

IDA RAHU

Bromine formation in inorganic  
bromide/nitrate mixtures and  
its application for oxidative aromatic  
bromination



DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS

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Press

Institute of Chemistry, Faculty of Science and Technology, University of Tartu,  
Estonia

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Supervisor: Prof. Jaak Järv (PhD)  
Institute of Chemistry, University of Tartu, Estonia

Opponent: Principle Investigator Alexey Khomutov (PhD, DSc)  
Engelhardt Institute of Molecular Biology,  
Russian Academy of Sciences, Moscow, Russia

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## TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS .....	7
ABBREVIATIONS .....	8
INTRODUCTION .....	9
1. LITERATURE OVERVIEW .....	11
1.1. Synthesis of brominated aromatic compounds .....	11
1.1.1. Bromination with molecular bromine .....	13
1.1.2. Bromination with bromo-organic compounds .....	15
1.1.3. Oxidative aromatic bromination methods .....	16
1.2. Oxidative properties of nitrate ions .....	17
1.3. Sigmoidal kinetic curve as a representation of an autocatalytic reaction .....	19
2. EXPERIMENTAL .....	21
2.1. Starting materials and equipment .....	21
2.2. General procedure .....	21
2.2.1. Time-course of acetanilide bromination in the presence of solvents .....	22
2.2.2. Brominating different substrates with $\text{KNO}_3$ and $\text{NaBr}$ mixture in the presence of solvents .....	23
2.2.3. Bromination in solvent-free conditions .....	24
2.2.4. Bromination with $\text{KNO}_3$ and $\text{AlBr}_3$ mixture .....	24
2.3. Data analysis .....	24
2.3.1. Analysing the sigmoidal kinetic curves received from the time-course of acetanilide bromination .....	25
3. RESULTS AND DISCUSSION .....	28
3.1. Preliminary experiments .....	28
3.2. Bromination of aromatic compounds with $\text{KNO}_3$ and $\text{NaBr}$ mixture .....	29
3.3. Time-course of acetanilide bromination .....	32
3.4. Acetanilide bromination in the presence of different solvents .....	33
3.5. The effect of amount and concentration of acid on lag phase duration .....	36
3.6. The effects of used salts ratio and amounts on bromine formation ..	38
3.7. The effect of nitrite on the formation of bromine .....	40
3.8. Possible applications of the studied bromination method to organic synthesis .....	44
3.9. Bromine formation in solvent-free conditions .....	44
3.9.1. Bromination of aromatic compounds in solvent-free conditions with the mixture of $\text{HBr}$ and $\text{KNO}_3$ .....	47

3.10. Bromination of non-activated aromatic compounds .....	48
3.10.1. The effect of different substrates and their amounts used in the reaction mixture .....	49
3.10.2. The effect of different amounts of nitrate and bromide used in the reaction mixture .....	52
3.10.3. The effect of water content on bromine formation .....	55
SUMMARY .....	57
CONCLUSIONS .....	59
REFERENCES .....	60
SUMMARY IN ESTONIAN .....	69
ACKNOWLEDGEMENTS .....	71
PUBLICATIONS .....	73
CURRICULUM VITAE .....	105
ELULOOKIRJELDUS .....	106

## LIST OF ORIGINAL PUBLICATIONS

- I Rahu, I.; Kekišev, O.; Järv, J.; Burk, P. Bromine Formation in Solid NaBr/KNO<sub>3</sub> Mixture and Assay of This Reaction via Bromination of Activated Aromatics. *Chem. Pap.*, **2018**, 72 (11), 2893–2898. <https://doi.org/10.1007/s11696-018-0526-3>.
- II Rahu, I.; Järv, J. Oxidative Bromination of Non-Activated Aromatic Compounds with AlBr<sub>3</sub>/KNO<sub>3</sub> Mixture. *Chem. Pap.*, **2020**, 74 (4), 1219–1227. <https://doi.org/10.1007/s11696-019-00965-w>.
- III Rahu, I.; Järv, J. Solvent-free Synthesis of Molecular Bromine and its Application for *in situ* Bromination of Aromatic Compounds. *P. Est. Acad. Sci.* **2020**, 69 (3), 208–214. <https://doi.org/10.3176/proc.2020.3.04> (*Available online*)

### Author's contribution:

- I The author planned and performed all the experiments and analysed their results. The author was also responsible for manuscript preparation.
- II Lead author of manuscript preparation. Also planned and performed all the experiments and analysed their results.
- III The author planned and performed all the experiments, analysed their results and prepared the manuscript.

## ABBREVIATIONS

1,2diBB	1,2-dibromobenzene
1,3diBB	1,3-dibromobenzene
1,4diBB	1,4-dibromobenzene
4NBB	4-nitrobromobenzene
B	benzene
BB	bromobenzene
BTPPMS	benzyltriphenylphosphonium peroxymonosulfate
CAN	diammonium cerium(IV) nitrate
CI <sub>95%</sub>	95% confidence interval
<i>Conv</i>	conversion value
<i>Conv</i> <sub>max</sub>	boundary-value
<i>Conv</i> <sub>t max</sub>	conversion value in the inflection point
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DMSO	dimethyl sulfoxide
Et <sub>2</sub> O	diethyl ether
F-W	Finke-Watzky
GC	gas chromatography
MeCN	acetonitrile
MS	mass spectrometry
NB	nitrobenzene
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
RMSE	root mean square error
SE	standard error
SEM	standard error of mean
SL	sulfolane
SMBI	sodium monobromoisocyanurate
TBAB	tetrabutylammonium bromide
TBATB	tetrabutylammonium tribromide
TBCA	tribromoisocyanuric acid
TBHP	<i>tert</i> -butyl hydroperoxide
<i>t<sub>i</sub></i>	induction time ( <i>i.e.</i> lag phase duration)
<i>t<sub>max</sub></i>	inflection point
TMSCl	chlorotrimethylsilane
TsNBr <sub>2</sub>	<i>N,N</i> -dibromo- <i>p</i> -toluenesulfonamide
<i>v</i> <sub>max</sub>	maximum rate ( <i>i.e.</i> slope of the burst phase)
$\sigma$	standard deviation

## INTRODUCTION

Application of sustainable chemistry concepts for improving the environmental and economic aspects of synthetic processes have significantly increased interest in unusual reaction conditions and synthetic approaches. [1] Primarily, the increase in atom efficiency of processes, the use of alternative reaction media or solvent-free reaction conditions, and application of reaction systems consisting of solid-solid, solid-liquid or solid-liquid-gas phases could be used for these purposes. In the present work, the application of sustainable chemistry concepts was investigated to improve the bromination of aromatic compounds.

Aromatic compounds with bromo-functional groups are used for the production of pharmaceuticals [2], flame retardants [3], and agrochemicals [4] because many aryl bromides have antioxidising, -tumour, -viral, -bacterial, and -fungal properties [5, 6]. Also, brominated aromatic compounds are important intermediates in organic chemistry. For example, they can be used in Heck reaction [7, 8], Sonogashira [9–11], Stille [12, 13], and Suzuki [14–16] couplings.

The traditional synthesis method for preparing brominated aromatic compounds uses molecular bromine and a Lewis acid catalyst [17]. Due to the high toxicity and corrosivity of molecular bromine, its handling is problematic [18, 19]. For this reason, an increasing number of attempts are made to develop procedures where bromination occurs *in situ*. Many of them use the approach where molecular bromine is generated in the reaction mixture by a reaction between bromide ions and a strong oxidising agent (*i.e.* so-called oxidative bromination methods). Besides the molecular bromine replacement, oxidative bromination methods provide higher atom efficiency in terms of bromine consumption (theoretically, it is up to 100%) compared to the traditional procedure [20]. However, the disadvantages of such methods are mainly related to the used oxidisers. They are often environmentally unfriendly reagents and can also cause several side reactions due to their strong oxidative properties.

In this work, oxidative aromatic bromination methods using inorganic nitrate as an oxidiser, are developed. The starting point of this study was our experiment, where  $\text{AlBr}_3$  was used instead of  $\text{AlCl}_3$  in the aromatics nitration procedure proposed by Olah *et al.* [21]. It was found that by replacing  $\text{AlCl}_3$  with  $\text{AlBr}_3$ , the main products formed in the reaction were brominated, not nitrated aromatic compounds. Our further studies revealed that aluminium bromide could be replaced with more stable bromide salts, like  $\text{NaBr}$ . This result indicated that nitrate acts as an oxidiser of bromide under certain conditions.

Nitrate ions have been previously used in aromatic bromination methods. However, most of those methods require strongly acidic and oxidative media. Based on the previous discussion, the bromination approach introduced in this work has several interesting aspects from a synthesis point of view. Indeed, inorganic salts ( $\text{KNO}_3$  and  $\text{NaBr}$ ) used in this system are low-cost, stable, safe, and can be considered as environmentally friendly chemicals. Also, a mild oxidising agent is used, and bromine formation occurs in different solvents at

room temperature and atmospheric pressure. For these reasons, further investigation of this method was undertaken.

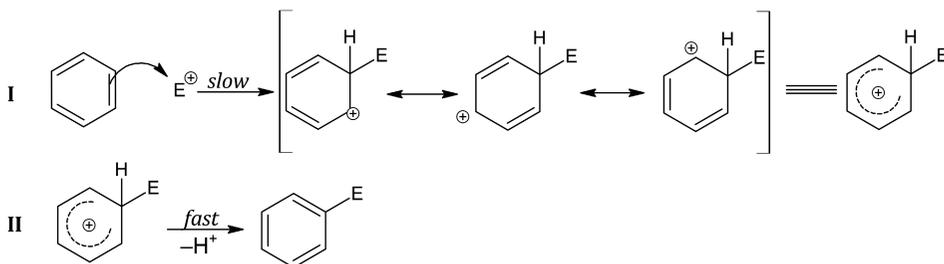
Accordingly, the aims of this study are:

- to specify the mechanism of this aromatic bromination reaction,
- to investigate the bromine formation process starting from solid nitrate and bromide salts in the reaction mixture,
- to clarify the scope and selectivity of this aromatic bromination process,
- to investigate the possibilities of using different inorganic bromides for this reaction in order to widen the application range of the method.

# 1. LITERATURE OVERVIEW

## 1.1. Synthesis of brominated aromatic compounds

Brominated aromatic compounds have several fields of applications, for example, flame retardants (*e.g.* tetrabromobisphenol A and decabromodiphenyl oxide) [3], agriculture chemicals (*e.g.* bromoxynil [4]), dyes (*e.g.* bromothymol blue), pharmaceuticals (*e.g.* nicergoline [2]), and intermediates in organic synthesis [18, 22]. Bromination of aromatic compounds takes place usually via electrophilic aromatic substitution mechanism. Generic electrophilic aromatic substitution occurs in two phases. In the first step, the electrophile is attacked by aromatic compound  $\pi$ -electrons, thus forming a positively charged intermediate (*i.e.* arenium ion). The second stage is the loss of a proton, during which aromaticity is restored. [17, 22–24]

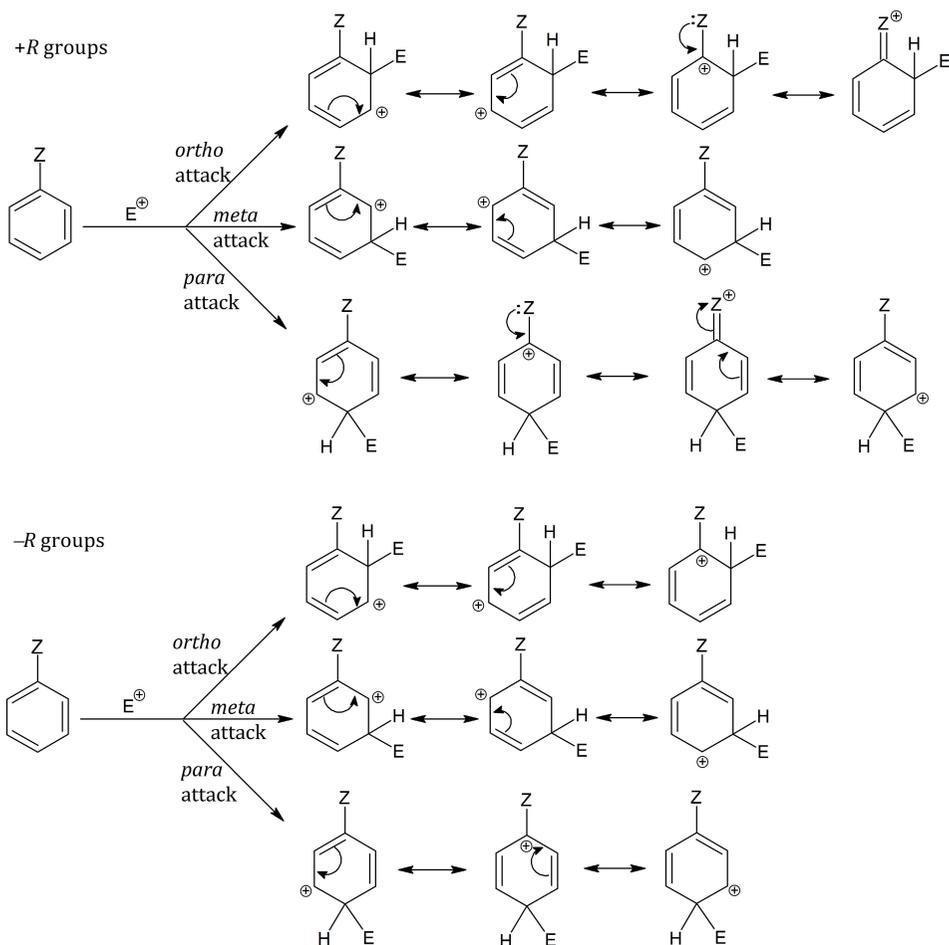


**Scheme 1.** Mechanism of electrophilic aromatic substitution. [17]

The rate of the electrophilic aromatic substitution reaction depends on the nature of the electrophile and the aromatic compound reactivity. The electrophile can be a cation or a molecule with a polarised covalent bond. The reactivity of aromatic compounds can be modified by changing the functional groups attached to the benzene ring. Effects of functional groups can be explained by field (or induction (*I*)) and resonance (*R*) effects, which change the stability of the arenium ion. Activating groups increase the reaction rate by stabilising the arenium ion compared to the non-substituted aromatic compound, whereas the groups decreasing the reaction rate are called deactivating groups. Induction and resonance effects also dictate the structure of the reaction product. When a monosubstituted aromatic compound is used as a substrate, electrophilic aromatic substitution can take place on *ortho*-, *meta*- or *para*-carbon and a mixture of three isomers with ratios 2:2:1, respectively, should form assuming the equal probability of reaction at each of these carbons. However, this ratio varies vastly and depends directly on the functional group. [17, 23, 24]

Resonance effects occur through the  $\pi$ -system. Groups which increase the density by resonance effect are called electron-donating groups ( $+R$  groups) and

groups which decrease the density electron withdrawal groups ( $-R$  groups). [17, 23, 24]



**Scheme 2.**  $+R$  and  $-R$  groups effects to the intermediates of electrophilic aromatic substitution. [23]

Inductive effects are caused by the difference between the electronegativities of atoms forming the  $\sigma$ -bond. Because of this difference, bond-forming electrons are unevenly distributed and shifted towards the more electronegative atom, causing a change in the electron density. Inductive effects fall off drastically with distance and are thus the strongest on the carbon directly connected to the functional group (*ipso*-carbon). Functional groups increasing the electron density of the aromatic ring by inductive effect are called  $+I$  groups and groups decreasing the density  $-I$  groups. [17, 23, 24]

Both effects should be considered together for a correct estimation of the overall effect of the functional group on the aromatic compound reactivity and final product structure. The effects of substituent groups are summarised in Table 1.

**Table 1.** Summarised effects of substituent groups. [23]

<i>ortho/para</i> directing groups	<i>meta</i> directing groups
<b>Strongly activating groups</b> -NR <sub>2</sub> , -NHR, -NH <sub>2</sub> , -NHCOCH <sub>3</sub> -O <sup>-</sup> , -OH, -OR, -OC <sub>6</sub> H <sub>5</sub> , -OCOCH <sub>3</sub>	<b>Strongly deactivating groups</b> -NO <sub>2</sub> , -NR <sub>3</sub> <sup>+</sup> -PR <sub>3</sub> <sup>+</sup>
<b>Weakly activating groups</b> Alkyl and phenyl groups	-SR <sub>2</sub> <sup>+</sup> , -SO <sub>3</sub> H, -SO <sub>2</sub> R -CO <sub>2</sub> H, -CO <sub>2</sub> R, -CONH <sub>2</sub> , -CHO, -COR, -CN, -CF <sub>3</sub>
<b>Weakly deactivating groups</b> -F, -Cl, -Br, -I	

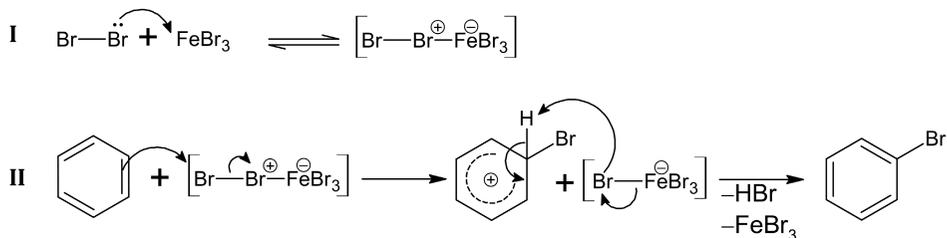
In addition to resonance and inductive effects, steric effects should also be taken into consideration when predicting the structure of the product. Electrophilic substitution is sterically hindered at *ortho* position if electrophile and/or substituent group(s) existing in the molecule are too large.

When benzene rings with more than one substituent are used as substrates, there are two possibilities: existing groups enhance or oppose each other. In the latter case, predicting the proportions of forming isomers can be very difficult. However, there are still some regularities:

- Strongly activating groups dominate over weakly activating or deactivating groups.
- When all other conditions are equal, because of steric hindrance, substitution is very unlikely to take place at a position between two groups.
- If a *meta* director is in a *meta* position to an *ortho/para* directing group, the substitution occurs mostly on the *ortho* position to the *meta* director. [17]

### 1.1.1. Bromination with molecular bromine

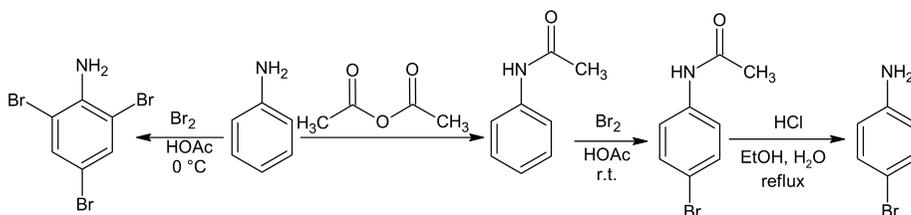
Benzene does not react with molecular bromine without a catalyst. Classically, Lewis acid catalysts (like FeBr<sub>3</sub>, AlBr<sub>3</sub>) are used to increase the electrophilic properties of bromine. [17, 23, 24] In the first stage, bromine forms a complex with a Lewis acid catalyst. As a result, the bromine atom connected to the Lewis acid has a formal positive charge. This makes the bromine atom a better electron acceptor and a better leaving group compared to bromine atoms in Br<sub>2</sub>. In the second step, the formed complex reacts with benzene. The overall mechanism can be described as follows: [23]



**Scheme 3.** Bromination of aromatic compounds with molecular bromine and a Lewis acid catalyst. [23]

Besides bromine atoms, oxygen and nitrogen atoms can also complex with a Lewis acid catalyst. Thus, Lewis acids are not usable in bromination methods for aromatic phenols and amines, because formed complexes withdraw electrons from the benzene ring and deactivate the substrate, especially in case of amines, because nitrogen gives stronger complexes than oxygen. [24]

Activated aromatic compounds can be brominated without catalysts. Electron-rich aromatic compounds used as a substrate polarise the  $\text{Br}_2$  molecule itself. [17] When very reactive aromatic compounds are brominated, monobromination is hard to achieve. For example, when aniline is used as a substrate, bromination with molecular bromine occurs very rapidly, and tri-brominated aniline is formed. For obtaining mono-brominated aniline, the amino group is usually acylated, and then the resulting amide is brominated. After that, the amide is hydrolysed back to the amine. [24]



**Scheme 4.** Aniline bromination with molecular bromine and synthesis strategy for its monobromination. [24]

Selectivity is another problem in these systems. Usually, more than one isomer forms during bromination of aromatic compounds. [17, 24] Several approaches have been developed to achieve high regioselectivity, but often very low temperatures [25, 26] or/and highly toxic reagents are needed [27]. The eco-friendlier methods involve using zeolites together with molecular bromine. For these procedures, the *ortho/para* ratio depends on the type of the cation, the extent of the cation exchange, the amount of the catalyst, the solvent used in the system, and the activation temperature. Varying these parameters enables to achieve high regioselectivity. [28–31]

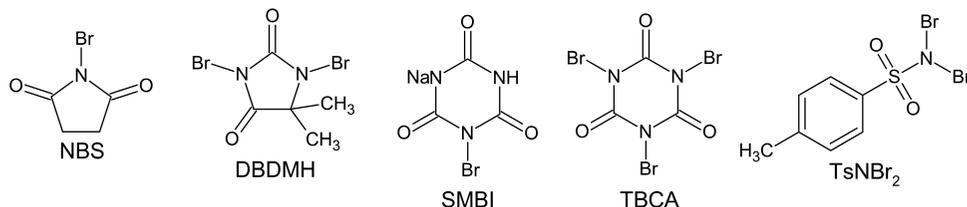
Molecular bromine is widely used in the synthesis of brominated aromatic compounds. However, the methods using molecular bromine present several limitations. For instance, the temperature needs to be controlled; applicable catalysts are often moisture-sensitive; molecular bromine itself is highly toxic and very reactive, its handling is complicated and presents many safety and environmental issues [18]. Also, it is important to keep in mind that the atom efficiency of those methods is only 50% [20, 32].

### 1.1.2. Bromination with bromo-organic compounds

In order to overcome the difficulties of handling molecular bromine, many bromination methods with bromo-organic compounds as reagents were introduced. The most popular and broadly used bromo-organic compound is *N*-bromosuccinimide (NBS). The common synthesis for aromatic bromination uses NBS in tetrachloromethane as a solvent [33–36]. But nowadays there are numerous alternative reaction mixtures containing NBS since its brominating properties can be controlled by many parameters like nature of the solvent [37–39], catalyst [40–44], or application of other activators such as microwave, ultrasound [43] or ultraviolet radiation [45, 46].

Bromination of activated aromatic compounds often shows a lack of selectivity, because reactions between an electrophile and activated aromatic compound occur rapidly. Using NBS for bromination could help to avoid such problems. For example, it is possible to brominate phenols and anilines with high para-selectivity and yield with NBS in acetonitrile using ammonium acetate as a catalyst [40]. Although handling NBS is easier and safer than Br<sub>2</sub>, there are still some negative aspects. The solid is irritant, and during some operations, Br<sub>2</sub> can be formed and released. Also, NBS should be stored in a refrigerator and kept away from moisture, to avoid its decomposition. [47]

In addition to NBS, several other bromo-organic compounds can be used for aromatic bromination: 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) [48–51], sodium monobromoisocyanurate (SMBI) [52], tribromoisocyanuric acid (TBCA) [53], and *N,N*-dibromo-*p*-toluenesulfonamide (TsNBr<sub>2</sub>) [54] to name some of them. All of them have many applications and advantages over each other, depending on the goal. For example, it was found that bromine formation with SMBI is faster compared to NBS in trifluoroacetic acid and therefore, bromination of aminomethylbenzoic acid derivative was achieved with SMBI but not with NBS. [52]



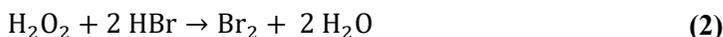
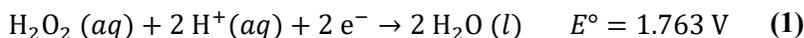
**Figure 1.** Bromo-organic compounds used for aromatic bromination.

The undesired side of using bromo-organic compounds is their synthesis in which molecular bromine is still often needed.

### 1.1.3. Oxidative aromatic bromination methods

Oxidative aromatic bromination is a term describing aromatic bromination methods in which molecular bromine is generated in the reaction mixture directly by oxidation of bromide ions. These methods have several superiorities. Inorganic bromide salts often used in these approaches are generally low-cost sources of bromine. With the classical bromination procedure (using molecular bromine), the maximum atom efficiency is 50% in terms of bromine consumption. With oxidative methods, the maximum atom efficiency can be up to 100%. For this reason, there are many further developments [55] of the traditional procedure, where HBr is recycled with an oxidising agent. [20]

Molecular bromine is a relatively strong oxidising agent. In aqueous solution at 298.15 K,  $\text{Br}_2(l)/\text{Br}^-(aq)$  standard electrode potential is 1.078 V [56]. Because of this high potential value, very strong oxidisers are usually required in oxidative bromination methods. The most commonly used oxidiser is  $\text{H}_2\text{O}_2$ . In those methods, hydrogen peroxide is used alone or together with some catalyst (for example vanadium(V) [57–59] or molybdenum(VI) [60, 61] compounds or boric acid [62]) depending on the field of application. [63–66] Other commonly used oxidising agents are *tert*-butyl hydroperoxide (TBHP) [66, 67], potassium peroxy sulfate (Oxone<sup>®</sup>) [68–71], benzyltriphenylphosphonium peroxy monosulfate (BTPPMS) [72], iodine or bromine compounds, where halogen appears in high oxidation state (for example  $\text{NaIO}_4$  [73],  $\text{I}_2\text{O}_5$  [74] or  $\text{H}_5\text{IO}_6$  [75] and bromates [76–78]), molecular oxygen in presence of catalyst [79], diammonium cerium(IV) nitrate (CAN) [80], dimethyl sulfoxide (DMSO) [81].



Most commonly, HBr or inorganic salts are used as a source of bromide ions. In addition, some quaternary ammonium bromides (like tetrabutylammonium bromide (TBAB) [59, 63] or tetrabutylammonium tribromide (TBATB) [82])

are also introduced. A typical solvent applied in those systems is water, because inorganic salts are soluble in it. Water-organic solvent mixtures are also used to prevent the problems with the solubilities of organic compounds.

A main practical limitation of such methods is the need for strong oxidising agents because these reagents can also oxidise some functional groups appearing in the organic substrate. Thus, unwanted side reactions could take place. Another issue is finding a suitable catalyst needed for aromatic bromination because Lewis acid catalysts are not applicable in aqueous conditions.

Besides, oxidative bromination methods where oxidation occurs because of irradiation have been implemented [83].

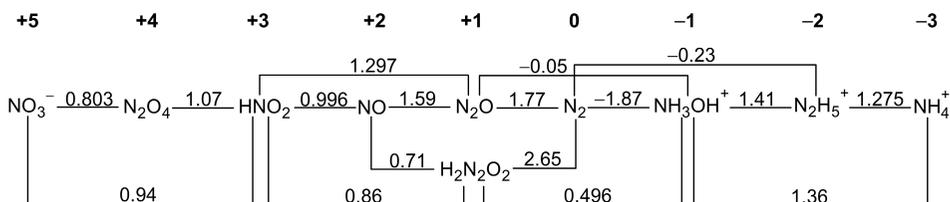
## 1.2. Oxidative properties of nitrate ions

Nitrogen can form compounds in many oxidation states. In nitrate ions, nitrogen is in its highest possible oxidation state V (+5). The main source of nitrate ions is nitric acid ( $\text{HNO}_3$ ).  $\text{NO}_3^-$  is considered as a moderately strong oxidising agent, but its oxidative properties are heavily pH-dependent. In diluted acid solutions, reduction of nitrate ions occurs relatively slowly, but the reaction is more rapid when acid concentration increases. An explanation is that the protonation of the oxygen atom promotes oxygen-nitrogen bond breaking and more  $\text{NO}_3^-$  will be protonated by increasing the acid concentration. [84]

**Table 2.** Oxidation states of nitrogen compounds with oxygen and hydrogen. [84, 85]

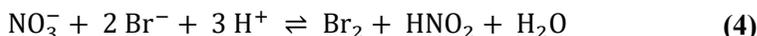
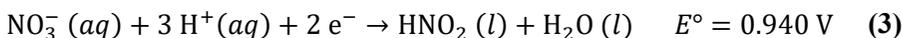
Oxidation state	Compounds
+5	$\text{NO}_2^+$ , $\text{NO}_3^-$ , $\text{HNO}_3$ , $\text{N}_2\text{O}_5$
+4	$\text{NO}_2$ , $\text{N}_2\text{O}_4$
+3	$\text{NO}^+$ , $\text{NO}_2^-$ , $\text{HNO}_2$ , $\text{N}_2\text{O}_3$
+2	$\text{NO}$
+1	$\text{N}_2\text{O}$ , $\text{H}_2\text{N}_2\text{O}_2$ , $\text{N}_2\text{O}_2^{2-}$
0	$\text{N}_2$
-1/3	$\text{HN}_3$ , $\text{N}_3^-$
-1	$\text{NH}_3\text{OH}^+$ , $\text{NH}_2\text{OH}$
-2	$\text{N}_2\text{H}_5^+$ , $\text{N}_2\text{H}_4$
-3	$\text{NH}_4^+$ , $\text{NH}_3$

Reduction of nitrates hardly ever gives only one product. The process appears to be very complicated because various reactions may occur due to the wide variety of possible lower oxidation states products [86]. Also, the reactivity of several nitrogen compounds is controlled kinetically, not thermodynamically [85]. Thus, the oxidation state of the final product of nitrate reduction hinges strongly on the properties of the reducing agent and the acid concentration. [84]



**Figure 2.** Latimer diagram connecting the different nitrogen species in acidic solution. [85]

The redox reaction between nitric acid and bromide ions has been extensively studied by Lengyel *et al.* [87]. They found that molecular bromine and nitrous acid form during the reaction. This is a reversible reaction (Equation (4)) described by the proton-independent equilibrium constant  $K(\text{H}^+) = (1.6 \pm 0.3) \cdot 10^{-6} \text{ M}^{-4}$  (Equation (5)). Thus, the reaction is strongly shifted towards the formation of bromide ions. This is also indicated by the corresponding standard potential values [56].



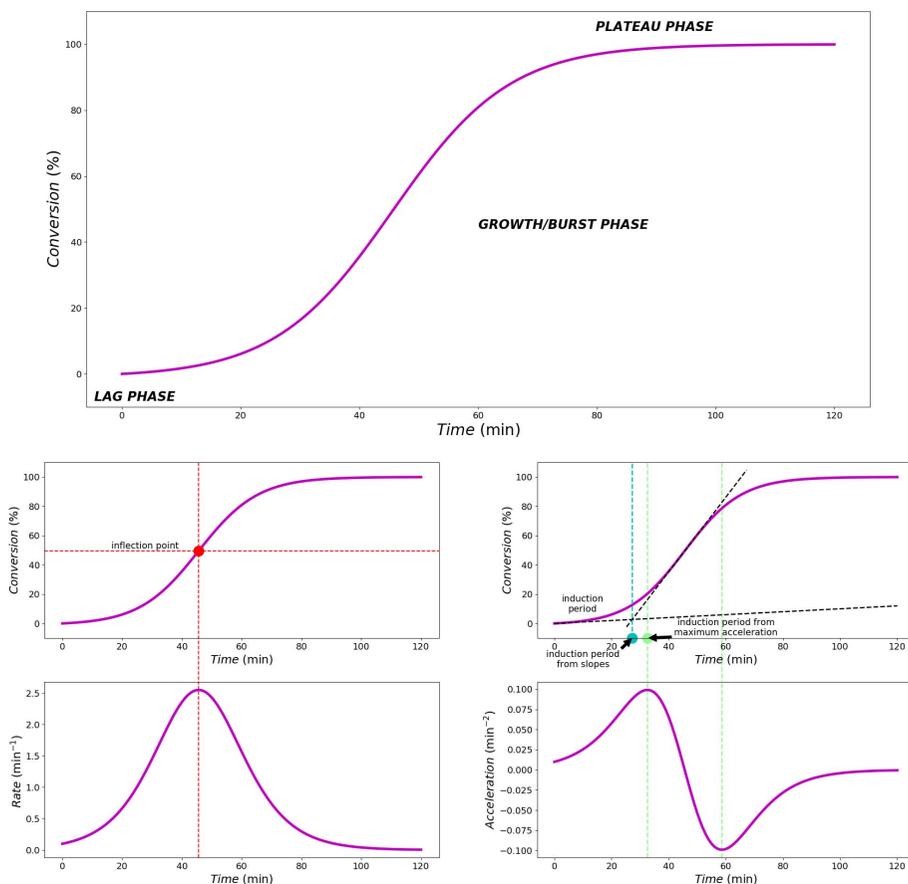
$$K(\text{H}^+) = \frac{[\text{HNO}_2][\text{Br}_2]}{[\text{NO}_3^-][\text{Br}^-]^2} \quad (5)$$

However, since the oxidising properties of nitrate ions are strongly dependent on the acid concentration, it is possible to shift the reaction towards the formation of bromine by increasing proton concentration [84, 87]. This property has also been used in many bromination processes, in which concentrated nitric acid is usually used alone or in combination with another strong acid to form bromine from the corresponding metal halide or hydrogen bromide [88–90]. Approaches using dilute nitric acid have also been developed. However, with these conditions, it has been found that, for example, acetic anhydride [91], a phase transfer catalyst [92], or quaternary ammonium bromides [93, 94] as a source of bromide ions, are also required. Fewer methods have been reported using nitrate salts instead of nitric acid as the source of nitrate ions. In these methods concentrated sulfuric acid, which itself can act as an oxidant, is often needed. [95] In addition, it has been found that nitric acid (alone or in combination with sulfuric acid) together with molecular bromine can be used for efficient bromination of deactivated aromatic compounds [88, 96, 97]. The main side reaction associated with the use of nitrate ions for the bromination of aromatic compounds is nitration, but it has been shown that it is possible to direct the reaction in a suitable path with a careful selection of the reaction conditions [97].

It is important to mention that the nitrogen compounds formed during the reduction of nitrate ions can also act as oxidants themselves. For example, sodium nitrite can be used in combination with potassium bromide to brominate pyrimidines [98]. As previously pointed out, the reduction of nitrate ions seldom results in a single product and, besides, often involves several autocatalytic cycles [99]. This autocatalytic nature of reduction of nitrate ions was also described by Lengyel *et al.* [87]. They found that the formation of bromine becomes autocatalytic after the formation of nitrous acid. Although this is an important aspect, it has not yet been observed or described in bromination processes using nitrate ions. To summarise, the use of nitrate ions in the oxidative aromatic bromination methods has several advantages, because  $\text{NO}_3^-$  is a moderate oxidising agent, and these methods can be considered as “green”. But the procedures implemented so far suffer from several drawbacks, such as a highly acidic and strongly oxidising reaction conditions, or the relatively expensive quaternary ammonium bromides (as compared to metal halides as bromine source). Replacing nitric acid with nitrate salts, which are much easier to handle, would also help to facilitate the application of the methods. Therefore, the study of the use of nitrate ions for the *in situ* generation of bromine is a very interesting field and needs further research.

### **1.3. Sigmoidal kinetic curve as a representation of an autocatalytic reaction**

Autocatalysis is a particular case of catalysis. During autocatalytic reactions, a reaction product (or an intermediate) also acts as a catalyst for this reaction [100]. In the early stages of the reaction, when only a little amount of catalyst is present, the reaction is proceeding slowly, *i.e.* the initial rate of reaction is low. However, the rate of the reaction will increase progressively as the catalytic product is formed. But after that, the reactants are consumed during the reaction, and the reaction will slow down again. The time-course of an autocatalytic process is represented by a sigmoidal/S-shaped curve. [101–105] This curve can be described in terms of three phases: a lag, a growth, and a plateau phase [106].



**Figure 3.** Sigmoidal curve analysis applied to autocatalytic reactions. [106]

In general, a lag phase refers to any slow phase, which is followed by a faster one [102]. In autocatalytic reactions, the induction period (*i.e.* duration of lag phase) can be defined in two ways: using the point of maximum acceleration or the point where initial and maximum slopes are crossing [106]. An inflection point is a point where the concavity of the curve changes [102]. In autocatalytic reactions, it represents the point where the maximum rate of the reaction is observed [106].

## 2. EXPERIMENTAL

### 2.1. Starting materials and equipment

Reagents and solvents were purchased from different commercial sources (specified in papers I, II, and III). Purities of all the organic compounds, used as substrates, were verified by gas chromatography-mass spectrometry (GC-MS). In addition, the purity of acetanilide, which was used as a reporter molecule, was checked by nuclear magnetic resonance (NMR) spectrometry, and also its melting point was measured. Dry NaBr and KNO<sub>3</sub>, used in solvent-free reactions, were obtained by drying these salts in an oven and stored in a desiccator.

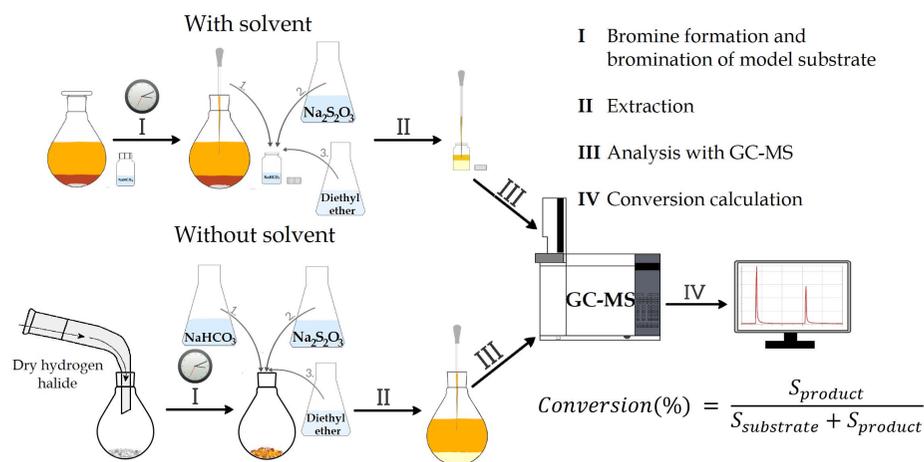
NMR spectra were recorded with Bruker Avance III HD (operating at 700.1 MHz for <sup>1</sup>H spectra and 176.0 MHz for <sup>13</sup>C spectra) at 25 °C in CDCl<sub>3</sub>, using a solvent residual signal as an internal reference.

GC-MS analyses were performed by using Agilent Technologies 7890A gas chromatograph equipped with quadrupole mass spectrometer. A nonpolar DB-5ms Ultra Inert column with dimensions of 30 m × 0.25 mm and film thickness of 0.25 μm was used. Three different temperature programmes were used. Programme I: 140 °C held for 4 min, followed by a temperature ramp of 10 °C/min to 240 °C, giving a total programme length of 14 min. Programme II: 50 °C held for 4 min, followed by a temperature ramp of 10 °C/min to 240 °C, followed by 240 °C held for 5 min, giving a total programme length of 28 min. Programme III: 50 °C held for 4 min, followed by a temperature ramp of 10 °C/min to 200 °C, followed by 200 °C held for 5 min, giving a total programme length of 24 min. Programme I was used, when acetanilide was used as substrate (papers I, II, and III). In paper III, programme I was also used for analysing the 4-hydroxy-3-methoxybenzaldehyde, and 1-bromo-2,4-dimethoxybenzene reaction mixtures. Programme III was used while benzene and bromobenzene were used as substrates (paper II). In all the other cases programme II was used. The GC-MS system was calibrated for acetanilide and its bromination product (*p*-bromoacetanilide), and all corresponding data was corrected. When benzene bromination reactions were assayed the standard substances (three dibromobenzene isomers) were used to distinguish between the isomers using their different retention times (paper II).

### 2.2. General procedure

The reaction mixture for aromatic bromination was prepared, and when the reaction was initiated, the timing was started. Since stirring in this system is perturbing bromine formation, in most cases, there was no constant stirring during experiments. Instead, stirring was applied 2 minutes before taking samples or ending the reaction. Samples or the overall reaction mixtures were then neutralised with saturated NaHCO<sub>3</sub> solution and treated with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution to remove possible excess of Br<sub>2</sub>. Then diethyl ether was used to

perform extraction, and the obtained organic layer was analysed with GC-MS. Exact volumes of used solutions and diethyl ether are given in papers I, II, and III.



**Figure 4.** Schematics of the general procedure with different reaction conditions.

### 2.2.1. Time-course of acetanilide bromination in the presence of solvents

To describe the parameters affecting bromine formation from bromide ions when nitrate is used as an oxidising agent, an indirect monitoring method was used. Instead of measuring the amount of formed  $\text{Br}_2$  directly, acetanilide was used as a model substrate, and its bromination product formation was assayed by taking samples (ca 0.5 mL) from the reaction mixture at fixed timesteps. This method is very convenient since the bromination of acetanilide occurs selectively and is a fast process compared to bromine formation.

Three different types of reaction mixtures were prepared in 100 mL pear-shaped flasks: (i) reaction mixtures with nitrate, (ii) reaction mixtures with nitrite, and (iii) reaction mixtures with nitrate and nitrite.

#### Reaction mixtures with nitrate

Acetanilide (5 mmol), NaBr (2.75 mmol, 5.5 mmol, or 11 mmol), and  $\text{KNO}_3$  (2.75 mmol, 5.5 mmol, or 11 mmol) were mixed together in 30 mL of organic solvent (diethyl ether, acetonitrile, or sulfolane). Reactions were started by adding hydrochloric acid (37wt% HCl in water; 5.5 mmol, 7.5 mmol, 15 mmol, 30 mmol, or 120 mmol). When diethyl ether was used as a solvent, durations of the experiments were 15 minutes (sampling after every minute) or 240 minutes

(sampling interval in those experiments was varied: 15, 30, 60, or 120 minutes). The duration of the experiments which were carried out in acetonitrile or sulfolane was 480 min, and samples were taken every 15 minutes.

#### **Reaction mixtures with nitrite**

Acetanilide (2.5 or 5 mmol), NaBr (5.5 mmol), and  $\text{KNO}_2$  (5.5 mmol or 11 mmol) were mixed together in 30 mL of organic solvent (diethyl ether or acetonitrile). Reactions were started by adding hydrochloric acid (37wt% HCl, 30 mmol). The duration of the experiments was 15 minutes (sampling after every minute).

#### **Reaction mixtures with nitrate and nitrite**

Acetanilide (5 mmol), NaBr (2.75 mmol, 5.5 mmol, or 11 mmol),  $\text{KNO}_3$  (2.75 mmol, 5.5 mmol, or 11 mmol), and  $\text{KNO}_2$  (0.275 mmol or 0.55 mmol) were mixed together in 30 mL of organic solvent (diethyl ether or acetonitrile). Reactions were started by adding hydrochloric acid (37wt% HCl, 30 mmol). Two different time-course experiments were carried out: short experiments (15 min) and long experiments (120 min). Sampling interval was 1 minute in short experiments and 5 minutes in long experiments.

For short experiments (total duration of 15 minutes and a sampling interval of 1 min), in most cases of the reaction mixtures described above, no stirring was done before sampling. For some experiments with nitrite in the reaction mixture, continuous stirring was applied.

In addition, to determine the effect of acid (concentration and amount) on bromine formation more thoroughly, a different experimental setup was used: equal amounts (1.5 mmol) of acetanilide,  $\text{KNO}_3$ , and NaBr were added to the 50 mL pear-shaped flask with 5 mL of hexane as a solvent. Reactions were started by adding hydrochloric acid and stirring the mixture thoroughly. In separate experiments, concentration and the amount of acid were varied. The reaction mixture was stirred 1 minute before ending the experiment. The duration of each experiment was 15 minutes.

### **2.2.2. Brominating different substrates with $\text{KNO}_3$ and NaBr mixture in the presence of solvents**

The substrate (2 mmol),  $\text{KNO}_3$  (2.2 mmol), and NaBr (2.2 mmol) were added to diethyl ether (10 mL), and the reaction was started by acidifying the reaction mixture with hydrochloric acid (1 mL, 37wt% HCl in water). Two samples (*ca.* 1 mL) were taken from the mixture (1 and 4 h after starting the reaction) to monitor the evolution of the reaction. After taking the second sample, the remaining reaction mixture was also treated as described in the general procedure. When toluene was used as a substrate, in addition to GC-MS analysis, NMR spectra were also recorded to identify the products.

### 2.2.3. Bromination in solvent-free conditions

Two different gaseous hydrogen halides (HBr and HCl) were used for this purpose. Reactions with HBr were performed in 50 mL flasks, which were connected to the source of dry hydrogen halide and contained different amounts of solid KNO<sub>3</sub> (1.1, 2.75, 5.5, or 11 mmol) as well as the bromination substrate (1, 5, or 10 mmol). The reaction was initiated by directing the gas into the vessel and keeping a constant flow rate during the reaction. Reactions were stopped by treating the overall reaction mixture like described in the general procedure. The duration of the experiments was varied. Reactions with HCl were performed similarly, with 1.1 mmol KNO<sub>3</sub>, 1.1 mmol NaBr, and 1 mmol acetanilide as bromination substrate in the reaction flask. The preparation of dry hydrogen halides is described in paper III.

### 2.2.4. Bromination with KNO<sub>3</sub> and AlBr<sub>3</sub> mixture

#### In liquid substrate

5 mL, 2.5 mL, or 1 mL of liquid substrate (benzene or bromobenzene) and KNO<sub>3</sub> (1.5 mmol, 2.5 mmol or 5 mmol) were added to the 50 mL round-bottom flask. Reactions were started by adding anhydrous AlBr<sub>3</sub> as a catalyst and a bromine source (3.75 mmol, 7.5 mmol, or 15 mmol). Reactions were stopped at different time points (15, 30, 60, 120, or 240 min) by applying the general procedure for the overall reaction mixture.

#### In solvent

As the results of preliminary experiments showed, water is needed when AlBr<sub>3</sub> is used as a source of bromide ions and catalyst, because during its hydrolysis, an acidic environment forms, which is required to enhance nitrate ions oxidising properties. In order to find the optimal amount of water, the following experiments were carried out. 1.5 mmol of a substrate (acetanilide or benzene) and the same amount of KNO<sub>3</sub> were added to the 50 mL round-bottom flask. In those experiments, hexane (5 mL) was used as a solvent. Then different amounts of water were added to the reaction mixture, and reactions were initiated by adding 7.5 mmol AlBr<sub>3</sub>. After 15 minutes, the overall reaction mixture was treated as described in the general procedure.

## 2.3. Data analysis

Results of GC-MS analyses were expressed in two ways, as conversion values or as peak area ratios. Conversion values were calculated as followed:

$$Conv (\%) = \frac{S_{\text{product}}}{S_{\text{sum}}} \cdot 100 \%, \quad (6)$$

$S_{\text{product}}$  refers to the peak area of product and  $S_{\text{sum}}$  is the sum of all the peak areas presented in the chromatogram. When acetanilide was used as a substrate,  $S_{\text{sum}}$  was the sum of peak areas which corresponded to the unreacted acetanilide and the *p*-bromoacetanilide, since this was the only product detected.

When benzene and bromobenzene were used as substrates in mixtures with  $\text{AlBr}_3$ , peak area ratios were used to present the results.

All experiments were carried out at least three times. Experimental data points shown in this work are the means of triplicate experiments. Error bars represent 95% confidence intervals (CI):

$$\text{CI}_{95\%} = \overline{\text{Conv}} \pm 2 \text{ SEM} \quad (7)$$

$$\text{SEM} = \frac{\sigma}{\sqrt{N}} \quad (8)$$

$$\sigma = \sqrt{\frac{\sum(\text{Conv} - \overline{\text{Conv}})^2}{N - 1}} \quad (9)$$

SEM – standard error of the mean,  $\sigma$  – standard deviation,  $N$  – number of experiments

### 2.3.1. Analysing the sigmoidal kinetic curves received from the time-course of acetanilide bromination

Curve fitting was done by using the Finke-Watzky two-step model [106] with integrated rate law:

$$\text{Conv} = \text{Conv}_{\text{max}} \left( 1 - \frac{k_1 + k_2 \text{Conv}_{\text{max}}}{k_2 \text{Conv}_{\text{max}} + k_1 e^{(k_1 + k_2 \text{Conv}_{\text{max}})t}} \right), \quad (10)$$

where  $k_1$  is a rate constant of slow continuous nucleation (describing the lag phase),  $k_2$  is a rate constant of fast autocatalytic growth (describing the burst phase), and  $\text{Conv}_{\text{max}}$  is the boundary-value.

Based on the results of long experiments it can be assumed that the expected final conversion of the system is 100%, except in the cases where the used bromide amount was smaller compared to the amount of acetanilide as model molecule. Therefore, to simplify the analysis of the experimental data, it can be assumed that  $\text{Conv}_{\text{max}}$  is 100%. In all calculations, for results of 15 minutes long experiments, this simplification was used, if not specified otherwise. The accuracy of the prediction was also checked by comparing the predicted curves with the experimentally obtained curves in selected cases.

It is also important to mention that if the calculated rate constant  $k_2$  is very small ( $k_2 \text{Conv}_{\text{max}} \ll k_1$ ), another simplification can be made ( $k_2 = 0$ ), resulting in the following equation:

$$Conv = Conv_{max} \left( 1 - \frac{1}{e^{k^*t}} \right) \quad (11)$$

The validity of this simplification was verified by calculating the value of  $k_1$  using Equations (10) and (11) and then comparing received values. The differences in calculated values were negligible. The calculated constant  $k_2$  was very small in some experiments in which diethyl ether was used as the solvent and sampling was made every 15 minutes. Because the duration of the lag phase was mostly shorter than 15 minutes, there was seemingly no lag period in the system, and the kinetic curve did not have an S-shape anymore but was described by a negative exponential curve. Therefore, it is understandable that the sigmoidal fitting model is not suitable for such cases. However, certain regularities were still revealed when  $k^*$  values were compared. Difficulties in determining the  $k_1$  value already appeared when the lag phase was very short and followed by a burst phase which had a very steep slope. In these cases, the other calculated parameters (like the induction time or maximum rate) were in good accordance with experimentally obtained results. So, it was still possible to compare the curves between them by using these parameters.

The values of  $k_1$  and  $k_2$  were used to calculate the duration of the lag phase in the two ways described in the literature:

$$t_{i1} = \frac{\ln \left[ (2 - \sqrt{3}) \cdot \frac{k_2 Conv_{max}}{k_1} \right]}{k_1 + k_2 Conv_{max}}, \quad (12)$$

$$t_{i2} = \frac{k_1 + k_2 Conv_{max}}{(k_1 - k_2 Conv_{max})^2} \cdot \ln \left( \frac{k_2 Conv_{max}}{k_1} \right) + \frac{2}{k_1 - k_2 Conv_{max}}, \quad (13)$$

Also, maximum rate ( $v_{max}$ ), inflection point ( $t_{max}$ ) and conversion value at the inflection point ( $Conv_{t_{max}}$ ) were calculated:

$$v_{max} = \frac{(k_1 + k_2 Conv_{max})^2}{4k_2}, \quad (14)$$

$$t_{max} = \frac{\ln \left( \frac{k_2 Conv_{max}}{k_1} \right)}{k_1 + k_2 Conv_{max}}, \quad (15)$$

$$Conv_{t_{max}} = \frac{1}{2} \left( Conv_{max} - \frac{k_1}{k_2} \right) \quad (16)$$

For general model prediction, the precision was evaluated by calculation of root mean square error (RMSE) and  $R^2$ .

For each predicted parameter, the goodness of the fit was estimated by calculating the standard errors (SE).

$$SE(\text{parameter}_i) = \sqrt{\frac{SS}{DF} \cdot Cov(i, i)}, \quad (17)$$

where  $ss$  is the sum of squared residuals,  $Cov(i,i)$  is  $i$ -th diagonal element of the covariance matrix, and  $DF$  is the number of degrees of freedom ( $DF = N_{\text{data points}} - N_{\text{predicted parameters}}$ ).

For fitting and plotting the curves, Python scientific computation library SciPy and visualisation library Matplotlib were used.

## 3. RESULTS AND DISCUSSION

### 3.1. Preliminary experiments

Olah *et al.* reported the possibility for nitration of aromatic compounds in mixtures of aluminium chloride, sodium nitrate, and chlorotrimethylsilane (TMSCl) [21]. In such nitration reactions, changing Lewis acid catalysts ( $\text{TiCl}_4$ ,  $\text{FeCl}_3$ ,  $\text{AlBr}_3$ , *etc.*) is possible [107, 108] and therefore attempts were made to replace aluminium chloride by aluminium bromide to nitrate activated aromatic compounds. As a result, it was found that brominated products were predominant in the obtained reaction mixture. Olah *et al.* suggested that nitril chloride forms due to the reaction between TMSCl and nitrate salt during the first stage of the nitration reaction. Then,  $\text{NO}_2\text{Cl}$  is activated by  $\text{AlCl}_3$ . [21] Previously, the formation of  $\text{NO}_2\text{Br}$ , as a result of halogen exchange between  $\text{NO}_2\text{Cl}$  and  $\text{KBr}$  has been described as well as its usage together with  $\text{TiBr}_4$  as a catalyst for nitration. However, in this study, ring bromination was also prevailing. [107] Halogenation can also occur as a side reaction while using nitril chloride for nitration. This is because the nature of the occurring reaction depends on the polarisation of the N–Cl bond and the way it has been cleaved [21]. Consequently, a wide scope of side reactions can be controlled by choice of solvent and catalyst. However, the use of nitril bromide for nitration gives significantly more halogenated products compared to the results obtained while using nitril chloride. This difference can be explained by the fact that nitril bromide decomposes easily and the reaction mixture constantly contains, in addition to  $\text{NO}_2\text{Br}$ , molecular bromine and nitric oxide. [107, 108]

In preliminary experiments, it was found that TMSCl is not necessary for bromination with  $\text{AlBr}_3/\text{KNO}_3$  mixture, and it even has some interfering effect. Therefore, it can be stated that bromine needed for bromination is not generated via halogen exchange with  $\text{NO}_2\text{Cl}$  in the studied reaction mixture, and the interfering effect of TMSCl is probably related to the formation of  $\text{NO}_2\text{Cl}$ .

Formation of nitril bromide also occurs in the reaction between bromine-containing Lewis acid and  $\text{HNO}_3$  [107]. Nitric acid, however, can only be formed in the studied reaction mixture when it contains water. The presence of water would hydrolyse  $\text{AlBr}_3$ , and an acidic environment would form. This is in correspondence with the preliminary experiments where it was found that no bromine forms in anhydrous conditions – neither the characteristic colour of bromine was noticed, nor brominated products were detected. In addition, it was found that increasing the polarity of the reaction media (adding sulfolane to the  $\text{CCl}_4$ ), higher conversions are obtained for bromination. Therefore, it can be assumed that increasing the solubility of salts is necessary for bromination.

Redox reaction between bromide ions and nitrate ions in acidic media has been studied (see Section 1.2., Equation (4)). Thus, it was necessary to clarify if bromine forms in a similar way via a redox reaction. For that reason,  $\text{AlBr}_3$  was replaced with  $\text{NaBr}$ , which is much more easily handled than aluminium bromide. Conducted experimental series showed that bromine formation does

not depend on the bromide source. However, the acidification of the reaction mixture is required. In this study, hydrochloric acid was used for this purpose. It is well known that some nitrogen species can also oxidise chloride ions, and thus chlorination side reactions could happen [56, 109]. However, no chlorinated products were obtained in this study. Also, it is important to notice, that by changing the bromide source, no nitrated products were detected anymore.

In the present work, attempts were made to investigate the bromine formation mechanism by iodometric titration to determine the amount of bromine produced. These attempts were unsuccessful due to the formed nitrogen compounds, even though scavengers of various nitrogen compounds were used. However, as a result of these experiments, it was found that nitrite ions and nitrogen dioxide form during nitrate reduction.

So far, oxidative bromination methods involving nitrate ions as oxidisers present several shortcomings. For example, strongly acidic conditions are needed, a strong oxidising agent (concentrated  $\text{HNO}_3$ ) as a source of nitrate ions is often used, *etc.* Therefore, it can be stated that the method using NaBr and  $\text{KNO}_3$  for aromatic bromination presented in this work clearly is characterised not only by interesting theoretical aspects but also has potential practical implications. Indeed, the process itself is straightforward as one should only add the reagents (solid NaBr and  $\text{KNO}_3$ ) together with the organic substrate and suitable solvent into the reaction flask and initiate the reaction by adding the hydrochloric acid. The reaction can be stopped by neutralising the reaction mixture with  $\text{NaHCO}_3$  solution, and the bromine excess is removed by treating the mixture with  $\text{Na}_2\text{S}_2\text{O}_3$  solution. The used solid reagents NaBr and  $\text{KNO}_3$  are easily handled, inexpensive and can be considered as green reagents. In addition, a wide variety of solvents can be used, and the reaction conditions are mild (room temperature, atmospheric pressure). Therefore, an in-depth, comprehensive study of the method was conducted.

### **3.2. Bromination of aromatic compounds with $\text{KNO}_3$ and NaBr mixture**

In order to find a range of applicability for the studied reaction mixture and understand the overall bromination mechanism, aromatic compounds with different reactivity were chosen for monitoring their bromination process. The results obtained after 4 hours are shown in Table 3.

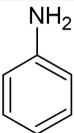
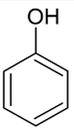
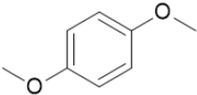
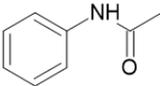
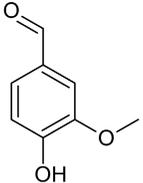
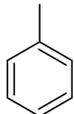
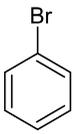
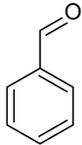
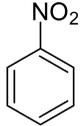
These results indicate that bromination of several activated aromatic compounds is possible in the studied reaction mixture. Also, they are in good accordance with the overall reactivity of the compounds by means of electrophilic aromatic substitution. The only exception is aniline, which bromination was impossible in such conditions. The probable reason is that aniline as a base reacts with hydrochloric acid, which is needed in the reaction mixture to improve oxidative properties of nitrate ions for bromine formation. Formed anilinium ion/salt is a deactivated compound, and this result is also in accordance

with the previous ones. However, it is also important to notice that in this reaction mixture, the characteristic colour of Br<sub>2</sub> was not observed. Therefore, it was assumed that no bromine formed in the reaction mixture. The reason could be that the oxidising properties of nitrate ions are not strong enough anymore since acid is consumed for protonation of aniline. However, this is rather unlikely the main reason, since the amount of acid utilised in this process is small compared to the overall amount of acid used in the reaction mixture. Therefore, another reason could be that the precipitation of anilinium chloride (aniline hydrochloride) could affect the dissolution process of salts needed for bromine formation.

It is also important to point out that while toluene was used as a substrate, no benzylic bromination occurred and only *ortho*- and *para*-brominated isomers were observed. With these results, the radical bromination mechanism could be excluded.

Relying on these results, it can be concluded that bromination of aromatic compounds occurs via a conventional electrophilic substitution mechanism, and the brominating agent is *in situ* generated molecular bromine.

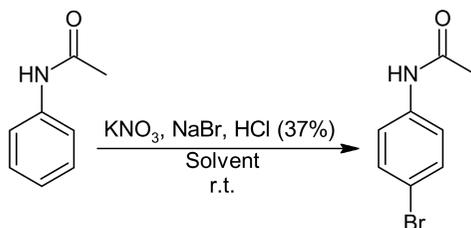
**Table 3.** Bromination of various aromatic compounds (2 mmol) with NaBr (2.2 mmol) and KNO<sub>3</sub> (2.2 mmol) in diethyl ether (10 mL) – hydrochloric acid (37wt% solution in water, 1 mL) mixture. Conversion values were calculated using raw data obtained from GC-MS analysis without systematic calibration (except for acetanilide). Conversion values and 95% confidence intervals are given with notation (*Conv* ± CI<sub>95%</sub> (%)) only when experiments were carried out three times. The duration of the experiments was 4 hours.

Substrate	Products and their conversion (%)	Substrate	Products and their conversion (%)
 Aniline	—	 Phenol	2-bromophenol (13%) 4-bromophenol (19%) 2,4-dibromophenol (8%) 2,4,6-tribromophenol (trace)
 1,4-dimethoxybenzene	2-bromo-1,4-dimethoxybenzene (27%) 2,5-dibromo-1,4-dimethoxybenzene (30%)	 Acetanilide	4-bromoacetanilide (99% ± 1%)
 4-hydroxy-3-methoxybenzaldehyde	5-bromo-4-hydroxy-3-methoxybenzaldehyde (98% ± 2%)	 Toluene	2-bromotoluene (2% ± 1%) 4-bromotoluene (3% ± 2%)
 Bromobenzene	—	 Benzaldehyde	—
 Nitrobenzene	—		

### 3.3. Time-course of acetanilide bromination

For the development of a new bromination method for aromatic compounds, it is essential to understand how different parameters affect the bromine formation. However, the studied reaction mixture, containing  $\text{KNO}_3$ ,  $\text{NaBr}$  and hydrochloric acid (37wt%) in the presence of an organic solvent, is very complex. It contains solid salts, a liquid phase (or several, depending on the used organic solvent), and several different nitrogen compounds (for example  $\text{NO}_2$  and nitrite ions, formation of which was proved by iodometric titration) which can form during reduction of nitrate ions. As there are several complications to monitor molecular bromine formation directly during the reaction, a different approach was used. This alternative method consists in monitoring the bromine formation indirectly by a fast and selective bromination reaction (so-called “reporter reaction”), assuming that the evolution of the brominated product over time describes the formation of molecular bromine well. This approach can only be used when bromine formation is slower than the bromination step.

In preliminary experiments, several activated aromatic compounds were tested. Acetanilide was chosen as a model substrate (“reporter molecule”) as it is possible to brominate it with this particular reaction mixture in the presence of different solvents (diethyl ether ( $\text{Et}_2\text{O}$ ), sulfolane (SL) and acetonitrile (MeCN)) with high *para*-selectivity and 100% conversion. Also, using acetanilide made the sampling procedure very convenient. In addition to all this, it is known from the literature [110, 111] that bromination of acetanilide is a very fast process and some results, which will be discussed later in this dissertation, show that bromination of acetanilide is faster than bromine formation. For these reasons, acetanilide was a reasonable choice as a model substrate for this work.



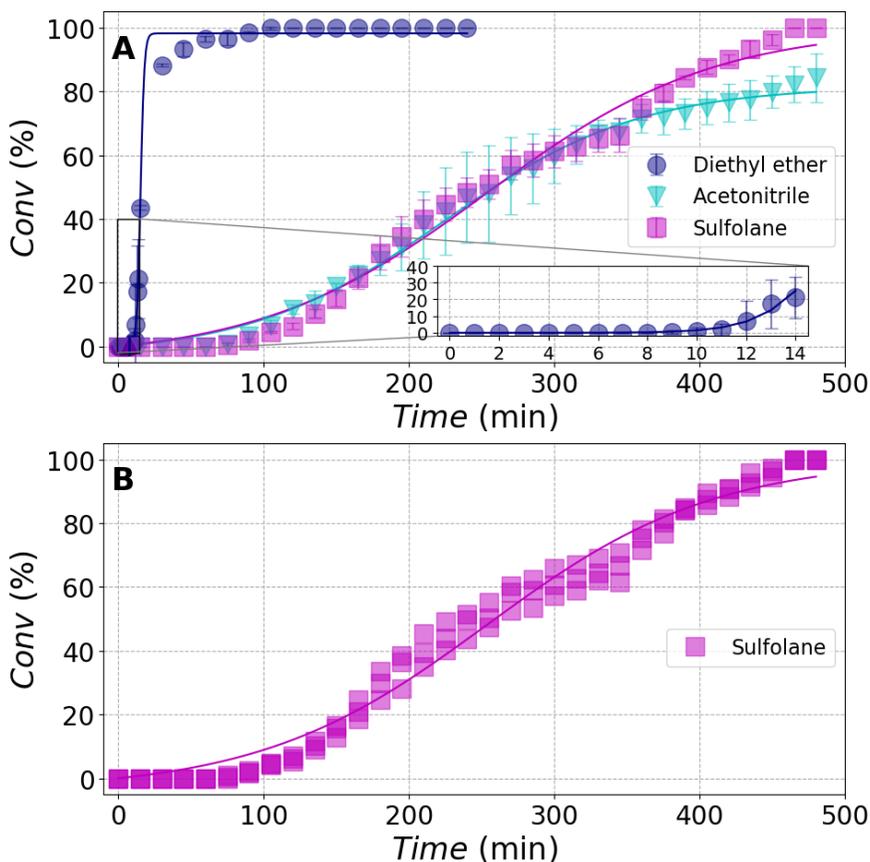
**Scheme 5.** Bromination of acetanilide with a  $\text{KNO}_3/\text{NaBr}$  mixture in acidic media.

Preliminary experiments were also conducted to scale-up the reaction mixture to have enough material for sampling and characterisation. These experiments showed that stirring the reaction mixture interfered with bromine formation. Without stirring, bromine formation was observed in the proximity of the surfaces of the solid salts. However, stirring is still required because the formed bromine and the substrate have to be distributed evenly for a reliable sampling. Therefore, 2 minutes before taking the sample, the mixture was stirred shortly.

In order to verify the sampling results, the remaining reaction mixture was always analysed after taking the final samples.

### 3.4. Acetanilide bromination in the presence of different solvents

Bromination of acetanilide was studied in the presence of three different solvents: diethyl ether, acetonitrile and sulfolane. These solvents were chosen because they do not react with molecular bromine and bromine formation as well as bromination processes occur in their presence.



**Figure 5.** Acetanilide (5 mmol) bromination with NaBr (5.5 mmol) and  $\text{KNO}_3$  (5.5 mmol) mixture in the presence of hydrochloric acid (37wt%, 2.5 mL) and organic solvent (diethyl ether, acetonitrile and sulfolane; 30 mL). **A** – Mean values of the experiments. Error bars are given for 95% confidence interval. Curve fitting was done using Finke-Watzky model. Inset: zoom on the lag phase in the presence of diethyl ether. **B** – Acetanilide bromination in the presence of sulfolane. Markers represent the three replicates and the continuous line is the result of curve fitting of the mean values presented in **A**.

Figure 5 shows that the acetanilide bromination has a lag phase in the presence of all three solvents and the reaction follows an S-shaped kinetic curve. The induction period and the sigmoidal kinetic curve are very characteristic to autocatalytic reactions. In the literature [87], it has already been reported that nitrate and bromide ions in acidic aqueous media react via an autocatalytic mechanism. In this mechanism, nitrous acid, which forms in the first step (Equation (4)), acts as a catalyst. Thus, it can be suggested that in the studied reaction mixture, bromine formation occurs similarly. However, the autocatalytic mechanism alone does not explain all the observed results such as the sensitivity of bromine formation to stirring and the bromine formation starting near the surfaces of solid salts.

To analyse the sigmoidal curves, the two-step generic Finke-Watzky (F-W) model [106] was used. This approach is based on the idea that the process involves two pseudo elementary steps. According to this model, a sigmoidal kinetic curve can be described by three parameters: a rate constant of slow continuous nucleation ( $A \xrightarrow{k_1} B$ ), a rate constant of fast autocatalytic growth ( $A + B \xrightarrow{k_2} 2B$ ) and a boundary-value, which in present work means the maximum conversion value ( $Conv_{max}$ ). With these three variables, it is possible to calculate the induction time ( $t_i$ ), inflection point ( $t_{max}$ ) and slope of the burst phase ( $v_{max}$ ) (see Section 2.3.1., Equations 12–15).

In the framework of this study, which uses “reporter reaction” for indirect bromine monitoring, A represents acetanilide and B is *p*-bromoacetanilide. At the starting point ( $t = 0$ ) the amount of *p*-bromoacetanilide is 0 ( $Conv = 0\%$ ). At time moment  $t$ , the following relationship applies: amount of *p*-bromoacetanilide + amount of acetanilide = amount of acetanilide at the starting point =  $Conv_{max}$ . Hence the integrated rate law, needed for curve fitting, can be expressed as given in Equation (10).

The Finke-Watzky model was used due to its minimalistic form because it allows to describe and approach very complex systems with relative ease. More advanced and sophisticated models exist to describe sigmoidal curves. However, it is often problematic to give a physical meaning and match the calculated parameters with existing physical models. For example, the reaction mechanism might be too complicated for an exact mathematical solution, or there is a lack of information about the individual steps occurring during the process. Models with increasing numbers of fitted parameters would indeed provide a better mathematical fit, but no physical meaning could be extracted from such models. Although F-W model has been criticised because of its oversimplified presentation, it is still widely used in very different fields for describing sigmoidal curves since this model provides a mathematical description and a good approach to the physical model even for systems which may contain hundreds of elementary steps [112–114].

In addition, it is important to notice that F-W model fits the experimental data received in this study with a satisfactory accuracy ( $R^2$  varied in range 0.87 to 1.00 and RMSE in range 0.73 to 5.1).

Figure 5 shows that the duration of the lag phase, as well as the slope of the burst phase, significantly depend on the organic solvent used. The results of processing the kinetic curves obtained under these different reaction conditions are listed in Table 4.

**Table 4.** Kinetic data obtained by fitting the experimental conversion curves with F-W model in the presence of different solvents. Experiments were conducted using 5.5 mmol of acetanilide, 5.5 mmol of NaBr, 5.5 mmol of KNO<sub>3</sub>, 2.5 mL hydrochloric acid (37wt%) and 30 mL of organic solvent (diethyl ether, acetonitrile or sulfolane).

Solvent	$Conv_{max} \pm SE$ (%)	$k_1 \pm SE$ (min <sup>-1</sup> )	$k_2 \pm SE$ (min <sup>-1</sup> )	$t_{i1}$ (min)	$t_{i2}$ (min)	$v_{max}$ (min <sup>-1</sup> )
Et <sub>2</sub> O	98.2 ± 1.8	(1.0 ± 0.2) · 10 <sup>-4</sup>	(5.1 ± 2.3) · 10 <sup>-3</sup>	14	13	12
MeCN	81.6 ± 2.9	(5.1 ± 1.3) · 10 <sup>-4</sup>	(1.8 ± 0.3) · 10 <sup>-4</sup>	136	114	0.32
SL	100.0 ± 18 <sup>a</sup>	(4.8 ± 3.8) · 10 <sup>-4</sup>	(1.2 ± 0.8) · 10 <sup>-4</sup>	150	127	0.33

<sup>a</sup> Conversion values larger than 100% are not realistic.

Based on the results presented in Figure 5 and Table 4, it can be emphasised that bromination occurs most rapidly when diethyl ether is used as an organic solvent in the reaction mixture. In the presence of acetonitrile and sulfolane, bromination (and therefore also bromine formation) happens in a similar manner since their induction time values and maximum rates are very similar. The most significant difference while using diethyl ether in these organic solvent–water mixtures is that there are two clearly distinguishable liquid phases in the reaction mixture – the organic phase and the acidic aqueous phase. It means that inorganic solid salts are in the acidic aqueous layer. It was already previously noted that acid must be present for the reaction to occur. Also, by increasing the proton concentration in the solution, the oxidising properties of nitrate ions are enhanced. This is a possible explanation to the results obtained above and a more detailed discussion about the effect of the acid concentration on bromine formation is presented in the next section. In addition, as the preliminary experiments showed (see Section 3.1.), the solubility of solid salts also affects the bromine formation.

Since the reaction is relatively fast in the presence of diethyl ether, the main part of this study was made by using this organic solvent.

It is important to add that, at the end of the kinetic curves, the assumption that bromination is a faster process than bromine formation does not apply because the amount of acetanilide used in the reaction mixture is smaller than the amount of bromide. However, this is not problematic in this approach since the focus of the investigation was on the lag phase and the beginning of the burst phase, which can be described with the first part of the curve. The statements that (i) bromination of acetanilide is faster than bromine formation and (ii) the first part of the kinetic curve describes only bromine formation kinetics, were both experimentally proven (see Section 3.7. for further discussions). Also, it is important to keep in mind, that the obtained curve analysis results

(like calculated rate constants, induction time *etc.*) are only rough estimations and are used solely for comparing the effects of the key factors.

### 3.5. The effect of amount and concentration of acid on lag phase duration

The oxidising properties of nitrate ions depend significantly on the concentration of hydrogen ions within the reaction mixture. For that reason, acidifying the reaction mixture is necessary to generate bromine from bromide ions. It was experimentally proven that without acid, bromine does not form in the reaction mixture.

According to Equation (4), bromine formation is a reversible reaction that can be shifted towards the formation of bromine by increasing the acid concentration in the mixture and keeping the water concentration as low as possible. By saying that, it is also important to notice that because of using a reporter reaction for assaying bromine formation, the equilibrium is already shifted towards bromine formation (formed bromine is consumed during the reporter reaction) to some extent. In the first experiments where the amount of acid was varied from 5.5 mmol to 120 mmol using 30 mL of diethyl ether as the organic solvent, no significant effect on the formation of bromine was evidenced. The probable reason for that was a too long sampling interval, which was longer than the lag phase duration. This statement is in accordance with the calculations of rate constants, where the calculated  $k_2$  values were very small. However, comparing the  $k^*$  values (see Table 5), it was found that larger amounts of acid increase the value of the constant to some extent. Therefore, more detailed studies were needed.

**Table 5.** Calculated  $k^*$  values as a function of the amount of acid in the reaction mixture. Experiments were conducted by using 5.5 mmol of acetanilide, 5.5 mmol of NaBr, 5.5 mmol of KNO<sub>3</sub>, hydrochloric acid (37wt%) and 30 mL of diethyl ether.

$n_{\text{H}^+}$ (mmol)	5.5	7.5	15	30	120
$k^* \pm \text{SE}$ (min <sup>-1</sup> )	0.052 ± 0.011	0.061 ± 0.003	0.063 ± 0.001	0.065 ± 0.002	0.077 ± 0.002
$\text{Conv}_{\text{max}} \pm \text{SE}$ (%)	97.3 ± 3.0	99.1 ± 0.5	99.5 ± 0.2	99.6 ± 0.4	99.3 ± 0.4

As mentioned before, when diethyl ether is used as a solvent, solid salts are in the acidic aqueous layer. For further studies, hexane (5 mL) was used as an even less polar solvent to assume that acid concentration in the aqueous layer is roughly the same as in the hydrochloric acid stock solution (37wt%) used in this work.

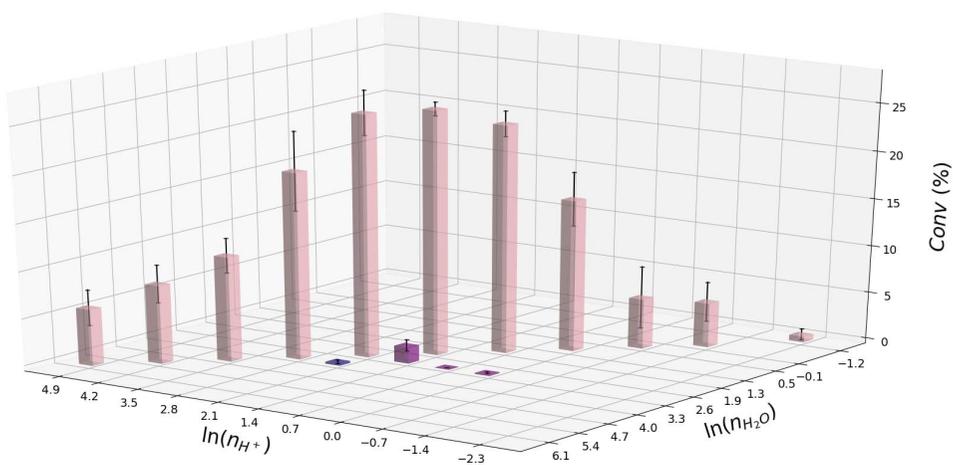
To investigate the effect of acid on bromine formation, two different sets of experiments were carried out. In the first series, the formation of bromine was studied in the reaction mixtures where the amount of acid ranged from

0.1 mmol to 128 mmol while holding the acid concentration constant. In the second set, the water content in the reaction mixture was changed while keeping the amount of acid the same (*i.e.* the total acid concentration varied but not the molar amount of acid). Results of these experiments are shown in Figure 6.

It can be seen, that an optimal amount of acid exists in the presence of which bromine formation is the fastest (light pink bars in Figure 6). The results (darker bars in Figure 6) clearly show that the addition of water (*i.e.* a lower acid concentration) slows down the formation of bromine, which is in good accordance with Equation (4).

The slowing down effect observed when smaller or larger amounts of acid solution were used compared to the optimal value, is not that straightforward. The explanation why smaller amounts of acid solution hinder the bromine formation could be related to the dissolution process of solid salts (important factor, as shown in Section 3.1.). Indeed, when using smaller volumes of acid, smaller amounts of salts can be dissolved over the same time interval. This means that in the total reaction volume, the regions where bromine can form, are very limited.

The slowing down effect observed when larger amounts of acid were used, could be explained by introducing the notion of “ignition volume”. An ignition volume is a small but finite heterogeneous region in the total volume, where the reaction is initiated. According to Equation (4), a high acid concentration and high concentrations in nitrate and bromide are required for bromine formation. The formation of these ignition volumes in which the nitrate, bromide and acid concentrations should be high enough is less probable during the same time interval when larger volumes of acid are used due to diffusion of dissolved salts over a larger region.



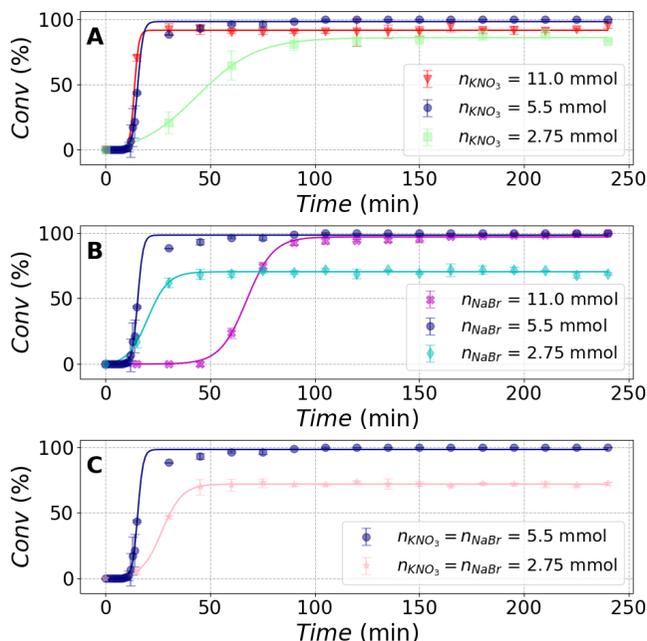
**Figure 6.** The effect of amount and concentration of acid on the bromine formation. Reactions were conducted using equal amounts (1.5 mmol) of acetanilide, NaBr and  $KNO_3$  in 5 mL of hexane. HCl 37wt% solution in water was used as acid. Duration of the experiments was 15 minutes. The error bars represent  $CI_{95\%}$  values.

Relying on the obtained results, it was assumed that the difference in acid concentration is one of the reasons why bromine formation is slower in acetonitrile and in sulfolane than in diethyl ether. When using these solvents, there is only one detectable liquid phase in the reaction mixture. In order to ascertain this speculation, experiments with acetonitrile (30 mL) as a solvent were carried out. In previous experiments with 30 mmol of HCl in the reaction mixture, brominated acetanilide was detected after 1 h. Adding five times as much acid shortened the lag period considerably and brominated acetanilide could be detected in less than 30 minutes. Thus, increasing the acid concentration does shorten the lag period. These results are in good agreement with the work of Lengyel *et al.* [87] in which they showed the significant impact of acid concentration on bromine formation.

From a synthesis point of view, it is essential to notice that a larger amount of acid can initiate side reactions. For example, in the studied system where acetanilide was used as a substrate together with larger amounts of hydrochloric acid, the formation of mono- and di-brominated aniline was detected as the reaction progressed in time.

### **3.6. The effects of used salts ratio and amounts on bromine formation**

The amounts of bromide and nitrate salts, as well as their ratio, were changed. Increasing the amount of nitrate accelerates the bromination process, and therefore also the bromine formation (Figure 7A). Based on the calculated results (see Table 6, series A), it can be stated that the maximum rate of the reaction strongly depends on the amount of nitrate used in the mixture. This regularity was also described in the literature [87]. However, side reactions could happen when using larger amounts of oxidising agent.



**Figure 7.** Experimental results obtained by changing the amounts and ratios of used solid salts in the mixture. **A** Changing nitrate amount while holding bromide amount (5.5 mmol) constant; **B** changing bromide amount while keeping nitrate amount (5.5 mmol) constant; **C** holding salts ratio constant and changing their amounts. In all experiments, the amount of acetanilide was 5 mmol, the volume of hydrochloric acid (37wt%) was 2.5 mL, and the volume of diethyl ether was 30 mL. Error bars are given as  $CI_{95\%}$ . Solid lines represent curve fitting results obtained by using F-W two-step model.

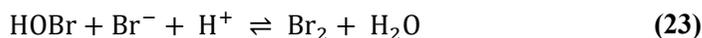
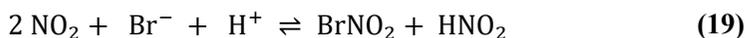
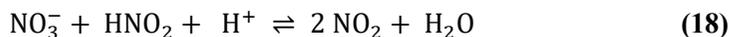
**Table 6.** Kinetic data obtained by F-W model while processing experimental results obtained in the experiments where the amounts of solid salts were changed. In all experiments, the amount of used acetanilide was 5 mmol.

Series	$n_{KNO_3}$ (mmol)	$n_{NaBr}$ (mmol)	$Conv_{max} \pm SE$ (%)	$k_1 \pm SE$ ( $min^{-1}$ )	$k_2 \pm SE$ ( $min^{-1}$ )	$t_{i1}$ (min)	$t_{i2}$ (min)	$v_{max}$ ( $min^{-1}$ )
<b>A</b>	11	5.5	$91.5 \pm 0.7$	$(2.0 \pm 0.3) \cdot 10^{-6}$	$(1.0 \pm 1.0) \cdot 10^{-2}$	12	12	22
	5.5	5.5	$98.2 \pm 1.8$	$(1.0 \pm 0.2) \cdot 10^{-4}$	$(5.1 \pm 2.3) \cdot 10^{-3}$	14	13	12
	2.75	5.5	$85.9 \pm 2.0$	$(3.2 \pm 1.7) \cdot 10^{-3}$	$(7.7 \pm 2.0) \cdot 10^{-4}$	25	21	1.6
<b>B</b>	11	5.5	$96.8 \pm 1.2$	$(4.0 \pm 2.1) \cdot 10^{-6}$	$(1.6 \pm 0.2) \cdot 10^{-3}$	59	55	3.8
	5.5	5.5	$98.2 \pm 1.8$	$(1.0 \pm 0.2) \cdot 10^{-4}$	$(5.1 \pm 2.3) \cdot 10^{-3}$	14	13	12
	2.75	5.5	$70.3 \pm 0.5$	$(3.3 \pm 1.1) \cdot 10^{-3}$	$(2.9 \pm 0.3) \cdot 10^{-3}$	14	11	3.7
<b>C</b>	5.5	5.5	$98.2 \pm 1.8$	$(1.0 \pm 0.2) \cdot 10^{-4}$	$(5.1 \pm 2.3) \cdot 10^{-3}$	14	13	12
	2.75	2.75	$71.8 \pm 0.2$	$(8.4 \pm 1.8) \cdot 10^{-4}$	$(2.8 \pm 0.1) \cdot 10^{-3}$	20	17	3.7

The effect of the amount of bromide on bromine formation cannot be easily described with the results obtained from calculations (Table 6, series **B**) because there are no clear trends in induction time and maximum rate values. However, it can be noted that larger amounts of bromide prolong the lag phase. A probable explanation for this phenomenon is given in the next section. Like expected, when more acetanilide compared to bromide is used (Table 6, series **B** and **C**), bromination never occurs with 100% conversion. Conversion values higher than theoretical ones indicate that acetanilide and 4-bromoacetanilide are distributed unevenly between aqueous and organic phases. This statement was confirmed by taking the samples also from the aqueous phase and by analysing the overall reaction mixture after taking the final sample – the conversion value in the latter case was around 53%.

### 3.7. The effect of nitrite on the formation of bromine

Lengyel *et al.* proposed that the formation of bromine is an autocatalytic process in which nitrous acid forming during the first stage (Equation (4)) acts as a catalyst. The whole process can be described as a sequence of the following reactions, as noted in the literature [87]:



It was previously determined that nitrite ions and nitrogen dioxide form in the studied reaction mixture, but further observations were needed for a better description of the process.

For that, nitrite ions, which form rapidly nitrous acid in an acidic medium, were added to the reaction mixture. Preliminary results showed that the addition of a small amount of nitrite salt significantly shortened the duration of the lag phase. This statement is also confirmed by the calculated induction time, which decreased about ten times with the addition of nitrite in the experiments where acetonitrile was used as a solvent (Table 7).

**Table 7.** Kinetic data for acetanilide (5 mmol) bromination in a reaction mixture containing solid  $\text{KNO}_3$  (5.5 mmol),  $\text{KNO}_2$  (0 or 0.55 mmol), and  $\text{NaBr}$  (5.5 mmol) in the presence of hydrochloric acid (37wt%, 2.5 mL) and organic solvent (diethyl ether or acetonitrile, 30 mL). Kinetic curves were processed by F-W model, and the obtained results together with calculated induction times are given.

Solvent	$n_{\text{KNO}_2}$ (mmol)	$\text{Conv}_{\text{max}} \pm \text{SE}$ (%)	$k_1 \pm \text{SE}$ ( $\text{min}^{-1}$ )	$k_2 \pm \text{SE}$ ( $\text{min}^{-1}$ )	$t_{i1}$ (min)	$t_{i2}$ (min)
$\text{Et}_2\text{O}$	0	$98.2 \pm 1.8$	$(1.0 \pm 0.2) \cdot 10^{-4}$	$(5.1 \pm 2.3) \cdot 10^{-3}$	14	13
	0.55	$94.5 \pm 6.5^a$	$(3.2 \pm 1.2) \cdot 10^{-3}$	$(2.7 \pm 0.4) \cdot 10^{-3}$	12	10
$\text{MeCN}$	0	$81.6 \pm 2.9$	$(5.1 \pm 1.3) \cdot 10^{-4}$	$(1.8 \pm 0.3) \cdot 10^{-4}$	136	114
	0.55	$100.0 \pm 6.9^a$	$(8.2 \pm 4.4) \cdot 10^{-3}$	$(4.9 \pm 2.9) \cdot 10^{-4}$	8.2	12

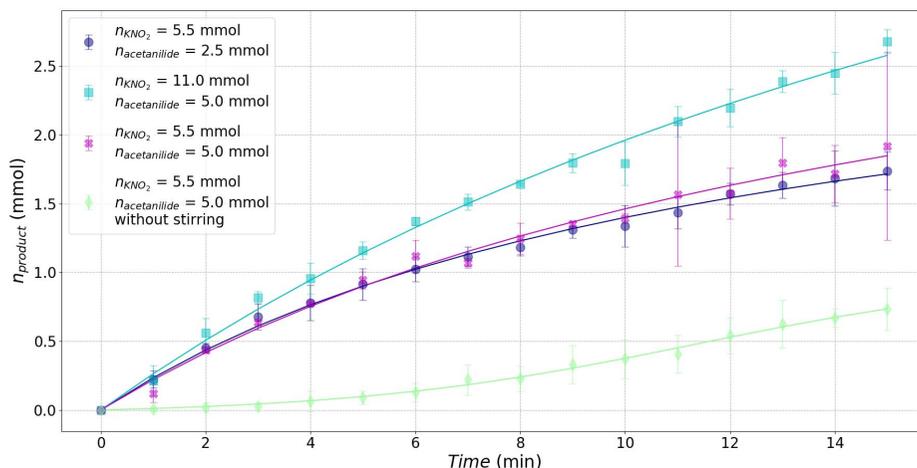
<sup>a</sup> Conversion values over 100% are not realistic.

When nitrites were added to the reaction mixture, an interesting phenomenon emerged: the interfering effect of stirring on the formation of bromine was eliminated. Stirring helps to disperse the formed  $\text{Br}_2$ . In addition, it accelerates the dissolution of solid salts. Therefore, in the experiments where the reaction mixture was stirred, the quantity of brominated product was higher during the same time interval compared to the experiments made without stirring while holding all other parameters constant (Figure 8). Stirring is needed for good reliability of sampling. For this reason, all the following data presented in this section is obtained from experiments in which reaction mixtures were stirred unless otherwise stated.

The effect of stirring on autocatalytic reactions has been previously studied [115–120]. It was shown that some reactions require a heterogeneous region where the reaction is initiated (previously mentioned as “ignition volume”). However, mixing does not favour the formation of such regions in the total volume. It was also shown that both the volume of the reaction mixture and the shape of the vessel have a significant effect on the formation of these required ignition volumes. This could explain why stirring effects appeared during an upscaling process.

Like mentioned before, formation of bromine as well as nitrous acid requires high bromide and nitrate ions concentrations in addition to high acid concentration. These conditions could be fulfilled in the studied reaction mixture thanks to slow diffusion, allowing for a steep concentration gradient near the surfaces of solid salts. However, in well-stirred reaction mixtures, concentration gradients could not form. The fact that a larger amount of bromide over nitrate prolonged the lag phase could mean that nitrate has the most critical role in forming those ignition volumes. It is known that in nitric acid, bromine forms from bromide ions and the reaction occurs faster when the concentration of nitric acid is high. It could mean that in the studied reaction mixture, a high nitrate concentration is needed to initiate the reaction. However, the presence of other salts (*e.g.* sodium bromide and anilinium chloride, when aniline was used

as a substrate) may affect the dissolution process<sup>1</sup> so that sufficiently high nitrate concentration forms slowly. Considering all these factors, it could be concluded that the formation of ignition volumes is necessary to allow the generation of nitrous acid in the studied system.

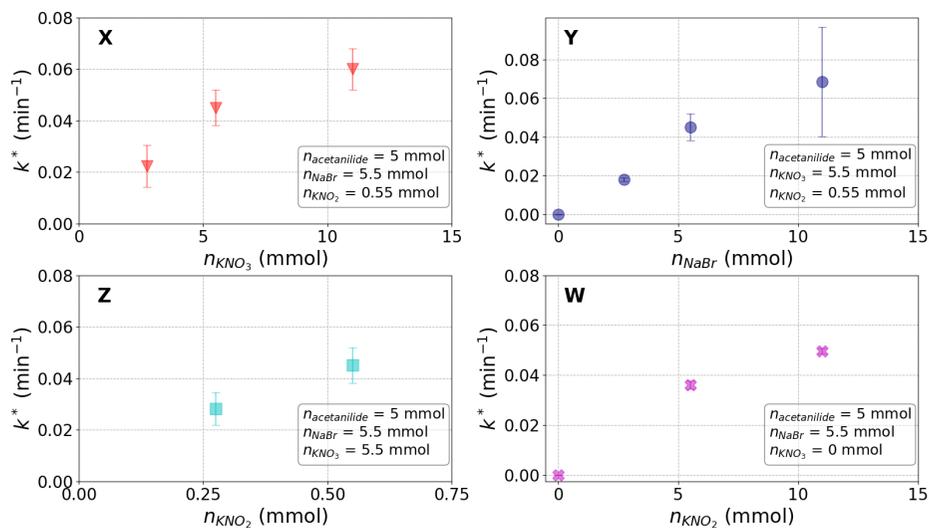


**Figure 8.** Kinetic curves obtained with nitrite as an oxidising agent in the reaction mixture. Error bars represent CI<sub>95%</sub>. Solid lines represent the results obtained while processing the experimental data with F-W model.

The addition of nitrite ions in the reaction mixture increased the rate of bromine formation significantly, and no lag phase was observed anymore (Figure 8). Therefore, when fitting the experimentally obtained kinetic curves with F-W model, only  $k^*$  values could be calculated. The  $k^*$  values observed from different experimental series (**X**, **Y**, **W**, **Z**) are presented in Figure 9.

In addition, from Figure 8 it can be seen that bromination is a faster reaction than bromine formation. Indeed, by lowering the acetanilide concentration in the mixture and holding other conditions unchanged, the first part of the obtained kinetic curve is not affected. However, changing the oxidiser amount has a significant impact on the observed kinetic curves. This is a major result since it confirms the validity of the approach used (*i.e.* the indirect bromine monitoring via reporter reaction).

<sup>1</sup> The presence of other salts can impact the dissolution rate as it depends on the surface area of the interface between solute and solvent. Also, the solubility of a substance strongly depends on the presence of other ionic species in the solvent (*i.e.* common ion effect or multiple equilibria system).



**Figure 9.** Kinetic data ( $k^* \pm SE$  (min<sup>-1</sup>)) obtained by processing experimental results with F-W model. Subplots represent the data obtained while the amounts of salts (nitrate – X, bromide – Y, nitrite in the presence of nitrate – Z, nitrite without nitrate in the reaction mixture – W) were changed in the reaction mixture.

It can be seen that the bromine formation becomes faster when the amount of salt in the mixture is increased, regardless of the nature of the salt. In order to confirm that nitrite certainly acts only as a catalyst in the reaction, control experiments were performed using nitrite in a catalytic amount without nitrate (5 mmol acetanilide, 5.5 mmol NaBr, 0.55 mmol KNO<sub>2</sub>, 30 mmol HCl). After 15 minutes, the conversion value was less than 1%. Thus, it could be concluded that nitrate acts as the oxidising agent, whereas nitrite acts only as a catalyst.

Due to the fact that adding a catalytic amount of nitrite to the reaction mixture affects mainly the value of  $k_1$ , not  $k_2$  (Table 7), the lag phase is shortened, but the maximum rate of the reaction does not vary significantly. By comparing the  $k^*$  values obtained in the experiments where nitrate with a catalytic amount of nitrite or only nitrite (Figure 9, X, Z and W) was used, it can be seen, that  $k^*$  values are similar. These results could indicate, that bromine formation occurs in a similar way during the burst phase in the mixtures where nitrates or nitrites are used. The only difference is the lag phase duration which depends on the formation of nitrous acid. The formation of nitrous acid is very fast when nitrites are used, but slow when nitrates are used, thus explaining the difference observed.

### 3.8. Possible applications of the studied bromination method to organic synthesis

From the point of view of organic synthesis, the goodness and suitability of a method are evaluated by the yield and atom efficiency of the process. Reaction conditions (temperature, used reagents, *etc.*) required for effective application of the method are also very important factors to consider.

For estimating the goodness and applicability of the studied reaction mixture for oxidative aromatic bromination, experiments were repeated with acetanilide, and the yield and purity were determined each time. In different experiments, the amounts of substrate and reagents ( $\text{KNO}_3$ ,  $\text{NaBr}$ ,  $\text{HCl}$ ), the volume of organic solvent and the reaction time were changed. Considering the effects of changeable parameters to bromine formation described previously, the average yield of *p*-bromoacetanilide was 80% with 100% conversion. The yield could be increased by changing the purification procedure (*i.e.* recrystallisation in this case) or improving it.

The real added value of the studied method, however, lies in the reaction conditions needed for the application. Indeed, this reaction is performed at the room temperature and atmospheric pressure, it uses a mild oxidising agent and allows to change organic solvents. Also, the possibility to change the rate of bromine formation easily by changing the parameters could open the opportunity to develop a method for selective bromination of more activated aromatic compounds. On the other hand, the possibility to shorten the lag phase by adding a catalytic amount of nitrite allows reducing the reaction times drastically.

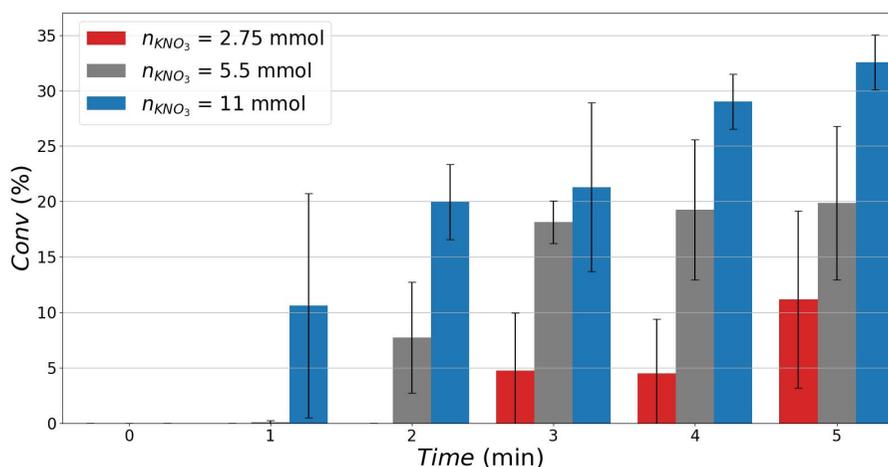
Eventually, even though this mixture can be used as such only for bromination of activated aromatic compounds, its applicability could be widened by introducing the suitable catalysts.

### 3.9. Bromine formation in solvent-free conditions

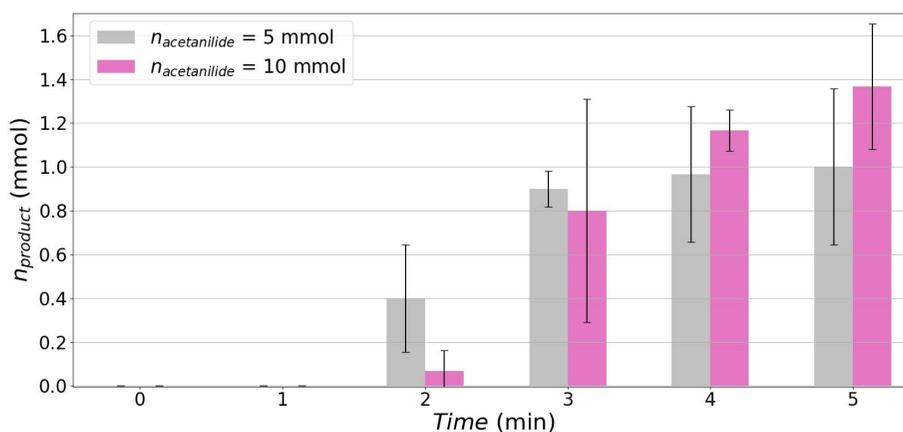
The use of nitrate salts for oxidative aromatic bromination is an interesting approach from the point of view of green chemistry. However, methods, where bromine is generated *in situ* in the reaction mixture, are often criticised, because organic solvents or organic solvent–water mixtures are required in the process. Such reactions in solvents often require additional purification steps of the product, increase the waste produced during the overall process and arise the demand for solvent reuse procedures. Solvent-free bromination methods have been developed to address these limitations [121–126]. Therefore, the opportunity to widen the scope of studied oxidative bromination procedure by using nitrates in solvent-free conditions was investigated.

In solvent-free reaction conditions, bromine was generated by using gaseous hydrogen halides ( $\text{HCl}$  or  $\text{HBr}$ ) and solid salts ( $\text{NaBr}/\text{KNO}_3$  mixture or  $\text{KNO}_3$ ). Bromine formation was assayed indirectly like in the presence of solvents, via acetanilide bromination. This method was convenient, due to the results ob-

tained in solvent-free conditions and in the presence of solvents were very similar showing that bromination is faster than bromine formation. This statement is also confirmed by the fact that the initial rate of acetanilide bromination (therefore also the initial rate of bromine formation) was controlled by the amount of oxidiser in the mixture (Figure 10) and not by the amount of acetanilide, since increasing its amount had no significant influence on the formation of brominated product (Figure 11).

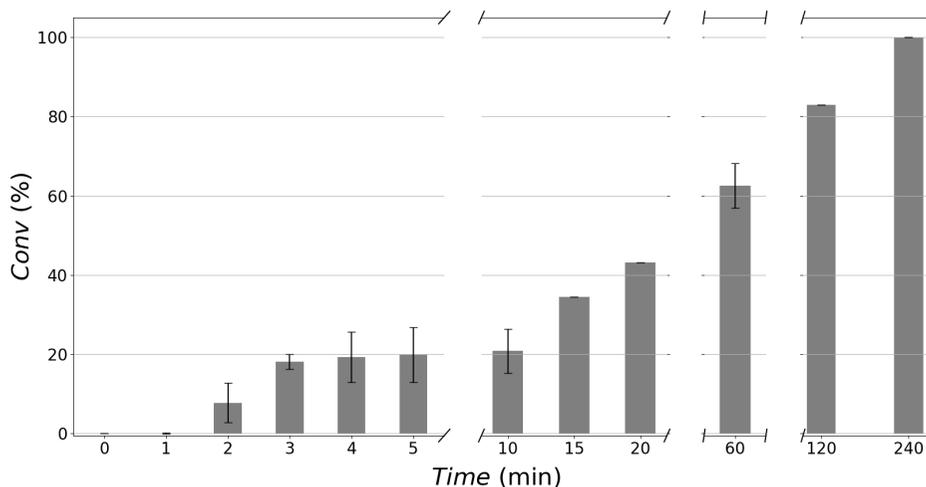


**Figure 10.** Results of acetanilide bromination in the reaction system, containing different amounts of  $KNO_3$  (2.75, 5.5, or 11 mmol), 5 mmol of acetanilide and at the continuous flow of gaseous HBr. The error bars were calculated from triplicate experiments and are represented as  $CI_{95\%}$ .



**Figure 11.** Bromination of different initial amounts (5 or 10 mmol) of acetanilide in the presence of 5.5 mmol  $KNO_3$  and at the continuous flow of gaseous HBr. The error bars were calculated from triplicate experiments and are represented as  $CI_{95\%}$ .

Time-course of acetanilide (5 mmol) bromination with gaseous HBr and KNO<sub>3</sub> (5.5 mmol) is shown in Figure 12. It can be seen that the conversion value increases until the 100% conversion is reached within about 4 hours. Thus, increasing the amount of KNO<sub>3</sub> accelerates the bromine formation (Figure 10) (like in the presence of solvents), it can be suggested that the time needed for the complete conversion can be reduced by adding more oxidising agent into the reaction mixture. This could be an important advantage while implementing the method to organic synthesis.



**Figure 12.** Acetanilide bromination in the reaction mixture, containing 5.5 mmol KNO<sub>3</sub> and 5 mmol acetanilide, and at constant HBr flow (normal pressure). The error bars were calculated from triplicate experiments and represent CI<sub>95%</sub>. Conversion values at 15, 20 and 120 min were calculated from single experiments, and therefore no error bars are given.

Harrison and Siddiqui [127] studied the following reaction:



They described that gaseous HCl rapidly exchanges bromide ions at the surface of solid sodium bromide and gaseous HBr is released (Equation (25)). The possibility to change the used gaseous hydrogen halides in the reaction mixture could broaden the field of application. Therefore, experiments for acetanilide bromination were performed by replacing gaseous HBr with gaseous HCl and solid NaBr in the reaction mixture. The results of these experiments are shown in Table 8. In addition, experimental results obtained by using NaBr and HBr together in the reaction mixture are also presented.

**Table 8.** Acetanilide bromination in the reaction mixture containing solid  $\text{KNO}_3$  (1.1 mmol),  $\text{NaBr}$  (1.1 mmol), acetanilide (1 mmol), under the continuous flow of  $\text{HBr}$  or  $\text{HCl}$  (normal pressure, 25 °C). Each experiment lasted 15 min. Results ( $\text{Conv} \pm \text{CI}_{95\%}$  (%)) of triplicate measurements are listed.

Reactants	Conv (%)
$\text{NaBr}$ (s) 1.1 mmol; $\text{KNO}_3$ (s) 1.1 mmol; $\text{HCl}$ (g)	$25 \pm 3$
$\text{NaBr}$ (s) 1.1 mmol; $\text{KNO}_3$ (s) 1.1 mmol; $\text{HBr}$ (g)	$28 \pm 1$
$\text{KNO}_3$ (s) 1.1 mmol; $\text{HBr}$ (g)	$29 \pm 2$

Firstly, it can be seen that  $\text{HCl}$  together with  $\text{NaBr}$  can be used for aromatic bromination. However, since trace amounts of chlorinated aromatic compounds were detected,  $\text{HBr}$  should be preferred for synthesis applications. Secondly, similar conversion values observed with all three experimental setups indicate that bromine formation occurs analogously in those reaction mixtures.

### 3.9.1. Bromination of aromatic compounds in solvent-free conditions with the mixture of $\text{HBr}$ and $\text{KNO}_3$

The range of applicability of this solvent-free method was tested by using a mixture of gaseous  $\text{HBr}$  and solid  $\text{KNO}_3$  for bromination of several aromatic compounds with different reactivity. Relying on the previous experiments, 11 mmol of  $\text{KNO}_3$  was used instead of 5.5 mmol. As suggested, using larger amounts of oxidising agent shortens the reaction time, as acetanilide was brominated with 100% conversion in 1 hour instead of 4 hours. All the results are summarised in Table 9. It appears that this reaction mixture is suitable for bromination of activated aromatic compounds. The bromination occurs via conventional electrophilic aromatic substitution mechanism, like in the presence of solvents.

A major advantage of this bromination method is definitely the simple purification process, especially if the formation of side-products can be controlled and minimised. In this work, acetanilide and 4-hydroxy-3-methoxybenzaldehyde were brominated several times in solvent-free conditions. After processing the crude product with  $\text{NaHCO}_3$  and  $\text{Na}_2\text{S}_2\text{O}_3$  solutions and extraction with diethyl ether, yields were 91% and 90% respectively.

**Table 9.** Bromination experiments with activated and deactivated aromatic compounds by using the solvent-free bromination method. Reactions were conducted by using 5 mmol of bromination substrate, 11 mmol of KNO<sub>3</sub>, and at constant flow of HBr.

Substrate	Reaction time (min)	Product(s) detected	Conv (%)
<i>N</i> -phenylacetamide (acetanilide)	60	4-bromoacetanilide	100
4-hydroxy-3-methoxybenzaldehyde	60	5-bromo-4-hydroxy-3-methoxybenzaldehyde	100
1,3-dimethoxybenzene	60	1-bromo-2,4-dimethoxybenzene	74
		1,5-dibromo-2,4-dimethoxybenzene	16
1-bromo-2,4-dimethoxybenzene	240	1,5-dibromo-2,4-dimethoxybenzene	50
toluene	240	4-bromotoluene	≤ 3
		2-bromotoluene	≤ 2
benzene	240	–	0
bromobenzene	240	–	0
benzaldehyde	240	–	0
benzoic acid	240	–	0

Conversion values are calculated without calibrating the GC-MS system for every compound.

### 3.10. Bromination of non-activated aromatic compounds

Possibility of applying the studied oxidative aromatic bromination procedure to non-activated compounds would be valuable. So far, it has been shown that the method is not suitable even for bromination of slightly activated compounds like toluene. Thus, the addition of a suitable catalyst in the reaction mixture is needed. In this work, an original approach was used to select a catalyst. First, one should remember the background of the studied method, which is based on a mixture of KNO<sub>3</sub> and AlBr<sub>3</sub> (see Section 3.1.). It was shown that the bromination of activated aromatic compounds is possible with that mixture. Also, AlBr<sub>3</sub> is a Lewis acid catalyst which can be used for aromatic bromination of deactivated compounds. Since AlBr<sub>3</sub> can act simultaneously as the catalyst and the source of bromide ions, it was a promising perspective to use the very same mixture for bromination of non-activated compounds. Especially because by limiting the reagents used in the mixture, side reactions might be avoided.

As it was previously shown, solvents have a significant impact on bromine formation. Therefore, the applicability of the described mixture was studied in solvent-free conditions. Liquid phase is still needed for using Lewis acids as catalysts. Indeed, the electrophilic properties of bromine are increased due to the formation of complex between Br<sub>2</sub> and AlBr<sub>3</sub>, which can occur only in the liquid phase. Hence, only liquid substrates were suitable for that purpose. After considering different model substrates, benzene, which is neither an activated nor a deactivated compound, and bromobenzene, as a slightly deactivated aromatic compound, were chosen. Bromobenzene was also selected because it is a bromination product of benzene. Thus, it can add some fascinating insight into the studied method.

Nitrate ions can be used for *in situ* generation of Br<sub>2</sub> in acidic media only. In preliminary experiments where an AlBr<sub>3</sub>/KNO<sub>3</sub> mixture was used it was shown that molecular bromine forms only in hydrous conditions. Due to aluminium bromide hydrolysis, an acidic environment is produced. Hydrolysis of Lewis acid catalyst is usually unwanted and prevented, but in this approach, it was turned into an advantage. For this reason, substrates without pre-drying were used. A more detailed study of water content effects on bromine formation will be discussed below.

In the first experiments with benzene, it was found that bromination of non-activated aromatic compounds with the AlBr<sub>3</sub>/KNO<sub>3</sub> mixture is possible since bromobenzene formed in the reaction mixture. However, a small amount of nitrobenzene, considered as an unwanted side product, was detected as well. This was not surprising, considering the starting point of the method. Nevertheless, these results were promising. Series of experiments in different conditions were carried out to investigate the possibilities to steer the reaction towards the desired outcome.

### **3.10.1. The effect of different substrates and their amounts used in the reaction mixture**

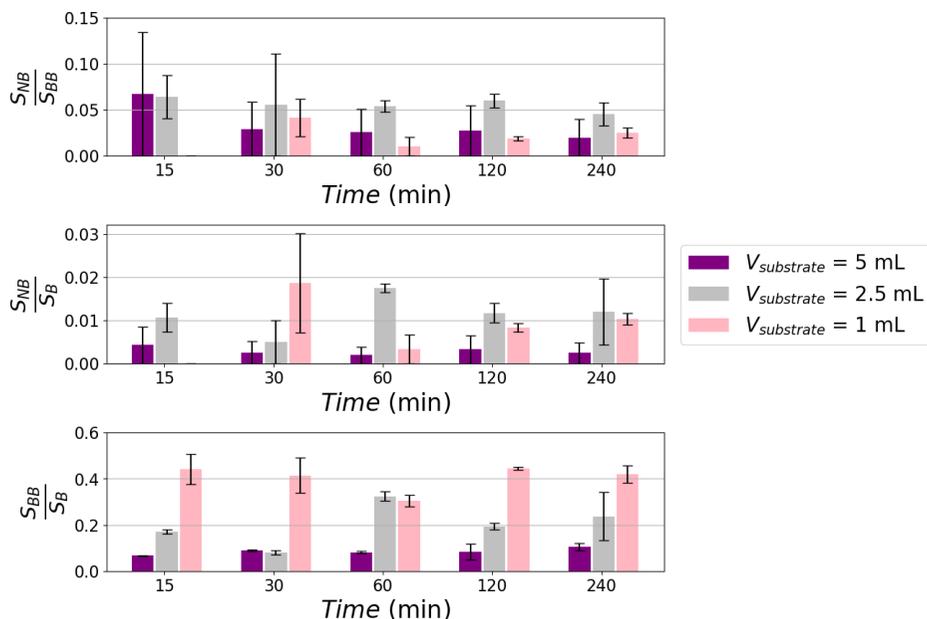
The results obtained in the experiments in which the amount (volume) of the substrate was changed show that the calculated product-substrate ratios were higher when less substrate was used (and *vice versa*). This regularity was expected because products should have larger percentages in mixtures containing less substrate (Figure 13 and Figure 14).

When benzene was used as a substrate, formation of bromobenzene occurred quickly. This statement is confirmed by the fact that the bromobenzene-benzene ratio stayed nearly constant in time (Figure 13). The main side product in this system was nitrobenzene. In Figure 13 it can be seen that nitration is also a fast process since the nitrobenzene-benzene and nitrobenzene-bromobenzene ratios remain almost constant in time.

In addition to nitrobenzene, di-brominated benzenes, biphenyl and 4-bromobiphenyl were also detected as side products for longer reaction times (Table 10). Biphenyl and 4-bromobiphenyl can form during Scholl reaction [128] which is a coupling of aromatic compounds in the presence of Lewis and protic acids. Couplings of halogenated benzenes have been studied before [129]. It was found that fluorobiphenyl is generated in the mixture of AlBr<sub>3</sub> and fluorobenzene whereas bromobiphenyl does not form in the mixture of aluminium bromide and bromobenzene. Therefore, it is suggested that in the present work, bromobiphenyl forms by bromination of biphenyl. This is also in accordance with the fact that no bromobiphenyl was obtained while bromobenzene was used as a substrate. From the point of view of the synthesis, it is important to add that as bromination occurs rather fast compared to other side reactions (except for nitration), the formation of unwanted side products could be minimised.

**Table 10.** Products detected in the reaction mixture containing benzene (1, 2.5 or 5 mL), 1.5 mmol of KNO<sub>3</sub> and 7.5 mmol of AlBr<sub>3</sub>.

$V_{\text{substrate}}$ (mL)	15 min	30 min	60 min	120 min	240 min
1	bromobenzene	bromobenzene nitrobenzene	bromobenzene nitrobenzene biphenyl 4-bromobiphenyl	bromobenzene nitrobenzene 1,3-dibromobenzene 1,4-dibromobenzene biphenyl 4-bromobiphenyl	bromobenzene nitrobenzene 1,3-dibromobenzene 1,4-dibromobenzene biphenyl 4-bromobiphenyl
2.5	bromobenzene nitrobenzene	bromobenzene nitrobenzene	bromobenzene nitrobenzene biphenyl 4-bromobiphenyl	bromobenzene nitrobenzene biphenyl 4-bromobiphenyl	bromobenzene nitrobenzene biphenyl 4-bromobiphenyl
5	bromobenzene nitrobenzene	bromobenzene nitrobenzene	bromobenzene nitrobenzene	bromobenzene nitrobenzene	bromobenzene nitrobenzene biphenyl 4-bromobiphenyl

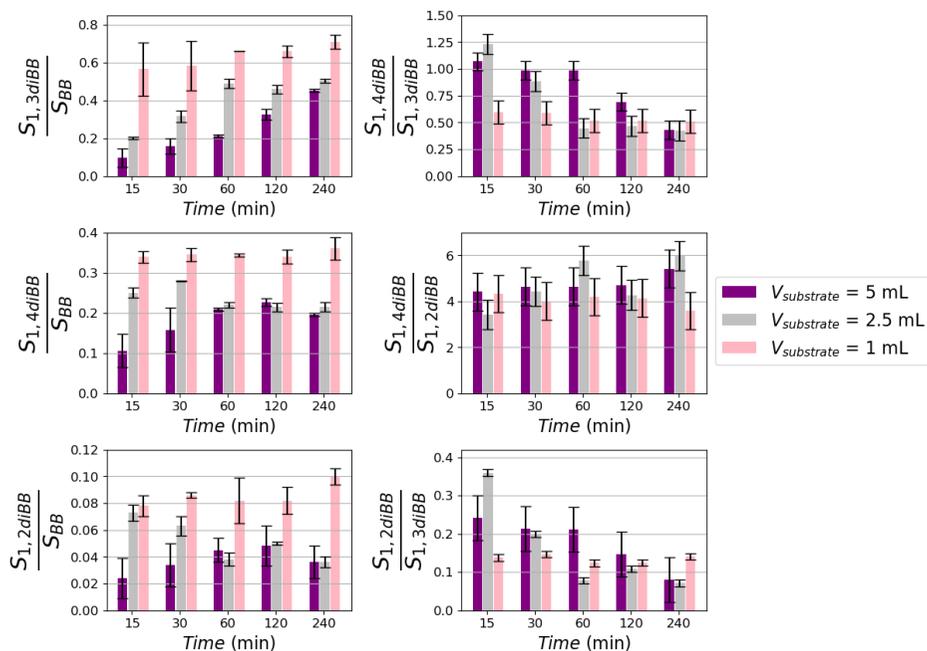


**Figure 13.** Experimental results obtained for different amounts of benzene (1, 2.5 or 5 mL) in the reaction mixture (1.5 mmol of  $\text{KNO}_3$  and 7.5 mmol of  $\text{AlBr}_3$ ). Error bars are given as  $\text{CI}_{95\%}$ . (NB – nitrobenzene, BB – bromobenzene, B – benzene)

Bromination of bromobenzene in the studied reaction mixture gave unanticipated results. All three di-brominated isomers and benzene were detected as products. Isomerisation of halogenated benzenes has been studied [129]. It was found that bromobenzene in the presence of  $\text{AlBr}_3$  isomerises easily. As a result of this, di-brominated benzenes (first *para*- and *ortho*-isomers and then *meta*-isomer) and benzene form. This reaction occurs extremely rapidly with water-promoted aluminium bromide. In 10 minutes, a 53% isomerisation was observed. In the formed mixture of dibromobenzenes, the molar percentages of *ortho*-, *meta*- and *para*-isomer were 4.3%, 62.5% and 33.2%, respectively. [129] In Figure 14, it can be seen that the *para*-*meta* and *ortho*-*meta* isomer ratios decrease in time, which is why it can be claimed that the obtained results are in very good agreement with the previous study. The *para*-*ortho* ratio stays nearly the same, and this confirms the results even more because the same tendency was observed in the study of halogenated benzenes isomerisation.

Di-brominated products were not formed on a large scale when benzene was used as a substrate. This result indicates that bromobenzene formed in the bromination reaction does not isomerise rapidly. A possible reason could be that  $\text{AlBr}_3$  is consumed in bromine formation and in benzene bromination. Thus, there is not enough catalyst left available for isomerisation. The fact that trace amounts of *meta*-dibromobenzene were detected in longer experiments (Table 10) shows that this side reaction can still occur to a smaller extent.

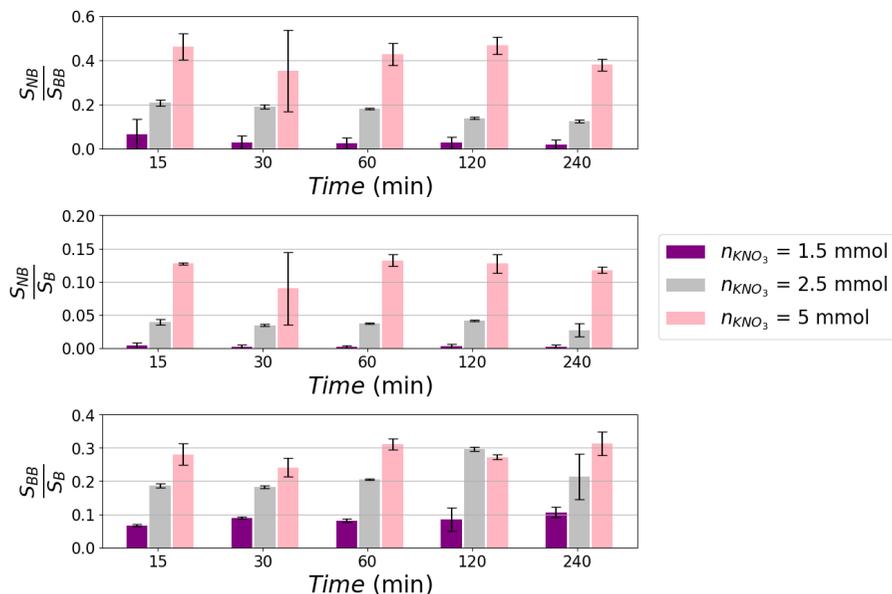
Besides this comprehensive isomerisation, nitration also occurred as a side reaction. During longer experiments, tri-brominated compounds were formed. This last result indicates that bromine is still generated in the reaction mixture and can be used for bromination.



**Figure 14.** Experimental results obtained for different amounts of bromobenzene (1, 2.5 or 5 mL) in the reaction mixture using 1.5 mmol of  $KNO_3$  and 7.5 mmol of  $AlBr_3$ . (BB – bromobenzene, 1,2*diBB* – 1,2-dibromobenzene, 1,3*diBB* – 1,3-dibromobenzene, 1,4*diBB* – 1,4-dibromobenzene)

### 3.10.2. The effect of different amounts of nitrate and bromide used in the reaction mixture

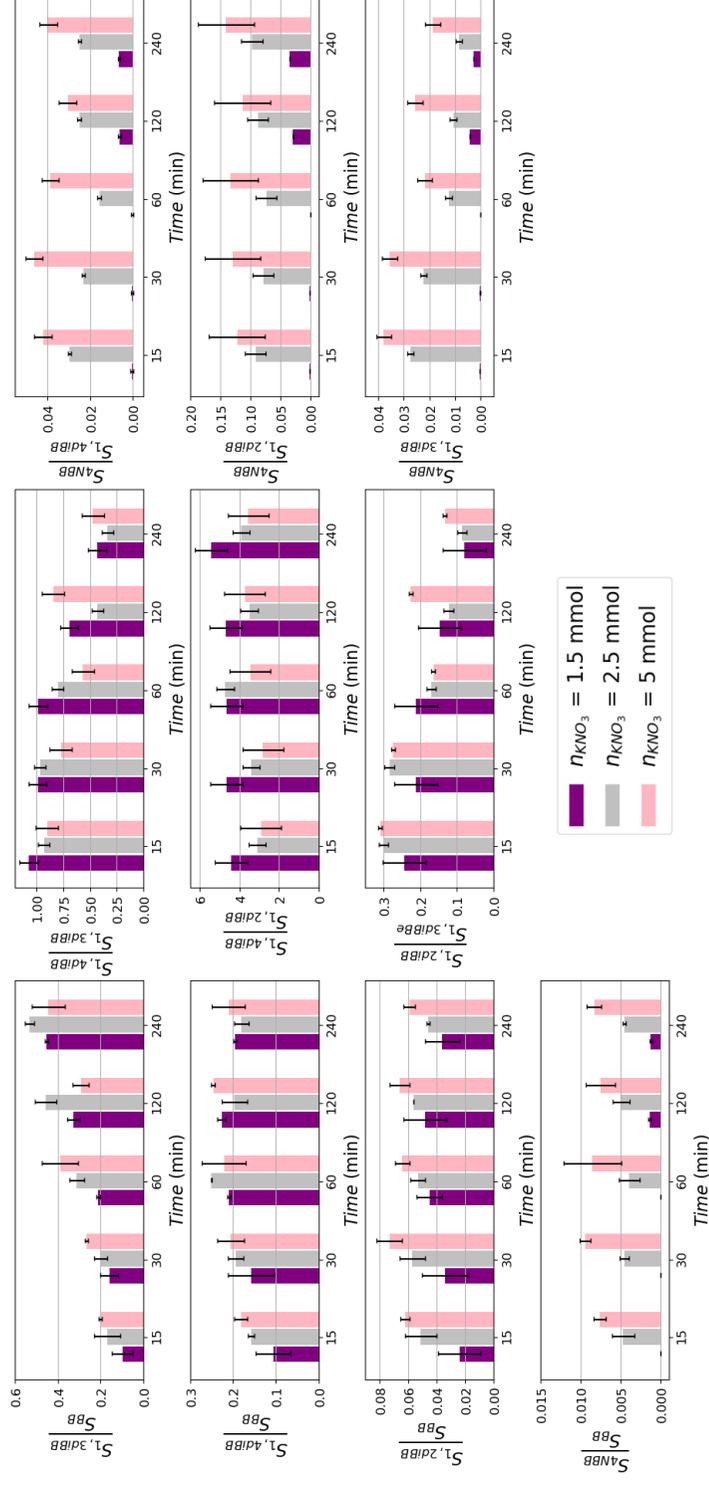
The results of the benzene and bromobenzene bromination experiments, in which the amount of nitrate was changed in the reaction mixture, are presented in Figure 15 and Figure 16, respectively. In benzene bromination experiments more bromobenzene forms in the presence of more nitrate. This was also observed regarding the formation of nitrobenzene. However, from the point of view of the synthesis, it is very important to notice that modifying the amount of oxidiser had no impact on other side reactions described before.



**Figure 15.** Experimental results obtained for different amounts of  $KNO_3$  (1.5, 2.5 or 5 mmol) for benzene bromination. Reactions were conducted using 5 mL of benzene and 7.5 mmol of  $AlBr_3$ . Error bars are given as  $CI_{95\%}$ . (NB – nitrobenzene, BB – bromobenzene, B – benzene)

The interpretation of data obtained from this series of experiments where bromobenzene was used as a substrate is complicated due to a large-scale isomerisation side reaction. However, it could be seen that decreasing the amount of nitrate in the reaction mixture also decreases the nitrated product formation. In addition, for shorter reaction times, it can be noticed that the amount of nitrate has a small influence on the formation of di-brominated products (especially the *ortho*- and *para*-isomers). This seems to indicate that bromine formation occurs faster when larger amounts of oxidising agent are introduced in the reaction mixture, and therefore bromination also occurs more quickly. No other fundamental conclusions can be made at this stage with these results.

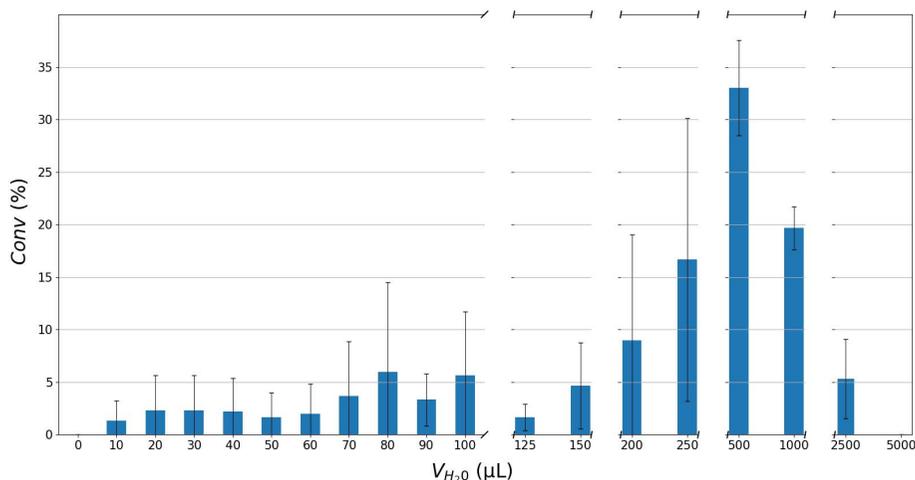
Eventually, experiments in which the amount of bromide was changed showed that larger amounts of  $AlBr_3$  cause side reactions on a larger scale. In experiments with benzene, more coupling of aromatic compounds was observed. In experiments with bromobenzene, isomerisation of halogenated benzenes occurred even more extensively. However, the nitration side reaction could be minimised by using larger amounts of  $AlBr_3$  over  $KNO_3$ . In a reaction mixture containing 1.5 mmol of potassium nitrate and 15 mmol of aluminium bromide for benzene bromination, no nitrobenzene was detected, even for experimental times as long as 240 min. Hence, side reactions might be avoided with careful selection of the ratios of salts used in the reaction mixture and keeping reaction times short.



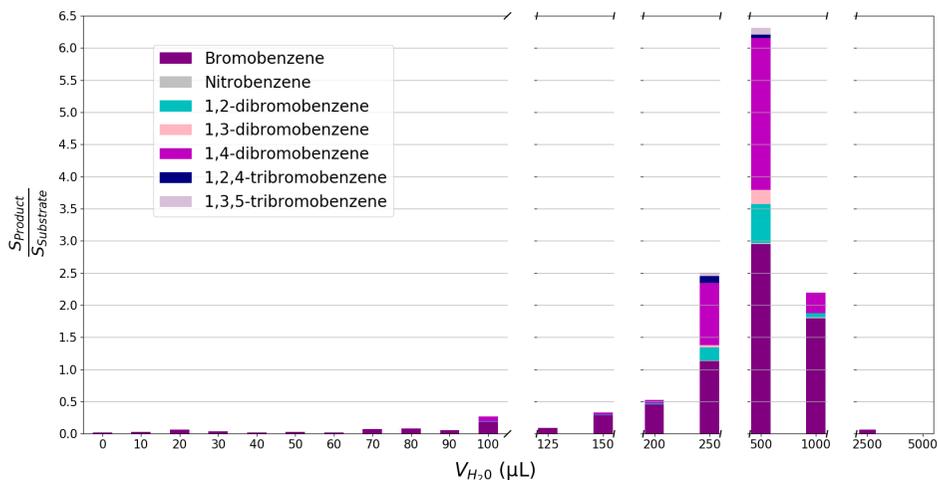
**Figure 16.** Experimental results obtained for different amounts of  $\text{KNO}_3$  (1.5, 2.5 or 5 mmol) for bromobenzene bromination. Reactions were conducted using 5 mL of benzene and 7.5 mmol of  $\text{AlBr}_3$ . (BB – bromobenzene, 1,2*di*BB – 1,2-dibromobenzene, 1,3*di*BB – 1,3-dibromobenzene, 1,4*di*BB – 1,4-dibromobenzene, 4NBB – 4-nitrobromobenzene)

### 3.10.3. The effect of water content on bromine formation

No bromine forms in anhydrous conditions, as mentioned previously, because the acidic environment, needed for bromine generation, is formed by hydrolysis of  $\text{AlBr}_3$ . In order to understand the effect of water, more thorough experiments were carried out where different amounts of water were added to the anhydrous reaction mixture. In those experiments, acetanilide was used as a model substrate. As it has already been shown in this work, it is very convenient to study bromine formation with nitrate ions as oxidising agents. It was observed that there is an optimal amount of water so that bromination occurs the most rapidly (Figure 17). Similar results were obtained in experiments where benzene was used as a substrate (Figure 18). The fact that bromination occurs the quickest in the two cases (for the same amount of added water), indicates that the aluminium bromide is not completely hydrolysed during the reaction. Indeed, there must be enough  $\text{AlBr}_3$  left for catalysis, or benzene bromination would not occur.



**Figure 17.** Acetanilide (1.5 mmol) bromination in a mixture of 1.5 mmol of  $\text{KNO}_3$  and 7.5 mmol of  $\text{AlBr}_3$ , 5 mL of hexane and different amounts of water (0 to 5000  $\mu\text{L}$ ). The duration of the experiments was 15 min. Reactions were conducted three times, and the mean values are presented. Error bars are given as  $\text{CI}_{95\%}$ .



**Figure 18.** Benzene (1.5 mmol) bromination in a mixture of 1.5 mmol of  $\text{KNO}_3$  and 7.5 mmol of  $\text{AlBr}_3$ , 5 mL of hexane and different amounts of water (0 to 5000  $\mu\text{L}$ ). The duration of the experiments was 15 min. Reactions were conducted three times, and the mean values are presented.

These results are very similar to the ones obtained in the solvent where  $\text{NaBr}$  was used instead of  $\text{AlBr}_3$  and hydrochloric acid was used for acidification of the reaction mixture (Section 3.5.). Therefore, it can be concluded there is also an optimal acid concentration even when  $\text{AlBr}_3$  is used instead of  $\text{NaBr}$ . In general, the acid concentration is a very important parameter for bromine generation with nitrates as oxidisers. In addition, it is important to notice that bromine formation was the fastest in mixtures where almost saturated  $\text{KNO}_3$  solution was used. This is in accordance with the results obtained in previous experiments where a mixture of  $\text{KNO}_3$ ,  $\text{NaBr}$  and  $\text{HCl}$  was used for acetanilide bromination. It was suggested that the dissolution process of nitrates is essential, and a high concentration in nitrate ions is needed for fast bromine formation.

To conclude, from the point of view of synthesis, this mixture, containing  $\text{AlBr}_3$  and  $\text{KNO}_3$  in hydrous conditions, could be used for bromination of non-activated aromatic compounds and steering the reaction is possible by a careful selection of the parameters presented above.

## SUMMARY

The current thesis sheds light on the oxidative aromatic bromination methods for activated and non-activated compounds where inorganic bromides are used together with  $\text{KNO}_3$  (and/or  $\text{KNO}_2$ ) as an oxidising agent. It was shown that bromination in the mixture of nitrates and different bromides occurs via conventional electrophilic aromatic substitution mechanism, where the brominating agent is *in situ* generated molecular bromine.

The focus of the first part of the work was the clarification of the nature of bromine formation reaction in a mixture of solid  $\text{KNO}_3$  and  $\text{NaBr}$  in the presence of organic solvents and concentrated hydrochloric acid. Due to the complexity of the system containing solid salts, one or several liquid phases and many nitrogen compounds, which form in the reduction process of nitrate ions, bromine formation was studied indirectly. A “reporter reaction”, where the formed bromine was consumed in a fast bromination reaction, was used and acetanilide was chosen as a “reporter molecule” for this approach. Bromination of acetanilide occurs selectively and quickly, and the process can be easily monitored by standard GC-MS analysis.

It was found that bromine formation in the mixture of solid  $\text{KNO}_3$  and  $\text{NaBr}$  is an autocatalytic reaction which presents a characteristic lag phase and the rate of reaction follows a sigmoidal kinetic curve. For analysing these sigmoidal kinetic curves, the two-step generic Finke-Watzky kinetic model was applied. The values of the observed rate constants, which describe the initiation phase and the following burst phase, were calculated. If the initiation phase was fast, the overall process was described with an exponential model, in line with the F-W model.

The key factors (nature of organic solvents, amounts of salts and acid), influencing bromine formation were investigated thoroughly. It was shown that the duration of bromine formation lag phase is mainly influenced by the amount of added nitrate salt and acid. Besides these factors, the stirring of the reaction mixture also affected the induction time.

It was found that adding catalytic amounts of nitrite into the reaction mixture shortens the lag phase duration. The obtained results confirmed the suggestion that nitrite (nitrous acid) may be the autocatalytic intermediate of the oxidation reaction, as it is formed in the reaction cascade of nitrate reduction.

The second part of the study focused on specifying the scope of this bromination reaction and investigates its broader applicability. In this part, three methods, based on the source of bromide ions ( $\text{NaBr}$ ,  $\text{HBr}$  and  $\text{AlBr}_3$ ), were developed.

For the first method, it was shown that a  $\text{NaBr}/\text{KNO}_3$  mixture can be used for bromination of activated aromatic compounds in the presence of different organic solvents. Due to the opportunity to control the rate of bromine formation in this mixture, it could be possible to develop a selective bromination method for highly activated aromatic compounds. On the other hand, this

mixture could also be used for fast bromination when a catalytic amount of nitrite is introduced into the reaction mixture.

The second method is based on green chemistry principle, which states that waste production should be minimised. Therefore, possibilities to generate bromine in solvent-free conditions in a mixture of gaseous hydrogen halides (HBr or HCl) and solid  $\text{KNO}_3$  (and NaBr, when HCl was used) were studied. It was shown that bromine formation occurs in those mixtures and that it can be used for bromination of activated aromatic compounds. The advantages of this method are (i) a simple purification process (especially when side reactions could be minimised) and (ii) the possibility to modify the rate of bromine formation easily by changing the amount of solid oxidising agent.

In order to widen the applicability of  $\text{KNO}_3$  for bromination of non-activated aromatic compounds, a third method was developed. For this last route,  $\text{AlBr}_3$  was chosen as a multirole key compound. In these mixtures,  $\text{AlBr}_3$  acts as (i) the catalyst needed for bromination of non-activated aromatic compounds, (ii) the source of bromide ions, and (iii) its hydrolysis in the hydrous environment allows for acidic medium to form and enhance the oxidative properties of nitrates. It was shown that bromination of non-activated compounds with this mixture is possible in solvents or in liquid substrates.

In addition, it is important to notice that all these methods are applicable at room temperature and atmospheric pressure, which makes them feasible from the point of view of synthesis.

Statistical analysis was performed to present standard errors and confidence intervals throughout this work. Repeatability of the results was demonstrated despite the complexity of reaction mixtures.

As a general conclusion, this work showed how nitrate salts can be used in oxidative aromatic bromination methods and how the reaction can be steered into a favourable path by changing the studied key factors affecting the bromine formation. Future work might consist of performing more experiments with different aromatic compounds to screen and study the possibilities to develop selective bromination methods thoroughly.

## CONCLUSIONS

1. Molecular bromine forms in the reaction mixtures containing solid salts (NaBr and KNO<sub>3</sub>) in the presence of different organic solvents and hydrochloric acid. Bromine formation occurs via autocatalytic mechanism, which includes nitrite (nitrous acid) as an autocatalytic intermediate. Several conditions which govern kinetics of this process have been studied in this work. These results are important for further optimisation of this process and its possible applications.
2. Bromination of acetanilide was used as a “reporter reaction” to monitor bromine formation process, as detection of the brominated product is convenient and simple by using GC-MS technique.
3. This reaction allows continuous *in situ* generation of molecular bromine as a brominating agent from stable precursors, and it was used for bromination of aromatic compounds in this study.
4. The bromine formation reaction is affected by solvents, which are added into the reaction mixture. However, the bromine formation process is also possible under solvent-free conditions. The latter option significantly increases the compliance of the whole process, consisting of the bromine formation and the coupled bromination reaction, with the principles of green chemistry.
5. The aromatic bromination reaction in studied reaction mixtures follows the conventional electrophilic aromatic substitution mechanism, where activated compounds react without the participation of catalyst, and for bromination of non-activated compounds, a catalyst is needed. In the present work, AlBr<sub>3</sub> was used simultaneously as the bromide source and the catalyst. Therefore, the proposed approach is rather universal in terms of substrate selection.

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## SUMMARY IN ESTONIAN

### **Broomi teke anorgaaniliste bromiidide ja nitraatide segudes ning selle rakendamine oksüdatiivseks aromaatsete ühendite broomimiseks**

Käesolevas doktoritöös uuriti reaktsioonisegude, mis koosnevad anorgaanilistest bromiididest ja oksüdeerijast  $\text{KNO}_3$  (ja/või  $\text{KNO}_2$ ), kasutamist aktiveeritud ja mitteaktiveeritud aromaatsete ühendite oksüdatiivseks broomimiseks. Töös leiti, et broomimine antud reaktsioonisegudega toimub elektrofiilse asendusreaktsiooni mehhanismi järgi ning broomiva reagendina käitub *in situ* genereeritud molekulaarne broom.

Doktoritöö esimeses osas uuriti broomi tekkereaktsiooni tahkete soolade  $\text{KNO}_3$  ja  $\text{NaBr}$  segus kontsentreeritud vesinikkloriidhappe ja orgaaniliste solventide juuresolekul. See süsteem on väga keerukas, kuna sisaldab tahkeid sooli, ühte või mitut vedelat faasi ja mitmeid nitraatioonide redutseerumisel tekkivaid lämmastikuühendeid. Seetõttu polnud broomi tekke otsene jälgimine võimalik, vaid tuli kasutada nn „reporterreaktsiooni“. „Reporterreaktsiooniks“ oli kiire broomimisreaktsioon, mille käigus reageerib tekkinud molekulaarne broom koheselt atsetaniliidiga. Atsetaniliidi broomimine on selektiivne ning kiire reaktsioon, mille toimumisulatus jälgimine ajas on lihtne, kasutades standardset GC-MS analüüsimeetodit.

Katsete tulemusena leiti, et broomi teke tahke  $\text{KNO}_3$  ja  $\text{NaBr}$  segus on autokatalüütiline reaktsioon, millele on iseloomulik induktsioonifaas, ning mille kineetika järgib sigmoidset kineetilist kõverat. Sigmoidsete kineetiliste kõverate analüüsiks kasutati kaheetapilist Finke-Watzky kineetilist mudelit, mille abil arvutati kiiruskonstandid, mis kirjeldavad induktsiooni- ja sellele järgnevat kasvufaasi. Olukorras, kus induktsioonifaas oli väga lühike, rakendati eelneva mudeliga kooskõlalist eksponentsiaalset mudelit.

Töö käigus uuriti põhjalikult võtmetegurite (erinevad orgaanilised solventid, soolade ja happe kogused) mõju broomi tekkele. Leiti, et induktsioonifaasi kestvus sõltub peamiselt lisatud nitraadi ja happe kogustest. Lisaks leiti, et ka reaktsioonisegu segamisel on induktsiooniajale oluline roll.

Reaktsioonisegusse katalüütilise koguse nitriti lisamine lühendas induktsioonifaasi pikkust. See kinnitab hüpoteesi, et nitritioonid (lämmastikuhape), mis tekivad nitraadi redutseerumisel toimivas reaktsioonide kaskaadis, võivad käituda autokatalüütiliste vaheühenditena.

Doktoritöö teises osas keskenduti broomimisreaktsiooni rakendusulatus vältimisele ja selle laiendamise võimaluste uurimisele. Selle käigus töötati välja kolm broomimismeetodit, mis põhinevad erinevatel bromiidioonide allikatel ( $\text{NaBr}$ ,  $\text{HBr}$  ja  $\text{AlBr}_3$ ).

Esimese meetodi puhul näidati, et  $\text{NaBr}/\text{KNO}_3$  seguga on võimalik broomida aktiveeritud aromaatsed ühendid erinevate orgaaniliste solventide juuresolekul. Antud reaktsioonisegu on võimalik broomi tekkekiirust kergesti variee-

rida. See võib aidata kaasa väga aktiveeritud aromaatsete ühendite selektiivseks broomimiseks mõeldud meetodi väljatöötamisele, lähtudes antud reaktsiooni-segust. Lisaks võimaldaks katalüütilise koguse nitriti lisamisega kaasnev induktsiooniaja lühenemine kiiret broomimist mainitud seguga.

Teine meetod tugineb rohelise keemia põhimõttele, mille kohaselt tuleb vähendada protsessi käigus tekkivate jääkide kogust. Sellest lähtuvalt uuriti broomi teket solvendivabades tingimustes gaasiliste vesinikhalogeniidide (HBr või HCl) ja tahke  $\text{KNO}_3$  (ja NaBr, kui kasutati HCl) segudes. Leiti, et mainitud reaktsioonisegudes tekib broomi ning neid segusid on võimalik kasutada aktiveeritud aromaatsete ühendite broomimiseks. Meetodi rakenduseelisteks on (i) lihtne puhastusprotsess (eriti juhul, kui kõrvalreaktsioonide toimumist saab vähendada) ja (ii) võimalus kergesti varieerida broomi tekkekiirust, muutes tahke oksüdeerija kogust segus.

Laiendamaks  $\text{KNO}_3$  rakendusvõimalusi ka mitteaktiveeritud ühendite broomimisele, töötati välja kolmas meetod, milles kasutatakse  $\text{AlBr}_3$ .  $\text{AlBr}_3$  on reaktsioonisegus (i) katalüsaator (vajalik mitteaktiveeritud ühendite broomimiseks), (ii) bromiidioonide allikas ja (iii) selle hüdrolüüsil tekib happeline keskkond (vajalik nitraatioonide oksüdeerivate omaduste tõstmiseks). Töö käigus näidati, et  $\text{AlBr}_3$  põhinevat segu on võimalik kasutada mitteaktiveeritud ühendite broomimiseks nii vedelates lähteainetes kui ka solventide juuresolekul.

Kõiki nimetatud meetodeid saab rakendada toatemperatuuril ja atmosfääri-rõhul, mis on oluline eelis nende potentsiaalseks rakendamiseks orgaanilises sünteesis.

Statistilist analüüsi kasutati läbivalt kogu töös, et kirjeldada andmeid standardvigade ning usaldusvahemikega. Hoolimata reaktsioonisegu keerukusest tõestati, et saadud tulemused on korratavad.

Kokkuvõtteks näidati käesolevas doktoritöös, kuidas saab kasutada nitraate oksüdatiivsetes aromaatsete ühendite broomimismeetodites, ning kuidas on võimalik reaktsiooni juhtida soovitud suunas, muutes võtmetegureid, mis mõjutavad broomi teket. Edaspidine töö võiks keskenduda erinevate aromaatsete ühendite broomimisele uuritud seguga, et leida võimalusi selektiivsete meetodite arendamiseks.

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## **PUBLICATIONS**

## CURRICULUM VITAE

**Name:** Ida Rahu  
**Date of birth:** November 6, 1991  
**Citizenship:** Estonian  
**Address:** Institute of Chemistry, Faculty of Science and Technology,  
University of Tartu, Ravila 14A, 50411, Tartu, Estonia  
**E-mail:** ida.rahu@ut.ee

### Education:

2016–present University of Tartu, PhD student in chemistry  
2014–2016 University of Tartu, MSc in chemistry, *cum laude*  
2011–2014 University of Tartu, BSc in chemistry, *cum laude*

### Professional employment:

2018–present Chairman of Committee of Estonian Chemistry Olympiad  
2018–2019 University of Tartu, lecturer (Research Project)  
2017–2019 Miina Härma Gymnasium, chemistry teacher  
2015–2016 University of Tartu, assistant teacher (Organic Chemistry I)  
2012–2013 University of Tartu, assistant teacher (Chemical Principles)

### Scientific publications:

1. Rahu, I.; Kekišev, O.; Järv, J.; Burk, P. Bromine Formation in Solid NaBr/KNO<sub>3</sub> Mixture and Assay of This Reaction via Bromination of Activated Aromatics. *Chem. Pap.*, **2018**, 72 (11), 2893–2898. <https://doi.org/10.1007/s11696-018-0526-3>.
2. Rahu, I.; Järv, J. Oxidative Bromination of Non-Activated Aromatic Compounds with AlBr<sub>3</sub>/KNO<sub>3</sub> Mixture. *Chem. Pap.*, **2020**, 74 (4), 1219–1227. <https://doi.org/10.1007/s11696-019-00965-w>.
3. Rahu, I.; Järv, J. Solvent-free Synthesis of Molecular Bromine and its Application for *in situ* Bromination of Aromatic Compounds. *P. Est. Acad. Sci.* **2020**, 69 (3), 208–214. <https://doi.org/10.3176/proc.2020.3.04> (*Available online*)

## ELULOOKIRJELDUS

**Nimi:** Ida Rahu  
**Sünniaeg:** 6. november 1991  
**Kodakondsus:** Eesti  
**Aadress:** Keemia instituut, Loodus- ja täppisteaduste valdkond,  
Tartu Ülikool, Ravila 14A, 50411, Tartu, Eesti  
**E-mail:** ida.rahu@ut.ee

### Haridustee:

2016– Tartu Ülikool, doktorant (keemia)  
2014–2016 Tartu Ülikool, magistriõpe (keemia), *cum laude*  
2011–2014 Tartu Ülikool, bakalaureuseõpe (keemia), *cum laude*

### Ametikäik:

2018– Eesti keemiaolümpiaadi komisjoni esimees  
2018–2019 Tartu Ülikool, õppejõud (Uurimisprojekt)  
2017–2019 Miina Härma Gümnaasium, keemiaõpetaja  
2015–2016 Tartu Ülikool, abiõppejõud (Orgaaniline keemia I)  
2012–2013 Tartu Ülikool, abiõppejõud (Keemia alused)

### Teaduspublikatsioonid:

1. Rahu, I.; Kekišev, O.; Järv, J.; Burk, P. Bromine Formation in Solid NaBr/KNO<sub>3</sub> Mixture and Assay of This Reaction via Bromination of Activated Aromatics. *Chem. Pap.*, **2018**, 72 (11), 2893–2898. <https://doi.org/10.1007/s11696-018-0526-3>.
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