Maastricht Science Programme

ORGANIC CHEMISTRY

SCI2017

2017-2018

Organic Chemistry
(SCI2017)

Maastricht Science Programme
Period 4
Spring 2018

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Course Overview

General

Meeting time:	Period 5, lectures and tutorial groups according to the official course schedule on Eleum.
Coordinator:	Dr. Hanne Diliën (hanne.dilien@maastrichtuniversity.nl)
Tutors:	TBA
	Do not hesitate to e-mail if you have questions about this class.

Required Course Materials

Book: Klein; "Organic Chemistry"; 2th edition; 2015; Wiley (ISBN: 9781118452288)

This book is one of the best organic textbooks available. It provides a logic description of organic chemistry, starting from the basics, ending with many complex reactions. The book has a very logical order of subjects, focusing on understanding and mastering of skills instead of memorization. The book has many useful illustrations and can readily be used as an organic chemistry encyclopedia. This book provides not only sufficient detail, but also tries to sketch a more general picture. We will cover the following material taken from the book; Chapters 1-5, 7-11, 13-14. This will give you a basis in organic chemistry for further studies in the natural sciences. The remainder of the book will be used for advanced courses and skills in organic reactions. As such, it is a worthwhile investment.

Other Material: The PowerPoint files will be available on Eleum.
These files form the core of this class and are as such, the most important study material.

Course Description and Objectives

This course intends to teach the basic principles of organic chemistry. It serves as an introduction to more advanced chemistry courses. In this course, a comprehensive description of the molecular structure, bonding and reactivity of the most important organic compounds and functional groups will be presented. In the first lecture, we may occasionally revisit chemistry topics, which have been part of your previous studies and our core class in chemistry. In lecture 1, we will discuss the language of organic chemistry before using it to explore concepts in structure and bonding particularly relevant to organic compounds. Lecture 2 will be entirely devoted to stereochemistry and its implications for organic reactivity. Subsequently, in lecture 3 we will focus on reactions involving radicals. The course will then proceed with two lectures (4 and 5) on the most important classes of organic reactions: those based on nucleophilic substitutions and eliminations. A logical review will be provided of the reactivity of the various functional groups, as applied in this type of reactions. In lecture 6, reactions involving alkenes, their reactivity and E/Z stereochemistry will be discussed. The main objective of this course is to provide the participants with an understanding of the basic concepts of organic chemistry. Knowledge of organic chemistry is important in the (life) sciences, since life itself is based on organic chemistry. Other specific course objectives are:

- To give you the ability to recognize organic compounds and to understand their basic physical and chemical properties.
- To enable you to understand typical organic reactions, and to be able to apply them to obtain well defined organic compounds.
- To understand the general framework in which organic reactions can be placed and understood.
- To be able to apply the concepts of stereochemistry to typical problems in organic chemistry and the life sciences.
- To prepare you for a career in science or industry and to provide you with sufficient background for more advanced courses in chemistry, biochemistry or the biomedical sciences.
- To assist you in developing and improving as a scientist by providing you with resources, which will enable you to identify, formulate and solve typical chemical problems.
- To help you improve your problem solving skills through the integration of multidisciplinary problems and their solutions into the course.

Course Procedures

Part of the class will be lecture oriented with PowerPoint presentations. PowerPoint files usually will be available on Eleum prior to the lecture. This allows you to print the slides out for use as notes. You are encouraged to read the material in the book, which will be presented in class, before coming to class. This will help you in learning the material, enable you to ask useful questions and ultimately save you a lot of study time. During the tutorial groups, students will work on large tasks as well as selected problems from the book. Some of the tasks will be linked to the co-requisite skills training, since they will form the preparation for the lab sessions occurring in period 4. In combination with the theory from the lectures, both the tasks and these problems are part of the material to be studied for examinations.

- You may ask questions at any time during the class. Do not wait until after the class, especially if you think your question is also useful for other students in the class.
- Seek help if you experience difficulties with particular concepts or problems.
- Attendance to the lectures is highly recommended in view of the fact that many students find it difficult to learn complex chemical concepts only by self-study.
- Attendance to the tutorial group meetings is required and only a limited number of absences is permitted (*cf.* Rules and Regulations). In case of more absences with a valid reason, additional assignments can be requested *via* the office of student affairs.
- It can be beneficial for you to work together with other students when working problems and preparing for a test. Try to find students to work with and meet regularly to go over the material presented in class. It has been proven that this is for many students a very effective learning strategy.

Course Requirements

Your learning will be assessed in the following ways, to emphasize the different learning styles and skills of each individual student. There will be:

- The ***midterm*** examination on lectures 1, 2 and 3 will take place in week 4 of period 4 (week 10 of 2018) and will count ***35 %*** towards the final grade. The midterm examination will consist of multiple choice questions.
- The ***final*** examination on all lectures will take place in exam week of period 4, and will count ***50 %*** towards the final grade. The final examination will consist of open questions.
- Your contributions to the ***tutorial*** group will count ***15 %*** towards the final grade.
- In case of a failing overall grade in this class, but a pass on attendance, a resit of the final will be permitted. However, your grades for the midterm and tutorial group will remain unchanged. The resit will cover all the topics of this course (so lectures and tutorials 1→6).

Though students are encouraged to work together on solving difficult problems, copying is strictly prohibited. All work submitted by you in this course is pledged as being your own work.

Course Schedule P4 2018

Week 6	Lecture 1: Basic Principles of Organic Chemistry
Week 7	carnival week: no education
Week 8	Lecture 2: Stereochemistry
Week 9	Lecture 3: Reaction Mechanisms & Radicals
Week 10	Lecture 4: Nucleophilic Substitution at Saturated Carbon
	Midterm Examination on Lectures 1, 2 and 3 and the corresponding problems/tasks
Week 11	Lecture 5: Conformations & Eliminations
Week 12	Lecture 6: Alkenes & Alkyne Structure and Reactivity
Week 13	F**INAL Examination** on all lectures, problems and tasks of this class. (with the focus on lectures 4, 5 & 6)

Lecture List

Lecture 1:

Organic Chemistry: Structure and Bonding

Topics

- The "*what*" and the "*why*" of organic chemistry
- Representation of organic structures
- Functional groups
- Orbitals and bonding
- Hybridization
- Delocalization and conjugation

Klein: Chapters 1, 2, 3, parts of chapter 4 & 18

This lecture will provide an introduction to organic chemistry and its place in modern science. The first part of the lecture will focus on the structure of organic compounds, their representation and the basic language of organic chemistry. Armed with this information, we will introduce functional groups as the structures responsible for the behaviour of molecules (in a chemical sense) before a quick refresher on orbitals and bonding. This will include a specific focus on the formation of the covalent bond, the interaction on which organic chemistry is founded.

The second part of the lecture will introduce basic molecular orbital theory, particularly as it relates to the hybridization of atomic orbitals, and how this explains the structure and geometry of carbon atoms in different functionalities, represented by alkanes, alkenes and alkynes. Finally, the concept of delocalization and conjugation will be discussed with reference to the structure and chemical properties of benzene and its role in molecules of paramount importance in biochemical systems (haemoglobin and chlorophyll).

Task:
Task 1 Separation of Mixtures of Organic Compounds

Suitable problems:

Problems will be handed out during the tutorial.

Lecture 2:

Stereochemistry

Topics

- Stereoisomers (*e.g.* diastereomers, enantiomers, cis/trans isomers)
- Nomenclature
- Polarization of light, specific rotation
- Absolute and relative configuration
- Conventions for writing R and S forms as well as E and Z forms
- Racemic mixtures, separation of enantiomers by biological means
- Stereochemistry of reactions

Klein: Chapter 5

When studying organic molecules it becomes apparent that certain different molecules look very similar and, on the other hand, some very similar molecules have different properties. For example, two forms of the molecule ibuprofen (a pain killer) exist. One of these forms is active; the other form, which has the same number of atoms, all connected in the same manner, is entirely inactive. Hence, a clear nomenclature is required to identify these types of similar/dissimilar molecules and distinguish their various apparent forms from each other: stereochemistry!
The first examples of such molecules are the alkenes. They are characterized by the restricted rotation along the double bond. As a result, in some cases the substituents on this double bond can be arranged in two different ways, leading to E/Z or cis/trans isomerism.
A molecule that does not contain a plain of symmetry and is not superimposable with its mirror image is called chiral and contains one or more chirality centers. Examples of such molecules are enantiomers: a pair of nonsuperimposable, mirror-image stereoisomers. Such enantiomers are difficult to separate (resolve) since they have identical physical properties. A special nomenclature has been developed to name enantiomeric compounds: the S/R configuration rules. Enantiomers are usually present in a 50:50 ratio (so called racemic mixtures). When molecules have multiple chirality centers, 2^n stereoisomers may be present. If two of these molecules are not mirror images of each other, they are called diastereomers. However, if they contain a plane of symmetry, they are achiral and referred to as meso compounds. Initially, the nomenclature may be somewhat confusing. However, if you have a reasonable 3D imagination, stereochemistry is straightforward. It is an essential area of expertise for researchers in the field of pharmaceutics and biomedical sciences.

Suitable problems:

Problems will be handed out during the tutorial.

Lecture 3:

Radicals

Topics

- Description (nomenclature and physical properties)
- Radical reactions of alkanes and alkenes
- Stability of free radicals
- Chain reaction mechanisms

Klein: Chapter 11

As we have seen in the previous lectures, alkanes, hydrocarbons with only single bonds, form the basis of many organic molecules. Alkanes are in general very stable, participating in only a limited number of reactions. Often these reactions involve radicals. Radical reactions can typically be divided in three steps: initiation, propagation and termination. In this way, alkyl halides can be prepared. The selectivity of the reaction is associated with the stability of intermediate radicals and can be predicted. It is good to keep in mind that other methods also exist to make alkyl halides in a more controlled manner. As we have seen in lecture 4, alkyl halides form an interesting starting point for further reactions. There are other areas of organic chemistry where one also finds radical reactions. Examples include polymerizations and antioxidants, topics which will also be discussed in this lecture.

Task:
Task 2: Radicals

Suitable problems

Problems will be handed out during the tutorial.

Lecture 4:

Nucleophilic Substitution at Saturated Carbon

Topics

- S_N1
- S_N2
- Leaving group
- Carbocation Stabilization
- Solvent Effect

Klein: (parts of) Chapter 7, (13, 14)

This lecture focuses on new types of reactions at saturated carbon. These reaction types are explained for alkyl halides, a common class of organic compounds. This class is useful for the demonstration of these basic reaction types in a comparatively straightforward and understandable manner. It should be noted that more complex reactions with a comparable mechanism do exist. However, focusing on the alkyl halides, the reaction discussed today is the nucleophilic substitution. Depending on the actual mechanism, one names these reactions S_N1 or S_N2. Which reaction occurs under which conditions depends on the nature of the substrate, the type of nucleophile, the actual leaving group and the solvent. It appears that the course of these reactions is highly predictable.

Task:
Task 3: Methylation

Suitable problems:

Problems will be handed out during the tutorial.

Lecture 5:

Eliminations & Conformations

Topics

- E1
- E2
- Conformations vs configuration
- Ring strain
- Cyclohexane (ring flip, axial, equatorial)

Klein: Chapters 4, 8

The last lecture will focus on conformational analysis and elimination reactions. In the first part of the lecture conformations will be analyzed. The shape of a molecule is not usually so well defined. Rotation is possible about single bonds and this rotation means that, while the localized arrangement of atoms stays the same, the molecule as a whole can adopt a number of different shapes. Yet, even though no two molecules have exactly the same shape at any one time, they are still all the same chemical compound. We call the different shapes of molecules of the same compound different conformations.

The second part of the lecture will focus on elimination reactions. Depending on the actual mechanism, one names these reactions E1 or E2. Which reaction occurs under which conditions depends on the nature of the substrate, the actual leaving group and the solvent. It appears that the course of these reactions is highly predictable. Furthermore the competition between substitutions (lecture 5) and these eliminations will be discussed.

Suitable problems:

Problems will be handed out during the tutorial.

Lecture 6:

Alkene and Alkyne Structure and Reactivity

Topics

- Structure of alkenes and alkynes
- Reactions of alkenes and alkynes
- Hydroboration
- Effect of delocalization on pKa, stability and reactivity
- Delocalized electrons and resonance in ions and molecules
- Conjugated dienes and aromaticity

Klein: (parts of) Chapters 2, 7,8, 9, 10

In the first week we encountered alkenes and alkynes in the context of molecular orbitals. Unsaturation is a unique property of carbon-based molecules. Today we will take a closer look at the properties and reactivity of this class of materials. Due to the fact that these materials have a large electron density, one can expect typical electrophilic reactions, in which species with fewer electrons, so-called electrophiles are added to the double or triple bond. These electrophiles can be positively charged, *e.g.* carbocations, or neutral, *e.g.* boranes. Typical reactions are the addition of halogens to alkenes and hydroborations. The above topic brings us a step closer to reactivity and chemical reactions in general. It is therefore useful to define what a chemical reaction entails and how we usually represent it on paper, either as a reaction equation or in an energy diagram
An important aspect in this context is delocalization. In this context it is noteworthy that some organic molecules exhibit a surprising stability or reactivity. Close scrutiny of the distribution of charges in these molecules gives the impression that different distributions exist, all contributing to an average, the actual molecule. Indeed, often multiple chemical structures can be written, although these structures do not represent different molecules and do not exist in reality. This phenomenon is usually referred to as resonance. Since the presence or absence of resonance has tremendous impact on the properties of molecules, it is the subject of many studies.

Task:
Task 4: Hydroboration

Suitable problems:

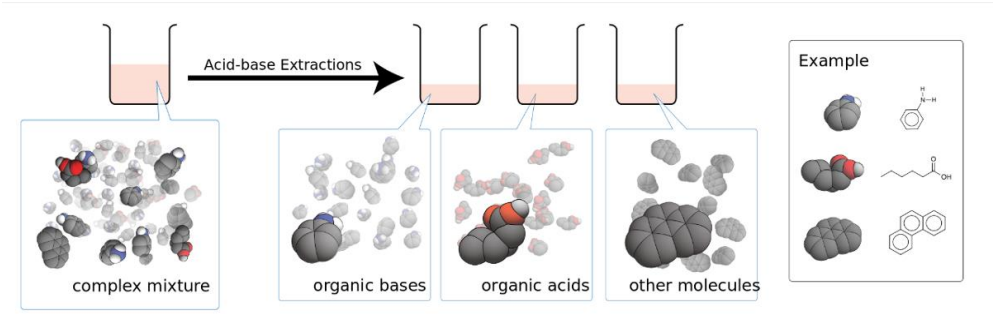
Problems will be handed out during the tutorial.

Tasks

Task 1: Separation of Mixtures of Organic Compounds

During the synthesis of organic compounds, often a complex mixture of organic compounds is obtained. This is not surprising, since some of the reactants may not have fully reacted, catalysts may have been added and, as we will see during this class, many reactions produce a mixture of compounds. Although one always prefers to optimize a reaction to make the yield as high as possible and limit subsequent purification steps, some purification afterwards is unavoidable.

During this class and the associated laboratory sessions, we will see many separation techniques. This task focuses on one of the most widely used techniques, the liquid-liquid extraction. The technique is based on two immiscible liquid phases. Once the mixture of organic compounds is mixed with (dissolved in) these solvents an unequal distribution of the solutes between the two immiscible solvents can occur. This process can be numerically described by the distributions coefficients of the organic compounds. As a result, this system can be used for the separation of the compounds, by separation of the solvents. Practical glassware exists to achieve this. Two important parameters affecting the separation are the occurrence of differences in polarity and density. It should be noted that often one of the phases is water, whereas the other phase is an organic solvent. As a result, the organic layers often have to be dried to avoid problems in, for example, IR and NMR analysis. If this would be all, the process would be quite straightforward to execute. However, it is often found that all compounds present dissolve best in only one of the phases, leading to almost no separation.

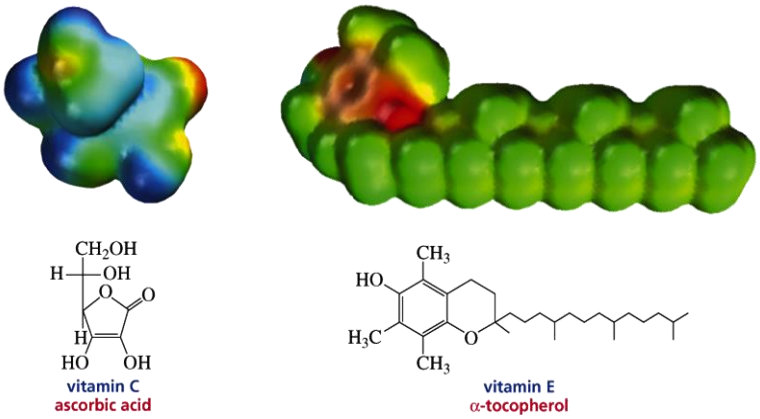


Fortunately, in many cases we can use the fact that many organic compounds are acids or bases, to facilitate an easy separation of the mixture. It can be easily seen that the solubility of an organic acid or base, may drastically change upon addition of an acid or a base. Sometimes this affects the distribution coefficients sufficiently to get a complete separation of a mixture of multiple compounds. After separation, the compounds can be recovered, with the exact procedure depending on whether we are dealing with a solid or a liquid compound. By fine-tuning the procedures, it is even possible to separate weak acids from stronger acids as well as weak bases from stronger bases according to their pKa values. When separating complex mixtures it is usually best to develop a separation scheme, to know which steps have to be performed in which order, and which compounds will be isolated when.

Task 2: Radicals

Since radicals are very reactive, biological systems contain many radical inhibitors to scavenge potentially harmful radicals, which can be formed for a variety of reasons (such as sitting too long in the sun!). Two examples of natural radical scavengers or antioxidants are vitamins C and E. One of these vitamins is soluble in water and can trap radicals formed in for example, the cell and blood plasma, the other usually traps radicals in apolar environments such as membranes. Sometimes it is even recommended to take supplements of these vitamins, although other sources suggest this is not the case and supplements may have an adversary effect. Notwithstanding, naturally present vitamins C and E as well as similar molecules definitely have a radical inhibiting effect.

Probably vitamin C is the best known radical scavenger and demonstrates the chemical working principle of many natural and synthetic antioxidants quite well. It can readily react with available radicals, leading to a resonance-stabilized intermediate. This intermediate is an antioxidant in itself and can react with another radical. After this process the ascorbic acid can be recovered using NADPH and the appropriate enzymes. vitamin C can be found in many fruits and vegetables.



Vitamin C and Vitamin E

After we understand the general working principle of vitamin C, it is interesting to look at the working principle of vitamin E and see whether this is the same. It is good to realize that the name vitamin E actually represents a group of eight different compounds, with some variations in the apolar side chains, with α-tocopherol being the most abundant and studied representative. α-Tocopherol can act as an antioxidant by reacting with lipid radicals produced in the lipid peroxidation chain reaction, which prevents the continuation of the oxidation process. (http://en.wikipedia.org/wiki/Vitamin_E) Once α-tocopherol reacts with a lipid radical, the lipid is recovered and resulting radical in the antioxidant is stabilized by electron delocalization. This type of reactions is typical for hydroquinones, or more general for many substituted phenollic compounds. The obtained radicals produced in this process may be recycled back to the active reduced form through reduction by, for example, vitamin C.

In view of the efficient mechanism of these natural antioxidants, it is not surprising that they are of considerable interest for the food industry. Vitamin C is added to many food products. However, it is not suitable to stabilize, for example, fats and oils. Although vitamin E possibly could do the job, synthetic alternatives have been developed with a similar action. This is a result of the fact that it is comparatively expensive to isolate vitamin E like substances in large quantities from natural products.

Our textbook mentions BHA (E320) and BHT (E321) as two of the most common representatives of synthetic antioxidants. Although commonly used in our food supply chain, their use is not without controversy. Already over 50 years, BHA and BHT have been added to fat-containing foods as an antioxidant. The addition of BHA and BHT prevents the fats from degrading and avoids that the food products become rancid and foul smelling. However, the US National Institutes of Health has reported that BHA is reasonably anticipated to be a human carcinogen based on evidence of carcinogenicity in experimental animals. It is unclear whether the low concentrations in food cause any adversary effects in humans, but the public opinion on these compounds is changing. Hence, an industrial quest is ongoing for alternative, but readily available, "natural" antioxidants. In all case, one searches for compounds with similar structural elements and the same working principle. Of particular interest are bioflavonoids, which can be found in many fruits, such as berries and oranges, and in other plant based products, such as green tea.

Task 3: Methylation

In nature many nucleophilic substitution reactions occur. Especially methylation is a commonly occurring reaction type. It is therefore of interest to look at this type of reaction in more detail. An introduction to the role of methylation in gene expression is provide in the following text, which is summarized from Phillips, T. (2008); Nature Education 1(1):

There are many ways that gene expression is controlled in eukaryotes, but methylation of DNA (not to be confused with histone methylation) is a common epigenetic signaling tool that cells use to lock genes in the "off" position. In recent decades, researchers have learned a great deal about DNA methylation, including how it occurs and where it occurs, and they have also discovered that methylation is an important component in numerous cellular processes, including embryonic development, genomic imprinting, X-chromosome inactivation, and preservation of chromosome stability. Given the many processes in which methylation plays a part, it is perhaps not surprising that researchers have also linked errors in methylation to a variety of devastating consequences, including several human diseases.

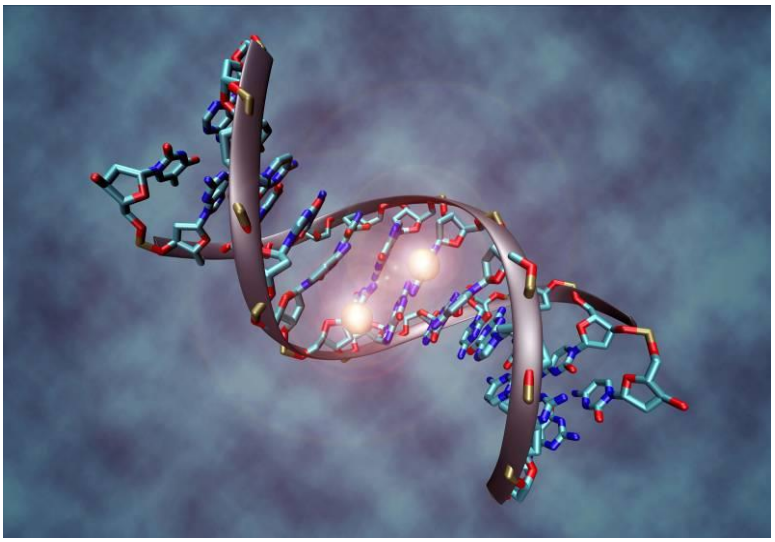


Illustration of a DNA molecule that is methylated at the two center cytosines (Source Christoph Bock, Max Planck Institute for Informatics; Wikipedia)

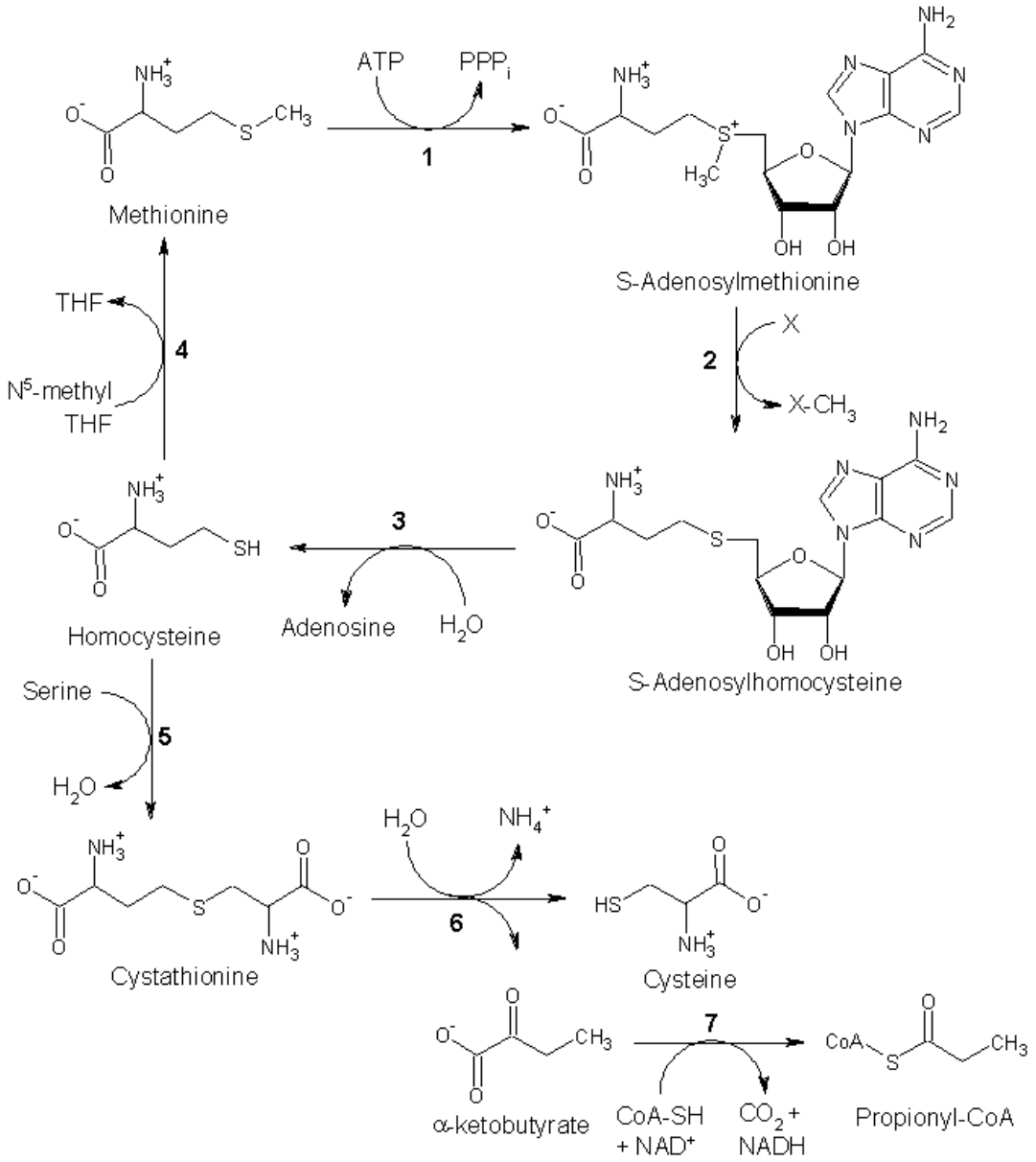
Today, researchers know that DNA methylation occurs at the cytosine bases of eukaryotic DNA, which are converted to 5-methylcytosine by DNA methyltransferase (DNMT) enzymes. The altered cytosine residues are usually immediately adjacent to a guanine nucleotide, resulting in two methylated cytosine residues sitting diagonally to each other on opposing DNA strands. Different members of the DNMT family of enzymes act either as de novo DNMTs, putting the initial pattern of methyl groups in place on a DNA sequence, or as maintenance DNMTs, copying the methylation from an existing DNA strand to its new partner after replication. Methylation can be observed by staining cells with an immunofluorescently labeled antibody for 5-methylcytosine. In mammals, methylation is found sparsely but globally, distributed in definite CpG sequences

throughout the entire genome, with the exception of CpG islands, or certain stretches (approximately 1 kilobase in length) where high CpG contents are found. The methylation of these sequences can lead to inappropriate gene silencing, such as the silencing of tumor suppressor genes in cancer cells.

Given the critical role of DNA methylation in gene expression and cell differentiation, it seems obvious that errors in methylation could give rise to a number of devastating consequences, including various diseases. Indeed, medical scientists are currently studying the connections between methylation abnormalities and diseases such as cancer, lupus, muscular dystrophy, and a range of birth defects that appear to be caused by defective imprinting mechanisms. The results of these studies will be invaluable for treating these disorders, as well as for understanding and preventing complications that can arise during embryonic development due to abnormalities in X-chromosome methylation and gene imprinting. To date, a large amount of research on DNA methylation and disease has focused on cancer and tumor suppressor genes. Tumor suppressor genes are often silenced in cancer cells due to hypermethylation. In contrast, the genomes of cancer cells have been shown to be hypomethylated overall when compared to normal cells, with the exception of hypermethylation events at genes involved in cell cycle regulation, tumor cell invasion, DNA repair, and others events in which silencing propagates metastasis. In fact, in certain cancers, such as that of the colon, hypermethylation is detectable early and might serve as a biomarker for the disease.

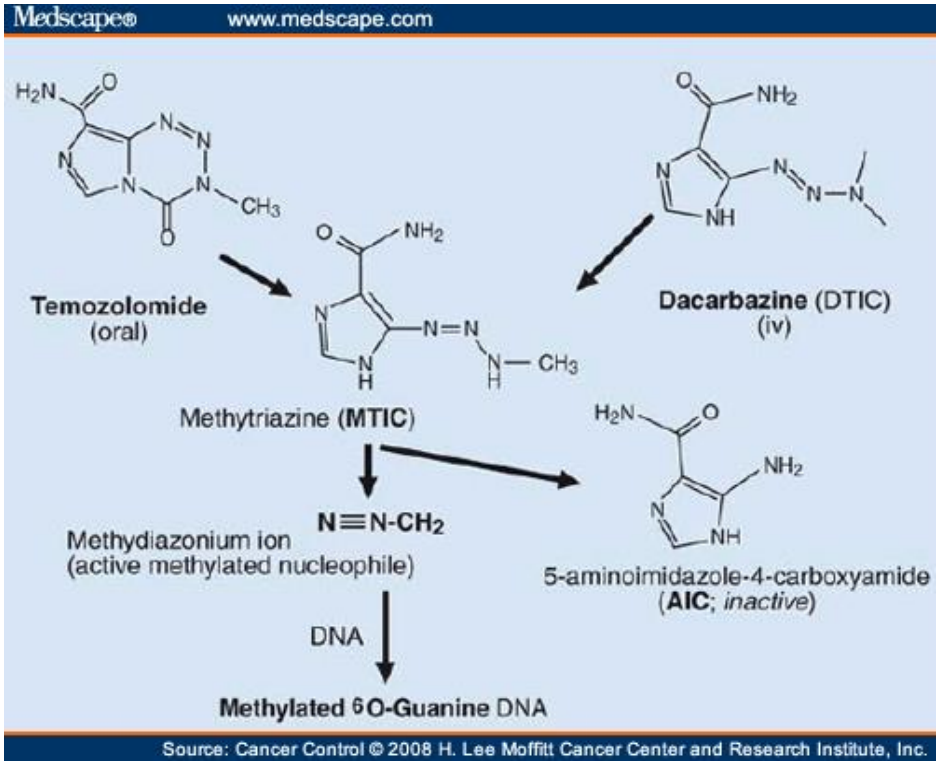
From the above text it is clear that methylation is a very important process in nature. Understanding of methylation can help us find cures for many different diseases. Hence, it is interesting to look from an organic chemical perspective to this process. According to the text DNA methyltransferases (DNMT) play a key role in this process. DNMT form a family of enzymes, which catalyze the transfer of methyl groups to DNA. All known DNA methyltransferases use S-adenosyl methionine (SAM) as the methyl donor. This is perhaps surprising, since in organic chemistry we use much more simple reagents for methylations. Based on the information provided in this lecture it is not difficult to find the best methylation agents and reaction conditions. Often S_N2 conditions are used to have a fast process with an excellent yield. It is important to realize that this is a reaction type, which should be rather carefully executed in the laboratory. However, these reagents are not necessarily suitable for biological methylations for a variety of reasons. As a result, SAM is commonly found in biochemical processes.

It is interesting to look at the methylation mechanism using SAM, which in essence is the same as other methylation reactions. One of the only differences is the perhaps rather uncommon leaving group. SAM is not only found in the methylation of DNA, but also in many other biological methylation reactions, such as the conversion of noradrenaline to adrenaline. A second well know biological methylation agent is N^5-methyltetrahydrofolate (Levomefolic acid). It is actually the compound used to methylate homcysteine back to methionine, an example of an alkylation of a thiol giving a thioether. This biochemical cycle is depicted in the scheme on the following page in steps 1-4.

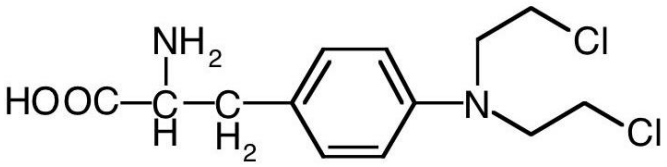


Regeneration of methionine from homocysteine and subsequent conversion with ATP to S-adenosyl methionine (SAM). The compound in the upper right corner is SAM. (Source Wikipedia)

As mentioned in the text from Phillips discussed on the first page, alkylation reactions can also be used as treatments for cancer. An excellent example is the drug Temozolomide (see scheme on following page). Although this scheme contains some errors, the methylation action of this drug is clear. Interestingly the drug is first converted to a different form (MTIC), before the actual reactive compound is obtained. Subsequently a very strong methylation agent is obtained. Many similar anticancer drugs can be found in which always the working mechanism is based on an alkylation step. One final compound of interest is melphalan. Similar to the others, this is an alkylation agent with chlorine being the leaving groups. The structure of this group allows a special type of DNA modifications.



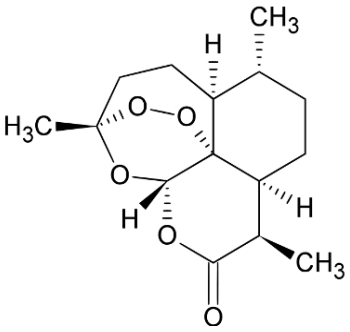
Use of Temozolomide as an anticancer drug.



Melphalan

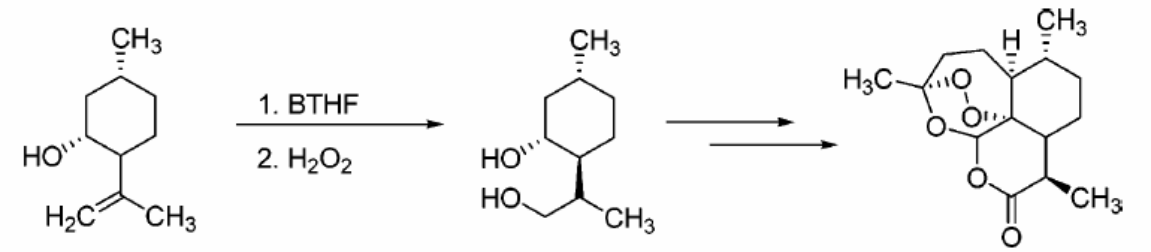
Task 4: Hydroboration

The successful treatment of malaria requires a cocktail of medicines. The most important component is Artemisinin, which is isolated from the herb *Artemisia annua*. In China, extracts from this plant have been used for over 2000 years to treat a variety of diseases. However, to reduce cost and improve availability of this compound and its derivatives for treatments across the world, a synthetic approach would be beneficial.



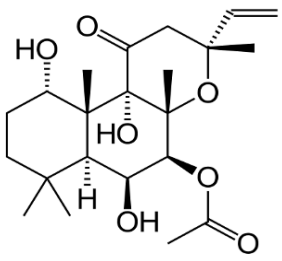
Artemisinin, a complex heterocyclic organic structure. The unusual peroxide bridge in the lactone ring, is believed to be responsible for the medical value of this compound.

However, the synthesis of such a complex natural compound is rather difficult. One has to design a multi-step reaction plan from available starting materials. Various approaches can be found in the literature, with the following reaction being an example of a potential step, early in the total synthesis.



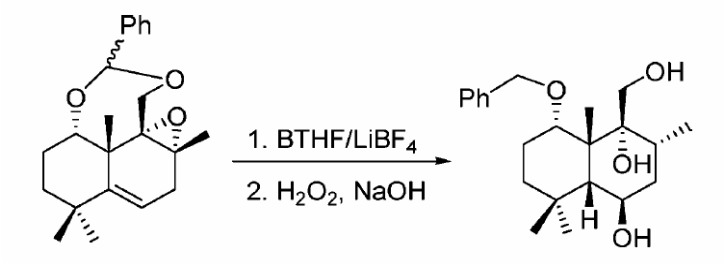
*One of the first steps in the total synthesis of Artemisinin on an industrial scale (Chem. Rev. **2006**, 106, 2617).*

In this step an electrophilic addition occurs. Perhaps surprisingly, the functionalization does not seem to follow Markovnikov's rule. This is not the only example of such a reaction. It is synthetically often extremely interesting to introduce an alcohol function at the least substituted carbon atom of a double bond. This is clearly demonstrated by a second example of an intermediate step in the total synthesis of forskolin.



Forskolin

This compound is used in cell physiology and has also several potential medical uses, such as an antiglaucoma agent. When we look at the step in the total synthesis of interests to us, we see that quite a few things take place. First of all an unusual ring opening occurs around the acetal. However, more interesting the alkene is converted to an alcohol and again this functionalization does not seem to follow Markovnikov's rule.



A proposed step in the total synthesis of Forskolin on an industrial scale (Chem. Rev. ***2006****, 106, 2617).*

It can be seen that this is again a two-step reaction with similar reagents. These reagents are typical for so- called hydroboration reactions (or hydroboration-oxidation reactions). The above two examples represent a very large group of reactions frequently used in pharmaceutical chemistry and natural product synthesis. They are very reproducible, have a high yield and are readily scalable.

In order to understand the perhaps somewhat complex hydroboration reaction, it is important to write out the full mechanism including the flow of electrons. This will allow you to identify all intermediates (there will be a cyclic intermediate!) and to understand why this reaction proceeds somewhat differently than some of the other electrophilic additions we have seen. Note that the actual regioselectivity occurs in the first step. This step is quite straightforward to understand with the knowledge you have gathered in lecture 2. The second step is a bit more complex, and requires some creative thinking, since we will not cover this type of reaction in this course.