Theory

REDUCTION and OXIDATION

1. The mechanism of the reduction of nitro compounds to amino compounds.
2. The main methods of the reduction in organic synthesis (e.g. catalytic reduction, Na/EtOH reduction, metal hydrogen complexes reduction: NaBH₄ and LiAlH₄).
4. The main oxidation reagents in the organic synthesis, e.g. KMnO₄, K₂Cr₂O₇, HNO₃, Ag₂O, SeO₂, KIO₄, O₃, PCC, PDC, OsO₄.

ELIMINATION and SUBSTITUTION

2. The mechanism and stereochemistry of elimination reaction unimolecular and bimolecular (E1, E2)
4. The mechanisms of the SN1 and SN2 reactions (spatial aspects of these reactions: racemic mixture production or inversion of configuration).
5. Carbocations and their comparison of their stability.

ELECTROPHILIC SUBSTITUTION

1. The most important reactions of electrophilic substitution of aromatic compounds (Friedel-Crafts reaction, nitration, sulfonation, halogenation, addition elimination).
2. General mechanism of electrophilic aromatic substitution.

CONDENSATION and ESTERIFICATION

1. The main types of condensation (reactions: aldol, Claisen, Knoevenagel) and their mechanisms.
2. Mechanism for acid catalysed esterification.
3. Transesterification.

NUCLEOPHILIC SUBSTITUTION TO CARBONYL GROUP

2. Nucleophilic addition to a carbonyl group (formation of cyanohydrins, acetics, oximes, hydrazones, Schiff bases, reactions with Grignard compounds).
3. Beckmann Rearrangement of with mechanism.

The literature:

Exercise 2

4-AMINO-BENZOIC ACID

The reaction has to be carry out under the hood!

\[ \text{NO}_2 \text{COOH} + 6 \text{FeSO}_4 + 12 \text{NH}_4^+ + 4 \text{H}_2\text{O} \rightarrow \text{NH}_2 \text{COOH} + 6 \text{Fe(OH)}_3 + 6 (\text{NH}_4)_2\text{SO}_4 \]

Reagents:
- 4-nitro-benzoic acid
- Ammonia solution 25%
- Iron(II) sulfate hydrate
- Acetic acid (glacial)

Equipment:
- beaker 150 ml
- dropping funnel 50 ml
- Büchner funnel
- conical flask with vacuum connector
- glass rod
- graduated cylinder

To a 150 ml beaker 30 mg iron(II) sulfate hydrate and 60 ml of water is added, and warmed in the heating mantle (until boiling). Then the mixture of 2.5 g 4-nitro-benzoic acid, 10 ml of 25% ammonia solution and 8 ml of water is drop-wise added. The solution becomes brown and 15 ml of 25% ammonia solution is next instilled (to achieve light alkaline pH). The resulted hot solution is filtered on the Büchner funnel and the precipitate is washed by small amount of hot water. To the filtrate a little amount of the activated carbon is added, and later the solution is concentrated by half (by evaporation) and filtered. When 2.5 ml of glacial acetic acid is drop-wise added, 4-amino-benzoic acid precipitates. After the mixture is cooled down, pure product is filtered and washed by small amount of cold water. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

You need to know (oral answers):
- Why do we perform the reaction in a beaker (not flask and condenser)?
- Why do we need to use water as a solvent for this reaction?
- When do we use the activated carbon?
- What role does the FeSO$_4$ play in this reaction?
Exercise 3

CYCLOHEXENE

The reaction has to be carry out under the hood!

\[
\begin{align*}
\text{OH} & \quad \xrightarrow{\text{H}_3\text{PO}_4} \\
\text{Cyclohexane} & \quad \quad \text{Cyclohexene}
\end{align*}
\]

**Reagents:**
- cyclohexanol: 20 ml
- phosphoric acid: 5 ml

**Equipment:**
- round-bottom flask: 250 ml
- Liebig Condenser
- fractionating column
- conical flask: 100 ml
- beaker: 100 ml
- thermometer
- dropping funnel
- heating mantle

We install a fractional distillation set, the receiver is placed in an ice bath. We pour 5 ml of concentrated orthophosphoric acid into the 2-neck flask and heat it to 160 °C on the heating jacket. Next, 20 ml of cyclohexanol are added dropwise over one hour. After the addition, the mixture is heated to about 200 °C for 30 min. The temperature of the distillate must not exceed 90 °C. Add water solution of sodium carbonate to the distillate, separate the upper layer and dry with sodium sulfate. The drying agent is filtered off and the product is obtained as colorless liquid.

**You need to know (oral answers):**
- What is the role of phosphoric acid in this reaction?
- Why should the distillate temperature not exceed 90°C?
- Why the receiver is cooled in ice water?
- What is the composition of the distillate obtained as a result of the first distillation? Why is the distillate washed with sodium carbonate solution?
Exercise 4

ADIPIC ACID

The reaction has to be carry out under the hood!

Reagents:
cyclohexanol 10 g (10.4 ml, 0.1 mol)
nitric acid conc. 54 g (38 ml)

Equipment:
two-neck round-bottom flask 250 ml
Liebig’s condenser
graduated cylinder 50 ml
beaker 150 ml
fritted funnel
conical flask with vacuum connector
dropping funnel 25 ml,
socket Ø 14
cap with the connector,
socket Ø 29

In the two-neck round-bottom flask (vol. 250 ml), equipped with condenser and dropping funnel, 38 ml of concentrated nitric acid is heated until boiling. Then the heater is stopped and 10.4 ml of cyclohexanol is dropwise added at the rate of slight boiling. (Caution! Cyclohexanol has to portioned slowly to avoid accumulation of not-reacted reagent). After instilling, the reaction mixture has to be heated for another 15 min and cooled down to 50 °C. The mixture is then poured into the beaker (vol. 100 ml) and chilled in the ice-water cooling bath. Precipitated adipic acid is filtered on the fritted funnel and washed by small amount of cold water. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

You need to know (oral answers):
- Why cyclohexanol is dropwise added at the rate of slight boiling?
- Why after portioning of the cyclohexanol the reaction mixture is additionally heated for 15 min?
- Why do we wash the adipic acid by small amount of cold water?
Exercise 5

*p-BROMONITROBENZENE*

The reaction has to be carry out under the hood!

![Chemical structure of p-bromonitrobenzene](image)

**Reagents:**
- bromobenzene: 4g
- nitric acid conc.: 15 ml
- sulphuric acid conc.: 15 ml

**Equipment:**
- round-bottom flask Ø29: 100 ml
- Liebig Condenser
- Büchner funnel
- vacuum flask with glass connector
- funnel stopcock Ø14: 25 ml
- funnel
- graduated cylinder: 25 ml
- beakers: 100+400 ml
- petri plate, glass rod
- glass stopper Ø14+Ø29

In a three-neck round-bottom flask (vol. 250 ml) equipped with a reflux condenser, dropping funnel and thermometer, concentrated nitric acid (5 ml) is placed and cautiously added concentrated sulphuric acid (5 ml). After cooling to room temperature bromobenzene (2.7 ml) is added dropwise over 15 min, with mixing the flask with by hand. The temperature increases spontaneously to around 60°C. If the temperature is too high, cool the flask with water. After the exothermic step, the mixture is heated for 30 min on a boiling water bath and left to cool. Then, it should be intensively mixed with the glass rod, the content of the flask is poured into a beaker containing 70 ml of cold water. The obtained precipitate is filtered using Büchner funnel and washed several times with small volumes of cold water. The crude product is purified by recrystallization from ethyl alcohol. After filtration of the precipitate and washing with cold ethanol, pure p-bromonitrobenzene is obtained. The mother liquor contains a mixture of isomers: ortho- and para-bromonitrobenzene. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

**ATTENTION:** Protective gloves should be wear during the exercise.

**You need to know (oral answers):**
- Why is H$_2$SO$_4$ added? Why should it be concentrated acid?
- What are the products that formed in this reaction?
- How to separate the resulting isomers?
- How do you perform the crystallization?
- Why should this synthesis be carried out under the hood?
Exercise 6

*tert*-BUTYL CHLORIDE

You need to know (oral answers):
- Where the reaction takes place?
- Why is the extract washed with sodium bicarbonate solution?
- Why does the product distilled?

In a separatory funnel 15.8 ml of *tert*-butanol and 42.5 ml concentrated hydrochloric acid are placed. The mixture is then shaken out for about 20 min. After a while the cap is removed to get rid of excess of gases and this activity is repeated every couple minutes (at the beginning even more often). Next, the resulted mixture is left for some time to separate two different phases. The down one is acidic and it is thrown aside, the top one is washed by 10 ml of 5% sodium bicarbonate, after separation 10 ml of water and finally the organic layer is dried under anhydrous sodium sulfate. The drying agent is then filtered by funnel and filter into the flask and the crude product is purified by fractional distillation (collect the fractions with the boiling point around 48-51°C).
Exercise 7a

CINNAMIC ACID

The reaction has to be carried out under the hood!

In the round-bottom flask (vol. 100 ml) are placed: benzaldehyde (5.3 g), malonic acid (6.25 g), pyridine (10 ml) and piperidine (0.25 ml) - the mixture warms up slightly. After connecting the Liebig condenser, the reaction mixture is heated on boiling water bath until the gas bubbles are bubbling (about 1.5 hours). Then the reaction mixture is poured out with a thin stream, stirring with a glass rod, into a beaker (vol. 250 ml) containing 50 g of crushed ice and 15 ml of concentrated hydrochloric acid. The solidified product is filtered off and recrystallized from water. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

You need to know (oral answers):
- What is the role of piperidine in this reaction?
- What gas is emitted from the reaction mixture and as a result of what process?
- How is the product purified?
Exercise 8

β-D-GLUCOSE PENTAACETATE

The reaction has to be carry out under the hood!

Reagents:
- D- (+)-glucose, anhydrous: 6 g
- sodium acetate, anhydrous: 4 g
- acetic anhydride: 27.5 ml
- methanol
- chloroform/ethyl acetate: 3:1, v/v

Equipment:
- round-bottom flask Ø29: 100 ml
- Liebig Condenser Ø29
- Büchner funnel
- conical flask with vacuum connector
- graduated cylinder: 50 ml
- beaker: 400 ml
- petri plate, glass rod
- thermometer
- chromatographic chamber
- porcelain mortar & pestle

Glucose (6 g) and sodium acetate (4 g) are rubbed together in a porcelain mortar. The mixture is then transferred to a round-bottom flask (vol. 100 ml) and added acetic anhydride (27.5 ml). The reaction mixture is heated under reflux until all solids dissolved (mix the contents of the flask every few minutes). The obtained solution is poured in a thin stream, stirring glass rod intensively into a beaker (vol. 400 ml) containing water (250 ml). The solidified product should be filtered on a Büchner funnel, transferred to a mortar and thoroughly ground with 50 ml of water. The resulting suspension is filtered again and washed twice with cold water. The crude product should be recrystallized from methanol. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

You need to know (oral answers):
- What form of glucose is in the aqueous solution?
- As evidenced by the dissolution of the precipitate in the reaction mixture?
- What is the purpose of crushing and subsequent grinding of the product obtained with water?
- Why do you use cold water to wash the obtained solid?
Exercise 9

BENZOPHENONE OXIME

In the round-bottom flask (vol. 100 ml) are placed: benzophenone (2.5 g), hydroxylamine hydrochloride (1.5 g), ethanol (5 ml) and water (1 ml). Then powdered sodium hydroxide (2.8 g) is added portion-wise. The reaction mixture is mixed by hand for a few minutes, and then the flask is connected to a Liebig condenser and heated under reflux over 5 minutes. After cooling to room temperature solution of hydrochloric acid concentrated (7.5 ml) in water (50 ml) is added. The solidified product is filtered off, washed with water, and recrystallized from methanol. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

You need to know (oral answers):
- Why is sodium hydroxide added to the reaction mixture?
- How is the product separated from the reaction mixture?
- How is the product purified?
Exercise 10

**BENZYLIDENE AZINE**

\[
\text{CHO} + \text{NH}_2\text{NH}_2\text{SO}_4 + \text{NH}_3 \rightarrow \text{H} \equiv \text{N} \equiv \text{N} \equiv \text{H}
\]

*Reagents:*
- Hydrazine sulfate: 1.7 g
- Ammonia solution 25%: 1.6 ml
- Benzaldehyde: 3.2 g
- Ethanol

*Equipment:*
- Round-bottom flask: 100 ml
- Liebig Condenser Ø29
- Büchner funnel
- Conical flask with vacuum connector
- Graduated cylinder: 50 ml
- Beaker: 150 ml
- Petri plate, glass rod, syringes and needles: 2x
- Magnetic stirrer
- Magnetic stir bar

In a 150 ml beaker, hydrazine sulfate (1.7 g), water (20 ml) and 25% ammonia solution (1.6 ml) are placed and mix with a glass rod until complete dissolution. To this solution, benzaldehyde is added (3.2 g) dropwise over 0.5-1 h and then stirred for a further 1.5 hours. The resulting precipitate is filtered on the Büchner funnel, washed several times with water. The crude product is purified by crystallization from ethanol. The resulting compound dries in an air atmosphere (to be weighed in the next laboratory).

**You need to know (oral answers):**
- Why is ammonia solution added to the reaction mixture?
- How is the product separated from the reaction mixture?
- How is the product purified?
Exercise number

TILTE

1. The reaction scheme

2. Reagents

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Molecular mass [g/mol]</th>
<th>Density* [g/ml]</th>
<th>Weight [g]</th>
<th>Volume* [ml]</th>
<th>Number of moles [mol]</th>
<th>Eq</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>106</td>
<td>1.039</td>
<td>5.3</td>
<td>5.1</td>
<td>0.05</td>
<td>1.0</td>
</tr>
<tr>
<td>Y</td>
<td>104</td>
<td>1.631</td>
<td>6.2</td>
<td>3.82</td>
<td>0.06</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*only for liquids

3. Procedure outline

   *The report should be written briefly in the past tense in an impersonal form.*

4. Results

   a) What does the product look like?
   b) The yield of the synthesis.

5. Discussion of Results (conclusion)

   *Comment on, whether or not the procedure was a good method to obtain the desired compound. If not, try to make suggestions to improve this method for future experimenters. Be sure to include a discussion of possible sources of error, and how that error would affect the overall yield.*