4-13-2018

Evaluation of Vaporization Enthalpies and Vapor Pressures of Various Aroma and Pharmacologically Active Compounds by Correlation Gas Chromatography

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B.S., Chemistry, University of Missouri- St. Louis, 2014

A Thesis Submitted to the Graduate School at the University of Missouri- St. Louis
in partial fulfillment of the requirements for the degree
Master of Science in Chemistry

May 2018

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Abstract

Scientists in the pharmaceutical, food, and aroma industries can benefit from reliable thermochemical data. Vaporization enthalpy and vapor pressure data are not available for all compounds. Furthermore, some literature data is conflicting. The goal of this work was to use a method called correlation gas chromatography (CGC) to generate reliable vaporization enthalpy data in instances where other experimental methods are not applicable. Vapor pressures of the targets were also calculated in cases where the required literature data on the standards used in this technique were available.

CGC involves making a standard cocktail that includes a mixture of standards and one or more unknowns. Reliable literature values for vaporization enthalpy must be available for the standards in order to evaluate the vaporization enthalpy of the targets. From the retention time of both the standards and their vapor pressures, it was possible to evaluate the vapor pressures of the targets. The compounds examined were structurally diverse. There included saturated and unsaturated compounds, cyclic and acyclic, aliphatic and aromatic, lactones, aldehydes, carboxylic acid derivatives, profens, and alcohols. Despite structural differences, their properties can be separated into two broad categories: aroma compounds and pharmacologically active compounds. Each class of compounds brought about unique challenges. Some were oils that were extracted and characterized prior to measurement. Aldehydes proved to be unstable. Some carboxylic acids gave poor peak shapes requiring a search for a suitable column. Additionally, some of the profens displayed liquid crystal behavior- adding additional complications.

Vaporization enthalpies were measured for nepetalactone, whiskey lactone, menthalactone, *trans*-2-hexenal, 2,6-dimethyl-5-heptenal, 2,6-nonadienal, *trans*-2-nonenal, *trans*,*trans*-2,4-decadienal, 2-butyl-2-octenal, patchouli alcohol, and Fenoprofen. Vapor pressures were measured for nepetalactone, whiskey lactone, menthalactone, and Fenoprofen. Vaporization enthalpy and vapor pressure values for the standards were all within experimental error of literature values, except in the case of 2-tetradecanol.

Chapter 1: Introduction

1.1. Introduction

The compounds examined in this work are structurally diverse. Many of the compounds are naturally occurring. The target analytes and many of the compounds used as standards are generally recognized as safe (GRAS). The GRAS compounds are safe enough to consume and examples studied in this work can be found in the food we eat, the beverages we drink, our medications, perfumes, and products we give to our pets.

Many of the lactones, aldehydes, and alcohols studied in this work are classified as aroma compounds. They are sufficiently volatile that even in relatively low concentrations at standard temperatures and pressures they can be perceived by the sense of smell. Many of these compounds are naturally occurring in foods and/or beverages.[1-6] Others are naturally extracted into food or beverage during cooking or through a maturation process.[6-9] Lactones of interest include catnip (nepetalactone), whiskey lactone (4β-methyl-γ-octalactone), and mint lactone (5,6,7,7a-tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone). Aliphatic aldehydes of interest include *trans*-2-hexenal, 2,6-dimethyl-5-heptenal, *trans*, *cis*-2,6-nonadienal, *trans*-2-nonenal, *trans*, *trans*-2,4-decadienal, 2-butyl-2-octenal, and lauric aldehyde while aromatic aldehydes of interest included *trans*-cinnamaldehyde, tolualdehyde, and cyclamen aldehyde. The major alcohol of interest is patchouli alcohol, which is used in the fragrance industry as well as a starting material for an anti-cancer drug, Taxol®.

Vapor pressure, its temperature dependence, and enthalpy of vaporization, are of importance to a variety of industries, including food science, the perfume industry, the chemical industry, and depending on the nature of the chemical, also to the

environmental protection agency (EPA). Vapor pressure governs the extent of exposure to chemicals, both benign and otherwise. Vapor pressure is the connecting link between the consumer's nose and palate to the aroma ingredients in foods and beverages. The aroma profile of a food not only depends on the concentrations of the aroma compounds, but also their affinity for the structural components (i.e. proteins, lipids, cellulose, etc.) of the food. Since many aroma compounds tend to be non-polar, or only moderately polar, the presence of lipids can influence the vaporization, and therefore the perception, of these compounds.[10] While the flavor profile of a food or beverage is comprised of both volatile and non-volatile components[11], this work examines materials that tend to be relatively volatile.

2-Arylpropionic acids (profens) and benzoic acid derivatives are another major category of compounds studied in this work. Several of these possess analgesic properties.[12-14] The target compound in this study was Fenoprofen, which is a nonsteroidal anti-inflammatory drug (NSAID). Better-known examples of NSAIDs are Naproxen (Aleve®) and Ibuprofen.[14] More broadly, NSAIDs belong to a class known as active pharmaceutical ingredients (APIs). APIs are the chemical(s) present in medication that are responsible for the therapeutic effect. For brevity in the remainder of this thesis, the profens and benzoic acid derivatives will be referred to as profens even though not all of the benzoic acid derivatives are profen compounds.

Enthalpy of vaporization data is useful in the pharmaceutical industry as well. Vaporization enthalpy data is usually compiled with other solvent properties. The compilation of data can then be used to select the best solvent for processing APIs. One group recently suggested using this data to find safer solvents relative to solvents

traditionally used.[15] Solvent vaporization enthalpy data can also be used to generate guidelines for drying APIs. This is typically a time/energy intensive process.[16]

The enthalpy of vaporization data of the API itself can also be useful. It is necessary, at times, to calculate the enthalpy of formation of reactants and products in the production of pharmaceutical compounds. The enthalpy of formation data is then, in turn, used to calculate the reaction heat.[17, 18] Estimation of the reaction heat is required prior to the first large-scale production run of pharmaceutical compounds as a safety measure. If the reaction heat is estimated to be large, then the equipment required for the reaction needs to be appropriately engineered to maintain conditions within accepted safety margins.[18]

A couple of the aroma compounds in this study have also seen some use as an analgesic. Menthalactone, also known as mintlactone, has undergone phase I, II, and III clinical trials and has been used to combat headache, toothache, and muscle pain [19]. Patchouli alcohol is perhaps most widely known for its application in the perfume industry. It has, however, also been used as a cold remedy [20] and has anti-inflammatory properties [21] among others.

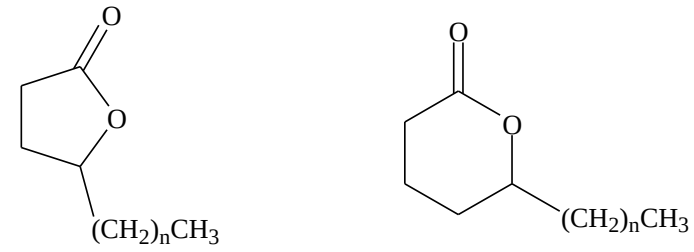
Aside from menthalactone and patchouli alcohol, the analgesic compounds and the aroma compounds are different not only in their application, but the physical properties are in stark contrast as well. An easily observable difference is that the lactones and aldehydes (aroma compounds) studied are all liquids at room temperature, whereas the 2-arylpropionic acid and benzoic acid derivatives (NSAIDs) are all solids. The alcohols gave varied results. Some of them are liquids at room temperature and others are solid. The aroma compounds studied have high vapor pressures that give a

strong (and often pleasant) odor even with small sample sizes. Accordingly, this means the enthalpies of vaporization are generally lower (42-84 kJ/mol) as compared to the sublimation enthalpies of the profens and benzoic acid derivatives which range between 96-140 kJ/mol at 25°C.[22] Thus, more energy is required to transfer the latter to the gas phase.

1.2. Structure and Properties

1.2.1. Lactone Aroma Compounds

Lactones are cyclic esters that occur naturally in a variety of ring sizes. Lactones examined in this study are of both of the γ- and δ- variety. The γ-lactone designation means the γ carbon is connected to the ring oxygen and forms a 5-membered ring. The δ-lactone designation means the δ carbon is connected to the ring oxygen forming a 6-membered ring. The carbonyl carbon is not considered in this system of nomenclature. Figure 1-1 depicts the difference between γ- and δ-lactones. As compared to smaller ring sizes (α or β), the γ- and δ-lactones are more structurally stable due to less ring strain resulting from a more favored bond angle geometry.[6] The standards that were utilized in these studies also had aliphatic side chains on the γ- and δ-positions.



Standards:
n = 1, 3, 5, 6

n = 2, 5, 6

FIGURE 1-1. The structures of the γ and δ-lactone standards.

Lactones are prepared synthetically by oxidizing the corresponding cyclic ketone in a Baeyer-Villager reaction.[23] Likewise lactones could also be produced by the reversible intramolecular esterification of the associated hydroxy acid. The reverse of this reaction would result in hydrolysis back to the acyclic form.[6]

As with acyclic esters, electron density is highest around the oxygen atoms, while the aliphatic side-chains are non-polar. In the compounds of Figure 1-1 there are stereocenters at the γ-position for γ-lactones and at the δ-position for δ-lactones. The target analytes, nepetalactone, whiskey lactone, and menthalactone each possess multiple stereocenters that are discussed further in section 2.1.1.

1.2.2. Aldehyde Aroma Compounds

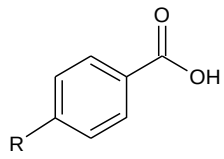
The aldehyde compounds examined in this study had simpler structures than the lactones and profens/benzoic acids. There is, however, still some variety in structure. Variations include saturated, mono-unsaturated, and polyunsaturated aldehydes. Both *cis* and *trans* double bonds are represented, although in the aliphatic aldehydes the double bonds have predominately *trans* stereochemistry. Examples of straight chain and branched aliphatic aldehydes are represented, as well as aromatic aldehydes.

In general, aldehydes can undergo many reactions similar to ketones, but are generally more reactive. These reactions are textbook reactions and usually involve nucleophilic attack at the carbonyl carbon. When compared to ketones, however, aldehydes are more prone to degradation by molecular oxygen. The degradation of aldehydes in the presence of oxygen can result in some interesting products through multiple reaction pathways that proceed via a radical mechanism. By far, the major

product is the corresponding carboxylic acid. However, the formate ester, primary or secondary alcohol, or ketone/aldehyde may also form under some conditions.[24]

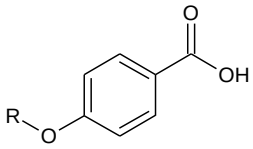
1.2.3. Profens and Benzoic Acids

The structures of profens and benzoic acids are very similar in that they both contain six-membered aromatic rings with carboxylate groups at the 1-position. The difference is, however, that the profens contain an extra ethylene group. The general class of arylpropionic compounds could have the aryl group attached to either the α- or β-carbon of the propionic acid. The profen nomenclature denotes that the aromatic group is attached at the α-carbon and therefore they are 2-arylpropionic acids. Figure 1-2 shows a comparison of benzoic acid derivatives (**1, 2**) and 2-arylpropionic acids (**3**).



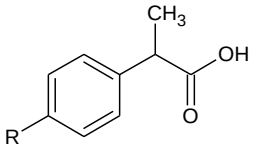
R= alkyl group

1



R= alkyl group

2



R= alkyl, phenyl, alkoxy

3

FIGURE 1-2. Compounds used in the analysis of Fenoprofen consisted of alkylbenzoic acid derivatives **1**, alkoxybenzoic acid derivatives **2**, and 2-arylpropionic acid derivatives **3**. The R groups listed represent the scope of compounds used.

Most of the profens and the benzoic acids used in this study were substituted at the *para* position. However, in the case of Fenoprofen, the substitution is an ether bridge to another aromatic group at the *meta* position. In the case of the benzoic acids, both alkyl and alkoxy substituted derivatives were used for standards. It is worth noting that another class of NSAIDs based on salicylic acid has a similar structure to benzoic acid. Salicylates are benzoic acids with an *o*-hydroxy group.

Lastly, it should be noted that unlike the benzoic acids the profens have a stereocenter at the α-carbon. The configuration that seems to have the largest biotherapeutic significance is the (S)-(+)-configuration[13, 25, 26]. Both R,S Fenoprofen and R,S flurbiprofen are administered by prescription in racemic form while both S (+)-ibuprofen and S (+)-naproxen are available over the counter.[27]

A fascinating and, admittedly, complicating point about the Fenoprofen salts commonly encountered is that they can form liquid crystals. Liquid crystals are a phase of matter between the solid crystalline and liquid state. Liquid crystals are less ordered than solid crystals in that they have orientational order, but lack positional order.[28] Liquid crystals are, however, more ordered than liquids or glass phases which are isotropic or amorphous. The complication is that the phase equilibrium for the one component system is no longer just a function of temperature and pressure, but now the phase transitions must be taken into account as well. Additionally, there is generally a lack of temperature-pressure data for liquid crystals[29] and they can undergo both first and second order solid-liquid phase transitions.[28]

Complicating matters even more, many liquid crystals can exist as several different polymorphs.[29] The Fenoprofen $Ca^{2+} \cdot 2H_2O$ salt is capable of forming thermotropic smectic liquid crystals[28, 30, 31]. The sodium salt, on the other hand, can form both thermotropic smectic and lyotropic lamellar liquid crystals.[28, 30] Interestingly, the potassium salt doesn't form the thermotropic liquid crystal, but it does form the lyotropic lamellar liquid crystal in the presence of water.[28] The different polymorphs have different physical properties and stabilities.[28, 30]

Thermotropic phases result from a temperature change.[28, 30] The intermolecular interaction of molecules in thermotropic smectic liquid crystals looks approximately like bundles of cigars stacked in layers. They are all oriented in the same direction, roughly parallel to each other; however, the bundles may not have long range positional order. The layers of bundles may be slightly askew from the perpendicular axis and can move with respect to one another.[28]

Lyotropic liquid crystals are more common in pharmaceuticals.[30] They are induced by the presence of solvent.[28, 30] In the aqueous lyotropic laminar arrangement, the Fenoprofen molecules would be arranged similar to a phospholipid bilayer found in cell membranes. The polar propionic group would be facing out and the non-polar phenyl rings would face the inside of the bilayer. Figure 1-3 shows the difference in intermolecular arrangement between the solid crystal, and the thermotropic smectic and lyotropic laminar liquid crystal structures.

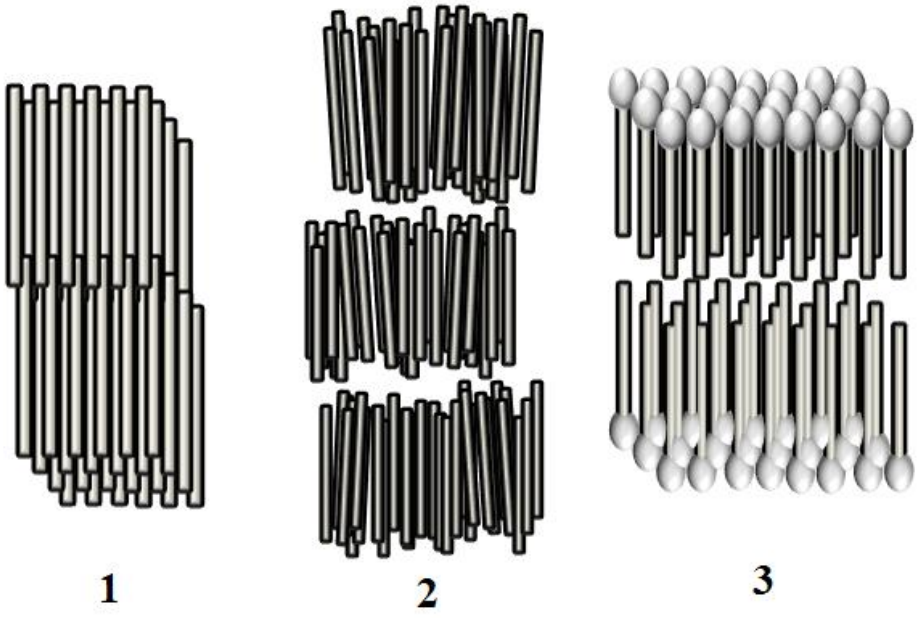


FIGURE 1-3. Fenoprofen salts have a rod-like shape and can take the form of crystals **1**, thermotropic smectic liquid crystals **2**, and lyotropic lamellar liquid crystals **3**.[28]

Fenoprofen exhibits a planar-rod shape in the liquid crystal state.[28] In this case, liquid crystals may be formed by heating the calcium dihydrate crystal to drive off the water.[30, 31] It is reported that the compound in this state, appears to be solid until it is under pressure.[30] Due to the possibility of liquid crystal formation, the melting of Fenoprofen sodium salt has a wide temperature range of 58-80 °C.[28] The liquid crystal nature of Fenoprofen was not observed in this study. In fact, the Fenoprofen calcium salt was first converted to the free acid as described in section 2.1.3. Although *S*-ibuprofen, *R*,*S*-flurbiprofen, and *S*-naproxen are all crystalline at standard temperature and pressure, the Fenoprofen neutral acid is a viscous liquid.

1.2.4. Alcohol Aroma Compounds

Most of the alcohol standards used for this study had simple structures. They were linear saturated primary alcohols. The exceptions were 2-tetradecanol, which of course is a secondary alcohol, and 1-adamantanol which is a tertiary alcohol.

1-Adamantanol has an interesting structure with three fused aliphatic rings and it also has some peculiar properties. For one, it undergoes a solid-solid phase transition at T = 357.1 K [32]. Also, consider a comparison to 1-decanol, which is the linear saturated alcohol with the same number of carbons. The boiling point of 1-adamantanol might be expected to be lower than that of 1-decanol. The orientation of the fused rings gives the 1-adamantanol molecule diamondoid geometry. This geometry presumably should lead to lower van der Waals forces because it has less surface area as compared to 1-decanol. Also, the primary alcohol should be more polarizable and more easily accessible for hydrogen bonding than the tertiary alcohol. The tertiary alcohol is more sterically

hindered and can better spread a dipole charge amongst three carbons instead of one. The lower van der Waals forces, less polarizability, and lower steric accessibility of the hydroxyl on 1-adamantanol should give it a lower boiling point as compared to 1-decanol. However, 1-adamantanol is a solid at room temperature and sublimes at 282-283°C[33] with an enthalpy of sublimation of 86.6 ± 0.3 kJ mol^{-1} [32]. ACD labs predicted a hypothetical boiling point of 245.8 ± 0.8°C for 1-adamantanol [34]. However, in a recent paper, Nelson and Chickos predict a hypothetical boiling point of 248.1 ± 0.5°C for 1-adamantanol using the CGC method. They note that the reported fusion temperature, T_{fus} = 279.8 °C, exceeds the predicted boiling point at one atmosphere and that 1-adamantanol likely behaves like $CO_2(s)$ by subliming at 1 atm.[35] More recent work also suggests that primary alcohols may not be good vapor pressure standards for polycyclic compounds, making the hypothetical boiling point of 1-adamantanol difficult to predict with confidence. 1-Decanol, on the other hand is a liquid at room temperature, with a boiling point of 231.1°C [36]. This collection of properties is intriguing as they tend to defy the usual predictors of relative boiling points.

The target compound in the alcohol study, patchouli alcohol, is also a tertiary alcohol with three fused aliphatic rings. Likewise, in this case the C_{15} patchouli alcohol has a higher predicted boiling point than 1-pentadecanol. Patchouli alcohol has a melting point of 55-56°C [37] and a predicted boiling point of 287.4 ± 0.8°C [34] whereas 1-pentadecanol has a melting point of 7°C and a boiling point of 229°C [38].

1.3. A Brief History, Natural Occurrence, and Overview of Uses

1.3.1. Lactone Aroma Compounds

Lactones are found in a range of biological organisms. Lactones occur as byproducts of metabolism in various animal milk fats[3] and in certain plants[39]. In plants they are derived from lignin[7] and they serve as natural defense mechanisms against various insects.[39] Fungi, however, synthesize lactones from a feedstock of sugars and lipids.[5]

Lactones are known for being aroma compounds. As seen in Table 1-1, many are associated with pleasant odors. Both γ- and δ-lactones contribute to the pleasant smell of butter oil. In fact, several of the standards used in this study such as: δ-octanolactone, δ-decanolactone, δ-dodecanolactone, and γ-dodecanolactone have been the interest in butter aroma research.[3] Many of the same lactones are present in olive oil as well. Olive oil lactones that are relevant to this study are δ-octanolactone, γ-nonanolactone, γ-decanolactone, δ-decanolactone, δ-dodecanolactone, and γ-dodecanolactone.[4]

Various fruits contain lactone aroma compounds. Many lactones are present in pineapple. The ones pertaining to this study are γ-hexanolactone, γ-octanolactone, δ-octanolactone, γ-decanolactone, γ-dodecanolactone, and δ-dodecanolactone.[1, 11] γ-Octanolactone is found in the essence oil of oranges (from orange juice concentrate).[2] As stated earlier, some aroma compounds are extracted during the preparation or maturation process for food or beverage. Whiskey lactone, as the name implies, is found in whiskey due to extraction from the whiskey barrels.[7] Among other functions, charring the inside of the oak barrels for aging whiskey increases availability of certain oak compounds that are extracted by the alcohol. One such compound is whiskey

lactone.[7] Whiskey lactone has a sweet woody aroma at low concentrations and a sweet coconut aroma at high concentrations.[7] In addition to whiskey lactone, American Bourbon whiskey also contains γ-nonalactone, δ-nonalactone, γ-decalactone, and γ-dodecalactone.[7] Chinese rice wine also contains lactones. Those which are relevant to this study include γ-hexanolactone, γ-nonanolactone, and γ-decanolactone.[8] Likewise, pineapple wine contains γ-nonanolactone.[11] γ-Nonanolactone, γ-decanolactone, and δ-decalactone have been reported to be present in some Sauvignon blanc and Merlot wine samples as well.[40] γ-Nonanolactone is also one of the key odorants of Tinta Negra Mole grapes, which account for 85-90% of Madeira wines produced.[9]

TABLE 1-1
Aroma profiles of lactone compounds used in this work.

Compound	CAS-registry no	Odor	Reference
γ-Hexanolactone	695-06-7	sweet, peach	[8]
γ-Octanolactone	104-50-7	fatty, herbal, caramel, coconut	[2, 5]
δ-Octanolactone	698-76-0	coconut-like	[41]
γ-Nonanolactone	104-61-0	coconut, cream, peach, strawberry	[7-9, 11]
γ-Decanolactone	706-14-9	peach, fruity	[3, 4, 7, 8]
γ-Undecanolactone	104-67-6	peach, coconut-like	[3, 41]
δ-Undecanolactone	710-04-3	sweet, milky	[42]
γ-Dodecanolactone	2305-05-7	peach, creamy, fruity	[3, 4, 7]
δ-Dodecanolactone	713-95-1	peach-like, sweet, flowery	[43]
cis-Whiskey Lactone	55013-32-6	wood, coconut	[7]
trans-Whiskey Lactone	39638-67-0	coconut, stale	[7]
Menthalactone isomers	13341-72-5	coconut, creamy, spearmint, sweet, tobacco	[44]
Nepetalactone isomers	490-10-8	citronella	[45]

As mentioned in section 1.2.1 the lactone standards used in this study are chiral. For at least some lactones both enantiomers can be found in nature. Although the enantiomers are mirror images of one another, they may possess different odor characteristics and are present in different foods. In the case of γ-decanolactone the S-

enantiomer is found in mango, while the R-enantiomer is found in many fruits- especially peaches.[6]

In other instances, different diastereomers are present in the same compound. One of the target analytes in this study is menthalactone, a mixture of 5,6,7,7a-tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone diastereomers. It originates from peppermint leaves among other sources and finds use as a flavorant, in cosmetics and, as stated earlier, has undergone phase I, II, and III clinical trials for use as an analgesic.[19]

Although lactones are abundant in nature, there has also been some interest in preparing them synthetically. Several different ways have been developed. In 1899 the Baeyer-Villager reaction was first used to oxidize menthone and carvomenthone to their corresponding lactones with peracids. [23, 46] More recent developments have allowed the use of aqueous hydrogen peroxide as the oxidizer in the presence of organometallic catalysts.[46] Besides natural extraction, menthalactone can be prepared synthetically from (+)-menthofuran. In the United States, menthalactone production is on large scale.[47]

Current research in lactone synthesis seems to be for the purpose of pest control chemicals.[39] Several lactones have shown promise for use as insect repellants. Both δ-octanolactone and δ-nonanolactone have been proven effective against tsetse flies that plague waterbuck.[48] The naturally occurring nepetalactone diastereomers have also shown promise as insect repellant against *Aedes aegypti* (yellow fever mosquito)[49] and *Anopheles gambiae* (Afro-tropical pathogen vector mosquitoes)[50].

The major active constituent of catnip oil, (4aS,7S,7aR)-nepetalactone, has been studied by several chemists over the years and was isolated by steam distillation. *Nepeta*

species that are known to contain nepetalactones have been used both as folk medicine for nervous, respiratory, and gastrointestinal diseases as well as traditional medicine for diuretic, anti-asthmatic, tonic, sedative, and others.[51] Essential oils from *N. Persica*, which contain (4aS,7S,7aR)-nepetalactone and (4aS,7S,7aS)-nepetalactone have also shown antibacterial properties against *E. coli, P. aeruginosa, S. aureus, S. typhi,* and *E. faecalis.*[51]

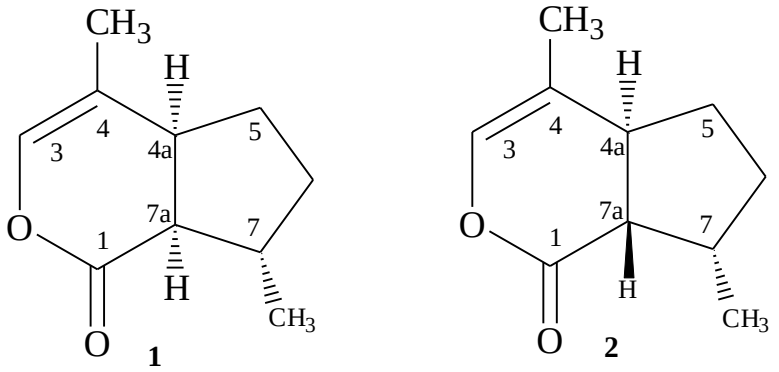


FIGURE 1-4. Essential oils from *N. Persica* can contain both (4aS,7S,7aR)- nepetalactone, **1**, and (4aS,7S,7aS)-nepetalactone, **2**.

1.3.2. Aldehyde Aroma Compounds

Aldehydes of the variety studied can be found in many types of foods and beverages commonly consumed. They are of interest to food scientists because they are known to be aroma compounds and often possess pleasant odors. The aroma profiles of the aldehyde aroma compounds utilized for this study are presented in Table 1-2. Hexanal is among the few volatile chemicals responsible for the aroma of butter.[3] Also found in butter oil are *trans*, *trans*-2,4-decadienal which provides a fatty[3, 7] or green note[2] and *trans*-2-nonenal which is described by flavorists as tasting like cardboard[3] or having a green note[7].

Alcoholic beverages also include aldehydes. American whiskeys contain many of the aldehydes used in this study. These include nonanal, *trans*-2-nonenal, *trans, cis-2,6*-nonadienal, *trans, trans*-2,4-decadienal, and *trans*-cinnamaldehyde.[7] Chinese rice wine contains hexanal, benzaldehyde and cinnamaldehyde.[8]

TABLE 1-2
Odors of aldehyde compounds in this study

Compound	CAS-registry no	Odor	Reference
Hexanal	66-25-1	green, cut grass	[2, 4, 8]
trans-2-Hexenal	6728-26-3	green, cut grass	[4]
Benzaldehyde	100-52-7	almond, bitter, cherry	[8, 9]
Octanal	124-13-0	citrus, lemon, green, soapy	[2, 4, 43]
2,6-Dimethyl-5-heptenal	106-72-9	Green, sweet, oily, melon	[52]
Nonanal	124-19-6	soapy, sweet, melon	[2, 7]
Tolualdehyde	104-87-0	fruity, cherry, phenolic	[44]
trans, cis-2,6-Nonadienal	17587-33-6	green	[7]
trans-2-Nonenal	18829-56-6	green, cardboard	[3, 7, 43]
trans-4-Decenal	65405-70-1	fresh, citrus, orange, madarin, tangerine, green, fatty	[53]
Decanal	112-31-2	lemon, fatty	[2]
trans-Cinnamaldehyde	14371-10-9	fruity	[7]
trans, trans-2,4-Decadienal	25152-84-5	fatty, solvent, green	[2-4, 7, 43]
2-Butyl-2-octenal	13019-16-4	fruity, pineapple, green, sweet, ripe, juicy	[54]
Lauric aldehyde	112-54-9	soapy, waxy, citrus, orange, madarin	[53]
Cyclamen aldehyde	103-95-7	floral, fresh, rhubarb, musty, green	[53]

Common fruits are also known to contain various aldehydes. For instance, pineapple contains hexanal, *trans*-2-hexenal, nonanal, decanal, and benzaldehyde.[1] Aldehydes are major contributors to the aroma of orange essence oil. The relevant aldehydes include hexanal, octanal, nonanal, *trans*-2-octenal, decanal, and *trans, trans*-2,4-decadienal. Of these, octanal and decanal are among the most aroma active compounds.[2]

Trans-2-hexenal is one of the key components responsible for the green aroma of virgin olive oil.[4] Other aldehydes from this study that are found in olive oil include hexanal, octanal, nonanal, benzaldehyde, *trans*-2-nonenal, *trans*-2-decenal, and *trans, trans*-2,4-decadienal.[4]

Hexanal is formed naturally by aldehyde-lyase.[4] Naturally occurring *trans*-2-hexenal comes from the enzymatic degradation of linolenic acid.[4]

Aldehydes have also seen use as fragrances in perfumes and colognes. Many of the aldehydes studied in this work were of natural origin and in recent years have been of interest to consumers in the form of essential oils. Essential oils are thought by some to be healthy sources of natural remedies.

1.3.3. Profens and Benzoic Acids

NSAIDs (nonsteroidal anti-inflammatory drugs) are some of the earliest and most widely prescribed drugs. Uses for NSAIDs include pain relief, anti-inflammatory, fever reduction, and some can be used as blood thinners.[14] The use of benzoic acids, in particular *o*-hydroxybenzoic acids, to relieve pain dates back to the ancient Egyptians. Bark and leaves from willow trees were used for stiff and painful joints. Salicin, seen in Figure 1-4, is a precursor to aspirin and was first isolated from willow tree bark in 1828 by Johann Buchner. It was not until 1857 that acetylsalicylic acid (aspirin) was first synthesized by Hammond Kolbe. In 1899 aspirin was patented and marketed by Bayer.[14]

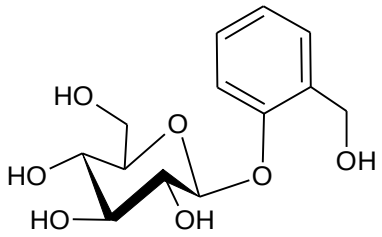


FIGURE 1-4. Salicin isolated from willow tree bark contains a glucose ether linkage that can be hydrolyzed to give salicyl alcohol. The salicyl alcohol is then oxidized to salicylic acid.

By 1939 a synthesis for a 2-arylpropionic acid (α-orthomethoxyphenyl-propionic acid) was described. The pathway was rather lengthy and involved converting a benzyl alcohol to the ethyl ester, then reacting with ethyl oxalate, evolution of carbon monoxide giving the rearrangement to the diethyl ester, addition of methyl iodide to methylate at the benzylic carbon, and finally hydrolysis of the diesters and decarboxylation of the diacid to give the monoacid.[55] At that time its biological activity was unknown.

By 1951, there were at least two synthetic routes to naproxen (β-(6-methoxy-1-naphthoyl)-propionic acid), one by reacting a napthalene cadmium reagent with the propionyl chloride and the other was an inverse Grignard reaction using the Grignard reagent generated from 1-bromo-6-methoxynapthalene and succinic anhydride. [56]

In 1959, John Nicholson and Stuart Adams first synthesized ibuprofen and it was marketed in 1969.[14] It wasn't until 1971 that the mechanism of aspirin-like compounds on inhibition of prostaglandin synthesis was explained by Sir John Robert Vane. In 1982 he shared the Nobel Prize in Physiology or Medicine for this discovery.[14]

In 1973, the absolute stereochemistry of (+)-naproxen was determined to be (+)-(*S*)-naproxen by degradation to the previously characterized (-)-(*S*)-2-phenyl-1-propanol.[57]

Some 2-arylpropionic acids such as Fenoprofen, naproxen, and ibuprofen belong to a class of compounds known as nonsteroidal anti-inflammatory drugs (NSAIDs).[14] The mechanism of these profens is thought to involve binding to the cyclooxygenase-2 (COX-2) receptor.[12] The specificity and mechanism of action of profens on COX-2 is different than other classes of NSAIDs such as fenamates or salicylates.[14, 58] This binding inhibits COX-2 from oxidizing arachidonic acid, 2-arachadonoylglycerol, and arachadonoylethanolamide into various prostagladins. Degradation of the prostagladins into metabolites are responsible for the pain and inflammation.[12]

Fenoprofen was developed by Eli Lilly and is sold commercially as the calcium dihydrate form under the name Nalfon.[25, 30] Fenoprofen is currently marketed to treat osteoarthritis and rheumatoid arthritis.[28] Like ibuprofen and naproxen, fenoprofen has only one stereocenter and it is found on the propionic acid moiety. Also like ibuprofen and naproxen, the active enantiomer for COX inhibition is the (*S*)-(+) isomer.[13, 25, 26] In the case of Fenoprofen, the (*S*)-(+) enantiomer shows 35 times more activity than (*R*)-(-) in COX inhibition.[25] The more common profens, naproxen and ibuprofen, were used as standards in the study as the vaporization enthalpies of these materials have previously been reported.[22]

1.3.4. Alcohol Aroma Compounds

Patchouli oil is an essential oil containing patchouli alcohol as well as a whole host of sesquiterpenes. The oil is described as having a powerful ambergris-type odor.[59] By 1925, the United States was already importing more than 25,000 pounds of patchouli oil.[60]

Patchouli oil is traditionally obtained by steam distillation of *Pogostemon cablin* leaves.[20] The conversion of α-patchoulene to patchouli alcohol was reported in 1961.[37] However, in 1964, the authors realized their 1961 conversion results were interpreted incorrectly. At this time they also gave a total synthesis of patchouli alcohol starting from (+)-camphor. The lengthy process took approximately 40 steps.[59]

Patchouli oil has many uses. One such use is as a natural insect repellant. It has been demonstrated to effectively repel termites and moths. Furthermore, it is actually toxic to termites causing tissue destruction inside the exoskeleton.[20] Patchouli oil has also been used in the perfume industry [20, 21] and to flavor toothpaste [21].

Patchouli oil has also been known to have pharmacological uses. It was historically used as a cold remedy in Asia [20] and has also shown anti-inflammatory, anti-allergic, immunomodulatory, and antimicrobial properties[21]. Patchouli alcohol, the main constituent of patchouli oil, has been studied in the enhancement of cognitive abilities and as a neuroprotective agent as well as an anti-inflammatory in both *in vitro* and *in vivo* animal studies.[21] Patchouli alcohol was also the starting material for the first total synthesis of Taxol (generic paclitaxel)[61, 62], which is a potent anti-tumor drug. Taxol is found in nature in the pacific yew tree. However, a synthetic method was

desired due to the scale necessary for production. It took approximately 12,000 trees to yield 2.5kg of Taxol.[63]

The Holton group reported the synthesis of Taxusin in 1988 from patchoulene oxide, which is derived from patchouli alcohol.[63] Then in 1994, the Holton group published usage of Taxusin as starting material for the total synthesis of Taxol, which is a total of 47 steps when starting from patchoulene oxide.[61, 62] The structure of patchouli alcohol can be seen in Figure 1-5.

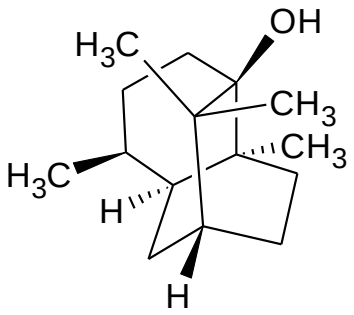


FIGURE 1-5. Patchouli alcohol was used as the starting material in the first total synthesis of the anti-tumor drug, Taxol.

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Chapter 2: Experimental Methods

2.1. Compounds

2.1.1. Lactone Compounds

Two lactone studies were conducted. In the first study, the target analyte was catnip oil (nepetalactone). Although nepetalactone has three chiral centers, there are only two naturally occurring diastereomers found in *Nepata cataria*. These are (4aS,7S,7aR)-nepetalactone (major), and (4aS,7S,7aS)-nepetalactone (minor). A comparison of the structures can be seen in Figure 2-1. [1]

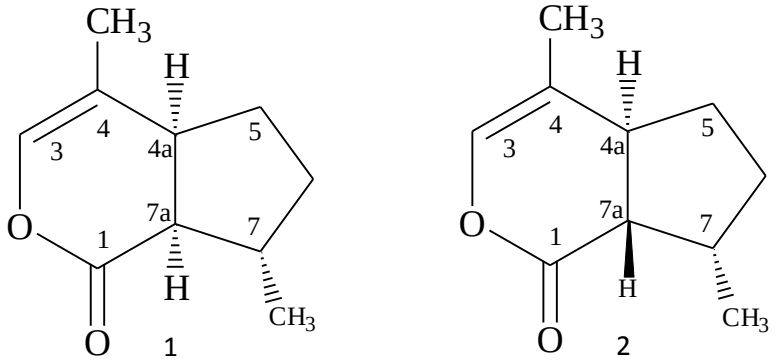

FIGURE 2-1. Structures of the major **1** and minor **2** diasteriomers of (4aS,7S,7aR) and (4aS,7S,7aS)-nepetalactone isolated from *Nepata catonia*, respectively.

The analytes of interest for the second study were whiskey lactone and menthalactone. The major diastereomers for whiskey lactone found in nature are *cis* (3*S*,4*S*)-4β-methyl-γ-octalactone (major) and *trans*(3S,4R)-4β-methyl-γ-octalactone (minor). The major diastereomers of menthalactone found in nature are (-)-mintlactone ((-)-(6*R*,7a*R*)- 5,6,7,7a-tetrahydro-3,6-dimethyl- 2(4*H*)-benzofuranone) and (+)-isomintlactone ((+)-(6*R*,7a*S*)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone). All possible whiskey lactone and menthalactone diastereomers are shown in Figure 2-2.

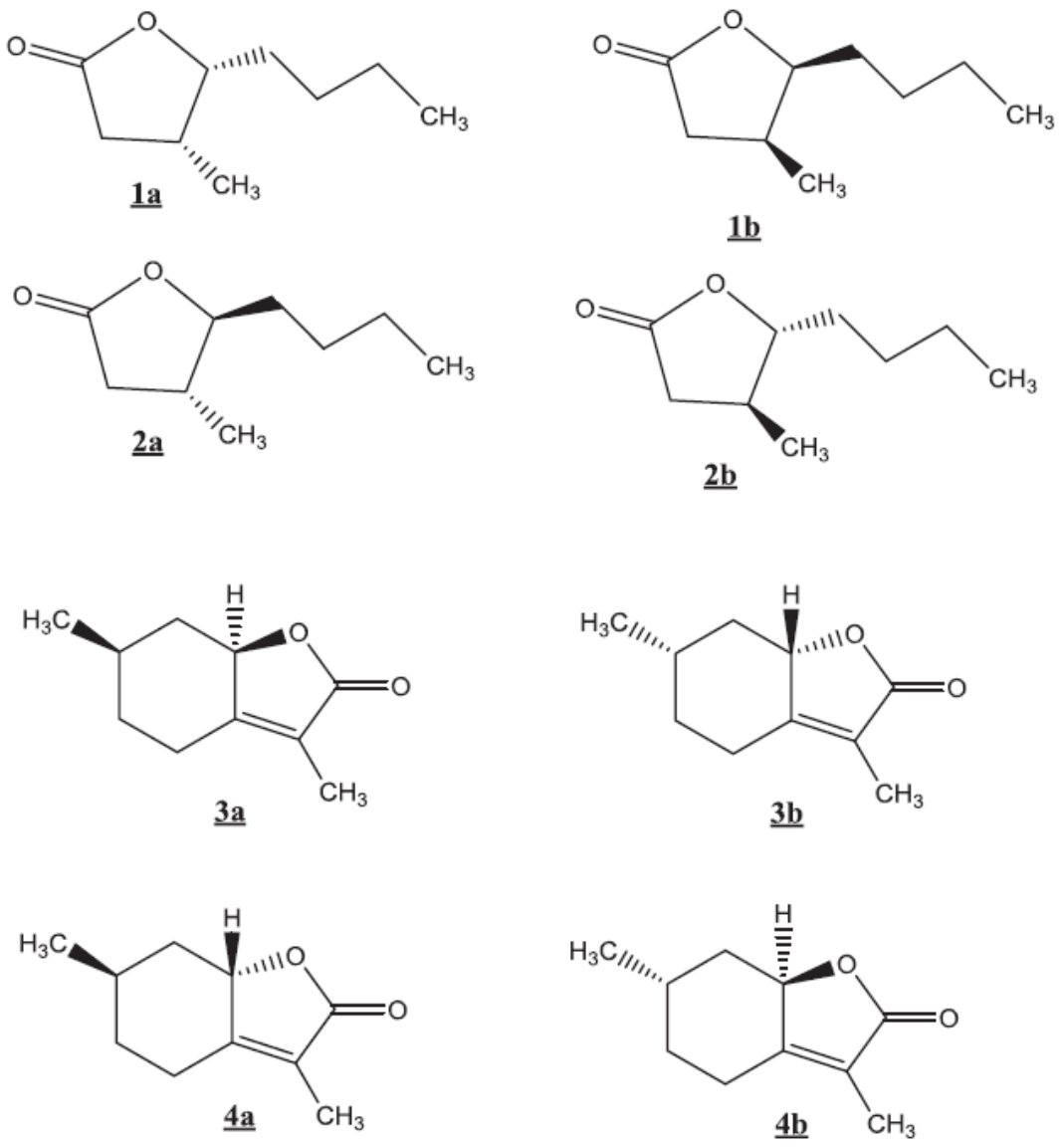

FIGURE 2-2. Top to bottom, left to right: Whiskey lactone major components [rel-(4R,5R)-5-butyldihydro-4-methyl-2(3H)-furanone] **1a + 1b**; Whiskey lactone minor components [rel-(4R,5S)-5-butyldihydro-4-methyl-2(3H)-furanone] **2a + 2b**; Mintlactone major enantiomer [(-)-(6R,7aR)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone] **3a**; Mintlactone minor enantiomer [(+)-(6S,7aS)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone] **3b**; Isomintlactone components (6R,7aS)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone **4a** and (6R,7aS)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone **4b**.

All lactone standards were purchased from commercial sources. The origin and purity of the standards are reported in Table 2-1. Most of the compounds were used unaltered. The catnip oil was isolated from a natural source and required removal of the

carrier which was tentatively identified by infrared spectroscopy as an alcohol or glycol. For catnip oil a few milliliters of oil was added to a few milliliters of methylene chloride. An emulsion formed and a few milliliters of deionized water were added to extract the carrier. The solution was allowed to phase separate and the water layer was discarded. This was repeated two more times. For storage, calcium chloride was added to the methylene chloride extract to dry the organic phase and prevent hydrolysis of the lactones.[1]

TABLE 2-1
Origin and purity of lactone compounds for this work.

Compound	CAS-registry no	Supplier	Mass Fraction Purity (Supplier)	Mass Fraction Purity (GC)
γ-Hexanolactone	695-06-7	Bedoukian	>0.98	0.993
γ-Octanolactone	104-50-7	Bedoukian	>0.97	0.996
δ-Octanolactone	698-76-0	Bedoukian	0.98[a]	0.989[a,b]
γ-Nonanolactone	104-61-0	Bedoukian	0.98	0.982
γ-Decanolactone	706-14-9	Bedoukian	0.97	0.984
γ-Undecanolactone	104-67-6	SAFC	>0.98	0.984
δ-Undecanolactone	710-04-3	Bedoukian	0.98[a]	0.948[a,c]
γ-Dodecanolactone	2305-05-7	Bedoukian	0.97	0.930
δ-Dodecanolactone	713-95-1	Bedoukian	0.98[a]	0.983[a,d]
Whiskey Lactone isomers	39212-23-2	Aldrich	≥0.98	0.995[e]
Menthalactone isomers	13341-72-5	Aldrich	≥0.99	0.999[f]
Nepetalactone isomers	490-10-8	Dr. Adorable, Inc.	e-Bay	

[a] Sum of isomers [2]
[b] Two isomers: 0.977, 0.023; the minor isomer separated, but was not identified.
[c] Two isomers: 0.928, 0.072; the minor isomer separated, but was not identified.
[d] Two isomers: 0.985, 0.015; the minor isomer separated, but was not identified.
[e] *Trans*-to-*cis* ratio: 0.516 : 0.484. Explanation in section 2.2.2.2. Purity is the sum of the isomers.
[f] (-)-menthalactone to (+)-menthalactone ratio: 93.3 : 6.7. Explanation in sections 2.2.2.3. Purity is the sum of diastereomers.

The whiskey lactone standard purchased from Sigma-Aldrich had a stated purity of ≥0.98 as a mixture of isomers and the menthalactone standard from the same company

had a stated purity of ≥0.99 as a mixture of isomers. The manufacturer, however, doesn't list any specifications for the ratios of these isomers or even identify which stereoisomer is present in the greatest proportion.[3] The identification of these stereoisomers is discussed in section 2.2.2.2 and 2.2.2.3 respectively.

2.1.2. Aldehyde Compounds

The compounds used in the aldehyde study were purchased from commercial sources. Although some were of synthetic origin, it should be noted that several of the aldehydes used are of natural origin. All were GRAS (generally recognized as safe) chemicals that could be used in flavors. Figure 2-3 shows the structural variety of aliphatic aldehydes used in this work and Figure 2-4 shows examples of aromatic aldehydes that were used in this work.

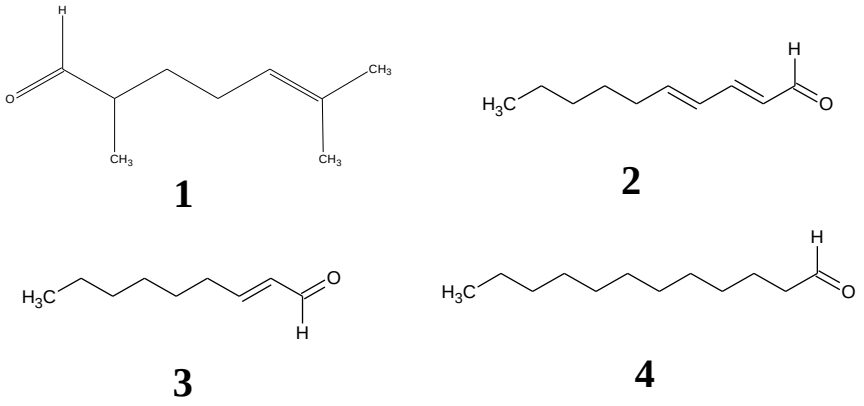

FIGURE 2-3. A sampling of aliphatic aldehydes used for aldehyde study: 2,6-dimethyl-5-heptenal **1**; *trans*,*trans*-2,4-decadienal **2**; *trans*-2-nonenal **3**; lauric aldehyde (dodecanal) **4**.

The ease with which aldehydes may be oxidized by molecular oxygen necessitated special handling. For this study, the samples were stored in the freezer, in the dark, and used unaltered in the analysis. The origin and purity of the standard and

target compounds may be seen in Table 2-2. Several compounds appeared to have lower purity than stated by their manufacturers. This could be due to sample degradation during storage. Although the samples were stored in the freezer and in the dark, they weren't stored under inert gas and some were older samples. The problem seems to be most evident in the straight chain saturated lower molecular weight aldehydes, regardless of manufacturer. However, a couple of the unsaturated aldehydes have the same problem, namely *trans*-2-hexenal and *trans, trans*-2,4-decadienal.

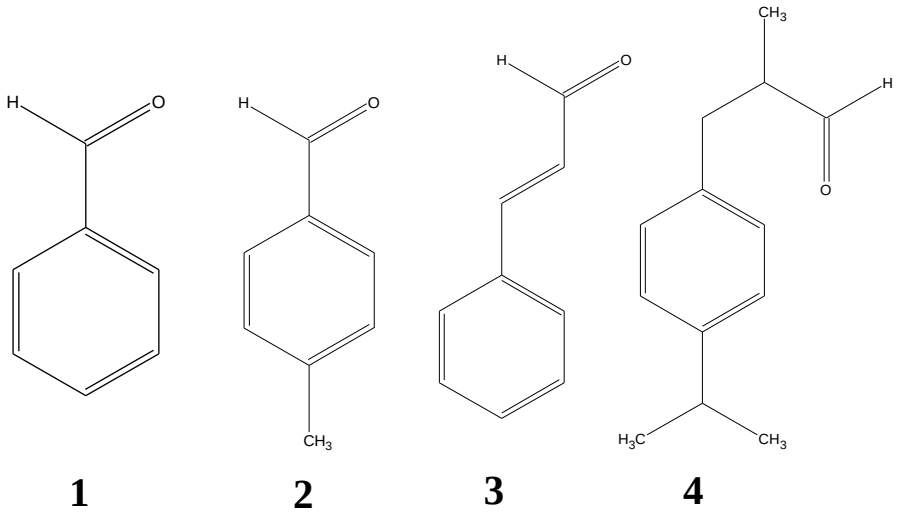

FIGURE 2-4. Select aromatic aldehydes used for aldehyde study: benzaldehyde, **1**; *p*-tolualdehyde (4-methylbenzaldehyde), **2;** *trans*-cinnamaldehyde (*trans*-3-phenylprop-2-enal), **3**; and cyclamen aldehyde (2-methyl-3-(*p*-isopropylphenyl)proprionaldehyde), **4**.

A few of the compounds were sold as a mixture of isomers. Those that separated on the gas chromatography column are noted in Table 2-2. The 2,6-dimethyl-5-heptenal used was of natural origin and contained unidentified isomers that separated. The *trans, cis*-2,6-nonadienal purchased is of synthetic origin with a minor isomer that separated. The manufacturer's specifications indicate the isomer is *trans, trans* in 0.1-7.0%

abundance. The *trans*-2-nonenal purchased is also of synthetic origin with a minor isomer that separated. The manufacturer identified this as the *cis* isomer in 0.1-3.5% abundance. The analysis was accomplished with two standard cocktails as outlined in section 2.2.3.

TABLE 2-2
Origin and purity of aldehyde compounds for this work.

Compound	CAS-registry no	Supplier	Mass Fraction Purity (Supplier)	Mass Fraction Purity (GC)
Hexanal	66-25-1	Advanced Biotech	≥ 0.95	0.899
trans-2-Hexenal	6728-26-3	Bedoukian	≥ 0.98	0.858
Benzaldehyde	100-52-7	SAFC	≥ 0.98	0.978
Octanal	124-13-0	Sigma Aldrich	≥ 0.92	0.727
2,6-Dimethyl-5-heptenal	106-72-9	Advanced Biotech	≥ 0.90[a]	0.833[a]
Nonanal	124-19-6	Advanced Biotech	≥ 0.95	0.837
Tolualdehyde	104-87-0	Sigma Aldrich	≥ 0.97	0.989
trans, cis-2,6-Nonadienal	557-48-2	Bedoukian	≥ 0.96[b]	0.946[b]
trans-2-Nonenal	18829-56-6	Bedoukian	≥ 0.97[c]	0.990[c]
trans-4-Decenal	65405-70-1	Bedoukian	≥ 0.95	0.993
Decanal	112-31-2	SAFC	≥ 0.95	0.857
trans-Cinnamaldehyde	14371-10-9	SAFC	≥ 0.99	0.993
trans, trans-2,4-Decadienal	25152-84-5	Sigma Aldrich	≥ 0.89	0.769
2-Butyl-2-octenal	13019-16-4	Alfrebro	--------	0.932
Lauric aldehyde	112-54-9	Sigma Aldrich	≥ 0.95	1.000
Cyclamen aldehyde	103-95-7	SAFC	≥ 0.90	0.984

[a] Sum of isomers: Isomers separated on column, but they were not identified.
[b] Sum of isomers: 0.0344 and 0.9118. Isomers separated on column, but they were not identified.
[c] Sum of isomers: 0.0707 and 0.9192. Isomers separated on column, but they were not identified.

2.1.3. Profens and Benzoic Acid Compounds

Previously, standard mixtures of alkylbenzoic acids and alkoxybenzoic acids had been used to determine vaporization enthalpies of S (+)-ibuprofen and S (+)-naproxen and both classes of standards seemed to correlate well.[4] However, subsequent work

has suggested that mixed standards may not be appropriate for evaluating the vapor pressure of the profens.[5] The liquid crystal nature of several compounds discussed earlier raises the question of whether they can be used as vapor pressure standards- considering the phase transition enthalpies involved from crystalline solid to liquid crystal phase(s), isotropic liquid and finally to gas phase.

Figure 2-5 shows the diversity of the structures used for the Fenoprofen study. Generally, the profens and benzoic acid derivatives were used as supplied in the free acid form. However, *R,S* Fenoprofen as received was the calcium salt hydrate. It was converted to the free acid, extracted and washed as follows. To a few milligrams of Fenoprofen were added 3 drops of 1N hydrochloric acid to convert the Fenoprofen calcium salt to the free acid. The Fenoprofen free acid precipitated from the solution forming a waxy resin. The resin was dissolved in a minimal amount of methylene chloride. The organic layer was allowed to phase separate from the aqueous layer and the organic layer was collected. This extract was used as the Fenoprofen reference and was subsequently mixed into the standard cocktail with the remaining standards.

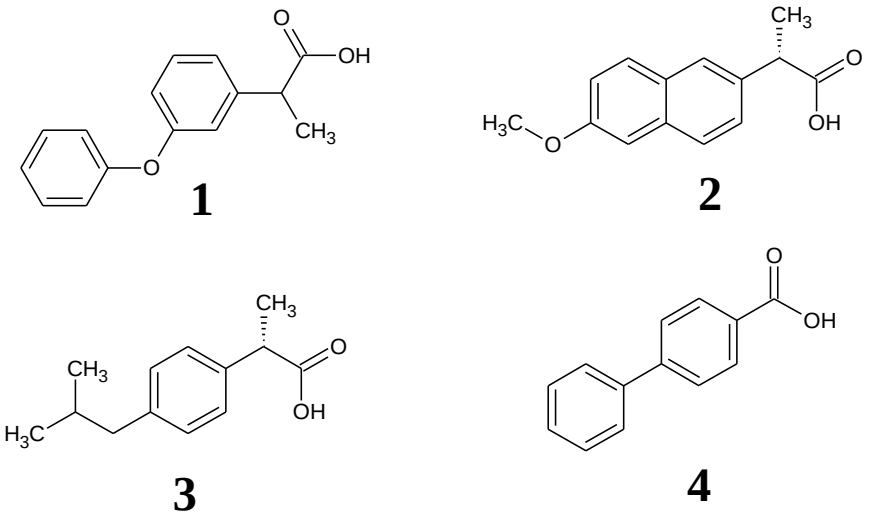

FIGURE 2-5. Some arylpropionic acid and benzoic acid derivatives utilized in the Fenoprofen study. Fenoprofen ((±)-2-(3-phenoxyphenyl)propionic acid) **1**; s-Naproxen ((s)-(+)-2-(6-methoxy-2-naphthyl)propionic acid) **2**; (s)-Ibuprofen ((s)-(+)-2-(4-isobutylphenyl)propionic acid) **3**; biphenyl-4-carboxylic acid **4**.

Figure 2-6 compares the absolute stereoconfigurations of the three analgesics used in the profen study.

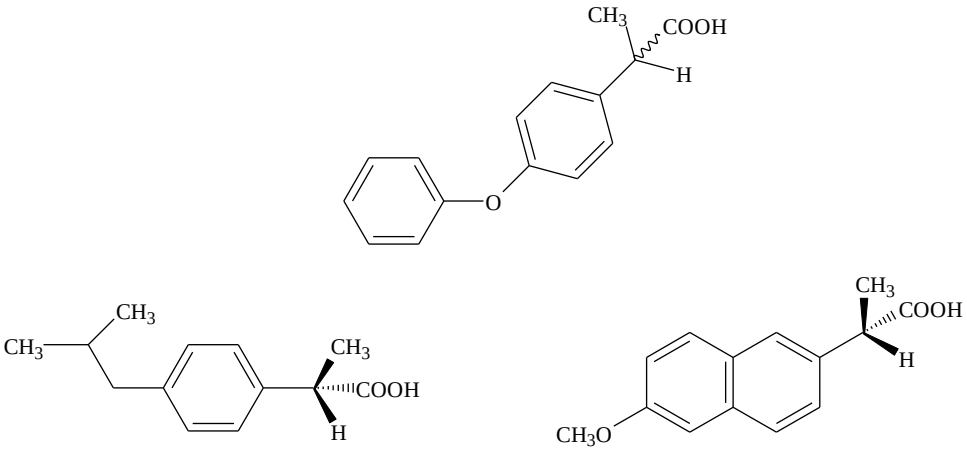

FIGURE 2-6. Top: *R*,*S* Fenoprofen; bottom: *S* ibuprofen, *S* naproxen.

The compounds used in the Fenoprofen study were purchased from commercial sources. The origin and purities of the compounds can be seen in Table 2-3.

TABLE 2-3
Origin and purity of alkyl- and alkoxybenzoic acid compounds originally screened for the Fenoprofen study.

Compound	CAS-registry no	Supplier	Mass Fraction Purity (Supplier)
4-Ethylbenzoic acid	619-64-7	Sigma Aldrich	≥0.99
4-Methoxybenzoic acid	100-09-4	Sigma Aldrich	≥0.99
4-Ethoxybenzoic acid	619-86-3	Sigma Aldrich	≥0.99
(*S*)-Ibuprofen	51146-56-6	Sigma Aldrich	≥0.99
4-Hexylbenzoic acid	21643-38-9	Sigma Aldrich	≥0.99
4-Propoxybenzoic acid	5438-19-7	Sigma Aldrich	≥0.98
4-Hexyloxybenzoic acid	1142-39-8	Alfa Aesar	≥0.98
Biphenyl-4-carboxylic acid	92-92-2	Sigma Aldrich	≥0.95
4-Heptyloxybenzoic acid	15872-42-1	Sigma Aldrich	≥0.98
4-Octylbenzoic acid	3575-31-3	Sigma Aldrich	≥0.99
Flurbiprofen	5104-49-4	Sigma-Aldrich	≥0.99
(R,S)-Fenoprofen·n·H2O; Ca+2 salt	53746-45-5	Sigma-Aldrich	≥0.97
4-Octyloxybenzoic acid	2493-84-7	Sigma Aldrich	≥0.98
(S)-(+)-Naproxen	22204-53-1	Sigma Aldrich	≥0.98

2.1.4. Alcohol Aroma Compounds

The compounds used in the alcohol study were purchased from commercial sources. All of the compounds were used without alteration. The origin and purities of the compounds can be seen in Table 2-4.

TABLE 2-4
Origin and purity of alcohol aroma compounds for the patchouli oil study.

Compound	CAS-registry no	Supplier	Mass Fraction Purity (Supplier)	Mass Fraction Purity (GC)
1-Adamantanol	768-95-6	Aldrich	0.99	1.00
1-Undecanol	112-42-5	Aldrich	0.99	0.96
2-Tetradecanol	4706-81-4	Aldrich	0.98	1.00
Patchouli Oil	----------	bulkapothecary.com	----------	0.36
1-Pentadecanol	629-76-5	Aldrich	0.99	0.99
1-Hexadecanol	36653-82-4	MCB	----------	0.98

The patchouli oil was a natural product that was obtained from Bulk Apothecary.com. The origin of the oil was from Indonesia. The components of the patchouli oil have previously been reported by Restek Corporation who also reported the gas chromatograph of the oil on their website. The identities of the components in patchouli oil were confirmed by GC-MS and they are described in section 2.2.5.1.

Patchouli alcohol was found to be one of the major components of patchouli oil. Conveniently, it eluted last on the GC column used, so extraction of the patchouli alcohol from the mixture was not necessary. Instead, patchouli oil was mixed together with the alcohols listed in Table 2-4. The standards bracketed patchouli alcohol without interference from the nine other major components in patchouli oil.

Figure 2-6 shows the main structural differences in the compounds used in the alcohol study. Most compounds were primary alcohols, one was a secondary, and the target compound and 1-adamantanol are tertiary compounds.

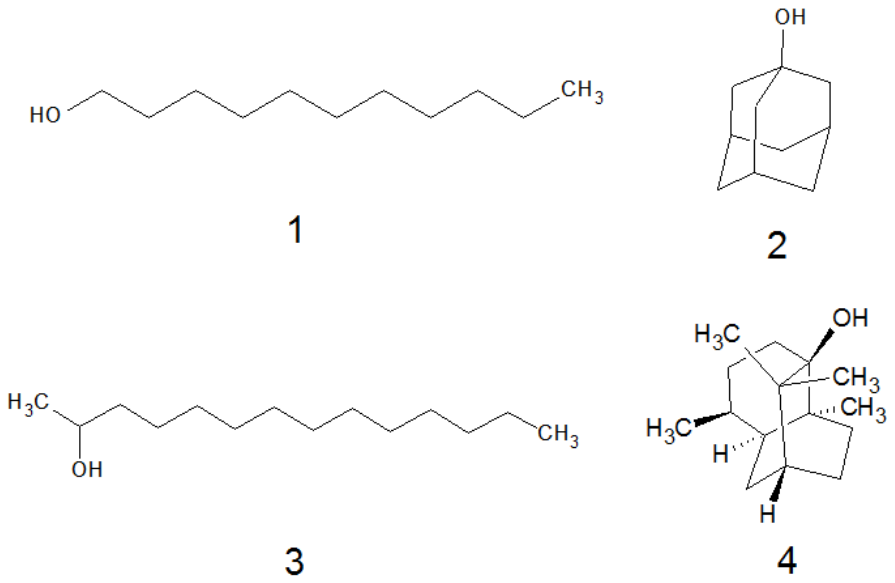

FIGURE 2-6. Compounds used in the alcohol study included primary alcohols such as 1-undecanol **1**, a tertiary alcohol, 1-adamantanol **2**, a secondary alcohol, 2-tetradecanol **3**, and the target compound patchouli alcohol **4**.

2.2. Instrumentation and Methods

2.2.1. General Methods

In general each study followed the same basic methodology. Each compound was diluted individually in an appropriate solvent. The solvent chosen for each group of compounds was chosen for solubility and volatility purposes. In each case, the solvent also functioned as a non-retained standard. Each diluted compound was injected to establish relative retention times at a convenient oven temperature for identification. Additionally, the single compound runs were used to determine compound purity as a way of comparison to the manufacturer's stated values.

After establishing a relative retention time for each compound, the standards and target compounds were combined into a cocktail and analyzed by gas chromatography at various oven temperatures in order to identify an optimal T = 30 K temperature range where the compounds would separate in a reasonable amount of time. Seven isothermal runs at T = 5 K intervals were run continuously to prevent instrumental drift. Oven temperatures were recorded with external digital thermometers purchased from Fluke or Vernier (GoLink!). The temperature was controlled to ±0.1 K by the gas chromatograph.

All gas chromatographic measurements were made on one of three instruments. Each instrument was a Hewlett Packard 5890 of various vintages. All instruments used flame ionization detectors (FID), helium for the carrier gas, and constant head pressures from 5-15psi depending on column length and desired retention times. A split ratio of approximately 100:1 was used for all measurements. Columns were chosen according to the class of compounds and the ability to separate those with similar boiling points. Column lengths used ranged from 10 meters to 30 meters. The exact columns and

conditions used for lactones are described in section 2.2.2, the conditions for aldehydes are described in section 2.2.3, the conditions for profens are described in section 2.2.4., and the conditions for alcohols are described in 2.2.5.

2.2.2. Methods for Lactone Compounds

For the nepetalacone study, each compound was diluted in methylene chloride and injected to establish retention times for each compound at the desired oven temperature for later identification when performing the official standard cocktail runs. Where necessary, compound purity assessment was taken from the single run chromatographs. In many cases, however, the lactone standards purity assessments were taken from previous papers published in the Chickos lab using the same vials of each compound. The results of this assessment can be seen in Table 2-1. The column used was a Supelco 15 m, 0.32 mm inner diameter, 1.0 μm film thickness SPB-5 capillary column. Seven isothermal runs were performed with an oven temperature range of T = 30 K at T = 5 K intervals from 398 – 428 K.[1]

For the whiskey lactone/menthalactone study, each compound was diluted in acetone and injected to establish retention times for each compound at the desired oven temperature for later identification. A Supelco SPB-5 15 m column with 0.32 mm inner diameter and 1.0 μm film thickness was also used for this analysis at a constant head pressure of 7.0 psi. The injector and detector were set to T = 473.15 K. Seven isothermal runs were performed with an oven temperature range of T = 30 K at T = 5 K intervals from 404 – 434 K.[3]

2.2.2.1. Identification of Nepetalactone Diastereomers

The nepetalactone diastereomers were identified by GC-MS and their structures were assigned based on their relative abundance as previously reported.[6] The instrument used was a Hewlett Packard GC/MS System Model 5698A. The GC portion was fitted with a Supelco SLBTM-5 MS capillary column (30 m x 0.25 mm; 0.5 μm film thickness). Helium was used for the carrier gas at an oven temperature of 298K. The mass spectrum was obtained by electron impact (EI) at 70 eV. Shafaghat and Oji noted that the nepetalactone diastereomers have a slightly longer retention time than dodecane.[7] Therefore, a small amount of dodecane was spiked into the catnip extract described in section 2.1.1. The dodecane peak was used as a reference on the chromatogram. Peaks that eluted after dodecane were analyzed by MS. Two of them were found to be the nepetalactones by comparing their mass spectra to the NIST library. The comparisons may be seen in section 3.1.1. Since the NIST library doesn't specify stereochemistry, the relative abundancies on the gas chromatograms were compared to the published ratios for structural identification.[1, 6] Caryophyllene appeared to be the only other material to elute after the nepetalactones.

2.2.2.2. Identification of cis/trans Whiskey Lactone Diastereomers

The whiskey lactone diastereomers present in the standard sample from Sigma-Aldrich were identified by GC peak area and relative retention order as compared to results published by Lahne. The referenced results indicated a slight excess (52.2%) of the *trans* isomer which eluted first on a DB-5 column with similar composition to the one used for this work.[8] The peak areas calculated for this work consist of the averages of

fourteen runs and can be seen in the Appendix Tables S3A and S3B. This work finds the first eluting peak to have a slight excess of (51.6% ± 0.5%, average of 14 runs), which is in good agreement with Lahne.[3]

2.2.2.3. Identification of cis/trans Menthalactone Diastereomers

Identification of the menthalactone diastereomers was accomplished by comparing GC peak areas to abundances found in literature. The natural abundance of mint lactone is 10:1 in favor of the (-)-mintlactone as compared to (+)-isomintlactone in peppermint oil. One synthetic pathway shows an abundance of 96:4, again in favor of (-)-mintlactone.[9] The 96:4 ratio compares favorably to the 93.3:6.7 average ratio observed in this study.[3] This data is presented in Appendix Tables S3C and S3D.

The rotational data for (-)-mintlactone and (+)-isomintlactone found in literature were also used to verify the correct assignment. (-)-mintlactone has a rotation of $[\alpha]_D^{20}$= -51.8° and (+)-isomintlactone has a rotation of $[\alpha]_D^{25}$= +76.9°.[9] The sample from Sigma-Aldrich was measured to be $[\alpha]_D^{20}$= -35°, again suggesting that (-)-mintlactone is in excess. Since the experimental conditions of the rotation measurements of both the Aldrich sample and the literature value are unknown, the optical purity of the Sigma-Aldrich standard could not be determined with certainty. In light of this, the enthalpies of vaporization and vapor pressures calculated for (-)-mintlactone and (+)-isomintlactone are expressed as the sums of their respective racemic mixtures.[3]

2.2.3. Methods for Aldehyde Compounds

For the aldehyde study, each compound was dissolved in methylene chloride and injected to establish retention times for each compound at the desired oven temperature. The results of this assessment can be seen in Table 2-2. The aldehyde runs were accomplished with two sets of two runs, utilizing data from the first set of runs to establish standard values for 2,6-dimethyl-5-heptenal. Then 2,6-dimethyl-5-heptenal was used as a standard in the second set of runs. An explanation of standards and target analytes for the aldehyde runs can be found in Table 2-4. All of the correlation gas chromatography (CGC) measurements were taken at a constant head pressure of 11psi on a J&W Scientific DB-5 30 m column with 0.53mm ID and 1.5μm film thickness at an oven temperature range of 358 – 388 K for cocktail 1 and 398 – 428 K for cocktail 2 as seen in Table 2-5.

TABLE 2-5
A summary of the compounds in each standard cocktail in order of elution on the J&W Scientific DB-5 column. Dichloromethane was used as the solvent.

Compound	Standard Cocktail 1 (T= 358 K to 388 K)	Standard Cocktail 2 (T= 398 K to 428 K)
Hexanal	Standard	Standard
trans-2-Hexenal	Target Analyte	----------
Octanal	Standard	----------
2,6-Dimethyl-5-heptenal	Target Analyte	Standard
Nonanal	Standard	----------
trans, cis-2,6-Nonadienal	Target Analyte	----------
trans-2-Nonenal	----------	Target Analyte
trans-4-Decenal	Standard	----------
Decanal	Standard	Standard
trans, trans-2,4-Decadienal	----------	Target Analyte
2-Butyl-2-octenal	----------	Target Analyte
Lauric aldehyde	----------	Target Analyte

2.2.4. Methods for Profen Compounds

It proved to be difficult to find a solvent that would work for all of the profen compounds. Namely, 4-biphenyl carboxylic acid was relatively insoluble in many solvents. DMSO and THF were found to work for this compound and THF was chosen as the safer alternative. Several of the other compounds were insoluble in THF, so a mixed solvent system was used. Therefore, each compound was dissolved in a mixture of methylene chloride/tetrahydrofuran and injected to establish retention times for each compound. Under these conditions methylene chloride and tetrahydrofuran co-elute and thus the retention time adjustments were still from a single peak.

Some selected standards were not able to be easily separated from the others. An example was flurbiprofen which did not separate from Fenoprofen. In order to get adequate resolution, the standards were split into two separate cocktails. Fenoprofen, for instance, could not be separated from 4-heptyloxybenzoic acid. Furthermore, naproxen was not able to be separated from 4-octyloxybenzoic acid. The standards that were eventually used in the calculation of vaporization enthalpy data are given in Table 2-6.

Three different columns were tried on the profen compounds due to the difficulty in obtaining good peak shapes. The first column tried was a 12m Supelco SPB-1 0.22mm ID and 0.33μm film thickness at 5psi head pressure. The SPB-1 column did not prove to give very reproducible peak shapes. The peaks for the later eluting compounds were very broad, and as a result the retention times weren't always consistent. The second column was a 15m 0.25mm ID J&W FFAP column run at 10psi head pressure. The elution order of the compounds changed from one column to the next. On the SPB-1 column 4-ethoxybenzoic acid elutes before ibuprofen, however, on the FFAP column

ibuprofen elutes before 4-ethoxybenzoic acid. Finally, the column that gave the best peak shapes was a 0.25mm inner diameter 30m DB-5MS at 11psi head pressure. The DB-5MS column stationary phase composition is 5% phenyl, 95% dimethyl arylene siloxane. The DB-5MS column afforded much sharper peaks and as a result it was possible to separate 4-octylbenzoic acid, Fenoprofen, and naproxen. On the DB-5MS, seven isothermal runs were performed for each standard cocktail at an oven temperature range of 464 - 494 K for Standard Cocktails 1 &2, and 480 – 510 K for Standard Cocktail 3. The injector and detector temperature were set at 573 K for each run.

TABLE 2-6
A summary of the profen compounds in each standard cocktail in order of elution (at T = 480K) on the DB-5MS column. A mixture of dichloromethane and tetrahydrofuran was used as the solvent.

Compound	Standard Cocktail 1 (T= 464 - 494 K)	Standard Cocktail 2 (T= 464 - 494 K)	Standard Cocktail 3 (T= 480 - 510 K)
4-Ethylbenzoic acid	----------	----------	Standard
4-Methoxybenzoic acid	Standard	Standard	Standard[a]
4-Ethoxybenzoic acid	Standard	Standard	Standard[a]
(s)-Ibuprofen	----------	----------	Target Analyte
4-Propoxybenzoic acid	Standard[a]	Standard[a]	----------
4-Hexylbenzoic acid	----------	----------	Standard
α-Naphthaleneacetic acid	----------	----------	Target Analyte [a]
4-Hexyloxybenzoic acid	Standard	Standard	----------
Biphenyl-4-carboxylic acid	----------	----------	Standard
4-Heptyloxybenzoic acid	----------	Standard	----------
4-Octylbenzoic acid	----------	----------	Standard
Fenoprofen	Target Analyte	----------	Target Analyte
4-Octyloxybenzoic acid	Standard	----------	----------
(s)-Naproxen	----------	Target Analyte	Target Analyte

[a]This compound was in the standard cocktail, but the data has been omitted from calculations due to poor fit.

2.2.5. Methods for Alcohol Compounds

For the alcohol study, each compound was dissolved in methylene chloride and injected to establish retention times for each compound at the desired oven temperature. Compound purity assessment was taken from the single run chromatographs. The results of this assessment can be seen in Table 2-4. All of the correlation gas chromatography

(CGC) measurements were at a constant head pressure of 7.0psi. The column was a Supelco 15 m, 0.32 mm inner diameter, 1.0 μm film thickness SPB-5 capillary column. Seven isothermal runs were performed at an oven temperature range of 419 - 449 K.

2.2.5.1. Identification of Compounds Present in Patchouli Oil

The compounds present in the patchouli oil sample were identified by GC-MS and their structures were assigned based on their mass spectra. The instrument used was a Hewlett Packard GC/MS System Model 5698A. The GC portion was fitted with a HP-1 Ultra capillary column (12 m x 0.20 mm; 0.33 μm film thickness). Helium was used for the carrier gas with an isothermal oven program at 413K. The mass spectrum was obtained by electron impact (EI) at 50eV. A lower than normal impact voltage was used to produce fewer fragments in an aging instrument. This allowed better agreement with NIST library structures. Positive identification of nine compounds was made in the GC/MS spectra. The most predominant included patchouli alcohol, δ-guaiene, α-guaiene, seychellene, and α-patchoulene. The compound identification results were compared to those that were published by Restek, which used a different column (Rtx-5; 10m 0.1mm ID, 0.1μm film thickness). The work by Restek was performed with a temperature ramp of 30K/min. Since the elution order is slightly different between the Rtx-5 column and the HP-1 Ultra column, the gas chromatogram peak areas were used to compare each compound to its counterpart on the other instrument. The compound identifications from this work were found to be in good agreement with the ones published by Restek. A summary of the compounds found in the patchouli oil sample is found in Section 3.4.1.

2.3. Calculations

2.3.1. Enthalpy of Vaporization

The calculations used for this study were adapted from those previously reported by Chickos.[10] To measure the time each analyte spends on the column, the retention time of the non-retained reference was subtracted from the retention time of each analyte to give the adjusted retention time, t_a. The time each analyte spends on the column is inversely proportional to the analyte's vapor pressure off the column. The adjusted retention time, reference time, t_0 = 60 s, and oven temperature, T, were then used to plot $\ln(t_0/t_a)$ vs $1/T$ for each analyte. The resulting plots were linear with $r^2 > 0.99$ in all cases. The actual r^2 values for each plot can be found in the data tables of Chapter 3. The slopes of those plots give rise to the following relationship seen in Eq (1), where $\Delta H_{trn}(T_m)$ is the enthalpy of transfer of the analyte from the column, at the mean temperature (T_m) of the T = 30K range to the gas phase. R is the gas law constant, 8.3145 $J \cdot mol^{-1} \cdot K^{-1}$.

$$-slope = \Delta H_{trn}(T_m)/R \quad (1)$$

It is interesting to note that occasionally two compounds will change elution order over the T = 30 K temperature range. This change of elution order is due to the fact that the compounds have different enthalpies of transfer on the column as evidenced by the differing slopes of the $\ln(t_o/t_a)$ vs $1/T$ plots. Since the slopes are different the lines must intersect at some point if the lines were extended indefinitely. Sometimes this happens to be within the range tested. Although this doesn't occur frequently, it is not completely uncommon and by comparing CGC generated vaporization enthalpies and vapor pressures with literature values the change in elution order does not seem to significantly affect the results. Likewise, if the two compounds changing elution order overlap at one

particular temperature the same peak can be used for the calculations in both compounds and it appears that the relationships are still linear and agree with literature data.

The enthalpy of transfer is related to the enthalpy of vaporization, $\Delta_l^g H(T_m)$, and the interaction enthalpy of analyte with the column, $\Delta H_{intr}(T_m)$, by Eq (2).

$$\Delta H_{trn}(T_m) = \Delta_l^g H(T_m) + \Delta H_{intr}(T_m) \quad (2)$$

The interaction enthalpy of the analyte with the column generally is much smaller than the enthalpy of vaporization, so the approximation may be made that $\Delta H_{trn}(T_m) \approx \Delta_l^g H(T_m)$ and $\Delta H_{intr}(T_m)$ is ignored.

A second plot of vaporization enthalpy of the standards versus their enthalpy of transfer is also found to be linear. The equation of this line combined with the experimentally determined enthalpy of transfer of the targets provides their vaporization enthalpy.

2.3.2. Vapor pressure

If the vapor pressure of the standards are available, plots of $\ln(p/p°)$ of the standards, where $p°$ = 101325 Pa, against $\ln(t_o/t_a)$ also results in a linear relationship. The equation of this line combined with $\ln(t_o/t_a)$ of the targets provides a measure of their vapor pressure. This correlation appears to remain linear over a range of temperatures.

2.3.2.1. Lactone Vapor pressures

Thermochemical properties for some of the lactone standards were available in the literature as seen in Table 2-7. Vapor pressures were calculated using equations (3) and (4). These equations were determined to be the best fit for the compounds by their

respective authors. Those compounds which have values for A, B, and C use equation (3) to calculate vapor pressure and those which have values for A ' and B ' use equation (4) to calculate vapor pressure.

$$\ln(p/\text{Pa}) = [\text{A} - \text{B}/T(\text{K}) - \text{C}\cdot\ln(T/(\text{K})/298.15)]/\text{R} \quad (3)$$

$$\ln(p/p_o) = \text{A'} - \text{B'}/T \quad (4)$$

The references in Table 2-7 explain the experimental methods and calculations used to arrive at the stated values. The literature data for the compounds were taken at various temperature ranges as shown in the last column of Table 2-7. In order to calculate the vapor pressures at a standard temperature of T = 298 K temperature adjustments were made as described in section 2.3.3.

TABLE 2-7

Thermochemical properties of the γ and δ lactones used as standards for the lactone studies.

	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}	A	B	C	T/K(range)
γ-Hexanolactone[a]	57.2±0.3	281.5	76317.1	64.3	283-353
δ-Octanolactone[b]	67.0±0.2	310.7	90681.9	79.3	288-353
γ-Nonanolactone[a]	70.3±0.3	325.1	96899.9	89.2	296-363
γ-Decanolactone[a]	75.6±0.3	342.0	104666.1	97.5	298-365
		A'	B'		
γ-Octanolactone[c]	66.1±0.5	15.32	7693.9		298-350
γ-Undecanolactone[c]	79.3±0.6	17.21	9204.7		298-350
δ-Undecanolactone[c]	79.8±0.6	17.23	9276.0		298-350
γ-Dodecanolactone[c]	83.7±0.6	17.85	9709.0		298-350
δ-Dodecanolactone[c]	84.2±0.6	17.87	9782.3		298-350

[a] Reference [11]
[b] Reference [12]
[c] Reference [13]

2.3.2.2. Profen Vapor pressures

For the Fenoprofen study, the vapor pressures of the solid standards were needed at the temperature where solid and liquid vapor pressures converge. For compounds that do not form liquid crystals this is the triple point, which was approximated as the fusion temperature. For those that formed liquid crystals, the temperature needed is the clearing temperature. Since the heat capacity of the isotropic liquid phase is reasonably close to the heat capacities of the smectic and nematic phases for liquid crystal forming compounds, the transition temperature at the lower of the two phases was chosen to approximate the clearing temperature. The reason this is thought to be a good approximation is that it is assumed the change in heat capacity as the liquid crystal reaches clearing temperature will cancel when the isotropic liquid cools back to the liquid crystal phase if all of the heat capacities of these phases are similar.[14]

Sub-cooled vapor pressures were calculated using modified Clausius-Clapeyron equations (5A) for liquids and (5B) for solids. The modification is a heat capacity correction which allows the vaporization enthalpy temperature to be adjusted to T = 298.15 K. The liquid heat capacity correction, eq (5A) has not been applied this way before. However, the solid heat capacity adjustment has been used before for calculating sublimation vapor pressures and found to reproduce experimental values within a factor of three.[10, 14] This liquid heat capacity correction would seem to have a similar degree of accuracy due to the strong agreement between calculated results using this method and literature results for ibuprofen as seen in section 3.3.

$$\ln(p/p^{o}) = -[\Delta_{l}^{g}H_{m}(T_{m}) + \Delta Cp\cdot\Delta T/2][1/T - 1/T_{fus}]/R + \ln(p/p^{o})_{T_{fus}} \quad (5)$$

$$\text{for liquids: } \Delta Cp(l)\cdot\Delta T = (10.58 + 0.26\cdot Cp(l))\cdot(T_{fus} - T) \quad (A)$$

for solids: $\Delta Cp(\mathrm{cr})\cdot\Delta T = (0.75 + 0.15\cdot Cp(\mathrm{cr}))\cdot(T_{\mathrm{fus}} - T)$ (B)

2.3.3. Temperature Corrections

Some standards (those in the profen study, for instance) are solid at T = 298.15 K. In order to calculate the vaporization enthalpy for the solids using equation (6) at T = 298.15 K, the sublimation and fusion enthalpies had to be adjusted to that temperature, using equations (7) and (8).[15] Equation (9) was used to adjust the enthalpy of vaporization to T = 298.15 K. C_p(l) is the heat capacity of the liquid and C_p(cr) is the heat capacity of the crystal. Since these values were not readily available, they were estimated using a group additivity approach[16] as described in section 2.3.4. Temperature corrections were also required to complete the vapor pressure calculations at the standard temperature.

$$\Delta_l^g H_{\mathrm{m}}(298.15\ \mathrm{K})/(\mathrm{kJ\cdot mol^{-1}}) = \Delta_{cr}^g H_{\mathrm{m}}(298.15\ \mathrm{K})/(\mathrm{kJ\cdot mol^{-1}}) - \Delta_{cr}^l H_{\mathrm{m}}(298.15\ \mathrm{K})/(\mathrm{kJ\cdot mol^{-1}}) \quad (6)$$

$$\Delta_{cr}^g H_{\mathrm{m}}(T/\mathrm{K})/(\mathrm{kJ\cdot mol^{-1}}) = \Delta_{cr}^g H_{\mathrm{m}}(T_{\mathrm{m}})/(\mathrm{kJ\cdot mol^{-1}}) + [(0.75 + 0.15\cdot C_p(\mathrm{cr})/(\mathrm{J\cdot K^{-1}\cdot mol^{-1}}))(T_{\mathrm{m}}/\mathrm{K} - T/\mathrm{K})]/1000 \quad (7)$$

$$\Delta_{cr}^l H_{\mathrm{m}}(298.15\ \mathrm{K})/(\mathrm{kJ\cdot mol^{-1}}) = \Delta_{cr}^l H_{\mathrm{m}}(T_{\mathrm{fus}})/(\mathrm{kJ\cdot mol^{-1}}) + [(0.15\cdot Cp(\mathrm{cr}) - 0.26\cdot C_p(\mathrm{l}))/(\mathrm{J\cdot mol^{-1}\cdot K^{-1}}) - 9.83)]\,[T_{\mathrm{fus}}/\mathrm{K} - 298.15]/1000 \quad (8)$$

$$\Delta_l^g H_{\mathrm{m}}(298.15\ \mathrm{K})/(\mathrm{kJ\cdot mol^{-1}}) = \Delta_l^g H_{\mathrm{m}}(T_{\mathrm{m}})/(\mathrm{kJ\cdot mol^{-1}}) + [(10.58 + 0.26\cdot C_p(\mathrm{l})/(\mathrm{J\cdot K^{-1}\cdot mol^{-1}}))(T_{\mathrm{m}}/\mathrm{K} - 298.15)]/1000 \quad (9)$$

Although these equations are generally used to correct temperatures to T = 298.15 K, they appear to give satisfactory results between approximately T = 250 K to T = 500 K. In this

range there is an uncertainty of 16 $J \cdot mol^{-1}$ associated with the bracketed term in eq (9).[15]

2.3.4. Group Additivity Approach for Estimating Heat Capacity

As noted above, equations (7), (8), and (9) require heat capacity corrections for the liquid and crystalline phases. Although heat capacity is sometimes ignored in estimating enthalpies of vaporiation or sublimation, Chickos, Hesse, and Liebman have found the error associated with the corrections to be less than estimations that do not include the heat capacity correction. They have provided a simple way to estimate the heat capacities of compounds which do not have experimental data available. This method involves adding together the group values for each carbon and functional group in the molecule. Group values are from literature.[16] An example can be seen using the data from Table 2-8 to estimate the heat capacity of whiskey lactone.

TABLE 2-8
Estimation of heat Capacities

Group Values (Γ) $J \cdot K^{-1} \cdot mol^{-1}$		Γ(l)	Γ(cr)
Cyclic secondary sp^3 carbon	**-C_cH_2-**	25.9	24.6
Cyclic tertiary sp^3 carbon	**-C_cH**(R)-	20.6	11.7
Cyclic quaternary sp^2 carbon	=**C_c**(R)-	21.2	4.7
Primary sp^3 C	**CH_3**-R	34.9	36.6
Lactone	***R*-[C(=O)O]$_c$-*R***	67.4	45.2

C_p (l) = 3*(25.9) + 2*(20.6) + 2*(21.2) + 2*(34.9) + (67.4) = 298.5 $J \cdot K^{-1} \cdot mol^{-1}$

C_p(cr) = 3*(24.6) + 2*(11.7) + 2*(4.7) + 2*(36.6) + (45.2) = 225 $J \cdot K^{-1} \cdot mol^{-1}$

2.3.5. Estimation of Vaporization Enthalpy

The target compounds of these studies did not have literature values available for vaporization enthalpies. In the case of whiskey lactone, it was possible to use a group

additivity approach to estimate the vaporization enthalpy. The estimated value was then compared to the experimental value. This calculation is based on the work of Emel'yanenko et al.[11], using the parent lactone, γ-butyrolactone. Each additional functional group is associated with a positive or negative enthalpy contribution and is added successively.[3] A more complete explanation of the process can be seen in Figure 2-7.

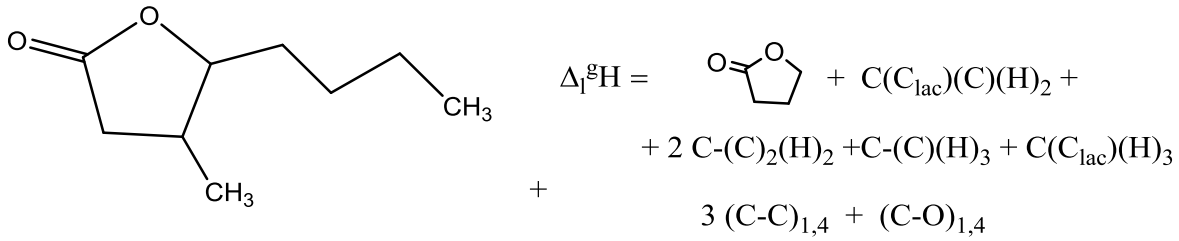

FIGURE 2-7. Estimation of whiskey lactone comprises of the vaporization enthalpy of γ-butyrolactone (53.9 kJ·mol^{-1}), the contribution of the methylene group adjacent to the lactone (-0.67 kJ·mol^{-1}), the contribution of two methylene groups (4.52/CH_2 kJ·mol^{-1}), two methyl groups , one on the butyl chain (6.33 kJ·mol^{-1}), and one adjacent to the lactone ring (1.11 kJ·mol^{-1}). Two non-bonded 1,4 C-C interactions are also included, two involving the butyl chain with carbon (0.26 kJ·mol^{-1} each) and one 1,4 interaction involving carbon with the oxygen atom (-3.26 kJ·mol^{-1}).

2.3.6. Estimation of Fusion and Sublimation Enthalpies for Lactones

Literature values for the fusion and sublimation enthalpies of isomintlactone were not available. Therefore, they were estimated. The fusion enthalpy, for instance, was taken as the product of the fusion temperature, T_{fus}, and the total phase change entropy, $\Delta_{tpch}S$. For isomintlactone, T_{fus} = 353K.[17] $\Delta_{tpch}S$ is not known, but is estimated by using a group additivity approach. First, entropy of the bicyclic backbone is calculated using the formula shown in Figure 2-8. Then it is adjusted with corrections for each

functional group. The bicyclic backbone used for isomintlactone is shown is Figure 2-8 and Table 2-9 shows the temperature adjustments.[3]

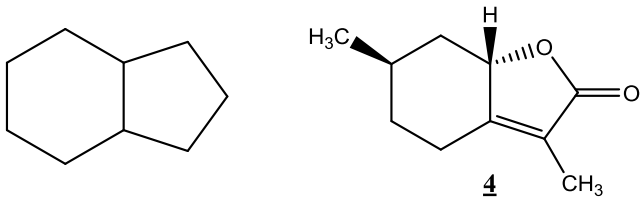

FIGURE 2-8. Polycyclic hydrocarbon ring systems: $\Delta_{tpce}S$ (ring) = [(33.4)R + 3.7(N-3R)] where R = number of rings and N = total number of ring atoms.

TABLE 2-9

Fusion Enthalpy Adjustments

Cyclic tertiary sp^3 carbon	**-C_cH**(R)-	-14.7
Cyclic quaternary sp^2 carbon	=**C_c**(R)-	-12.3
Primary sp^3 C	**CH_3**-R	17.6
Lactone	*R*-**[C(=O)O]$_c$**-*R*	3.1

The calculation: [(33.4)2 + 3.7(9-6)] + 3.1 -2*14.7 - 2*12.3 + 2*17.6 = (62.2±18.6) J·K·mol^{-1}

$\Delta_{cr}{}^{l}H$ (298.15 K)/(kJ·mol^{-1}) = [(62.2±18.6) J·K·mol^{-1}][353K]/1000 J/kJ = (22±6.5) kJ·mol^{-1}

2.3.7. Clarke and Glew Equation for Sublimation Vapor Pressures

The Clarke and Glew equation[18], eq (10), was used to calculate the sublimation vapor pressure of the solid standards and unknowns in the profen study. R is the molar gas constant, p^o = 10^5 Pa, p is the vapor pressure at temperature T, $\Delta_{cr}^{g}H_m$ is the sublimation enthalpy, $\Delta_{cr}^{g}G_m$ is the Gibbs free energy of sublimation, $\Delta_{cr}^{g}C_p$ is the heat capacity adjustment from the solid to gas phase, and θ is the temperature at which the vapor pressure is to be calculated. For this calculation, temperatures are all adjusted to θ = 298.15 K.[19, 20]

The parameters used for the standards may be seen in Table 2-10.[14]

$$R\cdot\ln(p/p^{o}) = \Delta_{cr}^{g}H_{m}(\theta)\cdot(1/\theta - 1/T) - \Delta_{cr}^{g}G_{m}(\theta)/\theta + \Delta_{cr}^{g}C_{p}(\theta)\cdot[\theta/T - 1 + \ln(T/\theta)] \quad (10)$$

TABLE 2-10

Parameters of the Clarke and Glew Equation Used, p^{o}/Pa = 10^{5}, θ/K = 298.15 [a]

Compound	$\Delta_{cr}^{g}H_{m}(\theta)$ kJ·mol^{-1}	$\Delta_{cr}^{g}G_{m}(\theta)$ kJ·mol^{-1}	$\Delta_{cr}^{g}Cp$ J·mol^{-1}·K^{-1}	$\Delta_{cr}^{g}H_{m}(T_{m}/K)$ [b] kJ·mol^{-1}
4-Ethylbenzoic acid	100.6±0.7	39.6±0.1	-40±11	99.3±0.5 (328.5)
4-Methoxybenzoic acid	112.6±0.6	48.1±0.1	-28±11	110.6±0.3 (351.3)
4-Ethoxybenzoic acid	121.9±1.0	52.5±0.1	-40±11	119.4±0.5 (361.2
4-Hexylbenzoic acid	122.3±0.9	50.4±0.1	-43±11	119.9±0.7 (355.1)
4-Hexyloxybenzoic acid	139.4±0.9	57.7±0.1	-36±11	130.8±0.4 (371.2)
4-Heptyloxybenzoic acid	157.2±1.2	62.5±0.2	-35±11	155.1±1.0 (358.3)
4-Octylbenzoic acid	133.3±1.6	56.3±0.3	-41±11	130.7±1.3 (361.2)
4-Octyloxybenzoic acid	161.4±1.2	64.8±0.2	-34±11	141.1±0.9 (367.8)

[a] Refs [19, 20]
[b] Sublimation enthalpy at the mean temperature of measurement.

2.3.8. Sublimation, Fusion, and Vaporization Enthalpies of Profen Standards

As an internal check, all sublimation enthalpies of the profen compounds with literature values were also calculated from the Clarke and Glew equation in 2.3.7.[19, 20]

Five compounds (4-hexylbenzoic acid, 4-hexyloxybenzoic acid, 4-heptyloxybenzoic acid, 4-octylbenzoic acid, 4-octyloxybenzoic acid) have cr – cr phase transitions below the oven temperatures used in this work. However, only the 3 alkoxy compounds were used as standards for later vaporization enthalpy calculations from the curves. This is discussed in section 3.3. Those enthalpies are included in their sublimation enthalpies at T/K =298.15. For comparison, temperature adjustments were also evaluated using equation (7) and compared to values from the Clarke and Glew

equation in Table 3-12 (Section 3.3). Comparisons between the two sublimation enthalpies calculated by eq (7) and the Clarke and Glew eq are within experimental error of each other also demonstrating the applicability of using eq (7) in this system as described in section 3.3. [14]

Equation (8) was used to adjust literature fusion enthalpies to T = 298.15 K to account for differences in heat capacity of the liquid vs. the solid. For the profens that were prone to form liquid crystals, this required an approximation. The $\Delta_{cr}^{l}H$ measurement for solid to isotropic liquid must include all enthalpy changes from cr – cr phase transitions. The assumption was made that the heat capacity of the liquid crystal regardless of its nature was approximately equal to that of the liquid phase. The heat capacity adjustment was therefore applied to the lowest liquid crystal phase transition temperature regardless of whether it was a smectic or nematic phase.[14]

2.3.9. Estimation of Error

Data processing was done in Microsoft Excel with the LINEST() function used to calculate the slopes, intercepts, and error associated with each best fit linear equation. The error expressed in the data tables in Chapter 3 are one standard deviation as recommended by the Guide to Expression of Uncertainty in Measurement.[21] Since the enthalpy of transfer is a function of the slope and gas law constant, R, the error for the enthalpy of transfer was calculated as the error in the slope times R. Error for enthalpy of vaporization must include the error in both the slope and intercept and therefore is calculated by Eq. (11), where u_1 is the error in the slope times the enthalpy of transfer and u_2 is the error in the intercept. Although standards bracketed the unknown retention

times, the confidence intervals were not adjusted for unknown values at the ends of the curve where uncertainty is potentially higher.

$$\sqrt{{u_1}^2 + {u_2}^2} \tag{11}$$

The error calculated from logarithmic values is reported as the average of the combined errors. If the average was larger than the measurement, the smaller of the two values was used. For the calculation of error in vapor pressure values, the error of each coefficient in the correlation equation was calculated at each temperature.[3]

The standard deviation associated with temperature adjustments for sublimation and fusion enthalpies has been estimated as 30% of the total adjustment.[16, 22] A standard deviation of ± 16 $J \cdot K^{-1} \cdot mol^{-1}$ is associated with estimates of $C_p(l)$.

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Chapter 3: Results and Discussion

3.1. Lactones

3.1.1. Oil of Catnip (Nepetalactone)

The oil of catnip sample received was a product of natural extraction, containing a mixture of compounds. Prior to measuring the enthalpy of vaporization or vapor pressure some preliminary characterization was performed. Initially, an IR spectrum was taken as shown in Figure 3-1. The large –OH stretch is likely due to the presence of an alcohol or glycol carrier. For this reason, the catnip sample was prepared as discussed in section 2.1.1 for use in the remaining experiments. Therefore, only the less-polar compounds are described below.[1]

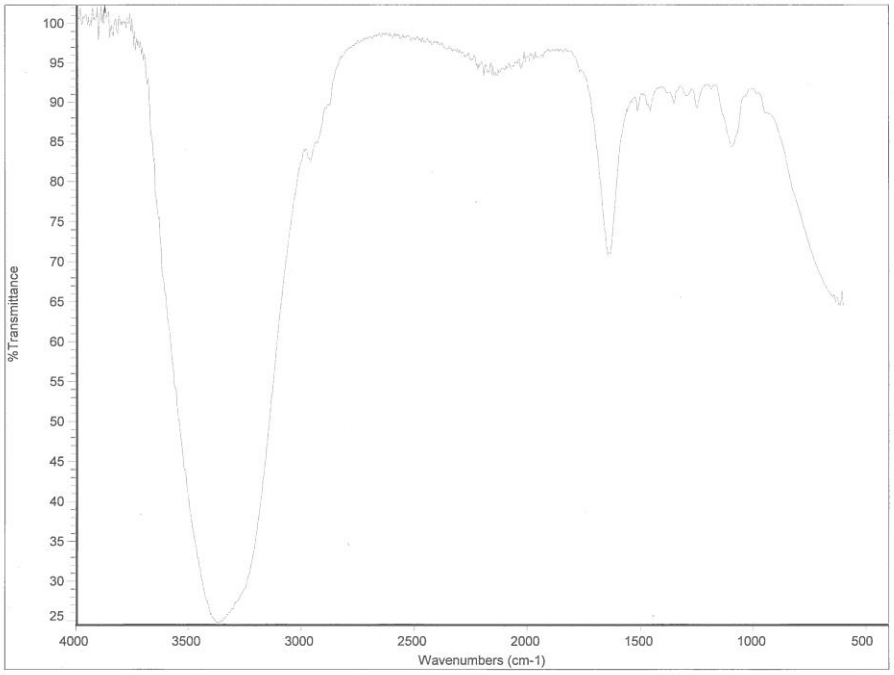

FIGURE 3-1. IR spectrum of the commercial catnip oil sample.

GC-MS spectra were acquired[(1)] and the oil was found to contain both major and minor nepetalactone isomers as well as caryophellene. Dodecane was added as an internal reference for ease of identification since it was anticipated that the natural product contained numerous other materials.[2] Such was not the case. Figure 3-2 shows the GC portion of this experiment and illustrates the large difference in abundance of the major (4aS,7S,7aR) and minor (4aS,7S,7aS) isomers of nepetalactone.[1]

[(1)]The author thanks Chase Gobble for his time and effort in collection of the nepetalactone GC-MS spectra.

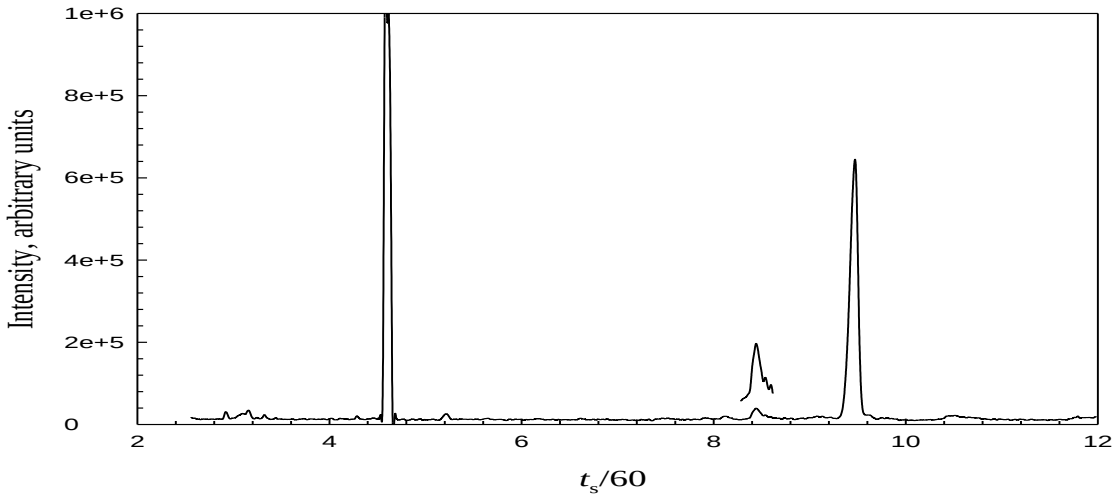

FIGURE 3-2. GC trace using total ion current detection. Retention times: 4.6min, dodecane standard; 8.46min, (4aS,7S,7aS)-nepetalactone; 9.46min, (4aS,7S,7aR)-nepetalactone; caryophyllene not shown.

Some sample mass spectra of the nepetalactone isomers are shown in Figure 3-3 (minor; 4aS,7S,7aS) and Figure 3-4 (major; 4aS,7S,7aR). The spectra were compared to those from the NIST library in order to confirm assignments.[1] It should be noted, however, that the fragmentation patterns of each diastereomer are quite similar. In fact, the NIST library doesn't specify stereochemistry on their mass spectra. Furthermore, Pettersson, *et al.* note that it is not possible to assign nepetalactone stereochemistry based

solely on mass specta.[3] Therefore, the nepetalactone compounds were merely identified by MS and the stereochemical assignment was made by GC peak area comparisons to the natural abundance in *N. Cataria* reported in the literature. The literature values were generated by separating the diastereomers on a silica gel column and comparing their ^{1}H and ^{13}C NMR spectra.[4]

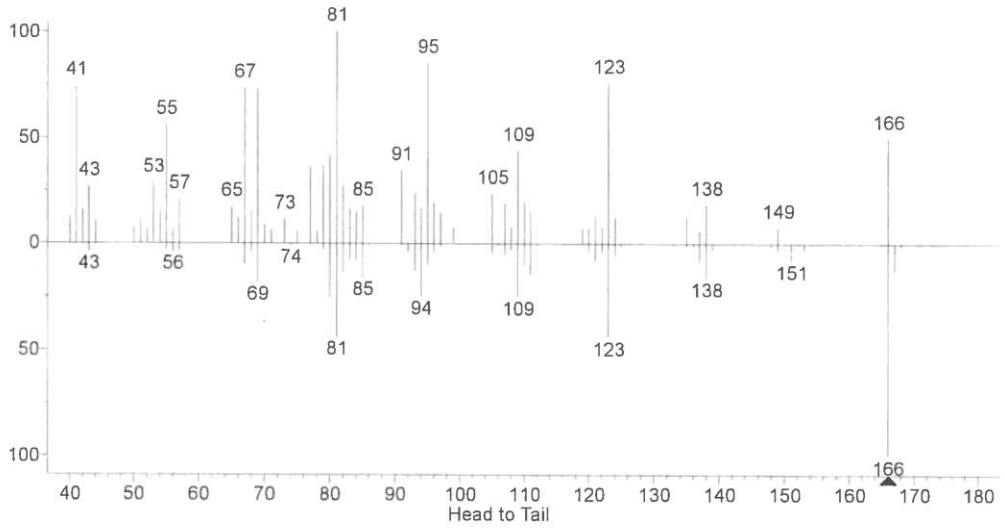

FIGURE 3-3. A comparison of the mass spectrum of the minor isomer of nepetalactone; retention time 8.46 (top) to nepetalactone from the NIST/EPA/NIH mass spectra database (bottom).

The similarities between the minor (4aS,7S,7aS) and major (4aS,7S,7aR) diastereomers can be seen by comparison of the top spectra in Figures 3-3 and 3-4. They are each compared to the NIST nepetalactone spectrum for reference.

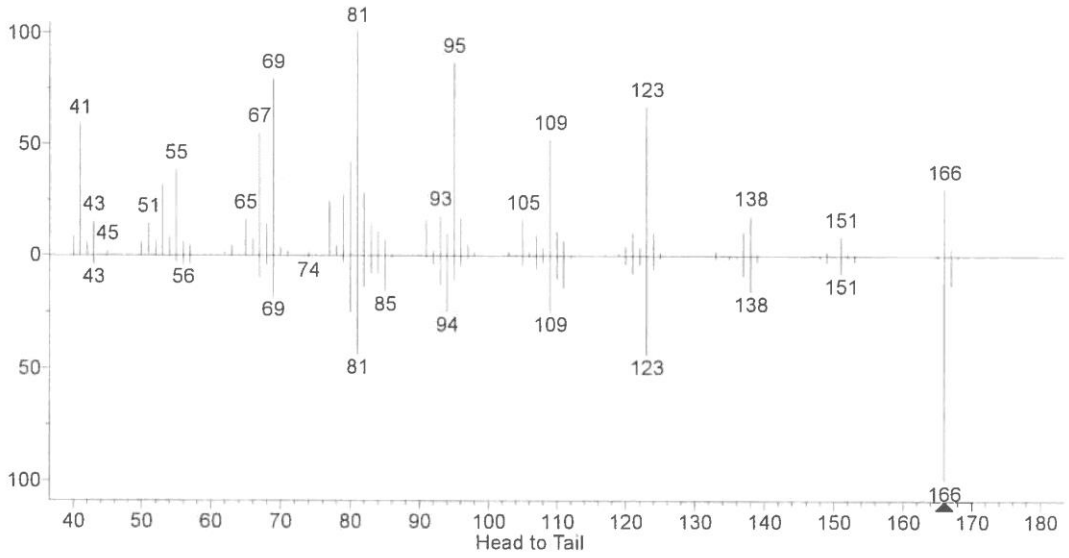

FIGURE 3-4. A comparison of the mass spectrum of the major isomer of nepetalactone; retention time 9.46 (top) to nepetalactone from the NIST/EPA/NIH mass spectra database (bottom).

Once the assignment of stereochemistry of the nepetalactones was achieved, the catnip oil extract was analyzed on an HP 5890 gas chromatograph (using a SPB-5 column described in section 2.2.2). Lactone standards were selected to bracket the nepetalactones and maintain reasonable retention times. An example of one of the resulting chromatograms is shown below in Figure 3-5. The standard cocktail was run isothermally over a T = 30 K temperature range at T = 5 K intervals. Each experiment was run in duplicate.[1]

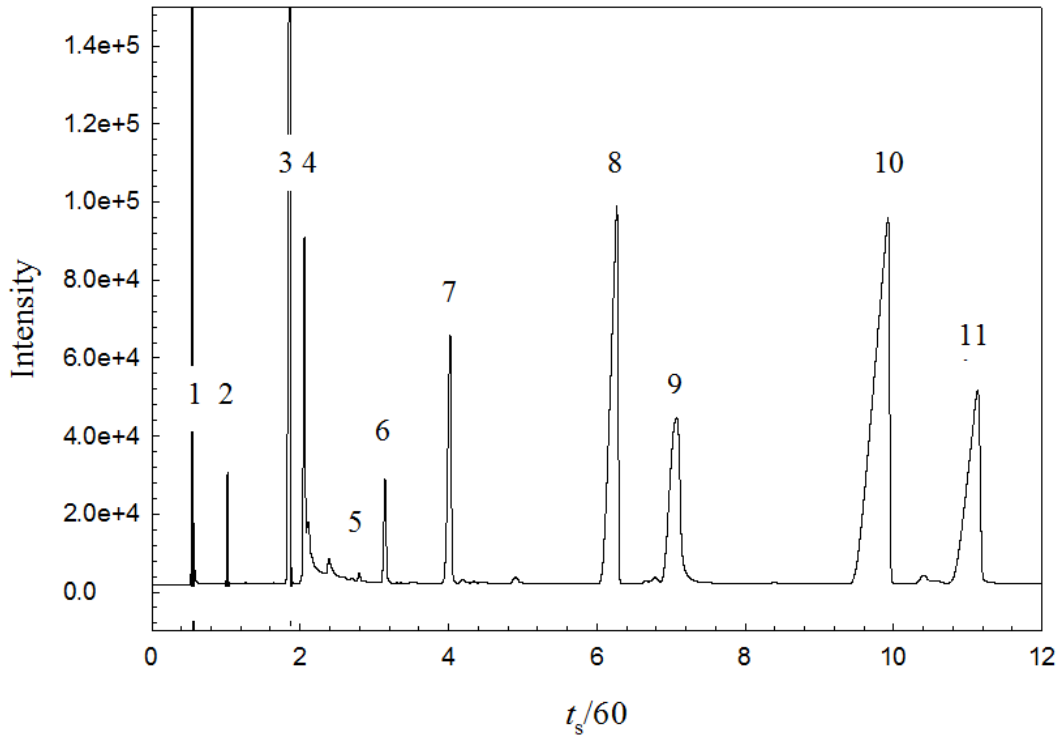

FIGURE 3-5. The gas chromatogram at T = 155.7 K. From left to right: (1) CH_2Cl_2; (2) γ-hexanolactone; (3) γ-octanolactone; (4) δ-octanolactone; (5) (4aS,7S,7aS)-nepetalactone; (6) (4aS,7S,7aR)–nepetalactone; (7) γ-decanolactone; (8) γ-undecanolactone; (9) δ-undecanolactone; (10) γ-dodecanolactone; (11) δ-dodecanolactone.

The retention times for each standard were plotted against the temperature of the run to obtain the enthalpy of transfer as described in section 2.3. Then the enthalpy of transfer was plotted against the enthalpy of vaporization literature values for each of the standards. This plot is shown in Figure 3-6. The figure includes the error bars for one standard deviation by the statistics generated by the software. The solid circles are the standards and the square boxes are the nepetalactone stereoisomers.

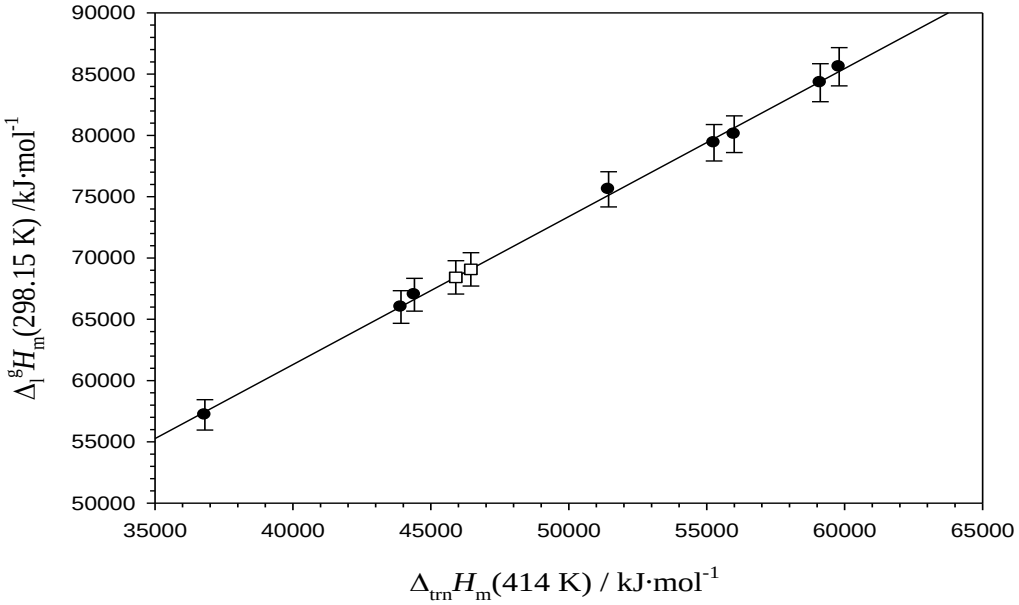

FIGURE 3-6. Enthalpy of transfer vs. enthalpy of vaporization for the nepetalactone study. The major and minor isomers of nepetalactone are the squares.

TABLE 3-1

Correlation of ΔH_{trn}(414K) with $\Delta_l^g H_m$(298 K) of the standards

Run 1	- slope *T*/K	intercept	ΔH_{trn}(414K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} (lit)	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}(calc)
γ-Hexanolactone	4427.5	11.085	36.81	57.2±0.3	57.5±1.2
γ-Octanolactone	5283.0	12.045	43.92	66.0±3.9	66.0±1.3
δ-Octanolactone	5341.4	12.058	44.41	67.0±0.2	66.6±1.3
(4aS,7S,7aS)-Nepetalactone	5522.0	12.100	45.91		68.4±1.4
(4aS,7S,7aR) -Nepetalactone	5587.3	12.105	46.45		69.1±1.4
γ-Decanolactone	6187.5	13.205	51.44	75.6±0.3	75.0±1.4
γ-Undecanolactone	6647.7	13.776	55.27	79.4±4.4	79.6±1.5
δ-Undecanolactone	6735.8	13.871	56.00	80.1±4.5	80.5±1.5
γ-Dodecanolactone	7110.7	14.361	59.12	84.3±4.6	84.2±1.5
δ-Dodecanolactone	7193.4	14.45	59.80	85.6±4.7	85.1±1.6
$\Delta_l^g H_m$(298.15 K)/kJ·mol^{-1} = (1.19±0.02)ΔH_{trn}(414 K) + (13.4±1.0)				r^2 = 0.9986	

The vaporization enthalpy of the nepetalactones was calculated from the product of the negative slope of the line and the gas constant derived from a plot of ΔH_{trn}(414K) vs $\Delta_l^g H_m$(298 K) by a linear least squares analysis. The bottom of Table 3-1 contains the

resulting equation and correlation coefficient, r^2, for Run 1. Table 3-2 summarizes the results for both runs, the averages, and provides a comparison to the known literature values for each compound.

TABLE 3-2
A summary of the slopes, intercepts and vaporization enthalpies at T = 298.15 K from runs 1 and 2; enthalpies in kJ·mol^{-1}

	-slope T/K	Intercept	$\Delta_l^g H_m$(298 K) Runs 1/2	$\Delta_l^g H_m(298\ K)_{avg}$ runs 1 and 2	$\Delta_l^g H_m$(298 K) Lit.
γ-Hexanolactone	4427.5	11.085	57.5±1.2		
	4607.2	11.496	57.8±2.0	57.7±1.6	57.2±0.3
γ-Octanolactone	5283.0	12.045	66.0±1.3		
	5389.2	12.290	65.5±2.1	66.3±1.7	66.0±3.9
δ-Octanolactone	5341.4	12.058	66.6±1.3		
	5503.3	12.425	66.7±2.2	66.7±1.8	67.0±0.2
(4aS,7S,7aS)-Nepetalactone	5522.0	12.100	68.4±1.4		
	5584.1	12.205	67.5±2.2	68.0±1.9	
(4aS,7S,7aR) -Nepetalactone	5587.3	12.105	69.1±1.4		
	5808.5	12.603	69.7±2.2	69.4±1.9	
γ-Decanolactone	6187.5	13.205	75.0±1.4		
	6363.8	13.603	75.2±2.3	75.1±1.9	75.6±0.3
γ-Undecanolactone	6647.7	13.776	79.6±1.5		
	6796.0	14.111	79.5±2.4	79.6±2.0	79.4±4.4
δ-Undecanolactone	6735.8	13.871	80.5±1.5		
	6955.0	14.361	81.1±2.4	80.8±2.0	80.1±4.5
γ-Dodecanolactone	7110.7	14.361	84.2±1.5		
	7240.0	14.653	83.9±2.5	84.6±2.0	84.3±4.6
δ-Dodecanolactone	7193.4	14.45	85.1±1.6		
	7389.5	14.888	85.4±2.5	85.3±2.1	85.6±4.7

Vapor pressures of the standards were calculated as described in section 2.3.2 using equations described in section 2.3.2.1 and the constants found in Table 2-7 to calculate vapor pressure of the standards as a function of temperature. Values of t_o/t_a calculated from the slopes and intercepts of the standards and targets were first averaged for both Runs 1 and 2 and then used in a plot of $\ln(p/p^o)$ vs $\ln(t_o/t_a)_{avg}$. The vapor pressures calculated from the slope and intercept of the plot for both targets and standards at T = 298.15 K are reported and compared to literature or predicted values in Table 3-3.

This plot was then repeated at T = 10 K intervals up to T = 350 K, the temperature range for which the vapor pressures of the standards are valid. The vapor pressures were then fit to a first order polynomial, eq 12.

$$\ln(p/p^{o}) = A' - B'/(T/K) \qquad \text{where } B = \Delta_l^g H_m(T_m/K)/R \qquad (12)$$

TABLE 3-3

Correlation of $\ln(t_o/t_a)_{avg}$ with $\ln(p/p_o)_{exp}$ of the standards at T = 298.15 K; p_o = 101325 Pa,

	$\ln(t_o/t_a)_{avg}$	$\ln(p/p_o)_{exp}$	$\ln(p/p_o)_{calc}$	p_{calc}(298 K)/Pa	p_{lit}(298 K)/Pa
γ-Hexanolactone	-3.856	-8.455	-8.45±0.03	21.9±0.6	21.6
γ-Octanolactone	-5.729	-10.485	-10.50±0.03	2.8±0.1	2.8
δ-Octanolactone	-5.941	-10.738	-10.74±0.03	2.2±0.1	2.2
(4aS,7S,7aS)-Nepetalactone	-6.472		-11.32±0.03	1.20±0.04	0.9[a], 0.67[b]
(4aS,7S,7aR)-Nepetalactone	-6.749		-11.62±0.03	0.91±0.03	0.9[a], 0.67[b]
γ-Decanolactone	-7.64	-12.615	-12.60±0.03	0.34±0.01	0.34
γ-Undecanolactone	-8.598	-13.663	-13.65±0.03	0.121±0.004	0.12
δ-Undecanolactone	-8.836	-13.882	-13.91±0.04	0.092±0.003	0.095
γ-Dodecanolactone	-9.557	-14.714	-14.70±0.04	0.042±0.002	0.041
δ-Dodecanolactone	-9.781	-14.94	-14.95±0.04	0.033±0.001	0.033

$\ln(p/p_o)_{calc}$ = (1.097±0.003) $\ln(p/p_o)_{exp}$ - (4.22±0.02)

[a] Predicted vapor pressure, reference [5]

[b] Predicted vapor pressure, reference [6].

The calculated vapor pressures were then used as an alternative means of calculating the vaporization enthalpy of the compounds. This secondary way of calculating vaporization enthalpy based on known vapor pressures is a way to compare results based on data from different measured properties. If the results are similar, then the vaporization enthalpy values have a higher level of certainty. The results of this comparison can be seen in Table 3-4. As can be seen the new vaporization enthalpies are all within the estimated experimental error for each method. Also given, are the A*'* and B*'* constant values needed to calculate the vapor pressures of each standard at the required temperature. The vaporization enthalpy at T = 324 K (the mean temperature of the seven runs) is given in the third column, the heat capacity corrections are given in

fourth column and the fifth and sixth columns give the calculated vaporization enthalpies at T = 298.15 K.

TABLE 3-4
A summary of the vaporization enthalpies calculated from vapor pressure calculations from T = 298.15 to 350 K adjusted from the mean temperature to T = 298.15 K.

	A'	B'/K	$\Delta_l^g H_m$(324 K) kJ·mol^{-1}	C_p(l) (J·K^{-1}·mol^{-1})	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}	
					From Vapor pressure (calc)	From Table 4 (calc)
(4aS,7S,7aS)-Nepetalactone	15.245	7916.9	65.8±0.2	298	68.1±0.5	68.0±1.9[a]
(4aS,7S,7aR)-Nepetalactone	15.443	8067.0	67.1±0.1	298	69.3±0.4	69.4±1.9[a]
Standards						(Lit)
γ-Hexanolactone	14.252	6764.2	56.2±0.3	206.6	57.9±0.5	57.2±0.3
γ-Octanolactone	15.249	7674.7	63.8±0.2	270.4	65.9±0.5	66.0±3.9
δ-Octanolactone	15.324	7766.7	64.6±0.2	264.4	66.6±0.5	67.0±0.2
γ-Decanolactone	16.615	8708.2	72.4±0.1	334.2	74.9±0.4	75.6±0.3
γ-Undecanolactone	17.223	9203.5	76.5±0.1	366.1	79.3±0.4	79.4±4.4
δ-Undecanolactone	17.398	9333.7	77.6±0.1	360.1	80.3±0.4	80.1±4.5
γ-Dodecanolactone	17.855	9706.1	80.7±0.1	398	83.6±0.4	84.3±4.6
δ-Dodecanolactone	18.022	9829.0	81.7±0.1	392	84.6±0.4	85.6±4.7

[a] A vaporization enthalpy of (50.9±0.3) kJ·mol^{-1} at the boiling temperature is predicted.

3.1.2. Whiskey Lactone and Menthalactone

An example chromatogram for the whiskey lactone and menthalactone compounds with standards can be seen in Figure 3-7. The retention times for these runs may be found in Appendix Tables S2A and S2B.

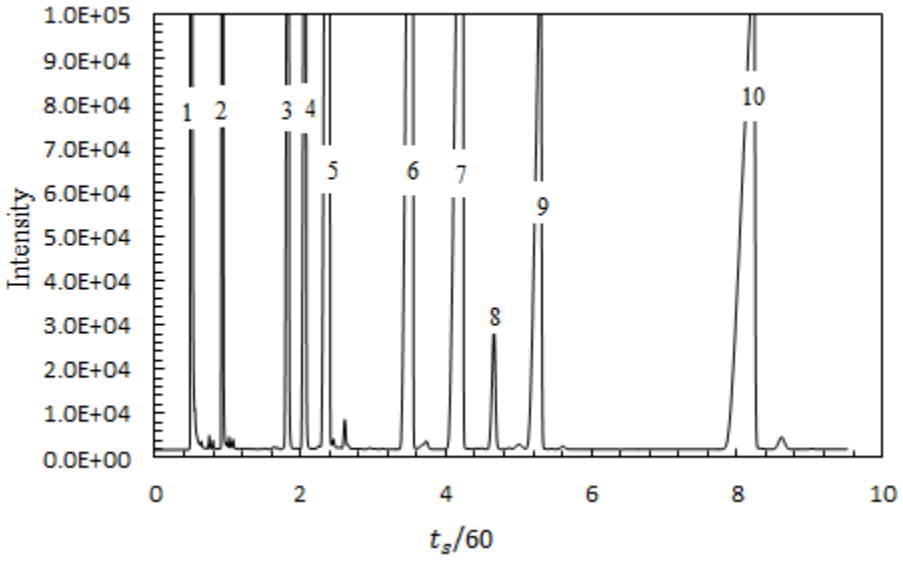

FIGURE 3-7. A representative gas chromatogram; Run 3 at T = 434.0 K. From left to right: (1) acetone; (2) γ-hexanolactone; (3) *trans*-whiskey lactone; (4) *cis*-whiskey lactone; (5) γ-nonanolactone; (6) γ-decanolactone; (7) (-)-mintlactone; (8) (+)-isomintlactone; (9) γ-undecanolactone; (10) γ-dodecanolactone. The chromatogram is scaled for ease of identification of (+)-isomintlactone (8).

As mentioned above in section 2.1.1, whiskey lactone and menthalactone each have four stereoisomers. Two diastereomers for each were able to be separated on the SPB-5 column. Figure 3-8 illustrates the structures of the major and minor isomers of whiskey lactone and isomintlactone shown previously.

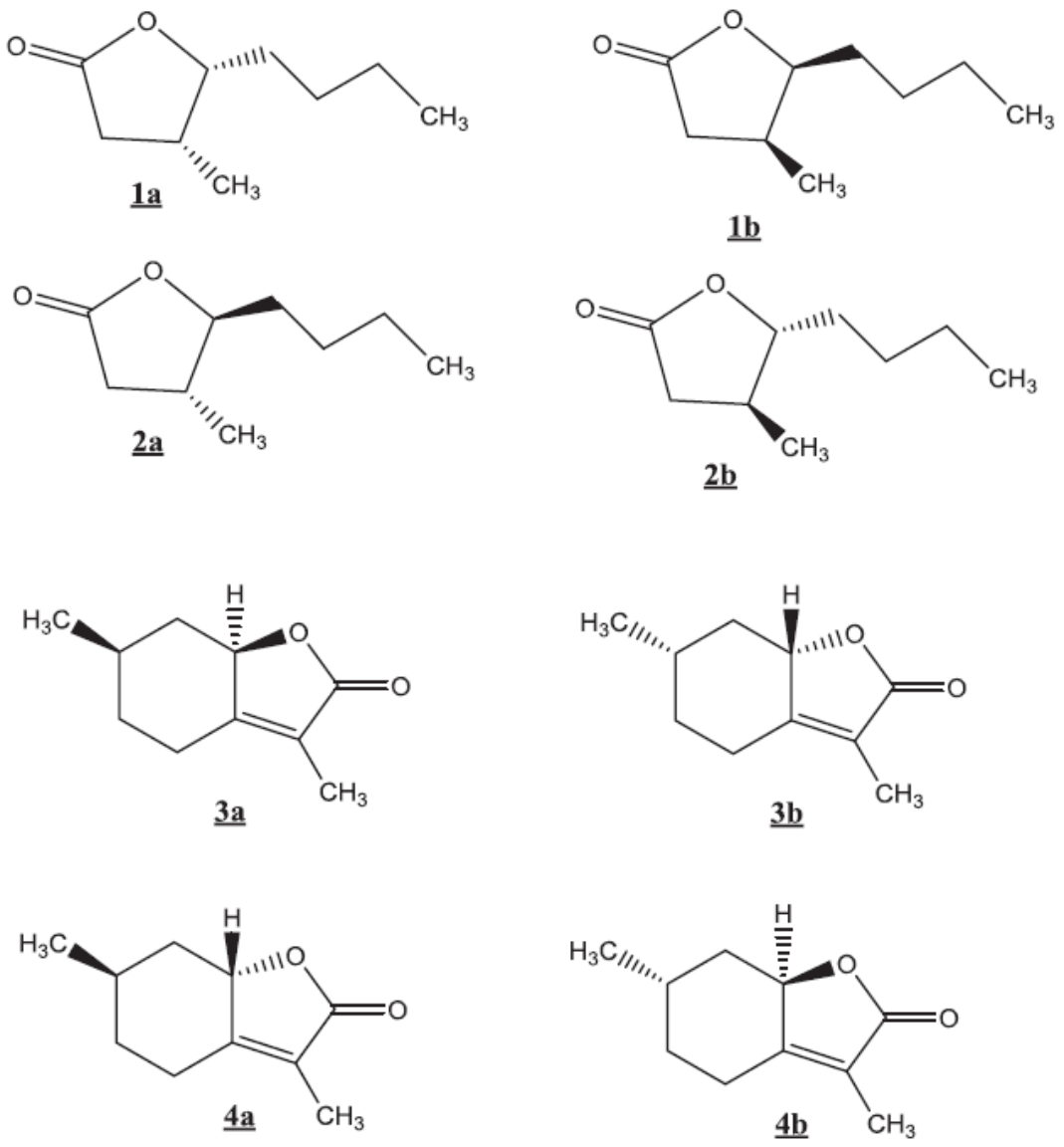

FIGURE 3-8. Top to bottom, left to right: Whiskey lactone major components [rel-(4R,5R)-5-butyldihydro-4-methyl-2(3H)-furanone] **1a + 1b**; Whiskey lactone minor components [rel-(4R,5S)-5-butyldihydro-4-methyl-2(3H)-furanone] **2a + 2b**; Mintlactone major enantiomer [(-)-(6R,7aR)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone] **3a**; Mintlactone minor enantiomer [(+)-(6S,7aS)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone] **3b**; Isomintlactone components (6R,7aS)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone **4a** and (6R,7aS)-5,6,7,7a-tetrahydro-3,6-dimethyl-2(4H)-benzofuranone **4b**.

Identification of the whiskey lactone diastereomer as *trans* was accomplished by comparing the GC peak area ratios and relative retention times to those found by

Lahne.[7] This is described in section 2.2.2.2. The data for this may be found in Appendix Tables S3A and S3B.

The identification of the mintlactone enantiomers was described in section 2.2.2.3, and was done by optical rotation and by comparing GC peak areas to those found in nature and previously used synthetic pathways.[8] This comparison can be seen in Appendix Tables S3C and S3D.

The relationship between the enthalpy of vaporization and the enthalpy of transfer is shown below in Figure 3-9. The error bars are relatively small and a discussion of the uncertainty calculations can be found in section 2.3.9.

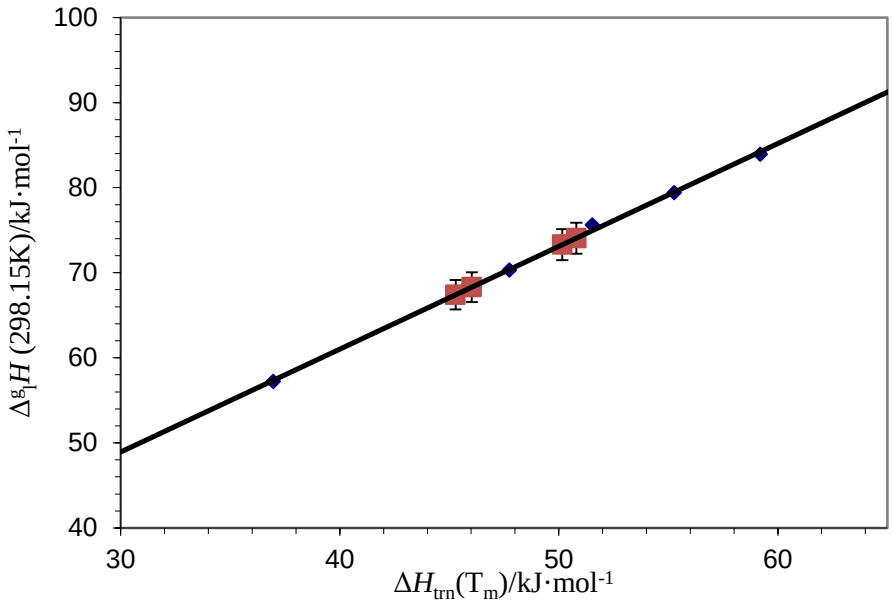

FIGURE 3-9. The relationship between the enthalpy of transfer at the oven temperatures and the enthalpy of vaporization at 298.15K of the lactone standards (diamonds) is used to calculate the enthalpy of vaporization of whiskey lactone and mintlactone (squares) at 298.15K. Uncertainties in the unknown values were calculated as discussed in section 2.3.9.

The calculated vaporization enthalpies for each of the compounds may be found in Table 3-5 for Run 3 and Table 3-6 for Run 4. The r^2 values are given in the tables and

are both greater than 0.99. The literature values for vaporization enthalpies are given for the known compounds and the back-calculated values from the best-fit curve are in good agreement within the stated uncertainties.

TABLE 3-5

Correlation of ΔH_{trn}(419K) with $\Delta_l^g H_m$(298 K) of the standards; uncertainties are one standard deviation; p^o =101325 Pa

Run 3	- slope *T*/K	intercept	ΔH_{trn}(419 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} (lit)	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}(calc)
γ-Hexalactone	4450±50	11.1±0.12	37.0±0.4	57.2±0.3	57±2
trans-Whiskey lactone[a]	5450±30	12.26±0.07	45.3±0.2		67±2
cis-Whiskey lactone[b]	5540±30	12.30±0.07	46.0±0.3		68±2
γ-Nonalactone	5740±40	12.59±0.09	47.8±0.3	70.3±0.3	70±2
γ-Decalactone	6200±40	13.2±0.10	51.5±0.3	75.6±0.3	75±2
(-)-Mintlactone[c]	6030±50	12.6±0.11	50.2±0.4		73±2
(+)-Isomintlactone[d]	6110±40	12.65±0.08	50.8±0.3		74±2
γ-Undecalactone	6650±40	13.75±0.01	55.3±0.4	79.4±4.4	80±2
γ-Dodecalactone	7120±50	14.4±0.12	59.2±0.4	83.9±4.6	84±2
$\Delta_l^g H_m$(298.15 K)/kJ·mol^{-1} = (1.21±0.03)ΔH_{trn}(419 K) + (12.7±1.3)					r^2 = 0.9987

[a] *cis* (4*S*,5*S*)-4β-Methyl-γ-octalactone.
[b] *trans* (4S,5R)-4β-Methyl-γ-octalactone.
[c] (-)-(6*R*,7a*R*)-5,6,7,7a-Tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone.
[d] (+)-(6*R*,7a*S*)- 5,6,7,7a-Tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone.

TABLE 3-6

Correlation of ΔH_{trn}(419K) with $\Delta_l^g H_m$(298 K) of the standards; uncertainties are one standard deviation; p^o =101325 Pa

Run 4	- slope *T*/K	intercept	ΔH_{trn}(419 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} (lit)	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}(calc)
γ-Hexalactone	4610±12	11.37±0.03	38.3±0.1	57.2±0.3	57±2
trans-Whiskey lactone[a]	5610±14	12.58±0.03	46.7±0.11		68±2
cis-Whiskey lactone[b]	5700±20	12.61±0.03	47.4±0.12		69±2
γ-Nonalactone	5880±20	12.85±0.05	48.9±0.2	70.3±0.3	70±2
γ-Decalactone	6340±20	13.43±0.05	52.7±0.2	75.6±0.3	75±2
(-)-Mintlactone[c]	6160±30	12.79±0.07	52.1±0.2		73±2
(+)-Isomintlactone[d]	6260±20	12.93±0.03	51.2±0.11		74±2
γ-Undecalactone	6780±30	13.98±0.07	56.4±0.2	79±4	80±2
γ-Dodecalactone	7250±20	14.59±0.06	60.3±0.2	84±5	84±2
$\Delta_l^g H_m$(298.15 K)/kJ·mol^{-1} = (1.22±0.03)ΔH_{trn}(419 K) + (11±1.3)					r^2 = 0.9988

[a] *cis* (4*S*,5*S*)-4β-Methyl-γ-octalactone.
[b] *trans* (4S,5R)-4β-Methyl-γ-octalactone.
[c] (-)-(6*R*,7a*R*)-5,6,7,7a-Tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone.
[d] (+)-(6*R*,7a*S*)- 5,6,7,7a-Tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone.

Literature values for the vaporization enthalpy of whiskey lactone were not available. A group additive approach was used to compare a theoretical value with the calculated experimental values[9]. This method was described in Figure 2-7. A value of 67.2 $kJ \cdot mol^{-1}$ was estimated and is relatively close to the experimental values of (68±2) $kJ \cdot mol^{-1}$ for *cis*-whiskey lactone and (69±2) $kJ \cdot mol^{-1}$ for *trans*-whiskey lactone. Suitable group values were not available for the menthalactones, therefore this comparison was not able to be made for them.

Vapor pressures were calculated as described in section 2.3.2 and using values found in Table 2-7. The retention times and vapor pressures of the standards were used to make a $\ln(t_o/t_a)$ vs. $\ln(p/p^o)$ plots as a function of temperature as described previously. The resulting linear relationships were used to calculate the vapor pressures of the whiskey lactone and menthalactone compounds at T = 298.15 K and at 10 K increments from T = (310 to 350) K. Table 3-7 illustrates the calculated vapor pressures for the lactone compounds at T = 298.15 K. Literature values are provided where available. All calculated pressures are within experimental error of the literature values.

TABLE 3-7
Correlation of $\ln(p/p^o)$ with $\ln(t_o/t_a)$; calculated and literature vapor pressures at T = 298.15 K[a]

	$\ln(t_o/t_a)$	$\ln(p/p^o)$	$\ln(p/p^o)_{calc}$	p/Pa	p/Pa_{lit}
γ-Hexalactone	-3.96	-8.46	-8.44±0.05	21.9±1.1	21.6
trans-Whiskey lactone	-6.12		-10.84±0.06	2.0±0.1	
cis-Whiskey lactone	-6.38		-11.12±0.06	1.5±0.1	
γ-Nonalactone	-6.77	-11.51	-11.55±0.06	1.0±0.1	1.01
γ-Decalactone	-7.72	-12.61	-12.61±0.07	0.34±0.02	0.337
(-)-Mintlactone	-7.75		-12.64±0.07	0.33±0.02	
(+)-Isomintlactone	-7.95		-12.86±0.07	0.26±0.01	
γ-Undecalactone	-8.66	-13.66	-13.65±0.07	0.12±0.01	0.118
γ-Dodecalactone	-9.62	-14.71	-14.71±0.07	0.041±0.003	0.041
$\ln(p/p^o) = 1.107 \cdot \ln(t_o/t_a)$ - 4.049		r^2 = 0.9999			(8)

[a] Uncertainties represent one standard deviation; p^o = 101325 Pa

The calculated vapor pressures were then used to calculate vaporization enthalpies. Heat capacity adjustments were needed to adjust the vaporization enthalpies from the mean temperature of measurement, 324 K to 298.15 K. When available, literature heat capacities were used. Vaporization enthalpies were calculated from vapor pressures using the Clapeyron equation (Eq 13). These results were then compared to the vaporization enthalpies calculated from the transfer enthalpies and found to be within experimental uncertainty. The comparison of vaporization enthalpies can be seen in Table 3-8.

$$\Delta_l^g H = -\frac{R \cdot \ln(\frac{P_2}{P_1})}{\frac{1}{T_2} - \frac{1}{T_1}} \quad (13)$$

TABLE 3-8
Adjustments of vaporization enthalpies from T = (324 to 298.15) K evaluated from vapor pressures; uncertainties reported are one standard deviation, p^o = 101325 Pa

	$\Delta_l^g H_m$(324 K)	C_p(l)	$\Delta Cp \Delta T$	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}	
	kJ·mol^{-1}	J·K^{-1}·mol^{-1}	kJ·mol^{-1}	Calcd	By Corr[e]
γ-Hexalactone	55. 8±0.2	206.6	1.7±0.4	57.4±0.4	57±1.6
trans-Whiskey lactone[a]	65.3±0.2	300	2.3±0.4	67.6±0.4	68±1.7
cis-Whiskey lactone[b]	66.2±0.2	300	2.3±0.4	68.5±0.4	69±1.7
γ-Nonalactone	68.1±0.1	302.3	2.3±0.4	70.4±0.4	70±0.3
γ-Decalactone	72.4±0.1	334.2	2.5±0.4	74.9±0.4	76±1.8
(-)-Mintlactone[c]	70.8±0.1	298.5	2.3±0.4	73.1±0.4	73±1.8
(+)-Isomintlactone[d]	71.7±0.1	298.5	2.3±0.4	74.0±0.4	74±1.8
γ-Undecalactone	76.7±0.1	366.1	2.7±0.4	79.4±0.4	80±1.9
γ-Dodecalactone	81.1±0.1	398	3.0±0.4	84.1±0.4	84±1.9

[a] *cis* (4*S*,5*S*)-4β-Methyl-γ-octalactone.
[b] *trans* (4S,5R)-4β-Methyl-γ-octalactone.
[c] (-)-(6*R*,7a*R*)-5,6,7,7a-Tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone.
[d] (+)-(6*R*,7a*S*)- 5,6,7,7a-Tetrahydro-3,6-dimethyl-2(4*H*)-benzofuranone.
[e] Obtained by correlation between $\Delta_{trn}H_m$(298 K) and $\Delta_l^g H_m$(298 K) of the standards.

(+)-Isomintlactone is a solid at room temperature requiring the fusion enthalpy for the calculation of its vapor pressure (see section 2.3.3.). Since the fusion enthalpy of (+)-isomintlactone was not available in the literature, it was estimated to be (22±7) kJ·mol^{-1} by the methods described in section 2.3.5. The vaporization enthalpy at T = 298.15 K was adjusted to T_{fus}, resulting in (70±2) kJ·mol^{-1}. Using these fusion and vaporization enthalpy values in equation 6, the sublimation enthalpy of (92±7) kJ·mol^{-1} is calculated at T_{fus}. When this is adjusted back to T = 298.15 K, the sublimation enthalpy is (93±7) kJ·mol^{-1}. At T_{fus} = 352 K, a vapor pressure of p = 24 Pa is calculated for (+)-isomintlactone using equation 14 and the isomintlactone constants given in Table 3-9.[8]

$$\ln(p/p_o) = A' - B'/T \qquad (14)$$

Table 3-9
Constants of Eq 14 obtained from correlations of $\ln(p/p^o)$ vs $\ln(t_o/t_a)$ from T= (298.15 to 350) K; p^o= 101325 Pa.[8]

	A'	B'
γ-Hexalactone	14.09±0.08	-6710±30
(±) *trans*-Whiskey lactone	15.54±0.06	-7860±20
(±) *cis*-Whiskey lactone	15.60±0.06	-7960±20
γ-Nonalactone	15.92±0.05	-8190±20
γ-Decalactone	16.61±0.04	-8710±13
(-)-Mintlactone	15.94±0.04	-8520±13
Isomintlactone	16.07±0.04	-8620±12
γ-Undecalactone	17.29±0.03	-9220±10
γ-Dodecalactone	18.02±0.02	-9760±10

For the remainder of these calculations T_{fus} = 352 K was approximated as the triple point. The fusion temperature and vapor pressure were used along with the sublimation enthalpy at T_{fus} to calculate the vapor pressure of the crystalline form at T =

298.15 K using equation 15. The vapor pressure of the crystalline form was calculated to be p/Pa ≈ (0.08±0.04).[8]

$$\ln(p_2/p^o) = -\Delta H_{sub}(T_{fus})/R[1/T_2 - 1/T_1] + \ln(p_1/p^o) \quad (15)$$

3.2. Aldehydes

As discussed above in section 2.1.2, many of the aldehydes were of natural origin and they are susceptible to oxidation. The samples were old and may have degraded some. Many of the samples were observed to have lower purity by GC than was reported by the manufacturers (see Table 2-2). The initial mixtures included both aliphatic and aromatic aldehydes. Literature values for the aromatic aldehydes did not correlate well in vaporization enthalpy vs. enthalpy of transfer plots. Therefore, their data has been omitted from the calculations. However, their retention times have still been included in the Appendix (Tables S4A – S4D) for reference.

An example chromatogram of mix 5 at T = 358.15 K is given in Figure 3-10. The elimination of the aromatic compounds left five standards for the mix 5 assessment and four standards for the mix 6 assessment. The correlation obtained seems very acceptable with $r^2 \geq 0.998$. An example plot is given in Figure 3-11. The standards are represented by diamonds and the targets by squares. The error bars are relatively small and were calculated as explained in section 2.3.9.

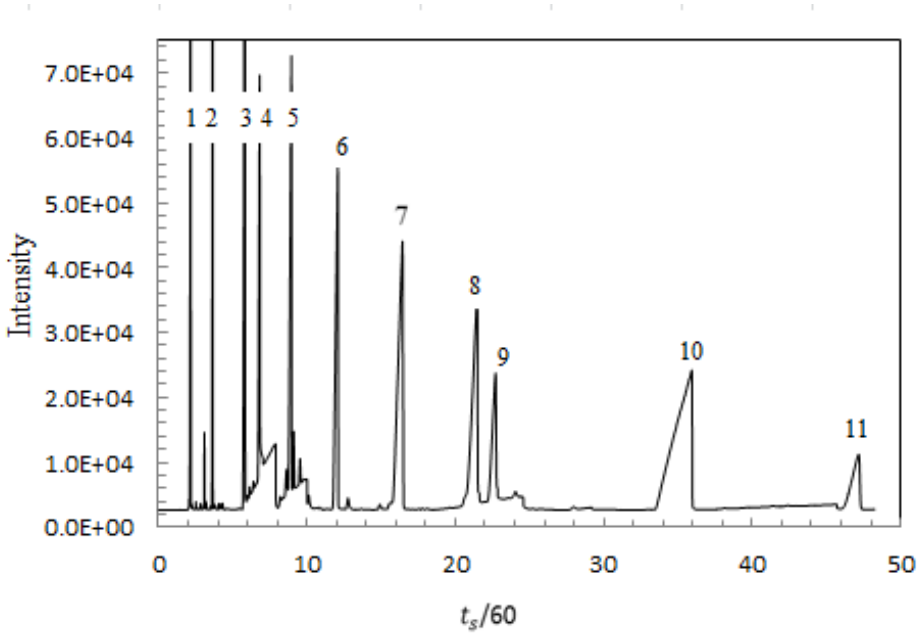

FIGURE 3-10. A representative gas chromatogram; Run 1 at T = 358.15 K. From left to right: (1) dichloromethane;(2) hexanal; (3) *trans*-2-hexenal; (4) benzaldehyde; (5) octanal; (6) 2,6-dimethyl-5-heptenal; (7) nonanal; (8) 2,6-nonadienal; (9) *trans*-4-decenal; (10) decanal; (11) *trans*-cinnamaldehyde

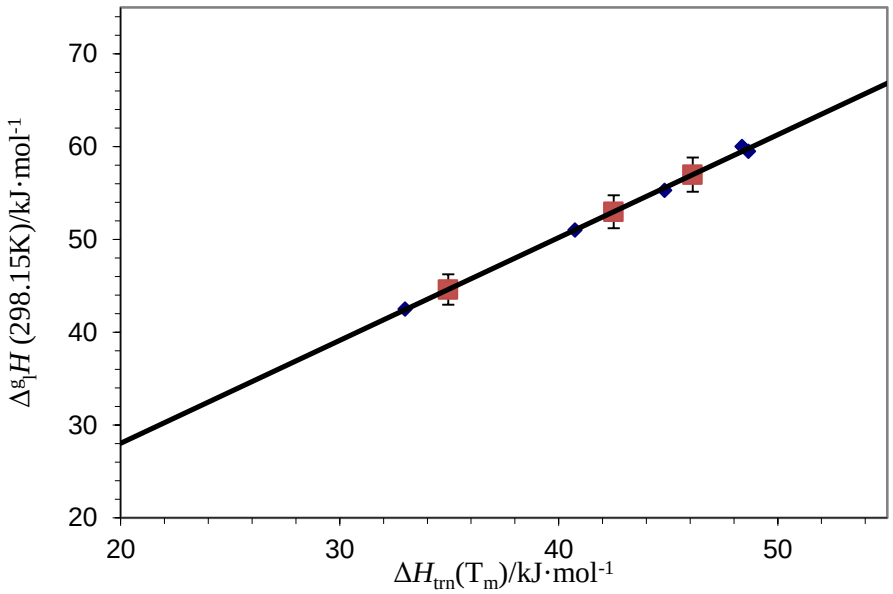

FIGURE 3-11. The relationship between the enthalpy of transfer at the oven temperatures and the enthalpy of vaporization at 298.15K of the aldehyde standards (diamonds) is used to calculate the enthalpy of vaporization of the target compounds (squares) at 298.15K. Uncertainties in the unknown values were calculated as discussed in section 2.3.9.

TABLE 3-10
Data showing relationship between the enthalpy of transfer at 374K and the enthalpy of vaporization at 298K for Aldehyde Run 5.

Run 5	- slope T/K	intercept	ΔH_{trn}(374 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} (lit)	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}(calc)
Hexanal	3970±40	11.1±0.1	33.0±0.3	42.5±0.4[a]	42±2
trans-2-Hexenal	4200±50	11.3±0.1	35.0±0.4		45±2
Octanal	4900±30	12.11±0.09	40.8±0.3	51.0±0.3[a]	51±2
2,6-Dimethyl-5-heptenal	5110±30	12.32±0.09	42.5±0.3		53±2
Nonanal	5390±30	12.72±0.09	44.8±0.3	55.3±0.3[a]	56±2
2,6-Nonadienal	5550±40	12.8±0.1	46.1±0.3		57±2
trans-4-Decenal	5820±40	13.2±0.1	48.4±0.3	60.0[b]	60±2
Decanal	5850±30	13.27±0.09	48.7±0.3	59.5±0.4[a]	60±2
Run 5: $\Delta_l^g H_m(298.15\ K)\ /\ kJ \cdot mol^{-1}$ = (1.11 ±0.03)$\Delta H_{trn}(374\ K)$ + (6±1) r^2 = 0.9979					
Run 6: $\Delta_l^g H_m(298.15\ K)\ /\ kJ \cdot mol^{-1}$ = (1.13 ±0.03)$\Delta H_{trn}(374\ K)$ + (5 ±1) r^2 = 0.9982					

[a] Reference [10]
[b] References [11, 12]

TABLE 3-11
Data showing relationship between the enthalpy of transfer at 410K and the enthalpy of vaporization at 298K for Aldehyde Run 7.

Run 7	- slope T/K	intercept	ΔH_{trn}(410 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} (lit)	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}(calc)
Hexanal	3820±40	10.82±0.09	31.8±0.3	42.5±0.4[a]	42.6±0.7
2,6-Dimethyl-5-heptenal	4830±20	11.72±0.05	40.2±0.2	52.9±1.8[b]	52.7±0.8
trans-2-Nonenal	5310±20	12.25±0.05	44.1±0.2		57.3±0.8
Decanal	5530±20	12.57±0.05	45.9±0.2	59.5±0.4[a]	59.5±0.8
trans,trans-2,4-Decadienal	5940±20	12.93±0.05	49.4±0.2		63.6±0.9
2-Butyl-2-octenal	6180±20	13.26±0.05	51.4±0.2		66.0±0.9
Lauric aldehyde	6430±20	13.68±0.06	53.4±0.2	68.3±0.9[a]	68.4±0.9
Run 7: $\Delta_l^g H_m(298.15\ K)\ /\ kJ \cdot mol^{-1}$ = (1.19 ±0.01)$\Delta H_{trn}(410\ K)$ + (4.9 ±0.6) r^2 = 0.9997					
Run 8: $\Delta_l^g H_m(298.15\ K)\ /\ kJ \cdot mol^{-1}$ = (1.19 ±0.01)$\Delta H_{trn}(410\ K)$ + (4.6 ±0.6) r^2 = 0.9998					

[a] Reference [10]
[b] Generated from Standard Cocktail 5 (mean of Runs 5 & 6)

The vaporization enthalpy data for Run 5 has been given in Table 3-10. Correlation equations for Run 5 and its duplicate are given at the bottom of the table. The vaporization enthalpies calculated are all within experimental error of the literature values that are available.

A second mixture in which one of the standards, 2,6-dimethyl-5-heptenal, was evaluated in the first mixture, is summarized in Table 3-11. Correlation equations for this run and its duplicate are provided at the bottom of the table. The vaporization enthalpies that were calculated for the compounds in Run 7 are given in Table 3-11. For both runs, $r^2 > 0.999$. All of the calculated vaporization enthalpies are within experimental error to literature values.

The retention times of the aldehydes in the form $\ln(t_o/t_a)$ did not seem to correlate well with $\ln (p/p^o)$ using vapor pressures that are currently available in the literature. One possible explanation is that data from literature and/or from this study may not be valid due to the ease of oxidation of the aldehydes. This is currently under further investigation.

3.3. Profens

In the profen study, Runs 9-12 (2 mixtures in duplicate) were run with alkoxybenzoic acid standards. The retention time data for these runs are reported in Appendix Tables S5A-S5D. Runs 13-14 were performed using a wider variety of standards. These included alkoxybenzoic acids, alkylbenzoic acids, and compounds with two rings such as α-napthaleneacetic acid, biphenyl-4-carboxylic acid, Fenoprofen, and naproxen. The retention times for these runs can be seen in Appendix Tables S5E-S5F.

Sublimation enthalpies available in the literature[13, 14] were first adjusted to T = 298.15 K using estimated heat capacities described in sections 2.3.3 and 2.3.4. Table 3-12 shows the adjustments of the literature sublimation enthalpies to T = 298.15 K.

TABLE 3-12

Adjustment of Literature Sublimation Enthalpies to T = 298.15 K, p^o/Pa = 10^5, Uncertainties are One Standard Deviation

Compound	$\Delta_{cr}^{g}H_m(T_m)$ kJ·mol^{-1}	T_m/K	Cp(cr) J·K·mol^{-1}	$\Delta Cp \cdot \Delta T$ kJ·mol^{-1}	$\Delta_{cr}^{g}H_m$(298 K)[a]/ kJ·mol^{-1} Eq 3	Eq 6	Ref
4-Ethylbenzoic acid	99.3±0.7	328.2	203.6	0.9±0.3	100.2±0.8	100.6±0.7	[13]
4-Methoxybenzoic acid	110.6±0.3	351.3	226.5	1.8±0.6	112.4±0.6	112.6±0.6	[14]
4-Ethoxybenzoic acid	119.4±0.5	361.2	253.2	2.4±0.7	121.8±0.9	121.9±1.0	[14]
4-Hexylbenzoic acid	119.9±0.2	355.1	311.2	3.0±0.9	122.9±1.3	122.3±0.9	[13]
4-Hexyloxybenzoic acid	130.8±0.4	371.2	361.2	4.0±1.2	140.8±1.3[b]	139.4±0.9[b]	[14]
4-Heptyloxybenzoic acid	155.1±1.0	358.3	387.9	3.5±1.1	158.6±1.5	157.2±1.2	[14]
4-Octylbenzoic acid	130.7±1.3	361.2	365	3.5±1.1	141.3±1.8[c]	140.4±1.3[c]	[13]
4-Octyloxybenzoic acid	141.1±0.9	367.8	414.8	4.4±1.3	163.4±1.6[d]	161.4±1.2[d]	[14]

[a] A comparison of the temperature adjustments using eq 7 and the Clarke and Glew equation (eq 10).
[b] Includes a cr-cr phase transition at T/K= 342.2 (5.95 kJ·mol^{-1}).
[c] Sublimation enthalpy of 4-octylbenzoic acid including solid-solid phase transitions at T/K= (305.6 and 366.6) (5.4±0.1 and 0.47±0.03 kJ·mol^{-1}, respectively) and a liquid crystal transition at T/K = 385.5 (1.2±0.12) kJ·mol^{-1}. The sublimation enthalpy reported in Table 2-10 was measured in between the two cr-cr transitions.
[d] Sublimation enthalpy of 4-octyloxybenzoic acid including a solid-solid phase transition at T = 346.7 K (17.9 kJ·mol^{-1}).

Table 3-13 shows the terms used to calculate the fusion enthalpy adjustments to T = 298.15 K. Adjustments were made as discussed in chapter 2 using equations (7) and (8). As noted in section 2.3.8, for profens that undergo a liquid crystal phase transition, the temperature at which the heat capacity correction was applied was the temperature of the first liquid crystal phase change (either smectic or nematic). In the top of column 2, T_{fus} refers to the temperature of fusion and T_f is the temperature that the material first converts to

liquid crystal. The footnotes at the bottom of the table identify the acids that form liquid crystals. Column 6 of Table 3-13 summarizes the fusion enthalpies at T/K = 298.15 [15]

TABLE 3-13
Adjustment of Literature Fusion Enthalpies to *T* = 298.15 K, Uncertainties are One Standard Deviation

Compound	$\Delta_{cr}^{l}H_m(T_{fus},T_f)$ kJ·mol^{-1}	T_{fus}/K[a]	Cp(l)/Cp(cr) J·mol^{-1}·K^{-1}	$\Delta_{cr}^{g}Cp\cdot\Delta T$ kJ·mol^{-1}	$\Delta_{cr}^{l}H_m$(298 K) kJ·mol^{-1}	Ref
4-Ethylbenzoic acid	12.79±0.03	385.2	272/203.6	-4.4±1.3	8.4±1.3	[13]
4-Methoxybenzoic acid	29.0±1.0	455.3	269.9/226.5	-7±2	21±2	[14]
4-Ethoxybenzoic acid	35.1±1.0	471.0	301.8/253.2	-9±3	26±3	[16]
4-Hexylbenzoic acid	13.8±0.1[b]	370.6	399.6/311.2	-5±2	9±2	[13]
4-Hexyloxybenzoic acid	22.7[c]	380.0	429.4/360.8	-6±2	17±2	[14]
4-Heptyloxybenzoic acid	31.65[d]	365.4	461.3/387.7	-5±1.4	26.8±1.4	[14]
Biphenyl-4-carboxylic acid	32.1±0.2	499.5	329.5/236.1	-12±4	20±4	[17]
4-Octylbenzoic acid	21.4±0.2[e]	373.3	463.4/365	-6±2	16±2	[13]
4-Octyloxybenzoic acid	32.2[f]	374.5	493.2/414.6	-6±2	26±2	[14]

[a] For compounds forming liquid crystals, T_{fus} refers to the temperature at which the crystal is converted to either the smectic or nematic phase, whichever is lower.
[b] Includes a liquid crystal to isotopic liquid transition at T/K = 385.9 (0.95±0.04 kJ·mol^{-1}).
[c] Includes a cr - cr phase transitions at T/K = 342.2 (5.95 kJ·mol^{-1}), cr –nematic transition at T/K = 380 (13.59 kJ·mol^{-1}), and a nematic – isotropic transition at T/K = 426.1 (3.16 kJ·mol^{-1}).
[d] Includes a cr - smectic phase transitions at T/K = 365.4 (27.59 kJ·mol^{-1}), smectic – nematic transition at T/K = 372.1 (1.94 kJ·mol^{-1}) and nematic – isotropic transition at T/K = 420.8 (2.11 kJ·mol^{-1}).
[e] Includes cr-cr phase transitions at T/K = 305.5 (5.40±0.1 kJ·mol^{-1}) and 366.6 (0.47±0.03 kJ·mol^{-1}), a crystal to liquid crystal transition at 373.3 K (14.32±0.17) kJ·mol^{-1}) and liquid crystal to isotropic transition at T/K = 385.4 (1.2±0.12 kJ·mol^{-1}).
[f] Includes a cr-cr phase transitions at T/K = 346.7 (17.87±0.1 kJ·mol^{-1}), a cr – smectic transition at T/K = 374.5 (11.57 kJ·mol^{-1}), a smectic - nematic transition at T/K = 381.6 (1.38 kJ·mol^{-1}), and a nematic to isotropic transition at T/K = 421.0 (1.38 kJ·mol^{-1}).

The vaporization enthalpies of the alkyl and alkoxyacids at T/K = 298.15 calculated with the aid of eq (6) are provided in Table 3-14. Also included in this table is

the vaporization enthalpy of 4-biphenylcarboxylic acid evaluated previously by correlation gas chromatography.[15, 17]

TABLE 3-14
Vaporization enthalpies of the standards at T = 298.15 K, p^o/Pa = 10^5, Uncertainties are One Standard Deviation

Compound	$\Delta_{cr}^{g}H_m$(298 K)[a] kJ·mol^{-1}	$\Delta_{cr}^{l}H_m$(298 K)[b] kJ·mol^{-1}	$\Delta_{l}^{g}H_m$(298 K)[c] kJ·mol^{-1}
4-Ethylbenzoic acid	100.6±0.7	8.4±1.3	92±2
4-Methoxybenzoic acid	112.6±0.6	22±2	91±3
4-Ethoxybenzoic acid	121.9±1.0	26±3	96±3
4-Hexylbenzoic acid	122.3±0.9	9±2	113±2
4-Hexyloxybenzoic acid	139.4±0.9[d]	17±2	122±2
4-Heptyloxybenzoic acid	157.2±1.2	26.8±1.4	130±2
Biphenyl-4-carboxylic acid			118±5[e]
4-Octylbenzoic acid	140.4±1.3	16±2	125±2
4-Octyloxybenzoic acid	161.4±1.2	26±2	135±2

[a] Ref [14]
[b] From Table 3-13
[c] Using eq (6).
[d] Includes a transition of 5.95 kJ·mol^{-1} at $T_{cr\text{-}cr}$/K = 348.
[e] Ref [17]

Examples of the vaporization enthalpy results for Runs 9, 11, and 13 are provided below in Table 3-15. The linear correlations all exceed an r^2 value of 0.999. This linearity suggests that the approximations made by adjusting the heat capacity from the temperature of the first liquid crystal phase transition in section 2.3.8 seem reasonable.

TABLE 3-15
Correlation of Vaporization Enthalpies with Enthalpies of Transfer, p^o/Pa = 10^5 [a]

Run 9	-slope/K	intercept	ΔH_{trn}(479 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}
4-Methoxybenzoic acid	5160±130	10.7±0.3	42.9±1.1	91±3	91.1±1.0
4-Ethoxybenzoic acid	5430±120	11.1±0.3	45.2±1.0	96±3	95.4±1.0
4-Hexyloxybenzoic acid	7090±130	13.0±0.3	59.0±1.1	122±2	121.9±1.2
Fenoprofen	7360±120	13.2±0.2	61.1±1.0		126.2±1.2
4-Octyloxybenzoic acid	7920±130	14.0±0.3	65.9±1.1	135±2	135.2±1.2
Run 11					
4-Methoxybenzoic acid	5620±80	11.7±0.2	46.8±0.7	91±3	90.9±0.7
4-Ethoxybenzoic acid	5900±70	12.1±0.2	49.0±0.6	96±3	95.5±0.7
4-Hexyloxybenzoic acid	7500±60	13.94±0.13	62.4±0.5	122±2	122.4±0.8
4-Heptyloxybenzoic acid	7970±80	14.5±0.2	66.3±0.6	130±2	130.3±0.8
(S)-Naproxen	8000±70	14.25±0.14	66.5±0.6		130.8±0.8
Run 13					
4-Ethylbenzoic acid	5080±90	10.8±0.2	42.3±0.7	92±2	92±2
S-Ibuprofen	6070±80	11.9±0.2	50.5±0.7		106±2
4-Hexylbenzoic acid	6620±80	12.5±0.2	55.0±0.6	113±2	113±2
Biphenyl-4-carboxylic acid	6960±70	12.62±0.13	57.8±0.5	118±5	118±2
4-Octylbenzoic acid	7420±70	13.4±0.2	61.7±0.6	125±2	124±2
Fenoprofen	7520±70	13.45±0.14	62.5±0.6		126±2
(S)-Naproxen	7730±60	13.54±0.12	64.3±0.5		129±2

Run 9: $\Delta_l^g H_m$(298.15 K)/kJ·mol^{-1} = (1.92±0.02)ΔH_{trn} (479 K) + (847±0.8); r^2 = 0.9999

Run 11: $\Delta_l^g H_m$(298.15 K)/kJ·mol^{-1} = (2.01±0.01)ΔH_{trn} (480 K) - (3.52±0.5); r^2 = 0.9999

Run 13: $\Delta_l^g H_m$(298.15 K)/kJ·mol^{-1} = (1.65±0.02)ΔH_{trn} (495 K) + (22.0±1.2); r^2 = 0.9996

[a] Uncertainties represent 1 standard deviation

Figure 3-12 shows a plot of the literature vaporization enthalpies vs. the enthalpies of transfer from the column to the gas phase. As can be seen there is a relatively large uncertainty associated with two of the standards.

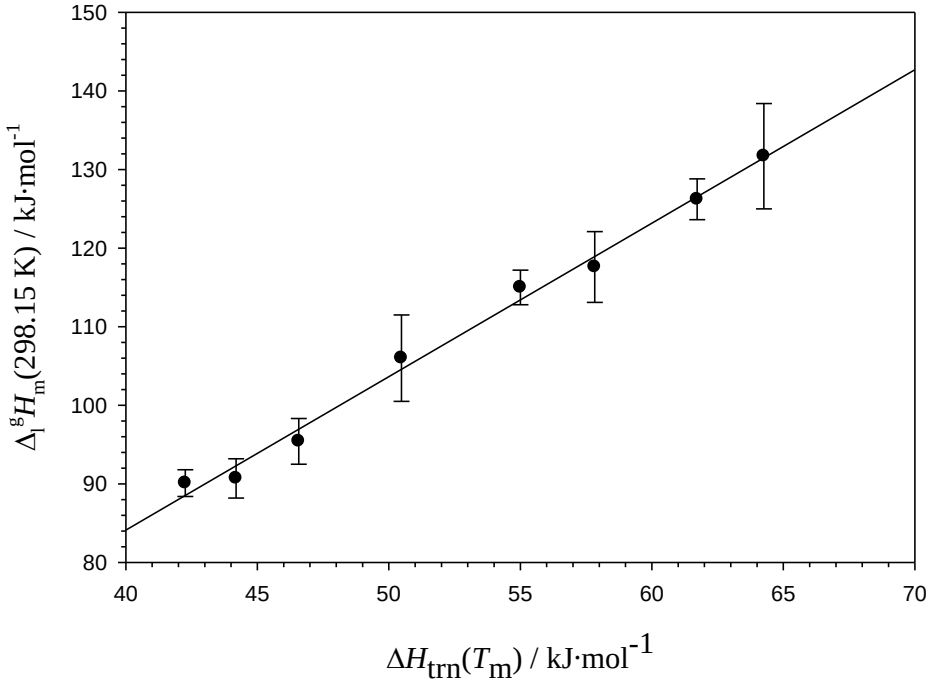

FIGURE 3-12. A plot of literature vaporization enthalpies vs enthalpies of transfer from the column to the gas phase for run 10.

R,S- Fenoprofen (Runs 9-10) and *S*- naproxen (Runs 11-12) vaporization enthalpies were evaluated using standards with similar functional groups. They were also both evaluated using only n-alkylbenzoic acids as standards in Runs 13-14. These results and the comparison can be seen in Table 3-16. The results for each compound calculated with both sets of standards are within experimental error of each other. The value for *S* naproxen is also in good agreement with the value of 132± 7 kJ·mol^{-1} kJ·mol^{-1} reported earlier using both alkyl and alkoxybenzoic acids as standards[18]. Similarly, the vaporization enthalpy for *S* ibuprofen of (105.7±1.3) kJ·mol^{-1}, evaluated using only alkylbenzoic acids as standards is also in good agreement with the previous value of (106±6) kJ·mol^{-1}[18].Replacement of a carbon atom by oxygen in the form of an ether

appears to provide successful correlations. *R,S* Fenoprofen, not measured previously has been found to have a vaporization enthalpy of (128±6) kJ·mol^{-1}at T/K = 298.15 [15].

TABLE 3-16
A Summary of the Vaporization Enthalpies at T/K = 298.15 (kJ·mol^{-1}, p^o = 101325)[a]

Targets	Run 9	Run 10	Run 11	Run 12	Avg[b]	Lit
Fenoprofen	126.2±1.2	125±2			125.6±1.2	
S Naproxen			130.8±0.8	131±2	131±2	131.7±6.7[c]
						132.1±1.8[d]
Standards						
4-Methoxybenzoic acid	91.1±1.0	91±2	90.9±0.7	91±2	91.0±1.4	90.9±2.5[e]
4-Ethoxybenzoic acid	95.4±1.0	96±2	95.5±0.7	96±2	95.5±1.4	95.5±3.0[e]
4-Hexyloxybenzoic acid	121.9±1.2	122±2	122.4±0.8	123±2	122±2	122.2±1.9[e]
4-Heptyloxybenzoic acid			130.3±0.8	130±2	130±2	130.4±1.8[e]
4-Octyloxybenzoic acid	135.2±1.2	135±2			135±2	135.0±2.1[e]
Targets	Run 13	Run 14				
S Ibuprofen	106±2	106±2			106±2	106.0±5.5[c]
Fenoprofen	126±2	126±2			126±2	
S Naproxen	129±2	129±2			129±2	131.7±6.7[c]
						132.1±1.8[d]
Standards						
4-Ethylbenzoic acid	92±2	92±2			92±2	92.2±1.5[f]
4-Hexylbenzoic acid	113±2	113±2			113±2	113.3±1.8[f]
Biphenyl-4-carboxylic acid	118±2	118±2			118±2	117.6±4.5[f]
4-Octylbenzoic acid	124±2	124±2			124±2	123.5±2.6[f]

[a] Uncertainties are one standard deviation.
[b] Average standard deviation.
[c] Ref [19]
[d] Ref [20]
[e] Ref [14]
[f] Ref [13]

Column 3 of Table 3-17 lists the vapor pressures of the standards in the form of ln(p/p^o) calculated from the Clarke and Glew eq at either their fusion temperature or for those forming liquid crystals, their respective crystal to nematic or smectic temperature,

T_f, whichever is lowest. The Clarke and Glew equation and the constants required (discussed in section 2.3.7) have been reprinted below as Eq 16 and Table 3-17.

$$R\cdot\ln(p/p^o) = \Delta^g_{cr}H_m(\theta)\cdot(1/\theta - 1/T) - \Delta^g_{cr}G_m(\theta)/\theta + \Delta^g_{cr}C_p(\theta)\cdot[\theta/T - 1 + \ln(T/\theta)] \quad (15)$$

TABLE 3-17
Parameters of the Clarke and Glew Equation Used, p^o/Pa = 10^5, T/K = 298.15 [a]

Compound	$\Delta_{cr}{}^{g}H_m(\theta)$ kJ·mol^{-1}	$\Delta_{cr}{}^{g}G_m(\theta)$ kJ·mol^{-1}	$\Delta_{cr}{}^{g}Cp$ J·mol^{-1}·K^{-1}	$\Delta_{cr}{}^{g}H_m(T_m/K)$[b] kJ·mol^{-1}
4-Ethylbenzoic acid	100.6±0.7	39.6±0.1	-40±11	99.3±0.5 (328.5)
4-Methoxybenzoic acid	112.6±0.6	48.1±0.1	-28±11	110.6±0.3 (351.3)
4-Ethoxybenzoic acid	121.9±1.0	52.5±0.1	-40±11	119.4±0.5 (361.2
4-Hexylbenzoic acid	122.3±0.9	50.4±0.1	-43±11	119.9±0.7 (355.1)
4-Hexyloxybenzoic acid	139.4±0.9	57.7±0.1	-36±11	130.8±0.4 (371.2)
4-Heptyloxybenzoic acid	157.2±1.2	62.5±0.2	-35±11	155.1±1.0 (358.3)
4-Octylbenzoic acid	133.3±1.6	56.3±0.3	-41±11	130.7±1.3 (361.2)
4-Octyloxybenzoic acid	161.4±1.2	64.8±0.2	-34±11	141.1±0.9 (367.8)

[a] Refs [13, 14]
[b] Sublimation enthalpy at the mean temperature of measurement.

Using the literature sublimation enthalpy measured at the mean temperature (provided in the last column of Table 2-10)[13, 14], the sublimation enthalpy of each standard was adjusted to each respective T_{fus} or T_f. Column four of Table 3-17 includes the temperature adjustment and the adjusted sublimation enthalpy at T_{fus} or (T_f) is reported in the fifth column. The corresponding vaporization enthalpies at T_{fus} (column 6 of Table 3-21) for 4-ethyl-, 4-methoxy, 4-ethoxy and 4-hexyloxybenzoic acids, were calculated by subtracting the fusion enthalpy (column 2 of Table 3-14) from the corresponding sublimation enthalpy, column 5 of Table 3-19 according to eq (6). For the benzoic acids that form liquid crystals, the fusion enthalpy included all phase change enthalpies

occurring from conversion of the crystal to the liquid crystal, T_f, including the transitions to the clearing temperature.[15]

The temperature dependence of the subcooled liquid vapor pressures of the standards were calculated using the integrated form of the Clausius-Clapeyron equation modified to include a heat capacity adjustment for liquids, eq 5A. This equation was then applied to calculate the subcooled vapor pressures of the standards at T/K = 298.15 and over the range of temperatures from T/K = (283.15 to 313.15). While eq 5A has not been used previously in this manner, a related equation, 5B dealing with sublimation vapor pressures has been found to reproduce experimental vapor pressures of a variety of crystalline materials within a factor of three[21]. A similar degree of accuracy for eq 5A is expected based on the results obtained for ibuprofen described below. The last column of Table 3-18 reports the sub-cooled liquid vapor pressure of the standards at T/K = 298.15 in the form of $\ln(p_l/p^o)$. The liquid vapor pressure equations evaluated for the standards over the temperature range T/K = (283.15 to 313.15) are provided in Table 3-19A. As a measure of quality control, the vaporization enthalpies calculated using these equations are compared to the values reported in Table 3-16 by direct correlation in the last two columns of Table 3-19A. Most results are within their experimental uncertainty.

TABLE 3-19
Parameters Used in Eq 5A for Calculating Liquid Vapor Pressures at *T*/K = 298.15

	T_m[a]/T_{fus}/T_f[b] / K	$\ln(p/p^o)_{Tfus}$[c]	$\Delta Cp(cr)\cdot\Delta T$[d] / kJ·mol^{-1}	$\Delta_{cr}{}^{g}H_m(T_{f,fus})$[e] / kJ·mol^{-1}	$\Delta_l{}^{g}H_m(T_{f,fus})$[f] / kJ·mol^{-1}	$\ln(p_l/p^o)_{298}$[g]
4-Ethylbenzoic acid	328/385.2	-7.0±0.3	-1.8±0.5	97.5±0.9	85±2	-15.1±0.1
4-Methoxybenzoic acid	351.3/455.3	-4.2±0.3	-3.6±1.1	107.0±1.1	78±3	-15.9±0.1
4-Ethoxybenzoic acid	377.8/471.8	-3.5±0.4	-3.6±1.1	116±2	81±3	-16.7±0.2
4-Hexylbenzoic acid	355.1/370.6[b]	-10.8±0.4	-0.7±0.2	119.2±0.3	105±2	-19.4±0.1
4-Hexyloxybenzoic acid	371.2/380[b]	-11.3±0.4	-0.5±0.1	130.3±0.4	114±2[g]	-21.6±0.1
4-Heptyloxybenzoic acid	358.3/365.4[b]	-13.6±0.5	-0.4±0.1	154.7±1.0	123±2	-23.1±0.1
4-Octylbenzoic acid	361.2/373.3[b]	-12.0±0.7	-0.1±0.2	135.9±1.3[f]	115±2[h]	-21.7±0.5
4-Octyloxybenzoic acid	367.8/374.5[b]	-13.5±0.5	-0.4±0.1	140.7±0.9	126±2	-24.3±0.5

[a] T_m: the mean temperature of vapor pressure measurements of the crystalline acid; T_{fus}: the fusion temperature;
[b] T_f: temperature of transition of the crystal to the nematic or smectic phase, whichever is lower.
[c] The sublimation vapor pressure relative to atmospheric pressure (10^5 Pa) at T_{fus} or T_f calculated by the Clarke and Glew equation ($p = p_{cr} = p_l$); for liquid crystals $T_f = T_{cr\rightarrow liquid\ crystal}$.
[d] Heat capacity adjustment from T_m to T_{fus} or T_f using eq 7.
[e] Sublimation enthalpy at T_{fus} calculated by adjusting the sublimation enthalpy measured at T_m (Table 2-10 , column 5) for temperature and adding any cr → cr transitions occurring above T_m.
[f] Vaporization enthalpy at T_{fus} calculated by subtracting the fusion enthalpy or total solid to isotropic liquid phase change enthalpy from column 5
[g] Sub-cooled liquid vapor pressure calculated at T/K = 298.15 using Eq 5A.

For the Fenoprofen study, the equations in Table 3-19A were used to evaluate $\ln(p_l/p^o)$ for the standards using calculated values of $\ln(t_o/t_a)_{avg}$ from standards and target analytes in Runs 9-14. Values of $(t_o/t_a)_{avg}$ were calculated from the slope and intercept of each run, averaged, then the logarithm was taken of the average. The last two columns of Table 3-19A compare the results of vaporization enthalpies calculated from equation 5A to the vaporization enthalpies summarized in Table 3-20. Most of these are within experimental error of each other.

TABLE 3-20

Slopes, Intercepts and Vaporization Enthalpies of Liquid Alkyl and Alkoxybenzoic Acids at T_m/K = 298.15 Calculated Using Equation 5A, p^o/Pa = 10^5

A. Standards	Sub-Cooled Vapor Pressure Equations from Runs 13/14 [a]	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} Eq 5A	Table 3-16
4-Ethylbenzoic acid	$\ln(p_l/p^o)$ =(21.80±0.05) - (10950±20)/T	91.0±0.1	92.2±0.7
4-Methoxybenzoic acid	$\ln(p_l/p^o)$ =(20.01±0.04) - (10650±12)/T	88.5±0.1	91±3
4-Ethoxybenzoic acid	$\ln(p_l/p^o)$ =(20.84±0.04) - (11149±13)/T	92.7±0.1	96±3
4-Hexylbenzoic acid	$\ln(p_l/p^o)$ =(26.10±0.07) - (13580±20)/T	112.9±0.2	113±2
4-Hexyloxybenzoic acid	$\ln(p_l/p^o)$ =(27.64±0.07) - (14740±20)/T	122.5±0.2	122±2
4-Heptyloxybenzoic acid	$\ln(p_l/p^o)$ =(29.78±0.08) - (15760±30)/T	131.1±0.2	130±2
4-Octylbenzoic acid	$\ln(p_l/p^o)$ =(30.54±0.09) - (16350±30)/T	123.4±0.2	124.1±0.7
4-Octyloxybenzoic acid	$\ln(p_l/p^o)$ =(30.53±0.09) - (16350±30)/T	135.9±0.2	135±2
	Sub-Cooled Liquid Vapor Pressure Equations [b]		
B. Targets		Eq 5A	Table 3-16
S Ibuprofen; Runs 13/14	$\ln(p_l/p^o)$ = (24.53±0.02) - (12630±0.5)/T	105.0±0.2	105.8±0.7
R,S Fenoprofen; Runs 9/10	$\ln(p_l/p^o)$ = (28.35±0.003) - (15228±0.4)/T	126.6±0.01	125.6±1.2
S Naproxen; Runs 11/12	$\ln(p_l/p^o)$ = (29.71±0.001) - (15938±1.0)/T	132.5±0.01	131±2
4-Biphenylcarboxylic acid; Runs 13/14	$\ln(p_l/p^o)$ = (26.49±0.01) - (14077±1.0)/T	117.0±0.2	118±5
C. Targets	Sub-Cooled and Liquid Vapor Pressure Equations from Runs 13/14[c]		
S Ibuprofen	$\ln(p_l/p^o)$ = (23.61±0.02) – (12366±0.02)/T	102.8±0.01	105.8±0.7
R,S Fenoprofen	$\ln(p_l/p^o)$ = (28.48±0.01) – (15070.5±0. 2)/T	125.3±0.01	125.6±1.2
S Naproxen;	$\ln(p_l/p^o)$ =(29.12±0.003) - (15494.7±1.0)/T	128.8±0.01	131±2
4-Biphenylcarboxylic acid	$\ln(p_l/p^o)$ = (26.49±0.01) – (14067.0±1.2)/T	116.9±0.01	118±5

[a] Sub-cooled liquid vapor pressure equations evaluated using the Clasius of the standards to calculate $\ln(p/p^o)$ at T_{fus} of each standard at the mean temperature of measurement, Eq 5A and the parameters reported in Table 3-17 to evaluate the vapor pressures over the temperature range T/K =(T_{fus} to 298.15).

[b] Vapor pressure equations evaluated from correlations between $\ln(p_l/p^o)$ and $\ln(t_o/t_a)$ of only standards in Table 3-19A with the same functional group also over the temperature range T/K = (283.15 to 313.15). All correlations characterized by $r^2 > 0.99$.

[c] Vapor pressure equations evaluated from correlations between $\ln(p_l/p^o)$ and $\ln(t_o/t_a)$ using all the standards in Table 3-19A in Runs 13/14 also over the temperature range T/K = (283.15 to 313.15). All correlations characterized by $r^2 > 0.99$.

The vapor pressure results of the Table 3-20 calculations are shown in Table 3-21. At the bottom of Table 3-21, the correlation equation has been given for each set of runs. As can be seen, the r^2 values are all greater than 0.999. The vapor pressures of the target compounds were calculated from these equations. The equations were generated from run data over the temperature range of T= 283.15 – 313.15 K. The calculated vapor pressures for compounds that were included in more than one mix are compared in the fifth and sixth columns. Slightly larger vapor pressures are predicted by the alkylbenzoic acids but the results still remain within the experimental uncertainties cited. There do not appear to be any experimental values available for either the standards or targets. *S* Ibuprofen and biphenyl-4-carboxylic acid were evaluated using only the alkylbenzoic acids as standards in Runs 13/14 while *R,S* Fenoprofen and *S* naproxen were evaluated using the alkoxybenzoic acids from Runs 9/10 and 11/12, respectively. Columns 5 and 7 of Table 3-21 compare the liquid vapor pressure values calculated in this work to estimated values.[22]These results do not agree as well. Differences are between two and three orders of magnitude for the larger acids. The vapor pressure of Fenoprofen, for instance, was calculated as (0.4±0.3)Pa vs. the estimate of 31.3Pa. Another way to put the experimental data into perspective is to look at the uncertainties, which in some cases are around 25% of the calculated values.[15]

TABLE 3-21
Results of Correlations Between $\ln(t_o/t_a)_{avg}$ and $\ln(p_l/p^o)$. Sub-cooled Liquid Vapor Pressures of *R*,*S* Fenoprofen, *S* Naproxen, *S* Ibuprofen and the Alkoxybenzoic Acids and a Comparison of Results Using Different Standards at *T*/K =298.15[a]

Run 9/10	$n(t_o/t_a)_{avg}$	$\ln(p_l/p^o)$	$\ln(p_l/p^o)_{calc}$	$10^4 \cdot p_l$/Pa (298.15 K) Run 9/10	$10^4 \cdot p_l$/Pa (298.15 K)	$10^4 \cdot p_l$/Pa [b] (298.15 K) Est
4-Methoxybenzoic acid	-6.86	-15.93	-15.9±0.3	130±30		9000
4-Ethoxybenzoic acid	-7.45	-16.65	-16.7±0.3	60±20		2800
4-Hexyloxybenzoic acid	-11.03	-21.59	-21.6±0.3	0.38±0.12		330
R,*S* Fenoprofen	-11.72		-22.7±0.3	0.14±0.05		31
4-Octyloxybenzoic acid	-12.83	-24.31	-24.2±0.4	0.03±0.01		48
Run 11/12					From Run 9/10	
4-Methoxybenzoic acid	-7.07	-15.93	-15.9±0.4	130±40	130±30	9000
4-Ethoxybenzoic acid	-7.67	-16.65	-16.7±0.5	60±20	60±20	2800
4-Hexyloxybenzoic acid	-11.17	-21.59	-21.7±0.5	0.39±0.13	0.38±0.12	330
4-Heptyloxybenzoic acid	-12.13	-23.09	-23.0±0.6	0.10±0.03		90
S Naproxen	-12.54		-23.6±0.6	0.06±0.02	0.12±0.001	34
Run 13/14					From 9/10 or 11/12	
4-Ethylbenzoic acid	-6.32	-15.00	-15.0±0.6	310±2		6500
4-Methoxybenzoic acid	-6.86		-15.7±0.6	150±1	130±30/130±30	9000
4-Ethoxybenzoic acid	-7.48		-16.5±0.6	69±0.4	60±20/60±20	2800
S Ibuprofen	-8.55		-17.9±0.7	17±0.1		760
4-Hexylbenzoic acid	-9.77	-19.44	19.4±0.7	3.6±0.02		330
Biphenyl-4-carboxylic acid	-10.75		-20.7±0.8	1.0±0.01		68
4-Octylbenzoic acid	-11.54	-21.72	-21.4±0.8	0.4±.002		92
R,*S* Fenoprofen	-11.82		-22.1±0.8	0.26±0.002	0.38±0.12	31
S Naproxen	-12.43		-22.9±0.8	0.12±0.001	0.06±0.02	0.0034

Runs 9/10: $\ln(p/p^o) = (1.40\pm0.02)\ln(t_o/t_a) - (6.3\pm0.2)$; $r^2 = 0.9995$
Runs 11/12: $\ln(p/p^o) = (1.42\pm0.02)\ln(t_o/t_a) - (5.9\pm0.2)$; $r^2 = 0.9995$
Runs 13/14: $\ln(p/p^o) = (1.26\pm0.03)\ln(t_o/t_a) - (7.2\pm0.2)$; $r^2 = 0.9987$

[a] Uncertainties represent 1 standard deviation; vapor pressures are believed accurate to within a factor of three.
[b] Estimated, ref [6]

While there are no experimental sub-cooled liquid vapor pressure data available in the literature for comparison of the result in Table 3-21, vapor pressures of crystalline racemic and chiral ibuprofen and chiral naproxen have been reported.[20, 23, 24]

Vapor pressures for both racemic and chiral ibuprofen are available at T/K = 298.15. The fusion temperature of *S* naproxen at T_{fus}/K = 482 lies well above the temperature range at which vapor pressures evaluated indirectly from the Clarke and Glew equation are likely applicable. However, T_{fus}/K = 324.3 for *S* ibuprofen falls within this range. Consequently, liquid vapor pressures of the alkylbenzoic acids from Runs 13/14 were also evaluated at the fusion temperature of *S* ibuprofen, T_{fus}/K = 324.3, using eq 5A, and the appropriate terms in columns 2, 3 and 6 of Table 3-19. Values of $\ln(p_l/p^o)$of the alkylbenzoic acids were then correlated with their corresponding values of $\ln(t_o/t_a)_{avg}$ evaluated at the fusion temperature of (S)-ibuprofen. The resulting equation in combination with the corresponding value of $\ln(t_o/t_a)_{avg}$ for (S)-ibuprofen was then used to evaluate its vapor pressure at this temperature. A value of $\ln(p_l/p^o)= \ln(p_{cr}/p^o)= -(14.4\pm0.6)$ at T/K = 324.3 was obtained. The vaporization enthalpy of (S)-ibuprofen was adjusted for temperature from T/K = 298.15 to T_{fus}/K = 324.3 using eq (9). A vaporization enthalpy of (102.4±1.4) kJ·mol^{-1} was calculated at this temperature. A sublimation enthalpy of (121±2) kJ·mol^{-1} is obtained by combining this value with the fusion enthalpy of (18.4±0.6) kJ·mol^{-1}. Applying the sublimation enthalpy and the value of $\ln(p_{cr}/p^o)$ evaluated at the fusion temperature to eq (5B) resulted in a value of $\ln(p/p^o)= -(18.3\pm0.6)$ at T/K = 298.15. These calculations are summarized in Table 3-22.[15]

Vaporization enthalpies of chiral and racemic materials are generally quite similar as are their liquid vapor pressures.[16] An approximate vapor pressure of (*R*,*S*)-ibuprofen was estimated in a similar manner, also summarized in Table 3-22. Liquid vapor pressures of the 4-alkylbenzoic acids were calculated at the fusion temperature of *R*,*S* ibuprofen, T_{fus}/K = 347.5, using eq (5A), the appropriate vaporization enthalpies and

liquid vapor pressures evaluated at fusion temperature of each respective 4-alkylbenzoic acid, Table 3-19 (columns 6 and 3 respectively). These values were then correlated with the corresponding values of $\ln(t_o/t_a)_{avg}$ also evaluated at T_{fus}/K using the value for *S* ibuprofen as a surrogate. A value of $\ln(p/p^o) = -(11.9\pm0.6)$ was obtained for *R*,*S* ibuprofen. Using the vaporization enthalpy of *S* ibuprofen at *T*/K = 298.15 for the racemic form and adjusting it to T_{fus} of the racemic mixture, resulted in a value of (100.2±1.3) kJ·mol^{-1}. Combined with a fusion enthalpy of (26.4±1.0) kJ·mol^{-1} for *R*,*S* ibuprofen,[19] a sublimation enthalpy of (127±2) kJ·mol^{-1} and the value of $\ln(p_{cr}/p^o)_{Tfus} = -(11.9\pm0.6)$ applied to eq (5B) resulted in a value of $\ln(p_{cr}/p^o) = -(19.2\pm0.6)$ at *T*/K = 298.15, Table 3-22.[15]

TABLE 3-22
Evaluation of the Vapor Pressure of Crystalline (*S*) and (*R*,*S*)-Ibuprofen at *T*/K = 298.15; Uncertainties are One Standard Deviation

	T_{fus} / K	$\ln(p/p^o)_{Tfus}$ [a]	$Cp(l)/Cp(cr)$ / J·K·mol^{-1}	$\Delta Cp(l)\cdot\Delta T$ / kJ·mol^{-1}	$\Delta_l^g H_m(T_{fus})$ / kJ·mol^{-1}	$\Delta_{cr}^l H_m(T_{fus})$ / kJ·mol^{-1}	$\Delta_{cr}^g H_m(T_{fus})$ / kJ·mol^{-1}	$\ln(p_l/p^o)_{298\ K}$
(S)	324.3	-14.48±0.03	386.6/294.8	-2.9±0.4	102.4±1.4	18.4±0.6	121±2	-18.3±0.6
(R,S)	347.5	-11.97±0.06	386.6/294.8	-5.5±0.8	100±2	26.4±1.0	127±2	-19.2±0.6

[a] $p = p_{cr} = p_l$.

The vapor pressures of racemic and chiral ibuprofen and their sublimation enthalpies estimated in this work are compared to literature values in Table 3-23. The literature values include sublimation enthalpies measured directly. Vapor pressures measured by Perlovitch et al.[23] are by transpiration and those by Ertel et al.[24] are by Knudsen effusion. For *S* ibuprofen, our vapor pressure estimate agrees within a factor of three despite the fact that our sublimation enthalpy is considerably larger than the value reported by Perlovitch et al. For *R*,*S* ibuprofen, our vapor pressure estimate is smaller but with consideration of the uncertainty cited, also differs within a factor of three. Our

sublimation enthalpies for racemic S ibuprofen are also somewhat larger than both literature values. While this agreement may be fortuitous, the statement made above regarding the accuracy of eq (5A) is based on this result. As noted by Perlovitch et al.[23], the sublimation enthalpy reported by Ertel on the racemic material combined Knudsen effusion measurements using two orifices. Segregating the measurements by orifice size resulted in measurements of (117±2) kJ·mol^{-1}, in better agreement with the transpiration results and (124 ±2) kJ·mol^{-1}, in better agreement with these estimates.[15, 23]

TABLE 3-23
A Comparison of Vapor Pressures of Crystalline *S* and *R,S* Ibuprofen Estimated in This Work With Literature Values

(S)-Ibuprofen	$10^4 \cdot (p_{cr})_{298\ K}$/Pa	$\Delta_{cr}^{g}H_m$(298 K) kJ·mol^{-1}	(R,S)-Ibuprofen	$10^4 \cdot (p_{cr})_{298\ K}$/Pa	$\Delta_{cr}^{g}H_m$(298 K) kJ·mol^{-1}
This work	11±7	122±2	This work	5±2	129±2[a]
Perlovitch et al.[b]	53±11	107.8±0.5	Perlovitch et al.[b]	18±4	115.8±0.6
			Ertel[d]	11.8	121.8[b]

[a] Evaluated by combining the vaporization enthalpy of *S* ibuprofen (100.2±1.3 kJ·mol^{-1}) with the fusion enthalpy of (R,S)-ibuprofen (26.4±1.0 kJ·mol^{-1}) both at T_{fus}/K = 347.5 and adjusting the sublimation enthalpy to *T*/K = 298.15 using Eq (7).
[b] Ref [23]
[c] Ref [24]
[d] Measured at an estimated mean temperature of *T*/K = 315. Adjusted to *T*/K = 298.15 results in a value of 122.6 kJ·mol^{-1}.

3.4. Alcohols

3.4.1. Patchouli Oil Components

Initially, the patchouli oil sample was dissolved in methylene chloride and injected on the gas chromatograph using a SPB-5 15m column to see if proper separation of compounds could be achieved. Figure 3-13 shows a typical chromatogram of the patchouli oil sample.

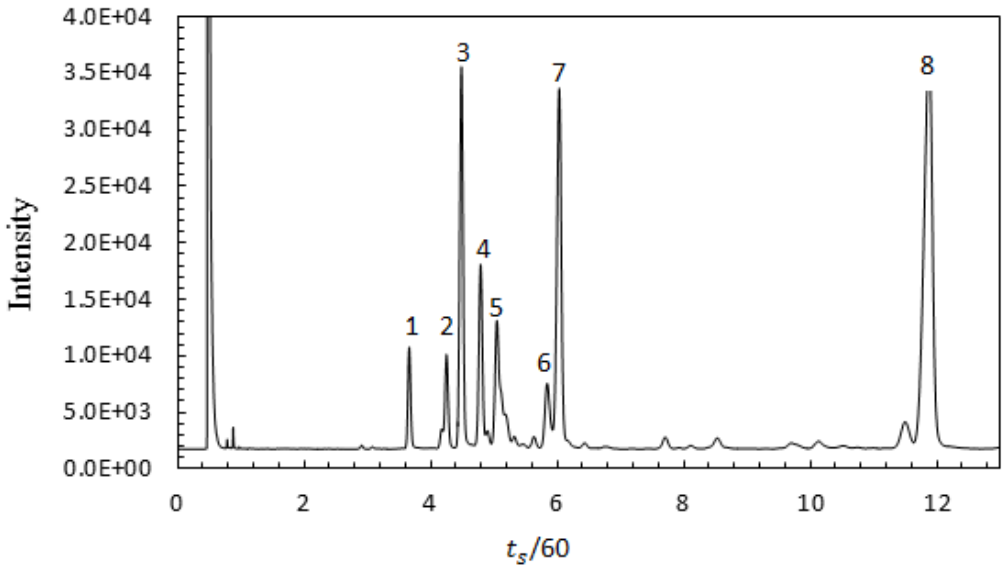

FIGURE 3-13. A gas chromatogram of the patchouli oil sample generated in this study with a 15m SPB-5 column at an oven temperature of T = 418.15 K. From left to right: (1) β-patchoulene; (2) caryophyllene; (3) α-guaiene (all *cis*); (4) seychellene; (5) α-patchoulene; (6) guaiene; (7) δ-guaiene; (8) patchouli alcohol

After the compounds were separated on the SPB-5 column, the sample was taken and injected on a GC-MS instrument with an 11m HP-1 Ultra column, electron impact (EI) ionization source and quadrupole mass analyzer. 50eV were used at the ionization source as opposed to the standard 70eV due to an aging instrument that was completely fragmenting the molecular ion. As many of the compounds present are structural isomers of each other, identification was a little difficult from the EI spectra alone. The experimental spectra were compared to those available from the NIST library. Example spectra compared to NIST library structures can be seen in Figures 3-14 and 3-15.

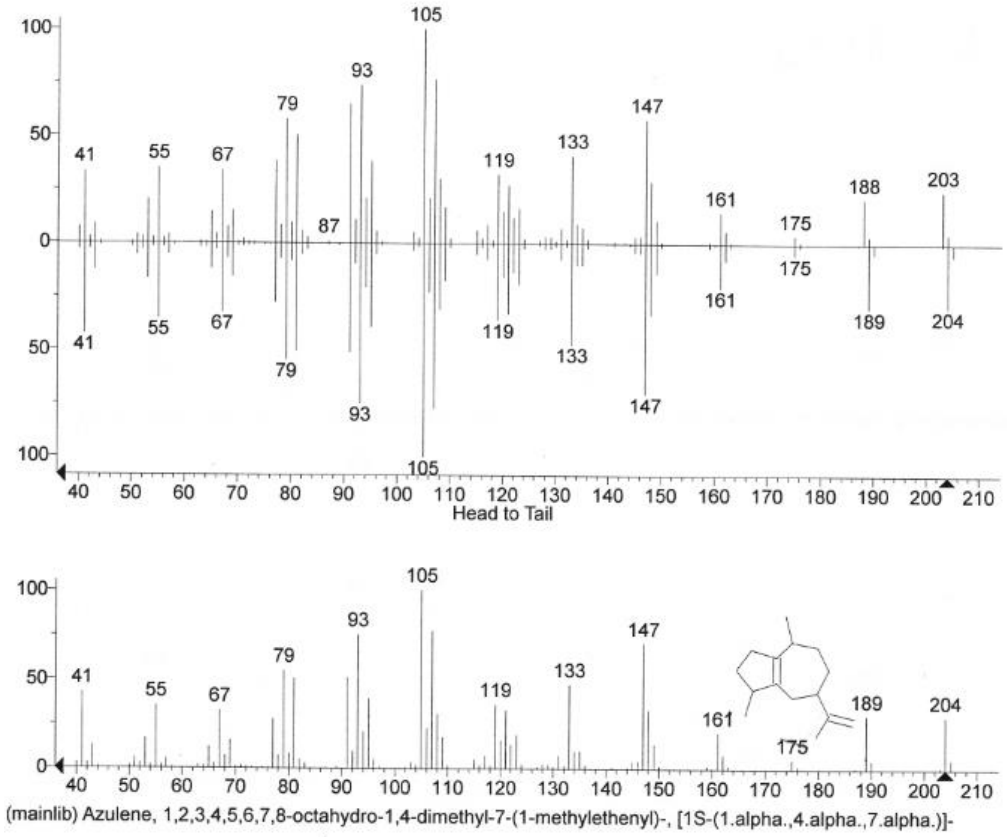

FIGURE 3-14. An example mass spectra is given and compared to the NIST library structure. This particular compound is α-guaiene. It is one of the more abundant compounds in the patchouli oil sample and it eluted third in Figure 3-13.

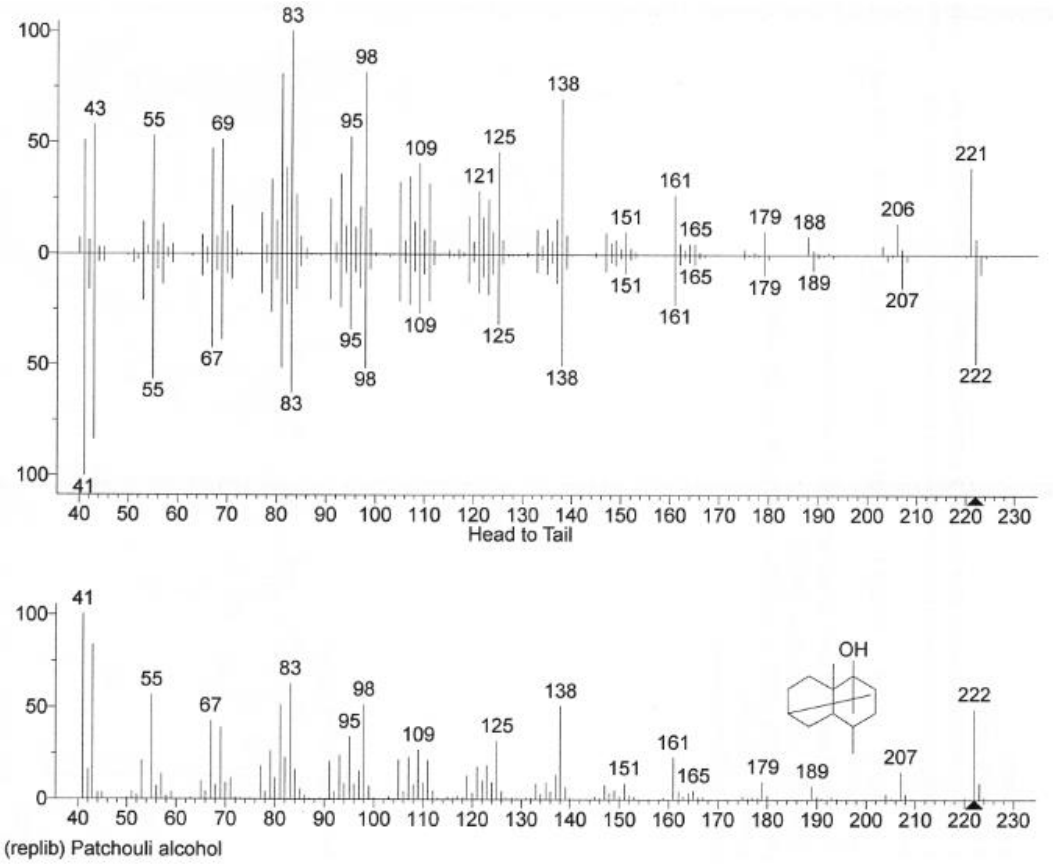

FIGURE 3-15. An example mass spectra is given and compared to the NIST library structure. This particular compound is patchouli alcohol. It is the most abundant compound in the patchouli oil sample and it eluted last as seen in Figure 3-13.

To further aid in identification, the relative peak areas and proposed structures were compared to literature published by Restek.[25] The experimental results on the 11m HP-1 Ultra column were favorable when compared to the Restek literature which used a Rtx-5SiMS. The elution order, however, was different. The Restek literature is reproduced below in Figure 3-16. [25] The closest that the Restek literature chromatogram could be matched using an isothermal oven temperature on the 15m SPB-5 column was at T = 393.15 K. This chromatogram has been provided in Figure 3-17.[15]

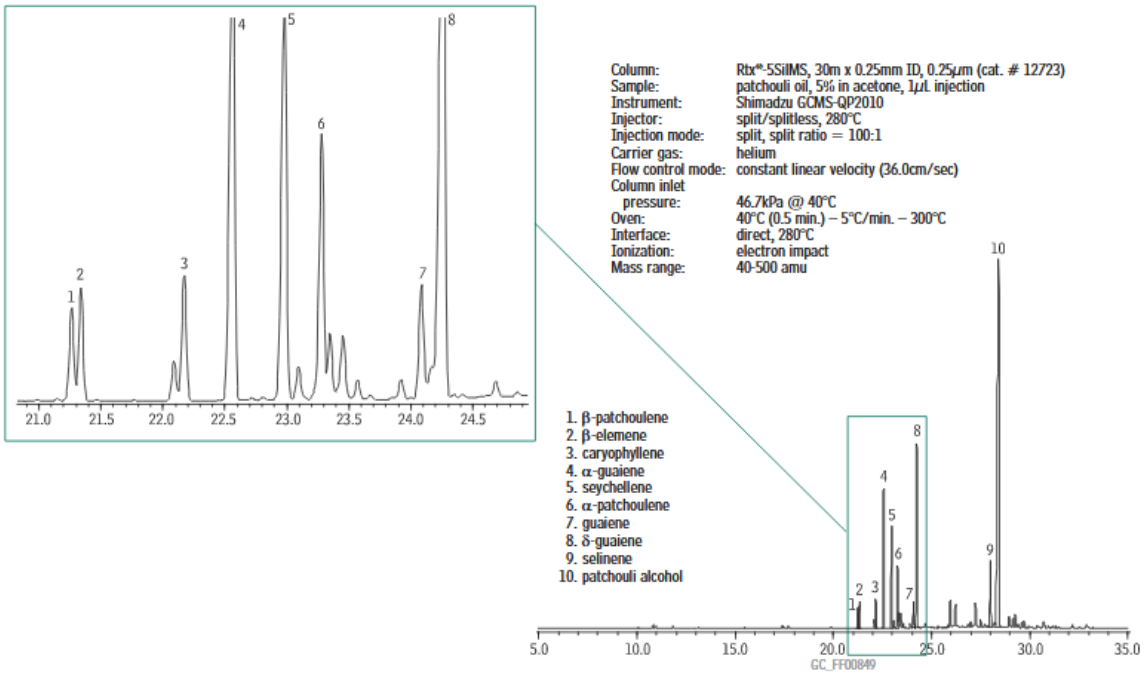

FIGURE 3-16. Restek has published this gas chromatogram of patchouli oil on their website. The column used was a Rtx-5SiMS. The elution order differs slightly from that seen in Figure 3-13.[25]

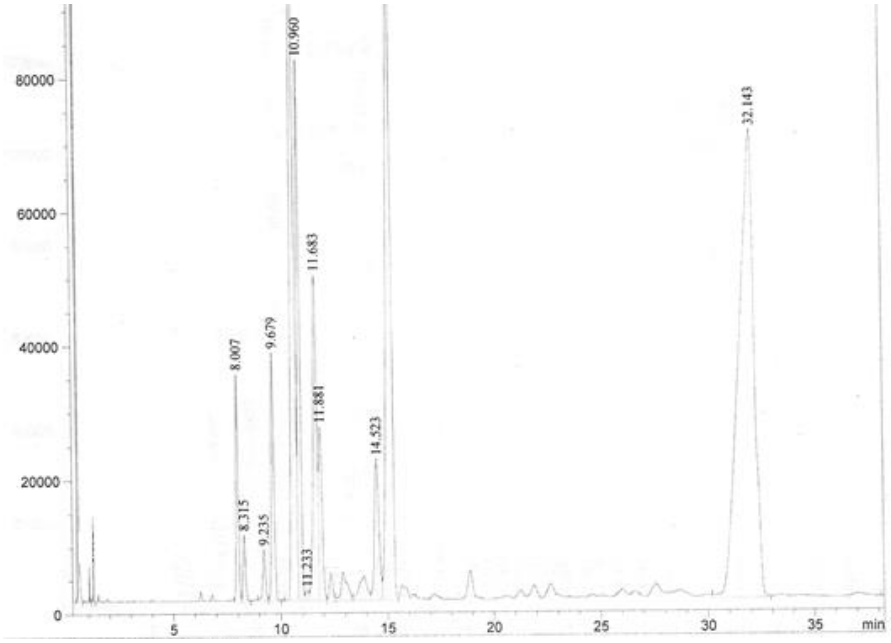

FIGURE 3-17. This chromatogram taken on a HP-5890 with a 15m SPB-5 column with an isothermal oven temp, T = 393.15 K, is the closest that the Restek chromatogram could be reproduced [15]. The Restek chromatogram in Fig 3-15 was generated on a different column and was done with a temperature ramp program.

Nine out of the ten compounds that Restek identified were found in the patchouli oil sample in this study. There was another compound that separated that could've been the one reported (selinene) by Restek, but it couldn't be positively identified in this analysis. Two different temperature programs were needed to identify all of the compounds as some compounds co-eluted at the lower temperature and different compounds co-eluted at the higher temperature. The Kovats Retention Index (RI) was taken for each of the compounds to further aid in identification. It should be noted, however, that the RI values are a function of temperature. Table 3-24 is a comparison of the compounds identified in each.

TABLE 3-24
Summary of compounds found in the patchouli oil sample. In order of elution from Restek literature.

Compound	Kovats Index		Present in	
	Lit	Exp	Restek Lit	This work
β-Patchoulene	1381[a]	1377[b]	Yes	Yes
β-Elemene	1390[a]	1383[b]	Yes	Yes[c]
Caryophyllene	1419[a]	1424[d]	Yes	Yes
α-Guaiene	1439[a]	1441[e]	Yes	Yes
Seychellene	1460[f]	1445[e]	Yes	Yes
α-Patchoulene	1456[a]	1456[e]	Yes	Yes
Guaiene	1490[f]	1453[d]	Yes	Yes
δ-Guaiene	1509[a]	1504[e]	Yes	Yes
Selinene	1517[g]	N/A[h]	Yes	No[g]
Patchouli Alcohol	1640[c]	1649	Yes	Yes

[a] Ref [26]
[b] The author thanks Manu Kuria for running the alkane retention index GC program on this compound.
[c] This peak identified in a different temperature program than the one shown in Figure 3-13. It co-elutes with peak 1 in Figure 3-13.
[d] The author thanks Megan Orf for running the alkane retention index GC program on this compound.
[e] The author thanks Lorna Espinosa for running the alkane retention index GC program on this compound.
[f] Ref [27]
[g] Ref [28]
[h] In a different temperature program than the one shown in Figure 3-13 a peak that co-eluted was able to be separated from patchouli alcohol. This peak was not able to be positively identified, but eluted shortly after patchouli alcohol and with a much lower abundance.

As can be seen in Table 3-24, many of the experimental and literature values for retention index are similar, however, there are a couple that differ by 15 or more; namely seychellene and guaiene. The literature numbers were all taken from DB-5 columns as was used in our lab. Although retention index numbers are often described to be independent of temperature, in reality there is some temperature dependence. The large retention index differences for those compounds could be due to a different temperature program using a ramp instead of isothermal conditions, or it could simply be due to a much higher or much lower oven temperature than was experimentally used in our lab. Even with these differences in mind, it should still be noted that all compounds still eluted between the same n-alkanes as reported in the literature.

3.4.2. Patchouli Alcohol Vaporization Enthalpy

When identification of the compounds was completed, the vaporization enthalpies were measured on the 15m SPB-5 column. Figure 3-18 shows a typical gas chromatogram of the patchouli oil with standards spiked in. The inset, labeled 4, are the compounds in patchouli oil which can be more clearly seen in Figure 3-13.

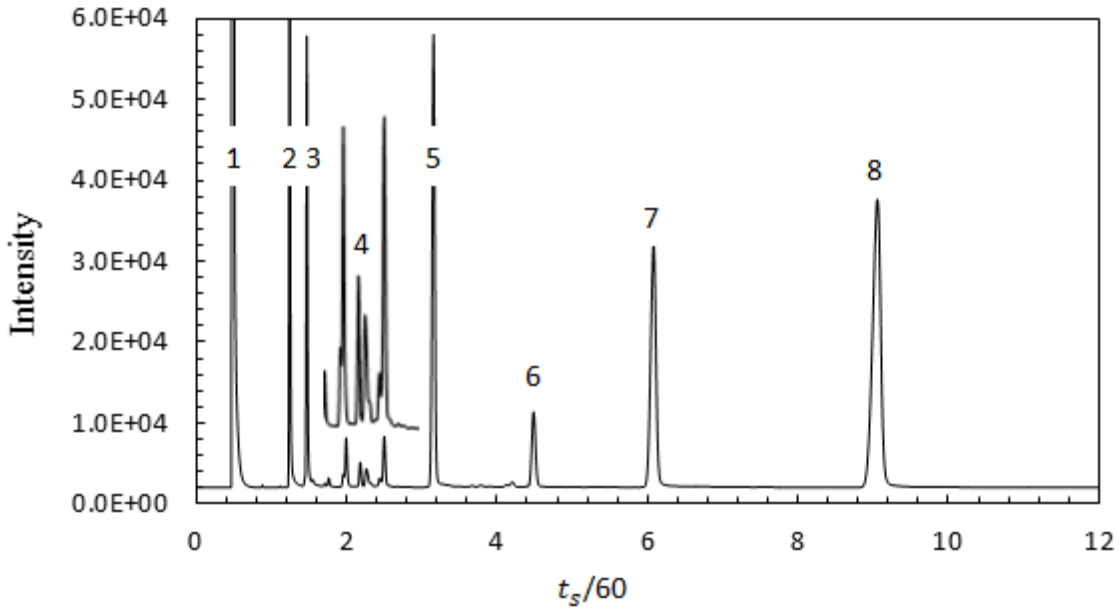

FIGURE 3-18. The initial patchouli oil runs were performed by simply spiking in standards and diluting with dichloromethane and run on a SPB-5 column at an oven temperature of T = 449 K. From left to right: (1) DCM; (2) 1-adamantanol; (3) 1-undecanol; (4) patchouli oil compounds-*see Figure 3-13*; (5) 2-tetradecanol; (6) patchouli alcohol; (7) 1-pentadecanol; (8) 1-hexadecanol

Primary, secondary, and tertiary alcohols were all introduced into the patchouli oil sample. Methylene chloride was used as the non-retained standard. Initially, all of the alcohol standards that had literature vaporization enthalpy data available were plotted in the vaporization enthalpies vs enthalpies of transfer plot shown in Figure 3-19. The correlation seems to be poor.

However, if 2-tetradecanol isn't included as a standard and the remaining three standards are used, the r^2 value increases significantly to 0.9999 and the error bars decrease significantly. This improved correlation can be seen in Figure 3-20.

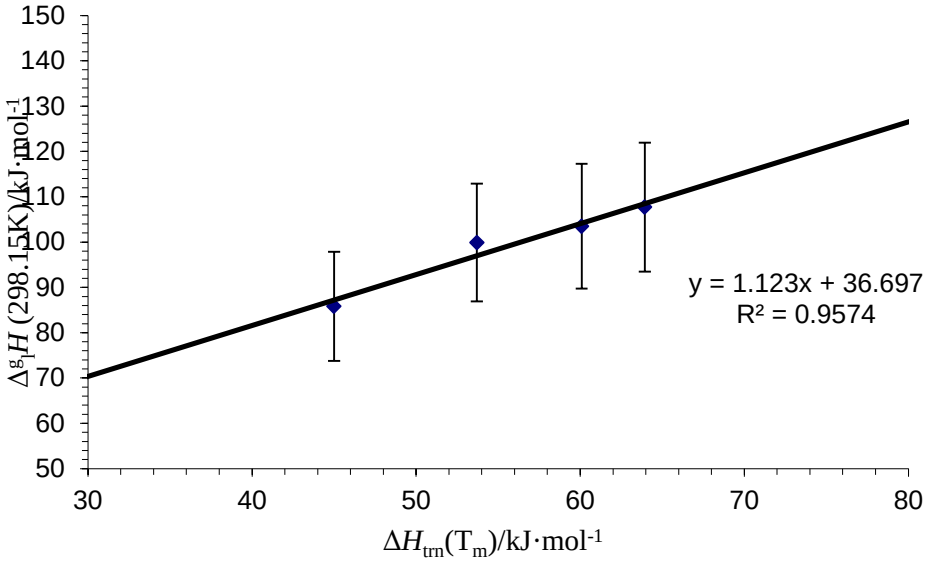

FIGURE 3-19. A plot of literature vaporization enthalpies vs enthalpies of transfer from the column to the gas phase. Using 1-pentadecanol, 1-undecanol, 1-hexadecanol, and 2-tetradecanol as standards, the $r^2 < 0.99$ is not ideal and the error for each standard is on the order of 12-14kJ/mol. 2-tetradecanol is the outlier and doesn't seem to be an appropriate choice for a standard when using primary alcohols.

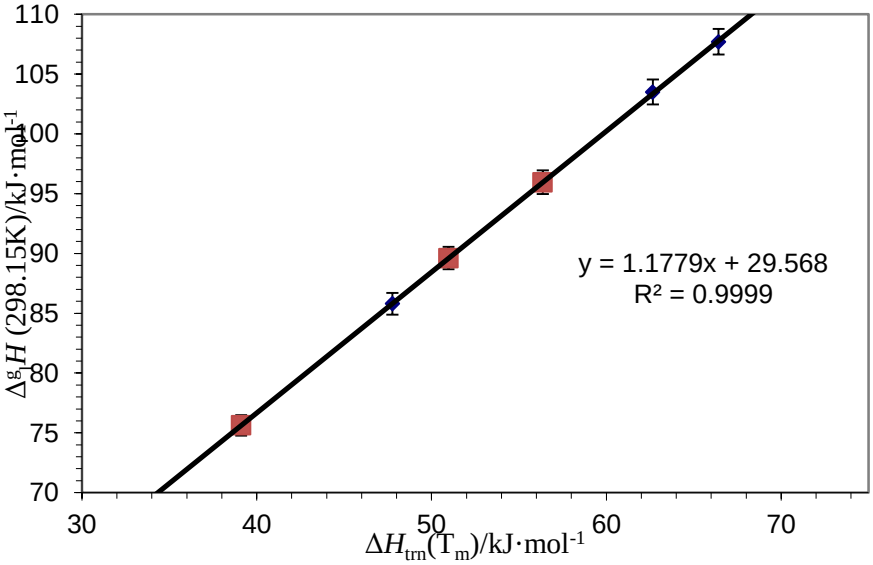

FIGURE 3-20. When taking out 2-tetradecanol, the other three standards correlate quite well. The r^2 value is much higher and the error bars are now on the order of 1kJ/mol. The blue diamonds are the standards and the red squares are the target analytes.

Although using only three standards is less than ideal, the calculations were carried out and the computed enthalpies from experimental data were compared to literature values. The calculated vaporization enthalpies for the standards and target analytes may be seen in Table 3-25. Since only three standards were used and since all of the standards are primary alcohols these vaporization enthalpy values should be used as a rough estimate. This experiment should be repeated with more appropriate standards such as secondary and tertiary alcohols if values are available in literature. Furthermore, the retention times measured for these compounds did not tend to correlate well enough for vapor pressure calculations.

TABLE 3-25

Data showing relationship between the enthalpy of transfer at 434K and the enthalpy of vaporization at 298K. *This data set was generated without using 2-tetradecanol as a standard.*

Runs 15 & 16	- slope *T*/K	intercept	ΔH_{trn}(374 K) kJ·mol^{-1}	$\Delta_l^g H_m$(298 K) kJ·mol^{-1} (lit)	$\Delta_l^g H_m$(298 K) kJ·mol^{-1}(calc)
1-Pentadecanol	7200±200	14.3±0.4	60±2	104±3[a]	103.4±1.1
	7540±40	15.08±0.08	62.7±0.3		103.4±1.0
1-Undecanol	5400±200	12.0±0.4	45±2	86±2[a]	85.8±1.0
	5740±30	12.82±0.08	47.8±0.3		85.8±0.9
1-Hexadecanol	7700±200	14.9±0.4	64±2	107.7±1.2[a]	107.8±1.2
	7990±40	15.67±0.08	66.4±0.3		107.8±1.1
2-Tetradecanol	6500±200	13.4±0.4	54±2	99.9[b]	95.9±1.1
	6780±30	14.13±0.07	56.4±0.3		96.0±1.0
Patchouli alcohol	5800±200	11.5±0.4	48.3±1.4		89.7±1.0
	6130±30	12.28±0.07	51.0±0.2		89.6±0.9
1-Adamantanol	4400±200	10.0±0.4	36±2		75.8±0.9
	4700±30	10.76±0.07	39.1±0.2		75.6±0.9

Run 15: $\Delta_l^g H_m(298.15\ K)\ /\ kJ \cdot mol^{-1}$ = (1.161 ±0.014)$\Delta H_{trn}(434\ K)$ + (33.6 ±0.8) r^2 = 0.9999

Run 16: $\Delta_l^g H_m(298.15\ K)\ /\ kJ \cdot mol^{-1}$ = (1.178 ±0.012)$\Delta H_{trn}(434\ K)$ + (29.6 ±0.7) r^2 = 0.9999

[a] Reference [29]

[b] References [30]

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Chapter 4: Summary

The nepetalactone sample was characterized by IR and GC-MS prior to CGC analysis. The IR analysis showed the presence of a compound containing a broad OH peak- possibly a carrier. The GC-MS analysis showed that the sample also contained caryophellene. The vaporization enthalpies at 298.15 K of (4aS,7S,7aS)-nepetalactone and (4aS,7S,7aR) –nepetalactone were found to be (68±2) kJ·mol^{-1} and (69±2) kJ·mol^{-1} respectively. The vapor pressures at 298.15 K for (4aS,7S,7aS)-nepetalactone and (4aS,7S,7aR) –nepetalactone were found to be (1.2±0.04) Pa and (0.91±0.03) Pa respectively. These compare favorably to literature predictions. The vaporization enthalpies calculated from the vapor pressures generated from correlations between $\ln(p/p^{o})$ and $\ln(t_o/t_a)$ were in good agreement with the ones calculated from the correlations between vaporization enthalpies and enthalpies of transfer from the condensed phase to the gas phase of the standards.

The vaporization enthalpies of whiskey lactone at 298.15 K were found to be (68±2) kJ·mol^{-1} and (69±2) kJ·mol^{-1} for *cis* (4*S*,5*S*)-4β-methyl-γ-octalactone and *trans* (4S,5R)-4β-methyl-γ-octalactone, respectively. These values compared favorably to the estimated value of 67.2 kJ·mol^{-1}. The vaporization enthalpies of menthalactone at 298.15 K were found to be (73±2) kJ·mol^{-1} and (74±2) kJ·mol^{-1} for (-)-mintlactone and (+)-isomintlactone respectively. The vapor pressures at 298.15 K of *cis* (4*S*,5*S*)-4β-methyl-γ-octalactone and *trans* (4S,5R)-4β-methyl-γ-octalactone were calculated to be (1.5±0.09) Pa and (2.0±0.1) Pa respectively. The vapor pressures at 295.15 K of (-)-mintlactone and (+)-isomintlactone were calculated to be (0.33±0.02) Pa and (0.26±0.012) Pa respectively. The vaporization enthalpies calculated from the vapor pressures were in

good agreement with the ones calculated from the vaporization enthalpies and enthalpies of transfer from the condensed phase to the gas phase of the standards.

Aliphatic aldehydes were found to correlate well for the purposes of calculating vaporization enthalpies. Aromatic aldehydes, however, did not correlate with the aliphatic data. Vaporization enthalpies were calculated for *trans*-2-hexenal (45±2 kJ·mol^{-1}); 2,6-dimethyl-5-heptenal (53±2 kJ·mol^{-1}); 2,6-nonadienal (57±2 kJ·mol^{-1}); *trans*-2-nonenal (57.3±0.8 kJ·mol^{-1}); *trans,trans*-2,4-decadienal (63.6±0.9 kJ·mol^{-1}); and 2-butyl-2-octenal (66.0±0.9 kJ·mol^{-1}). Calculation of vapor pressure data for the aldehydes was not possible due to the lack of a good correlation in the $\ln(p/p°)$ vs $\ln(t_o/t_a)$ plots.

The vaporization enthalpy and vapor pressure of *R,S*-Fenoprofen at 298.15 K were evaluated to be 125.6±1.2 kJ·mol^{-1} and $10^4 \cdot p_l$/Pa = (0.19±0.06) respectively. The vaporization enthalpies evaluated for *S* Ibuprofen and *S* Naproxen were calculated to be in agreement with literature values. Sub-cooled liquid vapor pressures for *S* Ibuprofen and *S* Naproxen were found to be $10^4 \cdot p_l$/Pa = (19±14) and (0.05±0.03) respectively at 298.15 K. A method to approximate heat capacity of liquid crystals for use as CGC standards was explained. The vapor pressure of crystalline *S* Ibuprofen was estimated by using vapor pressures of alkylbenzoic acid standards and other thermodynamic properties.

A patchouli oil sample from India was examined and its constituent compounds were identified by GC-MS using a NIST/EPA/NIH MS library. The compounds were compared to those identified by Restek®. A retention index of RI = 1633 was measured for patchouli alcohol to further establish its identity. Initial CGC runs using primary

alcohols, a secondary alcohol, and a polycyclic tertiary alcohol as standards were performed to see the feasibility of using primary n-alcohols as standards for polycyclic alcohols in the absence of reliable vaporization enthalpy data for polycyclic standards. The n-alcohols proved to work for calculating vaporization enthalpy; however, their reported vapor pressures did not correlate well enough to evaluate the corresponding vapor pressures.

APPENDIX: SUPPORTING DATA

TABLE S1A
Retention times for nepetalactone, Run 1

Run 1	398.4	403.5	408.8	413.8	418.8	423.9	429.0
t_o = 60 s				t_o/t			
CH_2Cl_2	0.501	0.504	0.508	0.510	0.510	0.517	0.517
γ-Hexanolactone	1.535	1.395	1.286	1.191	1.107	1.044	0.985
γ-Octanolactone	3.907	3.340	2.923	2.564	2.281	2.023	1.843
δ-Octanolactone	4.386	3.743	3.258	2.847	2.517	2.229	2.012
(4aS,7S,7aS)-Nepetalactone	6.342	5.376	4.615	3.988	3.466	3.046	2.690
(4aS,7S,7aR) -Nepetalactone	7.350	6.202	5.302	4.559	3.950	3.448	3.037
γ-Decanolactone	10.809	8.887	7.433	6.243	5.318	4.523	3.926
γ-Undecanolactone	19.034	15.312	12.568	10.349	8.680	7.209	6.161
δ-Undecanolactone	21.488	17.271	14.106	11.586	9.660	8.028	6.804
γ-Dodecanolactone	33.542	26.490	21.343	17.270	14.284	11.619	9.777
δ-Dodecanolactone	37.620	29.715	23.821	19.250	15.821	12.889	10.764

TABLE S1B
Retention times for nepetalactone, Run 2

Run 2	398.3	403.5	408.5	413.7	418.8	423.8	429.0
t_o = 60 s				t_o/t			
CH_2Cl_2	0.550	0.551	0.551	0.548	0.546	0.548	0.517
γ-Hexanolactone	1.626	1.478	1.354	1.248	1.159	1.086	0.985
γ-Octanolactone	4.029	3.469	3.008	2.637	2.328	2.076	1.843
δ-Octanolactone	4.581	3.926	3.390	2.957	2.599	2.305	2.012
(4aS,7S,7aS)-Nepetalactone	6.733	5.699	4.865	4.191	3.634	3.178	2.796
(4aS,7S,7aR) -Nepetalactone	7.783	6.562	5.574	4.782	4.128	3.592	3.037
γ-Decanolactone	11.307	9.321	7.736	6.495	5.490	4.681	3.926
γ-Undecanolactone	19.743	15.983	12.997	10.71	8.885	7.431	6.161
δ-Undecanolactone	22.742	18.342	14.896	12.21	10.103	8.416	6.804
γ-Dodecanolactone	34.611	27.564	22.012	17.834	14.548	11.955	9.777
δ-Dodecanolactone	39.591	31.392	25.066	20.229	16.448	13.474	10.764

TABLE S2A

Retention times for whiskey lactone/ menthalactone, Run 3

	404.2	409.2	414.2	419.2	424.1	429.1	434.0
t_o = 60 s				t/t_o			
Acetone	0.457	0.445	0.460	0.470	0.464	0.480	0.488
γ-Hexalactone	1.401	1.278	1.181	1.102	1.033	0.977	0.933
trans-Whiskey lactone	3.855	3.325	2.895	2.547	2.265	2.034	1.832
cis-Whiskey lactone	4.515	3.873	3.352	2.930	2.592	2.313	2.068
γ-Nonalactone	5.543	4.704	4.036	3.488	3.064	2.713	2.395
γ-Decalactone	9.258	7.696	6.476	5.480	4.717	4.101	3.539
(-)-Menthalactone	10.960	9.130	7.710	6.533	5.634	4.911	4.227
(+)-Isomenthalactone	12.292	10.233	8.594	7.278	6.242	5.405	4.660
γ-Undecalactone	15.442	12.612	10.427	8.670	7.325	6.261	5.299
γ-Dodecalactone	26.636	21.356	17.380	14.190	11.783	9.929	8.230

TABLE S2B

Retention times for whiskey lactone/ menthalactone, Run 4

	404.0	409.1	414.1	419.1	424.1	429.0	433.9
t_o = 60 s				t/t_o			
Acetone	0.518	0.520	0.517	0.524	0.539	0.531	0.532
γ-Hexalactone	1.554	1.416	1.298	1.210	1.141	1.064	1.003
trans-Whiskey lactone	4.260	3.655	3.170	2.792	2.470	2.194	1.965
cis-Whiskey lactone	4.985	4.251	3.668	3.210	2.820	2.492	2.218
γ-Nonalactone	6.055	5.110	4.371	3.799	3.298	2.897	2.556
γ-Decalactone	10.139	8.380	7.035	5.986	5.081	4.380	3.784
(-)-Menthalactone[c]	12.114	10.034	8.454	7.215	6.114	5.297	4.574
(+)-Isomenthalactone[d]	13.591	11.251	9.433	7.999	6.787	5.820	5.015
γ-Undecalactone	17.348	14.065	11.606	9.701	8.056	6.846	5.805
γ-Dodecalactone	29.352	23.422	19.018	15.618	12.753	10.650	8.882

TABLE S3A

Run 3 comparison of whiskey lactone isomer peak areas for isomer assignment.

Temp (K)	First Whiskey Lactone Peak		Second Whiskey Lactone Peak	
	Area Count	Area %	Area Count	Area %
434.0	655799	51.6%	614246	48.4%
429.1	713705	50.5%	700774	49.5%
424.1	763816	51.7%	712331	48.3%
419.2	603907	51.3%	574105	48.7%
414.2	693085	51.2%	661328	48.8%
409.2	687311	51.7%	642530	48.3%
404.2	697478	51.0%	670169	49.0%
Average		51.3%		48.7%

TABLE S3B

Run 4 comparison of whiskey lactone isomer peak areas for isomer assignment.

Temp (K)	First Whiskey Lactone Peak		Second Whiskey Lactone Peak	
	Area Count	Area %	Area Count	Area %
433.9	1173200	51.8%	1093280	48.2%
429.0	792697	51.8%	738602	48.2%
424.1	798204	52.2%	730709	47.8%
419.1	858121	52.1%	787705	47.9%
414.2	560679	52.0%	517256	48.0%
409.1	920684	51.6%	863099	48.4%
404.1	1085860	51.7%	1016460	48.3%
Average		51.9%		48.1%

TABLE S3C

Run 3 comparison of menthalactone isomer peak areas for isomer assignment.

Temp (K)	First Menthalactone Peak		Second Menthalactone Peak	
	Area Count	Area %	Area Count	Area %
434.0	1283480	93.3%	92331	6.7%
429.1	1808350	93.2%	132121	6.8%
424.1	1462620	93.3%	104794	6.7%
419.2	1279490	93.2%	93085	6.8%
414.2	1532530	93.2%	111529	6.8%
409.2	1349480	93.3%	97326	6.7%
404.2	1579340	93.2%	115192	6.8%
Average		93.2%		6.8%

TABLE S3D

Run 4 comparison of menthalactone isomer peak areas for isomer assignment.

Temp (K)	First Menthalactone Peak		Second Menthalactone Peak	
	Area Count	Area %	Area Count	Area %
433.9	2255930	93.3%	161237	6.7%
429.0	1517560	93.3%	108535	6.7%
424.1	1392940	93.3%	99262	6.7%
419.1	1507880	93.4%	105885	6.6%
414.2	996788	93.4%	70585	6.6%
409.1	1798440	93.3%	129132	6.7%
404.1	2148240	93.3%	154633	6.7%
Average		93.3%		6.7%

TABLE S4A

Retention times for aldehyde, Run 5 (low temp)

	359.3	364.3	369.3	374.3	379.3	384.4	389.4
t_o = 60 s				t/t_o			
CH_2Cl_2	2.130	2.198	2.203	2.201	2.205	2.230	2.235
Hexanal	3.086	3.016	2.903	2.811	2.743	2.690	2.641
trans-2-Hexenal	3.636	3.473	3.284	3.134	3.024	2.922	2.843
Benzaldehyde	5.825	5.296	4.810	4.420	4.127	3.840	3.645
Octanal	6.812	6.062	5.408	4.886	4.486	4.127	3.869
2,6-Dimethyl-5-heptenal	8.948	7.784	6.805	6.025	5.427	4.886	4.512
Nonanal	12.079	10.269	8.794	7.612	6.709	5.914	5.369
trans,*cis*-2,6-Nonadienal	16.434	13.752	11.589	9.858	8.532	7.370	6.609
trans-4-Decenal	21.468	17.648	14.627	12.237	10.411	8.854	7.807
Decanal	22.706	18.624	15.418	12.854	10.884	9.250	8.118
trans-Cinnamaldehyde	35.934	29.335	24.166	19.817	16.429	13.692	11.959

TABLE S4B

Retention times for aldehyde, Run 6 (low temp)

	357.4	362.4	367.5	372.5	377.6	382.7	387.6
t_o = 60 s				t/t_o			
CH_2Cl_2	2.200	2.194	2.218	2.225	2.232	2.243	2.254
Hexanal	3.147	3.007	2.911	2.826	2.751	2.695	2.651
trans-2-Hexenal	3.734	3.511	3.309	3.173	3.038	2.938	2.860
Benzaldehyde	6.016	5.448	4.865	4.525	4.167	3.902	3.684
Octanal	6.987	6.192	5.453	4.976	4.521	4.179	3.902
2,6-Dimethyl-5-heptenal	9.209	8.010	6.869	6.112	5.485	4.978	4.562
Nonanal	12.488	10.651	8.870	7.833	6.802	6.050	5.440
trans,*cis*-2,6-Nonadienal	17.182	14.493	11.693	10.231	8.692	7.606	6.717
trans-4-Decenal	22.286	18.470	14.729	12.648	10.595	9.119	7.923
Decanal	23.554	19.450	15.500	13.265	11.079	9.506	8.238
trans-Cinnamaldehyde	38.473	31.850	24.142	20.912	16.988	14.379	12.202

TABLE S4C
Retention times for aldehyde, Run 7

	395.7	400.7	405.6	410.5	415.3	420.3	425.2
t_o = 60 s				t/t_o			
CH_2Cl_2	2.289	2.330	2.332	2.361	2.365	2.381	2.375
Hexanal	2.602	2.606	2.580	2.582	2.563	2.557	2.536
Benzaldehyde	3.362	3.262	3.155	3.086	3.006	2.948	2.883
2,6-Dimethyl-5-heptenal	3.949	3.749	3.560	3.426	3.292	3.189	3.087
Tolualdehyde	4.521	4.243	3.993	3.806	3.622	3.475	3.343
trans-2-Nonenal	5.486	5.026	4.634	4.331	4.055	3.831	3.639
Decanal	6.362	5.742	5.219	4.815	4.459	4.171	3.924
trans-Cinnamaldehyde	8.913	7.894	7.040	6.358	5.768	5.273	4.885
trans, trans -2,4-Decadienal	10.317	8.983	7.893	7.029	6.300	5.700	5.220
2-Butyl-2-octenal	12.901	11.051	9.567	8.392	7.415	6.613	5.977
Lauric aldehyde	15.358	12.990	11.097	9.613	8.396	7.409	6.623
Cyclamen aldehyde	20.169	16.939	14.346	12.301	10.639	9.269	8.204

TABLE S4D
Retention times for aldehyde, Run 8

	395.7	400.6	405.6	410.5	415.3	420.2	425
t_o = 60 s				t/t_o			
CH_2Cl_2	2.307	2.325	2.335	2.344	2.358	2.371	2.378
Hexanal	2.619	2.600	2.580	2.562	2.555	2.548	2.537
Benzaldehyde	3.377	3.254	3.154	3.063	2.998	2.938	2.883
2,6-Dimethyl-5-heptenal	3.963	3.740	3.559	3.402	3.284	3.179	3.087
Tolualdehyde	4.536	4.229	3.991	3.774	3.616	3.468	3.341
trans-2-Nonenal	5.499	5.009	4.630	4.296	4.049	3.824	3.635
Decanal	6.371	5.724	5.214	4.784	4.451	4.163	3.922
trans-Cinnamaldehyde	8.929	7.830	7.019	6.293	5.763	5.271	4.870
trans, trans -2,4-Decadienal	10.324	8.932	7.874	6.974	6.294	5.696	5.208
2-Butyl-2-octenal	12.894	10.998	9.549	8.332	7.410	6.612	5.963
Lauric aldehyde	15.351	12.929	11.074	9.555	8.389	7.405	6.611
Cyclamen aldehyde	20.155	16.813	14.307	12.219	10.633	9.271	8.179

TABLE S5A
Retention times for Fenoprofen, Run 9

	464.2	469.3	474.4	479.4	484.5	489.5	494.5
t_o = 60 s				t/t_o			
DCM/THF	2.296	2.354	2.366	2.394	2.410	2.418	2.528
4-Methoxybenzoic acid	3.751	3.669	3.498	3.404	3.312	3.234	3.276
4-Ethoxybenzoic acid	4.195	4.054	3.827	3.687	3.558	3.451	3.469
4-Propoxybenzoic acid	5.100	4.846	4.478	4.251	4.042	3.874	3.843
4-Hexyloxybenzoic acid	11.913	10.669	9.201	8.262	7.416	6.773	6.360
Fenoprofen	16.725	14.717	12.519	11.040	9.743	8.758	8.076
4-Octyloxybenzoic acid	23.935	20.728	17.149	14.887	12.862	11.354	10.259

TABLE S5B
Retention times for Fenoprofen, Run 10

	464.7	469.6	474.7	479.6	484.6	489.4	494.2
t_o = 60 s				t/t_o			
DCM/THF	2.528	2.540	2.558	2.574	2.584	2.588	2.626
4-Methoxybenzoic acid	3.989	3.817	3.677	3.552	3.453	3.362	3.330
4-Ethoxybenzoic acid	4.423	4.185	3.990	3.820	3.684	3.563	3.507
4-Propoxybenzoic acid	5.300	4.926	4.615	4.351	4.139	3.953	3.852
4-Hexyloxybenzoic acid	11.802	10.306	9.058	8.066	7.257	6.578	6.139
Fenoprofen	16.167	13.916	12.050	10.565	9.355	8.348	7.649
4-Octyloxybenzoic acid	23.106	19.510	16.464	14.103	12.226	10.659	9.651

TABLE S5C
Retention times for Fenoprofen, Run 11

	464.8	469.8	474.7	479.7	484.6	489.6	494.5
t_o = 60 s				t/t_o			
DCM/THF	2.489	2.521	2.577	2.569	2.578	2.594	2.597
4-Methoxybenzoic acid	3.939	3.782	3.685	3.547	3.459	3.365	3.299
4-Ethoxybenzoic acid	4.364	4.147	3.996	3.814	3.690	3.565	3.474
4-Propoxybenzoic acid	5.266	4.906	4.637	4.356	4.166	3.956	3.825
4-Hexyloxybenzoic acid	11.497	10.083	8.933	7.965	7.221	6.522	6.027
4-Heptyloxybenzoic acid	16.116	13.842	11.977	10.466	9.321	8.226	7.486
Naproxen	22.160	18.847	16.132	13.959	12.282	10.700	9.620

TABLE S5D

Retention times for Fenoprofen, Run 12

	464.7	469.6	474.6	479.6	484.5	489.4	494.3
t_o = 60 s				t/t_o			
DCM/THF	2.537	2.543	2.566	2.575	2.577	2.591	2.605
4-Methoxybenzoic acid	3.960	3.814	3.668	3.541	3.444	3.378	3.302
4-Ethoxybenzoic acid	4.383	4.178	3.979	3.807	3.676	3.578	3.476
4-Propoxybenzoic acid	5.262	4.939	4.616	4.341	4.138	3.992	3.822
4-Hexyloxybenzoic acid	11.427	10.106	8.926	7.915	7.158	6.588	6.011
4-Heptyloxybenzoic acid	15.937	13.853	11.984	10.378	9.211	8.357	7.458
Naproxen	21.904	18.859	16.151	13.840	12.120	10.887	9.581

TABLE S5E

Retention times for Fenoprofen alkyl/alkoxy standards, Run 13, on a 30 m DB-5MS column with 11 psi head pressure.

	479.5	484.6	489.7	494.8	499.9	505.0	510.1
t_o = 60 s				t/t_o			
DCM + THF	2.618	2.658	2.691	2.725	2.725	2.757	2.667
4-Ethylbenzoic acid	3.460	3.411	3.372	3.337	3.279	3.256	3.108
4-Methoxybenzoic acid	3.687	3.609	3.545	3.489	3.413	3.375	3.211
4-Ethoxybenzoic acid	3.997	3.878	3.779	3.693	3.592	3.531	3.344
s-Ibuprofen	4.828	4.592	4.397	4.229	4.059	3.938	3.689
4-Hexylbenzoic acid	6.402	5.931	5.540	5.210	4.901	4.666	4.303
α-Naphthaleneacetic acid	7.031	6.487	6.037	5.651	5.297	5.020	4.611
Biphenyl-4-carboxylic acid	9.187	8.296	7.556	6.943	6.383	5.950	5.392
4-Octylbenzoic acid	10.624	9.463	8.511	7.714	7.018	6.466	5.797
Fenoprofen	11.948	10.578	9.476	8.507	7.690	7.035	6.277
Naproxen	15.842	13.830	12.176	10.815	9.620	8.679	7.655

TABLE S5F
Retention times for Fenoprofen alkyl/alkoxy standards, Run 14, on a 30 m DB-5MS column with 11 psi head pressure.

	479.5	484.7	489.7	494.8	499.9	505.0	510.1
t_o = 60 s				t/t_o			
DCM + THF	2.530	2.627	2.644	2.697	2.700	2.615	2.651
4-Ethylbenzoic acid	3.358	3.369	3.310	3.301	3.247	3.092	3.086
4-Methoxybenzoic acid	3.582	3.563	3.480	3.452	3.380	3.206	3.187
4-Ethoxybenzoic acid	3.887	3.828	3.710	3.653	3.557	3.354	3.318
s-Ibuprofen	4.702	4.530	4.317	4.183	4.017	3.741	3.656
4-Hexylbenzoic acid	6.251	5.841	5.434	5.149	4.852	4.435	4.261
α-Naphthaleneacetic acid	6.875	6.390	5.923	5.587	5.244	4.773	4.565
Biphenyl-4-carboxylic acid	8.996	8.157	7.406	6.860	6.333	5.664	5.327
4-Octylbenzoic acid	10.402	9.299	8.334	7.615	6.948	6.149	5.729
Fenoprofen	11.713	10.392	9.254	8.387	7.617	6.695	6.199
Naproxen	15.549	13.573	11.908	10.663	9.549	8.271	7.548

TABLE S6A
Retention times for Patchouli Alcohol, Run 15

	419.1	424.1	429.0	433.9	438.8	443.7	448.6
t_o = 60 s				t/t_o			
DCM	0.452	0.450	0.452	0.454	0.485	0.482	0.505
1-Adamantanol	2.112	1.869	1.704	1.539	1.508	1.397	1.326
1-Undecanol	2.987	2.555	2.256	1.975	1.880	1.698	1.571
2-Tetradecanol	8.500	6.935	5.862	4.892	4.442	3.841	3.378
Patchouli alcohol	11.303	9.371	8.012	6.785	6.210	5.423	4.792
1-Pentadecanol	19.402	15.395	12.649	10.265	9.057	7.623	6.504
1-Hexadecanol	31.664	24.729	20.025	15.993	13.916	11.536	9.693

TABLE S6B
Retention times for Patchouli Alcohol, Run 16

	419.1	424.1	429.0	433.9	438.8	443.7	448.6
t_o = 60 s				t/t_o			
DCM	0.443	0.447	0.458	0.460	0.464	0.475	0.480
1-Adamantanol	2.049	1.843	1.696	1.546	1.427	1.338	1.244
1-Undecanol	2.898	2.517	2.242	1.982	1.778	1.623	1.472
2-Tetradecanol	8.225	6.829	5.798	4.893	4.191	3.647	3.156
Patchouli alcohol	10.968	9.235	7.943	6.788	5.870	5.149	4.486
1-Pentadecanol	18.769	15.162	12.499	10.257	8.543	7.226	6.080
1-Hexadecanol	30.534	24.334	19.759	15.963	13.101	10.914	9.055