Zero Effluent Laboratory: An Educational Experiment
A Chemistry Professor's Viewpoint

Thomas Hellman Morton
Department of Chemistry
University of California, Riverside

I would like to discuss what is perhaps the major volume generator in the academic setting, namely the instructional laboratory. I want to describe an educational experiment that we ran some years ago in the mid 1970's. This experiment was entitled Zero Effluent Laboratory (ZEL), and its purpose was to see to what extent we could recycle solvents in an organic teaching laboratory. Our effort was to minimize the volume of waste material by running our introductory organic laboratory in a mode that minimized effluent. Today's talk will be a distillation of our recycling efforts. It is not realistic to expect that we could have run a laboratory with absolutely zero effluent, and I use "zero" to designate the asymptote that we were trying to approach in our efforts. This project was run while I was on the chemistry faculty of Brown University in Providence, Rhode Island, at a time when awareness and legal structures were on a much different level than today. Our recycling effort focused principally on solvents.

There was another important consideration, namely to balance the requirements of teaching with the necessity that the students not expose themselves to excess hazards in the laboratory. We wanted to address the question of whether recycling and trying to make the laboratory safe were compatible with our teaching goals.

I want to discuss the ground rules and the constraints under which we operated. The particular laboratory course was introductory organic chemistry, which, at the time, was offered in the second semester of the freshman year. The students with which we dealt had completed only one prior semester of college chemistry. The laboratories in which this course was given were built in the 1930's and, although there had been some subsequent remodeling, the facilities were limited. The hoods were not dependable. Consequently, all reactions had to be worked on the bench top. The plumbing was also quite unreliable, so we were obligated to limit the quantity of waste that was to be flushed down the drain.

In recycling solvents, one major question was whether it is preferable for each student to recycle his own solvent individually or whether wastes should be collected and redistilled in one large batch. This question of individual versus collective responsibility pertained to other aspects of the lab as well. With regard to safety, is it the instructor's responsibility to make sure that hazards don't exist, or can we ask the students to take some aspect of the responsibility upon themselves? In our own case, we required something akin to informed consent from our students.

The students were required to show in writing in their lab notebooks that they had checked all the pertinent references to the hazards of the chemicals with which they were working in the Merck Index and the CRC Handbook of Chemical Safety. Lab notebooks were inspected during pre-lab lecture by the Teaching Assistants, and students were not permitted to enter the laboratory unless their notebooks showed that they had, in fact, done the requisite background research. Students were also required to write a flow chart for the fate of every reagent and every solvent that they used.

Every student was issued a couple of hundred milliliters of each of the solvents he or she was going to use most during the course: Freon 113, cyclohexane, hexanes, and acetone. Students were expected in the course of the semester to use these solvents, to recover them by recycling, and to return them to the bottle in which they came. Part of our objective over several years during which this educational experiment was run was to find out if solvents recovered at the end of one semester were really reusable the next year. Freon 113 is a particular solvent in question, because although it is extremely hazard-free from the standpoint of day-to-day laboratory operations, it is also quite expensive. Recycling was, in fact, a cost-saving measure, not only from the standpoint of disposal cost but also from the standpoint of the capital cost of buying additional solvent. We found, after several years, that the Freon 113 was perfectly adequate for instructional labs even though it had been recycled repeatedly.

For safety, we did not want to have open flames in the laboratory. We chose to use infrared heat lamps connected to variable power supplied as a heat source for distillation. Now, given a choice between generating solid waste and liquid waste, we chose to recycle the liquid as much as possible even at the expense of creating additional solid waste. We found that this was possible and really quite successful, and we drew several conclusions from our experience.

Our first conclusion was that recycling not only is not an impediment to teaching, it is, in fact, a good teaching tool. Second, making the laboratory safe for the students is not incompatible with high pedagogical standards. Finally, in regard to the question of students doing individual versus batch recycling, we found that it was preferable to assign the task to the individual student to deal with his own individual waste rather than to collect a large batch of material for redistillation. The same holds true for waste treatment.

Let me give an example. One of the problems we had to deal with was disposal of cyanide left over from a benzoin condensation. Students could render the cyanide suitable for disposal by oxidizing it with hypochlorite. We chose to investigate doing this disposal procedure as a batch operation, having a large jug of calcium hypochlorite into which students dumped the cyanide wastes. This worked perfectly well as a collective operation. However, in the same lab period, students were also doing an oxidation of the benzoin to benzil, a procedure that used acetic acid as a solvent. A small amount of acetic acid needed to be disposed of following the experiment. One student accidentally disposed of her acetic acid into the jug of hypochlorite. The jug did not survive. The student did, however, owing to fast action by a teaching assistant. But this exemplified the difficulty with any kind of recycling or disposal procedure that involves collective responsibility. Namely, the error of one can propagate to vitiate the collective effort of many.

Zero Effluent Laboratory

Leonard R. Corwin, Ronald J. Roth, and Thomas H. Morton

TABLE OF CONTENTS

PREFACE: THE NATURE AND FUNCTION OF CHEMISTRY 11 LABORATORY

Chem 11 laboratory this semester is a continuing educational experiment that originated two years ago at Brown. This experiment, which bears the title Zero Effluent Laboratory, is being supported in part by the Exxon Education Foundation. We are trying to discover if a successful laboratory course can be taught without exposing students to serious health hazards, without polluting Providence, and without needlessly wasting chemicals, time, and effort. Extensive cooperation and patience will be required for this semester to be a valid test.

How is the laboratory run?

There will be a pre-lab lecture by your instructor before each laboratory, starting at 1:00. When the pre-lab lecture is through, the labs will be opened and work can be started. The experiments are notated regarding the amount of work that should be completed in an afternoon.

In order that we may insure that students understand what they are going to do before they enter the lab, we require that the laboratory notebooks have the following entries in advance:

1. Toxicities of all reagents, solvents, and products to be encountered.

2. A flow chart indicating the probable fate of all chemicals used.

3. Spaces alloted for writing in the % yields and recoveries as well as adequate space for observations.

4. Answers to any queries that can be decided before the laboratory.

Laboratory notebooks will be given to the teaching assistants for checking during the pre-lab lectures. You may not enter the lab and start working until the teaching assistant has approved your notebook.

When you have finished working for the afternoon, turn in signed and dated yellow carbon copies of the germane notebook pages to your teaching assistant. Your TA will inform you the next week whether you have done satisfactory work. If not, your TA will tell you what needs to be done to make your work satisfactory.

The laboratory notebook

A complete and accurate record of lab work is essential. The lab notebook must include all procedures tried--not only those that worked but also those that failed. If there is no comprehensible and durable record of your efforts in the lab, they will have been truly wasted, because it will not be possible for another investigator to reproduce your results.

Since Chem 11 is an educational experiment and most of the lab modules have never before been used in a large lab course, it is particularly important that a good lab notebook be kept. While performing an experiment, you may find a result that has been overlooked by previous workers. If you should vary the conditions of a reaction, you may cause the reaction to fail. In either case, the result is interesting and important and we request that you be as observant and truthful as possible.

In order to keep an orderly record of your experiences in the lab, you must be well prepared to perform the experiment before entering the lab. The lab modules should be studied carefully and a pre-lab write-up must be entered in your notebook. You may not commence work in the lab until your notebook has been approved. The write-up should include a flow chart for the experiments, toxicity data on the compounds you intend to encounter, and spaces for writing in quantities of material used or collected. The first

entry in your lab notebook should resemble the example shown on p. 4. This material should be entered in your notebook before you come to the first lab meeting. An example of a notebook page from a preparative experiment is given on p. 5.

Queries

In subsequent weeks, you will prepare your notebook in a similar fashion, including equations, molecular weights of starting materials and products, moles of starting materials, and theoretical yields of products, where applicable. There will also be clearly marked questions scattered throughout the body of the text. Some can (and ought to) be answered before coming to lab (e.g., "What is the empirical formula of trimyristin?") while others can be answered only through your observations in lab.

Yield

A recurrent calculation in chemistry is the yield of a reaction. This is useful for determining the feasibility of a reaction in a sequence, for elucidating mechanisms, or as a criterion of technique in isolating the product. The percentage yield is simply

$$\frac{\text{weight obtained}}{\text{theoretical weight}} \text{ x } 100$$

To determine the theoretical weight one must know the molecular weights of the starting materials and products, the measured weights of the starting materials, and the balanced equation for the reaction.

	CH_4	+	Cl_2	$\longrightarrow$	CH_3Cl	+	HCl
M.W.	16		71		50.5		36.5
measured weight	16g		71g		50.5 g (theor.)		
moles	1		1		1		1

ISOLATION OF NATURAL PRODUCTS FROM NUTMEG

FLOW CHART

WHOLE NUTMEGS → CRUSH → SOAK IN FREON 113 → REFLUX → FILTER

RESIDUAL NUTMEG HULLS

FREON 113 SOLUTION

——— WEEK 1 ———

WEEK 2

DISTILL

POT RESIDUE   RECOVERED FREON 113

RECRYSTALLIZE FROM ACETONE

TRIMYRISTIN   MOTHER LIQUOR → CONTINUED WEEK 4

CONTINUED, WEEK 3
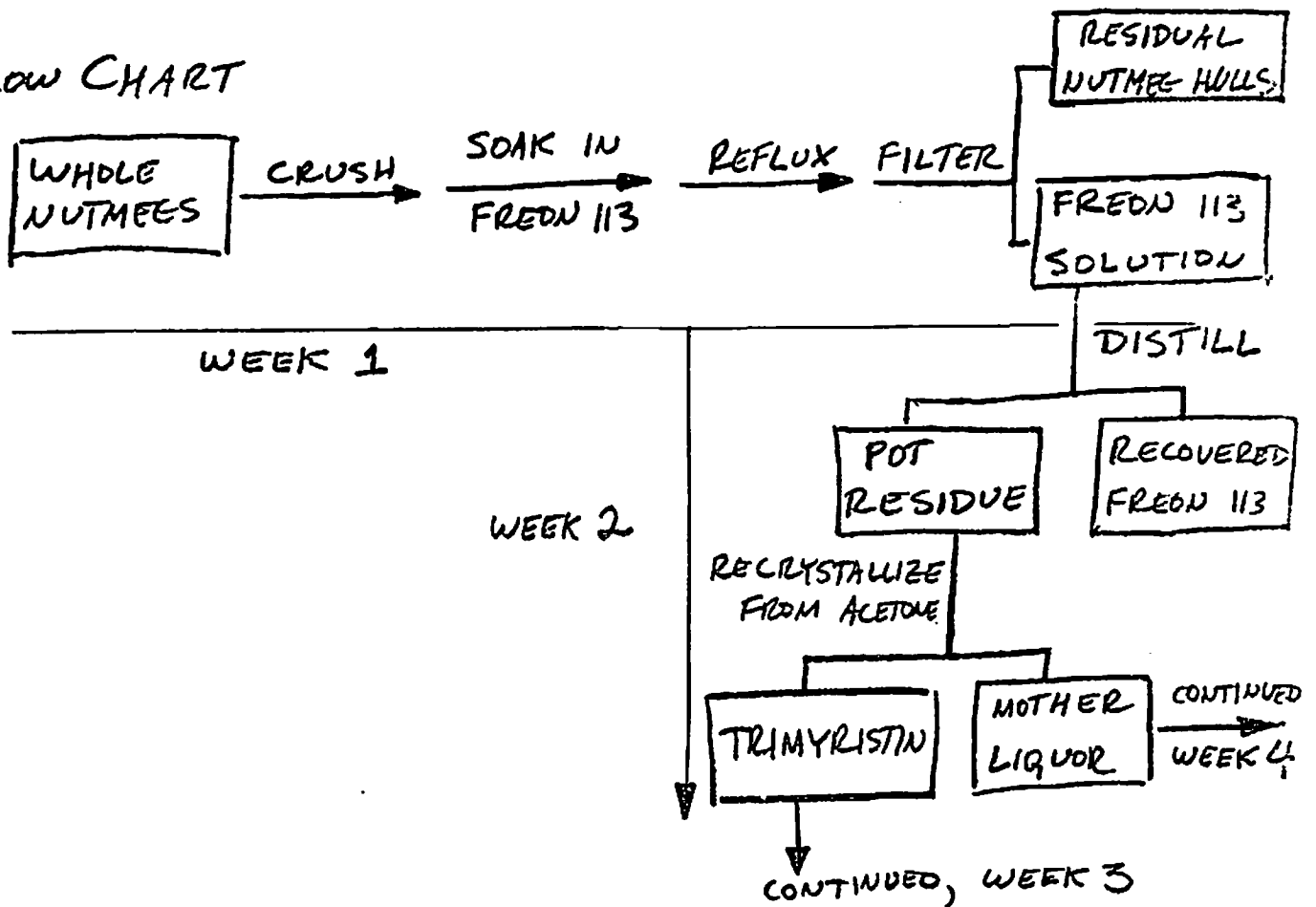
WEEK 1

TOXICITIES: FREON 113 [1,1,2-TRICHLOROTRIFLUOROETHANE, CRC]:

Minor inhalation toxicity hazard, Threshold limit value: 1000 ppm ($7600 \frac{mg}{M^3}$)

NUTMEG [MYRISTICA, MERCK INDEX]:
Ingestion of large quantities causes drowsiness, stupor, death.

DATA

of nutmegs received: Weight:

Volume of FREON 113 used:

Preparation of Methyl Cyclopropyl Ketone   Sept 10, 1974   CRM

over-all reaction

Flow chart - see next page

Toxicities

acetyl butyrolactone: skin irritant

HCl: corrosive solution & very irritating vapor

NaOH: caustic solution

Me cyclopropyl ketone: not listed. Other Me ketones with similar M.W. listed as
   irritating to eyes & mucous membranes, narcotic in high concns.

3-chloropropyl methyl ketone: not listed. Nothing similar. α-chloro methyl ketones are
                                                          lachrymators

Theoretical yield

starting acetyl butyrolactone   20 g = 0.16 mole
   flask tare weight   27.3 g
                        20.0
                        ‾‾‾‾‾‾
                        47.3 g final weight needed flask + lactone

1 mole acetyl butyrolactone ⇒ 1 mole Me cyclopropyl ketone   MW: C_5 60
                                                                  H_8 8
   0.16 mole × 84 g/mole = 13.4 g theor. yield   O   16
                                                                      ‾‾‾‾
Procedure   84

As in text: 20 g acetylbutyrolactone heated with 50 ml of 6N HCl.
Vigorous foaming, some of reaction mixture went up condenser.
Heated 25 min. Distilled ketone:

Time	Temp	Vol distillate	Time	Temp	Vol dist
2:45	97°	first drops	3:45	112°	30
2:50	99°	5 ml			
3:05	103°	10 ml		Distillation terminated. Pot contents	
3:15	105°	20		neutralized and discarded.	

Distillate consisted of 2 clear, colorless phases. Added 12 g NaOH &
refluxed 35 min. (Forgot boiling stone - cooled & added it). Added
12 g NaCl & sepd. layers.   Crude yield: flask + prod 36.5 g
Dried & distilled product, bp 108-113°,   tare   27.4 g
colorless, 7.0 g.   _ yield   ‾‾‾‾‾‾
                                                            9.1 g
Flask Made semicarbazone from 1.3 g of ketone   flask + prod 36.5
+ 0.5 g semicarbazide HCl + 0.8 g NaOAc. Beautiful   tare   29.5
rectangular or parallelogram plates pptd on scratching.   ‾‾‾‾‾
Filtered & left to dry (mp next week). Mp _____ .   7.0 g final

6

For example, if one mole of methane is allowed to react with one mole of chlorine, and if there are no side reactions and the reaction proceeds to 100% completion, one should obtain one mole of methyl chloride weighing 50.5g. If, in fact, one obtains only 25.25g of product, the yield is 50%. If the amount of CH_4 remained the same but 100g of Cl_2 (1.41 moles) was used instead, the chlorine would be present in excess and methane would be the limiting reagent. The maximum theoretical yield is still one mole or 50.5g of methyl chloride. If 50g of Cl_2 (0.71 mole) were used, it would be the limiting reagent and the maximum theoretical yield would be 0.71 mole or 35.8g of methyl chloride.

Before performing an experiment, you should write in your notebook the maximum theoretical yield in moles and in grams. After completing an experiment, you should record the actual yield of the dry product in grams and as a percent of the theoretical maximum (generally called, simply, the percent yield).

Is organic chemistry laboratory hazardous?

Definitely. One of the major objectives of the ZEL project is to eliminate some of the most blatant hazards. We have rid the laboratory of open flames: heat sources will be steam baths (up to 85°C) and infrared heat lamps. We have avoided solvents which are known to have serious effects from chronic exposure (benzene, carbon tetrachloride, chloroform) and those which pose grave fire and detonation threats (diethyl ether). We have avoided known carcinogens (benzidine, naphthylamine) and have tried to minimize skin irritation hazards. These sorts of safety hazards are part of most organic lab courses; the ZEL experiment is an effort to see if organic lab can be taught effectively without them.

There are plenty of hazards left. Most of the solvents (hexane, acetone, alcohol) are flammable. Some students may experience allergic skin reactions to certain reagents.

particularly organic halides. Some compounds are lachrymators: i.e., you will cry if their fumes get in your eyes (like onions). Some constitute severe inhalation hazards, e.g., bromine. These compounds may be used only in the fume hoods. Strong inorganic acids and bases can eat holes in your clothes or your skin. If, at any time, you suspect you have been physically affected by chemicals, tell your instructor at once.

All chemicals should be treated as if they are poison to ingest--even nutmeg (which, incidentally, is moderately toxic). Use a rubber bulb, not mouth suction, to fill a pipette. Furthermore, no smoking, eating, or drinking is allowed in the labs.

Some toxic chemicals may be absorbed through intact skin. If you get any chemical (even one you think is harmless) on your skin, wash it off immediately with large quantities of flowing water until you are positive the chemical is all gone (perhaps several minutes if the compound is not too water soluble). Chemicals in the eye may require washing for 15 minutes; do not hesitate to yell "Help!" to alert people around you in case you do need help finding a hose to bathe your eyes. There are no special eye-washing fountains in the laboratories. If you are drenched with a large volume of corrosive chemical, use a safety shower and do not let modesty deter you from getting the contaminated clothing off as quickly as possible.

As a primary protection for the eyes, you must wear safety glasses or goggles at all times in the laboratory! Contact lenses are forbidden; chemicals can get under them. Since you will have to step outside the lab if you take your goggles off, try to get a reasonably comfortable set. To protect the body wear a plastic apron, rubber gloves when appropriate, shoes, and clothing that does not expose large areas of the body.

A small fire not in contact with electrically live wires may be smothered with wet cloth or paper towels. Alert the teaching assistant, who will decide if a CO_2 extinguisher is needed. Note exit locations in case of need. Clothing fires can be extinguished with a

fire blanket or a safety shower (CO_2 can cause asphyxiation). Long hair can be a fire hazard and should be confined when in the laboratory.

Use of electrical equipment requires some caution, since some of the apparatus is not grounded, and there is often water about to serve as a conduction path. For example, if water gets into the socket of your infrared lamp, the socket and the ringstand to which it is clamped can become electrically live, and if you touched the ringstand and a ground such as a faucet at the same time, you could get a dangerous shock.

In addition to these precautions, we require that you look up the toxicities of all reagents and compounds you may handle in laboratory and write the information in your lab notebook before entering the laboratory. This information is to be found in CRC Handbook of Chemical Safety, the Merck Index, or the Toxic Substances List, copies of which are on 30-minute reserve at the Sciences Library.

We strongly urge that Chem 11 students refrain from drinking alcohol on their lab days (both before and after laboratory). Many toxic chemicals may interact with alcohol in the body and become much more poisonous. Two of the known examples are carbon tetrachloride and barbiturates. This effect may be due to the activation of certain enzyme systems to metabolize the alcohol.

Thermal burns occur occasionally. The best first-aid treatment is immediate (within seconds) immersion of the burned member in cold water or ice water.

Planning your lab time

In this laboratory you will gradually learn the economical use of time. Planning is as essential a part of good laboratory technique as manual dexterity. Some procedures require long blocks of time but relatively little attention once they are set up, such as heating a mixture for two hours. Some must be done in order, such as a sequence of short

reactions that require constant attention. In the former case, odd tasks can be accomplished while the major reaction is proceeding. In the latter case, it is best to concentrate on the reaction at hand or to set up equipment for the next step.

Although some time is needed to keep track of what you are doing, you should be busy most of the lab period. There is always glassware to wash, a bench to clean , a melting point to take, or an experiment to plan.

One problem that arises constantly is the cleaning and drying of glassware. You will find that it is worthwhile to wash glassware in odd free moments and at the end of the laboratory period. Wet glassware can be dried quickly (e.g., 5-15 minutes) in an electrically heated oven. Compressed air should not be used to hasten evaporation. Occasionally, a small amount of acetone may be used to rinse out water, followed by evaporation over a heat lamp (not the oven—fire hazard). However, we do not approve of this method for routine drying.

At the end of the lab period you should clean not only your own equipment but also the bench and sink near you. Spilled chemicals must be cleaned up immediately; for example, sodium or potassium hydroxide pellets rapidly absorb moisture from the air and turn into puddles of concentrated caustic solution that can cause severe chemical burns.

Chemicals stored in the locker must be labeled adequately, since their distinguishing characteristics are soon forgotten. Labels with moisture-sensitive adhesive are preferable to pressure sensitive ones, since the former can be removed with hot water. Wax pencils and felt pens may be used, but felt pen markings dissolve in organic solvents.

Why is the lab called Zero Effluent Laboratory?

Often, organic lab preparations contain the instruction, "Discard material X."
Even worse, there may be no instruction indicating what to do with material X. This is

usually wasteful, often damaging to the environment (as "discard" is generally taken to

mean "dump down the drain"), and never instructive. Chem 11 lab will generate some waste,

but our effluent will be much less than in previous years. Wastes that can not be recycled

will be disposed of in a legal fashion, sanctioned by the U.S. Environmental Protection Agency.

While minimizing the effluent from the laboratory, we also expect that students should

be able to account for all of the material consumed. If 5 grams of material went into the pot

and 3 grams were recovered at the end, what became of the other 2 grams? If you can't

find those 2 grams anywhere, then we expect you to try to provide an explanation for its

disappearance: "it evaporated," or "it reacted to form black tar at the bottom of the pot,

which I had to scrub out and discard." Try to substantiate your explanations.

Solvents will be distributed sparingly in Chem 11 in the expectation that recovery

operations will function well. At the beginning of the semester, every student will receive

one small bottle of each of the following solvents: cyclohexane, hexane, Freon 113,

and acetone. This should suffice for the entire semester. Hopefully, these bottles of

solvent will not be returned empty at the end of the semester.

The cost of a solvent is not the only expense associated with its use. Disposal of

used solvents by EPA (Environmental Protection Agency) authorized methods is not only

expensive, it is also wasteful.

Other solvents to be used in the laboratory include absolute (water-free) methanol,

95% ethanol, and tetrahydrofuran. On rare occasion, it may be necessary to dispose of

small quantities of these water-miscible solvents by flushing them down the drain.

What about environmental aspects of the lab?

In previous years, solvents and reagents left after isolation of a product usually went

down the drain. The ZEL laboratory is designed to recycle most solvents. This recycling

procedure is incorporated into the experiment when possible. In addition, large solvent recovery stills will be operated in the laboratories. The success of these communal batch recovery operations depends largely upon the care that each student takes.

In order for a recovery operation to function, the input must be carefully controlled. If, for instance, impure methanol is being purified by distillation, then it is vital that certain volatile impurities (such as Freon, acetone, or ethanol) be avoided.

There will be specially labelled cans for solvent recovery. You must not pour solvents into the wrong can, e.g., don't pour acetone into a methanol can. Details of this nature will be discussed in the individual experiments.

If, by accident, you dump the wrong stuff into a labelled can, tell your lab instructor at once. It may·be possible to salvage the recovery operation, provided that the identity and amount of·the impurity are known.

The batch operations will be run by the teaching assistants. Students are invited to investigate their operation during slack periods in their own experiments.

Is this recovery operation merely symbolic?

The logistics of Chem 11 laboratory are comparable to a small industrial concern; the course consumes large amounts of solvent. For example, each student uses about 250 ml of Freon 113 in the first experiment, the extraction of trimyristin from nutmeg. Freon 113 costs $10 a gallon. It is used because, in addition to being nonflammable, it is relatively nontoxic. The 450-500 students in Chem 11 will use 30-40 gallons of Freon 113—recovery of this solvent by distillation is certainly not symbolic.

Why is organic laboratory required?

This coming semester, the lecturers will outline some of the basic principles of organic chemistry. You may have heard that organic chemistry requires a lot of

memorization: in fact, there are unifying concepts which obviate much of this memori-
zation. These principles, though, were not handed down from heaven. It is vital to the
understanding of chemistry that their origins be visible. The gulf between the plausible
and the implausible has been created as much by experiment as by logic. This gulf is deep,
but narrow, and we feel that it is only through laboratory experience that one learns
which side is which.

But what do you get out of laboratory?

Chem laboratory is the place to learn from your mistakes. Since many principles
of science were discovered through trial and error (mostly error), we suspect that students
will learn in the traditional fashion. Most of you will soon discover that it is not trivial
to follow a recipe for an organic preparation. That which you can perform easily you
may consider already learned. That which gives you trouble you are learning.

What is there to learn?

Unlike most scholarly disciplines to which undergraduates are exposed, the field
of chemistry is intimately connected with an enormous industry. While the value of the
chemical industry (plastics, drugs, dyes, fuels, agricultural chemicals) to humanity is
much debated, the pervasive influence of chemistry upon every facet of life in the United
States is undeniable.

It has become a widespread belief over the past hundred years that the only way
to learn the techniques of chemistry is through laboratory experience. Chemistry 11
laboratory is the beginning of apprenticeship in organic chemistry. Regardless of
whether you choose to continue in this field, we feel that such experience is valuable.

What are "techniques of chemistry"?

Chemistry is a humanistic discipline. It is concerned with relations among our perceptions of reality, and it embraces a value system whose criteria are those derived from direct experience. All of the microscopic theory is related to some set of experiences: a color change, formation of crystals, deflection of a meter. Within the framework of the microscopic theory, the demonstration that a hypothesis is correct consists in the demonstration that alternative hypotheses are wrong within the limitations of human conception.

The connection between palpable reality and the microscopic theory is predicated upon the notion of the "pure compound." The purity of a compound often dictates the limits within which we may make inferences from its behavior. A great many of the techniques of chemistry are devoted to the isolation and purification of compounds. Of course, this means establishing operational definitions of purity. We hope that, in learning the techniques of chemistry, students will develop intuition regarding the meaning of the idea of a "pure compound."

In addition, the connection between the perception and the description of reality requires a feeling for the notion of change. Some things appear to change, yet we call these appearances illusory. The notion of change, like the notion of a pure compound, is difficult to define. Rather than provide canons for these notions, we present you, instead, with chemistry lab. The manipulations you perform in lab constitute chemical techniques: they provide the operational definitions for notions we cannot define.

Is this a "cookbook laboratory"?

The term "cookbook laboratory" connotes a course in which operations are specified to be followed unthinkingly. To avoid this mindlessness, the student must spend time

thinking about the experimental procedure until he actually understands not only what he is supposed to do but also why he is to do it a particular way. While most of the directions must be followed to obtain a certain product or result, some may be changed within limits. Understanding of the reasons for the procedure will permit some variation or correction of a mistake without beginning over.

As a consequence, we have attempted to write the Zero Effluent Laboratory modules in a rather detailed fashion. We are not trying to be patronizing: considerable skill is required to follow even a highly detailed preparative procedure. Moreover, the exercise of reproducing an experiment that someone else has already done is neither a simple - minded nor a trivial task: the fundamental criterion of value of an experiment is that it be reproducible. To be able to duplicate someone else's work (or to determine that it is not reproducible) is critically important for a chemist.

The lab experiments in Chem 11 are designed as paradigms for the development of laboratory technique. The written modules you receive this semester do not constitute a lab textbook so much as a chrestomathy, a collection of useful examples.

This calendar for the Chem 11 lab, 1977, shows the lab week (Roman numerals) for each day. The lab weeks do not correspond exactly to the numbered experiments; differences will be announced in the lab lecture.

Sun	Mon	Tue	Wed	Thu	Fri	Sat	
			2	3*	4	5	Feb
6	7 i	8 i	9 i	10 i	11 i	12	*Last day to change sections.
13	14 ii	15 ii	16 ii	17 ii	18 ii	19	
20	21 iii	22 iii	23 iii	24 iii	25 iii	26	
27	28 —	1 iv	2 iv	3 iv	4 iv	5	Mar
6	7 iv	8 v	9 v	10 v	11 v	12	
13	14 v	15 vi	16 vi	17 vi	18 vi	19	
20	21 vi	22 vii	23 vii	24 vii	25 vii	26	
27	28 vii	29 viii	30 viii	31 viii	1 viii	2	Apr
3	4	5	6	7	8	9	
		Spring recess					
10	11 viii	12 ix	13 ix	14 ix	15 ix	16	
17	18 ix	19 x	20 x	21 x	22 x	23	
24	25 x	26 xi	27 xi	28 xi	29 xi	30	
1	2 xi	3 xii	4 xii	5 xii	6 xii	7	May
8	9 xii	10 Check out	11	12 Check	13	14	
15	16 out						

1. ISOLATION OF TRIMYRISTIN FROM NUTMEG

The first five weeks of Chem 11 laboratory will be devoted to the extraction of two natural products from nutmeg, their purification, and the study of some of their reactions. This sort of work was typical of much chemical research prior to the 20th century, and in more refined form it continues to be of importance, especially in the search for new drugs or other biologically active compounds.

The experiments and background material have been divided into four large sections. There is some (but limited) flexibility in planning your time. We suggest the following division of lab work.

Week 1. Check in; pulverize nutmegs and reflux them in Freon

Week 2. Distill Freon, recrystallize trimyristin

Week 3. Saponify trimyristin, recrystallize myristic acid

Week 4. Purify and brominate myristicin

Week 5. Make myristic acid—urea inclusion complex; measure freezing point depression of "bromomyristicin" (optional).

Nutmeg is the common name of the seed from female Myristica fragrans, a tree native to the Spice Islands (the Moluccas, in the East Indies, now part of Indonesia). When the fruit of the tree matures, it splits in two, exposing a single seed sheathed in a crimson aril. The aril, a fibrous covering, constitutes the spice known as mace, and the seed is a whole nutmeg.

Nutmeg has been known as a spice in the Middle East for at least 2500 years, but it was not introduced into Europe until the Middle Ages. Dutch and Portuguese merchants monopolized the European nutmeg trade until 1843, when French and British interests succeeded in cultivating nutmeg trees in the West Indies. There is a decided
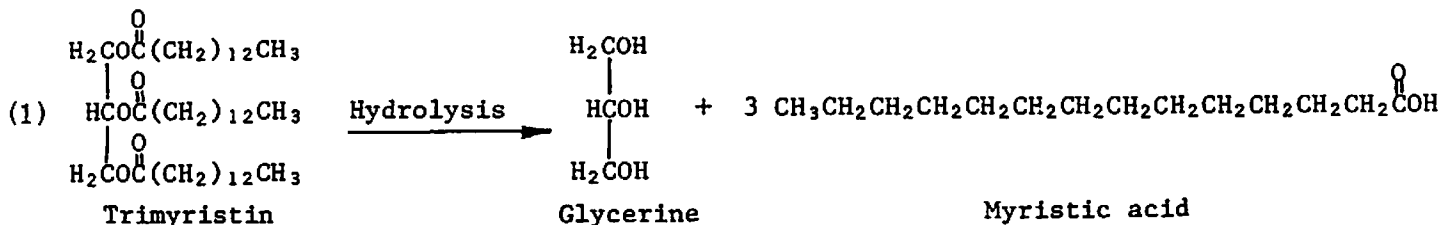
17

difference between East Indian and West Indian nutmeg.

Like many other spices, nutmeg has a long history of medicinal use. Preparations of nutmeg have been used as analgesics, digestive stimulants, aphrodisiacs, amenorrheal agents, and hypnotics. Medicinal use has declined since the 18th century, save for a brief period at the end of the 19th century, when it was rumored to be an effective abortifacient. Several medical journals of this period reported a high incidence of nutmeg poisoning among women. Recently, reports of nutmeg poisoning have again increased.

The nutmeg is about half cellulose. The other major components are fats, 25-40%, and essential oils, 8-15%. The former constitute the major portion of the expressed oil of nutmeg (obtained by pressing the seed), while the latter constitute the volatile oil of nutmeg (obtained by distilling the seed with steam).

Both of these components contain thousands of different compounds, only a handful of which have been identified. The expressed oil, also known as nutmeg butter, is composed principally of a lipid called trimyristin, the structural formula of which is illustrated in reaction 1. This fat also occurs in other plant and animal products, such as coconut oil and cow's milk.

Trimyristin is an example of a fundamental type of fat known as a triglyceride. Hydrolysis of one mole of a triglyceride affords one mole of 1,2,3-propanetriol (glycerine) and 3 moles of fatty acids, which are carboxylic acids containing the functional group $\overset{O}{\overset{\|}{C}}$——OH at the end of a long alkyl chain.

(1)

$$H_2CO\overset{O}{\overset{\|}{C}}(CH_2)_{12}CH_3$$
$$HCO\overset{O}{\overset{\|}{C}}(CH_2)_{12}CH_3$$
$$H_2CO\overset{O}{\overset{\|}{C}}(CH_2)_{12}CH_3$$
Trimyristin

Hydrolysis →

$$H_2COH$$
$$HCOH$$
$$H_2COH$$
Glycerine

$$+ \quad 3 \quad CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$
Myristic acid

The composition of the essential oil of nutmeg varies greatly, since chemical change accompanies some methods of isolation (e.g., steam distillation). When the oil is extracted from nutmeg with an organic solvent, its major components are the three compounds illustrated below, all derivatives of allylbenzene (elemicin is 3,4,5-trimethoxy-1-allylbenzene). Myristicin occurs in much higher concentration than elemicin or safrole.

MYRISTICIN

ELEMICIN

ALLYLBENZENE

SAFROLE
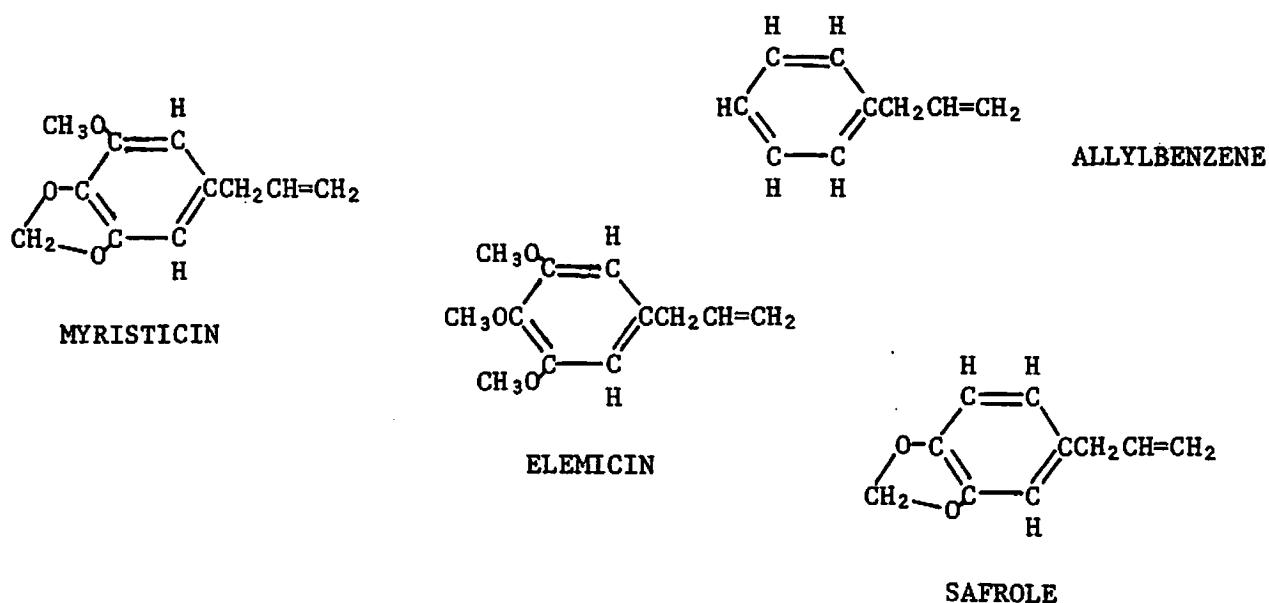
QUERY   What is the empirical formula $(C_xH_yO_z)$ of trimyristin? of myristicin?

Myristicin has been studied pharmacologically. In mice it inhibits the action of monoamine oxidase, an important enzyme in the central nervous system, and a distinct psychotomimetic effect has been detected in man. The effect of myristicin is reported to be stronger when the other constituents of the volatile oil are present. It has been suggested that the other components do not themselves contribute to the

psychotropic activity, but promote absorption of myristicin by irritating the gastrointestinal tract. One hypothesis regarding the hallucinogenic activity of allylbenzene derivatives is that they are metabolized to compounds related to amphetamine.

As for many pharmacologically active substances, the difference between an effective dose and a toxic does is not great. An aftereffect of ingestion of large quantities of nutmeg or myristicin is a lasting aversion to its taste or smell.

Procedure

Weigh 35-45 g of whole nutmegs to ± 0.1 g and crush and grind them, one at a time, with a mortar and pestle. Transfer the powder to a 500-ml round bottom (r.b.) flask and add 200 ml of Freon 113. Add a boiling stone to the mixture and fit the flask with the Liebig condenser (the fatter of the two in your kit--see Figure 1). Use a little stopcock grease on the condenser joint. Reflux the Freon 113 for 30 minutes over a heat lamp, then allow the mixture to cool for 15-20 minutes until the flask is warm to the touch. *

QUERY: When the refluxing is finished, you may notice a small patch of condensation remaining in the condenser. Using an eyedropper, drop some Freon 113 down the inside of the condenser. Does the Freon wash the condensation away? Remove the reflux condenser from the flask and drop some water down the inside. Does water wash away the condensation? What do you suppose the condensation to be? Where do you suppose it may have come from?

Then filter the suspension through a tared (preweighed), fluted, 18.5-cm filter paper into a 500-ml Erlenmeyer flask. Wipe the stopcock grease

---

* Work may be stopped here, but if possible continue to the place labelled **.

out of the neck of the r.b. flask with a piece of paper towel or a Kimwipe wet with

Freon before pouring the suspension into the filter. Then wash the r.b. flask with

two 10-ml portions of Freon to remove particles of nutmeg from the flask. Pour

these washings into the filter paper. Make sure that no particles of nutmeg get into

the filtrate. Wash out any particles of nutmeg remaining in the r.b. flask and dry

it before using it as a distillation pot. Set the residual nutmeg powder aside to dry.

Transfer the filtrate to your clean, dry 500-ml r.b. flask. Wash the 500-ml

Erlenmeyer flask with all your remaining Freon (there should be about 20 ml) and

add the washings to the still pot; add a boiling stone, too.**

With the regulated IR lamp as a heat source, distill the Freon 113 into a 250-ml

r.b. flask, using a West condenser (the smaller of the two). Surround the flask and

heat lamp with aluminum foil to conserve heat and to protect the plastic on the clamp

from the heat of the lamp (see Figure 3). Note the head temperature at the start of

distillation. Adjust the heat of the IR lamp so that the distillate comes over at a

rate of about two to four drops per second. Although this is faster than optimum,

the low vapor pressure of the extracted materials will prevent the Freon from being

too contaminated. Leave the heat constant and check the head temperature every 5

minutes until it has risen 6°C. This should not occur until most of the Freon has

distilled. Then turn off the heat.

While it is still warm, pour the yellow, oily pot residue into a 125-ml Erlen-

meyer flask. Rinse the pot with three 10-ml portions of acetone and add these wash-

ings to the pot residue. Swirl the clear, yellow solution for half a minute, set it

---

** You can stop here. Stopper the flask and store it until next week.

aside, and allow it to cool slowly to room temperature. A white precipitate should form within 30 minutes.

While crystallization is proceeding, record the volume of recovered Freon 113. Store the recovered Freon 113 for future use.

When the acetone solution has reached room temperature and a precipitate has formed, cool the flask further in an ice-water bath, swirling the flask occasionally. Be careful that the flask does not tip over. Collect the crystalline product by suction filtration using a Büchner funnel. Rinse the Erlenmeyer flask and wash the product with two 15-ml portions of cold acetone. Label and save the mother liquor -- it contains myristicin which will be isolated in a subsequent experiment.

Scrape the wet trimyristin onto a tared-watch glass and spread it out with a spatula. Record the weight of the dry nutmeg powder and of the wet trimyristin. Label the watch glass and store it in your lab locker for 1 week to dry. Dispose of the nutmeg powder in the designated containers (to be recycled via a compost heap).

If time permits, determine the melting point of the trimyristin. If it is less than 50°, purify the trimyristin by another recrystallization: dissolve the impure solid in 30 ml of hot acetone and allow the solution to cool slowly, undisturbed. Filter the solid on a Büchner funnel, wash with two 15-ml portions of cold acetone, and allow the white, crystalline product to dry on a watch glass.

Experimental Techniques

The procedure above employs several of the most commonly used techniques of organic chemistry: refluxing, gravity filtration, simple distillation, recrystallization, and suction filtration. It is hoped that you will come to understand all of these techniques in this experiment.

Refluxing

Trimyristin and myristicin are both quite soluble in Freon 113. However, simply soaking nutmeg in the solvent (even for one week) does not leach out large amounts of these compounds. For more efficient extraction, it is necessary to boil the suspension of nutmeg. In order that the solvent not be lost during the boiling, the flask is fitted with a reflux condenser, which is usually water cooled. This condenses the vapors and returns the liquid to the boiling mixture.
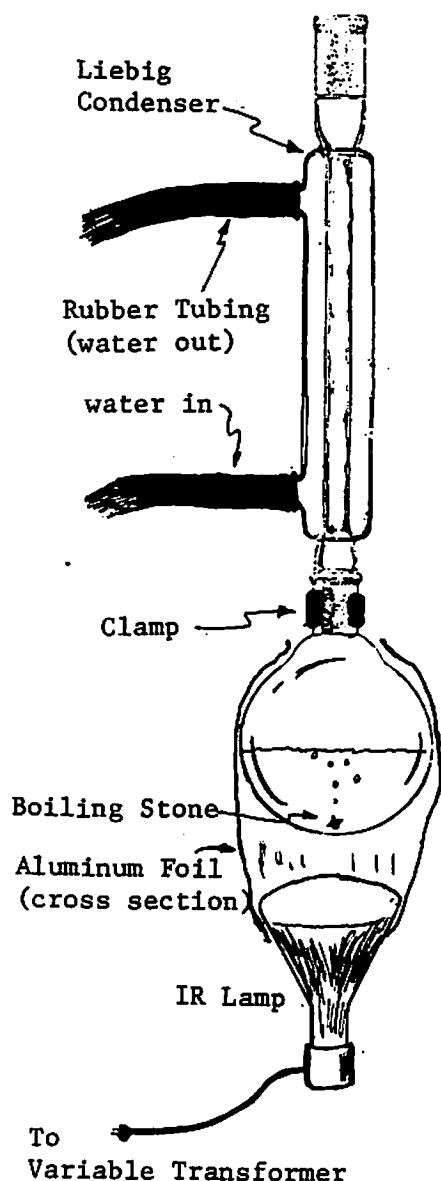
Rubber tubing for the condensers will be issued to you. The inlet hose connects the water tap and the bottom inlet of the condenser. The outlet hose runs from the top outlet of the condenser into the sink. Make sure that the hoses are attached securely. Do not turn on the water too rapidly; the hoses may burst or pop off the condenser. A trickle is sufficient.

Controlling a boiling liquid is not an entirely obvious procedure. The normal boiling point of a liquid is defined as the temperature at which the vapor pressure of the liquid equals atmospheric pressure (760 torr), but simply heating a liquid to its boiling point does not always cause ebullition. Instead many liquids become superheated. In this state they tend to burst into sudden, irregular, and often violent ebullition known as bumping. A porous object, such as a wooden stick or a small piece of jagged stone, is added to the liquid to prevent bumping. The

Liebig Condenser

Rubber Tubing (water out)

water in

Clamp

Boiling Stone

Aluminum Foil (cross section)

IR Lamp

To Variable Transformer

FIGURE 1. REFLUXING WITH A HEAT LAMP

bubbles of vapor form smoothly on the boiling aid; this increases the rate at which equilibrium is established between the liquid and vapor phases. Never add a boiling stone to a superheated liquid. The sudden eruption of boiling liquid that ensues may lead to a burn on your hand or a fire. If a boiling aid has been forgotten, cool the liquid before adding one.

The heat source for refluxing Freon 113 is an infrared (IR) heat lamp. This 220-watt lamp heats by radiation of photons which are not sufficiently energetic for the eye to see, but which can be absorbed by molecules and thereby converted to heat.

The heat lamp should be clamped to the ringstand after the boiling flask has been securely clamped on. The bulb of the heat lamp should be about one centimeter below the bottom of the boiling flask. The upper half of the bulb and the lower half of the flask should be wrapped in a cylinder of aluminum foil to minimize heat losses and conserve energy.

The heat output of the IR lamp is determined by controlling the input voltage with a variable transformer or solid-state controller (dimmer). Because the IR lamp also emits visible light, it is possible to gauge by eye the level of power output. The power output is not proportional to the dial setting of the controller.

As the flask warms, ebullition becomes evident and the contents of the flask are agitated. Gradually a column of refluxing vapor rises in the condenser. Then the output of the lamp should be set so that the top of the column of refluxing vapor is no higher than one-third the length of the condenser, or else there may be appreciable loss of solvent.
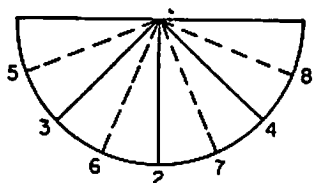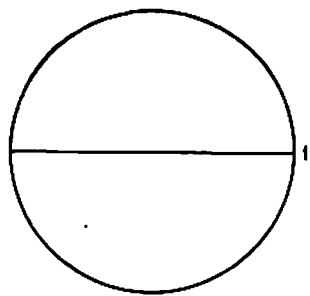
Fold in the order shown, fold downwards
on solid lines and upwards on broken lines

FIGURE 2: HOW TO
FLUTE FILTER PAPER

Gravity Filtration

Organic chemists use gravity filtration

only for rapid separation of coarse solids from

a liquid. The solid material left in the filter cone

is the residue. The liquid that has passed through

is the filtrate. The filter paper is ordinarily fluted,

so that the liquid will pass through quickly, to

minimize evaporation of the solvent. Fluting of

filter paper is not complicated and is illustrated

in Figure 2.

Simple Distillation

Distillation, an ancient art, is subject to many refinements. The distillation of

a volatile liquid from much less volatile substances is known as simple distillation, to

distinguish it from fractional distillation, a more complex technique for separating sub-

stances whose normal boiling points lie within 100°C of one another.

A set up for simple distillation is shown in Figure 3. The material to be

distilled is heated in a still pot. The condenser is connected to the pot by means of a

still head. A thermometer is inserted into the head to measure the temperature of the

vapors before they enter the condenser. For the thermometer to read the head

temperature accurately, the top of the bulb should be about half a centimeter below

the bottom of the sidearm. All joints should be lightly greased (apply enough with a

finger tip that you can see a thin film but no excess squeezes out of the joint). The

ringstands and clamps should be arranged so that all joints fit snugly but no strain is

put on the glass.

Vapors are condensed in a West condenser. The narrow jacket of the condenser provides for efficient cooling when the condenser is set at an angle. Liquid from the condenser flows into the collection flask via a receiver adapter. This adapter has an outlet to allow pressure equalization with the atmosphere (or evacuation, if the distillation is performed under reduced pressure). One must never distill or reflux in a closed system.

The boiling range of a distillation is the temperature span over which the distillation is carried out. The distillation is considered to have begun when liquid starts
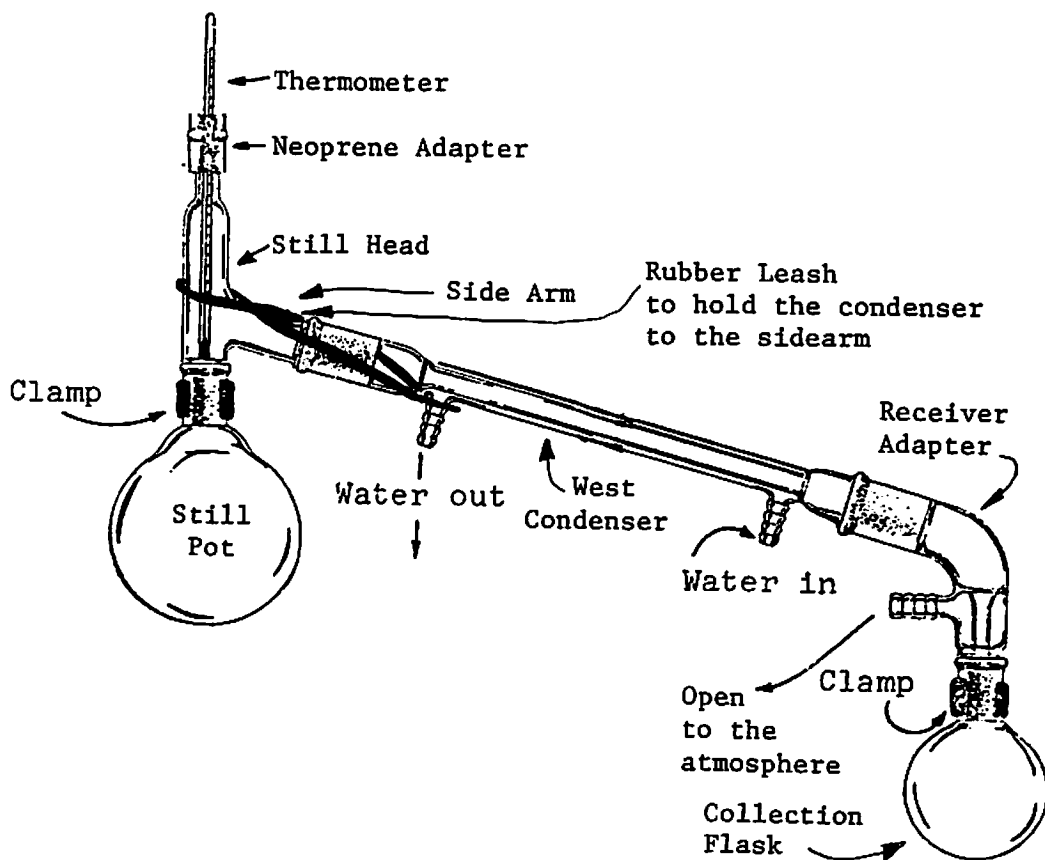
FIGURE 3: APPARATUS FOR SIMPLE DISTILLATION

to drip into the collection flask. It is extremely important that the bulb of the thermo-meter be well immersed in the column of refluxing vapors in the still head. For dis-tillations above 100°C, it is necessary to correct the observed temperature because the stem of the thermometer is at room temperature. This stem correction may amount to 3-5°C at 200°C and is necessary if the reported boiling range is to be accurate.

It is rare that even a pure liquid distills at a constant temperature, and a boiling range of 1°C is often considered quite good. When a pure liquid, or a pure liquid suspending an insoluble and nonvolatile substance, distills, the temperature of the boiling liquid (the pot temperature) and that of the vapor (the head temperature) will be about the same. The range of the head temperature is a very important piece of data and should always be recorded.

When the boiling liquid contains a soluble, but nonvolatile material, the pot temperature will rise as the concentration of solute increases. The range of the head temperature will be the same as for the distillation of the pure liquid, since the composi-tion of the vapors in both instances is identical. In other words, the range of the head temperature for distillation of the pure liquid and for distillation of the liquid containing nonvolatile solute will be the same. The ranges of the pot temperatures will be different.

Many simple distillations are performed on liquids containing solutes of slight volatility. As the mole fraction of solute in the liquid increases, the mole fraction of solute in the vapor increases as well. Very low concentrations of slightly volatile materials in the vapor will cause significant rises in head temperature.

It is possible to estimate the composition of the distillate at a given temperature if the boiling points of the components in the pot are known. For example, consider the distillate which is collected at a head temperature of 54°C from a solution of

myristicin in Freon 113. To estimate the composition of the distillate, using some

results from 19th century thermodynamics, the following values are determined in

four steps. First, the heat of vaporization, ΔH_{vap}, of each of the compounds in the

pot must be estimated. There is a useful approximation, known as Trouton's Rule,

which states that for nonpolar compounds,

(1) $$\Delta H_{vap} \approx 22\ T_b \text{ [calories/mole]}$$

where T_b is the normal boiling point in degrees Kelvin. For example, Freon 113

has a normal boiling point of $321^\circ K$ $(48^\circ + 273^\circ)$. By Trouton's Rule, it is estimated

that the heat of vaporization of Freon 113 is about 7000 calories/mole.

QUERY: The normal boiling point of myristicin is $280^\circ C$. What is its
boiling point in degrees Kelvin? Estimate the heat of vaporization of myristicin
using Trouton's Rule. In all queries of this type, include the equation, the
substitution, and the answer.

Once the heat of vaporization is known for each of the components in the pot,

the second step is to compute the vapor pressure of each component at the given head

temperature. To estimate the vapor pressure of a pure substance, one may use the

Clausius-Clapeyron Equation:

(2) $$\ln \frac{P_2}{P_1} = \frac{\Delta H_{vap}}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right)$$

where R is the gas constant (2.0 cal/mole-degree), while P_1 and P_2 are the vapor

pressures of the pure substance at T_1 and T_2, respectively. For example, the vapor

pressure P_1 of Freon 113 at $321^\circ K$ $(48^\circ C)$, or T_1, is 760 torr. Therefore, the vapor

pressure P_2 of Freon 113 at $327^\circ K$ $(54^\circ C)$ may be estimated as follows:

$$(2a) \qquad \ln(P_2/760) = \frac{7000 \text{ cal/mole}}{2.0 \text{ cal/mole-degree}} \cdot (\frac{1}{321^\circ K} - \frac{1}{327^\circ K}) = 0.20$$

From this, remembering that $\ln x = 2.3 \log x$, $\log (P_2/760) = 0.20/2.3 = 0.087$ and

$P_2 = 760 \cdot 1.22 = 930$ torr.

QUERY: What is the vapor pressure of myristicin at 54°C ?

The third step is to use Raoult's Law to calculate the mole fraction of myristicin,

X_A, and the mole fraction of Freon 113, X_B, in a mixture of the two compounds which

boils at 54°C. At the boiling point of a liquid, its vapor pressure is 760 torr. Raoult's

Law states that, at atmospheric pressure, the vapor pressure over an ideal solution

is equal to the sum of the products of the vapor pressures and the mole fractions of

each component, i.e.,

$$(3) \qquad 760 \text{ torr} = X_A^\ell P_A + X_B^\ell P_B$$

where P_A is the vapor pressure of myristicin at 54°C and P_B is the vapor pressure of

Freon 113 at 54°C.

Bearing in mind that we are considering only two components, Freon 113 and

myristicin, $X_A^\ell = 1 - X_B^\ell$. Since, from the last query, P_A is much smaller than P_B

$(P_A < 0.001 P_B)$ at 54°C, we may ignore the first term on the right in Eq. (3). Then

the mole fraction of Freon 113 in the boiling liquid is 760/930, i.e., $X_B^\ell = 0.82$, and

the fraction of myristicin in the pot is $X_A^\ell = 0.18$.

The vapor that is boiling from the Freon-myristicin solution at 54°C has a

different composition from the liquid. This is what makes distillation possible

as a method of purification, for the distillate has the same composition as the vapor.

The mole fractions of myristicin in the vapor, X_A^{vap}, and of Freon 113 in the

vapor, X_B^{vap}, are determined from Dalton's Law:

QUERY: At what pressure would myristicin boil at a temperature of 54°C ?
Hint: No further calculation is necessary.

Trimyristin has a normal boiling point of 311°C, only 31°C above that of myris-

ticin. At reduced pressure, the boiling point difference between the two compounds

will be smaller.

QUERY: Use the Clausius-Clapeyron equation to determine the boiling point of
trimyristin at the pressure you calculated in the previous query. Hint: you know P_1,
P_2, and T_1. Substitute to find T_2. What is the difference in boiling points at this
pressure?

Figure 4 illustrates the distillation characteristics of two compounds whose

boiling points are 26° apart and whose behavior is practically "ideal": i.e., it conforms

to the theoretical model. Distillation of a 1:1 mixture of the two compounds (point X on

the graph) gives a vapor and, hence, a distillate whose composition can be determined

by drawing a tie line from point X' to point Y on the condensation curve. The distillate

will not be pure substance B but about 70% compound B. A second distillation of this

distillate (point Y) will still not give a pure vapor and distillate but roughly 90% B

(point Z).

If the trimyristin-myristicin mixture were to behave ideally, the simple dis-

tillation of this mixture would behave like the isobutanol-isopropanol system depicted,

and the distillate would be a mixture of the two compounds. Nonideal behavior fre-

quently makes the distillation even less efficient.

Recrystallization

Myristicin and trimyristin may be separated more efficiently by taking advan-

tage of the fact that trimyristin is a solid at room temperature. The technique, known

as recrystallization, also makes use of the solubility characteristics of trimyristin in acetone.

The solubility of most solids in a liquid increases with temperature (as opposed to most gases, whose solubilities in a liquid decrease with increasing temperature). For instance, trimyristin is much more soluble in acetone at 50°C than at 0°C. Therefore, a saturated solution at 50°C will become supersaturated if the temperature is lowered to 0°C, and trimyristin will precipitate from the solution. The remaining solution is known as the mother liquor.

Of course, the solubilities of the other components of the mixture will also vary with temperature. However, it is often possible to find a solvent (acetone) in which the impurities (myristicin) are much more soluble than the substance to be purified (trimyristin).

Recrystallization has a distinct advantage over distillation. As Figure 4 shows, simple distillation of a 90:10 mixture cannot give one pure compound if the boiling points of the two components of the mixture are only 30° apart. It is clear that only multiple "stepwise" distillations (fractional distillation—to be discussed later) can give a product that even approaches 100% purity.

Recrystallization, however, should give a precipitate that is composed only of the compound in which the solution is supersaturated. Since myristicin is much more soluble in acetone than the trimyristin, the precipitate should be pure trimyristin. In other words, recrystallization "subtracts" the impurities from a mixture, while distillation "divides" them between the pot and the distillate.

The recrystallization of trimyristin from acetone is not a difficult procedure, since crystals of trimyristin ordinarily form within a reasonable length of time. Other recrystallizations do not always proceed so readily, since nucleation may take place

very slowly. Nucleation is the hypothetical process by which crystal growth starts: molecules cluster about microscopic sites called <u>nuclei</u>, and microscopic crystals are formed, which grow, by accretion, into macroscopic crystals. Once nucleation sites have been formed, a supersaturated solution will deposit crystals within a finite span of time.

If a supersaturated solution does not nucleate, it may become viscous and glassy, it may deposit an oil, or it may sit and do nothing. There are several ploys one may use to induce crystallization. The first is to reheat the solution and allow it to cool again slowly and undisturbed.

If this tactic fails, one tries <u>scratching</u>: insert a sharp glass rod into the supersaturated solution and rub the wall of the vessel repeatedly as the solution cools. Mysteriously, this sometimes works. It has been suggested that scratching dislodges tiny particles of glass, which act as nucleation sites.

Addition of a seed crystal to a supersaturated solution will induce crystallization. Obviously, this tactic is possible only if some of the solid to be crystallized is available. If it is not, the supersaturated solution should be set aside in a cool, dark place for a few days. Some crystallizations have taken years. Prayer is sometimes useful.

Alternatively, one can distill away the solvent and attempt the recrystallization using another solvent or a <u>two-solvent system</u>: a solvent which is miscible with the recrystallization solvent, but in which the substance to be purified is insoluble, is added to the supersaturated solution. This technique may result in formation of an oil.

There are two stages in a recrystallization where the purity of the isolated product may be lowered. If the saturated solution is cooled too quickly or disturbed, small pockets of mother liquor are trapped inside the crystals as they grow. This is known as <u>occlusion</u>. Thus a solution to be crystallized is allowed to cool by itself, and once
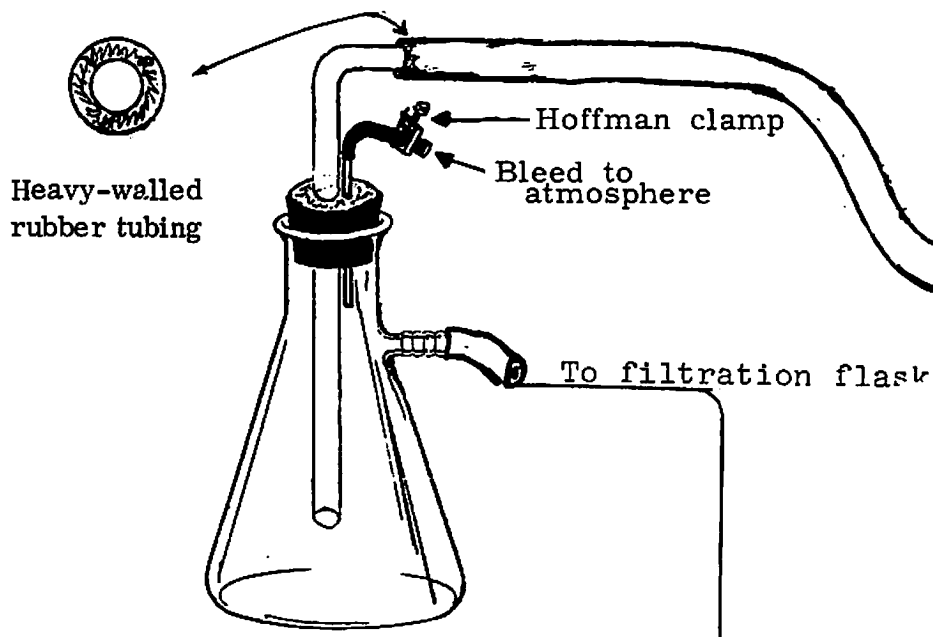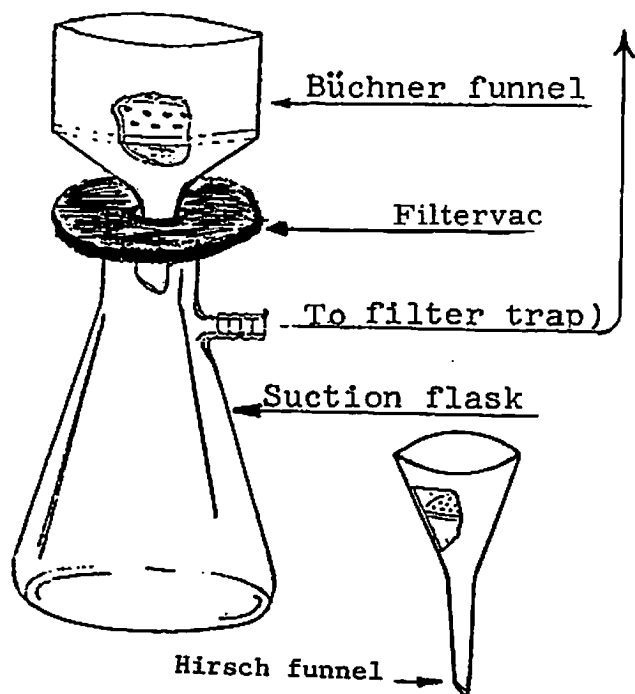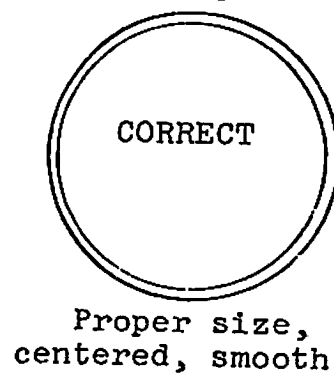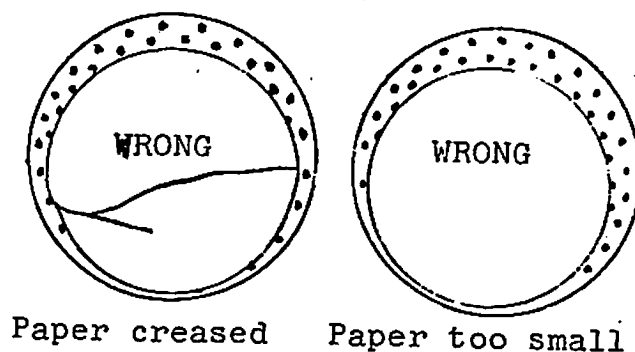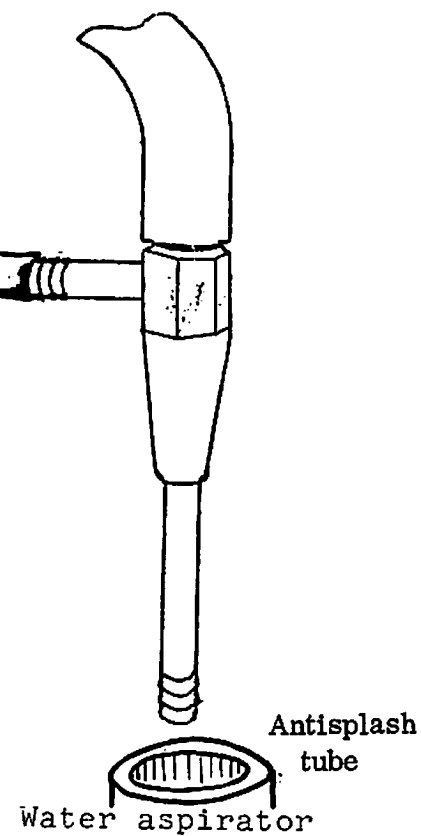
FIGURE 5: APPARATUS FOR SUCTION FILTRATION

FIGURE 6: POSITIONING THE FILTER PAPER

Connect the suction flask with the Büchner funnel to the filter trap and turn the aspirator water on full force. Close the Hoffman clamp to maximize the vacuum, make sure the filter paper is held firmly in place, open the clamp, and pour the suspension of crystals and mother liquor onto the filter paper in the Büchner funnel. Place your fingertip over the end of the bleed in the filter trap so that suction is applied. Do not suck the crystals dry before washing them. Instead of controlling the vacuum with the bleed, it may be easier to press the funnel more or less tightly against the Filtervac with the Hoffman clamp closed.

When most of the mother liquor has filtered through, take a small portion of cold solvent and wash out the rest of the solid in the recrystallization flask. Pour the washings and the solid into the Büchner funnel and again carefully apply suction. Again, do not suck the solid dry. Repeat the washing procedure until the filtrate is colorless (unless, of course, your product is colored). Do not wash with so much solvent, however, that your product dissolves. When the product has been adequately washed, suck the solid for a few minutes to dry it. Pressing the solid down with the bottom of a small flask or beaker will sometimes facilitate removal of solvent. Open the bleed valve or otherwise break the vacuum before shutting off the aspirator.

If filtration is very slow, check that the bleed valve is closed, and try pressing down on the funnel to make a vacuum-tight contact around the Filtervac. If the filter paper has clogged due to a fine precipitate, it should be removed and a new one inserted.

Melting Point

When the solid has dried, its melting point should be determined to test its purity. A micro melting point should be performed routinely on all solid products once they have dried.

A micro melting point is determined by filling the bottom of a 1-mm capillary tube

with sample, placing the capillary tube in a melting point block equipped with a mag-

nifying glass and a thermometer, and heating the block slowly until the solid within

the capillary tube melts. Under ordinary circumstances, only the bottom of the capillary
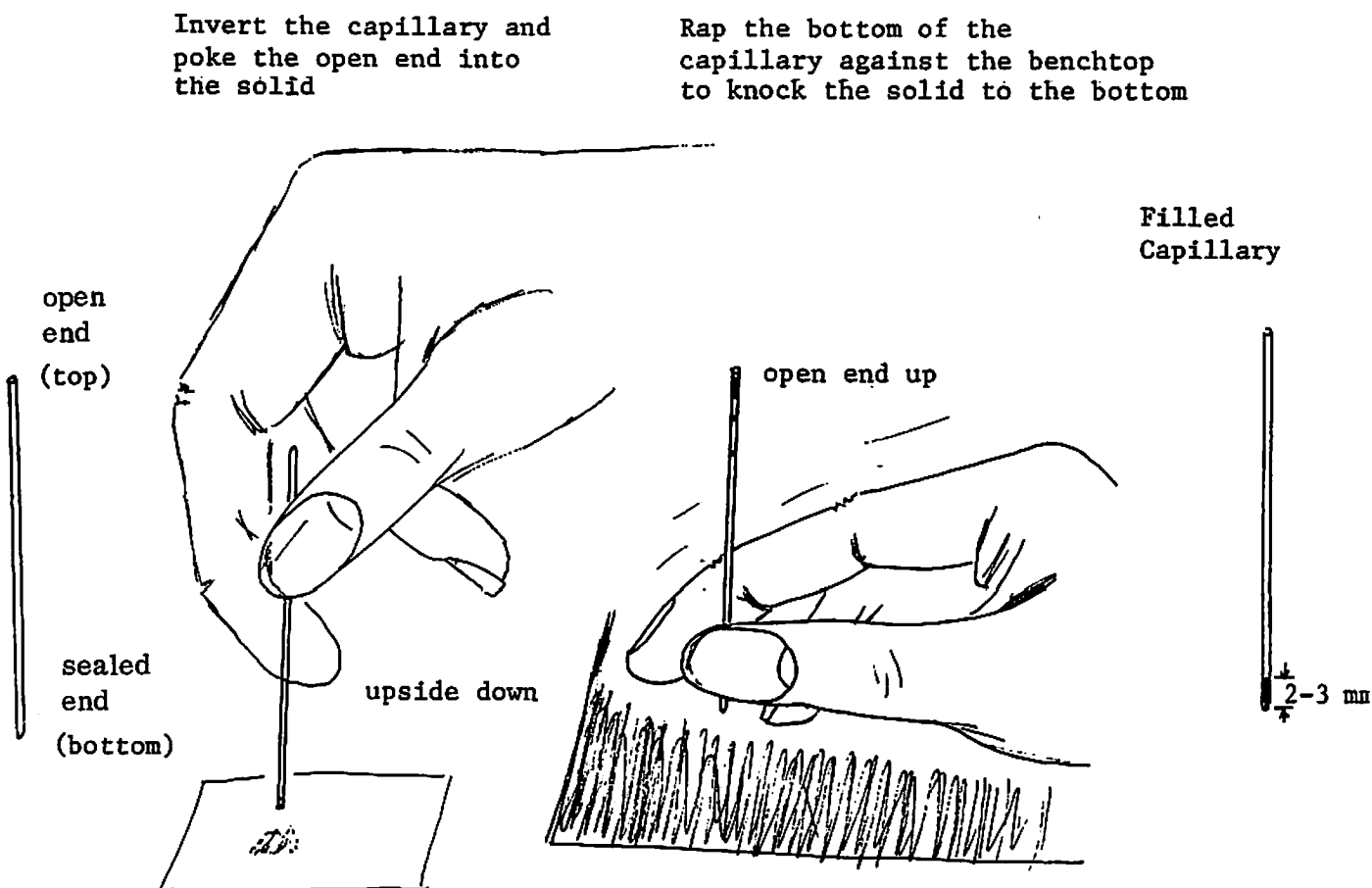
tube is sealed.

Invert the capillary and
poke the open end into
the solid

Rap the bottom of the
capillary against the benchtop
to knock the solid to the bottom

Filled
Capillary

open
end
(top)

open end up

sealed
end
(bottom)

upside down

2-3 mm

Figure 7: How to fill a melting point capillary

Most solids, even when quite pure, melt over a temperature range. Melting

is considered to have begun when the solid is observed to soften or lose shape; it is

not finished until all the solid has been converted to liquid. A melting range of 1°C

usually indicates satisfactory purity. Impure compounds melt over wider ranges.

When a compound is contaminated with solvent or an impurity, it will melt at

a lower temperature than the pure compound. The observed micro melting point of a

solid is usually a gauge of its purity.

In the trimyristin experiment, most of the solid compounds melt at relatively low temperatures and their melting point ranges can be determined accurately but quickly even though heat is being applied slowly and regularly $(2^{\circ}$ rise per minute). Many compounds have high melting points and, to avoid spending an inordinate amount of time measuring their melting points, you should take melting points of two samples. The first melting point is done crudely and quickly (perhaps $15-20^{\circ}$ rise per minute) to give an approximate melting point. The second sample is rapidly heated to a temperature 20° below the crudely determined melting point and then heated slowly $(2^{\circ}$ rise per minute) to determine the melting point range accurately. We repeat for emphasis that the recorded melting point comprises two numbers: the beginning of melting and the point of disappearance of the last bit of solid.

The proton nuclear magnetic resonance spectra of the four solvents used in the nutmeg experiments are given in Figure 8.
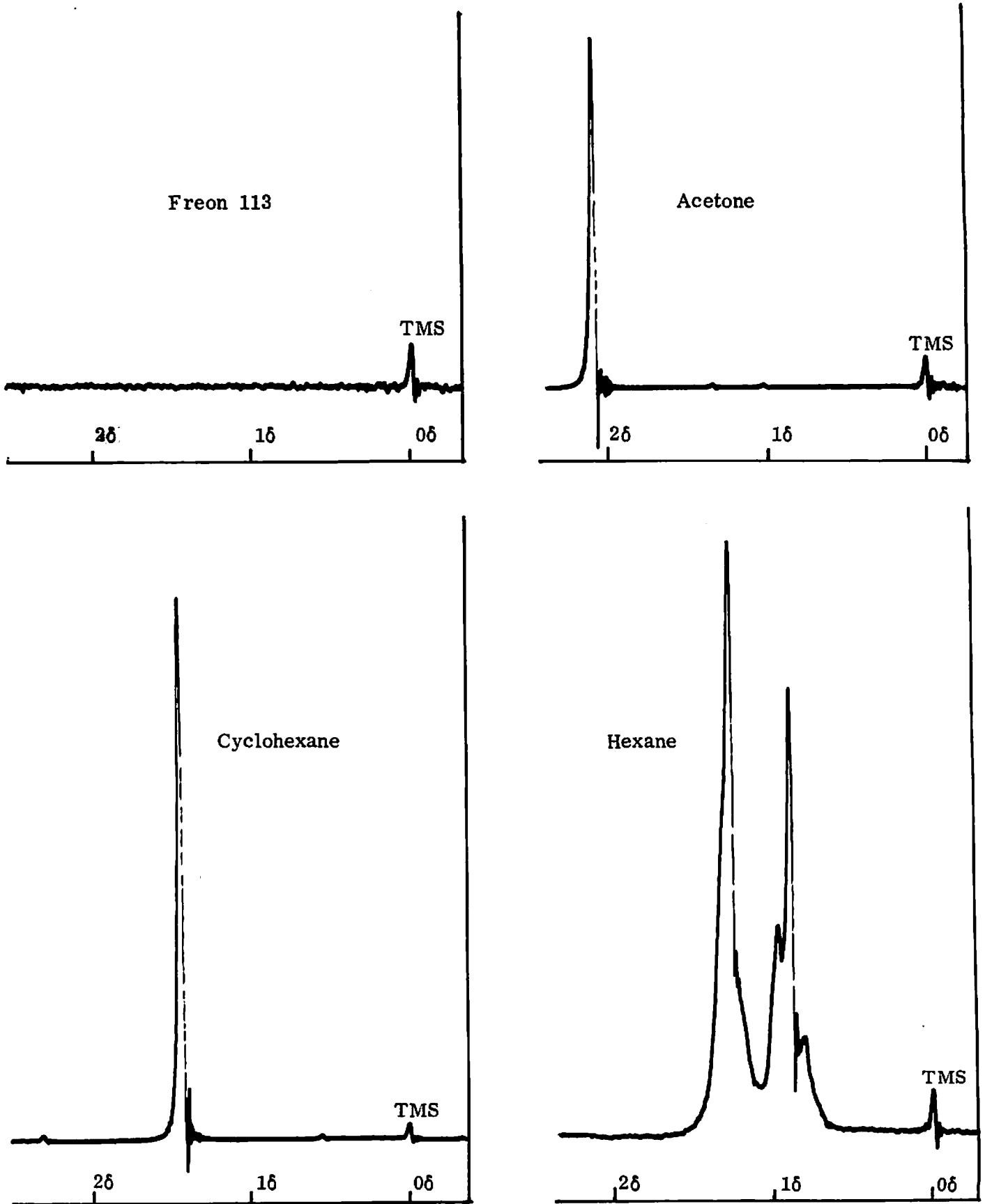
Figure 8:   Sixty MHz proton nmr spectra of solvents at 1000 Hz sweepwidth, in CCl_4

2. THE SAPONIFICATION OF TRIMYRISTIN: PREPARATION AND PURIFICATION OF MYRISTIC ACID AND AN INVESTIGATION OF ITS UREA INCLUSION COMPLEX

Soap, according to Pliny the Elder, was discovered by the Gauls, who used the substance as a cosmetic, particularly as an aid in dying their hair red. Although scholars have disagreed regarding the truth of Pliny's statement, there is no doubt that soapmaking, which is at least as old as Pliny (who died in the eruption of Vesuvius in 79 A.D.), is among the most ancient of organic chemical processes.

The basic reaction of soapmaking, called saponification, consists in the treatment of a fat with alkali. The products of the saponification of fats, glycerine and alkali metal salts of fatty acids, were first characterized by Michel Chevreul in 1815.

Saponification, historically, has been an important laboratory degradation, a reaction in which a natural product is broken down into recognizable parts. Chevreul's discovery led to the characterization of the chemical structure of fats and the recognition of the ester linkage, an extremely important functional group. An ester may be represented by the general formula $R-O\underset{O}{\overset{}{C}}-R'$, where R and R' symbolize organic groups. Trimyristin, for instance, like other triglycerides has three ester linkages ($-O\underset{O}{\overset{}{C}}-$ groups); in each one, R' is a long alkyl chain. The term saponification has come to refer to the reaction of any ester with base, Reaction 1.

$$(1) \quad R\underset{O}{\overset{}{C}}R' \quad + \quad OH^- \quad \rightarrow \quad ROH \quad + \quad {}^-O\underset{O}{\overset{}{C}}R'$$

$$\text{ester} \qquad\qquad\qquad\qquad \text{alcohol} \qquad \text{carboxylate anion}$$
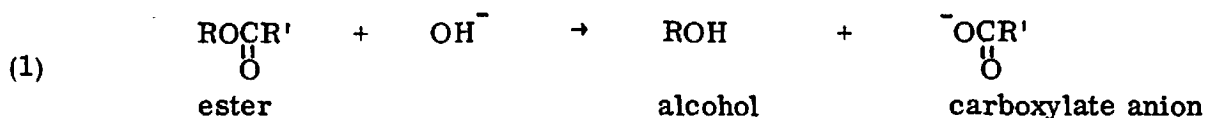
There is a great deal more to be learned about a chemical reaction than simply its products. One may, for example, inquire how the rate of the reaction is affected by alteration of the concentrations of the reactants. Saponification was among the

40

first reactions whose <u>kinetics</u> was studied; in 1881, R. B. Warder determined that

the reaction was first order in alkali and first order in ester, <u>viz.</u>

$$\frac{d[ester]}{dt} = -k[ester]\,[OH^-]$$

Suppose a saponification is run with one equivalent each of ester and base.

That is, at the start of the reaction, $[ester]_0 = [OH^-]_0 = X_0$. Let X represent the

concentration of ester at any time $t \geq 0$ ($t = 0$ is the start of the reaction). Because

of the stoichiometry of the reaction, one equivalent of base consumed for every equi-

valent of ester, $[OH^-]$ is also equal to X. Therefore

$$\frac{d[ester]}{dt} = \frac{dX}{dt} = -kX^2$$

This differential equation may be integrated to give X as a function of t,

$$X = \frac{1}{kt + C}$$

where C is a constant of integration. The value of C may be determined by remember-

ing that $X = X_0$ when $t = 0$. In other words, $C = 1/X_0$.

The half-life of the reaction, designated $\tau_{1/2}$, is the time required for X

to fall to half its initial value. Thus

$$X_0/2 = \frac{1}{k\,\tau_{1/2} + \frac{1}{X_0}}$$

which is easily rearranged to

$$\tau_{1/2} = \frac{1}{kX_0}.$$

QUERY: How many half-lives does it take for the reaction to go from the start
to 90% completion (i.e., to $X = X_0/10$)? to 95% completion? Hint: Calculate t in
terms of the constants and express it as a multiple of $\tau_{1/2}$. Suppose the reaction is

started with the initial concentrations of both reactants half as great, i.e., $[ester]_0 = [OH]^-_0 = X_0/2$. What will the half-life of this reaction be?

One may also inquire whether the oxygen in the alcohol product comes from the ester or the hydroxide ion reactant. This is a question of <u>mechanism</u>; that is, by what steps does the reaction occur? This question was answered in 1934 by Michael Polanyi and A. L. Szabo, who saponified an ester with hydroxide ion <u>labelled</u> with the isotope ^{18}O (the normal isotope of oxygen is, of course, ^{16}O). None of the ^{18}O was in the alcohol product—all of the isotopic label was found in the carboxylate anion. On this basis, the following steps are proposed for the saponification reaction (the asterisk denotes the labelled oxygen):

(2)

$$HO^-_* + RO\underset{O}{\overset{}{C}}R' \rightarrow RO\underset{\underset{*}{OH}}{\overset{O^-}{C}}R' \rightarrow ROH + \underset{\underset{*}{O}}{\overset{^-O}{C}}R' \leftrightarrow \underset{\underset{*}{-O}}{\overset{O}{C}}R'$$
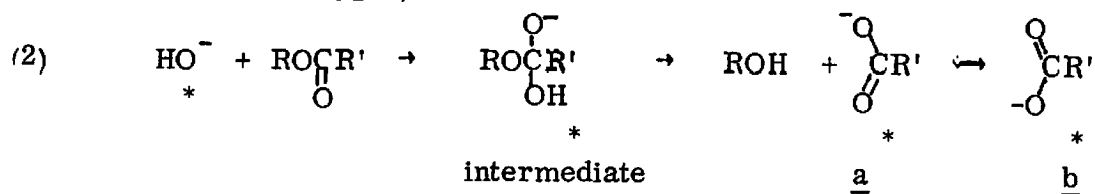
intermediate   <u>a</u>   <u>b</u>

There are two salient features of Reaction 2. First, there is an <u>intermediate</u>, an anion formed by attack of hydroxide on the ester. Nobody has ever isolated this intermediate; it remains a hypothetical species whose existence is presumed from the experiments by Warder, Polanyi and Szabo, and others.

A second feature of Reaction 2, not related to the question of mechanism, is that the carboxylate anion product is represented by two equivalent structures, <u>a</u> and <u>b</u>. They are known as <u>resonance structures</u>, and are connected by a double-headed arrow, ↔ , rather than by "equilibrium arrows," ⇌ , to distinguish between resonance and equilibrium, two concepts which are of great importance in theoretical

organic chemistry. This difference will be discussed extensively in the lecture; suffice it to say, at this point, that resonance delocalizes the negative charge in the anion, making it a more stable species.

Because of the stability of carboxylate anions, most carboxylic acids have dissociation constants (K_a's) on the order of 10^{-4} to 10^{-5}.

QUERY: What is the dissociation constant (K_a) of water? The K_a of myristic acid in water is about 10^{-5}. How much myristic acid is present in a 0.1 $\underline{M}$ solution of potassium myristate? What is the pH of a 0.1 $\underline{M}$ solution of potassium myristate?

Hint: To solve this seemingly impossible problem, remember that the operative equation is

$$Myr^- + H_2O \; \rightleftharpoons \; HMyr + OH^-$$
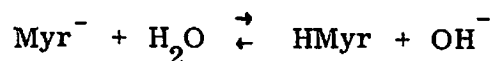
To find the equilibrium constant for this equation, make use of K_a found above. To determine [HMyr], remember that the concentration of potassium myristate is 0.1 $\underline{M}$ (and assume it does not vary) and also that, for every molecule of HMyr formed, a hydroxide ion is generated. The amount of hydroxide ion formed by self-ionization of water is very small and can be ignored.

Soaps

Carboxylate anions from fatty acids have some peculiar characteristics. The carboxylate end of the molecule is quite water soluble (hydrophilic), while the long alkyl chain is very water-insoluble (hydrophobic or lipophilic). In aqueous solution, the hydrophilic end of the molecule is solvated, but the water-repellent hydrophobic end will perform a variety of maneuvers to minimize the repulsion (Figure 9). The molecule tends to come to the surface of the water, where the hydrophobic tail may break the surface and jut out of the water. This lowers the surface tension of the water; substances that do this are called surfactants.

Myristate anion, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2C$

represented schematically as

Hydrophobic region

Hydrophilic end

SURFACE

Single surfactant molecule, near the surface of the solvent

Surfactant dimer

Micelle (cross section)
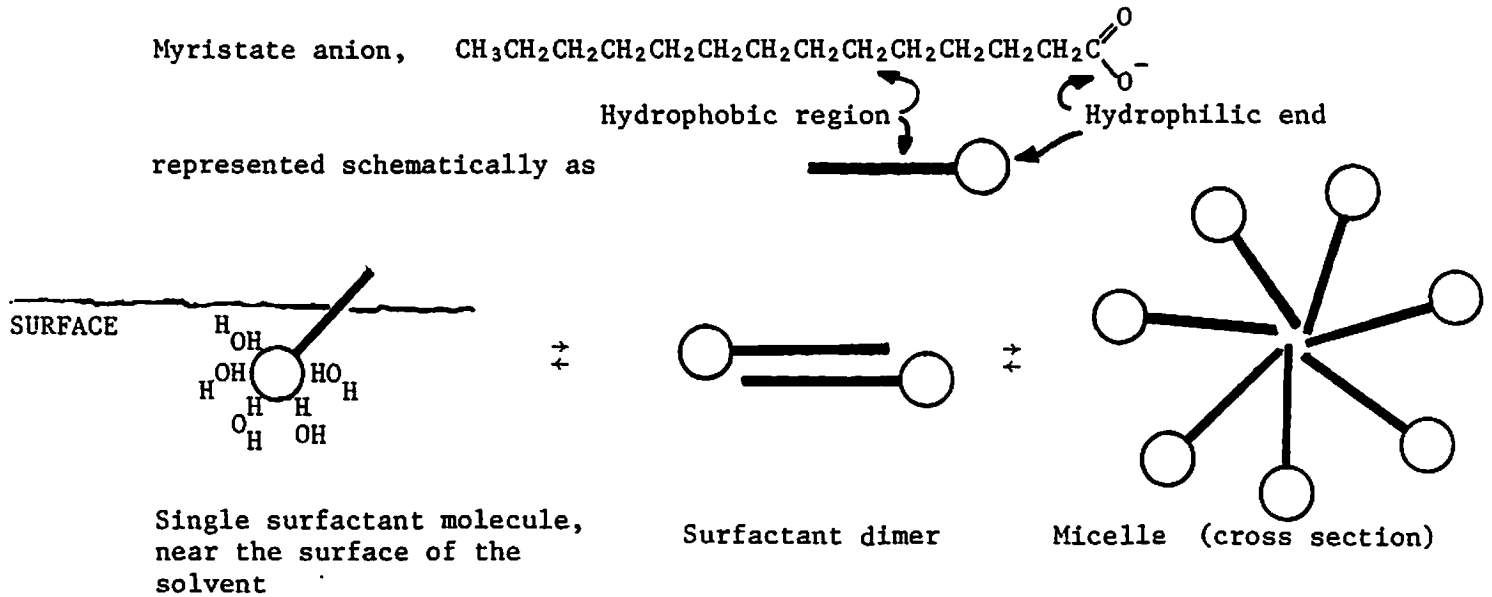
FIGURE 9 : MYRISTATE ANION AS A SURFACTANT: 3 PHASES IN EQUILIBRIUM

There are several other phases in equilibrium with this surface phase.

The surfactant molecules may form dimers; that is, two anions will aggregate

with their hydrophobic tails towards one another. If the concentration of surfactant

is great enough, the anions will form spherical clusters called micelles (from the

Latin work for "little crumb"), in which the hydrophobic tails are all pointed into

the center, away from the water. This may be considered analogous to the be-

havior of a Hollywood wagon train under attack: the wagons form a circle to corral

the horses and provide a barricade.

The presence of micelles in a solvent changes its properties, often dramatically;

this is a subject of much current research. The most prominent effect is that

the micelles will suspend in water substances that are ordinarily insoluble, such

as dirt and grease. Although desirable for cleaning dirty hands, the formation

of such suspensions, called emulsions, can be frustrating when one wishes to

separate two ordinarily immiscible solvents in the laboratory. For example, if

an aqueous solution of potassium myristate (which is a good soap) is shaken with

hexane, an emulsion forms which will not separate into layers.

Fatty Acids

A fatty acid may be prepared by saponification of a triglyceride, followed

by acidification of the aqueous solution of the alkali metal carboxylate. For ex-

ample, treatment of trimyristin with potassium hydroxide in water affords an aqueous

solution of potassium myristate, the acidification of which precipitates myristic

acid. The glycerine produced in the saponification is completely miscible with water,

even at low pH.

Since many fatty acids have long, straight alkyl chains (e.g., myristic acid:

$CH_3(CH_2)_{12}$), they are able to form inclusion complexes with urea, H_2NCONH_2.

An inclusion complex is a chemical combination in which one component, the guest,

is trapped inside the other, the host. There are no ordinary (covalent) chemical

bonds between the host and the guest, but, if the hydrocarbon chain has the appro-

priate dimensions and shape, it will just fit into the channels formed when the urea

crystallizes, maximizing the weak surface forces sufficiently to form a stable complex.

As a urea crystal grows, a lattice is built up that resembles a honeycomb with

long vacant cavities or canals, as shown in Figure 10. The urea molecules are held

together by hydrogen bonds. The inside diameter of the channels is about 5 A, the
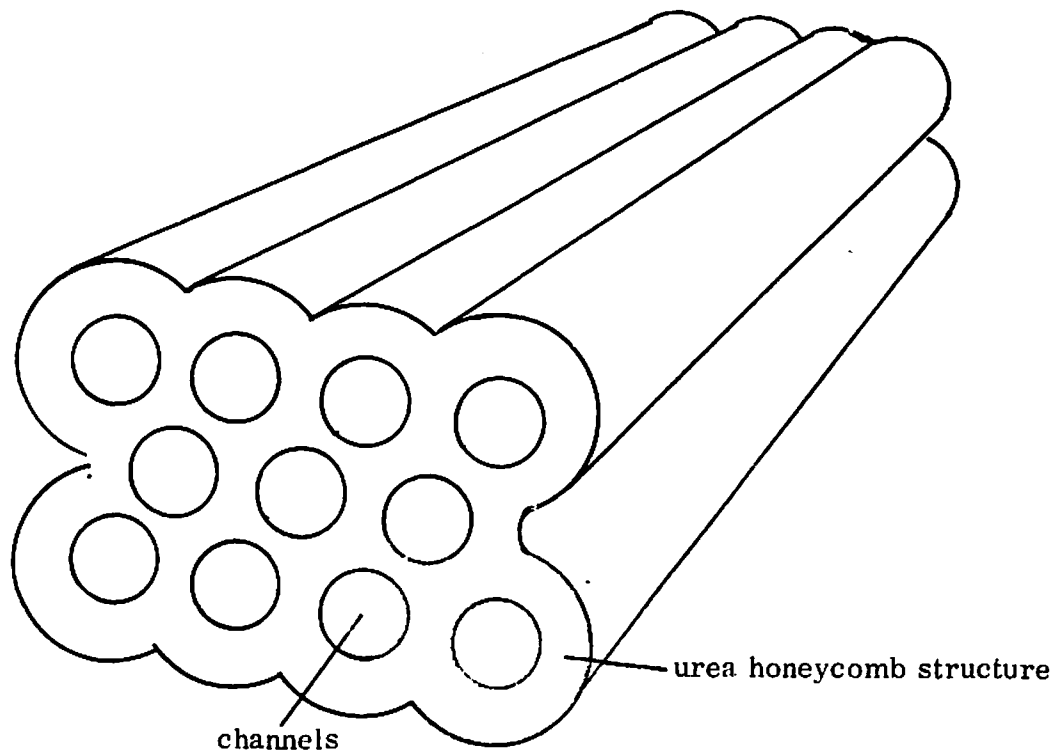
Schematic representation
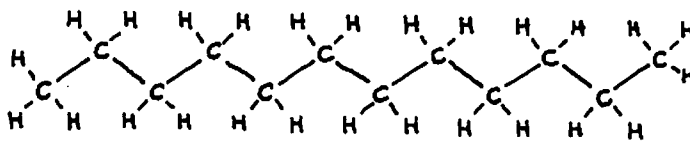
Conventional representation of a linear hydrocarbon (dodecane)

end view
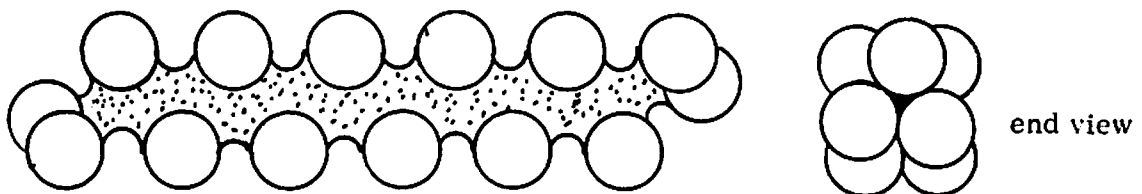
Shape of a space-filling model of a linear hydrocarbon (dodecane)

Figure 10: Approximate spatial structure of a urea inclusion complex of a straight-chain hydrocarbon

right size to accomodate a long straight-chain hydrocarbon or fatty acid. Compounds with bent or branched chains will not form inclusion complexes with urea.

Although urea inclusion complexes are not stoichiometric, the molar ratio of urea to fatty acid is generally reproducible to two significant figures. The melting point range of urea inclusion complexes is usually quite large, but it is often possible to detect a <u>decomposition</u> temperature considerably below the melting point of pure urea, $135^{\circ}C$. As the complex decomposes, beads (or sometimes a mist) of melted fatty acid are extruded from the channels and are deposited on the walls of the capillary.

Procedure

Add 3.0 g of trimyristin to 20 ml of 95% ethanol in a 100-ml round-bottom flask. Add a solution of 20 g of potassium hydroxide in 20 ml of water, and reflux the mixture for two hours (with a boiling stone), using the apparatus that was used to extract the nutmegs. Weigh the 20 g of KOH in a 150-ml beaker on a centigram or triple-beam balance; clean up any spilled pellets immediately for the safety of your fellow students. Be sure the condenser joint is well greased; test it from time to time to see that it has not frozen solid (due to dissolution of the glass by the strong base). After the flask has cooled, dilute the reaction mixture with 75 ml of water and transfer it to a 250-ml separatory funnel. Wash the aqueous solution with 10 ml of Freon 113. Wait for the emulsion to separate into two layers, then drain the organic layer into a tared (preweighed) 50-ml Erlenmeyer. Store the flask unstoppered to let the solvent evaporate, and weigh the residue of trimyristin next week.

Transfer the aqueous layer to a 250-ml Erlenmeyer and carefully acidify the solution by adding concentrated hydrochloric acid (about 40 ml) in small portions

while swirling the flask. The neutralization reaction will evolve heat. Be careful. The myristic acid does not precipitate but separates as an organic phase or oil. If the initial precipitate is solid, warm the flask on a steam bath until it melts. When the aqueous solution is acidic, cool the flask in ice until the myristic acid freezes. Agitate the flask by swirling or with a stirring rod so that the myristic acid forms small crystals rather than a solid cake. Collect the product by suction filtration, rinse the flask with three 50-ml portions of water, and wash the crystals with the rinsings. Press down on the crystals with something flat (e. g. a clean spatula) to promote drying. Save a small portion of the crude product for a melting point determination next week.

Recrystallization. Divide the crude product into two weighed portions. Recrystallize at least one gram from methanol-water using the following procedure. In a test tube, dissolve the crude myristic acid in 10 ml of methanol. If the solution is slightly yellow, add a spatula tipful of decolorizing charcoal (Norit), carefully boil for a minute, and gravity filter the hot solution into a 50-ml Erlenmeyer flask. Wash the test tube and filter paper with 1 ml of methanol. Boil the methanol solution (use a boiling stick) and add water in drops until the solution just turns cloudy. Add more methanol in drops until the boiling solution just becomes clear again. Allow the solution to cool slowly to room temperature, then cool and swirl the flask in an ice-water bath. Collect the purified product by suction filtration, wash with two 10-ml portions of water, press, and air dry. Spread the residue on a tared watchglass and allow the material to dry in your locker over the week. When dry, determine the melting point, and calculate the percent yield based on trimyristin. Pour the mother liquor into the designated receptacles.

A urea inclusion complex* is prepared from the other portion of the crude myristic acid. Use 4.0 g of urea and 20 ml of methanol for every gram of crude myristic acid used. Dissolve the urea in the hot methanol and add the crude myristic acid to the boiling solution. Continue to heat and swirl the mixture until all the solid has dissolved. Allow the hot solution to reach room temperature slowly, then cool it thoroughly in an ice bath with swirling. Collect the crystals by suction filtration and rinse the flask with the filtrate to remove all of the solid. Wash the residue with 2 ml of ice-cold methanol. Press the crystals and air dry. Allow the crystals to dry on a tared watchglass (30 minutes should be long enough) and determine the melting point range. Note the onset temperature of decomposition, if you see it. Pour the mother liquor into the designated receptacle for recycling.

QUERY: Place a few crystals of the urea inclusion complex in a small test tube and add a few drops of water. Do the crystals dissolve? Is urea soluble in water? Place a few crystals of the inclusion complex in another small test tube and add a few drops of Freon. Do the crystals dissolve? Is myristic acid soluble in Freon?

Weigh the rest of the complex to the nearest milligram on a microbalance. Transfer the material to a 60-ml separatory funnel, add 15 ml water, and swirl vigorously. Add 10 ml Freon and shake vigorously. The inclusion complex will dissociate and partition between the two layers: the urea will dissolve in the water, while the myristic acid will dissolve in the Freon. If an emulsion develops, it should break up slowly. Separate the two clear layers. Ignore any traces of mutually insoluble material. Drain the organic layer and gravity filter it through a fluted filter cone containing two or three spatula tipfuls of anhydrous magnesium sulfate ($MgSO_4$ is a

---

*This experiment may be deferred to week 5.

desiccating agent; it will absorb traces of water in the Freon layer). Wash the

aqueous layer with another 10-ml portion of Freon, and drain the Freon layer

through the magnesium sulfate cone. Both filtrates should be collected in a 50-ml

Erlenmeyer flask which has been tared to the nearest milligram. Store the

Erlenmeyer flask in your lab locker over the week to allow the Freon to evaporate.

Weigh the recovered myristic acid to the nearest milligram, record its melting

point, and calculate the molar ratio of urea to myristic acid in the inclusion com-

plex. Also save the aqueous layer in a tared 50-ml beaker and record the weight

of recovered urea when the water has completely evaporated. Determine the per-

cent yield, based on trimyristin, of myristic acid purified via the urea inclusion

complex.

QUERY: Using the melting point as a criterion, compare the purity of the
crude myristic acid and that purified by recrystallization and through the inclusion
complex. How do the weights of recovered urea and myristic acid compare to the
weight of complex with which you started?

Note on Recycling and Disposal

Methanol consumed in this experiment will be collected and recycled by batch

distillation. The recycling stills are operated by the teaching assistants and are

situated in the fume hoods. You should take a look at them to see how they work.

The aqueous filtrate from the preparation of myristic acid is acidic. It should be

neutralized with sodium bicarbonate and poured down the drain.

Experimental Techniques

The preceding procedure requires refinement of techniques encountered in the

previous experiment. Care must be taken in the suction filtration of the aqueous suspension of myristic acid or the fine crystals will pass through the filter. The recrystallization of myristic acid, involving the use of Norit and a hot filtration, requires some expertise. Another type of extraction, liquid-liquid extraction, is introduced.

Recrystallization

Recrystallization is such a routine technique in organic chemistry that detailed descriptions of the procedure are rarely given in experimental write-ups. There are six general steps in a recrystallization: 1) selection of a solvent, 2) dissolution of the solid in the minimum quantity of hot solvent, 3) clarification and decoloration of the solution, 4) crystallization, 5) suction filtration and drying, and 6) determination of a micro melting point. The last three of these procedures were described in detail in the prevous experiment. The first three merit amplification.

1. Selection of a solvent

The most crucial factor affecting the success of a recrystallization is the selection of a solvent. In cases where the recrystallizing solvent is not specified (or where a new compound is to be purified), an effort must be made to find the best solvent. The best recrystallization solvent is one that will dissolve a moderate amount of material when hot, but only a small amount of the desired compound when cold. If a large amount of solid is soluble in a very small amount of hot solvent, very little material may precipitate on cooling because the solution is not saturated, or a great deal of material may precipitate very quickly and as one congealed mass. In the former instance, purification will have been effected but the

recovery is unacceptably low. In the latter, a good recovery of impure material is achieved. A better recrystallization solvent must be found.

Obviously, the solvent of choice should not react with the compound to be purified. Ideally, impurities should be either completely insoluble (easily removed by filtration) or completely soluble, even at low temperatures (retained in the mother liquor). The best solvent should be volatile and easily removed from the crystals of the purified substance, cheap, nonflammable, and nontoxic. Since it is unlikely that all of the above criteria can be satisfied, compromises are necessary.

When confronted with a new compound to be recrystallized, a number of solvents must be tested on a small scale. If, after much travail, it is found that no one solvent is satisfactory, it may be necessary to use a two-solvent system. In this case, the material to be recrystallized is dissolved in a solvent in which it is soluble and then brought to the boiling point. A second solvent, which is completely miscible with the first but in which the compound to be purified is insoluble, is added in drops until the boiling solution just becomes turbid (saturated). A few drops of the first solvent are added until the solution is clear. It is then set aside to crystallize.

To test a recrystallization solvent, add a few drops of the cold solvent to a small amount of the solid in a test tube. Crush the solid with a glass stirring rod and agitate the test tube to make sure the solid does not dissolve completely at room temperature. Then heat and agitate the sample on a steam bath to see if it all dissolves. If it does not, add a few more drops of solvent to the suspension and again heat to boiling. If the solid is absolutely insoluble, try another solvent. If it eventually dissolves and the solution slowly deposits crystals as it cools, the solvent may be satisfactory.

2. Dissolution of the solid in the minimum quantity of hot solvent

Estimate the minimum quantity of solvent that will be needed, add the solid to

be purified, and heat the solvent to boiling. The estimate should be small since

a frequent error in recrystallizations is the use of too much solvent. Dissolve

the material in the hot solvent, crushing and stirring the solid with a glass rod.

Really try to force all of the solid into solution before adding more solvent. Do

not add large quantities of solvent to the boiling solution to make the last little bit

of solid dissolve; this may be an impurity which is insoluble in the recrystallization

solvent. If an insoluble impurity is present, it should be removed by gravity filtra-

tion of the hot solution. The crystallization flask and filter should be rinsed with

a small amount of hot solvent.

3. Clarification and decoloration of the solution

When the compound to be purified contains a small amount of highly colored

impurities which become evident once the sample dissolves, or the solution is turbid,

rather than clear, the impurities can sometimes be removed by adding a small amount

of decolorizing charcoal (Norit) to the solution and then boiling it for a few minutes.

The danger of bumping is great when Norit is present; therefore, the hot flask must

be continuously swirled. Boiling aids are insufficient. The decolorizing charcoal

and other insoluble particles are removed when the hot solution is gravity filtered

through a large piece of fluted filter paper. There are two methods to prevent the

product from precipitating on the filter or the stemless glass funnel: a large excess

of recrystallizing solvent can be used, or the receiver on which the funnel rests can

contain a small amount of boiling solvent that continuously bathes the funnel and filter

with hot solvent vapors. The latter method is favored since much less solvent is lost

when the solution is concentrated. The recrystallization flask and filter should be

rinsed with a small amount of hot solvent in either case. Once the excess solvent

has been boiled away, the hot solution is set aside for slow and undisturbed

crystallization to take place.

Liquid-Liquid Extraction.

Liquid-liquid extraction is a frequently used technique wherein a solute is

transferred from one solvent to another. The terms extract and wash are often

used interchangeably to denote this technique. Specifically, though, a solution is

washed with a solvent if the product remains in the original solution and impurities

are removed by the wash solvent. A solution is extracted with a solvent if the pro-

duct is removed from the original solution into the extracting solvent.

The solute partitions itself between the two solvents in a ratio that depends on its affinity for each of the solvents. If the ratio of these affinities (the partition coefficient) is great, a single extraction step may suffice to transfer the solute from one solvent to the other; in other cases, repeated extractions are necessary.
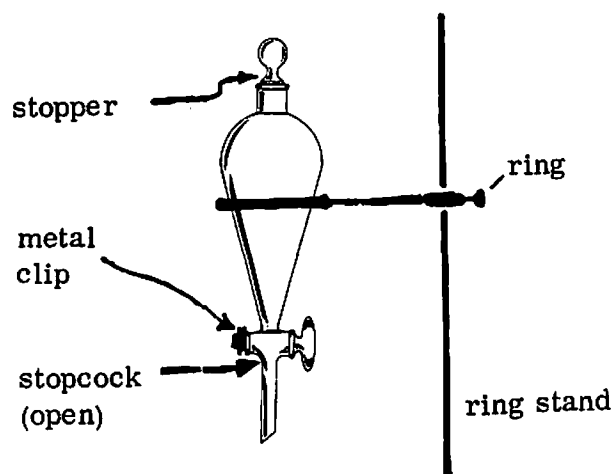
FIGURE 11: SEPARATORY FUNNEL

To perform an extraction or washing, first be sure that the stopcock is closed.

Glass (but not Teflon) stopcocks should have a small film of stopcock grease to seal,

lubricate, and retain the stopcock. A metal clip also helps to retain the stopcock.

Pour in the solution to be extracted and a second, immiscible solvent. Stopper the

funnel. Then invert it gently and vent it immediately. To do this, the funnel is held

with one finger or the palm of the left hand holding the stopper, while the right hand turns the stopcock (for most right-handed persons). Close the stopcock, shake once, and vent again. Repeat until you are sure that further shaking will not build up a large amount of pressure, then shake the funnel vigorously for 5-10 seconds. Finally set the funnel upright in an iron ring or wide open burette clamp and remove the stopper while you wait for the two phases to separate. Do not point the funnel stem at yourself or anyone else when you are venting the funnel; it may spit.

The separation of layers does not always occur cleanly. Surface-active materials may form stable emulsions , or films of insoluble materials may surround large globules of solvent. Although little can be done in the former case, films may be broken up with a stirring rod or spatula.

When two well-defined layers have formed and separated completely, the lower layer is drawn off slowly. Droplets remaining after separation may be removed by rotating the separatory funnel with a few short twisting motions and drawing off the small layer which forms at the bottom. The upper layer, which should now be the only layer in the funnel, is poured through the top into a receiving flask.

A recurrent problem in extractions is: which layer should I save? Organic compounds may be denser or lighter than water or aqueous solutions. Solutions may change in density as a component is extracted out. It may happen that your organic layer is above one washing solution and below another. Although, with practice, you may be able to judge which layer is which visually, the safer test is to add a drop of water and see with which layer it mixes.

Be sure that you understand completely what is happening in each step of the saponification reaction and, therefore, which layer contains the product during the

washing. Ordinarily, organic compounds are distributed largely into the organic solvent, while salts, acids, and bases remain in the water layer. Both layers should be saved until you are certain which one contains the desired material.

The proton nuclear magnetic resonance spectra of trimyristin and myristic acid are given in Figures 12 and 13.
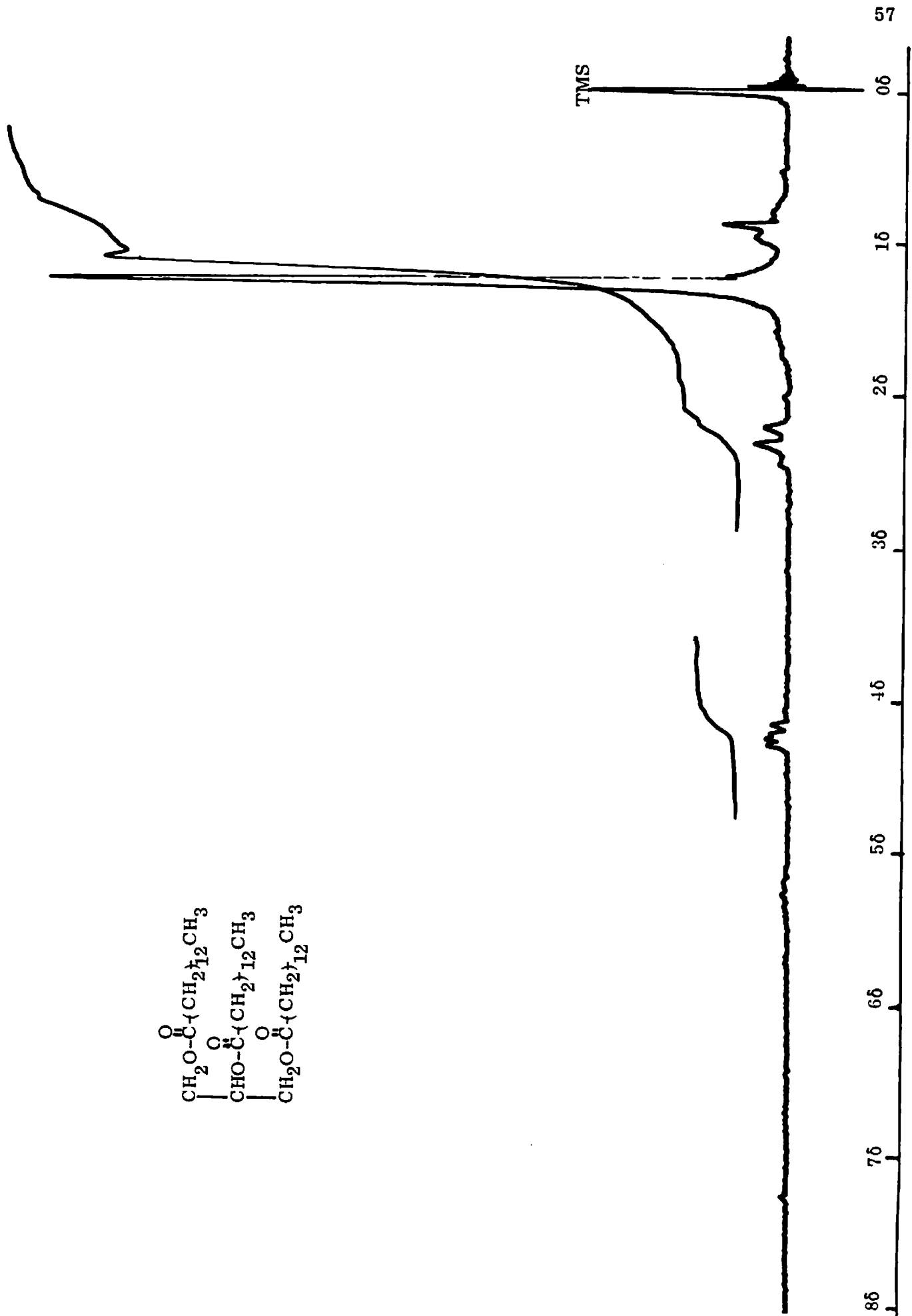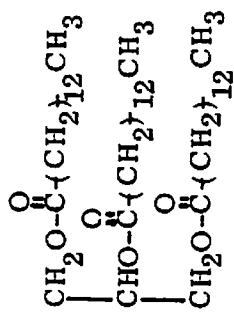
Figure 12: A 60 MHz proton nmr spectrum of trimyristin at 1000 Hz sweepwidth, solvent CDCl$_3$

$$CH_2O-\underset{\underset{O}{\|}}{C}(CH_2)_{12}CH_3$$
$$CHO-\underset{\underset{O}{\|}}{C}(CH_2)_{12}CH_3$$
$$CH_2O-\underset{\underset{O}{\|}}{C}(CH_2)_{12}CH_3$$

57
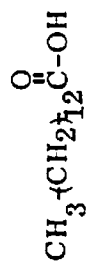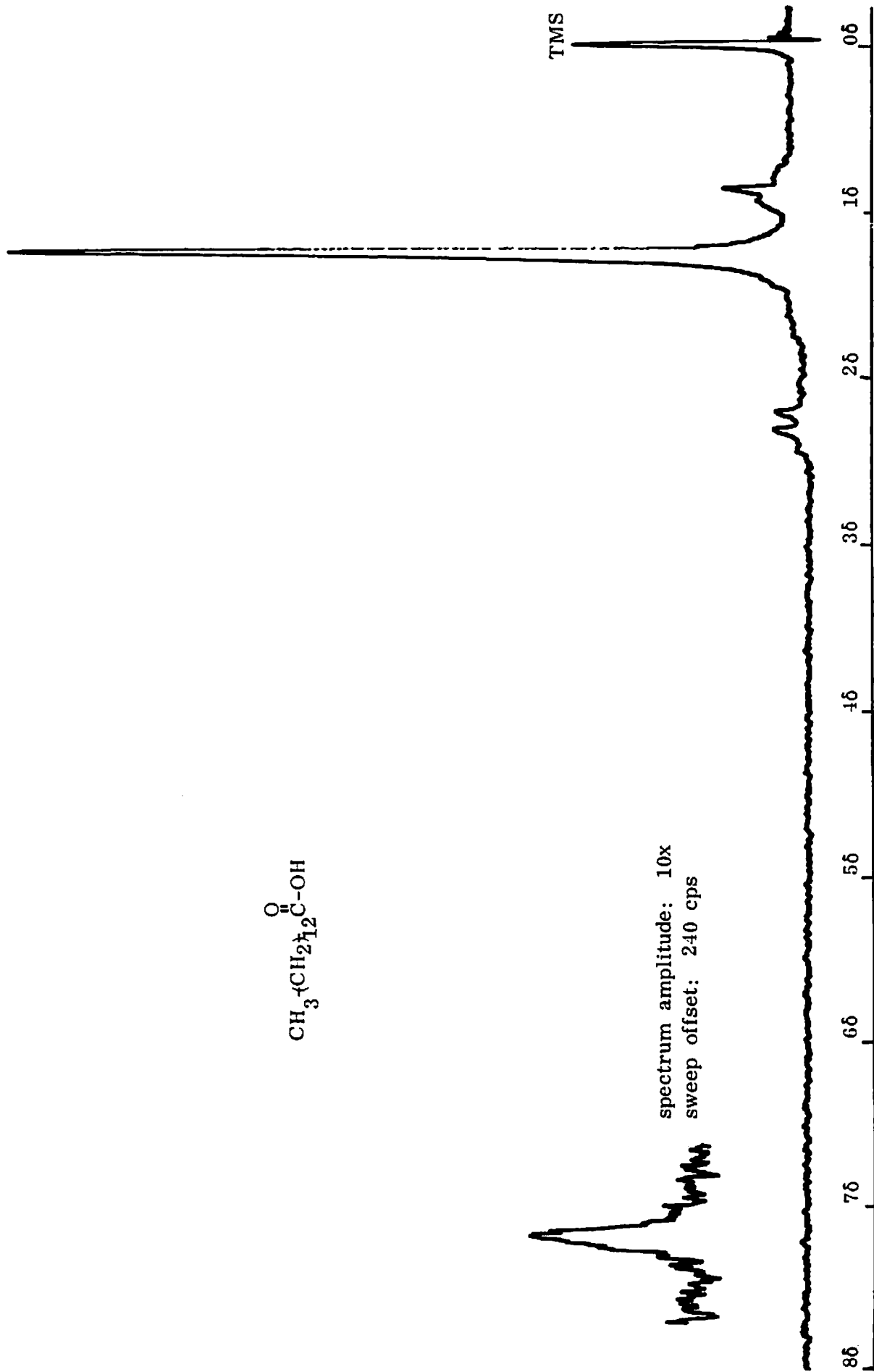
Figure 13: A 60 MHz proton nmr spectrum of myristic acid at 1000 Hz sweepwidth, solvent $CDCl_3$

3. ISOLATION AND BROMINATION OF MYRISTICIN

In the previous weeks, several techniques for the isolation and purification

of organic compounds have been discussed: extraction, distillation, and recrystalli-

zation. Myristicin is separated from other natural products in nutmeg by means of

a fourth technique, known as chromatography. There are many different types of

chromatography, but they are all based on the same principle: different compounds

move at different rates through certain special porous media.

Toward the end of the 19th century, when industry began to show serious in-

terest in locating and tapping subterranean petroleum supplies, David Talbot Day,

a chemist with the U.S. Geological Survey, noted that crude petroleum from different

locations often showed different properties. For example, drillers at one site might

find black petroleum, while at a nearby site they found red petroleum. How might

this be explained if, on the basis of geological evidence, it was believed that both

drillers had tapped the same deposit?

In 1897, Day proposed an ingenious explanation: petroleum, forced up through

layers of limestone or clay by subterranean pressure, was separated by what he called

"fractional diffusion." That is, some components of the petroleum travelled upward

at a greater rate than others. To test his hypothesis, Day forced a petroleum sample

through a tube packed with fuller's earth (an aluminum silicate) and found that the

sample was separated into fractions: light oil, heavy oil, petroleum jelly. Day

suggested that such a method of separation might be used to analyze an oil sample into its

individual hydrocarbon constituents. This prediction has been realized to a considerable

extent. Today, chromatography is used extensively by both the petroleum industry and

by pollution monitors to analyze oil samples and to ascertain their origin.

The term "chromatography" was introduced not by Day, but by Mikhail

Tswett, a professor of botany at Warsaw, who developed the technique completely

independently about the first decade of the 20th century. Tswett wished to isolate

pigments from chloroplasts, and he devised a technique by which he was able to

obtain quantities of nonvolatile materials too tiny to isolate by recrystallization.

Tswett's chromatography was much the same as is used today. A crude mixture

is put at the top of a glass column packed with a porous adsorbent (Tswett at

first used calcium carbonate). A solvent, known as an eluent, is passed through the

column and the components are eluted (washed through the column) at different rates

and can be collected in separate receivers. This process is schematically illustrated

in Figure 14. The adsorbent that we will use is alumina (aluminum oxide, Al_2O_3)

that has been activated by heating. The details of the adsorption process are not well

understood, but this does not limit the usefulness of the technique.
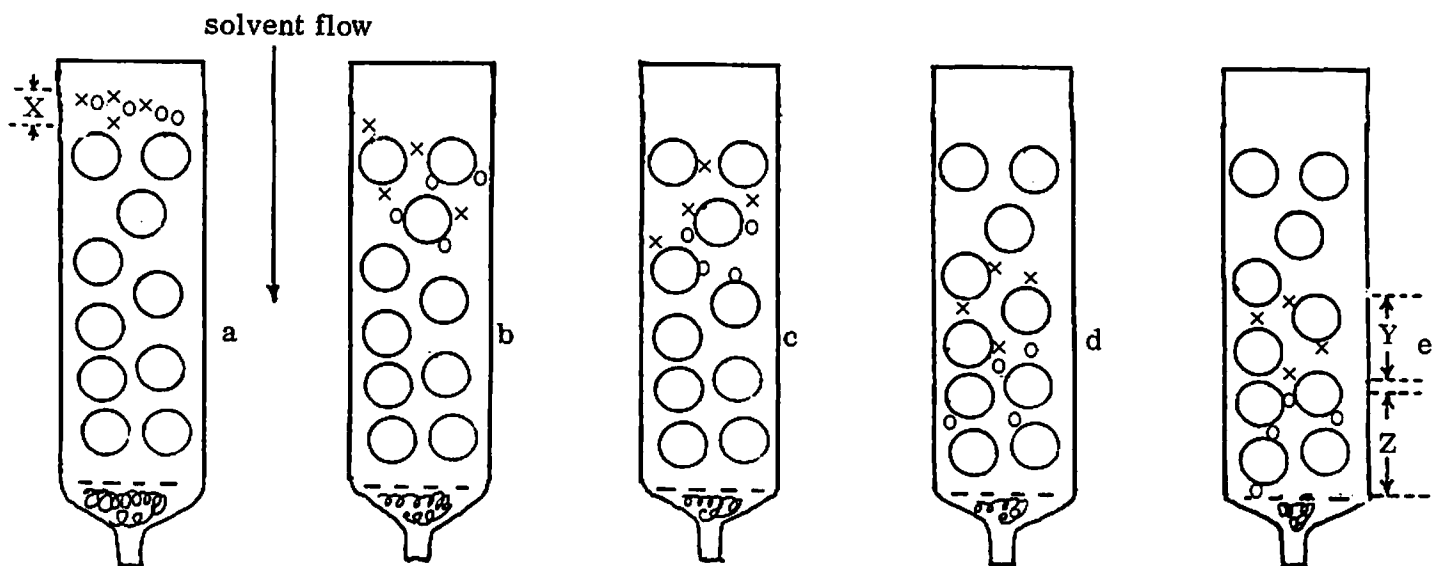
FIGURE 14: Separation of a two-component mixture (x and o) on a column of adsorbent (O). a—column loaded with mixture; b-e—successive stages in elution.

In Tswett's investigations, the compounds were highly colored (hence the name "chromatography"), and their progress through the column and the extent of separation could be monitored visually. As Tswett realized, chromatography is equally applicable to colorless materials; however, their elution cannot be so easily monitored. It has been found that the ratio of rates of elution of compounds and solvent is generally reproducible. Hence, in the chromatography of colorless compounds, it is sometimes sufficient to specify the size of the column, the amount of adsorbent, and the amount of eluent needed in order to reproduce an efficient separation. For example, in the isolation of myristicin below, monitoring the volume of eluent should effect a satisfactory separation.

Once the myristicin has been isolated, the product of its reaction with bromine will be investigated. There are two fundamental reactions of elemental bromine with organic compounds, substitution, Reaction 1, and addition, Reaction 2.

$$(1) \quad RH + Br_2 \rightarrow RBr + HBr$$

$$(2) \quad \overset{\diagdown}{\diagup}C=C\overset{\diagup}{\diagdown} + Br_2 \rightarrow -\overset{|}{\underset{|}{C}}-\overset{Br}{\underset{Br}{\overset{|}{C}}}-$$
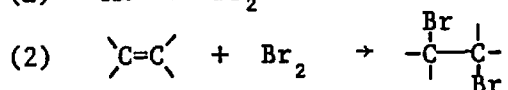
Substitution affords a mole of hydrogen bromide for each mole of bromine consumed, and it occurs with both saturated and unsaturated compounds. The HBr evolved in this reaction can be detected with moist indicator paper. Addition occurs only between bromine and an unsaturated compound. This reaction is often used as a diagnostic test for double and triple bonds. In the case of a highly substituted aromatic compound such as myristicin, both reactions may occur.

PROCEDURE

Myristicin is isolated from the mother liquor residue of the trimyristin

62

Hexane

Sand

Alumina

Sand

Glass
wool

O-Ring

Removable tip

Stopcock
assembly
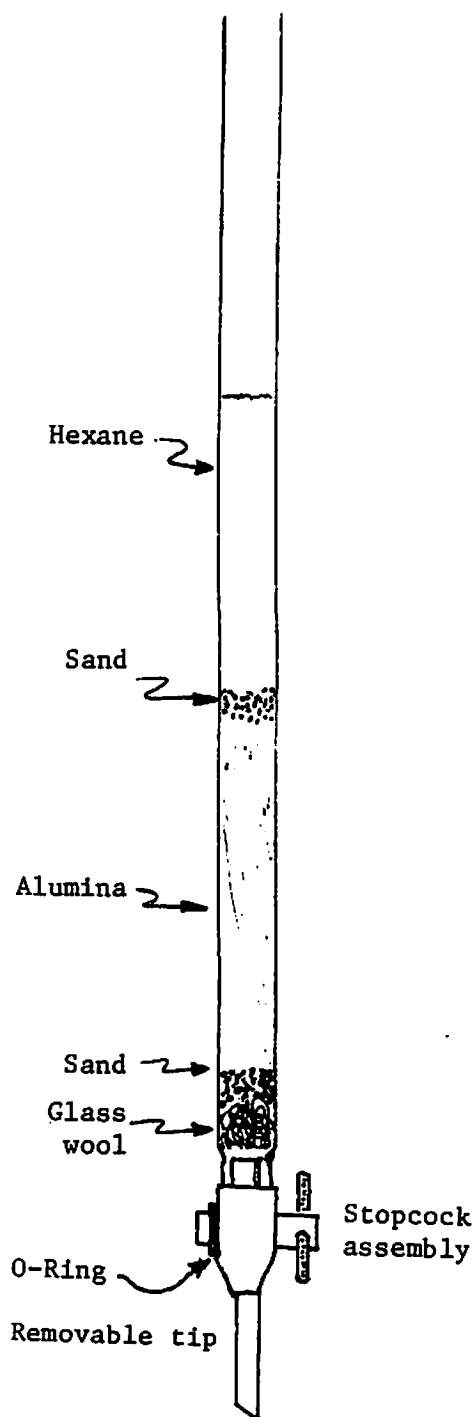
Figure 15: Chromatography
column

experiment by column chromatography. If time
and water pressure permit, it may be further purified
by distillation at reduced pressure.

To Prepare a Column

A chromatography column must be carefully
prepared in order to work efficiently. The column
is packed under hexane to promote the formation of
a uniform bed of adsorbent that is free from channels
(bubbles or fissures). Channels worsen separation.

Fill the column about half full of hexane (not cy-
clohexane) and push a wad of glass wool (sometimes
called angel hair) to the bottom with a long glass rod.
The wad should be just large enough to support a
5-to 10-mm layer of sand and to prevent any particles
from passing into the stopcock of the column.

Weigh 10 + 0.2 g of the adsorbent, alumina,
into a tared beaker. Pour about 1 ml of sand through
a funnel into the column. Tap the column lightly to level
the sand. Pour the alumina slowly and evenly through
the funnel into the column, tapping the side gently so that
the alumina settles evenly. During the addition
of the alumina, make sure that the level of hexane is
always higher than that of adsorbent. Add more hexane

if necessary. If too much hexane has been added to the column, drain it so that it does not overflow. When all the alumina has settled, cover the top of the adsorbent with another 5- to 10-mm layer of sand.

Open the stopcock and drain the hexane until the solvent level just coincides with the upper edge of the top sand layer. The column should be ready for use. The hexane that was used to pack the column is not contaminated and should be reused as eluent.

To Load the Column

The acetone should have evaporated from the mother liquor of the trimyristin recrystallization to leave an orange oil. If not, evaporate the acetone in a 50-ml beaker on the steam bath. If the residue is predominantly crystalline, it contains a large amount of trimyristin, which should be removed by recrystallization from acetone. Dissolve the residue in the minimum amount (5-10 ml) of acetone while heating on a steam bath; chill the solution in ice, filter off the trimyristin with suction on a Hirsch funnel, washing with a little cold acetone, and evaporate the filtrate in a 50-ml beaker on the steam bath. Add 5 ml of hexane to this residue and stir the mixture thoroughly with a spatula to insure that all material soluble in hexane has dissolved. The hexane-insoluble material usually separates at first so that the liquid appears cloudy and then precipitates in large oily drops. Add a few drops of hexane to see that no more cloudiness forms. If it does, add more hexane until no more precipitate forms. If you fail to do this, the precipitate may form within the column and clog it. Then add the supernatant hexane solution in drops to the top layer of sand with a 1-ml pipette. Be careful not to disturb the sand layer. Now open the stopcock carefully and let the solvent level come down just to the upper edge of the top sand layer. Extract the mother liquor residue with

another 5-ml portion of hexane, add this hexane solution to the top of the column, and again run the level of the solvent down to the top of the upper layer of sand. The solvent layer must never fall below the top of the sand layer, or channels will develop in the column and the purification will be incomplete or nonexistent.

The two portions of hexane should have contained most of the myristicin, as well as some trimyristin and other impurities. The column has now been loaded and is ready for elution (see Figure 15).

To Elute the Myristicin

Fill the column with hexane, taking care not to disturb the upper layer of sand. Open the stopcock and collect the eluent in a 100-ml r.b. flask. This flask should have a 75-ml level marked on the outside (i.e., fill the flask with 75 ml of hexane and mark the 75-ml level; then pour the hexane into a clean 125-ml Erlenmeyer and use it as eluent). The elution may take 15-30 minutes. Don't let your attention wander too far from the elution; the solvent level must never fall below the top of the sand layer.

Place a boiling stone in the collected hexane solution and distill the hexane until no more comes over (set up as in Figure 3). Record the head temperature every 5 minutes. Distillation should be stopped if the head temperature rises more than 10° C above the boiling point of hexane.

QUERY : What is the normal boiling point of hexane ?

Optional Experiment: Vacuum Distillation

A vacuum distillation may be performed on the pot residue, provided that more than two hours remain in the laboratory period and that the water pressure in the laboratory is adequate for aspirator vacuum to reach 25 torr (mm Hg). Remove the condenser

from the simple distillation assembly used above, attach the female end of the

receiver adapter to the side arm of the still head and connect the tubulation of the

receiver adapter to the hose from the aspirator filter trap. Use a tared ($\pm$ 0.001 g)

50-ml r.b. flask as the collection flask. No condenser is used in this distillation.

Add a fresh boiling stone to the pot and evacuate the system with the aspirator.

Close off the bleed on the filter trap with a Hoffmann clamp. Make sure that all

joints of the still have been properly greased to prevent leaks. Also grease the

neoprene thermometer adapter. After 5-10 minutes, the ultimate vacuum of the

system should be reached. Heat the pot with the IR lamp and record the boiling

range of the liquid as it distills. Stop the distillation when distillate ceases coming

over (detectable by a rapid fall of the head temperature) or when the head tempera-

ture reaches 200°C. Weigh the distillate and record the yield as a percentage of

the weight of the original nutmegs. The nuclear magnetic resonance spectrum of

myristicin purified in this way is given in the discussion section.

Bromination

Add 5 ml of cyclohexane to the crude, concentrated sample in the 100-ml r.b.

flask. Cool the cyclohexane solution of myristicin by swirling the flask in an ice-water

slush. (Pure cyclohexane freezes at 6°.)

The following steps must be performed in the hood. Add 0.5 ml of a 10%

solution of bromine in cyclohexane to the continuously cooled solution of myristicin.

Burets filled with bromine solution will be situated in the fume hoods. Do not pour

the bromine solution yourself; call a teaching assistant to do it if the buret needs filling.

Bromine is extraordinarily corrosive, and it will cause painful burns and leave distinct

scars if it spills onto your skin! Be sure to record the proper treatment of bromine burns

(detailed in lurid color in the <u>CRC Handbook of Laboratory Safety</u>, pp. 108-9) in your

laboratory notebook. If you should get any on your skin, cover with glycerol and wash off

the glycerol with plenty of water. Note that grease and neutralizing agents are contra-

indicated in the treatment of bromine burns.

After the first portion of bromine solution has been added to the myristicin

solution, swirl the flask and note the discharging of the color of the bromine. Add

more bromine solution in drops to the cooled myristicin solution; after 2 ml has been

added, swirl the flask again until the color is again discharged. Continue to add 2-ml

portions, followed by swirling, until the bromine color remains. Record the volume

of bromine solution that was used. Hold a piece of moist litmus or mixed indicator

paper near the mouth of the flask.

QUERY: Does red litmus paper turn blue? Does blue litmus paper turn red?
Hold a piece of moist litmus paper over the bromine solution in the buret. Does
red litmus paper turn blue? Does blue litmus turn red?

The bromination product may precipitate from the cold cyclohexane solution.

When no more precipitate forms, decant the supernatant into a separatory funnel containing

10 ml of 5% aqueous sodium bisulfite to reduce the bromine to bromide. Be careful not to

pour any of the crystals into the separatory funnel. Also add 10 ml of 5% sodium bisulfite

solution to the suspension of crystals and swirl until the bromine color is discharged.

<u>Do not remove any vessels from the hood until the bromine is all gone.</u> Collect the crystals

by suction filtration on a Hirsch funnel, wash them with a few milliliters of bisulfite solution

followed by 10-20 ml of water, and suck the crystals dry. Add the filtrate to the mixture in

the separatory funnel, stopper, vent, and agitate. Add more bisulfite solution if the bromine

color is not completely discharged.

<u>If no crystals are deposited by the bromination reaction,</u> pour the entire reaction

mixture into a separatory funnel containing 10 ml of 5% aqueous sodium bisulfite

solution. Vent the funnel; once the bromine color has been discharged, the remainder

of the experiment may be performed at your lab bench. Be sure not to discard any

layers from the liquid-liquid extractions until you are sure which layer is which.

QUERY: What is the formula of sodium bicarbonate? What do you think is
the purpose of washing the crystals with sodium bicarbonate solution?

Separate the layers in the separatory funnel and wash the cyclohexane solution

with 10 ml of 5% aqueous sodium bicarbonate, followed by 15 ml of water, and filter the

cyclohexane solution through a cone of magnesium sulfate. Concentrate the filtrate

to about 15 ml or less by boiling off some of the cyclohexane on a steam bath (use a

boiling stick), and allow the solution to cool to room temperature. Then cool the solution

in an ice bath. If a precipitate does not form, induce crystallization by scratching the

cold solution with a sharp glass stirring rod. Collect the solid product by suction

filtration on a Hirsch funnel, wash with 2 ml of cold cyclohexane, and air dry. Determine

the melting point, and, if time permits, recrystallize the bromomyristicin in a small

test tube from a minimum amount of 95% ethanol.

RECYCLING AND DISPOSAL

If the myristicin was purified by vacuum distillation, the only volatile solvent

present in the mother liquor after the crystals of bromomyristicin have been filtered

off is cyclohexane. It will be recovered by batch simple distillation. Place the mother

liquor in the clearly labelled container.

If the myristicin was purified by column chromatography, the mother liquor

contains cyclohexane, hexane, and other volatile impurities. The hexane (bp 69°)

and cyclohexane (bp 81°) will be recovered by batch fractional distillation. Place the mother liquor in a <u>different</u> clearly labelled container.

The inorganic waste solutions—sodium bisulfite and sodium bicarbonate layers from washing the bromination product—may be flushed down the drain. It is important to bear in mind that both solutions liberate gas when acidified. In the latter case, the gas is CO_2, which is relatively innocuous. Sodium bisulfite solution, however, liberates SO_2 when acidified. This gas is poisonous and is used as a fumigant. Aside from being obnoxious, SO_2 has played a prominent role in several ecological disasters, the most notorious of which have been the "killer fogs" of London.

Effluents such as sodium bisulfite are tolerable in small quantities so long as the medium is not acidic. Not surprisingly, the pH of liquid waste is an important consideration, and, if the pH of the Providence River were to fall below 6, an enormous stench would probably permeate the city.

Neutral solid waste, such as used magnesium sulfate, may be deposited in the wastebaskets, as the quantity used should not exceed 0.2 g per student. The disposal of used alumina, however, presents a greater problem. To clean out your chromatography column, you should invert it, remove the stopcock assembly, and allow the slurry to ooze out. It may be necessary to blow the solids out with your large rubber bulb. Then rinse the column with water and leave it in the designated place to be dried.

Because the alumina becomes mixed with sand, it cannot be recycled for laboratory use. The slurry should be deposited in designated receptacles in the fume hoods, where the hexane may evaporate away. Admittedly, this contributes to air pollution; however, we have not devised a satisfactory alternative. Suggestions are appreciated.

The alumina, once dry, will be disposed of as conventional noncombustible solid waste. It is nontoxic and plentiful; nevertheless, we lament having to throw it out. Again, we welcome suggestions.

EXPERIMENTAL TECHNIQUES

Chromatography

The techniques of chromatography have become highly refined in the past thirty years. Applications in organic and biochemistry have been pioneered by Arne Tiselius (who received a Nobel prize for the development of electrophoresis) and by Lazlo Zechmeister, and a quantitative theory has been developed by A. J. P. Martin and R. L. M. Synge (who shared a Nobel prize in chemistry for the development of partition chromatography).

The principle on which chromatography is based is that different compounds move through an active, porous medium at different rates. There are three physical properties that determine this rate: solubility, adsorption, and volatility. Depending on the type of chromatography, two of them are employed simultaneously. For example, in adsorption chromatography, compounds are separated on the basis of their different degrees of adsorption on a solid phase (here alumina) and solubility in a moving, eluting solvent (here hexane). In liquid-liquid partition chromatography, the rates of elution of different compounds depend on their different solubilities in two liquid phases (one stationary and one mobile). In gas-liquid partition chromatography (glpc), different compounds move at different rates because they do not have the same volatility and solubility in the stationary liquid phase. Gas-solid adsorption chromatography is also used occasionally.

The concept of adsorption was introduced in the charcoal decoloration step of a recrystallization: colored impurities are removed from solution when they "adhere"

to the finely divided particles of charcoal, which have a large surface area. In adsorption column chromatography, the tendency of a compound to "stick" to the surface of the adsorbent competes with its tendency to dissolve in the eluting solvent and move down the column. What makes column chromatography an effective method of purification is that compounds to be separated rarely have exactly the same tendency to be adsorbed on the stationary phase and desorbed (dissolved) by the solvent (eluent). Since the technique involves many repeated adsorptions and desorptions as the compounds move down the column, these differences are magnified and, with care and some luck, well-defined (separated and narrow) bands of pure material can be collected in different receivers.

The movement of solute through a chromatographic column is depicted schematically in Figure 14 above. The figure shows the separation of two substances represented as x's and o's. The mixture is "loaded" onto the column in a narrow band designated as X. At the end, the x's and o's have been separated into bands of width Y and Z which are much broader than X. This broadening affects the resolution of the column and is a limiting factor in a chromatographic separation. Both the stationary and mobile phases should be chosen to maximize separation of bands and minimize broadening.

Glpc is probably the most versatile chromatographic method for separating volatile organic compounds because of the large number and variety of stationary liquid phases available. Although one generally thinks of a liquid as being highly mobile and rather volatile, the stationary liquid phase in glpc is usually a viscous oil (Apiezon, silicone) or low-melting solid (Carbowax) with a very high boiling point.

An inert, porous solid material acts as a support and is coated with a thin film of the viscous, nonvolatile liquid, which comprises the stationary liquid phase. The coated support is the material with which the column is packed.
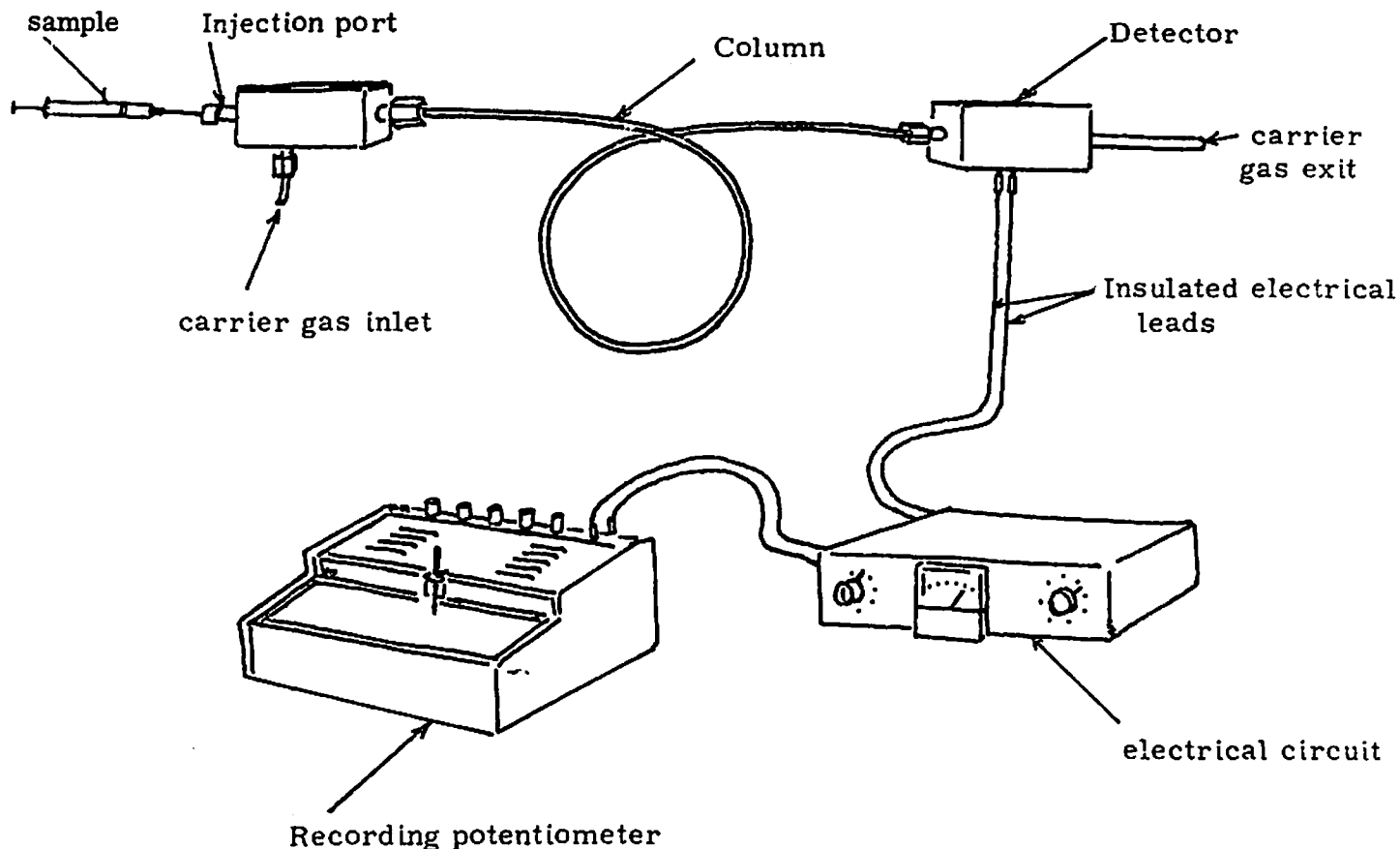
FIGURE 16: GLPC SCHEMATIC

The sample to be analyzed (see Figure 16) is injected into the machine with a gas-tight syringe through a rubber septum on the heated injection port. There it is volatilized and carried by a flow of inert carrier gas (nitrogen or helium) onto the column. The column is usually two to ten feet long and packed with a nonvolatile liquid coated on an inert solid support (firebrick, diatomaceous earth). If the components of the mixture have different solubilities in (affinities for) the liquid phase, they will move through the column at different rates and therefore separate into bands.

Each of the components is only partially dissolved in the liquid phase at any particular instant since the column is heated and most of the sample is in the gas phase. In column chromatography, separation of the components of a mixture is effected by repeated and selective adsorptions and desorptions. In glpc, separation is effected by repeated and selective dissolution and vaporization of the components. The more soluble and/or less volatile component moves more slowly through the column. As the separated components emerge from the column in the vapor phase, they pass . through a detector block which is very sensitive to changes in thermal conductivity and these changes are electrically transmitted to a recorder. Other types of detectors are available. The area of the trace (peak) is proportional to the amount of material coming off the column. The major limitation of glpc is the relatively small size of the sample that can be separated: for analytical work, 1-5 μl (microliters) and for preparative work, usually less than 500 μl.

There are many other types of chromatography that are used routinely in the organic chemistry lab. One that will be used in a subsequent experiment is thin-layer chromatography.

The NMR of myristicin, which is shown in Figure 17, shows some subtleties. The broad singlet at 6.25 δ is from the two ring protons. The sharp singlet at 5.85 δ is from the two methylene protons in the $-OCH_2O-$ function. Buried underneath this large singlet are the resonances from the C-CH=C proton, which is highly split into a multiplet. Two small peaks from this multiplet can be seen at 5.65 δ and 5.55 δ. Both of the vinyl methylene protons, $=CH_2$, have about the same chemical shift, 5.0 δ. This resonance is split into a doublet, J $\approx$ 13 Hz, by the vicinal vinyl proton. The methoxy protons give a sharp singlet at 3.9δ. The allylic methylene protons show a resonance at 3.25δ, which is split into a doublet, J = 7Hz, by the vicinal vinyl proton.
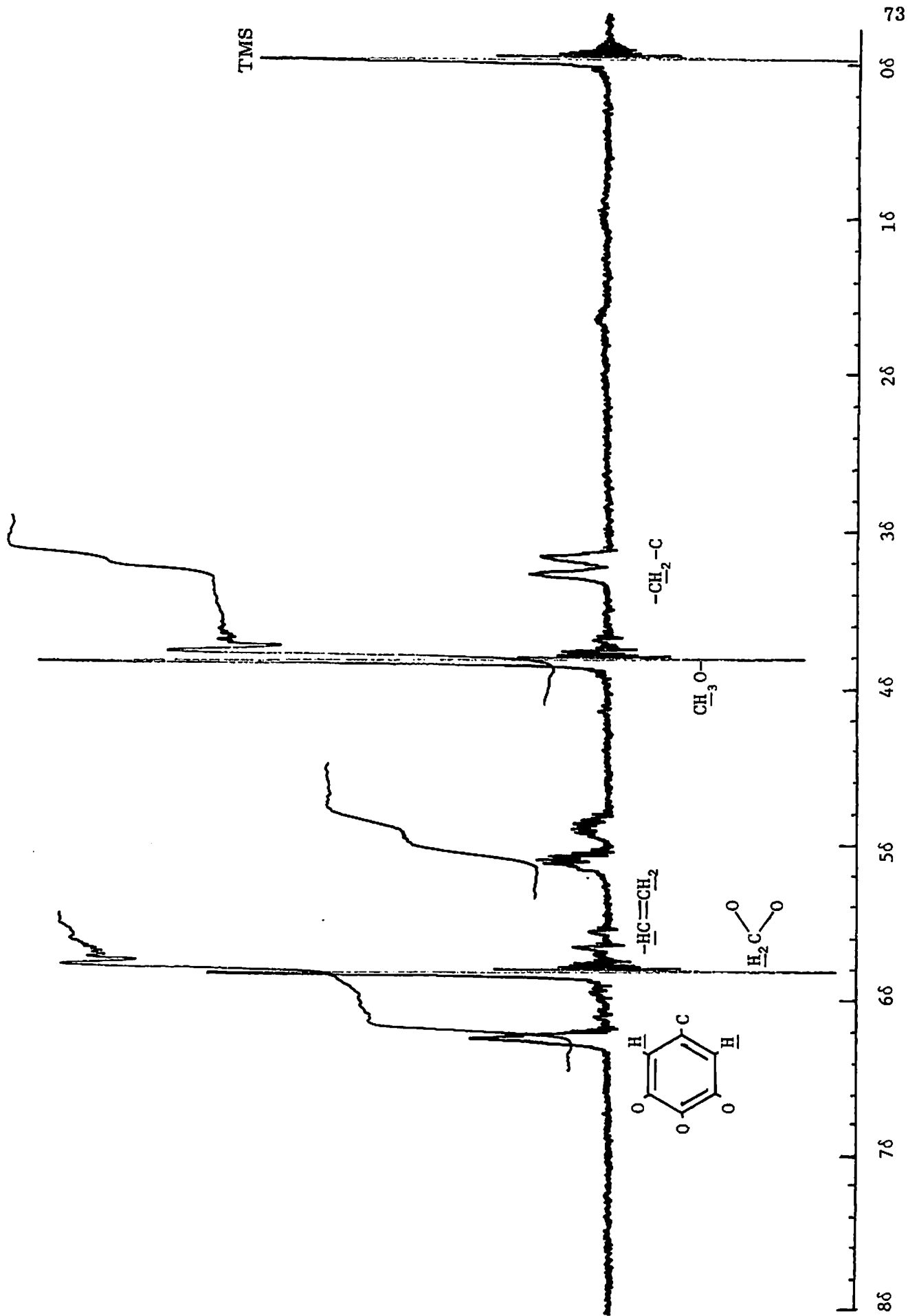
Figure 17: A 60 MHz proton nmr spectrum of myristicin at 1000 Hz sweepwidth, solvent $CDCl_3$

Depending on the conditions under which the experiment is run, the bromination of myristicin can give a number of different products. The NMR of the tribromide (mp 100°) is shown in Figure 18. Compare the spectrum of the tribromide with that of myristicin (Figure 17). Indicate which peaks have been significantly shifted and try to explain why. Assign the peaks and calculate the number of protons under each peak or group of overlapping peaks.
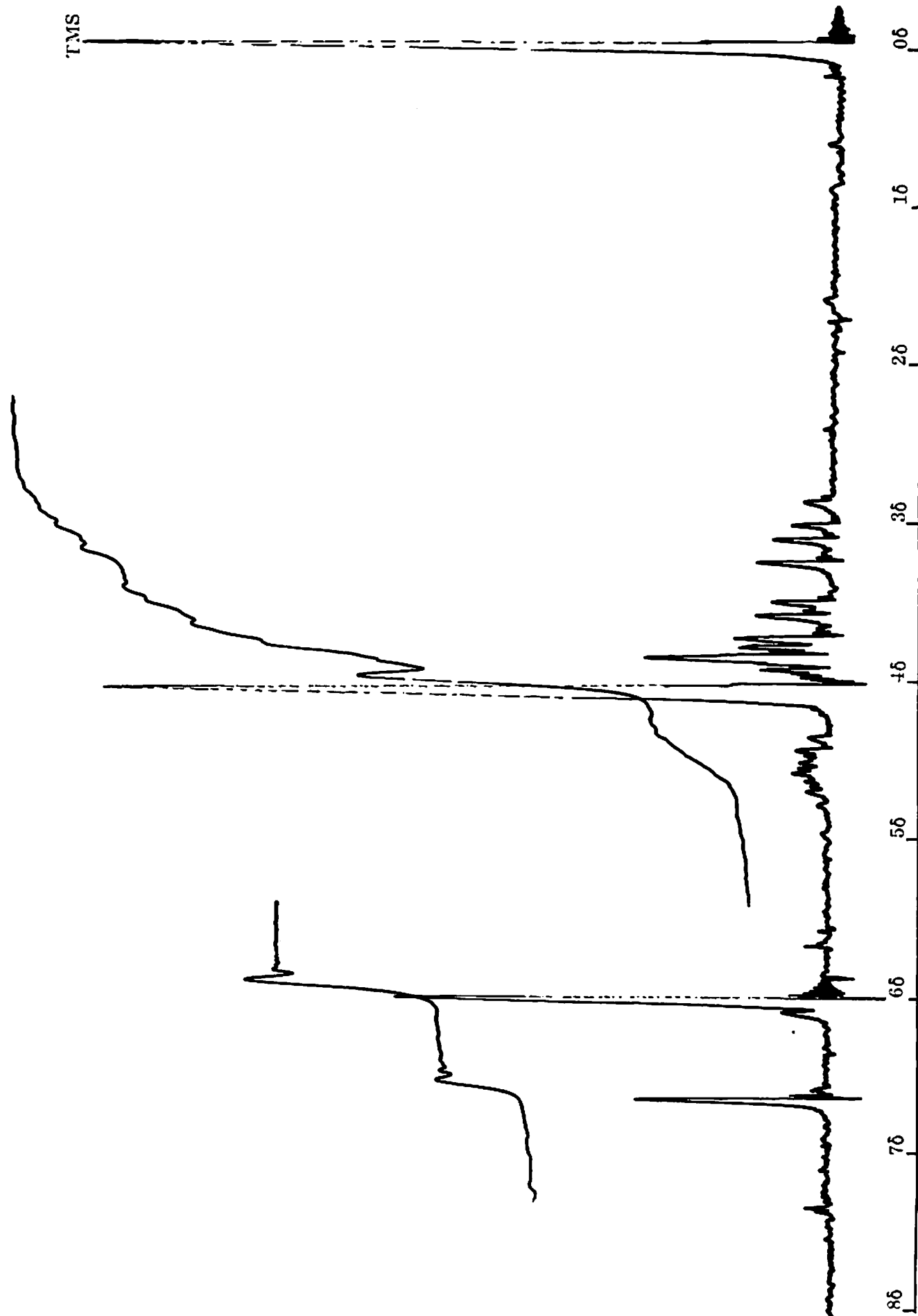
Figure 18: A 60 MHz proton nmr spectrum of bromomyristicin at 1000 Hz sweepwidth, solvent CDCl₃

4. INVESTIGATION OF THE STRUCTURE OF BROMOMYRISTICIN

In the previous weeks, two Freon-soluble natural products have been isolated

from nutmeg, trimyristin and myristicin. Trimyristin is a solid, melting point 56°C, while

myristicin is a liquid, boiling point 280°C. The trimyristin was saponified to afford

myristic acid, and myristicin was reacted with 10% bromine in cyclohexane to give

a white crystalline derivative, which will be called bromomyristicin. This week,

the structure of bromomyristicin will be investigated.

As noted in the Week 4 writeup, bromine can react with organic compounds in

two ways: substitution and addition. Myristicin is an allylbenzene derivative (see the

Week 2 writeup) containing carbon-hydrogen bonds, C-H, and carbon-carbon double

bonds, C=C. Thus, it is possible that it may undergo either or both of the bromination

reactions.

The first question to ask regarding the structure of bromomyristicin is: how

many bromine atoms does the molecule contain? This question may be answered by

a determination of the molecular weight of bromomyristicin.

QUERY: What is the molecular weight of myristicin? If one mole of bromine were to
react with one mole of myristicin via substitution, what would the molecular weight
of the mono-bromo product be? What would be the molecular weight of the di-bromo
product from addition of one mole of bromine to myristicin? What would be the
molecular weight of the tri-bromo product from reaction of myristicin with two moles
of bromine via one addition and one substitution reaction? The tetra-bromo product
from addition of two moles of bromine to myristicin? The tetra-bromo product from
reaction of myristicin with three moles of bromine via one addition and two substitution
reactions?

The molecular weight of bromomyristicin will be determined by the freezing

point depression of a cyclohexane solution of bromomyristicin. This method is based

upon Raoult's Law: the presence of solute in a pure liquid lowers the freezing point

by an amount proportional to the molal concentration of solute (moles of solute per

1000 grams of solvent).

The Freezing Point

The observation of phase changes is an important technique of organic chemistry. In the distillation of Freon 113, a boiling point curve similar to Figure 19 was observed; the head temperature rose from room temperature to ca. 48°, remained constant throughout most of the distillation, and then rose again when most of the Freon had been collected and the concentration of trimyristin and myristicin in the pot and in the vapor increased.
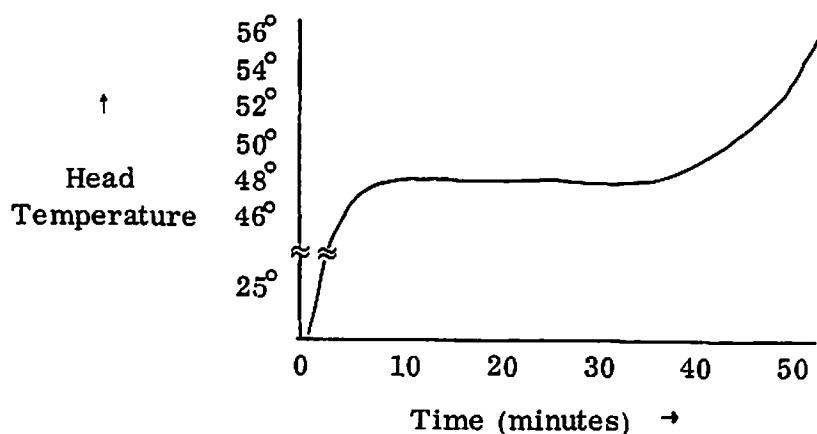
FIGURE 19: HEAD TEMPERATURE VERSUS TIME FOR THE DISTILLATION OF FREON 113 FROM NUTMEG EXTRACT

Two phenomena characteristic of the phase change from liquid to vapor were observed, ebullition (bubbling and frothing) and the temperature plateau while most of the Freon 113 distilled. Heat added to the pot first raised the temperature of the solution to the boiling point, and then vaporized the Freon at a constant temperature before the temperature rose again. Temperature plateaus are characteristic of all phase changes.

The freezing of a liquid is accompanied by two similar phenomena: the appearance of a new phase (solid) and the levelling off of the temperature as heat is withdrawn from the system. The time versus temperature cooling curve for an ideal pure liquid freezing to a solid is shown in Figure 20.
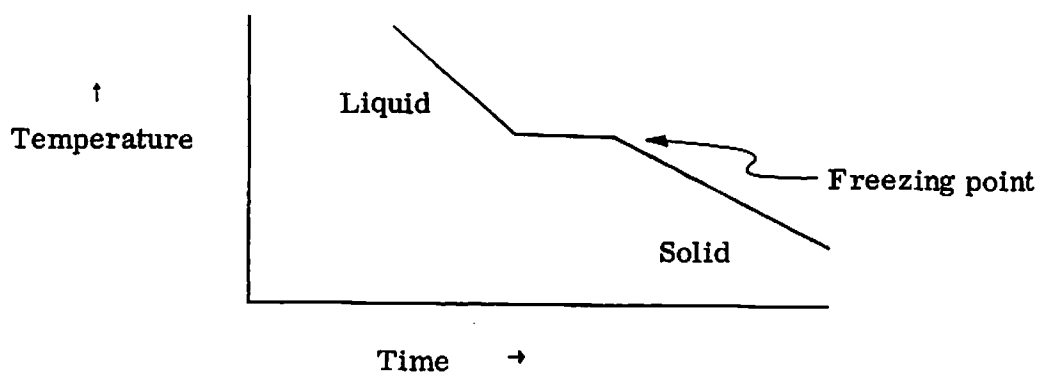
FIGURE 20: IDEALIZED COOLING CURVE FOR A PURE SUBSTANCE

The freezing point (or melting point) of a substance is defined as that temperature at which the solid and liquid phases are at equilibrium with each other at an external pressure of one atmosphere (760 torr). Experimentally, the freezing point is defined as the temperature at which a plateau is observed in the cooling curve of the liquid, while the melting point is defined as the temperature at which a plateau is observed in the heating curve of the solid.

The definition of melting point presented above differs considerably from that of micro melting point , which has been used to characterize solids in previous experiments. The micro melting point has been described as the temperature range over which a solid is converted completely to liquid, and the phase change is monitored by watching the appearance of the liquid phase and disappearance of the solid. The micro melting point is an observation of the behavior of the solid upon heating, and it is a crude . approximation to the melting point.

The determination of a freezing point, however, is a measurement. In order to determine the freezing point accurately, one should plot a cooling curve of the liquid-solid phase transition. For a molecular weight determination, the freezing point of the pure solvent must be measured. Then, the freezing point of a solution of the unknown substance, whose concentration in grams per liter is known, should be measured.

Freezing Point Depression

Experimentally, it has been observed that the freezing points of solutions are lower than the freezing points of the pure solvents. This depression of the freezing point was studied extensively in the nineteenth century by Francois Raoult, a professor of chemistry at the University of Grenoble. In 1883, Raoult demonstrated that, for dilute solutions, the amount by which the freezing point is depressed is proportional to the ratio of the number of solute molecules to the number of solvent molecules, regardless of the identity of the solute. Consequently, the freezing point depression of a solution may be used to determine the molecular weight of the solute by means of Equation 1:

$$(1) \qquad M = \frac{1000 \ w \ K_f}{W \Delta T}$$

where M is the molecular weight of the solute, w is the weight of solute, W the weight of solvent, ΔT the observed freezing point depression (in degrees), and K_f the cryoscopic constant. The cryoscopic constant is a characteristic of the solvent: the freezing point depression of a 1.0 molal solution (1.0 mole of solute per 1000 grams of solvent). The cryoscopic constant of a solvent is inversely proportional to the heat of fusion of the solvent, ΔH_a : the number of calories required to convert one mole of solidified pure solvent at the melting point completely to liquid at the same temperature. The specific formula by which the cryoscopic constant is determined is given by Equation 2:

$$(2) \qquad K_f = \frac{mRT^2}{1000 \ \Delta H_a}$$

where m is the molecular weight of the solvent, R the gas constant (1.99 cal/mole-degree), and T the freezing point of the pure solvent in degrees Kelvin.

QUERY: The freezing point of pure cyclohexane is 6.5° C, and the heat of fusion is 640 calories/mole. What is the cryoscopic constant of cyclohexane ?

The Freezing Point of a Solution

The cooling curve of a solution generally shows a less pronounced plateau than the cooling curve of a pure liquid. A set of experimental data points for a solution of bromomyristicin in cyclohexane is plotted in Figure 21. At $4.8°C$, the curve has a slope of zero ($\frac{d[temperature]}{d[time]} = 0$); this is taken as the experimentally determined freezing point of the solution.
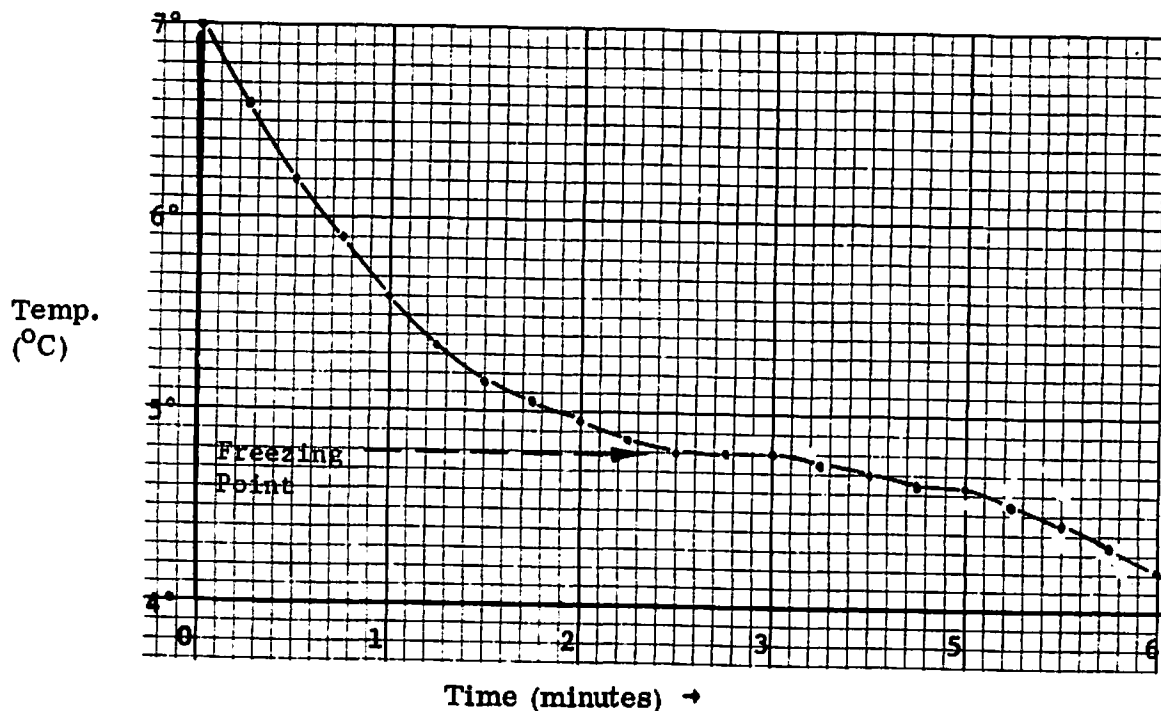
FIGURE 21: COOLING CURVE OF A SOLUTION OF BROMOMYRISTICIN IN CYCLOHEXANE

It is possible that the cooling curve for a solution may not level off. A second set of data points determined for the same solution is plotted in Figure 22. There is no obvious plateau. In this case, it is necessary to find the point where the curve has the minimum rate of change. This point is represented by Z in Figure 22;a line drawn through the point before Z and the point after Z has a smaller slope than any other line drawn through any other pair of data points. This point of minimum slope (also known as an inflection point) is the freezing point of the solution.
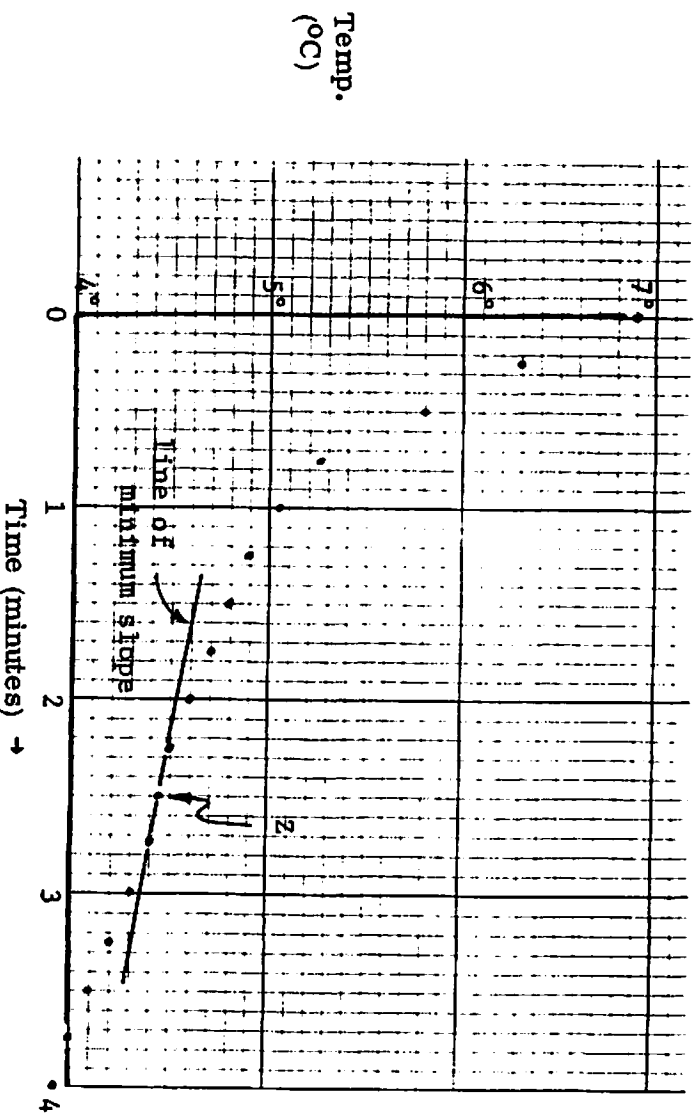
FIGURE 22: DATA POINTS PLOTTED FOR THE COOLING OF A SOLUTION OF BROMOMYRISTICIN IN CYCLOHEXANE

Sometimes _supercooling_ is observed in the determination of freezing points: the liquid drops below its freezing point without solidifying. When solid finally starts to form, the temperature rises and then begins to fall again. This is shown in Figure 23. In such an instance, a straight line should be drawn through the three points after the supercooling. The freezing point is the point of intersection of this line with the cooling curve before the supercooling.
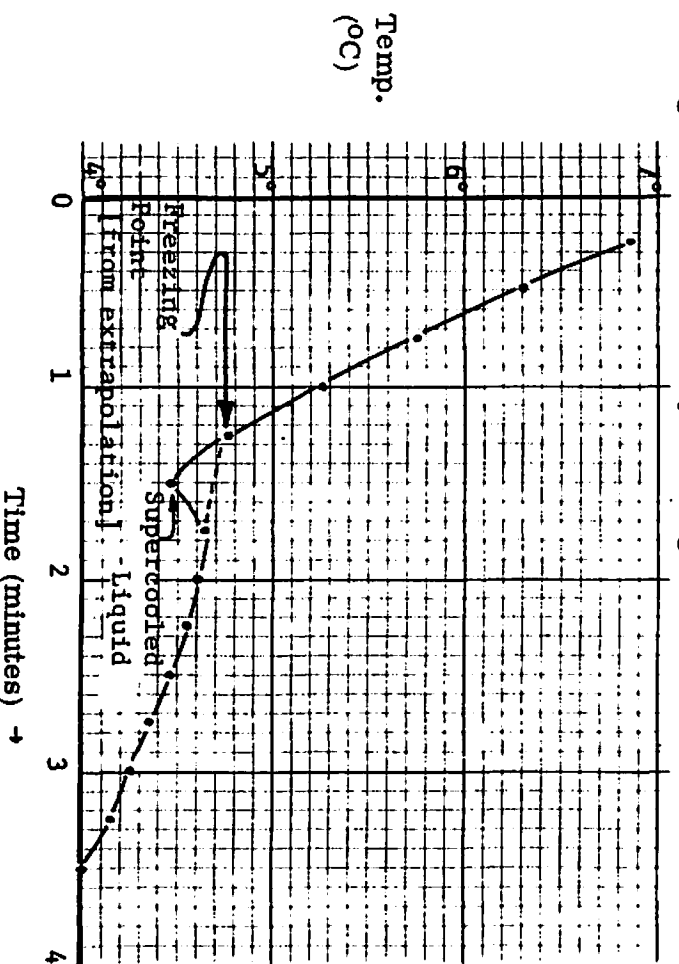
FIGURE 23: COOLING CURVE SHOWING SUPERCOOLING

81

Experimental Uncertainty and Experimental Error

The thermometer which will be used in this experiment is identical to the one utilized in determining the data points shown in Figures 21-23. The scale of the thermometer is calibrated in $0.1°C$ intervals and can be read to only half an interval. This implies that the temperature can be read to only the nearest $0.05°C$. This is the uncertainty of any reading of the thermometer and of any freezing point determined with it. In other words, no value of the temperature can be determined more precisely than $\pm 0.025°$ C.

Suppose the freezing points determined from Figures 21-23 represent the results of three independent trials of the same solution. This means that each experiment has given a different answer: $4.80°C$, $4.35°C$, and $4.75°C$. It is important to know how precise the average of these three temperatures is in order to decide whether further trials need be made.

The mean value of the three temperatures, $\overline{T}$ (sum of the three ÷ 3) is $4.65°C$. The standard deviation, σ, is given by Equation 3:

$$(3) \qquad \sigma = \sqrt{\sum_1^n \frac{(T_i - \overline{T})^2}{n-1}} = \sqrt{\frac{(4.80-4.65)^2 + (4.35-4.65)^2 + (4.75-4.65)^2}{2}} = 0.25°$$

T_i is the value determined in the ith trial and n is the total number of independent trials. The statistical theory of sampling says that σ has the following meaning: odds are about 2 to 1 that any future independent trial will give a value within $\pm 0.25°C$ of $4.65°C$. In other words, σ represents a confidence limit on $\overline{T}$.

Statistical analysis is an extremely powerful tool, for it estimates the precision ("precision" means "reproducibility") of an experimental value. This sort of analysis depends upon an important assumption, namely, that deviations of the experimentally determined value from the "real" value are random. The value of σ

is a measure of the <u>random error</u> of a set of experimental measurements. Experimental measurements should never be reported without specifying the magnitude of the random error.

QUERY: Consider a solution of 0.200 grams of bromomyristicin in 5.00 grams of cyclohexane. How many degrees freezing point depression (to the nearest $0.05°C$) should be observed if the solute is monobromomyristicin (whose molecular weight was calculated in a previous query)? if the solute is dibromomyristicin? tribromomyristicin? either of the tetrabromomyristicins?

PROCEDURE

This experiment should be performed with a partner, since it requires 0.2 g of bromomyristicin. Choose a partner (or partners, if need be) whose bromomyristicin has the same melting point, within $2-3°C$, as yours. Each group of partners should sign out a -10 to $50°C$ thermometer from the stockroom. This thermometer must be returned in perfect shape at the end of the period, or else the person who signed it out will be charged $10 for its loss.

Weigh a clean, dry 18 x 150 mm test tube (held upright in a beaker) on a Mettler balance. Add 7.5 ml of cyclohexane to the test tube and weigh the cyclohexane to the nearest milligram. Determine a cooling curve of the cyclohexane.

Fold a paper towel lengthwise into thirds and wrap it around the top of the test tube. Use this plug of paper towel to support the test tube containing cyclohexane inside a larger test tube (25x200 mm) filled about halfway with tap water. Insert this larger test tube into a 500 ml Erlenmeyer flask filled with an ice-water slush. Insert a -10 to $50°$ thermometer into the cyclohexane and clamp it into position. The assembly should resemble Figure 24.

paper towel wrapped around thermometer to hold it in the clamp

clamp

$-10°$ to $50°$ thermometer

smaller test tube (18x150 mm)

paper towel plug

larger test tube (25x200 mm)

water level in larger test tube

ice level in 500 ml flask

500 ml Erlenmeyer flask filled with ice slush

cyclo-hexane level in smaller test tube

FIGURE 24: COOLING ASSEMBLY

The thermometer is held in the clamp by a paper towel (folded lengthwise into thirds) wrapped around the thermometer. The bulb of the thermometer should be wholly immersed in the cyclohexane, but it should not touch the bottom or the side of the smaller test tube. The water in the larger test tube and the ice slush in the flask should not overflow. Please be careful with the thermometer.

Once the temperature has fallen below $10°C$, it should be recorded to the nearest $0.05°C$ at regular intervals of 15 seconds. In about 10 or 15 minutes the cyclohexane should be completely solidified. Quickly plot the cooling curve in your lab notebook and determine the freezing point. Allow the cyclohexane to liquefy completely before performing another trial. Replace the water in the larger test tube with room temperature tap water before doing another run. QUERY: What is the purpose of the larger test tube filled with tap water?

Each partner should do at least two cooling curves for pure cyclohexane. While one partner is reading the temperature, the other should be plotting. When the freezing point of the sample of pure cyclohexane has been determined with reasonable precision ($\sigma \leq 0.1°C$; quickly estimate the standard deviation), weigh 0.2g of bromomyristicin to the nearest milligram and add it to the cyclohexane in the smaller test tube. The test tube must be heated gently to dissolve the bromomyristicin. Don't worry if a tiny amount of insoluble impurity remains.

As the bromomyristicin solution cools, it becomes supersaturated. If it is not scratched, the liquid will not deposit crystals until it has solidified. If a precipitate forms in the liquid, stop this trial, reheat the bromomyristicin solution to redissolve the precipitate, and commence a new trial. Each partner should perform at least two trials. Determine the mean value of the freezing point and estimate the molecular weight of bromomyristicin.

Once you feel that you can make a clearcut choice whether bromomyristicin

has one, two, three, four, or N bromine atoms in it, you should recover the solid

bromomyristicin by **recrystallization.** Heat the cyclohexane solution to dissolve

the bromomyristicin and filter the hot solution if any insoluble material remains.

Allow the solution to cool to room temperature; scratch the solution to induce

crystallization, if necessary. Collect the crystals by suction filtration in a

Hirsch funnel and suck them dry. Redetermine the melting point.

Don't forget to turn in your -10 to 50°C thermometer when you have finished with it.

When the bromomyristicin crystals have dried, let your teaching assistant know.

He may take a sample and run an NMR spectrum of it. Try to analyze the spectrum

and decide if it is consistent with the formula you infer from your cryoscopic

determination of the molecular weight. For comparison, the NMR spectrum of bromo-

myristicin is reproduced on page 59. During the coming week, propose the

structures you feel are plausible for bromomyristicin. Turn in the yellow carbon

copies from your laboratory notebook, with the cryoscopic data analyzed (including

standard deviations of freezing points and molecular weights) and proposed structures,

to your teaching assistant at the beginning of the next laboratory period. Try to explain

the NMR of bromomyristicin.

Note on Recycling

This week's experiment should be short enough to leave time to finish work

left from previous weeks. Please dispose of all waste in the fashions described in

previous writeups. Solid samples - trimyristin, myristic acid, bromomyristicin,

the urea inclusion complex, etc. - should be packed into glassine envelopes, and labelled

with your name, the name of the compound, and the weight of the contents. Staple .

these glassine envelopes to the yellow carbon copies you hand in next week.

The cyclohexane mother liquor left from this week's experiment will be collected in designated containers and recycled by batch distillation.

Note on Data Analysis

To determine the standard deviation of the cryoscopically determined molecular weight, it is necessary to determine the standard deviation of the freezing point depression. The freezing point depression is, of course, the difference between the freezing points of pure cyclohexane and of the solution of bromomyristicin in cyclohexane. Both of these freezing points have standard deviations of their own.

The standard deviation of the difference of two values, each with its own standard deviation, is computed as shown in Equation 4:

$$(4) \qquad \sigma_{\text{freezing point depression}} = \sqrt{\sigma^2_{\substack{\text{cyclohexane} \\ \text{freezing point}}} + \sigma^2_{\substack{\text{solution} \\ \text{freezing point}}}}$$

The standard deviation of any value found by multiplying one quantity (with a known standard deviation) by a constant that is known to a higher precision than the first quantity is equal to the product of the standard deviation of the first quantity and the same constant. More succinctly,

$$\text{if} \qquad M = k \cdot (\text{freezing point depression})$$

$$\text{then} \qquad \sigma_M = k \cdot \sigma_{\text{freezing point depression}}$$

5. SYNTHESIS AND PURIFICATION OF CYCLOPROPYL KETONES

Introduction

In the sequence of nutmeg experiments you have seen how compounds may be

obtained from natural sources and purified. These compounds may be characterized

and identified by degradation to simpler compounds (e.g., trimyristin → myristic acid),

by reactivity toward diagnostic reagents (e.g., myristicin → bromomyristicin), and by

spectroscopic analysis (e.g., nmr). A number of important purification techniques

were introduced (distillation, recrystallization and chromatography) and one test of

purity, the micro melting point.

The elucidation of the structures of organic compounds is an important branch of

organic chemistry. The painstaking degradation of natural products to simpler compounds

was a major occupation of 19th century organic chemists, and this effort, aided by

spectroscopic methods, continues today. However, synthesis of organic compounds

is now of greater importance. For example, the discovery and eventual synthesis of

sulfa drugs, antibiotics, steroid hormones, and a variety of other drugs not only have

helped to create a large pharmaceutical industry but also have stimulated the discovery

of new synthetic methods.

Synthesis of organic molecules is generally divided into two areas: transformation

of functional groups and the formation of new carbon--carbon bonds. The reactions that

you have already performed (saponification and bromination) belong to the former class.

The three reactions in the dicyclopropyl ketone synthetic sequence involve both types:

A. γ-butyrolactone ($C_4H_6O_2$) $\xrightarrow[\text{in methanol}]{\text{sodium methoxide}}$ dibutyrolactone ($C_8H_{10}O_3$)

B. dibutyrolactone ($C_8H_{10}O_3$) $\xrightarrow{\text{hydrochloric acid}}$ 1,7-dichloro-4-heptanone ($C_7H_{12}Cl_2O$)

C. 1,7-dichloro-4-heptanone ($C_7H_{12}Cl_2O$) $\xrightarrow[\text{in water}]{\text{sodium hydroxide}}$ dicyclopropyl ketone ($C_7H_{10}O$)
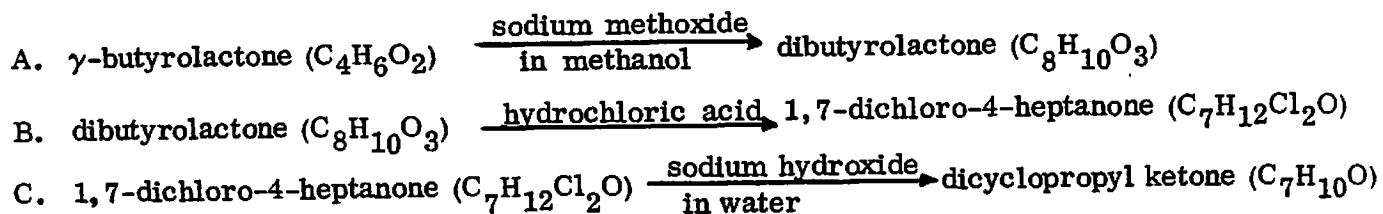
The starting material for this experiment is γ-butyrolactone. A lactone is a cyclic ester, and the prefix "γ" indicates that an oxygen in the $-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-$ group is attached to the γ-position of the hydrocarbon chain of the ester (the carbon atoms are numbered with Greek letters, as shown in the drawing of butyrolactone below).

	Aldehyde	$CH_3CH_2CH_2\overset{\overset{\text{O}}{\|}}{C}H$	butyraldehyde
	Ketone	$CH_3CH_2\overset{\overset{\text{O}}{\|}}{C}CH_3$	2-butanone (methyl ethyl ketone)
	Carboxylic Acid	$CH_3CH_2CH_2\overset{\overset{\text{O}}{\|}}{C}OH$	butyric acid
γ-butyrolactone	Amide	$CH_3CH_2CH_2\overset{\overset{\text{O}}{\|}}{C}NH_2$	butyramide
CARBONYL COMPOUNDS	Ester	$CH_3CH_2CH_2\overset{\overset{\text{O}}{\|}}{C}OCH_3$	methyl butyrate
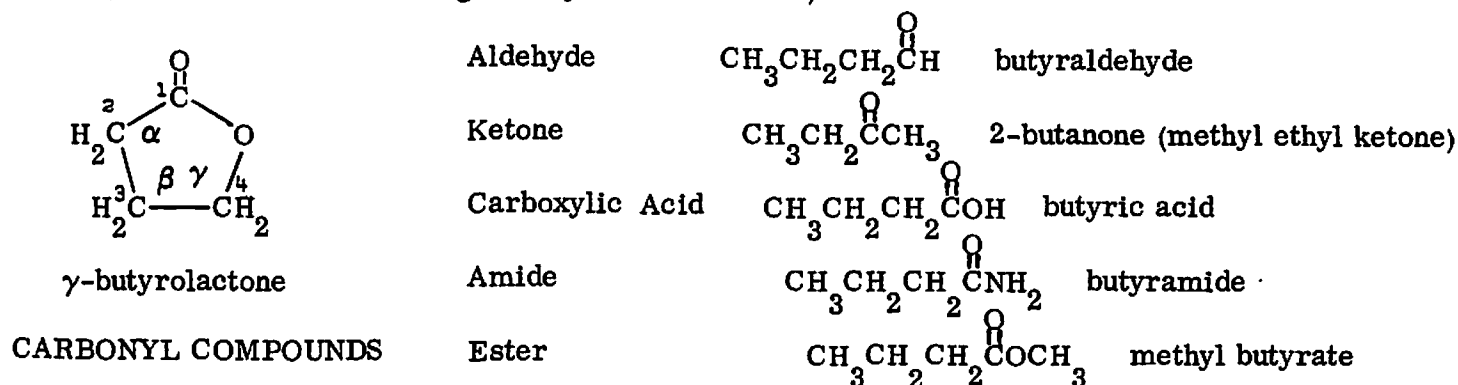
Esters and lactones are members of the class of compounds containing the <u>carbonyl</u> (C= O) group. Other carbonyl compounds include aldehydes, ketones, carboxylic acids, and amides. There are two important characteristics that all carbonyl compounds share: the carbon is Lewis acidic, and hydrogens in the α-position are Brønsted acidic.

The concept of Lewis acidity should be familiar from Chem 3. To review briefly, all first-row elements seek to acquire, through bonding, eight electrons in their outer shells. For this reason carbon has a valence of four, nitrogen a valence of three, et cetera. An element such as boron, however, can bind covalently only with a valence of three, but trivalent boron has only six electrons in its outer shell. This is shown in the dot structure of BF_3 below. The vacant p-orbital in BF_3 can easily accept an electron pair; for example, BF_3 forms a very strong bond with ammonia, which has a lone pair in its outer shell. An electron pair donor is called a <u>Lewis base</u>; an electron pair acceptor is a <u>Lewis acid.</u>
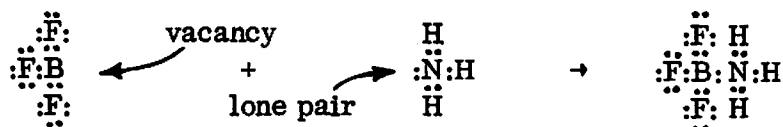
Many organic compounds are much weaker Lewis acids than BF_3 and much

weaker Lewis bases than NH_3. Consequently, many of the covalent bonds formed by

electron pair donation in organic reactions are much weaker than the bond formed

between ammonia and BF_3. Organic chemists generally avoid the terms "Lewis acids"

and "Lewis bases" for this reason. Also, a large molecule may have one site that is

acidic and another site that is basic. Instead, sites within molecules are called

electrophilic (Lewis acidic) or nucleophilic (Lewis basic). In a carbonyl compound, the

dot structure suggests that both the carbon and oxygen have eight electrons in their

outer shells, and equally share the four electrons in the double bond. However, oxygen

is more electronegative than carbon, and a large amount of electron density is localized

on the oxygen. This charge separation in the C=O bond renders the oxygen nucleophilic and

the carbon electrophilic.

Various representations of the carbonyl group
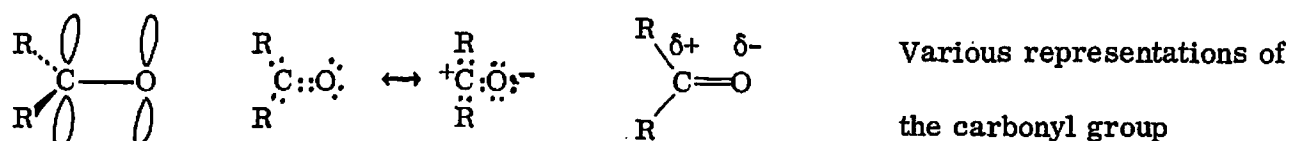
You have already encountered an example of the electrophilic character of the carbonyl

group in the saponification of esters, for the hydroxide anion acts as a nucleophile (Lewis

base) when it forms a bond to the carbonyl carbon (cf. reaction 2 on page 42 of the nutmeg

experiment) of trimyristin.

Brønsted acidity, as you recall from Chem 3, refers to proton-donating ability.

Hydrogen chloride (a very poor Lewis acid) is a very strong Brønsted acid, for it ionizes

completely in aqueous solution. Hydrogens on atoms attached to carbonyl groups

(α-hydrogens) tend to be Brønsted acidic. For example, the hydrogens in water are weakly

acidic (pK_a=15.7), while the O-H hydrogen of butyric acid is moderately acidic (pK_a=5).

This Brønsted acidity results from the combined effects of the partial positive charge on the

carbonyl carbon and stabilization of the conjugate base (the carboxylate anion) by delocalization

90

of the negative charge through resonance (cf. structures a and b in reaction 2, page 42 of the nutmeg sequence).

Similarly, the N-H hydrogens of butyramide are much more acidic ($pK_a = 25$) than ammonia itself ($pK_a = 36$). Even C-H hydrogens, when α to a carbonyl, become acidic: the pK_a of 2-butanone is 20 and the pK_a of methyl butyrate is 24.5, while the pK_a of butane itself is greater than 40. This "activation" of α-hydrogens by a carbonyl function is of particular importance in the chemical reactions of carbonyl compounds.

Suppose γ-butyrolactone is allowed to react with base. If the base acts as a nucleophile, saponification takes place; if the base acts as a Brønsted base, one of the two α-hydrogens is removed. In the synthetic sequence which you are performing, we wish the latter reaction to occur to the exclusion of the former. Hence, the base used is sodium methoxide, NaOCH$_3$, for $^-$OCH$_3$ is much more reactive as a Brønsted base than as a nucleophile. The reaction between γ-butyrolactone and methoxide in methanol is shown in reaction 1. Note the line drawings which may be used to represent butyrolactone.

QUERY Suppose hydroxide were used and saponification took place. What product would result? Because this product is undesirable and because water reacts with methoxide to form hydroxide, the methanolic solution of sodium methoxide must be kept rigorously free from water.

I
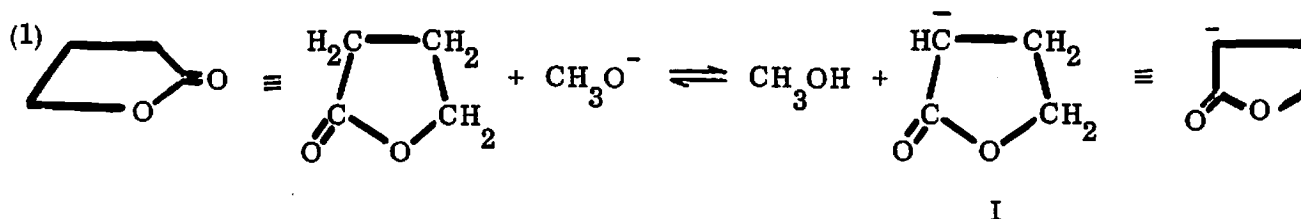
The anion I is the conjugate base of γ-butyrolactone. Because it has a negative charge on carbon, it is called a carbanion. Carbanions, as a rule, are quite nucleophilic, particularly toward electrophilic carbon. Consequently, the equilibrium shown in reaction 2 favors the condensed intermediate II.

I   II
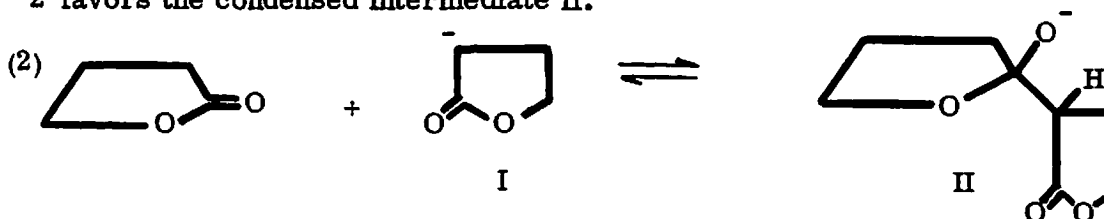
The condensed intermediate II undergoes internal proton transfer and loss of

hydroxide to yield the product dibutyrolactone, as shown in reaction 3.

(3) II ⇌ [structure with OH] ⇌ OH⁻ + [Ring A, Ring B structure] Dibutyrolactone

ether oxygen   carbonyl oxygen   ester oxygen
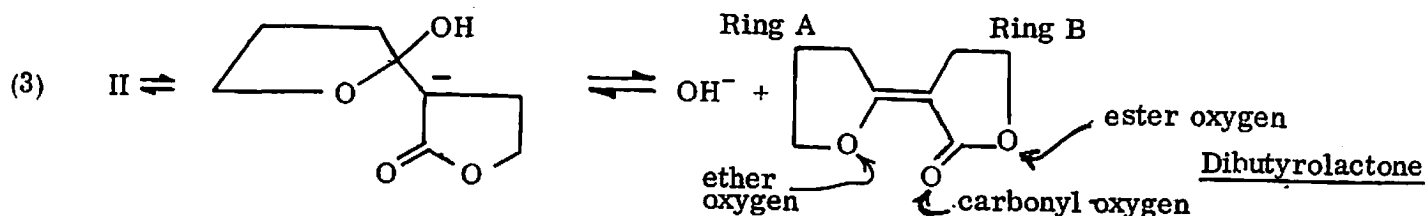
QUERY: There are two geometric isomers of dibutyrolactone, of which only one is drawn in reaction 3. Draw the structure of the other geometric isomer. In all likelihood, the condensation of γ-butyrolactone produces a mixture of these isomers.

As you can see, dibutyrolactone has two rings, which we shall call Ring A

and Ring B. It has three different oxygen atoms: a carbonyl oxygen, an ester oxygen and

an ether oxygen. The ether oxygen is bound to a carbon which is part of a double bond

(called a vinyl carbon). Vinyl ethers have several properties that are unusual. First,

they are easily hydrolyzed by hydrochloric acid, whereas most other ethers are not

attacked by HCl. Second, the hydrolysis product, a vinyl alcohol, is not stable, but

rearranges (tautomerizes) to an isomeric carbonyl compound. These reactions are ex-

emplified by the acid hydrolysis of 2-propenyl methyl ether, reaction 4, shown below.

(4) $H_2C=C$(OCH$_3$)(CH$_3$) + HCl ⇌ $H_2C=C$(OCH$_3$)(CH$_3$) + Cl⁻ → CH_3Cl + $H_2C=C$(OH)(CH$_3$) ⇌ H_3C-C(O)(CH$_3$)
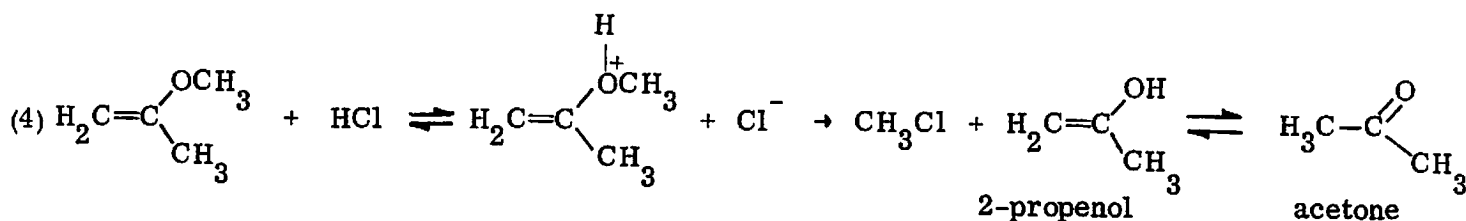
2-propenol   acetone

The equilibrium constant for conversion of 2-propenol to acetone is greater than 50,000. In

general, such "enols" (ene + ol) prefer to exist as the isomeric carbonyl compounds.

QUERY: Predict the product from hydrolysis of Ring A of dibutyrolactone in aqueous HCl. Does it matter which isomer of dibutyrolactone you start with ?

Reaction of dibutyrolactone with HCl is the second step in the synthetic sequence to

prepare dicyclopropyl ketone. Both Ring A and Ring B are opened; the opening of Ring B

proceeds in the same fashion as the reaction of γ-butyrolactone with HCl shown in reaction 5.

(5) [lactone structure] + HCl ⇌ [protonated structure] + Cl⁻ → $HOCCH_2CH_2CH_2Cl$

4-chlorobutyric acid
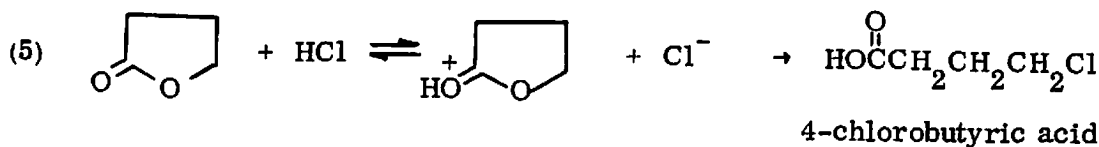
QUERY   Knowing that enol ethers hydrolyze to ketones and γ-butyrolactone opens to give 4-chlorobutyric acid with HCl, predict (and draw) the initial product formed when dibutyrolactone is refluxed with hydrochloric acid.
Hint: It is a β-keto carboxylic acid.

All β-keto carboxylic acids are unstable at temperatures above $100^{\circ}C$, for they rearrange via an intramolecular hydrogen transfer to expel carbon dioxide. This decarboxylation reaction is exemplified by reaction 6, the conversion of acetoacetic acid (3-oxo-butyric acid) to acetone via the intermediacy of 2-propenol.

(6) $$O=\overset{O}{\underset{CH_2}{\overset{\diagup}{C}}}\kern-1em\overset{H}{\diagup}\kern-1em\overset{O}{\diagdown}CCH_3 \rightarrow \overset{O}{\underset{O}{\overset{\parallel}{C}}} + \underset{H_2C}{\overset{H-O}{\diagup}}C\text{-}CH_3 \rightarrow \underset{H_3C}{\overset{O}{\diagdown}}C\text{-}CH_3$$
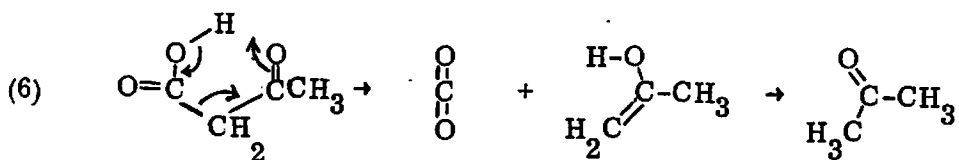
The curved arrows drawn in reaction 6 are supposed to indicate that the hydrogen transfer occurs at the same time as the expulsion of carbon dioxide. Such a reaction, in which several bonds are made and broken synchronously, is called concerted. The arrows are drawn from the bonds that are breaking to the places where bonds are forming. They represent the flow of electron pairs in the transition state; their tails are at the bonds which disappear and their heads are at the bonds that appear in the product. Thus, the final product formed when dibutyrolactone is refluxed in aqueous hydrochloric acid is 1,7-dichloro-4-heptanone, $ClCH_2CH_2CH_2\overset{O}{\overset{\parallel}{C}}CH_2CH_2CH_2Cl$.

The final step in the synthesis of dicyclopropyl ketone is the reaction of 1,7-dichloro-4-heptanone with aqueous base. As noted above, the α-hydrogens of a carbonyl compound are somewhat acidic, and the conjugate base of 1,7-dichloro-4-heptanone is drawn as the carbanion III in reaction 7. The anionic site of III is nucleophilic, and it attacks the nearest and most electrophilic site in the molecule, which happens to be one of the carbons bearing a chlorine. This type of reaction is known as nucleophilic displacement and the chloride that is displaced is called the leaving group.

(7)

III → Cl⁻ + IV
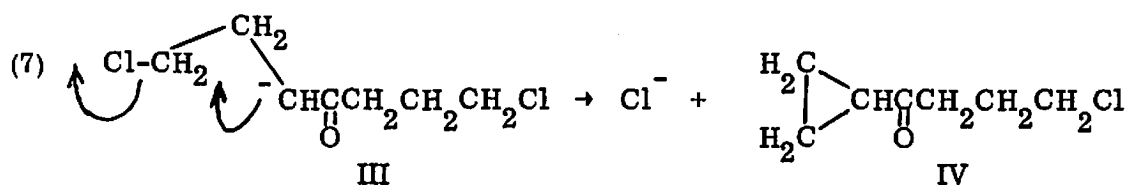
The product of reaction 7, ketone IV, reacts with a second mole of hydroxide to

form its conjugate base, V, which undergoes a second intramolecular nucleophilic

displacement to yield the product, dicyclopropyl ketone, as depicted in reaction 8.

(8)

V

Dicyclopropyl ketone
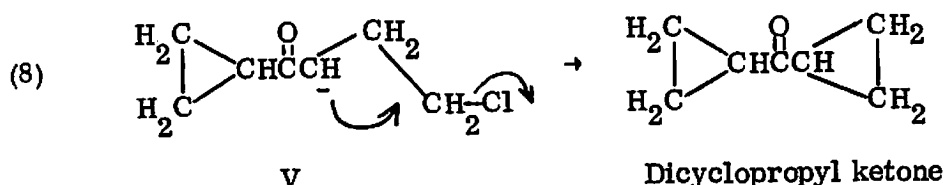
It should be noted that, in reaction 7, there were two equivalently electrophilic

carbon atoms in the carbanion III: the $ClCH_2$ at the 1-position and the $ClCH_2$ at the

7-position. The nucleophilic carbanion attacks the closer of the two to form a three-

member ring. This preference or choice is known as regioselectivity; it reflects the

fact that the transition state for formation of a three-member ring by nucleophilic

displacement is more accessible than the transition state for formation of a five-member

ring (which would have resulted from attack on the farther of the two $ClCH_2$ carbons),

even though the latter product is thermodynamically more stable than the former.

The observed regioselectivity represents kinetic control of the nucleophilic

displacement reaction rather than thermodynamic control.

QUERY   Reaction of acetylbutyrolactone with hydrochloric acid, followed by treatment of
the reaction product with aqueous sodium hydroxide, yields methyl cyclopropyl ketone.
Draw the mechanism for this reaction, with a structure for every intermediate.
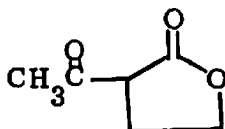
Acetylbutyrolactone

Fractional Distillation

As discussed in the nutmeg experiment (p. 30), simple distillation of a mixture

of two liquids will often give a distillate that consists of a mixture. For example, simple

distillation of a 1:1 mixture of isobutanol and isopropanol affords a 1:2 mixture as distillate

(Figure 4, nutmegs). A second distillation of this distillate gives a 1:5 mixture, and "pure"

isopropanol can be recovered only after a number of sequential distillations.

Fractional distillation is a technique whereby

successive distillations are carried out automatically

without collecting or transferring the intermediate

fractions. At the start of the distillation, hot vapors

rise from the still pot and condense on the fractionating

column. As the condensate returns to the pot, it

encounters hotter vapors and is partially vaporized

again, as shown in Figure 25. However, the portion

Vapor from
condensate 2

Condensate 2

Vapor from
condensate 1

Condensate 1
heated by
vapor from pot

Vapor from pot
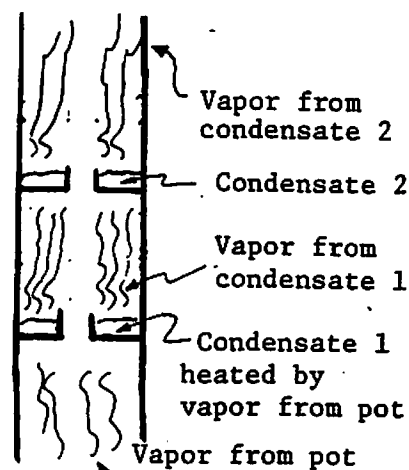
Figure 25: Idealized fractionation column

of the condensate that is revaporized contains a larger fraction of the more volatile

component than the original vapor. Repeated vaporizations and condensations over the

length of the column eventually give a vapor at the top of the column that is considerably

enriched with the more volatile component, while the still pot contains a larger fraction of

the less volatile component than the original mixture. Obviously, the longer the column

and the slower the takeoff at the top, the better the separation will be. If the pot is over-

heated or the boil-up rate is too fast, the vapor and liquid in the column do not have time to

equilibrate and the efficiency of the column is much reduced. Fractionating columns are

often packed with some inert material (glass beads or helices) that provides a surface for

condensation. Since the boiling point difference between Freon and dicyclopropyl ketone

is large (about 100°), the reduced efficiency of a non-packed column is still sufficient

to effect separation.

Steam Distillation

Steam distillation is a clever technique for distilling a high-molecular-weight or heat-sensitive compound at a temperature below the boiling point of water. The major requirement is that the compound to be distilled be insoluble in water. Under these circumstances, the degree of separation is about the same as that obtained through a simple distillation at reduced pressure. Steam distillation is particularly useful when separating a volatile compound from nonvolatile impurities, for instance tarry reaction residues or inorganic salts.

Steam distillation is a technique of codistillation. You will recall, from the discussion of simple distillation on pp. 25-31 of the nutmeg sequence, that a solution of Freon 113 and myristicin boils at 54°C when the mole fraction of myristicin in solution is 0.18. Also, using Dalton's Law (Equation 4, p. 30), you calculated that only a tiny amount of myristicin (mole fraction about 10^{-4}) codistills with the Freon 113 at 54°C.

Now suppose you are distilling a mixture of myristicin and water. Since these two liquids are insoluble, the total vapor pressure over the mixture is simply the sum of the vapor pressures of each component. In other words, if two pure liquids are completely immiscible, the mole fraction of each, in its respective phase, is unity. Therefore, the expression of Dalton's Law for a two-phase system of phases A and B is

$$X_A^{vap} = \frac{P_A}{760} \quad \text{and} \quad X_B^{vap} = \frac{P_B}{760}.$$

One may calculate how much steam is needed to codistill a given amount of immiscible organic material. For example, the total vapor pressure above the two-phase system myristicin + water is 760 torr at 99.8°C. The vapor pressure of water at this temperature is 755 torr; therefore, the vapor pressure of myristicin is 5 torr. The mole fraction of water in the vapor from this boiling mixture is 755/760, and the mole fraction of myristicin

in the vapor is 5/760. Consequently, 5/755 mole of myristicin is distilled for every mole

of water distilled. Since the molecular weight of water is 18 and the molecular weight of

myristicin is 192, this means that 1.3 g of myristicin codistills with 18 g of water.

QUERY   The mixture of dicyclopropyl ketone and water boils at $96^\circ C$. How much water (in grams)
is needed to codistill 5 g of ketone ? The vapor pressure of water at $96^\circ C$ is 660 torr.

The steam used in a codistillation may be generated externally and passed into the

system, or it can be generated in situ. The former method is preferable if a great

deal of steam is required to distill a small quantity of material. In steam distillation of

dicyclopropyl ketone, however, distillation of a mixture of ketone and water is adequate.

Drying of Liquids

Drying of organic liquids that have been in contact with moisture is often a

necessary pretreatment before distillation or further reactions, since water can cause

undesired side reactions with many reagents. Liquids are dried through use of inorganic

salts that form hydrates ($MgSO_4$, Na_2SO_4, $CaCl_2$), as well as minerallike compounds

(Molecular Sieves), adsorbents (Al_2O_3), substances that react irreversibly with water

(Na, $LiAlH_4$, P_2O_5), and by other means.

Both neat liquids and solutions in an organic solvent may be dried with hydrating

salts. No good rules of thumb exist for the amount needed, but if more than 5% of drying

agent is added, liquid clinging to the salt will be lost. Necessary drying time may vary

from 10 minutes to several hours. Simple criteria for completeness of drying include

clearing up of cloudiness in the liquid and (for $MgSO_4$ only) cessation of clumping of the

powdery drying agent. The laboratory directions will tell you the drying agent to use and

the length of time thought necessary. The drying agent is commonly estimated by eye (in

spatulatipfuls) and added to the liquid with occasional swirling.

Dried liqids are filtered before distillation or reaction. Gravity filtration may be

used, but suction filtration is usually preferable to recover the most material.

PROCEDURE — Dicyclopropyl ketone

Since sodium methoxide is very sensitive to moisture, its exposure to the sodden atmosphere of Providence must be minimized. Have all the necessary glassware on the benchtop and ready for rapid assembly before beginning the experiment.

Measure out 43 ml (34 g, 0.40 mole) of γ-butyrolactone into a 500-ml r.b. flask. Quickly measure out 52 ml of 25% sodium methoxide in methanol solution and pour it into the flask also. Swirl the mixture, add a boiling stone, fit the flask with the apparatus for a simple distillation (still head, condenser, receiver adapter, and 100-ml graduated cylinder as a receiver) and begin to heat the mixture with the regulated ir lamp. Collect approximately 50 ml of distillate and note the head temperature every few minutes as the distillation proceeds. The brown residue that remains in the pot contains the butyrolactone dimer. * Fit the cooled pot with a Claisen adapter topped with an addition funnel and a reflux condenser with a gas trap, as shown in Figure 26. You may use an ice bath to hasten cooling, but be sure the residue does not set to a hard, glassy mass.

In the hood, carefully measure out 80 ml of concentrated hydrochloric acid and pour it into the addition funnel (stopcock closed!). Return to your bench and very carefully (dropwise) begin to add the acid to the brown pot residue. After a few drops have been added, agitate the flask without dismantling the apparatus either by picking up the ringstand or by loosening the clamps. A great deal of CO_2 gas is evolved at this stage and it will carry hydrogen chloride fumes into the lab if the gas trap is not properly set up. If too much acid is added at once, the reaction mixture is likely to erupt out of the flask and onto the benchtop. Be careful! If the reaction should get out of hand, stand back and wait for it to subside. Make sure that water from the gas trap does not back up into the reaction flask. If there is a pressure drop and the water begins to rise in the inverted funnel, simply lift the funnel above the surface of the water.

---

*You could stop here, but try to continue to the place marked ** on the next page.

After adding all the acid, reflux the mixture for 20 minutes with occasional agitation, then remove the gas trap and thoroughly cool the reaction flask by swirling it in an ice bath. Try not to disassemble all the glassware since the same setup (minus the gas trap) is used in the next step. Neutralize the aqueous acid in the gas trap with sodium bicarbonate and discard. Rinse out the acid-containing addition funnel with bicarbonate solution and water.

Prepare a concentrated solution of aqueous base as follows. Weigh 48 g of NaOH in a beaker on a triple-beam balance and add it to 60 ml of water, with swirling, in an Erlenmeyer flask. Then cool the flask in an ice bath. Prepare this solution 20 minutes before you need it in order to give it time to cool. Pour the cold ($0-5^\circ$C) solution into the 125-ml addition funnel and set the funnel atop the Claisen adapter as in Figure 26. While cooling the 500-ml flask that contains the mixture of HCl and dichloroketone in an ice-water bath, add the NaOH solution slowly and carefully (exothermic). After adding all the base, ** reflux the mixture for 30 minutes; turn off the lamp and allow the mixture to cool for a few minutes. A great deal of sodium chloride may precipitate while the basic solution is refluxing. Do not be alarmed, but if the mixture tends to bump violently, lower the heat or cool and filter off the precipitate.

Using the same flask and contents, arrange an apparatus for simple distillation and distill into a 250-ml Erlenmeyer flask until about 100 ml of the dicyclopropyl ketone—water mixture has collected. Add sufficient NaCl to saturate the aqueous layer (about 20 g) and decant the supernanant liquid from the Erlenmeyer into a separatory funnel. Add 25 ml of Freon, vent the funnel, shake vigorously, and allow the layers to separate. Drain the Freon directly into a 100-ml r.b. flask. Extract the aqueous phase with a second 25-ml portion of Freon and again drain the Freon into the r.b. flask. Add a boiling stone to the flask and fit it with a fractionating column, still head, condenser, and receiver adapter

---

**You may stop here. If you do, transfer the mixture to an Erlenmeyer flask and stopper for storage.

as in Figure 27. Carefully distill and collect the Freon, while watching the head temperature, until the temperature drops to about 40°C. Return the recovered Freon to the bottle. Turn off the lamp and remove the fractionating column and the condenser. (If the yield of product is very low, skip the next step.) Connect the still head directly to the receiver adapter and continue the "short-path" distillation into a tared 50-ml r.b. flask or sample bottle until no more distillate comes over (dicyclopropyl ketone boiling point is 165-170°C).
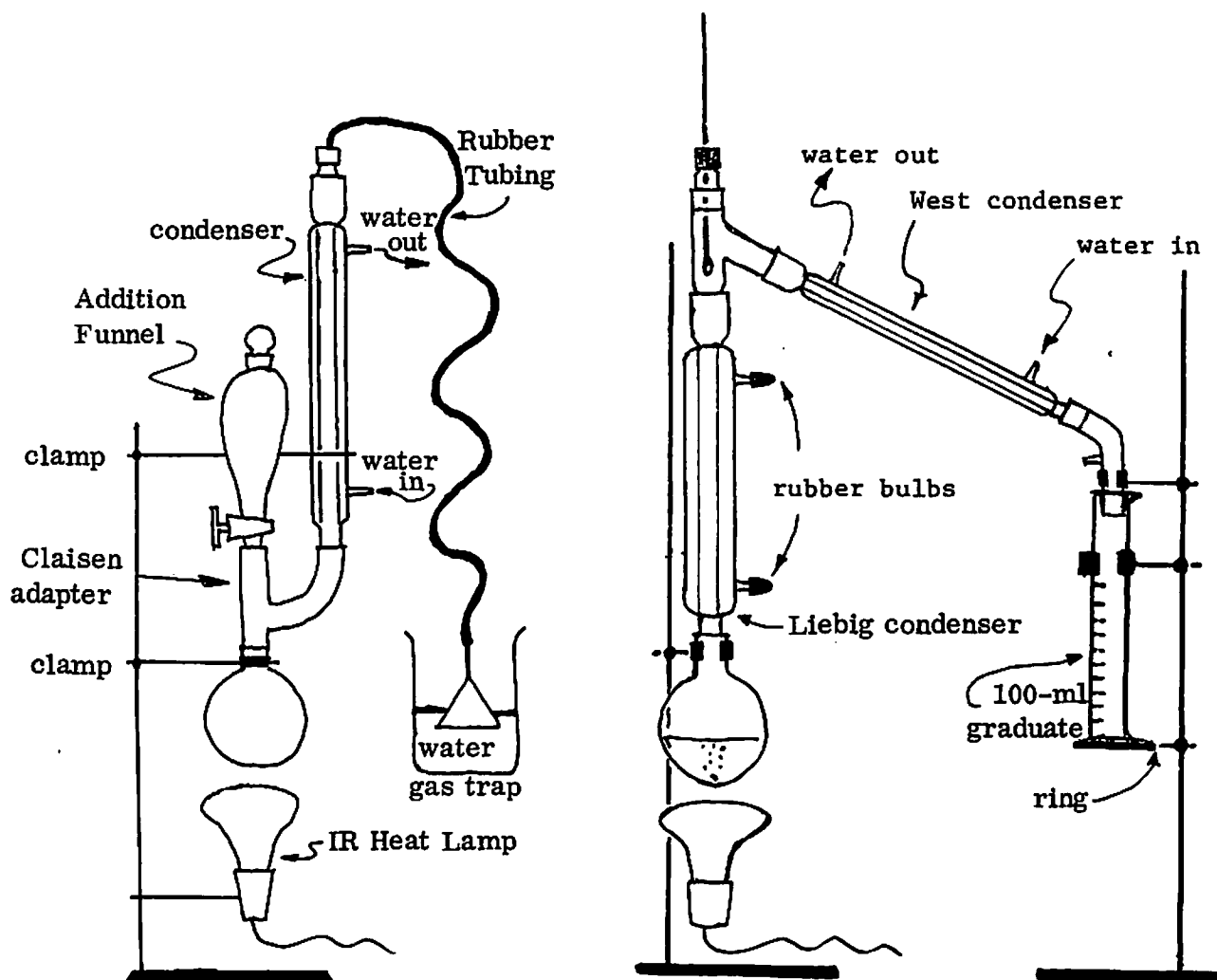
Figure 26: Apparatus for reactions.

Figure 27: Fractional distillation setup.

100

PROCEDURE — Dicyclopropyl Ketone Semicarbazone (A taste of Chem. 12)

Dissolve 0.5 g of semicarbazide hydrochloride and 0.75 g of sodium acetate in 5 ml of water in a test tube. Add about 0.5 ml (10 drops) of dicyclopropyl ketone* to the aqueous solution. It will form a small second layer over the water. Add 95% ethanol dropwise (about 0.5 ml) until the mixture is homogeneous (only one layer) at room temperature. Heat the test tube in a hot water bath (about 75 ^{o}C) atop a steam bath for 30 minutes. Allow the solution to slowly cool to room temperature, then cool it by swirling in an ice-water bath. If crystals of semicarbazone do not precipitate, even with scratching, place the solution in your locker. By next week, crystals will form. Isolate them by suction filtration and report the weight and melting point of the semicarbazone obtained.

---

*If only a very small amount (less than 1 ml) of dicyclopropyl ketone remains after fractional distillation to remove the Freon, add the aqueous solution of semicarbazide hydrochloride and sodium acetate directly to the crude ketone in the 100-ml r.b. flask.
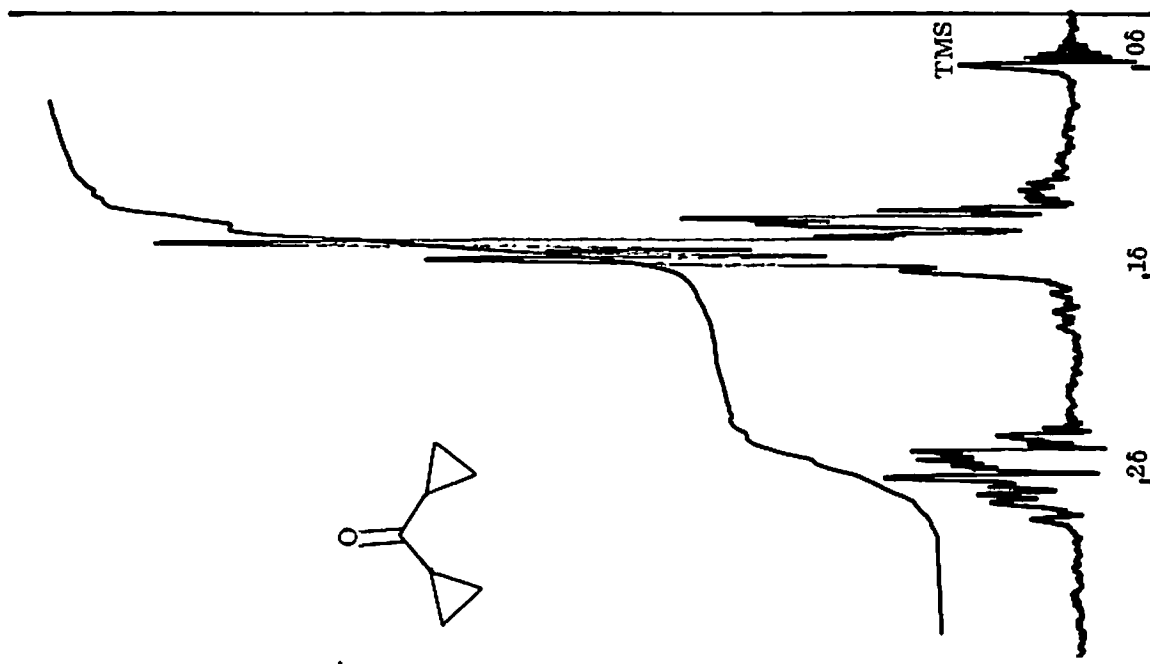
Figure 29: 60-MHz proton nmr spectrum of dicyclopropyl ketone in CCl$_4$
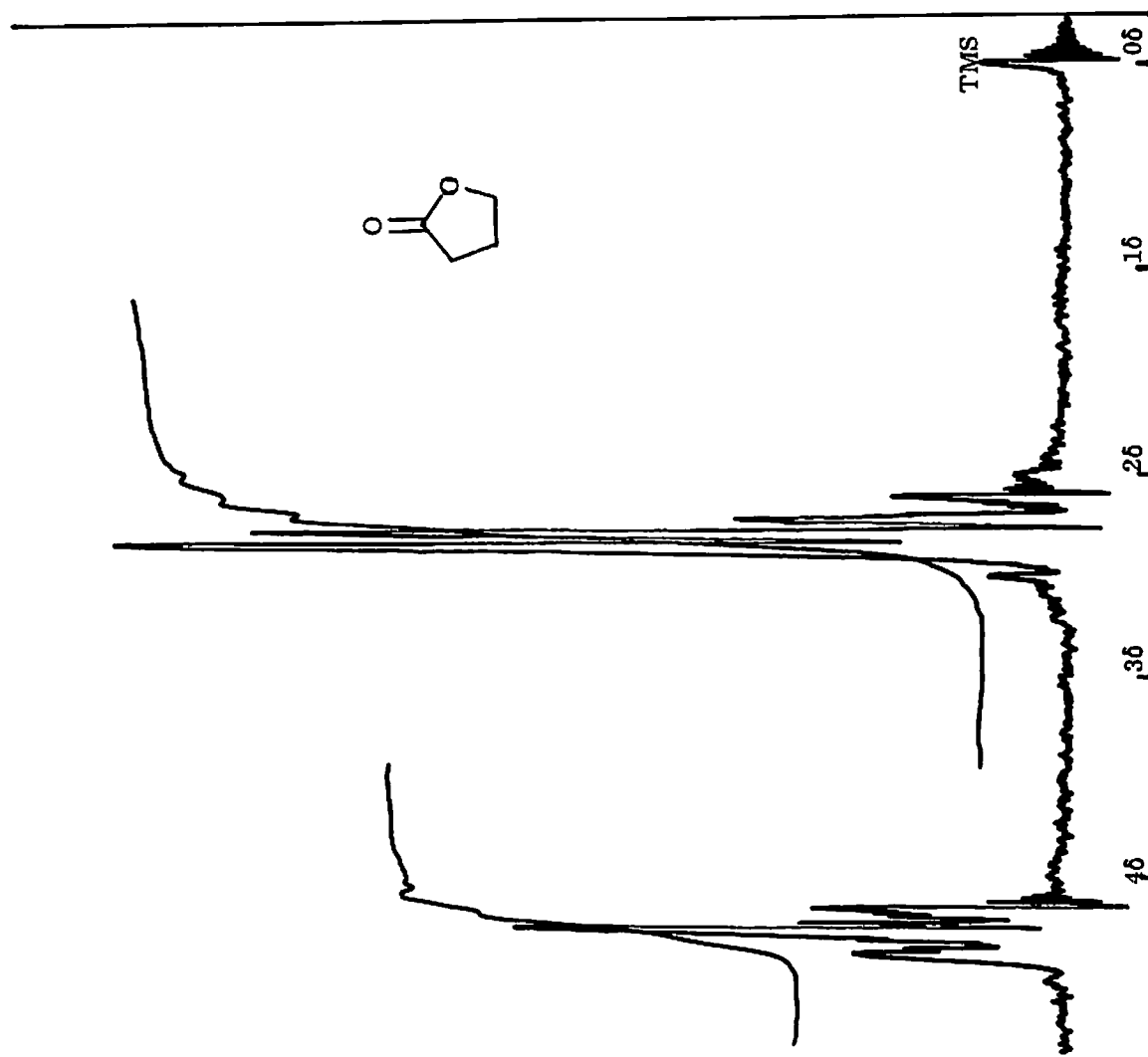
Figure 28: 60-MHz proton nmr spectrum of γ-butyrolactone in CCl$_4$

102
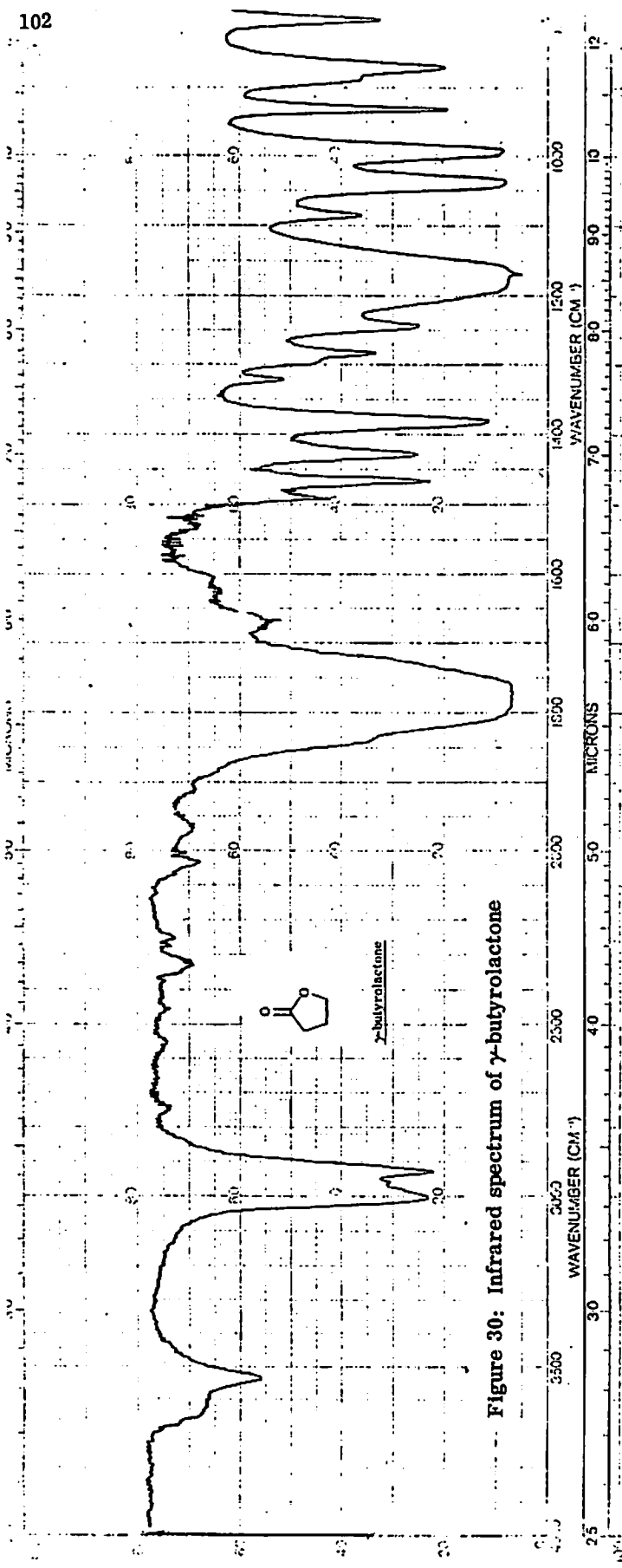
Figure 30: Infrared spectrum of γ-butyrolactone
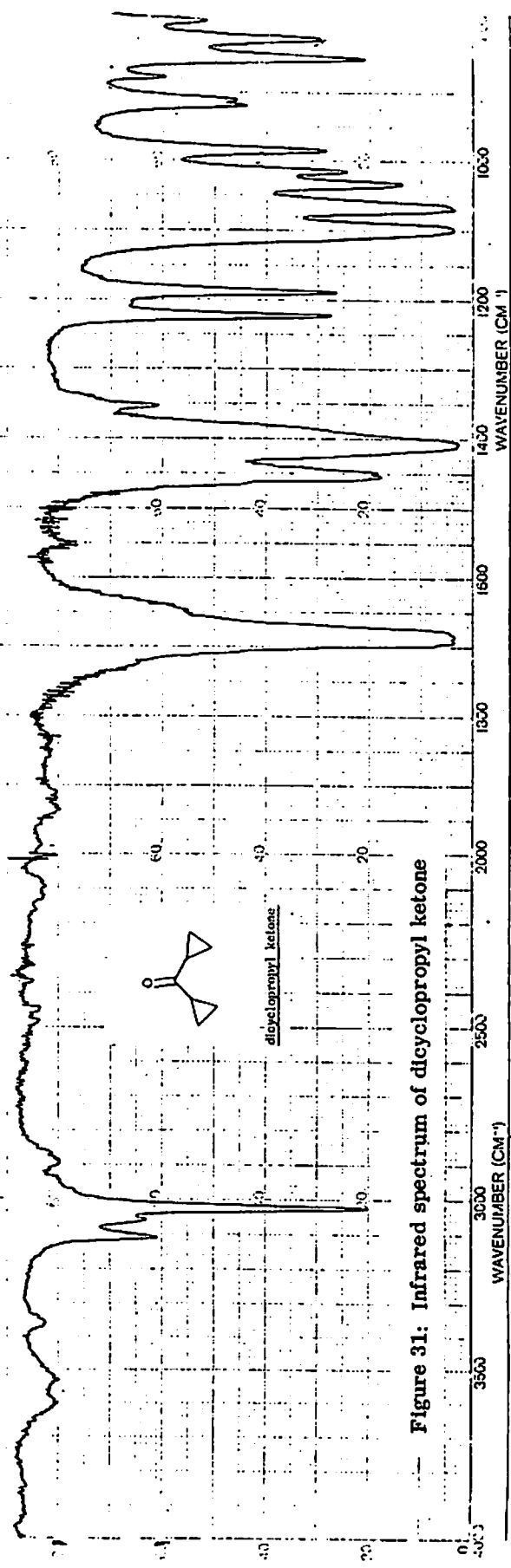
γ-butyrolactone

Figure 31: Infrared spectrum of dicyclopropyl ketone

dicyclopropyl ketone

PROCEDURE — methyl cyclopropyl ketone

Measure out 24 ml (20 g, 0.16 mole) of 2-acetylbutyrolactone into a 500-ml r.b. flask. Add a boiling stone and fit the flask with the apparatus for a simple distillation (still head, condenser, receiver adapter) as in Figure 2 but with a 250-ml r.b. flask immersed ice-water bath as a receiver. Remove the adapter with the thermometer and pour 50 ml of 6 N HCl down a funnel into the reaction flask. Quickly replace the thermometer and adapter since CO_2 is rapidly evolved. Gently warm the mixture with the ir lamp, controlling the vigor of the reaction with the voltage regulator. Once the CO_2 evolution has subsided, turn up the heat to codistill about 65 ml of water--chloroketone mixture. Add 12 g of NaOH pellets to the cold two-phase mixture in the 250-ml r.b. flask. Swirl the flask in the ice water bath until all the base has dissolved. Remove the bath, clamp the flask to a ringstand, add a boiling stone, fit the flask with a reflux condenser, and reflux for 30 minutes. Cool for five minutes and then fit the flask with the apparatus for a simple distillation (Figure 2). Again, codistill the mixture, using an ice water-cooled 100-ml r.b. flask as the receiver. Collect about 50 ml of distillate and saturate the solution with NaCl (about 15 g). Allow the mixture to warm to room temperature; add more salt if necessary to saturate the aqueous solution. Transfer the liquid mixture to a 60-ml separatory funnel and separate the layers. About 10 g of yellow methyl cyclopropyl ketone should be isolated. Purification by simple distillation (bp 110-112°C) should be done if time permits.

A semicarbazone should be made by the procedure given for dicyclopropyl ketone semicarbazone, using 1.3 ml of methyl cyclopropyl ketone.

Figure 34: 60-MHz pmr spectrum
of methyl cyclopropyl ketone

Figure 33: 60-MHz pmr spectrum of
5-chloro-2-pentanone

Figure 32: 60-MHz pmr spectrum of
2-acetylbutyrolactone
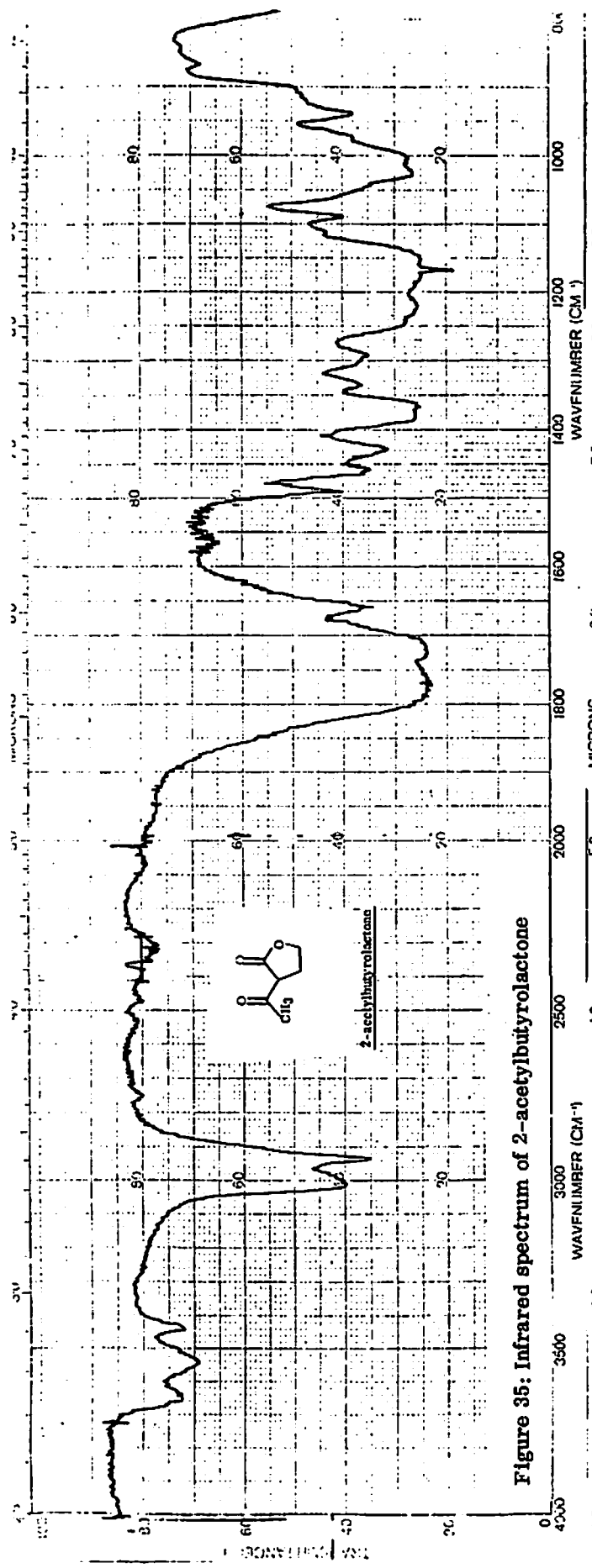
Figure 35: Infrared spectrum of 2-acetylbutyrolactone

2-acetylbutyrolactone
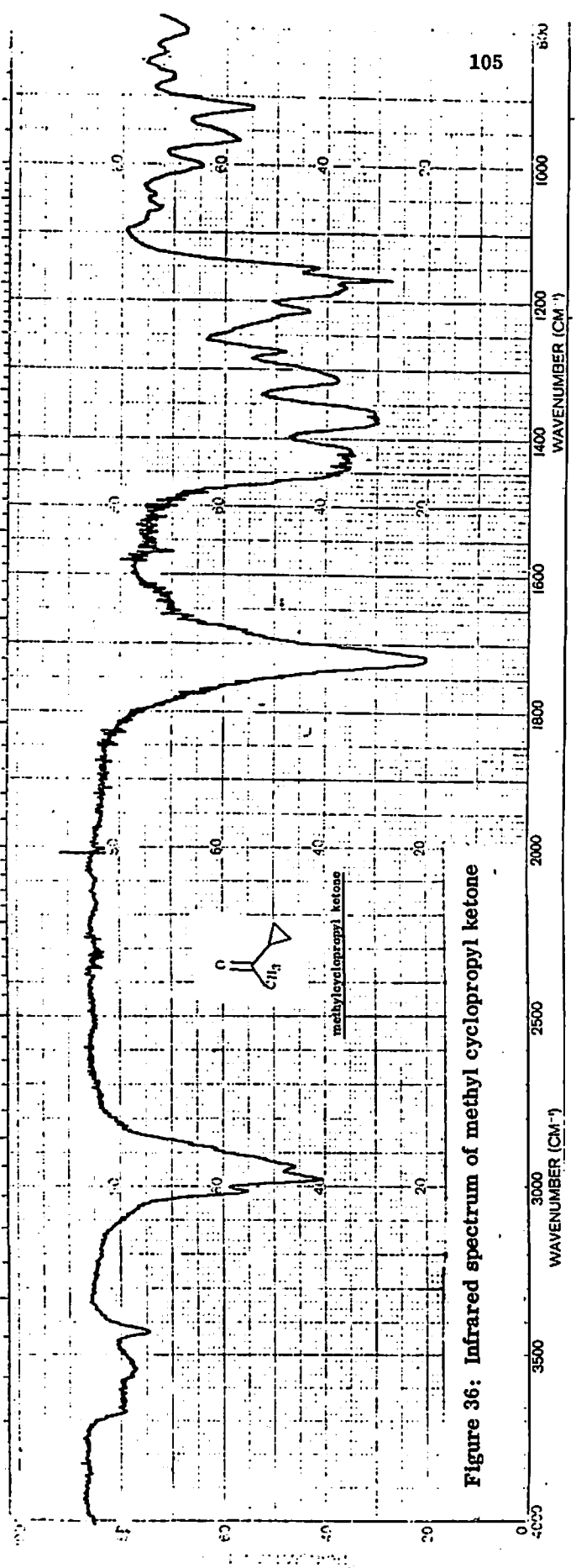
Figure 36: Infrared spectrum of methyl cyclopropyl ketone

methylcyclopropyl ketone

6. SYNTHESIS OF 6,6-DIPHENYLFULVENE

Introduction

In the previous weeks, we have examined organic reactions with mechanisms

that involve nucleophilic attack. Such mechanisms are based upon the concepts of Lewis

acid—base theory (discussed in the cyclopropyl ketones experiment), and the term

"nucleophile" denotes a Lewis base that attaches itself to carbon. Reactions involving

nucleophilic attack have synthetic utility (the saponification of trimyristin, the dimerization

of butyrolactone), a simple example being the trapping step in the conversion of alcohols

to halides (ROH + HX → RX + H_2O) as well as the reverse reaction, the conversion of

organic halides to alcohols (RX + H_2O → ROH + HX).

Reactions involving nucleophilic attack are also important in forming new carbon—

carbon bonds. The dimerization of γ-butyrolactone may be considered a nucleophilic

attack by a carbanion upon a carbonyl group as depicted in Reaction 1.

(1)

$$\xrightarrow[\text{addition}]{\text{Nucleophilic}}$$
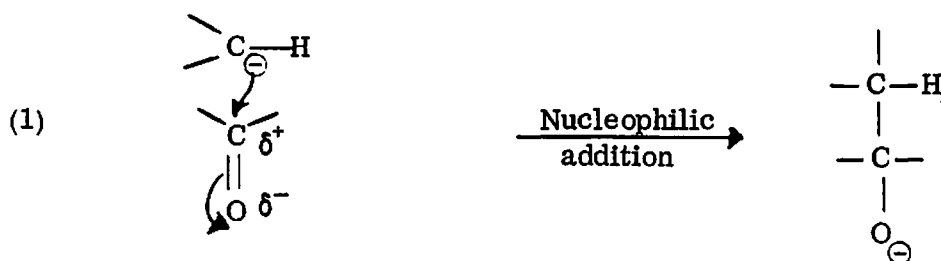
In reaction 1, the nucleophile is the negatively charged carbon. The carbon of the carbonyl

function bears a partial positive charge. The linkage of the two carbons bearing opposite

charges is an example of nucleophilic addition to the carbonyl group. This week,

nucleophilic addition of a carbanion to a carbonyl group will be used in the synthesis

of 6,6-diphenylfulvene from cyclopentadiene and benzophenone. These compounds are

illustrated at the top of the next page.

FULVENE
(positions numbered)

6,6-DIPHENYLFULVENE

CYCLOPENTADIENE

BENZOPHENONE
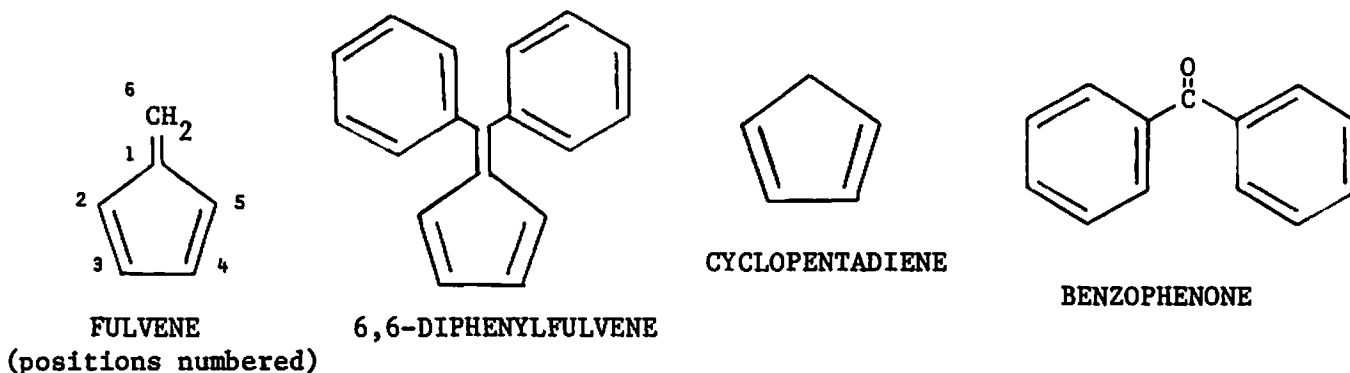
Cyclopentadiene

Cyclopentadiene is a hydrocarbon which possesses several unusual characteristics. Two aspects of its reactivity are of importance in the present experiment: its tendency to dimerize and its high acidity ($pK_a \sim 15$, more acidic than water!)

Cyclopentadiene is a planar conjugated diene in which the two double bonds are held cis to one another. Such compounds readily undergo a reaction with the π-system of another alkene or alkyne to form new σ-bonds. For instance, cyclopentadiene (in the role of conjugated diene) reacts with itself (in the role of alkene) to form a dimer, which is named, by IUPAC convention, tricyclo[5.2.1.0^{2,6}]deca-3,8-diene (Reaction 2). This type of reaction was discovered by Otto Diels and Kurt Alder, two German chemists, who received the Nobel prize in 1950 for their discoveries, and the reaction is named the Diels-Alder reaction. In the dimerization of cyclopentadiene, the equilibrium lies far to the right.

(2)

Diels-Alder

Cyclopentadiene Dimer
(Tricyclo[5.2.1.0^{2,6}]deca-3,8-diene)
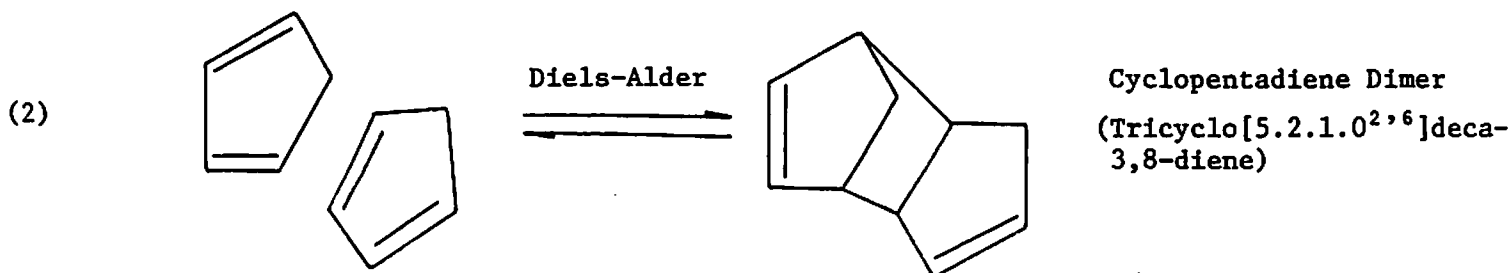
QUERY   How many stereoisomers exist for cyclopentadiene dimer?

Commercial cyclopentadiene is sold as the dimer, which boils at 170 °C with

considerable decomposition to the monomer. The monomer, which boils at $42°$ C, may

be fractionally distilled away from the dimer; it is by this _cracking_ of the dimer that

cyclopentadiene monomer will be isolated for this week's experiment.

QUERY   The density of cyclopentadiene monomer is 0.8 gram/cm^3. What is the molarity
(moles per liter) of pure cyclopentadiene monomer?

As you have learned in Chem 3, the temperature dependence of a rate constant, k, is given by the _Arrhenius equation_· $k = A \exp[-E_a/RT]$. For the second-order reaction, dimerization of cyclopentadiene monomer, the value of the _pre-exponential factor_, $A = 10^{4.9}$ liters/mole-second, while the value of the _activation energy_, $E_a = 14.9$ kcal/mole. What is the value of the second order rate constant, k, for dimerization of cyclopentadiene at room temperature $(300°K)$? at $0°$ C? The value of R is 2.0 cal/mole-degree. Don't forget to convert all temperatures to degrees Kelvin.

In the Week 3 write up, some discussion was devoted to half-lives of second-order reactions. What is the half-life of pure cyclopentadiene at room temperature? at $0°$ C?

As noted above, cyclopentadiene is remarkably acidic for a hydrocarbon. This

acidity is attributed to _resonance stabilization_ of the conjugate base, the _cyclopentadienide_

anion, i.e., the fact that it can be drawn as any one of the several structures below

(discussed in Morrison and Boyd, Section 10.7). Although resonance stabilization of this

sort does not occur in all analogous systems (discussed in Morrison and Boyd, Section 10.10)

it does occur in the cyclopentadienide anion. As a consequence, the negative charge is

not localized on any one carbon atom, but is equally distributed among all five. Hence,

the cyclopentadienide anion is · often drawn as a pentagon with a circle inside, structure a.
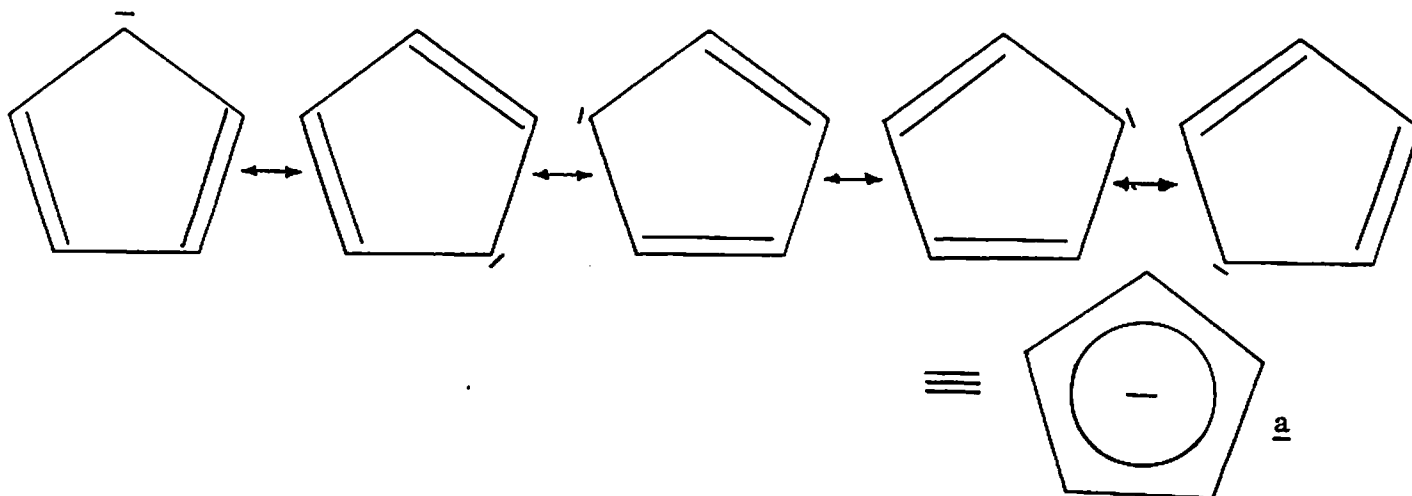
Formation of 6,6-Diphenylfulvene from Cyclopentadiene and Benzophenone

A likely reaction pathway for the formation of 6,6-diphenylfulvene is depicted in the equations below. The reversible formation of cyclopentadienide anion from cyclopentadiene takes place in ethanolic potassium hydroxide (Reaction 3).

φ stands for phenyl
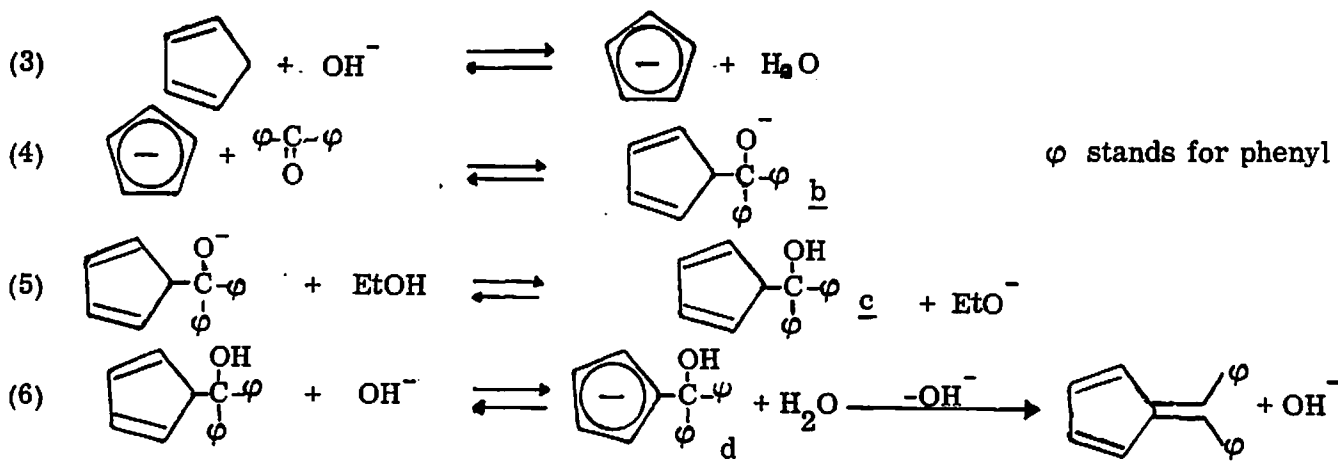
Benzophenone undergoes reversible nucleophilic attack by cyclopentadienide to form the alkoxide anion $\underline{b}$, Reaction 4. Anion $\underline{b}$ abstracts a proton from the solvent, Reaction 5. The resulting alcohol, $\underline{c}$, is presumably as acidic as cyclopentadiene, and hydroxide abstracts a proton from the cyclopentadiene ring of $\underline{c}$ to form the anion $\underline{d}$, which irreversibly eliminates hydroxide to form the product, as shown in Reaction 6. This last step, elimination of hydroxide ion from $\underline{d}$, is represented as irreversible because the 6,6-diphenylfulvene precipitates from solution.

The nmr spectrum of the product is given in Figure 37.

EXPERIMENTAL PROCEDURE

The cracking of cyclopentadiene dimer and the preparation of ethanolic KOH should be performed by two people working as partners. The reaction of benzophenone with cyclopentadiene in ethanolic KOH and recrystallization of the product should be performed individually by each student.

110

One partner should measure 20 ml of Dicyclopentadiene (cyclopentadiene dimer) into a 100-ml r,b, flask, add a boiling stone, and assemble a fractional distillation apparatus as shown in Figure 27, Experiment 5. Fit the flask with a fractionating column (Liebig condenser) packed with stainless steel wool or sponge,* and use a 10-ml graduate containing about 1 g of $CaCl_2$ (to remove traces of water from the distillate) and immersed in an ice-filled beaker as a receiver. Heat the Dicyclopentadiene with an IR lamp at high power, concentrating the heat on the bottom half of the still pot by means of a cone of aluminum foil. Within 15-20 minutes, cyclopentadiene monomer should start to distill. Lower the heat so that the column does not flood (bubbling of vapor up through large quantities of condensed liquid) and the head temperature does not rise above 50°C (cyclopentadiene b.p. 42°C). About 4-5 ml of cyclopentadiene should distill within 30-45 minutes. Keep the cyclopentadiene in the ice bath until it is needed. Allow the pot to cool to about 60°C (hot to touch but can be handled) and promptly pour the contents into the bottle labeled Used Dicyclopentadiene in the hood. Rinse out the flask with several small portions of absolute ethanol and pour the washings in the bottle labeled Ethanol—Dicyclopentadiene. If any residue remains in the flask, it may be removed with alcoholic KOH.

While the cracking is proceeding, the other partner should dissolve 3.0 g of potassium hydroxide in 30 ml of absolute (100%) ethanol by heating and swirling over a steam bath. Two 4.5-g portions of benzophenone (one for each partner) should be weighed into 125-ml Erlenmeyer flasks and each dissolved in 20 ml of absolute ethanol. The solutions must be cooled in an ice-water bath to 0°C before the cyclopentadiene is added; some of the benzophenone will crystallize out.

*The stainless steel wool is very sharp and will cut you if you attempt to pull it apart with your bare hands. Use scissors if necessary to cut off some, and use a wire hook to pull some into the fractionating column.

Each student should add 2 ml of cyclopentadiene to his benzophenone solution and then add half (15 ml) of the freshly prepared ethanolic KOH solution. Warm the dark solution on a steam bath for 30 minutes; a gentle boil is adequate.

Remove the brown solution from the steam bath and allow it to cool slowly to room temperature for about 20 minutes until the fulvene precipitates. If it does not precipitate, stirring with a stirring rod dipped in a mixture that has started to crystallize will start it. Then chill and swirl the flask in an ice bath. Collect the crude product by suction filtration on a Büchner funnel and wash it with 10 ml of cold absolute ethanol. Recrystallize the product from the minimum amount of ethanol, and determine the melting point of the deep orange recrystallized material (review recrystallization and melting point technique). Calculate the percent yield and hand in your product in a labeled glassine envelope.

Recycling and Disposal

Pour any unused cyclopentadiene monomer into the "Used Dicyclopentadiene" bottle. Set up a simple distillation and recover the ethanol from the filtrates of the reaction mixture and the mother liquor. Pour the recovered ethanol into the labeled bottle in the hood (not the one used for ethanol washings of the Dicyclopentadiene) and the pot residue into the waste jar. Carefully remove the stainless steel sponge from the fractionating column with a wire hook and place it in the large evaporating dish in the hood.

Preparation for Next Week's Experiment

Do not leave the laboratory without starting next week's experiment. In a test tube, dissolve 0.30 g of N-phenylmaleimide in 8 ml of hot 95% (or absolute) ethanol. Gravity filter the hot solution through a small fluted filter into another test tube and cool the solution in an ice-water bath. Add 1 ml of furan, stopper tightly, and set aside until next week.
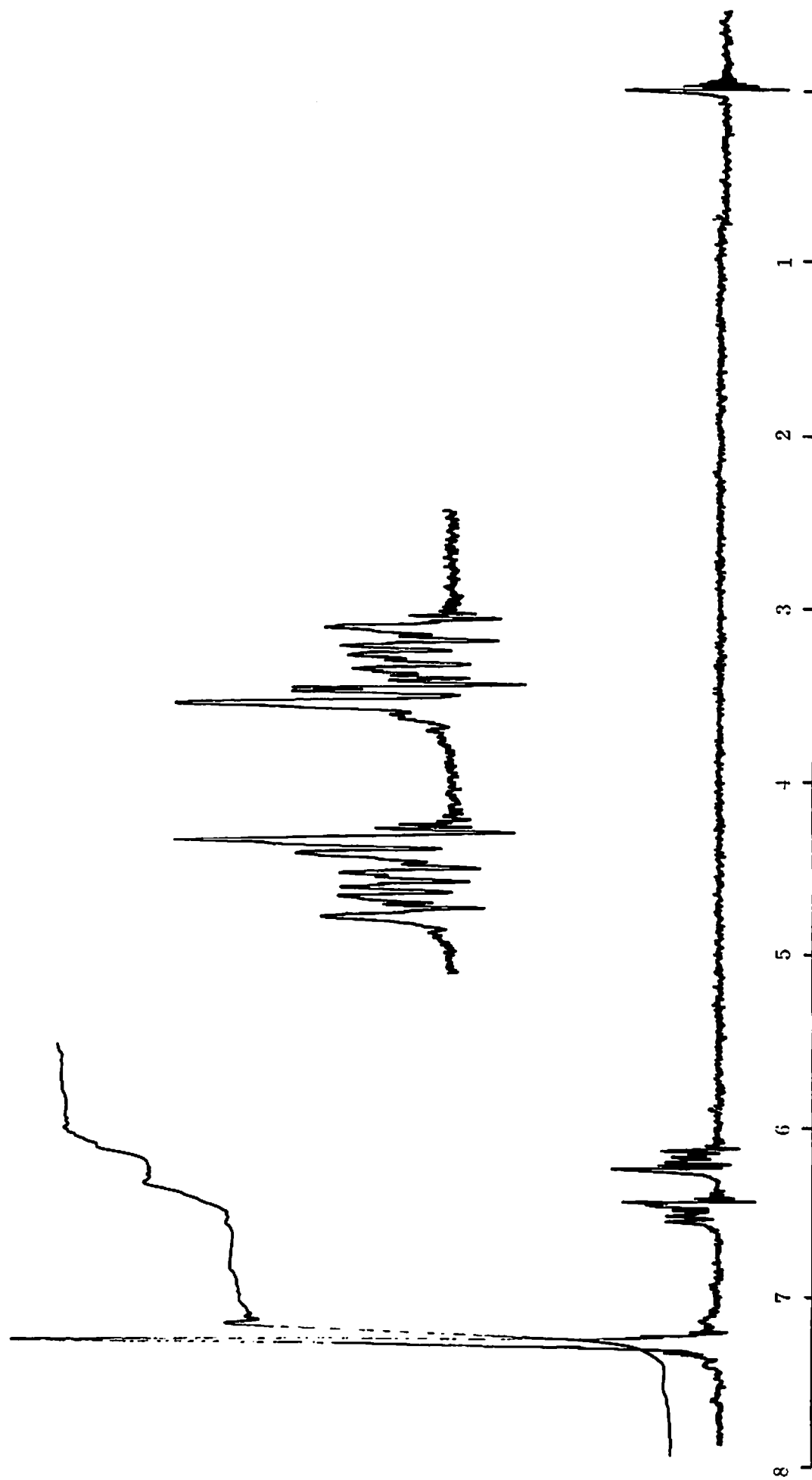
Figure 37: 60-MHz pmr spectrum of 6,6-diphenylfulvene. Upper trace shows the upfield multiplets enlarged.

7. KINETIC CONTROL VERSUS THERMODYNAMIC CONTROL
IN THE DIELS-ALDER REACTION

The Diels-Alder reaction is a member of a large class of reactions called

cycloadditions. The reverse of the Diels-Alder reaction (e.g., the cracking of

cyclopentadiene dimer) is called a retro-Diels-Alder reaction and is an example of a

cycloreversion. The term "cycloaddition" is used because a new cyclic structure is

formed. Other common cycloadditions lead to 3-, 4-, and 5-member rings. In the Diels-

Alder reaction a 6-member ring is formed by the addition of a double bond to the ends of

a diene system; e.g., ethylene adds in a 1,4 fashion to butadiene. The overall result is

the conversion of two π bonds into two σ bonds, as shown in equation (1). The Diels-

Alder reaction is described as requiring two partners, a diene and a dienophile.

(1)
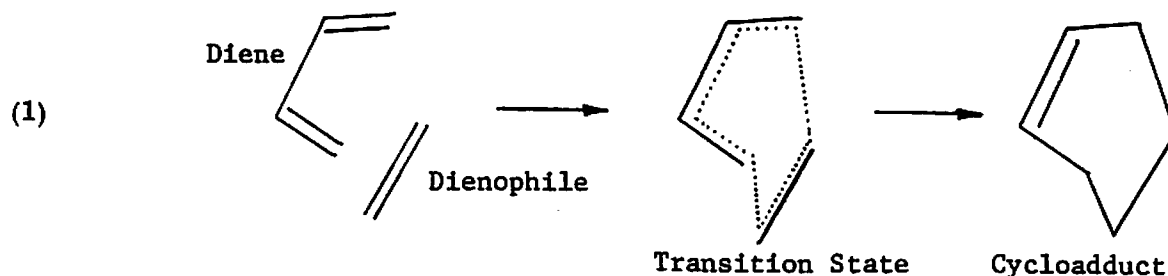
Cyclopentadiene plays both roles in its dimerization. The cycloaddition reaction to be

examined this week is shown in equation (2).

(2)

furan   N-phenylmaleimide

4-phenyl-4-aza-10-oxatricyclo-
[5.2.1.0^{2,6}]dec-8-ene-3,5-dione
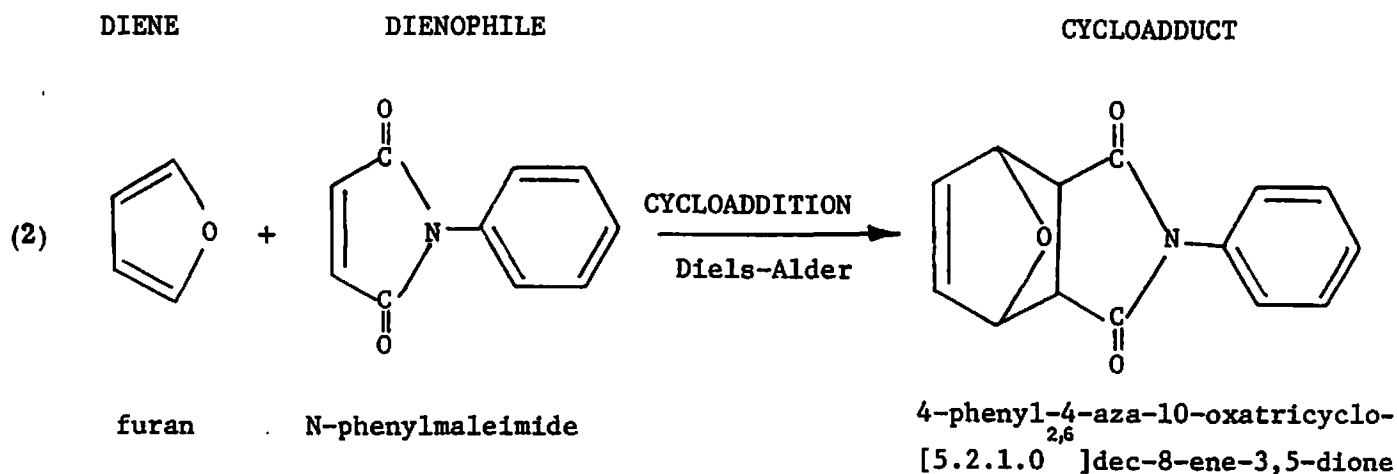
In reaction (2), the diene is furan, a five-member ring compound containing oxygen. A derivative, tetrahydrofuran (THF), will be used as a solvent later in the semester. Furan was originally derived from products of destructive distillation of oat hulls and bran, for which the Latin word is furfur.

The dienophile in reaction (2) is N-phenylmaleimide. It is derived from maleic acid, which in turn, may be prepared from malic acid, a constituent of unripe apples (the name comes from malum, Latin for apple). The suffix "-mide" denotes that the -OH of the

maleic acid   malic acid   maleimide
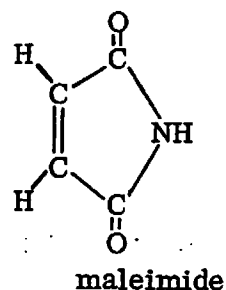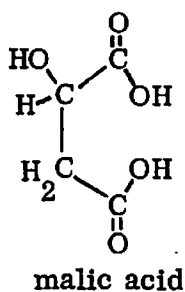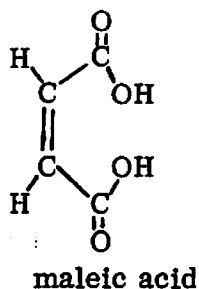
carboxylic acid groups has been replaced by nitrogen. The prefix "N-phenyl" denotes the substitution of a phenyl group on the nitrogen of maleimide.

The systematic name of the cycloadduct of reaction (2) is derived from the systematic name of the corresponding hydrocarbon (which has the same carbon skeleton as cyclopentadiene dimer). One $-CH_2-$ group is replaced by nitrogen (aza) and the bridge $-CH_2-$ is replaced by oxygen (oxa).

Stereochemistry

The four conceivable stereoisomers of the cycloadduct formed in reaction (2) are illustrated in Figure 38. The trans isomers are exceedingly strained and have never been synthesized; it is doubtful whether they can exist at all.

The cycloaddition of furan and N-phenylmaleimide at room temperature produces a mixture of both cis isomers. They are meso compounds. In the more stable isomer, the dienophile moiety is on the same side of the ring as the oxygen bridge; this is the cis, exo isomer. In the less stable isomer, the dienophile moiety is on the side of the ring opposite to the oxygen bridge; this is the less stable cis, endo isomer.
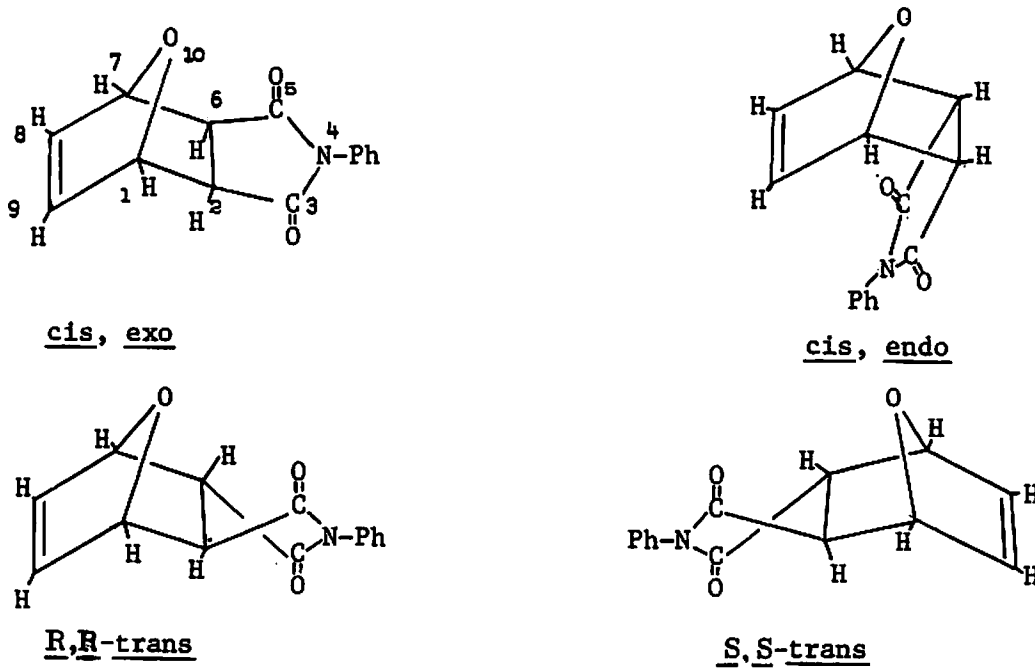
Figure 38: Stereoisomers of the cycloadduct of furan and N-phenylmaleimide

QUERY (if you have studied nmr spectra): The 60-MHz pmr spectrum of the pure cis, exo isomer is reproduced on the next page. Assign the peaks and explain the spectrum. Measure the integrals and determine how many hydrogens each peak represents. Hint: The sharp singlet at 3.0 δ is the resonance of the hydrogens α to the carbonyl groups and represents two hydrogens.

The pmr spectrum of the crude reaction product containing both the cis, exo and cis, endo isomers is on the following page. The spectrum of a mixture appears as a superposition of the individual spectra, with relative integrals of each spectrum proportional to the relative amounts of each component. By difference, one can assign peaks to the endo isomer; for example, the four-line multiplet at 3.7 δ corresponds to the hydrogens α to the carbonyl groups of the endo isomer. Similarly, the distortion of the peak at 5.5 δ in the spectrum of the mixture suggests that the C-1, C-7 protons of the two isomers have slightly different yet overlapping chemical shifts. Assign the rest of the peaks in the spectrum of the mixture.

What is the ratio of the cis, endo to the cis, exo isomer in the mixture? Hint: Use the integral traces above the peaks at 3.0 and 3.7 δ in the spectrum of the mixture. The isomer ratio is equal to the ratio of integrals A and B in the spectrum.

Kinetic Control of a Chemical Reaction

It is significant to note that the less stable of the cis isomers is produced in greater abundance when the cycloaddition is performed at room temperature. Clearly, the reaction is not thermodynamically controlled; that is, the reaction does not give an equilibrium distribution of the products. In such a case, the product distribution reflects the relative rates of formation of the cycloadducts rather than their relative stabilities and the reaction

Figure 39: 60-MHz pmr spectrum of cis, exo-cycloadduct
of furan and N-phenylmaleimide
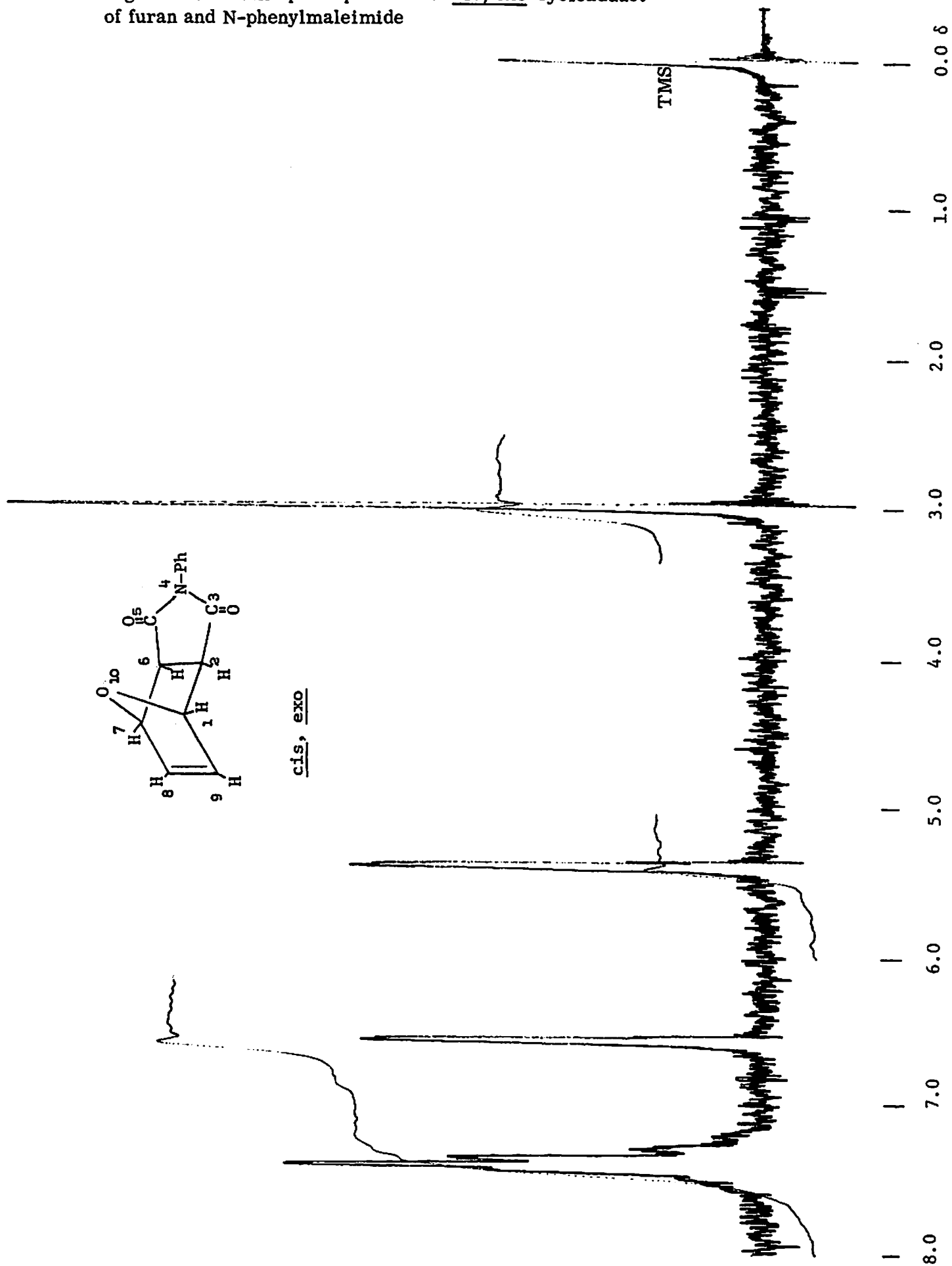
Figure 40: 60-MHz pmr spectrum of mixture of
cycloadducts of furan and N-phenylmaleimide
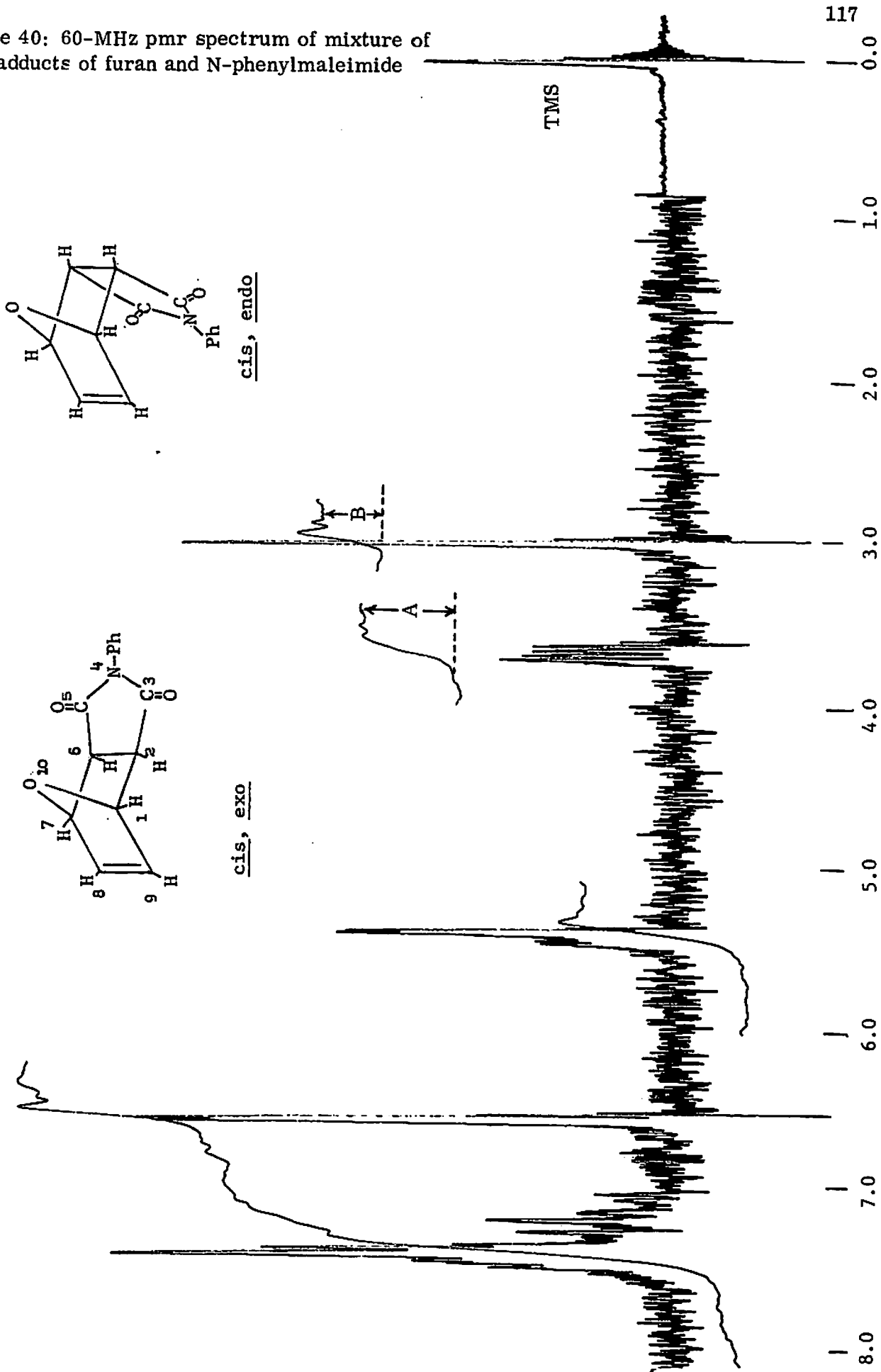
is, therefore, kinetically controlled. A free energy diagram for a case where kinetic control and thermodynamic control give different products is shown in Figure 41.
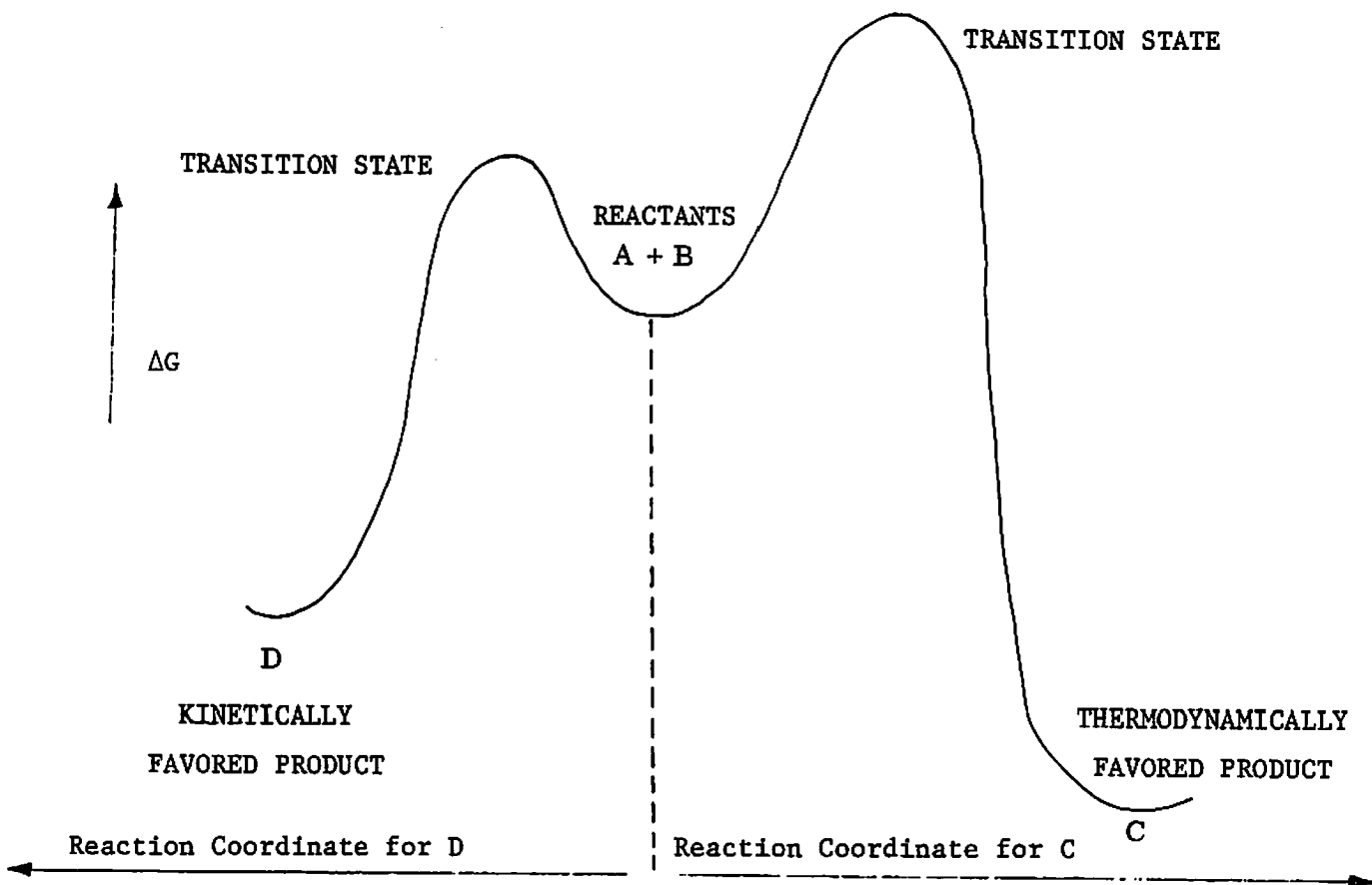

Figure 41: Free energy diagram for a general reaction A + B → C or D where kinetic control gives predominantly the less stable product.

The hypothesis of kinetic control is based upon the following supposition: chemical reactions do not occur instantaneously because there is an energy barrier that must be surmounted by the reactants in order for reaction to occur. This is often represented by a free energy diagram such as Figure 41, which graphs the free energy of the reactants as a function of the progress of the reaction. The abscissa of the graph is called the reaction coordinate.

At some point along the reaction coordinate the free energy is at a maximum. This is the point of demarcation between reactants and product, and it is usually called the transition state. Chemists often pretend that the transition state represents a discrete, albeit evanescent, species whose heat of formation can be related to the activation energy of the reaction. Therefore, the higher the energy of the transition state, the slower the reaction at a given temperature.

If two reactions are in competition, the reaction with the lower-energy transition state will proceed faster. If the reverse reaction (e.g., cycloreversion of the adduct to furan and N-phenylmaleimide) is very slow, then the product distribution reflects only the relative rates of the competing routes of reaction. This constitutes kinetic control of the reaction. The ratio of the two products, C and D in Figure 41, is equal to $C/D = k_c/k_d$, where k_c is the rate of formation of C and k_d is the rate of formation of D.

QUERY   Suppose that the product distribution under conditions of kinetic control reflects only the difference in Arrhenius activation energy (E_a) between the competing routes [and that the pre-exponential factors (A) for the competing routes are the same]. Since the Arrhenius rate law asserts that $k = A\exp(-E_a/RT)$, the product ratio $C/D = \exp[-(E_a^C - E_a^D)/RT]$, where E_a^C and E_a^D are the activation energies for formation of products C and D, respectively, and $\exp(X) \equiv e^X$. What activation energy difference will account for the product ratio observed in the nmr spectrum of Figure 40?

Thermodynamic Control of a Chemical Reaction

Since most chemical reaction rates increase with temperature, cycloaddition of furan and N-phenylmaleimide takes place more swiftly as the temperature is raised from ambient to, say, 77°C. However, at 77°C, the interconversion of cis,endo and cis,exo isomers is also faster. Under such conditions, equilibrium is established between the two isomers. When products can equilibrate, the final product ratio reflects their relative stabilities. This constitutes thermodynamic control of the reaction.

Several mechanisms may be postulated for the interconversion of the exo and endo isomers. One class of mechanisms involves unimolecular interconversion of

the isomers, as exemplified in equation (3).

(3)

endo   broken bond intermediate   exo
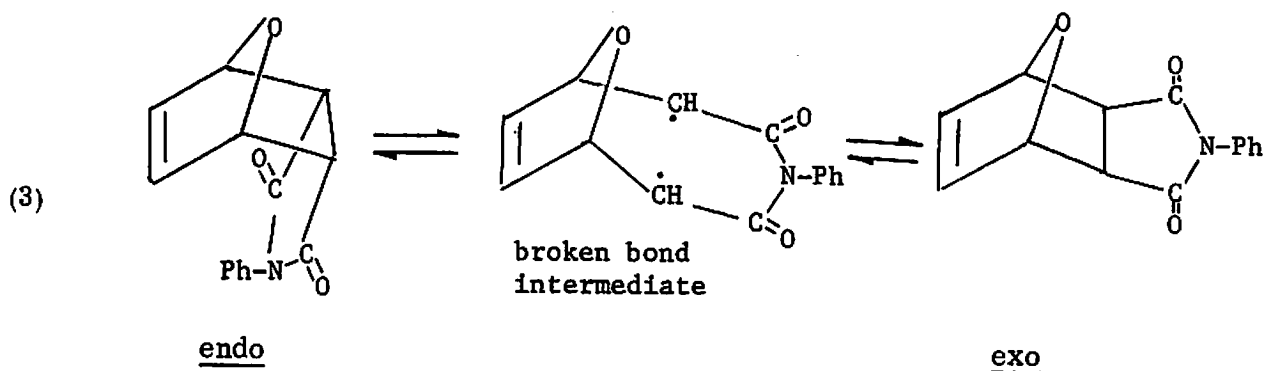
A different sort of mechanism posits that the interconversion of exo and endo isomers takes place via cycloreversion to the starting materials, furan and N-phenyl-maleimide, followed by recombination. Such a mechanism implies a unimolecular dissociation of the cycloadduct followed by a bimolecular recombination step.

How might these two mechanisms be distinguished? One method is to look for uncombined cycloreversion products from the heating of the cycloadduct at 77°C. In order to perform such an investigation, a method must be devised for the separation and identification of the components of a reaction mixture. Such a method is found in chromatography, and the products of reaction (2) will be examined by means of thin-layer chromatography.

Thin-Layer Chromatography

Two technical problems have plagued experimental chemistry since its beginning as a science: the determination of the number of components in a given system and the separation of the mixture into its pure components. In the last 50 years, a number of chromatographic techniques have been developed in response to these problems. All have advantages and limitations. Of those discussed previously, column chromatography is good for large-scale separations but is not very effective in separating components that are similar. Gas chromatography is very effective in separating similar compounds but the materials

must be thermally stable and sufficiently volatile. A new technique, thin layer chromatography, will be introduced this week as a diagnostic tool (to determine the number of components in a system) rather than a preparative one, although it can be used to separate samples weighing up to 100 milligrams. For diagnostic purposes, TLC is a powerful method because microgram quantities can be detected easily and rapidly. TLC is widely used in industrial, medical, forensic, food, and research chemistry.

The principles involved in TLC are the same as those in other forms of chromatography: a mobile phase (liquid solvent) moves in contact with a stationary phase (solid silica gel), and the components to be separated are partitioned between the two on the basis of their relative tendencies to be adsorbed and dissolved. Components are separated and identified by their rate of travel along the adsorbent layer. The retention factor or R_f value is a measure of the distance each component has moved along the plate, and is characteristic for a given compound under a particular set of conditions.

The adsorbent is a powder (usually silica gel or alumina), much finer than that used in column chromatography, that is spread in a thin layer on a glass or plastic plate. It usually contains a binder ($CaSO_4$ or polyvinyl alcohol) to hold the adsorbent on the plate. The commercial plates used in this experiment are preferable to homemade plates because the coatings are more uniform and the R_f values reproducible. They are plastic-backed, readily cut with scissors, and contain an insoluble fluorescent compound (for UV visualization).

To separate a mixture by TLC, a small sample of the mixture is applied near one end of a plate, and the plate is set in a thin pool of solvent. The solvent rises slowly up the adsorbent, and the components of the mixture travel various distances up the plate. When the development has proceeded sufficiently, the plate is removed from the solvent and allowed to dry, and the developed spots are made visible in one of a number of ways.

Techniques

Spotting the plates. First, examine the plates under UV light to see that they are free from blemishes, fingerprints, or other interfering marks. Random specks of dust are unavoidable. The sample, dissolved in a small amount of solvent, is applied to the bottom of the plate (spotted) with a spotter. Proper spotting technique must be adhered to closely in order to obtain good results. Most important, the spot should be no bigger than 3 mm in diameter. Any solvent will do, as long as it forms a concentrated solution of the sample and evaporates quickly.

Draw a light line with a soft pencil 1 cm from the bottom of the TLC plate and place the spots along the line. Do not chisel the adsorbent off the plate. A small amount of sample is delivered to the plate by dipping a piece of drawn-out capillary tubing (spotter) into the sample solution and then touching it to the plate. Capillary action causes a small quantity of solution to enter the tube; touching the capillary tip to the plate delivers a spot of solution. The capillary should be touched to the plate lightly and quickly. Do not scratch the adsorbent with the capillary or poor solvent flow and loss of resolution will result. After the solvent has evaporated, examine the spot under UV light to see if a sufficient amount of sample has been delivered. If the spot is very pale, the solution is too dilute and the spot must be retouched several times, each time allowing the previous spot to dry. Each respotting must be exactly on center and must be very brief or needless spreading will occur. If the solution is too concentrated and too much sample is spotted on the plate, a deep purple spot will be visible under UV light. In this case, the plate is probably overloaded and the spot will streak when developed. A streaking sample, instead of moving as a discrete spot, leaves a long smear or tail on the plate, usually stretching from the origin to some point along the plate.

Making spotters. Use a file or scorer to scratch the closed end of a melting point capillary, and break off the end. Rotate the capillary in a small flame until the glass softens; remove the tube from the heat and pull out the glass before it hardens (Figure 42). Pulling the tube in the flame will not work. Break the feather capillary to give two spotters.

Developing the plates. To help speed equilibration of the solvent and vapor in the developing tank, a piece of filter paper should be placed in the tank. The tank (screw cap bottle) should contain a few milliliters of solvent to a depth of 2-4 millimeters. Carefully place each slide in the developing tank (in which solvent should be equilibrated with vapor). It is essential that the solvent level lie below the spots, or else the sample will be extracted into the solution instead of being eluted up the plate. The elution of sample on the TLC plate is called development. The solvent front immediately begins

Rotate the capillary in a
Bunsen burner flame until
the glass is soft
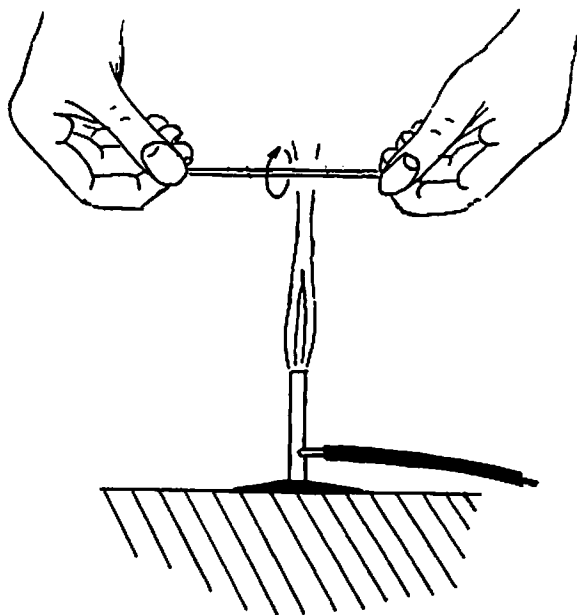
Remove the softened capillary
from the flame and quickly pull
to make a fine "feather" capillary

Break in two
to make a pair of
TLC spotters
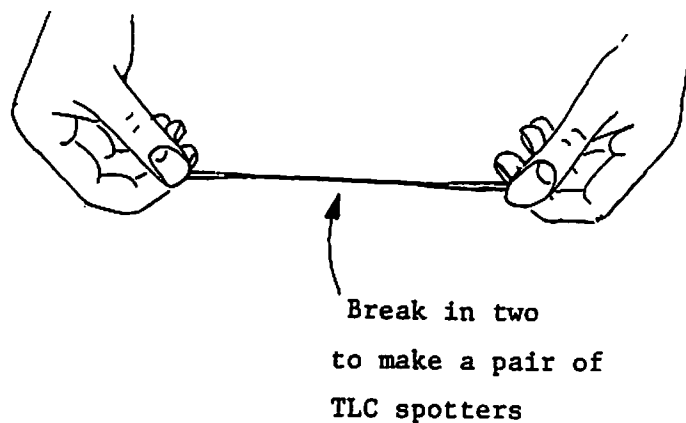
Figure 42: Making TLC spotters
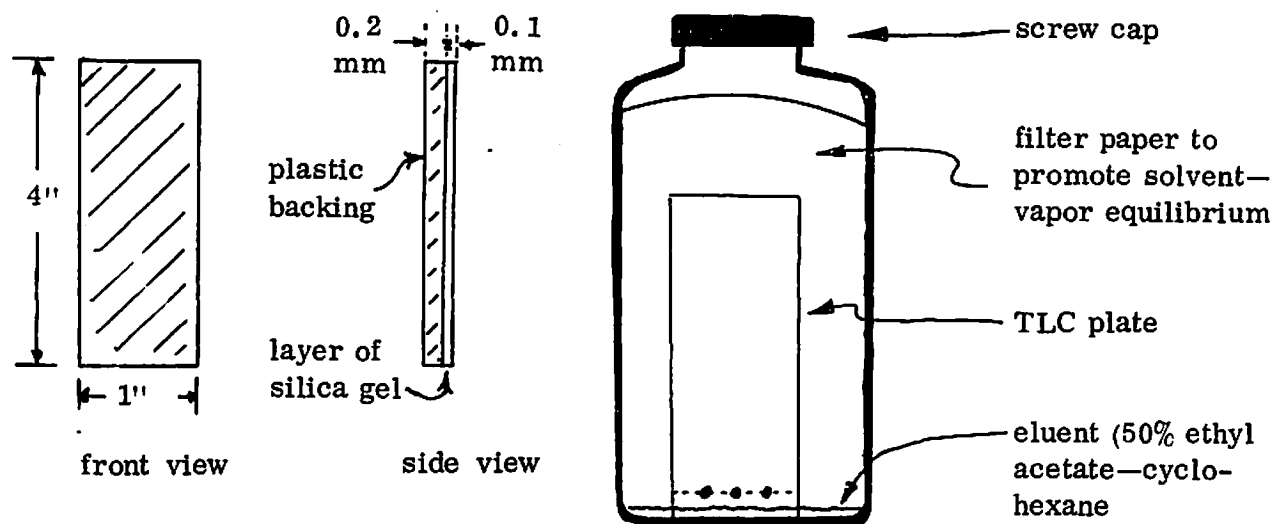
TLC plates   Developing chamber
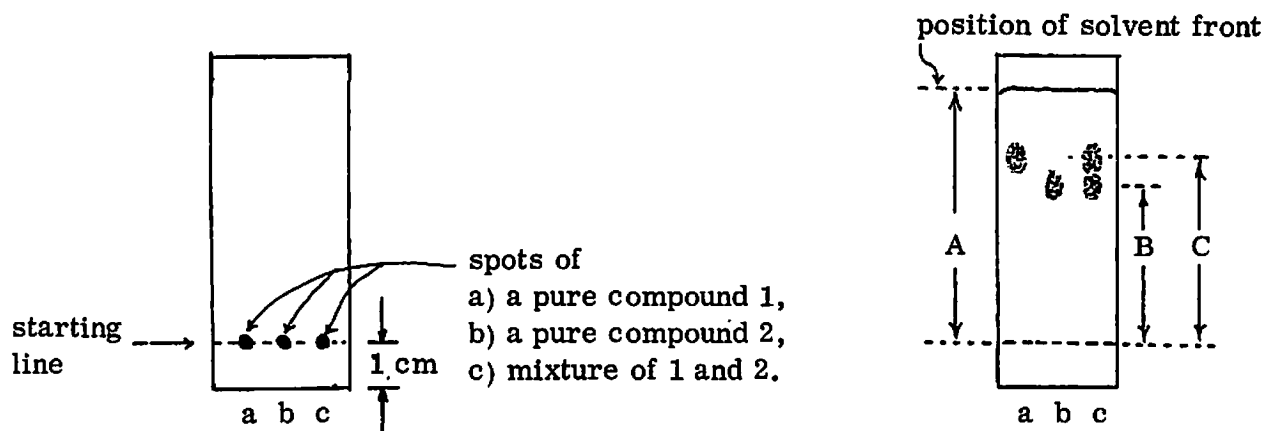
Spotting a plate

Appearance of same plate
when developed and visualized

$$R_f^1 = C/A$$
$$R_f^2 = B/A$$

Figure 43: TLC paraphernalia

to move up the plate. When the solvent front nears the upper edge, carefully remove the plate and immediately mark the level of the solvent front with a pencil. <u>Do not let the solvent front overrun the top edge of the coating</u>, or you will be unable to calculate the R_f value. Dry the plate in air and visualize the spots with UV light.

<u>Visualization of the compounds on the plates.</u> A number of physical and chemical means are employed to make compounds on TLC plates visible. For the plates we will use, illumination of the dry plate with UV light will cause the plate to fluoresce, except in regions where spots lie. <u>Be careful not to look directly at the UV light source, since ultraviolet is harmful to the retina.</u> Examination of the TLC plate under the light should reveal the eluted fractions as dark purple spots on a colored background. Circle the spots with pencil and determine the R_f values (distance spot moved ÷ distance solvent moved; see Figure 43). If the R_f value is 0.2 or less, or the suspected components are poorly separated, the plate may be redeveloped, several times if necessary. This should not be necessary in the present experiment.

EXPERIMENTAL PROCEDURE

Dissolve 300 mg of N-phenylmaleimide in 8 ml of hot 95% ethanol and filter the hot solution to remove insoluble impurities. Add 1 ml of furan to the cool solution in a test tube, stopper, and allow to sit a few days for the adduct to crystallize. If your laboratory section does not meet until after the spring recess, the test tube should be stored in a refrigerator.

Isolate the white, crystalline, Diels-Alder adduct of furan and N-phenylmaleimide by suction filtration through a Hirsch funnel. Wash the platelets with cold 95% ethanol and press down on the crystals to promote drying. Transfer the product to a tared watch glass or piece of filter paper and air dry.

While the adduct is drying, assemble a small TLC developing tank (screw cap bottle with a piece of filter paper moistened with solvent) containing several milliliters of 50/50 ethyl acetate—cyclohexane to a depth of a few millimeters. Close the bottle tightly to allow the liquid and vapor to equilibrate. Draw out several melting point tube capillaries over a microburner set up in the hood. They will be used as TLC spotters. Prepare a reference solution of N-phenylmaleimide by dissolving two or three crystals in ten drops of ethyl acetate in a small test tube. A number of students may use the same reference solution if they are careful not to contaminate it. Clearly label the solution and its spotter.

Weigh the dry adduct and determine the melting point. Place a few of the crystals in a small test tube and dissolve them in several drops of ethyl acetate. <u>Do not warm the solution.</u> Practice spotting the solutions of NPM and adduct mixture on the small (1 x 1 in) practice plates. If too much material is on the plate, it will streak and no useful information will be obtained. If too little is used, no spots will be visible after development. Then spot a full size silica gel plate (4 x 1 in) with appropriate amounts of these two solutions. Visualize the spots under UV light before development.

Develop the plate with 50/50 ethyl acetate—cyclohexane solvent until the the solvent front is about a centimeter from the upper edge of the plate. Remove the plate from the tank carefully, quickly mark the solvent front, and allow the plate to air dry. Examine the plate under UV light, lightly circle the visualized spots in pencil, and calculate the R_f value of each.

Weigh out approximately 3/4 of the cycloadduct and dissolve it in 5 ml of ethyl acetate in a 50-ml r.b. flask. Fit the flask with a water-cooled reflux condenser and reflux the solution for 30 minutes. Remove a small amount of the solution with a TLC spotter and spot a plate with this solution. Also spot the plate with two reference samples: N-phenylmaleimide solution and the solution of the original cycloadduct. Develop the plate, dry it, visualize the spots, and determine the R_f values.

Allow the ethyl acetate solution to cool and isolate the white crystals formed by suction filtration with a Hirsch funnel. Wash the crystals with 2 ml of cold ethyl acetate and allow them to air dry. Determine the melting point; dissolve several crystals in a few drops of ethyl acetate and spot a TLC plate with the solution. Also spot the plate with N-phenylmaleimide reference solution and the solution of the original cycloadduct. Record the R_f values.

Dissolve a few crystals of the recrystallized material in several drops of ethyl acetate in a small test tube and boil the solution on a steam bath for 5 minutes. Spot a TLC plate with this solution and with the two reference samples; record the R_f values.

Describe the results in your lab notebook and present an explanation. Remember, the purpose of this experiment is to distinguish between two different mechanisms for the conversion of the endo to the exo cycloadduct. One possible mechanism involves unimolecular bond breakage and the other involves cycloreversion. You will need a total of four good plates to rationalize the results:

PLATE 1 PLATE 2 PLATE 3 PLATE 4

128

PLATE 1 two spots: NPM and initially formed crystalline adduct (A)

PLATE 2 three spots: NPM, (A), and ethyl acetate solution after 30 minute reflux (B)

PLATE 3 three spots: NPM, (A), and crystals precipitated from refluxed ethyl acetate (C)

PLATE 4 three spots: NPM, (A), and solution of (C) in ethyl acetate boiled 5 minutes

When analyzing your results, keep in mind the following facts:

1) A single pure compound will appear as one spot after development and visualization.

2) A mixture of compounds should appear as several spots, ideally, each spot corresponding
to one compound. If the compounds are very similar, the spots will not be well
separated; they will probably overlap.

3) The reference spots serve a purpose. If two spots on the same plate have the same R_f
value, they correspond to the same compound (in this experiment).

Note on toxicity: You will probably not be able to find toxicities for the compounds
used in this week's experiment. However, one possible metabolic route for the cyclo-
adducts would be reversion to starting materials and hydrolysis of N-phenylmaleimide
to maleic acid and aniline. Toxicities for these compounds are known.

8. SYNTHESIS OF A TERPENOID ALCOHOL: (±)-DIHYDROLINALOOL

Many of the fragrances from natural sources arise from hydrocarbons. In the 19th century, chemists recognized that most of these hydrocarbons contained 10, 15, or 20 carbon atoms in their molecular formulas. In 1866, August Kekule suggested the name terpenes* to designate the large class of naturally occurring $C_{10}H_{16}$ isomers. The C_{15} homologues came to be called sesquiterpenes (the prefix sesqui- from the Latin semisque, one and one half), the C_{20} homologues called diterpenes, and so forth.

Since the number of carbon atoms in many natural products is a multiple of 5, chemists (numerologists at heart) suspected a common biosynthetic origin and designated all natural products with C_{5n} (n≥2) skeletons as terpenoids. In 1877, the German chemist Otto Wallach, considering the structural formulas known at the time, proposed that the C_5 fragment common to all terpene derivatives was the isoprene unit, ⟋⟍. Wallach, who received the Nobel prize in chemistry in 1910, hypothesized that the structure of all terpenoids could be built up by simply connecting the required number of isoprene units, ⟋⟍; subsequent variation of oxidation states and addition of functional groups produced exact structural formulas. For example, the terpene limonene (the principal constituent of oil of oranges) is the Diels-Alder adduct of two isoprenes, while natural rubber is a polyisoprene.

isoprene
(2-methyl-
1,3-butadiene)

natural rubber

limonene

---
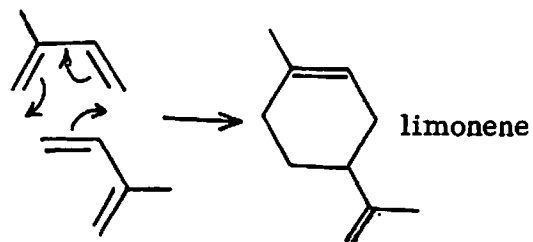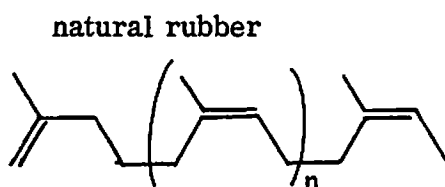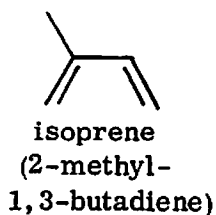
* The word "terpene" comes from "turpentine", whose etymological root is the Greek word TERMINTHOS, the name for the species of pine from which turpentine was originally extracted. Incidentally, the -INTHOS suffix is characteristic of words which have been in the Greek language since the Mycenaean period, prior to 1200 B.C.

Wallach's "isoprene rule" is valid in a large number of cases, and nearly all

deviations can be explained. Laboratory synthesis of terpenoid compounds has been a

lively research area for the past century and is still a subject of current interest;

for example, Prof. K. A. Parker at Brown is pursuing the synthesis of antileukemic

terpenoid drugs. Investigation of the routes by which terpenoid compounds arise in

nature is another subject of ongoing research; for instance, Prof. D. E. Cane at Brown

is using isotopic labelling techniques to elucidate the biosynthetic pathways for formation

of terpenoid fungal metabolites.

Many terpenes have peculiar names, which are usually derived from their natural

sources and are often used in place of the much longer systematic names. The terpenoid

linalool was originally isolated from oil of linaloe, which in turn is extracted from both

North and South American trees (the word linaloe is derived from Latin lignum aloes,

aloe wood). The North and South American linalools have opposite signs of optical

rotation. Linalool and its acetate occur in many other natural oils used in perfumes

and flavorings. Other fragrant terpenoid alcohols with closely related structures are

geraniol, nerol, and citronellol.
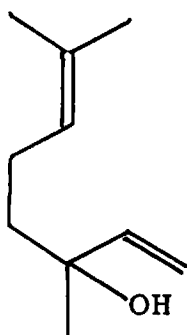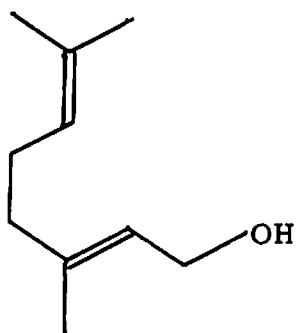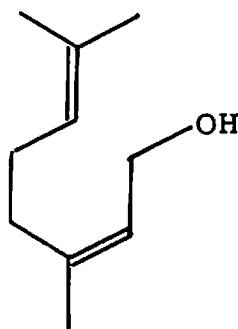
linalool   geraniol   nerol   citronellol
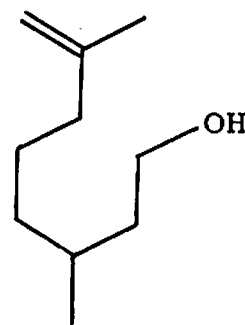
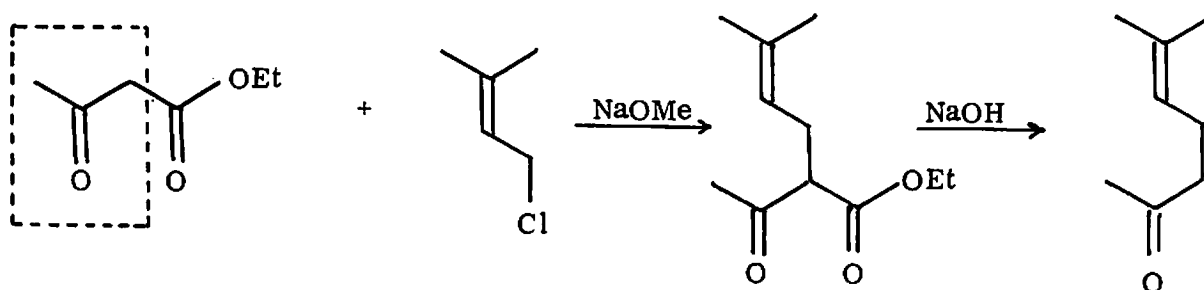## Plan of the Synthesis of Dihydrolinalool

Strategies for laboratory syntheses of terpenoids rarely imitate the biosynthetic

pathways. In the present synthetic sequence the 10-carbon skeleton of the terpenoid is

constructed from three fragments. The largest is the 5-carbon unit from methylbutenol

A. The reaction of this alcohol with hydrochloric acid results in an allylic rearrangement,
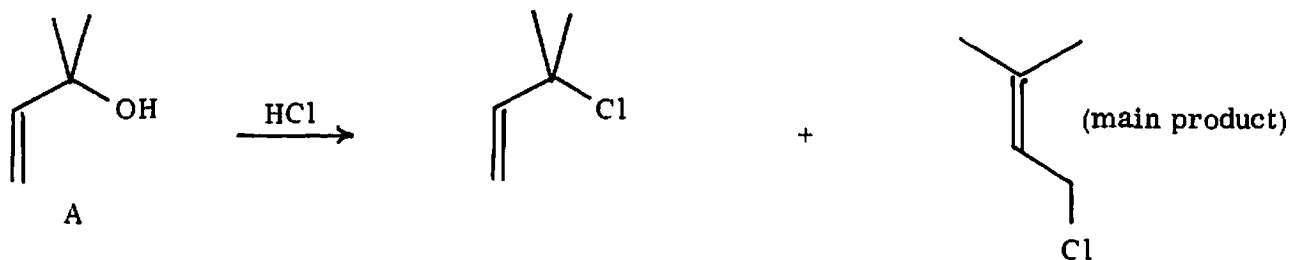
in which the double bond changes position during the nucleophilic substitution, although

the carbon skeleton retains the basic isoprene structure.

Next this unit is joined with a 3-carbon unit (enclosed in dotted line) from ethyl

acetoacetate. In a subsequent step the rest of the ethyl acetoacetate molecule is

removed by conversion into ethanol and carbon dioxide.

Finally, a two-carbon ethyl group is added to the methylheptenone by means of

the Grignard reagent formed from ethyl bromide and magnesium. The product, dihydro-

linalool, has not been discovered in nature. However, its synthesis is much easier than

that of the natural terpenoid, and it retains the property of a pleasant floral fragrance.

<u>Preparation of chloromethylbutene from methylbutenol</u>. The starting material is
available commercially because of its importance in the synthesis of methylheptenone
(our synthesis differs slightly from the industrial one), which is a precursor to synthetic
vitamin A. The methylbutenol is ultimately made from acetone and acetylene, followed
by partial hydrogenation.
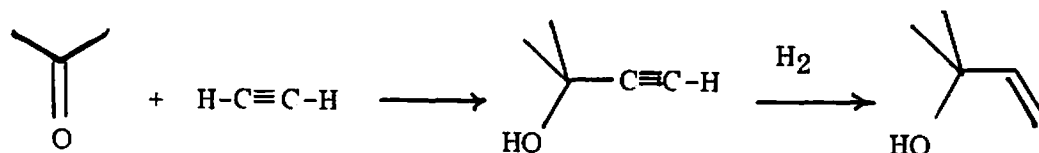
The product, also called 1,1-dimethylallyl alcohol, is a tertiary allylic alcohol
and thus extremely reactive to acids, forming the resonance-stabilized 1,1-dimethyl-
allyl cation:
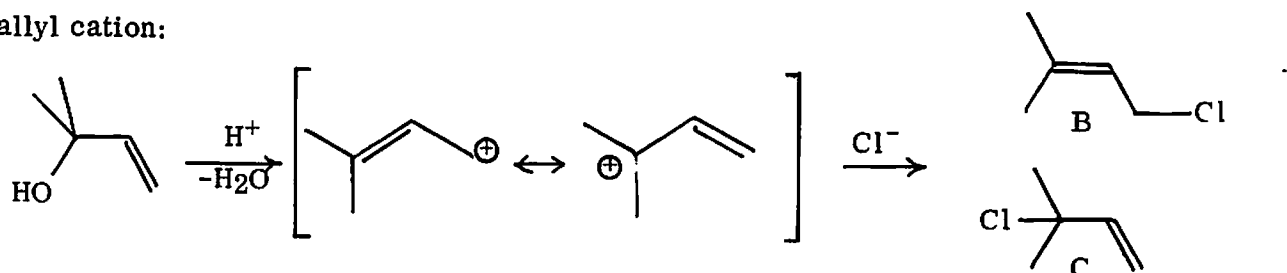
This cation can be attacked at either end by chloride to form products B or C. In fact,
the main product formed is the primary halide B resulting from attack at the less
hindered position. If the reaction mixture is allowed to stand, the hydrochloric acid
will add to the double bond, giving 1,3-dichloro-3-methylbutane.

<u>Preparation of methylheptenone from ethyl acetoacetate and chloromethylbutene</u>.
The initial step here is the formation of the anion D by removal of a proton from the

+ MeOH
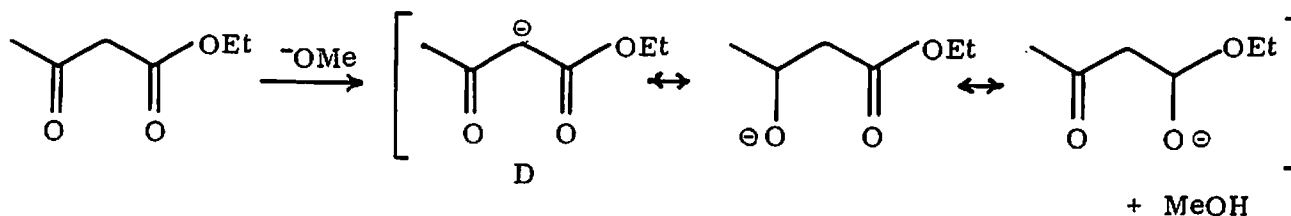
ethyl acetoacetate. Protons that are in a position α to two carbonyls are much more acidic than the α protons of a simple ketone since the anion formed is stabilized by two resonance structures with the negative charge on oxygen. This reaction occurs immediately on mixing of the ethyl acetoacetate with the strong base sodium methoxide.

The next step is the nucleophilic displacement of the chlorine by the anion D:
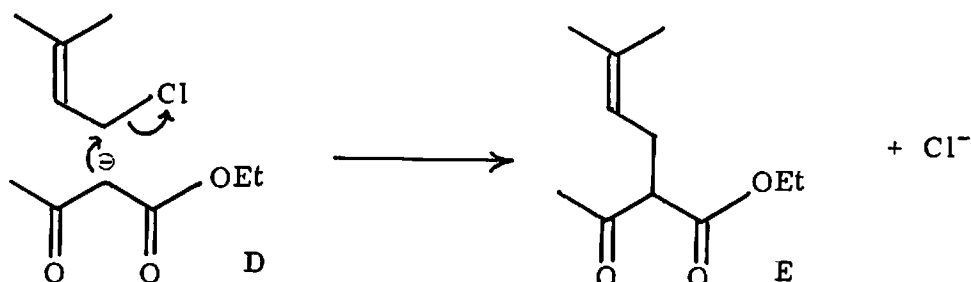
This yields the complex intermediate compound E, which is not quite what we were after. But it happens that, if the β-keto ester E is saponified with aqueous base, the β-keto acid F is produced.
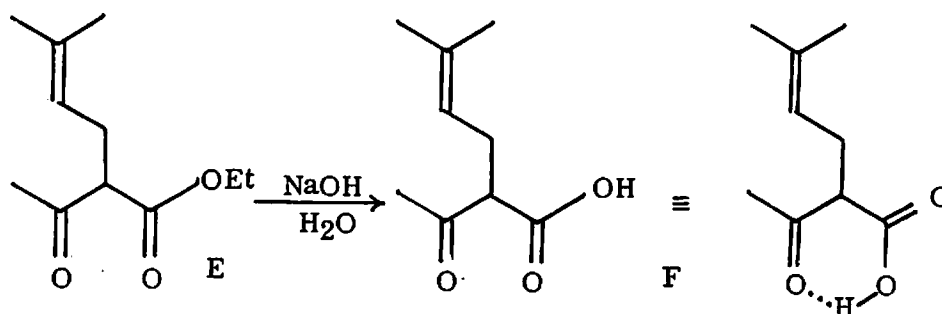
This β-keto acid is unstable and loses carbon dioxide to form the vinyl alcohol (enol) G. The acid F is stabilized in the proper conformation to undergo this reaction by the hydrogen bond (dotted line) between the carboxyl hydrogen and the ketone oxygen.


F   G   H

134
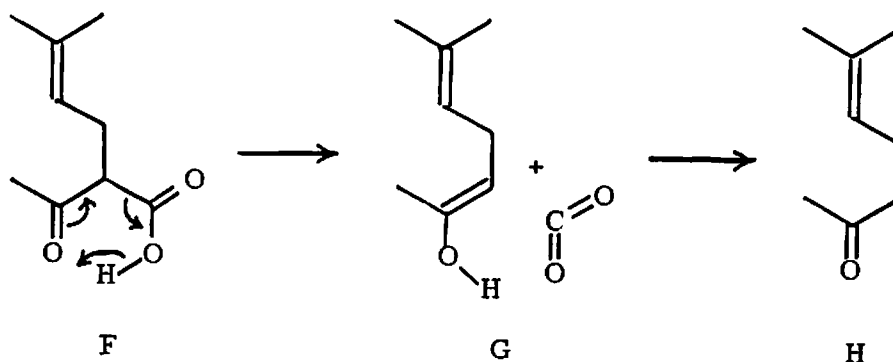
The vinyl alcohol G is also unstable and tautomerizes by exchanging a proton, resulting in the desired ketone H, 6-methyl-5-hepten-2-one.

QUERY: If any ethyl acetoacetate should remain unreacted, it will be saponified and decarboxylated just like F. Write the three carbon-containing products of this reaction.

In our preparation, we take advantage of the low volatility of the intermediate E and combine the steps of hydrolysis—decarboxylation and steam distillation. The hydrolysis step is carried out in a distillation apparatus instead of a refluxing setup; as the methylheptenone is formed, it distills along with the water.

Preparation of dihydrolinalool from methylheptenone. The final assembly of dihydrolinalool is accomplished by means of a Grignard reaction. This is an example of the use of an organometallic reagent to form a new carbon—carbon bond. Grignard reagents are organomagnesium compounds generally represented as RMgX, where R is alkyl or aryl and X is a halide. Grignard reagents are versatile in synthesis because they can be made from a wide variety of organic compounds and because they react with many different functional groups.

Grignard reagents are usually prepared by the reaction of an organic halide with magnesium metal in an ether solvent, usually diethyl ether or, as in our case,

$$C_2H_5Br \xrightarrow[\text{THF}]{\text{Mg}} C_2H_5MgBr$$

furan   tetrahydrofuran
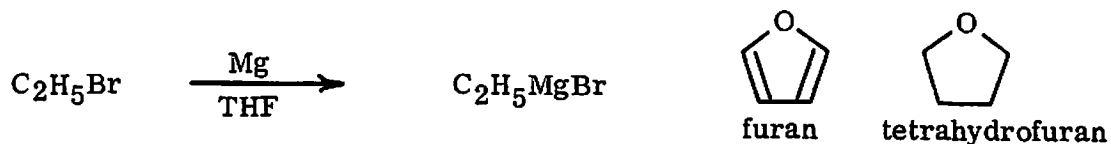
tetrahydrofuran (THF). The details of the mechanism of the formation of Grignard reagents remain obscure, despite intense investigation over the past fifty years. It is believed that the oxygen lone pairs in the solvent molecules form a complex with the Grignard reagent (or some intermediate) to drive the reaction to completion.

Once the Grignard reagent is prepared, it may be used in a variety of reactions; the one that you will use is shown below. The reaction proceeds in two steps: first,
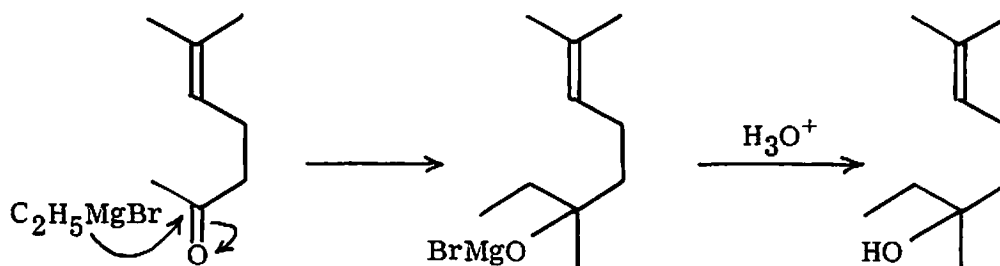
addition of the ketone to the Grignard reagent; second, hydrolysis of the magnesium alkoxide with acid. Ordinarily a very weak acid (water) is used, since strong acids may catalyze the dehydration of the alcohol. Ammonium chloride solution is employed instead of water because the magnesium salt precipitate formed with water alone is often gelatinous and hard to filter.

The most difficult step in this preparation will be getting the Grignard reagent to start forming. Once started, the process goes spontaneously and exothermically. Grignard reagents react vigorously with active hydrogens and will not even form in the presence of water. That is why both reagents are carefully dried before use. Furthermore, considerable attention is given to drying (and keeping dry) the solvent, since ethers readily absorb water, even from the air. The apparatus devised to accomplish these ends in convenient fashion is illustrated in Figure 44. The arrangement is a setup for refluxing, with a device called an aludel (derived from the Arabic for "the vessel") inter- posed between the flask and the condenser. A drying tube at the condenser outlet excludes atmospheric moisture, and a chemical drying agent is suspended in the solvent. The drying agent (e. g. , calcium hydride or sodium metal) reacts irreversibly with water. When the reaction is finished, the flask is heated,
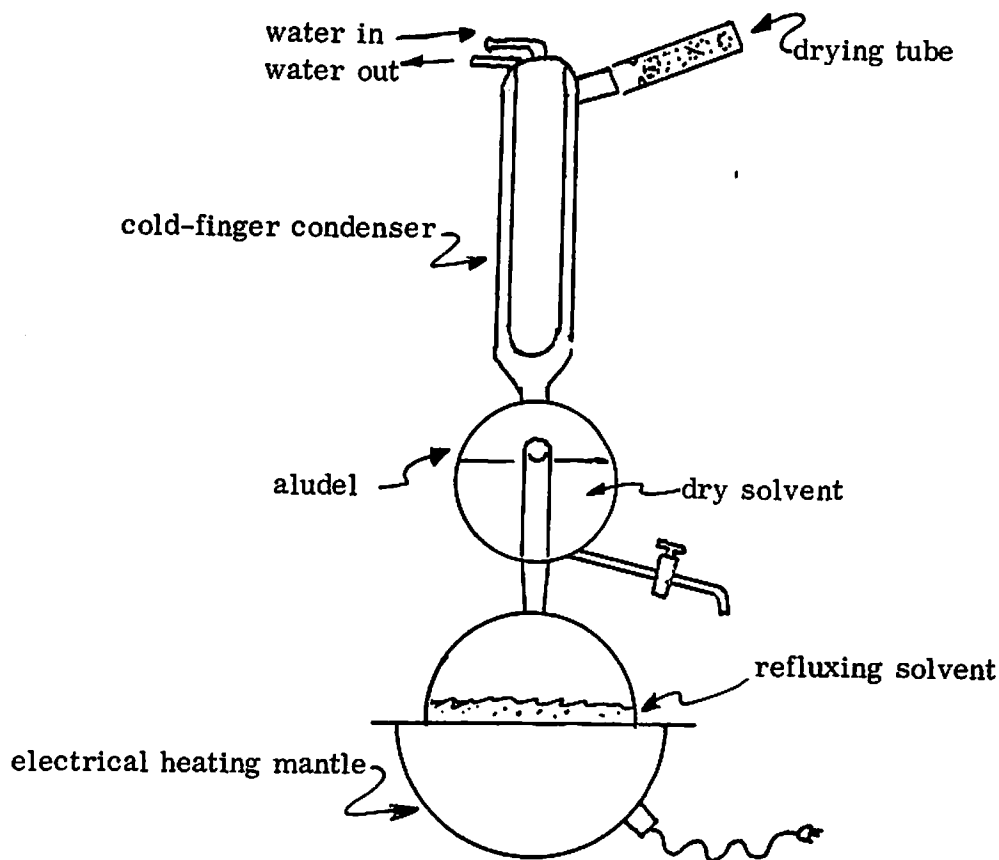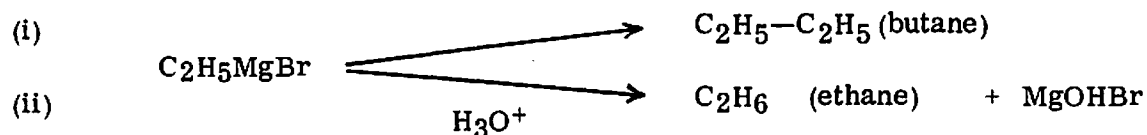
Figure 44. Solvent drying still.

distilling the solvent into the aludel, from which it is removed immediately before it is needed, in order to minimize exposure to the atmospheric moisture.

To start the Grignard reaction, various tricks are employed. The oxide layer that forms on magnesium (usually sold to chemists in the form of turnings cut from a cast cylinder) is unreactive. Thus the magnesium is crushed to expose fresh metal surface, either in a mortar and pestle or with a glass rod under the solvent surface. The reaction may be started with a high concentration of the halide, although a lower concentration is used, once started, in order to minimize such side reactions as coupling (reaction i). Other measures involve addition of traces of very reactive organic halides, such as methyl iodide or 1,2-dibromoethane.

(i)

(ii)

$$C_2H_5MgBr \rightleftharpoons$$

$$\xrightarrow{} C_2H_5{-}C_2H_5 \text{ (butane)}$$

$$\xrightarrow{H_3O^+} C_2H_6 \quad \text{(ethane)} \quad + \text{ MgOHBr}$$

After the Grignard reagent has formed, it is allowed to react with the

methylheptenone to form the magnesium salt of dihydrolinalool. This reaction is

rapid and does not pose any particular problems. Although any water in the methyl-

heptenone will destroy the Grignard reagent and form ethane, the Grignard reagent

will be in excess, and the volatile ethane will not contaminate the product.

When the addition is complete, the magnesium salt is "quenched" with saturated

aqueous ammonium chloride, which liberates the free alcohol and precipitates magnesium

salts, which are filtered off and washed with THF. The excess Grignard gives ethane

(reaction ii). Most of the THF is recovered by simple distillation. The pot residue is

fairly pure dihydrolinalool, as may be shown by gas chromatography.

The pmr spectra of the starting materials, intermediates, and final product

are given in Figures 45-51. It is worth comparing these figures to see which spectral

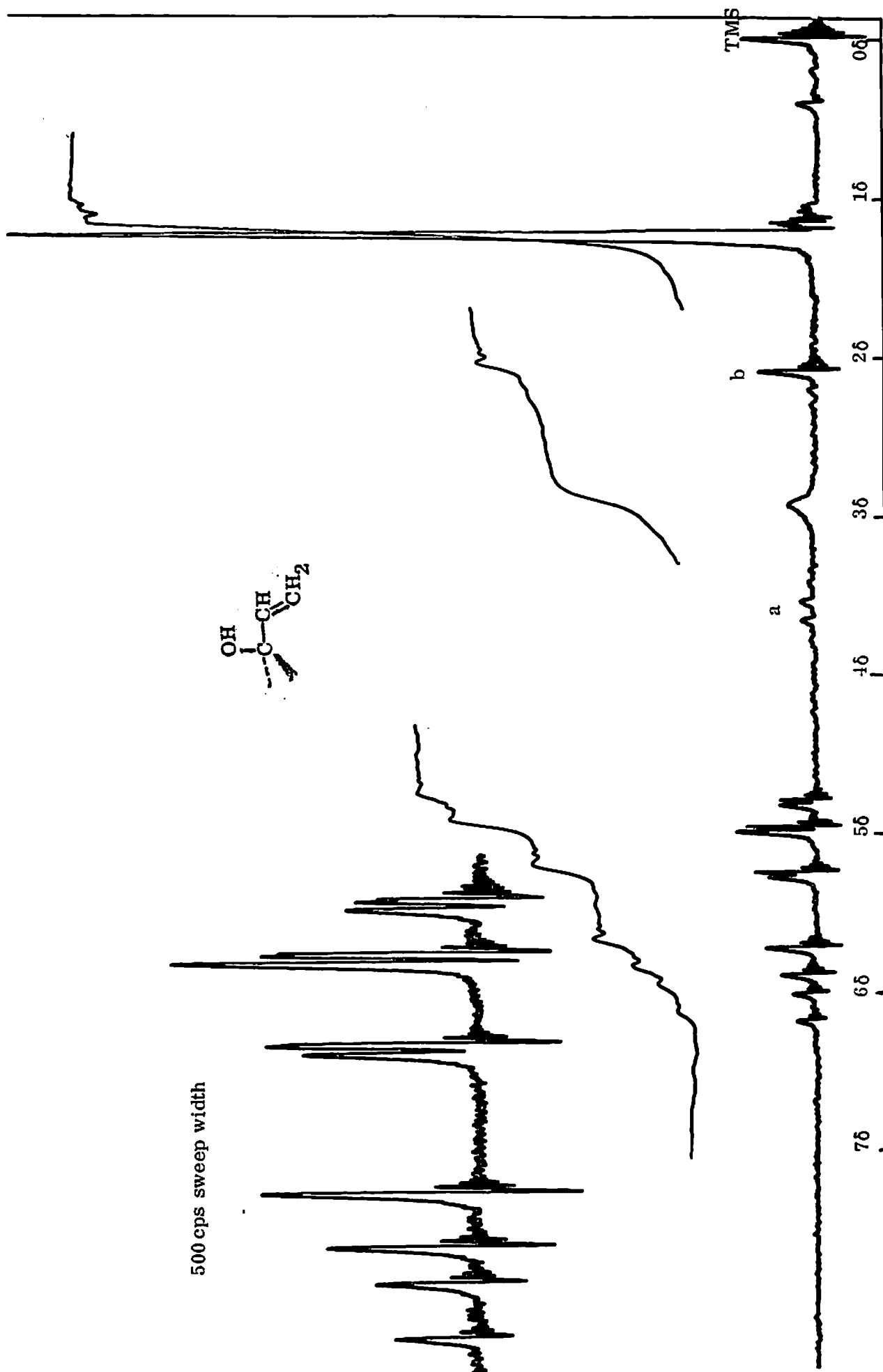features change and which do not as the various parts of the molecule are modified.

Figure 45: 60-MHz pmr spectrum of 2-methyl-3-buten-2-ol. Peaks labeled a and b are probably due to the allylic isomer, 3-methyl-2-buten-1-ol; compare Figure 46.
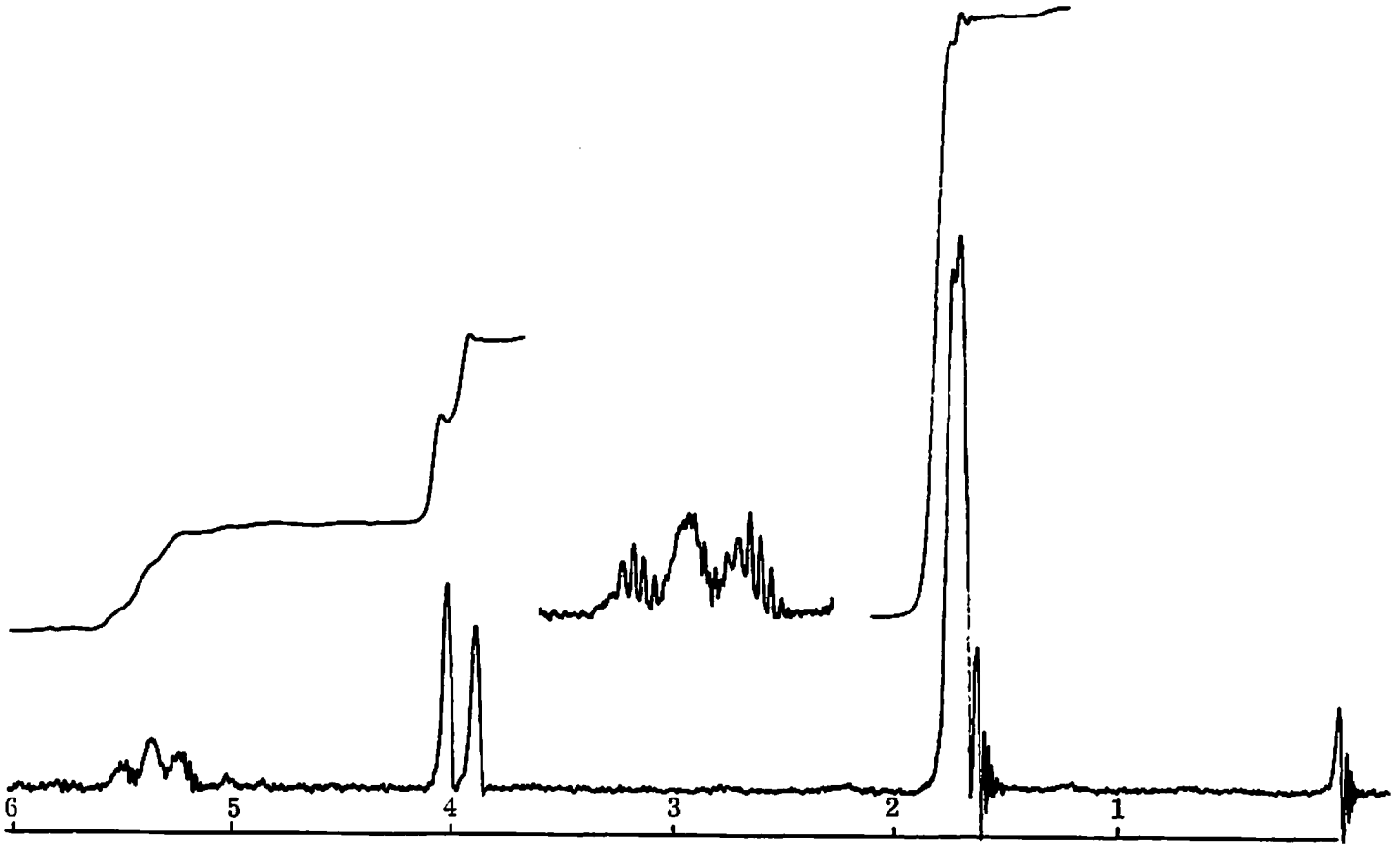
Figure 46: 60-MHz pmr spectrum of 4-chloro-2-methyl-2-butene.
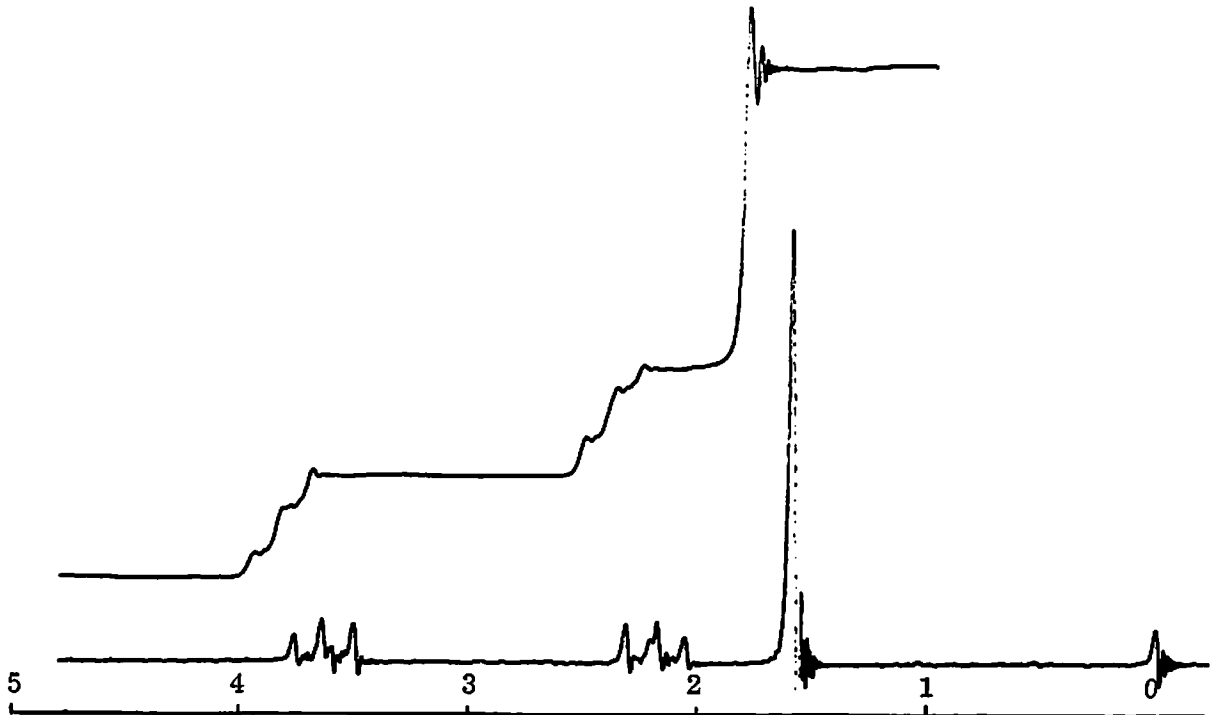Insert above: downfield multiplet expanded by a factor of two.

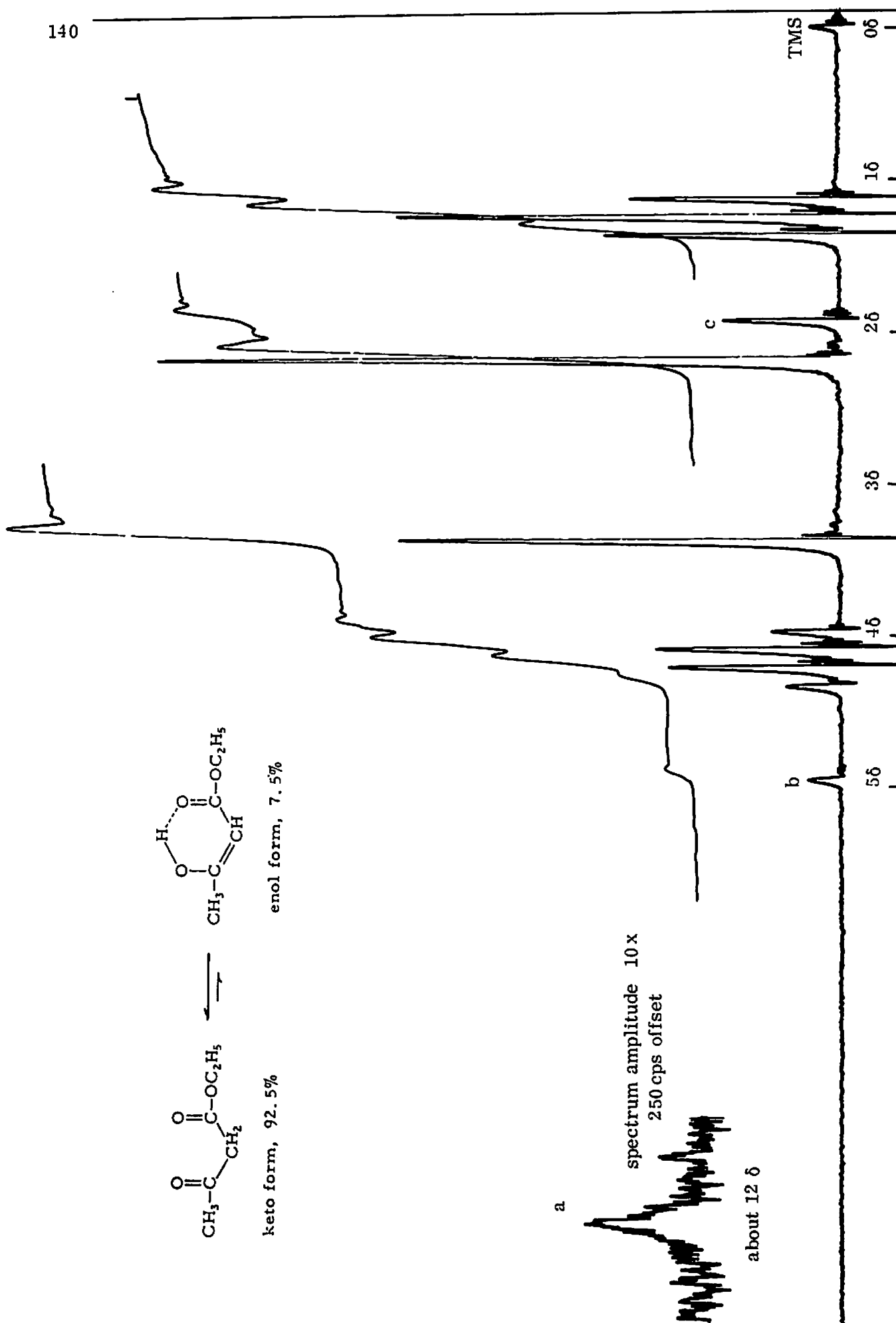Figure 47: 60-MHz pmr spectrum of 1,3-dichloro-3-methylbutane.

Figure 48: 60-MHz pmr spectrum of ethyl acetoacetate. Peaks labeled a, b, and c are due to the enol tautomer.
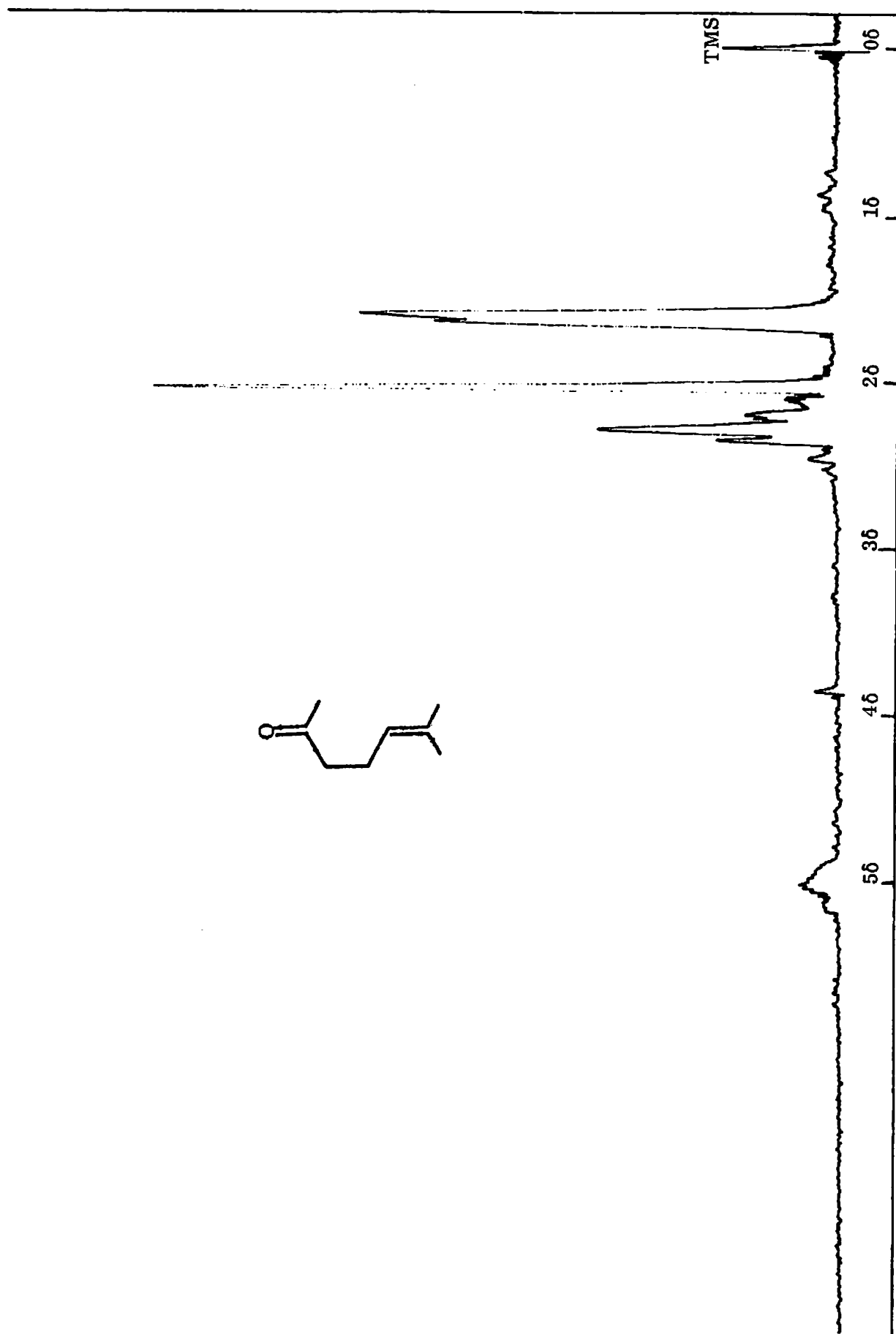
Figure 49: 60-MHz pmr spectrum of 6-methyl-5-hepten-2-one.
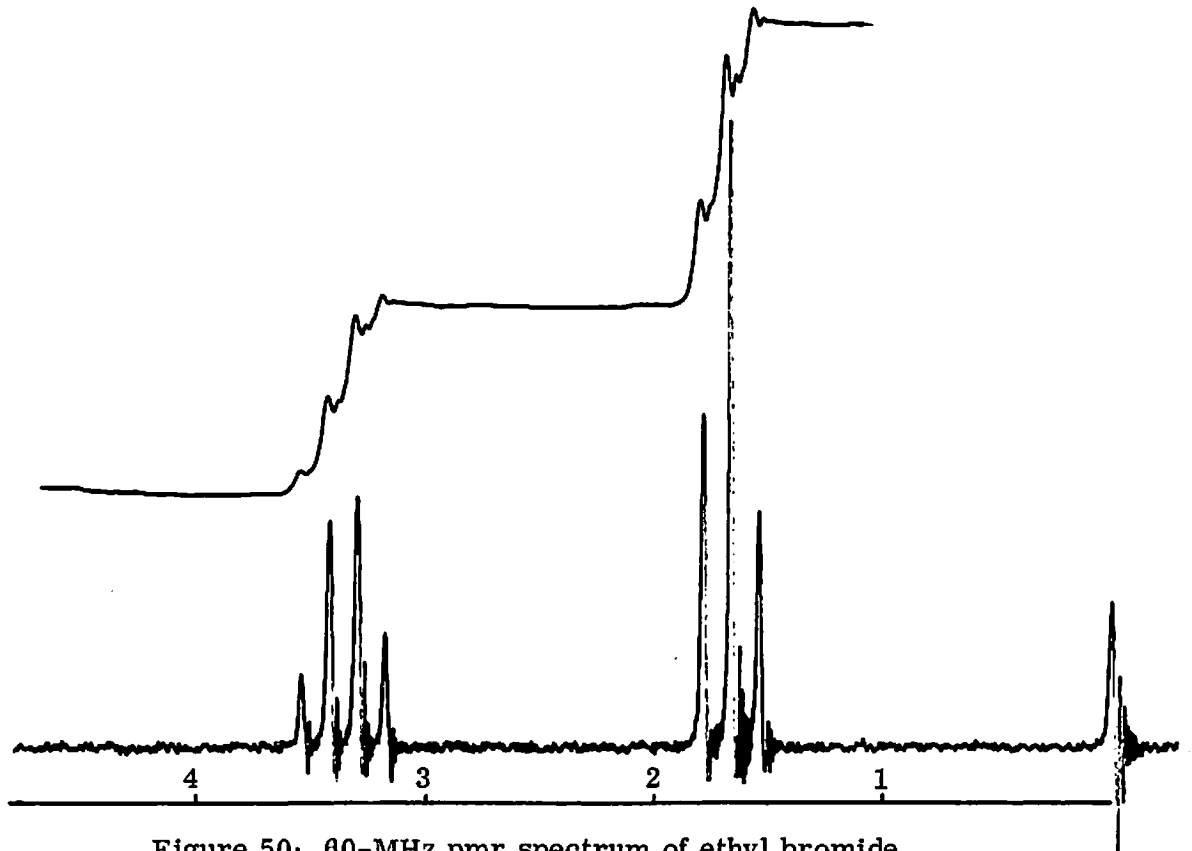
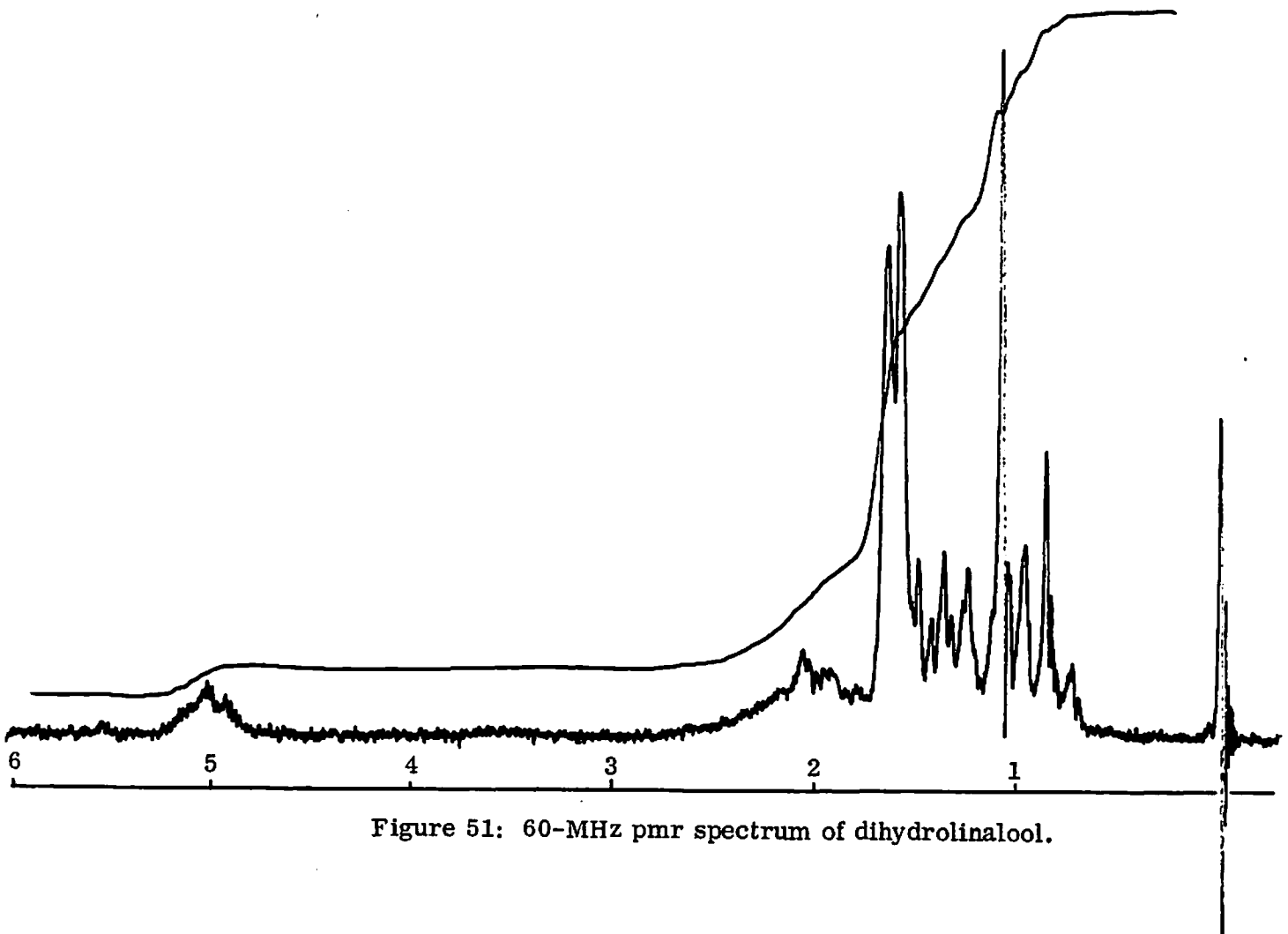Figure 50: 60-MHz pmr spectrum of ethyl bromide.

Figure 51: 60-MHz pmr spectrum of dihydrolinalool.

EXPERIMENTAL PROCEDURE

This experiment will take two weeks to complete. The first week you should

complete the preparation of methylheptenone; the second, that of dihydrolinalool. The

preparation of the methylheptenone derivatives and their purification may be fitted

around the lengthier preparations in either week as convenient.

4-Chloro-2-methyl-2-butene from 2-methyl-3-buten-2-ol

Review separatory funnel technique, p. 54. The following procedure, as far as

the asterisk, should be performed in the hood. There will be ring stands in the hoods

and prepared solution of hydrochloric acid containing 10% (weight/volume) calcium

chloride. Provide a ring or clamp for your 125-ml separatory funnel. Add 12 ml of

methylbutenol (d=0.824) to the funnel. The following steps must be performed

rapidly in order to minimize by-product formation. Add 50 ml of the hydrochloric

acid-calcium chloride solution to the funnel. Immediately stopper it, invert it,

open and close the stopcock, and shake vigorously for 30 seconds. Vent once more.

After shaking it for 30 seconds, place the funnel in a ring or clamp and wait for

the layers to start to separate. Draw off the lower, acid layer, and leave it in the hood

until you neutralize it (see"Recycling and Disposal" at end of procedure). Add 25 ml of

distilled water (measured roughly beforehand, to the product in the funnel, shake vigorously

for a few seconds, let the layers separate, and add the water to the hydrochloric acid

solution. Repeat once, this time carefully removing all the water from the separatory

funnel. * Decant the product, without getting any water drops in the flask, into a 50-ml

Erlenmeyer flask containing 1-2 g of anydrous sodium sulfate granules to dry the product.

The chloromethylbutene may be distilled when it is quite dry, but it is satisfactory for the

next experiments after a brief drying period without distillation if the above steps have been

followed carefully.

For the solvolysis experiment, set aside 1 ml of chloromethylbutene in a tightly closed vial containing a few granules of anhydrous potassium carbonate.

6-Methyl-5-hepten-2-one from chloromethylbutene and ethyl acetoacetate

If the amount of chloromethylbutene that you obtained is different from that specified here, scale the other reagents in proportion. Set up the apparatus shown in Figure 26, p. 99, without the gas trap at the top of the condenser, and using a 100-ml flask. Measure into the flask 13 ml of ethyl acetoacetate and 25 ml of 25% sodium methoxide in methanol (caustic—clean up spills). Put 10 ml of chloromethylbutene in the addition funnel. Add the chloromethylbutene slowly in drops to the flask while swirling it as much as possible (you will have to loosen the clamps or shake the ring stand). The mixture will become hot and a precipitate of sodium chloride will form. When the addition is complete (about 10 minutes), heat the mixture (do not reflux!) for 20 minutes while setting up a Büchner funnel for suction filtration. Cool, remove the salt by suction filtration, and return the filtrate to the 100-ml flask after rinsing it out with water.

On the 100-ml flask, set up a simple distillation apparatus, using the Claisen adapter between the flask and the still head (Figure 52). Distill off about 15 ml of methanol fairly rapidly (2 drops/sec). The head temperature will rise from the methanol boiling point of 64°C, but the distillate is still primarily methanol. If the temperature exceeds 74°C, stop the distillation.
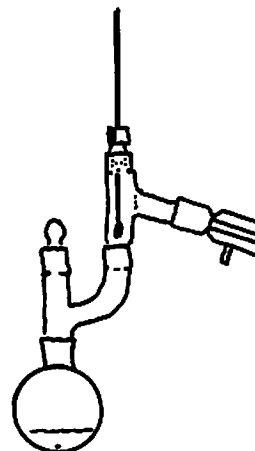

Figure 52: Simple distillation with a Claisen head.

Hydrolysis, decarboxylation, and steam distillation of methylheptenone. Let the flask cool for a minute and then add 40 ml of 3 M sodium hydroxide solution (caustic). Heat the flask and continue the distillation (2 drops/sec), using the 100-ml graduate as the receiver. In half an hour, most of the methylheptenone should have distilled (two liquid phases in the receiver, total volume 30-40 ml). If you have time, continue the distillation to recover a little more methylheptenone.

Add an equal volume of saturated sodium chloride solution to the distillate, mix well, and separate the layers in a separatory funnel. Store the product over a small amount of sodium sulfate. Calculate the yield (typically 35-70%, based on chloromethylbutene, $\underline{d}$ 0.926). The methylheptenone does not need to be dry for the preparation of a derivative, so you can start immediately on this if you have time.

Preparation of solid derivatives of 6-methyl-5-hepten-2-one

Semicarbazone. Methylheptenone (0.63 g, 5 mmol) is dissolved in 10 ml of 50% aqueous ethanol in a test tube. Then 0.56 g (5 mmol) of semicarbazide hydrochloride and 0.9 g of sodium acetate (buffer) are added. The test tube is heated on a steam bath for 10 minutes and allowed to cool. The product is often slow to crystallize; after it has cooled to room temperature, scratching the test tube or chilling it in ice or simply waiting may be necessary. When crystallization appears to be complete, suction-filter the chilled solution on a Hirsch funnel. A second crop of crystals should be obtained by heating the filtrate, adding water by drops until the solution is barely turbid, and allowing it to cool (procedure on p. 52). The isolated semicarbazone is recrystallized at least once from ethanol—water. The literature value for the melting point is 136-137°C.

<u>2,4-Dinitrophenylhydrazone</u>. Methylheptenone (0.32 g, 2.5 mmol) is dissolved

in 10 ml of ethanol in a 50-ml Erlenmeyer flask. To the solution is added a solution of

0.5 g (2.5 mmol) of 2,4-dinitrophenylhydrazine, 2 ml of concentrated sulfuric acid, 3 ml

of water, and 12 ml of ethanol (or 17 ml of a solution made up in these proportions). The

orange precipitate of the dinitrophenylhydrazone usually forms at once. After the precipi-

tate has settled, it should be filtered off on a Hirsch funnel and recrystallized from

ethanol. Literature m.p.: 86-87°C.

This dinitrophenylhydrazone may sometimes precipitate in part as an oil that
solidifies to dark masses on cooling to room temperature. Possible remedies for this
are: use of more solvent, so that the compound precipitates at a lower temperature,
below the melting point of the oil; separation of the oil from the flask with a pipet;
separation of the solidified masses from the purer, flaky crystals after filtration.
Although several recrystallizations may then be necessary to purify the compound,
they can be performed fairly quickly in succession.

Note on toxicity: The dinitrophenylhydrazine and most dinitrophenylhydrazones
are toxic (the former causing anemia) and are rapidly absorbed through the skin. If a
solution of either is spilled on the skin, <u>immediate</u> washing with soap and water will
remove most of the compound.

<u>Preparation of dihydrolinalool from methylheptenone via a Grignard reaction</u>

<u>Ethylmagnesium bromide.</u> Use the same apparatus as for the methylheptenone

preparation, with a 100-ml flask and a drying tube filled with a little calcium chloride

on top of the condenser. Magnesium turnings (0.52 g) are weighed, crushed with a

mortar and pestle, and placed in the flask. Obtain 25 ml of the tetrahydrofuran solution

of ethyl bromide (25 ml of solution contains 1.8 g of EtBr), and add 3 ml to the flask.

The reaction should start spontaneously or on heating or crushing the turnings further

with a glass rod (support the flask with your hand so that you do not poke a hole in it).

Pour the rest of the ethyl bromide—THF solution into the addition funnel and add it to

the flask at such a rate that the THF refluxes moderately. After the solution has been

added, heat the flask to reflux the THF for 15-20 minutes. Most but not all of the

magnesium should have dissolved. Turn off the heat. The flask contains the ethyl Grignard reagent.

Addition of the Grignard reagent to the methylheptenone and hydrolysis of the magnesium alkoxide. Dissolve 1 g of methylheptenone in 10 ml of dry THF and add it via the addition funnel, slowly and with swirling, to the cooled Grignard reagent. The reaction is quite rapid, but the mixture should be refluxed for 5 minutes to be sure it is complete. Cool the flask and add 2.5 ml of saturated aqueous ammonium chloride solution, one drop at a time at first, swirling to mix the solution after each addition. A precipitate will form. Suction-filter the precipitate on a Hirsch funnel and distill off the THF from the filtrate, using a simple distillation apparatus with a 50-ml flask until no more will distill (but do not overheat the still pot). The product remaining in the pot is reasonably pure ($\pm$)-dihydrolinalool (typically 90-95% by gas chromatography).

Recycling and Disposal

The hydrochloric acid—calcium chloride solution and the washings from the same preparation are placed in a large beaker. The 3 M sodium hydroxide solution from the hydrolysis is added cautiously to the beaker (exothermic reaction). The neutralization is completed with solid sodium bicarbonate, and the solution is flushed down the drain with plenty of running water.

The aqueous phase (plus sodium chloride) from the steam distillation of the methylheptenone is discarded without treatment. The mother liquors from the derivative preparations are collected for recovery of ethanol. This may be combined with the recovery of ethanol used in experiment 7.

The methanol distilled from the reaction mixture should be put in the labeled bottles in the hood. It may be used for drying glassware or redistilled.

The THF recovered from the Grignard reaction should be placed in bottles labeled "Recovered THF" in the hood, to be dried and redistilled. The solid residue of excess magnesium and basic magnesium chloride should be placed in a large evaporating dish in the hood. It will be discarded once the solvent has evaporated.

Turn in labeled samples of unused compounds, the dihydrolinalool, and the methylheptenone derivatives. The labels should include the compound name and a boiling or melting point if determined on that sample, as well as your name.

9. SOLVOLYSIS OF AN ALLYLIC HALIDE: 4-CHLORO-2-METHYL-2-BUTENE

When an ionic solid, such as NaCl, is dissolved in water, the solute is found (by freezing-point depression or conductance measurements) to be completely dissociated into ions. Similarly, many covalent compounds, for example HCl, also dissociate when dissolved in water; this phenomenon is sometimes called <u>hydrolysis</u>. Can organic halides (abbreviated as RX) also dissociate into ions? The answer, as you might expect, is that some do and some do not, but the experimental justification of this answer is not trivial. In the first place, most organic halides are rather insoluble in pure H_2O, precluding meaningful freezing-point depression or conductance measurements. In the second place, organic cations, R^+, which would be formed by dissociation of RX, are usually unstable in solution. In other words, the equilibrium $RX \rightleftharpoons R^+ + X^-$ cannot be attained, because the cation reacts with the solvent.

The dissociation of a covalent compound in any solvent is termed a <u>solvolysis</u> (by analogy to hydrolysis). This experiment is designed to explore the kinetics of solvolysis of an allylic halide.

Last week, 4-chloro-2-methyl-2-butene was prepared by reaction of 2-methyl-3-buten-1-ol with hydrochloric acid. That reaction was described as proceeding through an allylic cation. This week the reverse reaction will be studied in an effort to demonstrate the existence of such an intermediate.

As shown in the scheme on the next page, the solvolysis of chloromethylbutene may proceed via three types of pathways. Path i is, except for the asymmetry of the dimethylallyl cation, simply the reverse of the reaction by which the chloromethylbutene was prepared. The cation is trapped by water acting as a Lewis base; i.e., its lone-pair

149

150
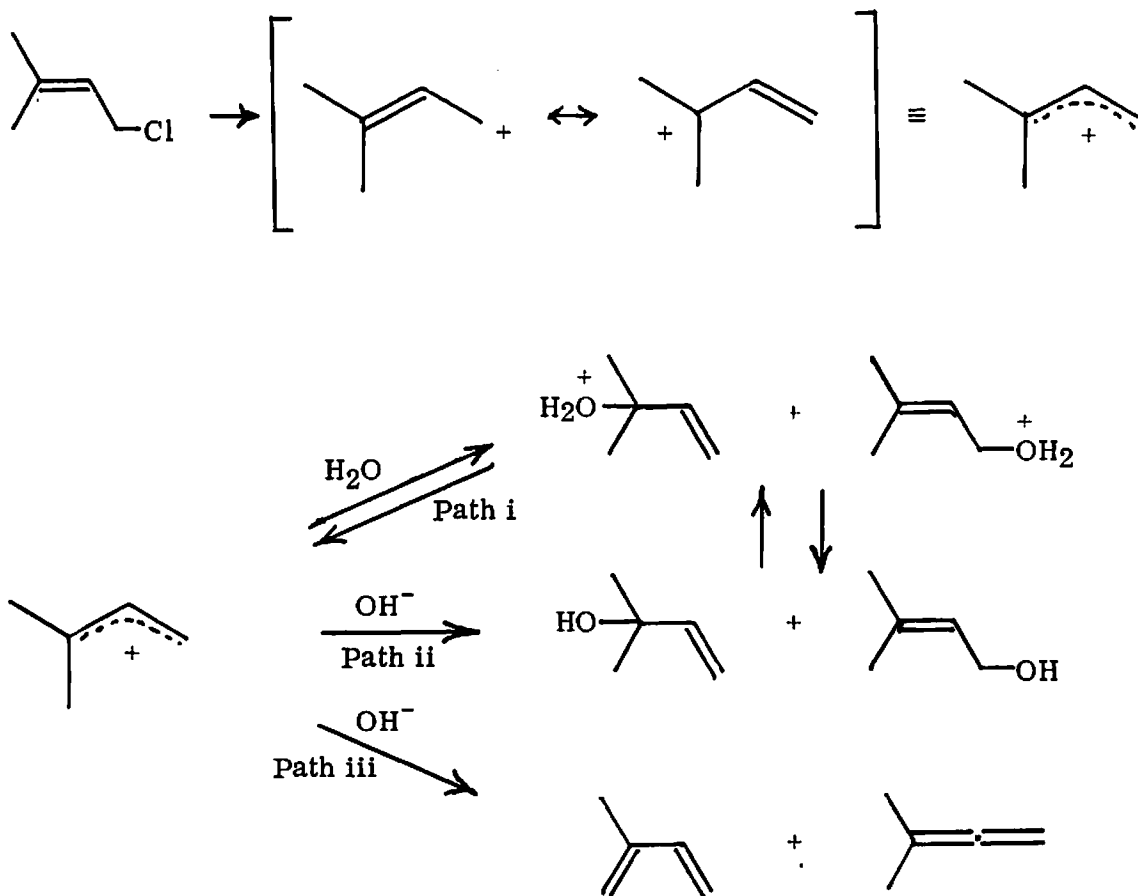
electrons form a bond with one of the vacant p orbitals of the cation. The water in this

step is called a nucleophile, and the process is a nucleophilic attack on the cation by

water. The over-all reaction via path i is substitution of chlorine by hydroxy and is

designated an S_N1 reaction (S_N stands for "substitution, nucleophilic").

Path ii in the scheme represents trapping of the cation by another nucleophile,

hydroxide ion. This reaction is represented as irreversible because the dissociation

of alcohols to cations in the absence of an acid is an exceedingly endothermic reaction.

Organic chemists distinguish between "nucleophile" and "Brønsted base" on the

basis of the type of reaction undergone. In path iii, hydroxide ion acts as a base,

adding a proton, rather than as a nucleophile, to give 2-methyl-1,3-butadiene (isoprene).

Clearly this type of reaction is very different from i and ii, and the over-all result of reaction by path iii is the elimination of HCl from chloromethylbutene. This is designated an E1 reaction (E stands for "elimination").

This complex scheme was elaborated to explain a number of experimental observations in the solvolysis of chloromethylbutene. If the reaction is run in a mixture of acetone and water with no base present, reaction via path i occurs much more often than reaction via paths ii or iii, since hydroxide ion will be present in only very low concentrations. If base is added, reaction via paths ii and iii increases, and the isoprene/methylbutenols ratio increases. In other words, the rate of isoprene production increases with increasing base concentration.

Consider, however, the rate of cation formation. The scheme depicts this dissociation step as occurring without participation of hydroxide ion. If dissociation is the slowest step in the solvolysis, as it happens to be, then this step is the "bottleneck" of the reaction. Such a bottleneck is called a rate-determining step. Since the cation is trapped much more efficiently by water than by chloride ion, the rate of disappearance of chloromethylbutene is equal to the rate of cation formation.

If our scheme is an accurate representation of the solvolysis mechanism in 70% acetone—water, then addition of hydroxide will not affect the rate of disappearance of chloromethylbutene (or the rate of appearance of HCl, which is produced at the same time). The over-all rate of solvolysis is independent of base concentration. This sort of rate law has been observed experimentally for the conversion of many tertiary and allylic halides to the alcohols, and it is part of the evidence for the mechanism shown in the scheme. Because the dissociation of the covalent carbon—chlorine bond is promoted by the solvent rather than hydroxide ion, the over-all reaction is called a solvolysis.

As noted above, the fraction of isoprene formed is a function of hydroxide concentration; that is, the product-determining steps depend on hydroxide concentration, while the rate-determining step does not. Such a situation—where the rate-determining and product-determining steps show different rate laws—necessarily implies the existence of an intermediate.

The rate-determining step of the scheme is depicted as a unimolecular process. For this reason the postscript "1" is applied to the over-all reactions via paths i and ii (S_N1) and path iii (E1). Bimolecular mechanisms (S_N2 and E2) are also common, but they are not operative in the case of chloromethylbutene.

Apart from the question of mechanism, there are practical reasons for investigating the rate of hydrolysis of chloromethylbutene. In the spirit of Zero Effluent Laboratory, the acidic solution remaining from the preparation of chloromethylbutene was neutralized with sodium hydroxide and sodium bicarbonate before it was flushed down the drain. The reason for avoiding acidic effluents was discussed in previous experiments: sulfur-containing compounds from decomposed sewage and industrial waste would generate a revolting stench if the pH of the local rivers were to fall drastically.

It is apparent that chloromethylbutene is an "acid carrier"; although not acidic itself, it hydrolyzes to hydrochloric acid. Unavoidably, a small amount of chloromethylbutene was discarded from the laboratory last week. Was most of it hydrolyzed, and thus neutralized by the bicarbonate, before the aqueous waste was poured down the drain? Or did this laboratory generate a potential—if small scale—pollution problem? In order to answer such troubling questions, the rate of hydrolysis of chloromethylbutene will be measured this week.

There is an additional question regarding disposal. Suppose one had a large

quantity of chloromethylbutene which, for some reason, had to be disposed of.

Hydrolysis would be a reasonable way to convert this compound to a relatively

harmless one, since methylbutenol and isoprene are far less toxic than chloro-

methylbutene. Would hydrolysis proceed faster if the chloro compound were mixed

with base before hydrolysis? In this week's experiment, you should determine the

answer to that question experimentally.

QUERY: Suppose, for the purpose of disposal of chloromethylbutene, that you wished
to convert it to methylbutenol and neutralize the solution, yet have a minimal quantity of
isoprene produced. Would you add base to the mixture of chloro compound and water
before, during, or after the hydrolysis?
   Suppose you wished to maximize the quantity of isoprene produced (trading
water pollution for air pollution). Would you add base to the reaction mixture before,
during, or after the hydrolysis?

Since there is no way of calculating chemical rates from first principles, a

body of information on rates of known reactions would at least permit a rough predic-

tion of rates for new and unknown reactions. This would be useful, for example, in

planning a laboratory synthesis or estimating the costs and feasibility of a planned

industrial production method.

Rates of chemical reactions in solution depend on a large number of factors.

The most important are the structure of the reactants, the temperature, the solvent

composition, including the presence of catalysts, and the concentration of reactants

and catalysts.

Structure of reactants. The high reactivity of allylic halides is an example of

this type of effect. The structure of the leaving group also affects the rate. For

example, iodides usually react faster than bromides, which react faster than chlorides,

and fluorides rarely react at all.

Temperature. The rates of most reactions increase with temperature in a regular way. In fact, rate measurements at different temperatures make it possible to calculate in a simple way the activation energy of a reaction. However for a single kinetic "run" or measured reaction, the temperature is held as constant as possible.

Solvent composition. When writing down reactions, the solvent is often ignored. However, for many reactions the solvent chosen has a large effect on the rate or product distribution. For a solvolysis in which a positively charged intermediate is formed from neutral reactants, solvents that solvate well (related to the dipole moment or dielectric constant) increase the rate tremendously. The solvent mixture chosen for this reaction involved a number of compromises among rate and solubility of methylchlorobutene and of sodium hydroxide.

Concentration of reactants and catalysts. Chemical rates in solution commonly start at a relatively high rate and decrease smoothly. The reaction rate is usually proportional to some product of reactant concentrations, each raised to some power (usually one or two, zero if the reactant does not participate in the rate-determining step). This dependence is understood to reflect the number of molecules, ions, etc., involved in the rate-determining step.

Measuring Reaction Rates

It is rarely possible to measure the rate of a chemical reaction directly. What we can do is measure the concentration or perhaps absolute amount of a particular reactant or product at a number of points in time. By plotting these points versus time and drawing a smooth curve through them, one could determine the rate at any point from the tangent to the curve.

However, a further simplification is possible. By integrating the various rate expressions, which are differential equations, one can obtain expressions for how the concentration will change with time. These expressions can be arranged to be straight lines, and so it is easy to see if a set of data points, when plotted in a particular way, forms a straight line or not.

For example, consider our reaction

(1) $RC1 + H_2O \rightarrow ROH + HC1$

If the reaction is first order in RC1 (i.e., the rate is proportional to the first power of RC1), and considering the stoichiometry of the reaction, we may write

$$\text{rate} = \frac{d([RC1]_0 - [RC1])}{dt} = -\frac{d[RC1]}{dt} = \frac{d[ROH]}{dt} = \frac{d[HC1]}{dt} = k[RC1]$$

where $[RC1]_0$ is the initial concentration of halide.

$$\text{If} \quad -\frac{d[RC1]}{d[RC1]_0} = kdt, \text{ then } \ln\frac{[RC1]}{[RC1]_0} = -kt$$

The negative sign appears since [RC1] decreases as time increases (k is positive).

But $[RC1] + [HC1] = [RC1]_0$, so $\frac{[RC1]}{[RC1]_0} = 1 - \frac{[HC1]}{[RC1]_0}$

(2) $\ln(1 - \frac{[HC1]}{[RC1]_0}) = -kt$

Thus, for a first-order reaction, if we plot $\ln[1 - ([HC1]/[RC1]_0)]$ versus time, we should get a linear plot with slope $-k$.

In this experiment, however, we determine not [RC1] but [HC1] (or $[H^+]$). Since the number of moles of RC1 reacted is equal to the number of moles of HC1 formed, and thus equal to the product of the volume of base consumed to neutralize the HC1 and its molarity M, we can set

(3) $\frac{[RC1]}{[RC1]_0} = \frac{MV}{MV_\infty} = \frac{V}{V_\infty}$

Here V_∞ is the volume of base required to titrate the HC1 released when all the RC1 has reacted. Thus one may plot $\ln[1 - (V/V_\infty)]$ without converting to [RC1].

EXPERIMENTAL PROCEDURE

A solvolysis run is conducted as follows. A quantity of chloro compound is added to the mixed solvent and the clock time t_0 is recorded. Phenolphthalein and sodium hydroxide solution are added until the mixture is basic (pink color). As the solvolysis proceeds, HCl is released, the solution becomes more acid, and the indicator color disappears. The time of disappearance is recorded, together with the volume of base added. Then more base is added, and the process is repeated until the solvolysis has proceeded sufficiently far. Finally the solution is warmed to hasten the completion of the reaction, and the HCl liberated is titrated in the usual way, giving the infinity titer V_{∞}. The further treatment of the data thus obtained is described later in the experiment.

Three independent trials of the solvolysis reaction should be run. For each trial 50 ml of 70:30 acetone—water will be used. Fill a dishpan about half full of tap water, insert a thermometer, and allow the water to reach room temperature. This will serve as a constant-temperature bath for the solvolyses.

In a 500-ml Erlenmeyer flask, prepare 300 ml of 0.025 M sodium hydroxide solution by diluting 90 ml of aqueous 0.083 M sodium hydroxide (in the hood) with 210 ml of acetone. Stopper the flask and swirl the contents until the solution is homogeneous. The stopper reduces diffusion of carbon dioxide into the solution. Clean the buret with two 10-ml portions of the diluted sodium hydroxide solution. Be sure that the tip is not clogged and that the stopcock does not leak. Fill the buret with the basic solution and fill the tip also by briefly opening the stopcock. Adjust the liquid level exactly to zero.

When you are about to start a run, add 4-5 drops of phenolphthalein indicator solution to a 125-ml Erlenmeyer containing 50 ml of 70:30 acetone—water. Leave the

flask in the constant-temperature bath until its temperature is constant, then clamp it

to a ring stand so that it does not tip over. Since the titration end point is signaled by

a color change, it will be easier to see if you have a white dishpan or a piece of white

paper or tile under the flask. Clamp the buret so that the end of the tip is at the level
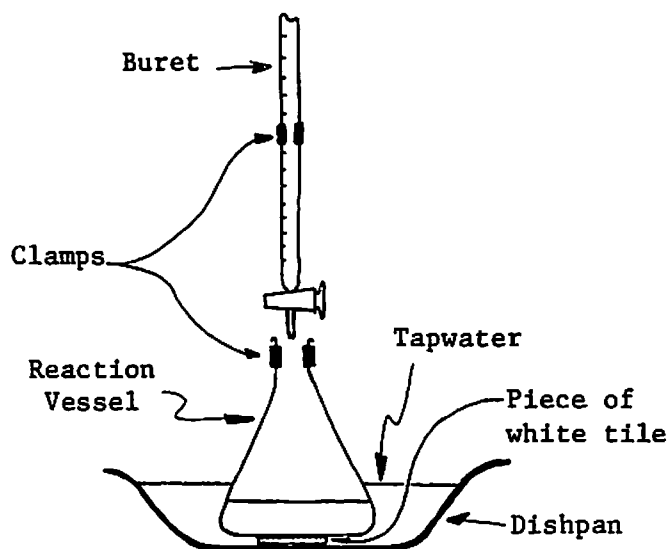
of the rim of the 125-ml Erlenmeyer so that the flask may be swirled without breaking off the buret tip (Figure 53). Add 0.1 ml of chloromethylbutene from a graduated pipet to the acetone— water solution and record the clock time t_0. Then add 1-2 ml of the 0.025 M NaOH solution from the buret to the flask and mix thoroughly. If the solution remains colorless, add more base in 1-ml portions until the solution remains pink after mixing.

Figure 53: Apparatus set up for measuring solvolysis kinetics.

The color of the solution should fade slowly. When the pink color has just completely dis-

appeared, record the clock time and the buret reading (see "Treatment of Data" for a

convenient way of doing this). Holding a white card with a black stripe behind the buret

will make the bottom of the meniscus easier to see. Add another milliliter of base and

again record the time when the pink color has just disappeared.

In the first run, continue adding 1-ml portions of base and recording time and

volume readings. In the second run use 3-ml portions of base, and in the third run, 5-ml

portions. This will permit an estimate of the effect of hydroxide ion concentration on the

reaction rate. Discuss the effect in your writeup of the experiment.

Continue each run for 40 minutes or until 30 ml of base has been added (about

two half-lives or 75% completion). A small number of accurate readings is better than

a large number of haphazard ones. To miss a point (time of color disappearance) is not

a tragedy; simply add more base, swirl, and record the time and volume at the next

fading.

When the first kinetic run is completed, warm the solution on a steam bath for

10 minutes to drive the reaction to completion. Allow the solution to cool to room

temperature and determine the infinity titer (V_{∞}) by titrating to a faint pink end point.

While this solution is cooling, start the second kinetic run in another Erlenmeyer flask.

Since V_{∞} enters all the calculated values, this titration is more critical than the others

and should be done slowly near the end point. If time permits, determine V_{∞} for the

second and third kinetic runs also.

Treatment of Data

It is convenient to record data in tabular form, leaving room for further calcu-

lations so that numbers do not need to be recopied. One way to do this would be to use

headings as follows.

Clock time $[t_0]$	V	V/V_{∞}	$1-(V/V_{\infty})$	log or $\ln[1-(V/V_{\infty})]$	t

Record your data in the first two columns and your calculations from them in the others.

If you do not have a convenient source of natural logarithms (a calculator or log-log slide

rule), use a 3- or 4-place table of base 10 logarithms.

If the initial buret reading was zero, then the subsequent readings during the

reaction represent the volume of base consumed in titrating the hydrochloric acid formed

in the reaction at time $\underline{t}$. The difference between the clock time and t_0 is the elapsed time t.

Using the graph paper in your laboratory book, make graphs of V (ordinate) versus t (abscissa) and of log or ln [1 — (V/V$_\infty$)] vs. t for your three runs. If you have more than 20 points in the first run you may skip a few nonadjacent ones. The smoothness of the graph of V vs. t is a rough indicator of the quality of the data.

From the plot of log or ln [1 — (V/V$_\infty$) vs. t, find the slope and calculate the rate constant from Eqs. 2 and 3. If you used base 10 logarithms, recall that ln x = 2.30 log x. Determine the average value of the three rate constants, and determine the standard deviation of the mean using the following expression (see p. 82):

$$\sigma = \sqrt{\frac{\Sigma (\Delta k_i)^2}{n-1}}$$

where $\Sigma (\Delta k_i)^2 = (\Delta k_1)^2 + (\Delta k_2)^2 + (\Delta k_3)^2$ is the sum of the squares of the differences of the calculated values from the average, i.e., $\Delta k_i = k_{av} - k_i$ (i = 1, 2, 3); $k_{av} = (k_1 + k_2 + k_3)/3$, and n = 3. In your writeup you should discuss the differences, if any, among your three experimental runs.

Hints on Drawing Graphs

Graphs are easier to draw and read if the units are conveniently chosen. Use the graph paper in your lab notebook. Label the axes with the proper units and add a title, so that someone who hasn't done the lab can tell what the graph represents. Draw a line through the experimentally determined data points so that an equal number of points lie above and below your line.

Recycling and Disposal

Put the used solvolysis mixture in the labeled jugs in the hood. The acetone will be recovered by batch distillation. Any left over chloromethylbutene should be put in the appropriate bottle in the hood. Rinse out the buret with water.