University of Tartu
Institute of Chemistry

Mari Ojakivi

Charged Droplets – Novel Media for Studying Reactions between Aldehydes and Amines/Hydrazines

Master's Thesis in Chemistry (30 EAP)

Supervisors: Anneli Kruve, PhD
Jaanus Liigand, MSc

Tartu 2019

Information sheet

Charged Droplets – Novel Media for Studying Reactions between Aldehydes and Amines/Hydrazines

Within the framework of this study, reactions between 7 aldehydes and 4 nitrogen bases were carried out in charged droplets. For this, an in-house built electrospray system was designed and built. For comparison, the same reactions were also carried out in bulk phase under similar conditions. The results show, that charged droplets are a new potent media for carrying out reactions, since the reactions were accelerated compared to bulk phase. Also, new reaction pathways may be found, as several new products were observed.

Keywords: synthesis, electrospray, charged droplets

Laetud tilgad – uudne keskkond reaktsioonide läbiviimiseks aldehüüdide ja amiinide/hüdrasiinide vahel

Töö raames uuriti 7 aldehüüdi ja 4 lämmastikaluse vahelisi reaktsioone laetud tilkades. Selleks disainiti ja ehitati oma elektropihustussüsteem, mis võimaldas reaktsiooniproduktide kogumist. Võrdluseks viidi samu reaktsioone läbi ka lahusefaasis sarnastel tingimustel. Tulemused näitavad, et laetud tilgad on uudne võimalusterohke keskkond orgaaniliste reaktsioonide läbiviimiseks, kuna toimus reaktsioonide oluline kiirenemine. Samuti on võimalik avastada uusi reaktsiooniteid, sest mitmetel reaktsioonidel tekkis uusi produkte.

Märksõnad: süntees, elektropihustus, laetud tilgad

Table of Contents

Abbreviations

LC/MS – Liquid Chromatography/Mass Spectrometry

ESI – Electrospray Ionisation

NMR – Nuclear Magnetic Resonance

MeCN – Acetonitrile

MeOH – Methanol

1. Introduction

Synthesis of new compounds is essential in many fields from material sciences to pharmaceutical industries. Thus, scientists are continuously working on finding synthesis procedures that lead to higher reaction yields, are faster, cheaper, safer and more environmentally benign. Besides, a good synthesis procedure is diverse, yet selective and as simple as possible (less steps, readily available starting materials and without the need for extraordinary conditions).

These days, most synthetic pathways are carried out in a solvent, a gas phase or an ionic liquid. In this work, I studied a novel media for carrying out reactions: charged droplets or electrospray in other words. Electrospray is a liquid aerosol, where liquid droplets in the gas phase are charged either positively or negatively with the help of electrochemical processes. Furthermore, electrospray synthesis has been demonstrated to be more selective, faster and might need less starting material (lower concentrations) and no catalysts to take place compared to the same synthesis in bulk phase. This makes charged droplets a valuable media for carrying out reactions as one step in a multistep synthesis or to totally change the common pathways of some reactions.

Charged droplets occur in nature; they are produced during thunderstorms and found near rapidly moving water masses such as waterfalls, sea waves (also called sea spray aerosol), etc. Electrospray can also be produced in a laboratory in order to study its properties and find other applications. For example, an electrospray source of mass spectrometers (MS) produces a spray of charged droplets. In this study, I used an in-house built electrospray source to carry out reactions.

My aim in this study was to see if and which reactions proceed in charged droplets. To do so, I designed an electrospray source, set it up, designed the procedure for conducting the reactions and analysing the results. I studied the reactions between 7 aldehydes and 4 amines/hydrazines in charged droplets in acetonitrile (MeCN) solution without any catalysts. I chose the reactions that are known to proceed in bulk phase with high yield, but usually need high temperatures and acidic or basic conditions. I observed the acceleration of the reactions compared to bulk phase even at room temperature and without any catalyst. The results of this study have influenced to start a much bigger project in this field, where many more reactions are studied, and various parameters optimised in order to shift reaction pathways, get better yields, and allow conducting reactions in a scalable manner.

2. Literature Review

Over the last decades, novel catalysts have improved the yields and selectivity of chemical synthesis tremendously. However, the ability to speed up highly selective and high-yield synthesis with cheap, simple and accessible means is insufficient. A new promising method to minimise above-mentioned problems is carrying out synthesis in confined spaces, including charged droplets.

2.1. Synthesis in Confined Spaces

Confined spaces, such as microemulsions [1,2], droplets on surfaces [3], levitated droplets [4,5] and droplets formed in microfluidics [6], can be beneficial for carrying out synthesis due to various reasons. Confined spaces limit the phase boundaries [7] and change the local concentrations of the reagent; therefore, usually accelerating the reactions [8,9]. Additionally, confined spaces may help to improve regioselectivity [10,11] and overcome reagent incompatibilities [6].

Most thoroughly studied microcompartments for organic syntheses are microemulsions. This thermodynamically stable medium was originally used to overcome reagent incompatibility, but it also offers two additional benefits. Firstly, significant enhancement in reaction rates has been reported [1,2]. This phenomenon has been related to the compartmentalisation of the reagents on droplets surface, as reaction rates in microemulsions increase with decreasing droplet radius [7]. Secondly, microemulsions can be used to increase the regioselectivity during bond formation in Diels-Alder reaction [12,13], nitration [11], bromination [14], and photocycloaddition of substituted anthracenes [10]. These beneficial properties have been described to result from concentration and orientation of the reagents on the interface of water droplets in microemulsions. Though the chemical nature of the surfactants used in preparation of microemulsions affects the reaction rate and yield, experiments carried out with droplets demonstrate that the main reason for abovementioned advantages rely on other properties of microcompartments. A major drawback of microemulsions turns out to be the thermodynamic stability of microemulsions, resulting in tedious clean-up and separation of the reaction products from the reaction media [15].

Nanodroplets carry most of the advantages of microemulsions, but do not require complex clean-up step after syntheses. Nanodroplets on surfaces have been shown to enhance the reaction rates of aza-Michael and Mannich reactions [3], though properties of the surface have

been presented to influence the reaction rates. Lately, acoustically levitated [4] and Leidenfrost levitated [5] droplets that are not in contact with solid surface, have been studied as a reaction medium for accelerating reactions. Though droplets of this type are very useful for studying pure effect of microcompartments and carrying out small-scale test syntheses, they are impractical for large-scale production of chemicals, due to the limited number of droplets that can be simultaneously generated.

2.1.1. Synthesis in Charged Droplets

Compared to previously described confined spaces, the generation of charged droplets with electrospray is fast, efficient, may produce several grams of matter within minutes, and tolerates solvents with a wide range of polarity from water to dichloromethane [16]. Similar technology, also called electrospinning or electrohydrodynamic atomisation, is widely used in polymer industry to produce fine fibres on a large scale. Even handheld and battery-powered electrospray sources, used for electrospinning grams of polymeric material in a few minutes, have been reported [17]. Therefore, such a source can be conveniently implemented into automated or semi-automated synthesis apparatuses and still remain cheap and simple to use.

Charged droplets produced by electrospray are a highly potent reaction medium, as the properties of these droplets have been found to significantly deviate from the bulk solution properties. Firstly, charged droplets provide compartmentalisation of the reagents to a small volume similarly to levitated droplets and microemulsions.

Secondly, charged nanodroplets carry an excess charge. This excess charge is located near the surface of the droplet and forms a medium with superacidic properties. These features have been recognized generally to produce a unique medium for the production of protonated molecules even for very weak bases (sugars [18], carboxylic acids [19], esters [19], etc.) for mass spectrometry (MS).

Thirdly, several molecules have multiple different functional groups that may be ionised. The functional group ionised in charged droplets may differ from the one observed in bulk solution phase, both for protonation [20–24] and deprotonation [20, 25–27]. This would allow access to the reactivity of completely different functional groups than observed in bulk solution phase.

Fourthly, due to solvent evaporation, the droplets become more concentrated during syntheses; therefore, increasing the reaction rate. [3].

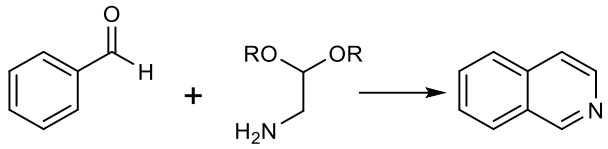
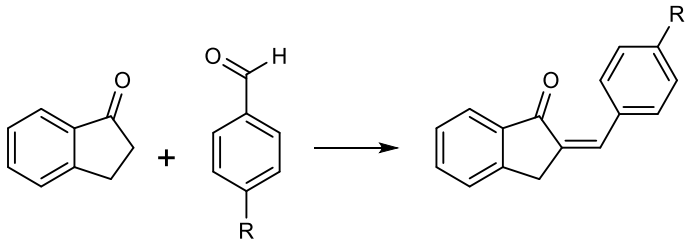
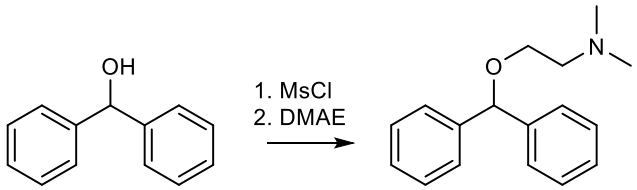
Lastly, due to electrospray process the solvent and volatile additives are removed from the reaction mixture during the procedure, leading to a simplified clean-up procedure.

From these properties, it is obvious that charged droplets possess extremely high but still undeveloped potential for organic synthesis. The possibility to form covalent bonds in charged droplets was only recently discovered in Prof. Zare's research group, where Perry et al. [28] discovered that one of the reagents had reacted with the solvent (both with methanol and water) in the charged droplets while monitoring a transfer hydrogenation in the presence of Ru organometallic catalysts. Later, the same group used electrospray coupled to MS for carrying out Stevens oxidation [29], for cycloaddition of diethyl azodicarboxylate and quadricyclane [30], and for preparation of isoquinoline [31] and substituted quinolines [32]. The same group has demonstrated that some reactions in charged droplets follow a different route compared to the bulk solution [33].

Only a year after the discovery of Perry et al. [28], Müller et al. [34] from Prof. Cooks's group observed that electrospray droplets can be used for carbon-carbon bond formation by the Claisen–Schmidt condensation. For the first time, reaction products were collected and analysed with chromatography, assuring that the reaction was actually occurring in the droplets. Additionally, chromatographic analysis revealed different by-products in bulk solution phase and in charged droplets [33,34]. Though additional by-products are not directly advantageous for application of such reactions in the framework of organic synthesis, it shows that a new type of chemistry is happening in charged droplets. Later the same group optimized some of the electrospray parameters (flow rate, temperature and collection distance) on the Hantzsch reaction [35] and described hydrazone [36] and amide [37] formation in charged nanodroplets.

The area of reactions carried out in charged droplets is increasing fast [38–40] but the scope of reactions studied in charged droplets so far is mostly limited to C-N, C-O, and C-C bond formation (Table 1). Though the list of investigated reactions is far from complete, most of the studied reactions have been accelerated from 100 to 1 000 000 times in charged droplets compared with bulk solution phase reactions [33, 41]. This has led to increased atom efficiency, as reactions that otherwise require additional reagents or catalysts can be run without them. For example, Wleklinski et al. [37] have observed significantly increased conversion rates for *N*-acylation reaction without the need for coupling reagents.

Table 1. Selected examples of the C-N, C-O, and C-C bond formation reactions carried out in charged droplets.

Reaction	Scheme	Reference
C-N bond formation: preparation of isoquinoline		[31, 32]
C-C bond formation: Claisen–Schmidt condensation		[34, 42]
C-O bond formation: ether formation		[37]

The mechanism of the reactions in charged droplets is scarcely investigated. However, it is known that increasing distance between the spray source and collection plate increases the conversion while the concentration of the compounds increases along the spray [36]. An efficient acceleration is associated with three key properties of the charged droplets: (1) the compartmentalisation of the compounds on the droplet surface together with solvent evaporation, (2) the superacidic properties (so far only positively charged droplets have been studied), and (3) induction of structural changes at the 2D surface of the droplets. [41] Additionally, the reactions appear not to be limited to compounds that are known to ionise in charged droplets [30, 34, 43]. Nam et al. [44] recently observed a significant shift in equilibrium for phosphorylation of various sugars. In solution phase, the reaction is disfavoured due to an unfavourable entropic component; however, carrying out the reaction in charged droplets allows overcoming this impediment.

2.2. Imide/Hydrazone Synthesis by Conventional Methods

The condensation reaction of aldehydes and amines is the most common and best way to prepare imines, it is straightforward and gives high yields. It is thoroughly studied, and several

methods have been found, but usually high temperatures and acid or base catalysts are needed [45].

Likewise, the formation of hydrazones from aldehydes and hydrazines is a well-known, straightforward reaction that proceeds in high yields and is usually acid- or base-catalysed. The only exception there is, that hydrazine itself does not react with aldehydes forming hydrazones, but azines (a product where the second amine group condenses with a second equivalent of carbonyl group) [45].

2.3. The Importance of Studying Reactions in Charged Droplets

In addition to being a promising new media for doing synthesis faster, cheaper, with higher selectivity and with more environmentally benign catalysts and solvents, the studies of electrospray syntheses provide additional benefits.

Firstly, reactions in such a novel media might proceed through novel reaction pathways. This can lead to formation of completely new products or even materials. This is extremely beneficial in many fields starting from pharmaceutical industry up to the production of chemicals or polymers.

Secondly, natural aerosols are found abundantly around us. Some of the most interesting fields being environmental aerosols [46] and atmosphere abiogenesis [47]. For instance, micro- and nanodroplets are considered extremely important in the synthesis of amino acids, carboxylic acids, and other compounds in atmosphere during abiogenesis [47]. However, these fields often lack the possibility to study the mechanisms of reactions under well-defined conditions. Therefore, the studies of reactions in electrospray might give insight about the origin of life, the changes in climate and what happens in atmospheric aerosols [48–50].

Thirdly, fast reactions occurring in charged droplets give the possibility to use on-site derivatisation of analytes in MS. This can tremendously improve the sensitivity and selectivity of MS analysis.

Fourthly, the acceleration of the reactions and a small mixing time of the reagents inside a droplet gives the possibility to study reaction intermediates and kinetics easily and with high resolution [41].

3. Methods

3.1. Reagents and Solvents

The following reagents were used for carrying out syntheses: benzaldehyde (Sigma-Aldrich, assay: ≥ 99%), 2-methoxybenzaldehyde (Sigma-Aldrich, assay: 98%), 2-hydroxybenzaldehyde (Sigma-Aldrich, assay: 98%), 4-hydroxybenzaldehyde (Sigma-Aldrich, assay: ≥ 95% (HPLC)), 2-nitrobenzaldehyde (Sigma-Aldrich, assay: 98%), 4-nitrobenzaldehyde (Sigma-Aldrich, assay: 98%), hydrazine hydrate solution (Sigma-Aldrich, concentration: 35 wt. % in H2O), phenylhydrazine (Sigma-Aldrich, assay: 97%), aniline (Sigma-Aldrich, assay: ≥ 99.5% (GC)), *n*-hexylamine (Sigma-Aldrich, assay 99%).

For MS analyses, acetonitrile (Sigma-Aldrich, assay: ≥ 99.9%) and methanol (Sigma-Aldrich, assay: ≥ 99.9%) were used as solvents, formic acid (Sigma-Aldrich, assay: 98.0–100%) and ammonium acetate (Sigma-Aldrich, assay: ≥ 99.0%) were used as additives. Ultra-pure water (purified with in-house Millipore Advantage A10 MILLIPORE GmbH system) was used in the LC water phase.

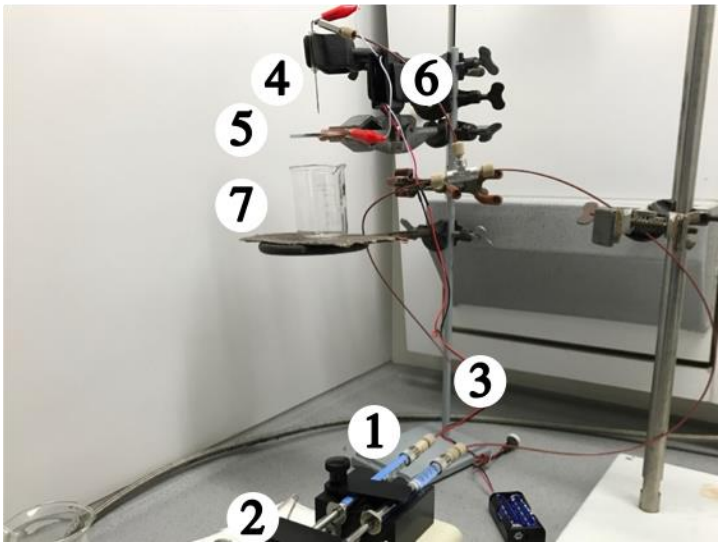
For nuclear magnetic resonance analyses, deuterated acetonitrile-d3 (Eurisotop, 99.80% D) and deuterated dimethyl sulfoxide-d6 (Deutero, 99.8% D) were used as solvents.

All reagents and solvents were used without further purification. Structural information together with *m/z* values of the reagents can be found in Table SI 1.1.

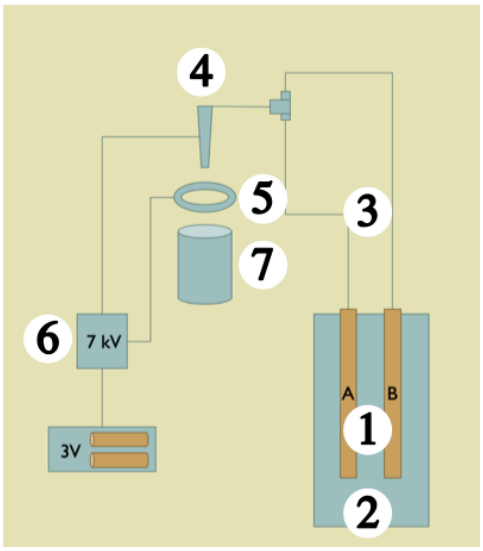
3.2. In-house Built Electrospray System

In this work I used an in-house built electrospray source (see Photo 1 and Scheme 1).

Photo 1. In-house built electrospray system used in this study.



Scheme 1. The scheme of the in-house built electrospray system used in this study.



1. syringes (Agilent manual syringe PN 5190-1530)
2. infusion pump (kdScientific)
3. PEEK tubing with T junction (the two PEEK tubings connecting syringes to T-junction are of the same length)
4. electrospray needle (The autosampler needle from Agilent 1100 series LC was used - type G1313A)
5. counter electrode (galvanized steel, outer diameter – 49.2 mm, inner diameter – 17.4 mm, width – 2.6 mm)
6. High-voltage generator 3 V to 7 kV (purchased from eBay [51])
7. glass beaker

The reagent solutions from the syringes were channelled with the help of infusion pumps via PEEK tubing until the T-junction where the solutions were mixed. After ca. 0.14 seconds, the mixture of two solutions reached the ES needle. High voltage was applied between the needle and the counter electrode through high voltage. The electrospray was formed between the needle tip and the counter electrode. Distance between ESI needle tip and counter electrode (the area where reactions occur) was kept as constant as possible between experiments (8 – 10 mm). The stand was used to adjust the distance between the electrodes and the switch was used to turn the voltage on and off.

The system was placed under the hood, kept on room temperature and the spray was formed without the help of any gas flow. The formation of the spray can be seen on the video on our webpage https://kruvelab.com/spray-video/.

3.2.1. Experimental method

Reagent solutions in MeCN of concentrations around 500 ppm were prepared (at most, one-day old solutions were used) and inserted into syringes.

Two syringes were either filled both with the same reagent (later called "procedure for reagent A" and "procedure for reagent B") or with different reagents (later called "reaction") and connected to the system. First, fast forward was used to make sure the new solutions arrive to ES needle tip and then the voltage was applied between the ES needle and the counter electrode, infusion pumps were turned on at flow rate 0.75 mL/h for 1 hour and the presence and stability of the spray were checked with a light torch.

The presence and stability of the spray were checked several times during the procedure or synthesis and after one hour, the flow rate and spray voltage were turned off (the procedure or synthesis was stopped).

Then, the beaker and the counter electrode were removed from the system and the formed products were washed off with pure solvent (MeCN, if not specified otherwise). The reaction mixture from the beaker and from the counter electrode were analysed separately with LC/MS.

3.2.2. Cleaning the System

Before every procedure or reaction, the system was cleaned thoroughly. Syringes were cleaned between all syntheses by washing them 3 times with pure solvent and before inserting new solution, the new solution was used to rinse the syringe 3 times. PEEK tubing was cleaned by flushing MeCN through the system (from both syringes) for at least 10 minutes. ES needle was cleaned with ethanol-infused paper before each procedure or reaction. Counter-electrode and

the beaker were thoroughly scrubbed with fine sand paper before each procedure or reaction, then cleaned under distilled water, then cleaned with hexane and put into ultrasound in the mixture of distilled water and MeCN for at least 5 minutes under at least 30 degrees. After that, the counter electrode and the beaker were cleaned with hexane and distilled water again and as a last step, rinsed two times with pure solution.

3.3. Bulk Phase Reactions

Bulk phase reactions were done for comparison. For them, the same concentration was used as in the reactions in charged droplets. The reactions in bulk phase were done with the help of the autosampler of the MS. Specifically, the autosampler took 1 μL of both solutions, mixed them, then diluted with 8 μL of the solvent and inserted into MS.

3.4. Instrumentation for Analysis

3.4.1. Liquid Chromatography / Mass Spectrometry (LC/MS)

The LC/MS analyses were carried out in the positive ion mode, on one of two different mass spectrometers. The first MS instrument was an Agilent ion trap mass spectrometer (LC/MSD Trap XCT) with ESI source. It was coupled to Agilent liquid chromatograph (Agilent 1100 series). For instrument control, Agilent ChemStation for LC 3D Rev. A. 10.02 and MSD Trap Control Version 5.2 were used. The column used in this set was Eclipse XDB-C18 (4.6 x 150 mm) with particle size of 5 μm. The solvent flow rate was 0.8 mL/min. The chromatographic gradient started with 5% of organic solvent, that was increased to 100% by 10th minute and kept so until 15th minute. After that, the organic solvent content was brought back down to 5% by 20th minute. Every run was followed by a 5-minute post run. The MS parameters for this set were as follows: injection volume 10 μL, nebulizer gas pressure 60 psi, drying gas flow rate 11 L/min and temperature 350 °C, needle voltage 3500 V, target mass 15 m/z and scan range 50–500 m/z.

The second MS instrument was an Agilent triple quadrupole mass spectrometer (6495 Triple Quad LC/MS) with ESI source (Agilent Jet Stream). It was coupled to Agilent liquid chromatograph (Agilent 1290 Infinity series). For instrument control, Agilent MassHunter Workstation LC/MS Data Acquisition for 6400 Series Triple Quadrupole Version B.07.00 and Qualitative Analysis version B.07.00 were used. The column used in this set was Agilent Zorbax RRHD SB-C18 (2.1 x 50 mm) with particle size of 1.8 μm. The solvent flow rate was 0.3 mL/min. The chromatographic gradient started with 5% of organic solvent, that was increased to 100% by 10th minute and kept so until 15th minute. After that, the organic solvent

content was brought back down to 5% by 17th minute. Every run was followed by a 2-minute post run. The MS parameters for this set were as follows: injection volume 1 μL, nebulizer gas pressure 20 psi, drying gas flow rate 14 L/min and temperature 200 °C, sheath gas flow rate 11 L/min and temperature 250 °C, needle voltage 3000 V and scan range 100 – 500 m/z.

Fragmentation was performed on LC/MSD Trap XCT instrument with the same parameters as described above. Isolation width was 2.0 m/z and amplitude ranging between 0.6 – 1.0 V.

If needed and for preliminary experiments, direct infusion analyses were performed using kdScientific infusion pump coupled to LC/MSD Trap XCT instrument, where MS parameters were kept the same as in LC/MS analysis. Flow rate in this case was 0.5 mL/h.

3.4.2. Nuclear Magnetic Resonance Spectroscopy

Some structural analysis was performed on Bruker Avance III HD instrument. ^{1}H spectra were obtained on the frequency of 700 MHz. As a solvent, deuterated acetonitrile-d3 or deuterated dimethyl sulfoxide-d6 were used. To process spectra, Bruker TopSpin 3.2 program was used.

3.5. Interpretation of the Results

In order to obtain information about the formed products during the syntheses, the following workflow was followed. First, procedure A, procedure B and reaction were carried out separately on our system and the respective product mixtures were collected (all according to section 3.2) and analysed with LC/MS. The chromatogram of the reaction solution was then compared to the chromatograms of the solutions from procedure A, procedure B and new peaks (peaks that were not apparent in the chromatograms of the procedures A and B but do appear in the chromatogram of the reaction) were analysed further. For 3 – 4 most intensive new peaks, fragmentation was carried out in order to identify the products further. In some cases, NMR was used for structural identification of the products.

4. Results

The results were collected from two to three measurements in the time frame of half a year. Before that, preliminary syntheses were carried out, and several parameters were optimised. For example, during the first year, I studied the effect of flow rate and distance between the needle and counter electrode to the appearance of the spray. Different solvents were tested, such as methanol and acetonitrile/formic acid 0.1% mixture on the example of a couple of reactions. From that data collection I can say that the same products formed reproducibly. Additionally, alternative LC/MS and MS instruments were used to verify the results for a couple of reactions; a good agreement was observed. The data represented here is based on two to three replicates: the results of two experiments were analysed with LC/MS and of one experiment additionally LC/MS/MS (the fragmentation experiment) was used. The exceptions are syntheses with 4-methoxybenzaldehyde and 4-nitrobenzaldehyde, for which only one experiment was carried out due to different technical reasons. I thought it is better to include these preliminary data, as experiments with other reactants showed very good repeatability.

The results are presented here by reactions and sorted by amine/hydrazine (first all reactions with hydrazine, then with phenylhydrazine, aniline and hexylamine).

For all reactions, firstly a reaction scheme with most probable products is shown together with a table showing the products that were seen in my experiments (see sections 4.1–4.4). In the tables, “yes” means that the structure is confirmed by fragmentation patterns and “possibly” means that fragmentation experiments were not performed, but the *m/z* of the peaks observed in LC/MS is consistent with the *m/z* of proposed reaction products. Secondly, additional information such as the most intensive peak for each experiment or information from NMR is specified under each table. More specific information about fragmentation experiments and possible side products can be found in the supplementary information (Tables SI2).

4.1. Reactions with Hydrazine

4.1.1. Hydrazine + Benzaldehyde – Reaction Number 1

Scheme 2. The most probable reaction products of hydrazine and benzaldehyde.

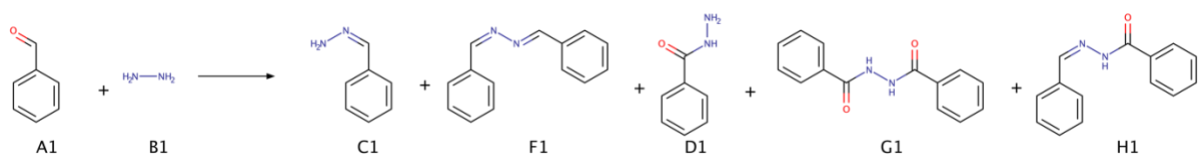


Table 2. Hydrazine and benzaldehyde reaction products seen in my experiments.

	m/z 121 (C1)	m/z 209 (F1)	m/z 137 (D1)	m/z 241 (G1)	m/z 225 (H1)	Side products
Vial	-	Possibly	-	-	-	-
Beaker	-	Possibly	-	-	Possibly	m/z 203 m/z 239
Counter electrode	-	Yes	-	-	-	m/z 151 m/z 191 m/z 239

The most intensive peak both from the beaker and the counter electrode is m/z 209 (product F1).

4.1.2. Hydrazine + 2-Methoxybenzaldehyde – Reaction Number 5

Scheme 3. The most probable reaction products of hydrazine and 2-methoxybenzaldehyde.

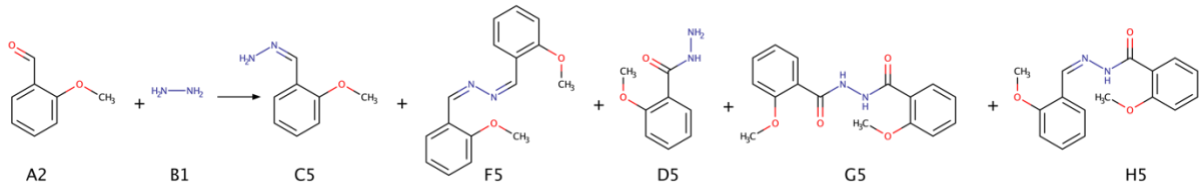


Table 3. Hydrazine and 2-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 151 (C5)	m/z 269 (F5)	m/z 167 (D5)	m/z 301 (G5)	m/z 285 (H5)	Side products
Vial	-	Possibly	-	-	-	-
Beaker	Yes	Yes	-	-	-	m/z 152 m/z 174
Counter electrode	Yes	Yes	-	-	-	-

The most intensive peak both from the beaker and the counter electrode is m/z 269 (product F5).

4.1.3. Hydrazine + 4-Methoxybenzaldehyde – Reaction Number 9

Scheme 4. The most probable reaction products of hydrazine and 4-methoxybenzaldehyde.

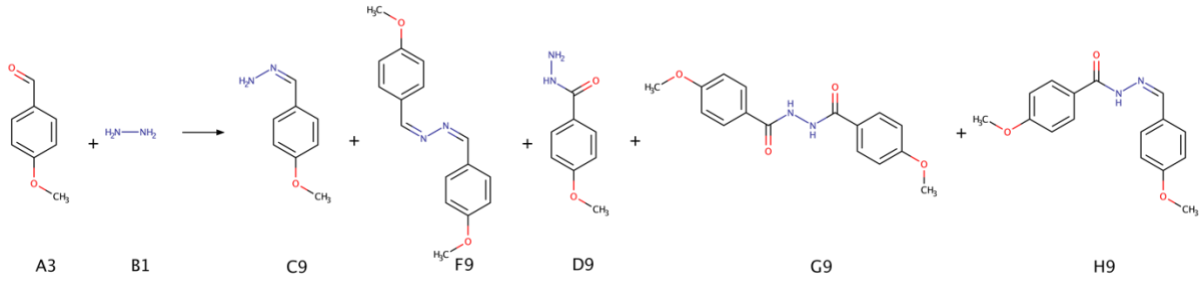


Table 4. Hydrazine and 4-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 151 (C9)	m/z 269 (F9)	m/z 167 (D9)	m/z 301 (G9)	m/z 285 (H9)	Side products
Vial	Not done	Not done	Not done	Not done	Not done	Not done
Beaker	Yes	Yes	-	-	-	-
Counter electrode	-	Yes	-	-	-	-

The most intensive peak both from the beaker and the counter electrode is m/z 269 (product F9).

4.1.4. Hydrazine + 2-Hydroxybenzaldehyde – Reaction Number 13

Scheme 5. The most probable reaction products of hydrazine and 2-hydroxybenzaldehyde.

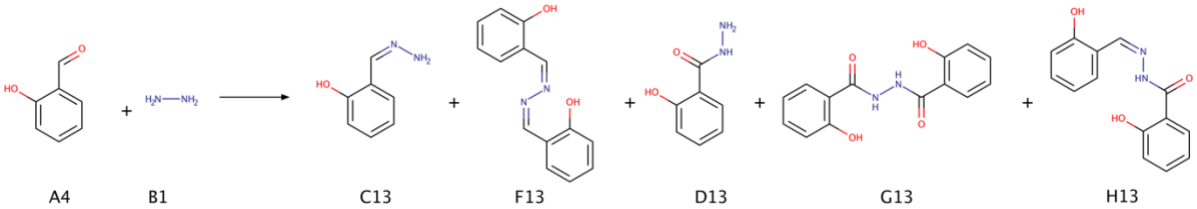


Table 5. Hydrazine and 2-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 137 (C13)	m/z 241 (F13)	m/z 153 (D13)	m/z 273 (G13)	m/z 257 (H13)	Side products
Vial	-	-	-	-	-	-
Beaker	-	Yes	-	-	-	m/z 255
Counter electrode	-	Yes	-	-	-	m/z 255

The most intensive peak both from the beaker and the counter electrode is m/z 241 (product F13).

4.1.5. Hydrazine + 4-Hydroxybenzaldehyde – Reaction Number 17

Scheme 6. The most probable reaction products of hydrazine and 4-hydroxybenzaldehyde.

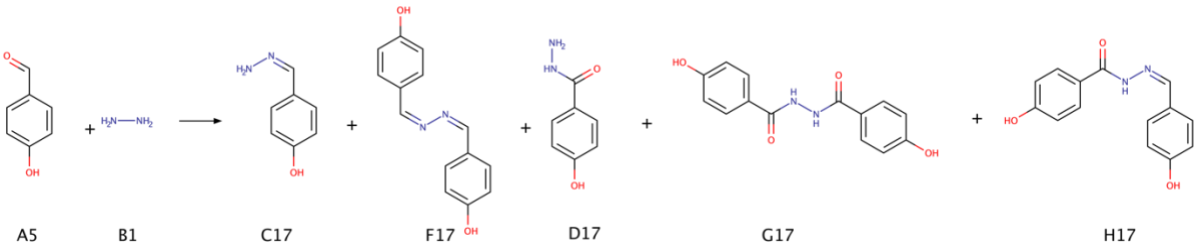


Table 6. Hydrazine and 4-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 137 (C17)	m/z 241 (F17)	m/z 153 (D17)	m/z 273 (G17)	m/z 257 (H17)	Side products
Vial	-	-	-	-	-	-
Beaker	-	Yes	-	-	-	-
Counter electrode	-	Yes	-	-	-	m/z 255

The most intensive peak both from the beaker and the counter electrode is m/z 241 (product F17).

4.1.6. Hydrazine + 2-Nitrobenzaldehyde – Reaction Number 21

Scheme 7. The most probable reaction products of hydrazine and 2-nitrobenzaldehyde.

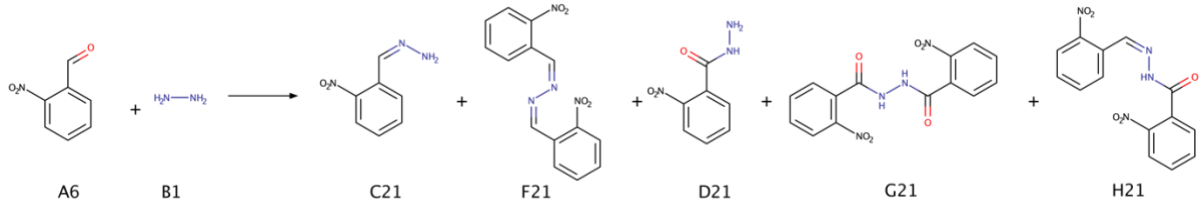


Table 7. Hydrazine and 2-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 166 (C21)	m/z 299 (F21)	m/z 182 (D21)	m/z 331 (G21)	m/z 315 (H21)	Side products
Vial	-	-	-	-	-	-
Beaker	Yes	Yes	-	-	-	-
Counter electrode	Yes	Yes	-	-	-	-

The most intensive peak both from the beaker and the counter electrode is m/z 166 (product C21).

4.1.7. Hydrazine + 4-Nitrobenzaldehyde – Reaction Number 25

Scheme 8. The most probable reaction products of hydrazine and 4-nitrobenzaldehyde.

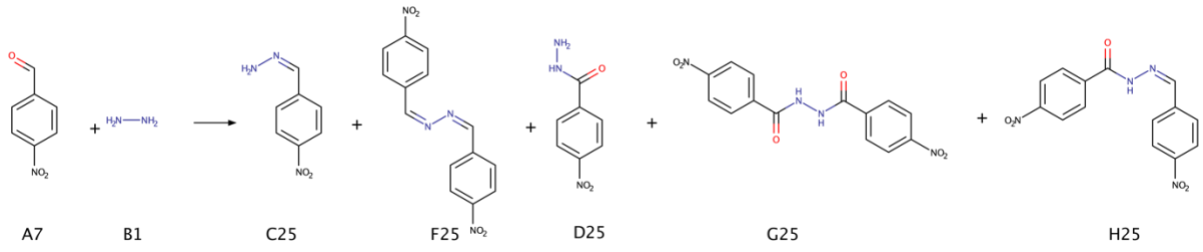


Table 8. Hydrazine and 4-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 166 (C25)	m/z 299 (F25)	m/z 182 (D25)	m/z 331 (G25)	m/z 315 (H25)	Side products
Vial	-	-	-	-	-	-
Beaker	Possibly	-	-	-	-	-
Counter electrode	Possibly	Possibly	Possibly	-	-	-

The most intensive peak both from the beaker and the counter electrode is m/z 166 (product C25).

4.2. Reactions with Phenylhydrazine

4.2.1. Phenylhydrazine + Benzaldehyde – Reaction Number 2

Scheme 9. The most probable reaction products of phenylhydrazine and benzaldehyde.

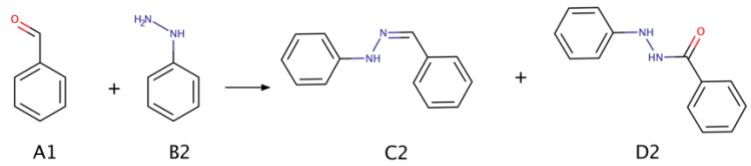


Table 9. Phenylhydrazine and benzaldehyde reaction products seen in my experiments.

	m/z 197 (C2)	m/z 213 (D2)	Side products
Vial	-	-	-
Beaker	Yes	Yes	m/z 191 m/z 195
Counter electrode	Yes	Yes	m/z 191 m/z 195

The most intensive peak from the beaker is m/z 213 (product D2) but from the counter electrode is m/z 197 (product C2).

In order to confirm the reaction products, this reaction was performed in bulk phase by conventional method [52] and then both mixtures of reaction products were analysed using NMR (see SI 3). The spectra show the production of the imine in both cases.

4.2.2. Phenylhydrazine + 2-Methoxybenzaldehyde – Reaction Number 6

Scheme 10. The most probable reaction products of phenylhydrazine and 2-methoxybenzaldehyde.

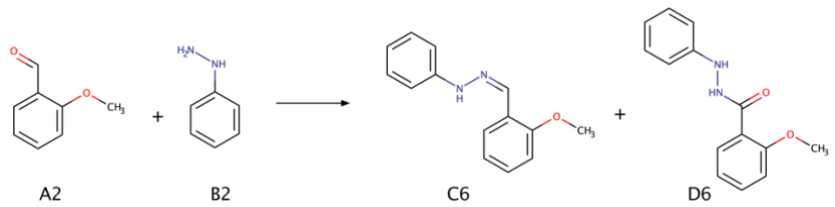


Table 10. Phenylhydrazine and 2-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 227 (C6)	m/z 243 (D6)	Side products
Vial	-	-	-
Beaker	Yes	-	m/z 225
Counter electrode	Yes	-	m/z 225

The most intensive peak both from the beaker and the counter electrode is m/z 227 (product C6).

4.2.3. Phenylhydrazine + 4-Methoxybenzaldehyde – Reaction Number 10

Scheme 11. The most probable reaction products of phenylhydrazine and 4-methoxybenzaldehyde.

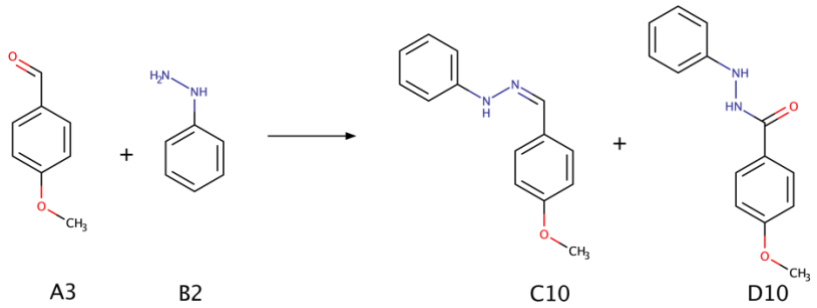


Table 11. Phenylhydrazine and 4-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 227 (C10)	m/z 243 (D10)	Side products
Vial	Not done	Not done	Not done
Beaker	Yes	Possibly	-
Counter electrode	Yes	Possibly	m/z 241

The most intensive peak both from the beaker and the counter electrode is m/z 227 (product C10).

4.2.4. Phenylhydrazine + 2-Hydroxybenzaldehyde – Reaction Number 14

Scheme 12. The most probable reaction products of phenylhydrazine and 2-hydroxybenzaldehyde.

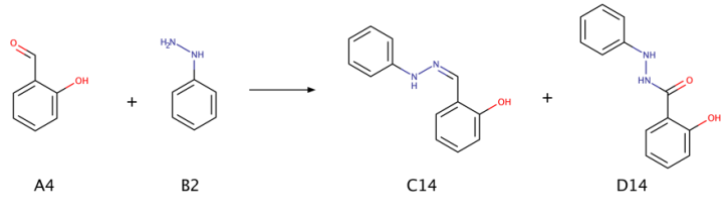


Table 12. Phenylhydrazine and 2-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 213 (C14)	m/z 229 (D14)	Side products
Vial	Possibly	-	-
Beaker	Yes	-	-
Counter electrode	Yes	-	m/z 227 m/z 229

The most intensive peak both from the beaker and the counter electrode is m/z 213 (product C14).

4.2.5. Phenylhydrazine + 4-Hydroxybenzaldehyde – Reaction Number 18

Scheme 13. The most probable reaction products of phenylhydrazine and 4-hydroxybenzaldehyde.

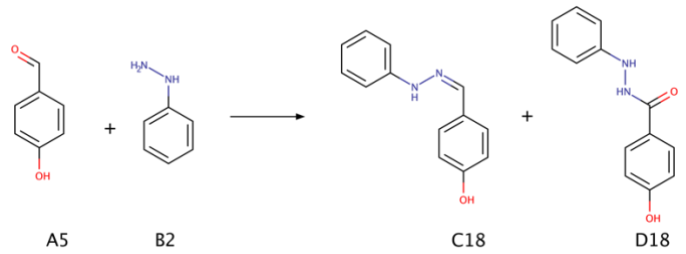


Table 13. Phenylhydrazine and 4-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 213 (C18)	m/z 229 (D18)	Side products
Vial	Possibly	-	-
Beaker	Yes	-	-
Counter electrode	Yes	-	m/z 227 m/z 229

The most intensive peak both from the beaker and the counter electrode is m/z 213 (product C18).

4.2.6. Phenylhydrazine + 2-Nitrobenzaldehyde – Reaction Number 22

Scheme 14. The most probable reaction products of phenylhydrazine and 2-nitrobenzaldehyde.

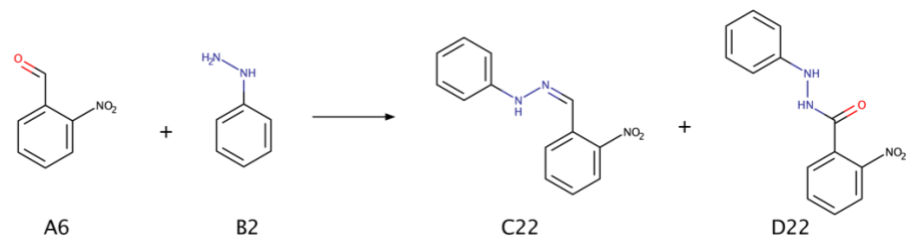


Table 14. Phenylhydrazine and 2-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 242 (C22)	m/z 258 (D22)	Side products
Vial	-	Possibly	-
Beaker	Yes	Possibly	m/z 262
Counter electrode	Yes	Possibly	m/z 262

Peaks with m/z 242 (C22) and m/z 258 (D22) are equally intensive for both the beaker and the counter electrode.

4.2.7. Phenylhydrazine + 4-Nitrobenzaldehyde – Reaction Number 26

Scheme 15. The most probable reaction products of phenylhydrazine and 4-nitrobenzaldehyde.

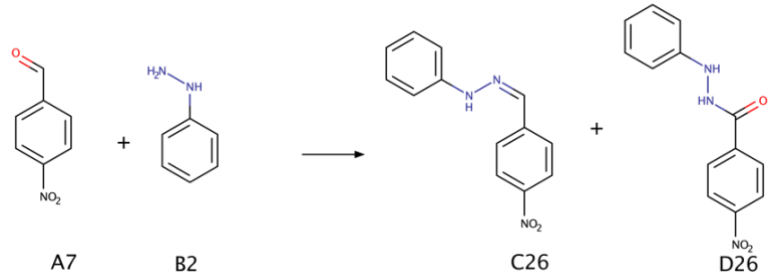


Table 15. Phenylhydrazine and 4-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 242 (C26)	m/z 258 (D26)	Side products
Vial	-	-	-
Beaker	-	-	-
Counter electrode	Possibly	Possibly	-

Peaks with m/z 242 (C26) and m/z 258 (D26) are equally intensive for both the beaker and the counter electrode.

4.3. Reactions with Aniline

4.3.1. Aniline + Benzaldehyde – Reaction Number 3

Scheme 16. The most probable reaction products of aniline and benzaldehyde.

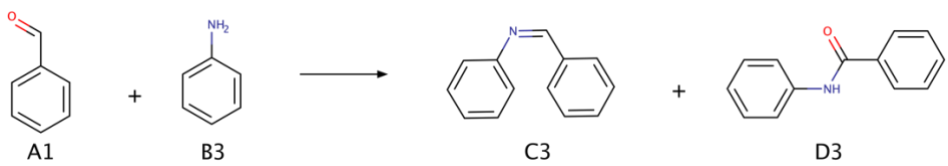


Table 16. Aniline and benzaldehyde reaction products seen in my experiments.

	m/z 182 (C3)	m/z 198 (D3)	Side products
Vial	-	-	-
Beaker	-	Yes	-
Counter electrode	-	Yes	-

The only product observed is a peak with m/z 198 (product D3).

4.3.2. Aniline + 2-Methoxybenzaldehyde – Reaction Number 7

Scheme 17. The most probable reaction products of aniline and 2-methoxybenzaldehyde.

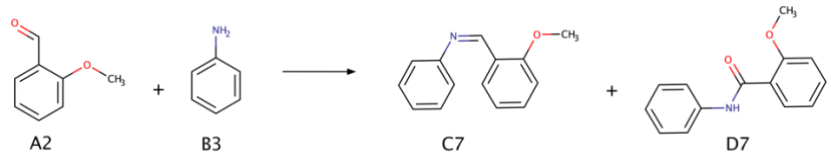


Table 17. Aniline and 2-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 212 (C7)	m/z 228 (D7)	Side products
Vial	Possibly	-	-
Beaker	-	-	-
Counter electrode	Yes	-	-

The only product observed is a peak with m/z 212 (product C7).

4.3.3. Aniline + 4-Methoxybenzaldehyde – Reaction Number 11

Scheme 18. The most probable reaction products of aniline and 4-methoxybenzaldehyde.

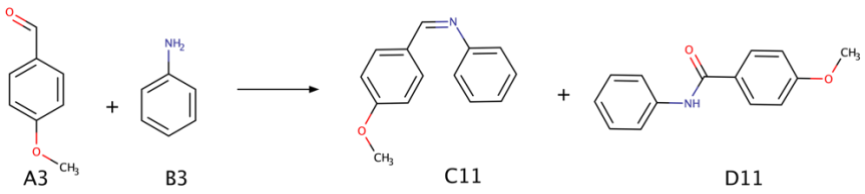


Table 18. Aniline and 4-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 212 (C11)	m/z 228 (D11)	Side products
Vial	Not done	Not done	Not done
Beaker	-	-	-
Counter electrode	-	-	-

No new products were observed.

4.3.4. Aniline + 2-Hydroxybenzaldehyde – Reaction Number 15

Scheme 19. The most probable reaction products of aniline and 2-hydroxybenzaldehyde.

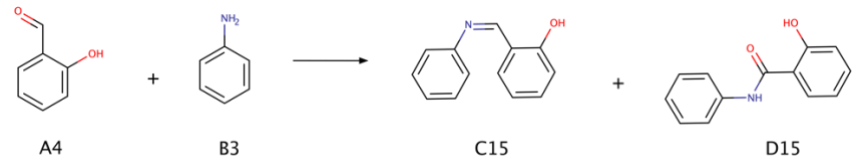


Table 19. Aniline and 2-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 198 (C15)	m/z 214 (D15)	Side products
Vial	-	-	-
Beaker	Yes	Possibly	-
Counter electrode	Yes	Possibly	-

The most intensive peak both from the beaker and the counter electrode is m/z 198 (product C15).

4.3.5. Aniline + 4-Hydroxybenzaldehyde – Reaction Number 19

Scheme 20. The most probable reaction products of aniline and 4-hydroxybenzaldehyde.

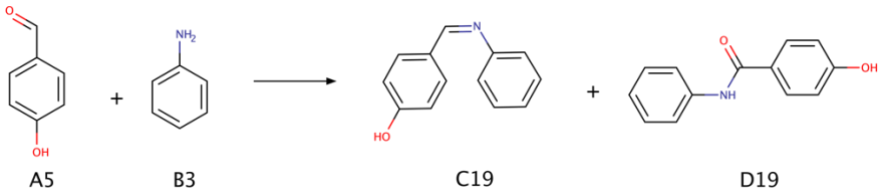


Table 20. Aniline and 4-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 198 (C19)	m/z 214 (D19)	Side products
Vial	-	-	-
Beaker	-	-	-
Counter electrode	Yes	-	-

The only product observed is a peak with m/z 198 (product C19).

4.3.6. Aniline + 2-Nitrobenzaldehyde – Reaction Number 23

Scheme 21. The most probable reaction products of aniline and 2-nitrobenzaldehyde.

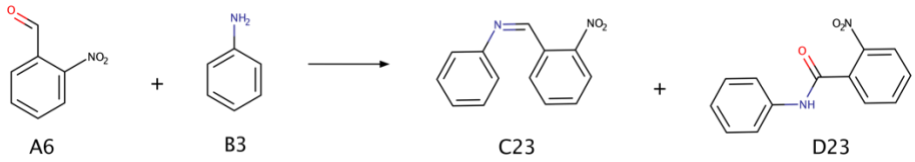


Table 21. Aniline and 2-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 227 (C23)	m/z 243 (D23)	Side products
Vial	-	-	-
Beaker	-	-	-
Counter electrode	Possibly	-	-

The only possible product observed is a peak with m/z 227 (product C23).

4.3.7. Aniline + 4-Nitrobenzaldehyde – Reaction Number 27

Scheme 22. The most probable reaction products of aniline and 4-nitrobenzaldehyde.

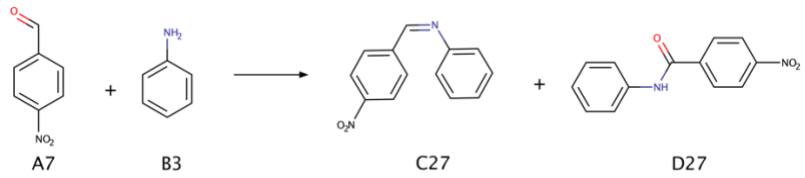


Table 22. Aniline and 4-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 227 (C27)	m/z 243 (D27)	Side products
Vial	-	-	-
Beaker	-	-	-
Counter electrode	-	-	-

No new products were observed.

4.4. Reactions with Hexylamine

4.4.1. Hexylamine + Benzaldehyde – Reaction Number 4

Scheme 23. The most probable reaction products of hexylamine and benzaldehyde.

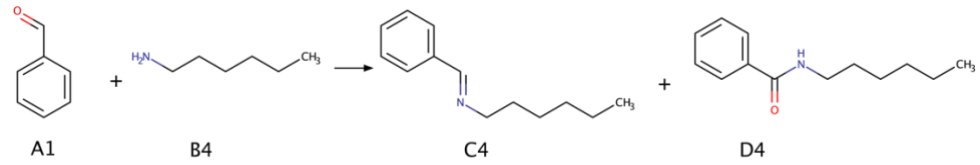


Table 23. Hexylamine and benzaldehyde reaction products seen in my experiments.

	m/z 190 (C4)	m/z 206 (D4)	Side products
Vial	-	-	-
Beaker	Yes	Possibly	m/z 217
Counter electrode	Yes	Possibly	m/z 217

The most intensive peak both from the beaker and the counter electrode is m/z 217 (see discussion).

In order to obtain the structure of the molecule with m/z 217, I measured its NMR spectrum of ^{1}H (see SI 3). The peaks indicate a mixture of the corresponding imine and amide.

4.4.2. Hexylamine + 2-Methoxybenzaldehyde – Reaction Number 8

Scheme 24. The most probable reaction products of hexylamine and 2-methoxybenzaldehyde.

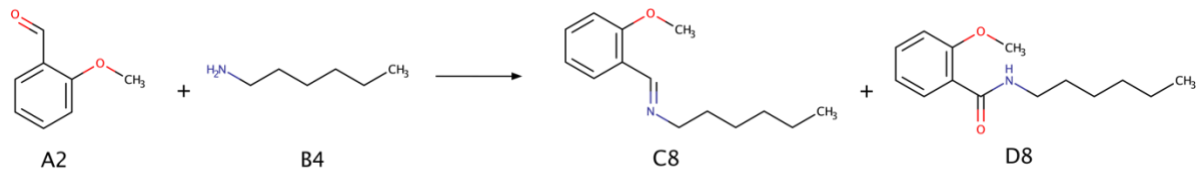


Table 24. Hexylamine and 2-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 220 (C8)	m/z 236 (D8)	Side products
Vial	-	-	-
Beaker	Yes	-	m/z 247
Counter electrode	Yes	-	m/z 247

The most intensive peak both from the beaker and the counter electrode is m/z 247 (see discussion).

4.4.3. Hexylamine + 4-Methoxybenzaldehyde – Reaction Number 12

Scheme 25. The most probable reaction products of hexylamine and 4-methoxybenzaldehyde.

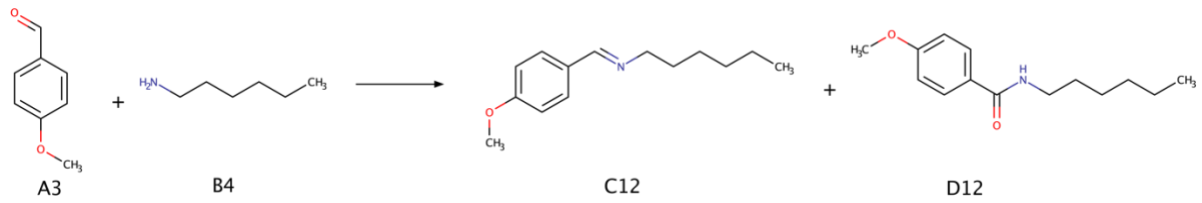


Table 25. Hexylamine and 4-methoxybenzaldehyde reaction products seen in my experiments.

	m/z 220 (C12)	m/z 236 (D12)	Side products
Vial	Not done	Not done	Not done
Beaker	Yes	Yes	m/z 247
Counter electrode	Yes	-	m/z 247

The most intensive peak both from the beaker and the counter electrode is m/z 220 (product C12).

4.4.4. Hexylamine + 2-Hydroxybenzaldehyde – Reaction Number 16

Scheme 26. The most probable reaction products of hexylamine and 2-hydroxybenzaldehyde.

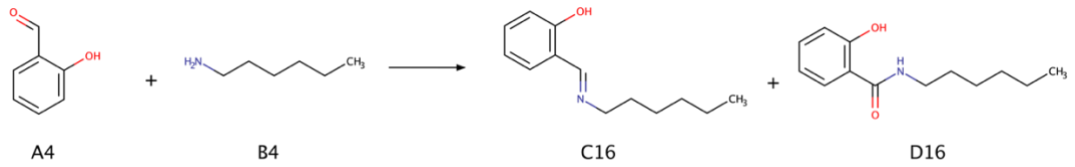


Table 26. Hexylamine and 2-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 206 (C16)	m/z 222 (D16)	Side products
Vial	-	-	-
Beaker	Yes	-	m/z 250 m/z 220
Counter electrode	Yes	-	m/z 250 m/z 220

The most intensive peak both from the beaker and the counter electrode is m/z 206 (product C16).

4.4.5. Hexylamine + 4-Hydroxybenzaldehyde – Reaction Number 20

Scheme 27. The most probable reaction products of hexylamine and 4-hydroxybenzaldehyde.

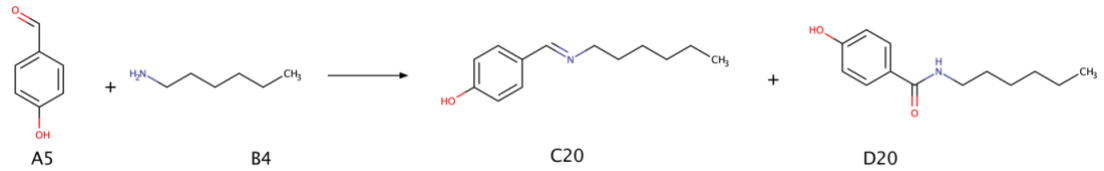


Table 27. Hexylamine and 4-hydroxybenzaldehyde reaction products seen in my experiments.

	m/z 206 (C20)	m/z 222 (D20)	Side products
Vial	-	-	-
Beaker	Yes	-	m/z 233
Counter electrode	Yes	-	m/z 233

The most intensive peak both from the beaker and the counter electrode is m/z 206 (product C20).

4.4.6. Hexylamine + 2-Nitrobenzaldehyde – Reaction Number 24

Scheme 28. The most probable reaction products of hexylamine and 2-nitrobenzaldehyde.

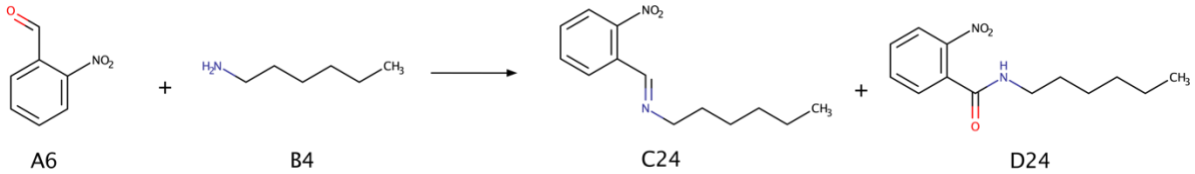


Table 28. Hexylamine and 2-nitrobenzaldehyde reaction products seen in my experiments.

	m/z 235 (C24)	m/z 251 (D24)	Side products
Vial	-	-	-
Beaker	Possibly	Yes	m/z 262
Counter electrode	Possibly	Yes	m/z 262 m/z 221

The most intensive peak both from the beaker and the counter electrode is m/z 262 (see discussion).

4.4.7. Hexylamine + 4-Nitrobenzaldehyde – Reaction Number 28

Scheme 29. The most probable reaction products of hexylamine and 4-nitrobenzaldehyde.

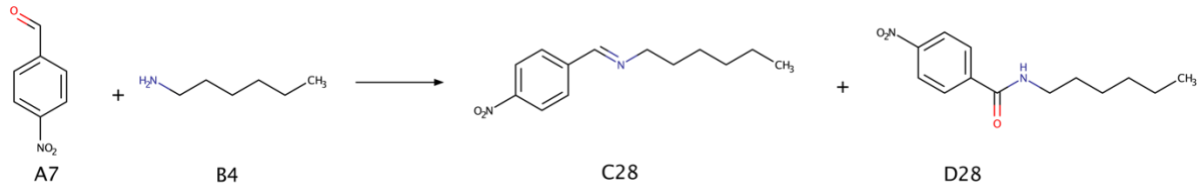


Table 29. Hexylamine and 4-nitrobenzaldehyde reaction products seen in my experiments.

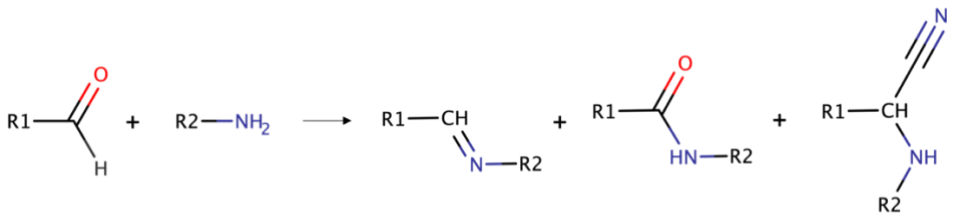
	m/z 235 (C28)	m/z 251 (D28)	Side products
Vial	-	-	-
Beaker	-	-	-
Counter electrode	-	Possibly	m/z 262 m/z 233

No new products were observed from the beaker. The most intensive peak from the counter electrode is m/z 262 (see discussion).

4.5. Summarised results

Based on the results represented above, it is seen that mostly imines and amides are produced and for hexylamine, a [M+27] product is formed. Based on the fragmentation spectra, this product can be a nitrile. The mostly seen products are shown on scheme 30.

Scheme 30. Mostly seen products in the reactions carried out.



The following tables represent the overall results of the syntheses done in charged droplets (Table 30) and in the bulk phase (Table 31).

As seen from Table 30, imine was formed in 24 reactions out of 28, amide was formed in 11 reactions out of 28 and a nitrile was formed in 6 reactions out of 28. At the same time, corresponding to Table 31, in bulk phase reactions, imine was seen in 5 reactions out of 28, amide only once and nitrile was never found to be produced.

Table 30. The overview of the reaction products observed in charged droplets.

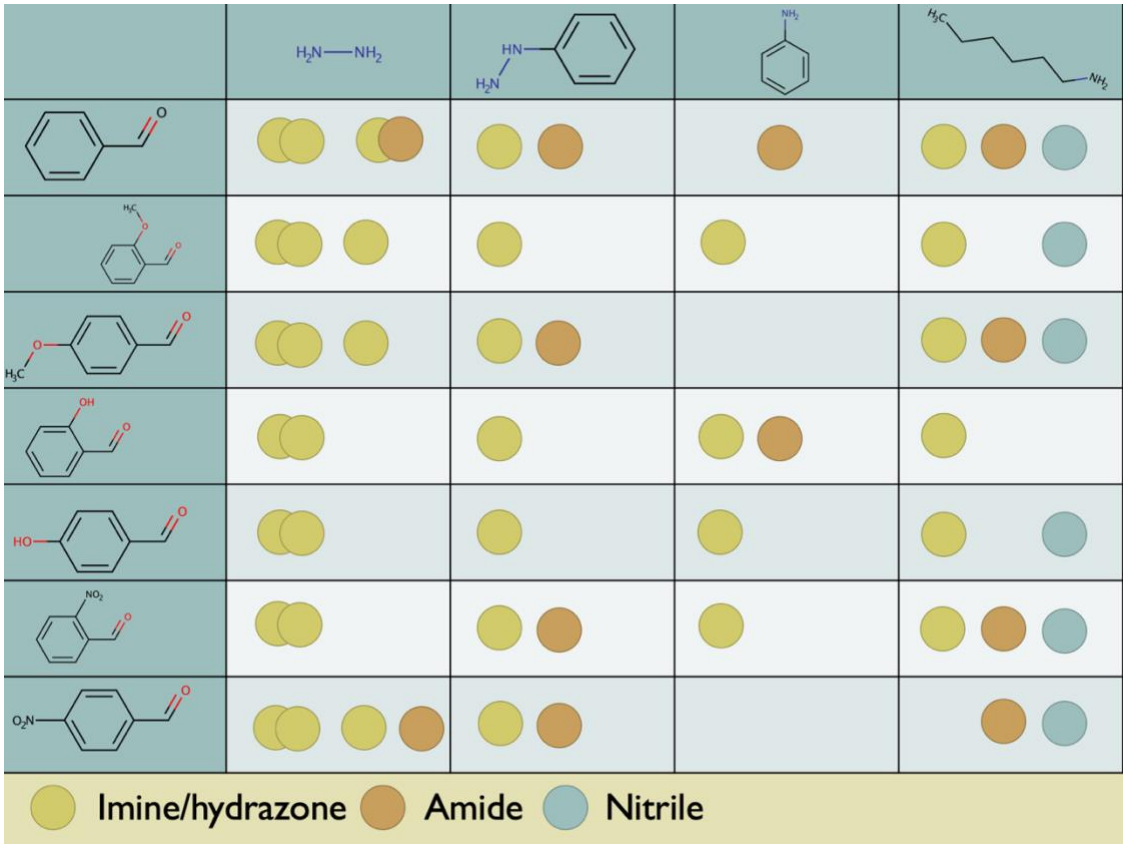
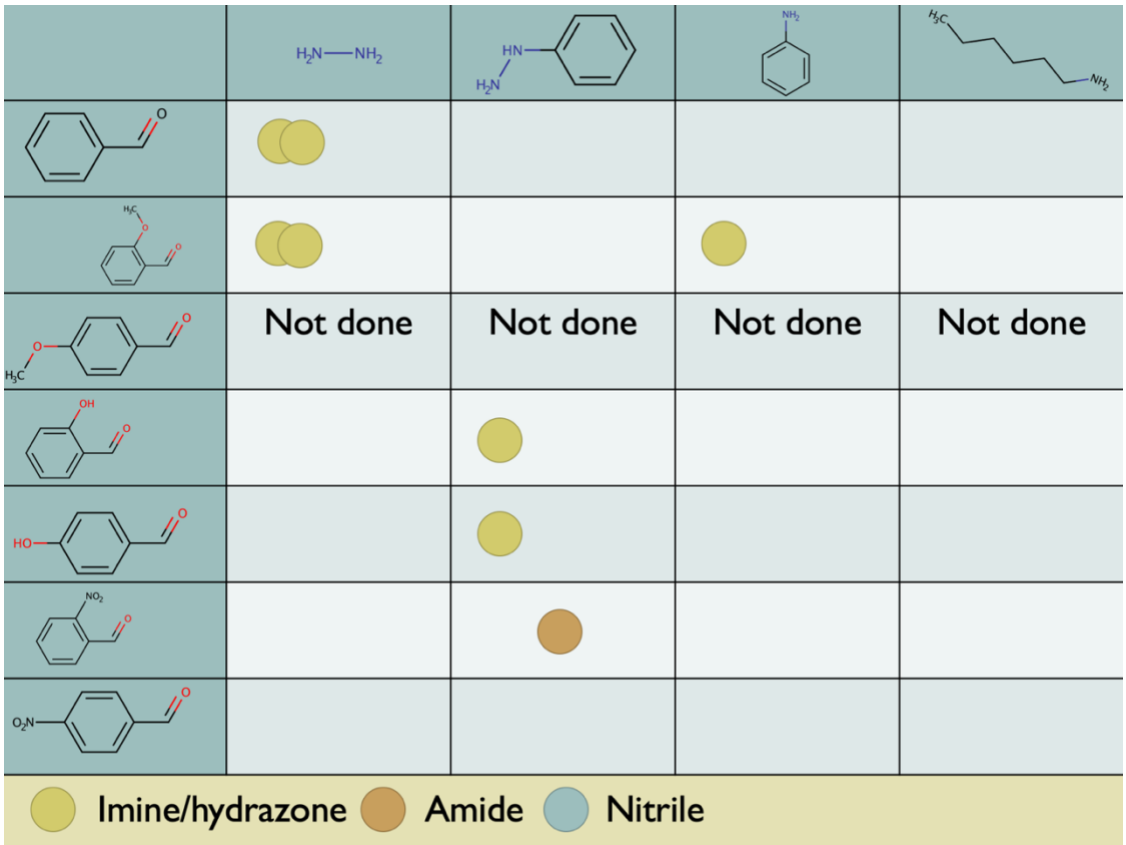


Table 31. The overview of the reaction products observed in bulk phase.



5. Discussion

5.1. General Observations

Within this study, an in-house built electrospray source was designed, installed in our laboratory and used for abovementioned syntheses. It can be seen from the results that the system works; most of the reactions give at least one product. It is necessary to mention, that this work was only qualitative and no quantitative data (yields, assays, etc.) was collected.

In general, more intensive peaks were seen in the sample collected from the counter electrode and the same samples yielded more peaks corresponding to side products. The analysis of the product from beaker usually resulted in "cleaner" chromatograms (less other smaller peaks). This is probably because (1) the counter electrode is closer to the spray and, therefore, more of the product as well as side products precipitates on the counter electrode, (2) the metal was not as clean as beaker or (3) electrochemical reactions can take place on the counter electrode.

During the reactions, mostly imines or hydrazones are produced, but also amides were seen as reaction products. Most interestingly, [M+27] side product in reactions with hexylamine was observed. This product corresponds to a nitrile according to MS/MS fragmentation patterns.

Moreover, when comparing the results from the syntheses in charged droplets to the syntheses in bulk phase under similar conditions (same concentration of the reactants, similar time-frame and temperature) it can be seen that more products are formed from the syntheses in charged droplets. This confirms that reactions are accelerated in charged droplets compared to bulk phase. Moreover, additional reaction products have been observed for reactions in charged droplets which means that new reaction pathways open in this medium.

5.2. Discussion by Amines/Hydrazines

Hydrazine reacts with aldehydes by producing hydrazones and/or azines. In four reactions out of seven, one-to-one product (hydrazone) was observed, but two-to-one product (azine) where an aldehyde has reacted to both nitrogens of hydrazine, was seen in all reactions (the concentration ratio was approximately 1:1). Amide was only seen in the reaction with 4-nitrobenzaldehyde. A very interesting product is observed in the reaction with benzaldehyde where one nitrogen of the hydrazine seems to be reacted as an imine and the other as amide; however, this product needs to be verified in the future with NMR analysis.

Phenylhydrazine reacts with aldehydes by producing imines in all studied reactions and amide is produced in four reactions out of seven.

Aniline reacts with aldehydes by producing imines in four reactions out of seven and amides in two reactions out of seven. Here, no products were observed in the reactions with 4-methoxybenzaldehyde and 4-nitrobenzaldehyde and overall not so many products are seen for all reactions. This suggests that aniline is the less reactive of the amines/hydrazines studied. Aniline's nucleophilic reactivity is lower compared to other nucleophiles used in this study because the lone pair of electrons on nitrogen is in resonance with the π system and thus decreases the nucleophilic reactivity of the nitrogen and aniline in general [53].

Hexylamine reacts with aldehydes by producing imines in all reactions except with 4-nitrobenzaldehyde. Amide is also produced in four reactions out of seven. One of the most interesting findings in our study was a [M+27] side product in hexylamine reaction with almost all aldehydes, the only exception being 2-hydroxybenzaldehyde. This product corresponds to a nitrile according to MS/MS fragmentation patterns. Still, this structure needs to be verified by NMR.

5.3. Discussion by Aldehydes

5.3.1. Isomeric Effects

I was also interested in studying the isomeric effect on the reactivity of the aldehyde in charged droplets. The para- and ortho-substituted aldehydes possessed different reactivity (products formed); however, the isomeric effect is dependent on the exact functional group of the aldehyde. Yet, from the reactions with aniline, it can be said that para-isomers are in general less reactive than ortho-isomers. For ortho-isomers, reaction products were observed in charged droplets while the products were not observed for para-isomers. In bulk phase neither of the isomers yielded detectable amounts of product.

It is known that isomer effects exist also in the protonation of the compounds in charged droplets generated in ESI/MS. It is interesting to compare the measured ionisation efficiency values for different aldehydes with the reactivity. J. Liigand has measured the ionisation efficiency values of the aldehydes used in this study (see Table 32). For the reaction of aniline and nitrobenzaldehydes the difference in reactivity is supported by the ionisation efficiency values of the two aldehydes. The ionisation efficiency for para-nitrobenzaldehyde is ca 10 times lower than is observed for corresponding ortho-isomer and the reaction product is observed only for the ortho-isomer. It is expected that the protonation increases the reactivity of the

aldehyde. On the other hand, the ionisation efficiencies of ortho- and para-methoxybenzaldehyde are very similar, but the reaction product was observed only for the ortho-isomer. Therefore, the isomer effect needs further validation with a wider range of aldehydes.

Table 32. Ionisation efficiency values for the aldehydes used in this study.

Compound	Ionisation efficiency (log*IE*)	*s*
Benzaldehyde	-	-
2-methoxybenzaldehyde	1.18	0.14
4-methoxybenzaldehyde	1.46	0.05
2-hydroxybenzaldehyde	-	-
4-hydroxybenzaldehyde	1.13	0.12
2-nitrobenzaldehyde	0.78	0.12
4-nitrobenzaldehyde	-0.09	0.27

5.4. Questions Remaining Fuzzy

The formation of [M+27] product in hexylamine reactions is still not fully understood. One possibility is the formation of a nitrile according to Stecker synthesis [54], but this reaction pathway needs hydrogen cyanide (HCN) in order to proceed. In my reactions, it is hard to say where the cyano group might come from, though one probability is MeCN used as a solvent. Thus the mechanism of the reactions is still fuzzy.

Another interesting finding was the formation of the product with m/z 225 in the reaction between hydrazine and benzaldehyde. According to fragmentation seems to be a product where one nitrogen has reacted as an imine and the other as amide. Yet, this was the only reaction where this structure was obtained and thus it needs to be studied further.

5.5. NMR analysis

NMR was used to identify products for only two reactions. This is due to the reason that it was very difficult to collect sufficient amount of the product with the current electrospray system. To start with, the concentrations used were low and the spraying time was insufficient to collect enough product. Also, some of the products were liquids and evaporated during the collection

of the products. Therefore, in this pilot study LC/MS proved to be more suitable tool for analysing the collected reaction mixtures.

However, for some selected cases it was possible to verify the results with NMR analysis (see SI 3). For the reaction of benzaldehyde with phenylhydrazine and benzaldehyde with hexylamine, the product mixture was collected from four consequent repetitive reactions. No further purification was done, yet the analysis results confirm the production of the products which were observed by MS/MS analysis. This indicates that although from MS spectra smaller side product peaks are observed, the main products are dominant.

For the detection of smaller side products, further purification needs to be done. I tried to collect some products from the mixtures with chromatographic column, but the quantities were too low and collecting sample size sufficient for NMR analysis was impossible. The purification is planned for the continuing project.

The NMR spectra of the reaction mixture of phenylhydrazine and benzaldehyde (see SI 3) match the spectra of the same reaction done by conventional method [52] in a bulk phase and the peaks correspond to the imine.

In order to obtain structural information on the products of the reaction between hexylamine and benzaldehyde, ^{1}H spectrum was measured. The spectrum shows peaks of the corresponding imine and amide but does not verify the presence of the possible nitrile product. This might be due to low concentration of the product or some other unknown reason. Further studies on these [M+27] products in the reactions with hexylamine have to be done.

Conclusion

Charged Droplets – Novel Media for Studying Reactions between Aldehydes and Amines/Hydrazines

In this work, an in-house built electrospray system was designed and set up. Then, 28 reactions between aldehydes and nitrogen bases were carried out. Mostly imines were observed as reaction products, but also amides were found in some reactions. Most interestingly, reactions with hexylamine gave a [M+27] product, possibly a nitrile. All of the above shows that reactions occur and are accelerated in charged droplets compared to the reactions happening in bulk phase under similar conditions. Moreover, the reaction pathways are different compared to bulk solution reactions. Though the mechanisms of the reactions are still unknown, it shows the possible value of this new reaction media.

I believe that in the future the reactions can be made even more repeatable using a more robust system and syntheses can be shifted towards certain products by optimising physical parameters of the electrospray system. Parameters that can be adjusted include the distance between the electrodes, voltage applied to the electrodes, other solvent systems, different concentrations of the reactants and the use of gases in the spray system.

The described new and more powerful system (the system allows the collection of products with a speed of 200 mg per hour) is already installed in our laboratory based on my results and experience. Around 20 different reactions have already been tested and I will continue studying charged droplets as a novel reaction media.

Keywords: synthesis, electrospray, charged droplets

CERCS code and name: P390 Organic Chemistry

References

1. Holmberg, K. Organic Reactions in Microemulsions. *Curr. Opin. Colloid Interface Sci.* **2003**, *8*, 187–196.
2. Holmberg, K. Organic Reactions in Microemulsions. *Eur. J. Org. Chem.* **2007**, *5*, 731–742.
3. Badu-Tawiah, A. K.; Campbell, D. I.; Cooks, R. G. Accelerated C–N Bond Formation in Dropcast Thin Films on Ambient Surfaces. *J. Am. Soc. Mass Spectrom.* **2012**, *23* (9), 1461–1468.
4. Crawford, E. A.; Esen, C.; Volmer, D. A. Real Time Monitoring of Containerless Microreactions in Acoustically Levitated Droplets via Ambient Ionization Mass Spectrometry. *Anal. Chem.* **2016**, *88* (17), 8396–8403.
5. Bain, R. M.; Pulliam, C. J.; Thery, F.; Cooks, R. G. Accelerated Chemical Reactions and Organic Synthesis in Leidenfrost Droplets. *Angew. Chem. Int. Ed.* **2016**, *55* (35), 10478–10482.
6. Song, H.; Chen, D. L.; Ismagilov, R. F. Reactions in Droplets in Microfluidic Channels. *Angew. Chem. Int. Ed.* **2006**, *45* (44), 7336–7356.
7. Fallah-Araghi, A.; Meguellati, K.; Baret, J.-C.; Harrak, A. E.; Mangeat, T.; Karplus, M.; Ladame, S.; Marques, C. M.; Griffiths, A. D. Enhanced Chemical Synthesis at Soft Interfaces: A Universal Reaction-Adsorption Mechanism in Microcompartments. *Phys. Rev. Lett.* **2014**, *112* (2).
8. Dwars, T.; Paetzold, E.; Oehme, G. Reactions in Micellar Systems. *Angew. Chem. Int. Ed.* **2005**, *44* (44), 7174–7199.
9. Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. "On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem. Int. Ed.* **2005**, *44* (21), 3275–3279.
10. Wu, D.-Y.; Zhang, L.-P.; Wu, L.-Z.; Wang, B.; Tung, C.-H. Water-in-Oil Microemulsions as Microreactors to Control the Regioselectivity in the Photocycloaddition of 9-Substituted Anthracenes. *Tetrahedron Lett.* **2002**, *43* (7), 1281–1283.
11. Currie, F.; Holmberg, K.; Westman, G. Regioselective Nitration of Phenols and Anisols in Microemulsion. *Colloids Surf. Physicochem. Eng. Asp.* **2001**, *182* (1–3), 321–327.
12. Jaeger, D. A.; Su, D.; Zafar, A.; Piknova, B.; Hall, S. B. Regioselectivity Control in Diels−Alder Reactions of Surfactant 1,3-Dienes with Surfactant Dienophiles. *J. Am. Chem. Soc.* **2000**, *122* (12), 2749–2757.
13. Jaeger, D. A.; Wang, J. Micellar Effects on the Regiochemistry of a Diels-Alder Reaction. *Tetrahedron Lett.* **1992**, *33* (43), 6415–6418.
14. Currie, F.; Holmberg, K.; Westman, G. Bromination in Microemulsion. *Colloids Surf. Physicochem. Eng. Asp.* **2003**, *215* (1–3), 51–54.
15. La Sorella, G.; Strukul, G.; Scarso, A. Recent Advances in Catalysis in Micellar Media. *Green Chem.* **2015**, *17* (2), 644–683.
16. Xie, J.; Jiang, J.; Davoodi, P.; Srinivasan, M. P.; Wang, C.-H. Electrohydrodynamic Atomization: A Two-Decade Effort to Produce and Process Micro-/Nanoparticulate Materials. *Chem. Eng. Sci.* **2015**, *125*, 32–57.

17. Xu, S.-C.; Qin, C.-C.; Yu, M.; Dong, R.-H.; Yan, X.; Zhao, H.; Han, W.-P.; Zhang, H.-D.; Long, Y.-Z. A Battery-Operated Portable Handheld Electrospinning Apparatus. *Nanoscale* **2015**, *7* (29), 12351–12355.

18. Bahr, U.; Pfenninger, A.; Karas, M.; Stahl, B. High-Sensitivity Analysis of Neutral Underivatized Oligosaccharides by Nanoelectrospray Mass Spectrometry. *Anal. Chem.* **1997**, *69* (22), 4530–4535.

19. Oss, M.; Kruve, A.; Herodes, K.; Leito, I. Electrospray Ionization Efficiency Scale of Organic Compounds. *Anal. Chem.* **2010**, *82* (7), 2865–2872.

20. Yao, H.; Steill, J. D.; Oomens, J.; Jockusch, R. A. Infrared Multiple Photon Dissociation Action Spectroscopy and Computational Studies of Mass-Selected Gas-Phase Fluorescein and 2′,7′-Dichlorofluorescein Ions. *J. Phys. Chem. A* **2011**, *115* (34), 9739–9747.

21. Warnke, S.; Seo, J.; Boschmans, J.; Sobott, F.; Scrivens, J. H.; Bleiholder, C.; Bowers, M. T.; Gewinner, S.; Schöllkopf, W.; Pagel, K.; von Helden, G. Protomers of Benzocaine: Solvent and Permittivity Dependence. *J. Am. Chem. Soc.* **2015**, *137* (12), 4236–4242.

22. Schmidt, J.; Meyer, M. M.; Spector, I.; Kass, S. R. Infrared Multiphoton Dissociation Spectroscopy Study of Protonated *p* -Aminobenzoic Acid: Does Electrospray Ionization Afford the Amino- or Carboxy-Protonated Ion? *J. Phys. Chem. A* **2011**, *115* (26), 7625–7632.

23. Chang, T. M.; Prell, J. S.; Warrick, E. R.; Williams, E. R. Where's the Charge? Protonation Sites in Gaseous Ions Change with Hydration. *J. Am. Chem. Soc.* **2012**, *134* (38), 15805–15813.

24. Boschmans, J.; Jacobs, S.; Williams, J. P.; Palmer, M.; Richardson, K.; Giles, K.; Lapthorn, C.; Herrebout, W. A.; Lemière, F.; Sobott, F. Combining Density Functional Theory (DFT) and Collision Cross-Section (CCS) Calculations to Analyze the Gas-Phase Behaviour of Small Molecules and Their Protonation Site Isomers. *The Analyst* **2016**, *141* (13), 4044–4054.

25. Schröder, D.; Buděšínský, M.; Roithová, J. Deprotonation of *p*- Hydroxybenzoic Acid: Does Electrospray Ionization Sample Solution or Gas-Phase Structures? *J. Am. Chem. Soc.* **2012**, *134* (38), 15897–15905.

26. Steill, J. D.; Oomens, J. Gas-Phase Deprotonation of *p* -Hydroxybenzoic Acid Investigated by IR Spectroscopy: Solution-Phase Structure Is Retained upon ESI. *J. Am. Chem. Soc.* **2009**, *131* (38), 13570–13571.

27. Xia, H.; Attygalle, A. B. Effect of Electrospray Ionization Source Conditions on the Tautomer Distribution of Deprotonated *p* -Hydroxybenzoic Acid in the Gas Phase. *Anal. Chem.* **2016**, *88* (11), 6035–6043.

28. Perry, R. H.; Splendore, M.; Chien, A.; Davis, N. K.; Zare, R. N. Detecting Reaction Intermediates in Liquids on the Millisecond Time Scale Using Desorption Electrospray Ionization. *Angew. Chem. Int. Ed.* **2011**, *50* (1), 250–254.

29. Yan, X.; Cheng, H.; Zare, R. N. Two-Phase Reactions in Microdroplets without the Use of Phase-Transfer Catalysts. *Angew. Chem. Int. Ed.* **2017**, *56* (13), 3562–3565.

30. Bain, R. M.; Sathyamoorthi, S.; Zare, R. N. "On-Droplet" Chemistry: The Cycloaddition of Diethyl Azodicarboxylate and Quadricyclane. *Angew. Chem. Int. Ed.* **2017**, *56* (47), 15083–15087.

31. Lee, J. K.; Banerjee, S.; Nam, H. G.; Zare, R. N. Acceleration of Reaction in Charged Microdroplets. *Q. Rev. Biophys.* **2015**, *48* (04), 437–444.

32. Banerjee, S.; Zare, R. N. Syntheses of Isoquinoline and Substituted Quinolines in Charged Microdroplets. *Angew. Chem. Int. Ed.* **2015**, *54* (49), 14795–14799.

33. Banerjee, S.; Gnanamani, E.; Yan, X.; Zare, R. N. Can All Bulk-Phase Reactions Be Accelerated in Microdroplets? *The Analyst* **2017**, *142* (9), 1399–1402.

34. Müller, T.; Badu-Tawiah, A.; Cooks, R. G. Accelerated Carbon□Carbon Bond-Forming Reactions in Preparative Electrospray. *Angew. Chem. Int. Ed.* **2012**, *51* (47), 11832–11835.

35. Bain, R. M.; Pulliam, C. J.; Cooks, R. G. Accelerated Hantzsch Electrospray Synthesis with Temporal Control of Reaction Intermediates. *Chem. Sci.* **2015**, *6* (1), 397–401.

36. Bain, R. M.; Pulliam, C. J.; Ayrton, S. T.; Bain, K.; Cooks, R. G. Accelerated Hydrazone Formation in Charged Microdroplets: Accelerated Reactions in Charged Microdroplets. *Rapid Commun. Mass Spectrom.* **2016**, *30* (16), 1875–1878.

37. Wleklinski, M.; Falcone, C. E.; Loren, B. P.; Jaman, Z.; Iyer, K.; Ewan, H. S.; Hyun, S.-H.; Thompson, D. H.; Cooks, R. G. Can Accelerated Reactions in Droplets Guide Chemistry at Scale? *Eur. J. Org. Chem.* **2016**, *2016* (33), 5480–5484.

38. Rashid, S.; Mayer, P. M. Dual-Electrospray Synthesis: A Method of Studying Unique Coordination Complexes in the Gas Phase. *Int. J. Mass Spectrom.* **2018**, *429*, 107–114.

39. Lai, Y.-H.; Sathyamoorthi, S.; Bain, R. M.; Zare, R. N. Microdroplets Accelerate Ring Opening of Epoxides. *J. Am. Soc. Mass Spectrom.* **2018**, *29* (5), 1036–1043.

40. Iyer, K.; Yi, J.; Bogdan, A.; Talaty, N.; Djuric, S. W.; Cooks, R. G. Accelerated Multi-Reagent Copper Catalysed Coupling Reactions in Micro Droplets and Thin Films. *React. Chem. Eng.* **2018**, *3* (2), 206–209.

41. Yan, X.; Bain, R. M.; Cooks, R. G. Organic Reactions in Microdroplets: Reaction Acceleration Revealed by Mass Spectrometry. *Angew. Chem. Int. Ed.* **2016**, *55* (42), 12960–12972.

42. Wei, Z.; Wleklinski, M.; Ferreira, C.; Cooks, R. G. Reaction Acceleration in Thin Films with Continuous Product Deposition for Organic Synthesis. *Angew. Chem. Int. Ed.* **2017**, *56* (32), 9386–9390.

43. Girod, M.; Moyano, E.; Campbell, D. I.; Cooks, R. G. Accelerated Bimolecular Reactions in Microdroplets Studied by Desorption Electrospray Ionization Mass Spectrometry. *Chem Sci* **2011**, *2* (3), 501–510.

44. Nam, I.; Lee, J. K.; Nam, H. G.; Zare, R. N. Abiotic Production of Sugar Phosphates and Uridine Ribonucleoside in Aqueous Microdroplets. *Proc. Natl. Acad. Sci.* **2017**, *114* (47), 12396–12400.

45. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2006.

46. Cochran, R. E.; Ryder, O. S.; Grassian, V. H.; Prather, K. A. Sea Spray Aerosol: The Chemical Link between the Oceans, Atmosphere, and Climate. *Acc. Chem. Res.* **2017**, *50* (3), 599–604.

47. Tuck, A. The Role of Atmospheric Aerosols in the Origin Of Life. *Surv. Geophys.* **2002**, *23*, 379–409.

48. Mmereki, B. T.; Donaldson, D. J.; Gilman, J. B.; Eliason, T. L.; Vaida, V. Kinetics and Products of the Reaction of Gas-Phase Ozone with Anthracene Adsorbed at the Air–Aqueous Interface. *Atmos. Environ.* **2004**, *38* (36), 6091–6103.

49. Scott, C. E.; Arnold, S. R.; Monks, S. A.; Asmi, A.; Paasonen, P.; Spracklen, D. V. Substantial Large-Scale Feedbacks between Natural Aerosols and Climate. *Nat. Geosci.* **2018**, *11* (1), 44–48.

50. Rastelli, E.; Corinaldesi, C.; Dell'Anno, A.; Lo Martire, M.; Greco, S.; Cristina Facchini, M.; Rinaldi, M.; O'Dowd, C.; Ceburnis, D.; Danovaro, R. Transfer of Labile Organic Matter and Microbes from the Ocean Surface to the Marine Aerosol: An Experimental Approach. *Sci. Rep.* **2017**, *7* (1).

51. High-Voltage Generator from e-Bay https://www.ebay.com/itm/DC-3V-to-7KV-7000V-Boost-Step-up-Power-Module-High-voltage-Generator-/111146930592 (accessed May 20, 2019).

52. Ramakrishna, E.; Dev, K.; Maurya, S. W.; Siddiqui, I. R.; Maurya, R. Hypervalent Iodine (III)-Mediated Oxidation of Aryl Sulfonylhydrazones: A Facile Synthesis of N-Aroyl-N′-Acyl Arylsulfonylhydrazides. *Tetrahedron Lett.* **2017**, *58* (6), 570–573.

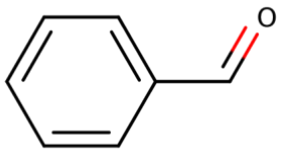
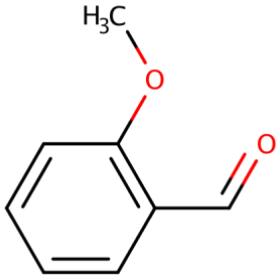
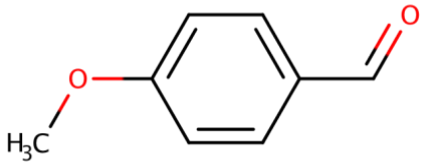
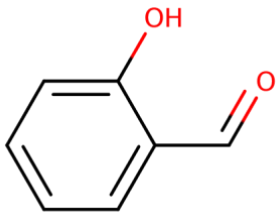
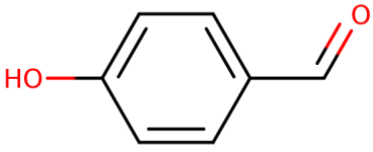
53. Bunnett, J. F.; Davis, G. T. The Nucleophilic Reactivity of Aniline, Hydrazine and Phenoxide Ion toward 2,4-Dinitrochlorobenzene [1]. *J. Am. Chem. Soc.* **1958**, *80* (16), 4337–4339.

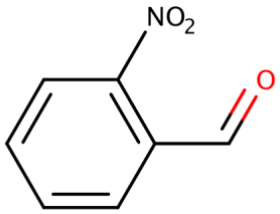
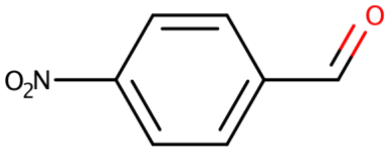
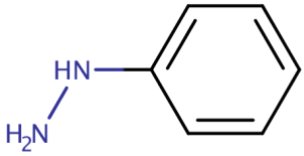
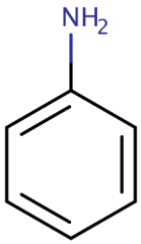
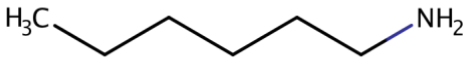
54. Stecker Synthesis on Organic Chemistry Portal https://www.organic-chemistry.org/namedreactions/strecker-synthesis.shtm (accessed May 21, 2019).

Supplementary Information

SI 1. Compounds

Table SI 1.1. The compounds used in this study with their CAS nr, *m/z* value and structure.

Name	CAS number	*m/z* value	Structure
Benzaldehyde	100-52-7	107	
2-Methoxybenzaldehyde	135-02-4	137	
4-Methoxybenzaldehyde	123-11-5	137	
2-Hydroxybenzaldehyde	90-02-8	123	
4-Hydroxybenzaldehyde	123-08-0	123	

Name	CAS number	*m/z* value	Structure
2-Nitrobenzaldehyde	552-89-6	152	
4-Nitrobenzaldehyde	555-16-8	152	
Hydrazine	302-01-2	33	
Phenylhydrazine	100-63-0	109	
Aniline	62-53-3	94	
Hexylamine	111-26-2	102	

SI 2. Results

All reactions were performed according to the experimental methods described in sections 3.2 and 3.3. Here I represent the results on a flowchart, where the most intensive m/z values of MS1 and their MS2 fragment ion m/z values are shown together with proposed structures. The structures of MS1 are proposed based on the fragment ions' m/z values and checked occasionally with NMR spectroscopy. Under every reaction, reaction products from bulk phase reaction (vial) and from charged droplets (collected from the counter electrode and from the beaker separately) are shown in separate flowcharts.

Reactions with Hydrazine

Table SI 2.1. Results for the reaction between hydrazine and benzaldehyde in bulk phase.

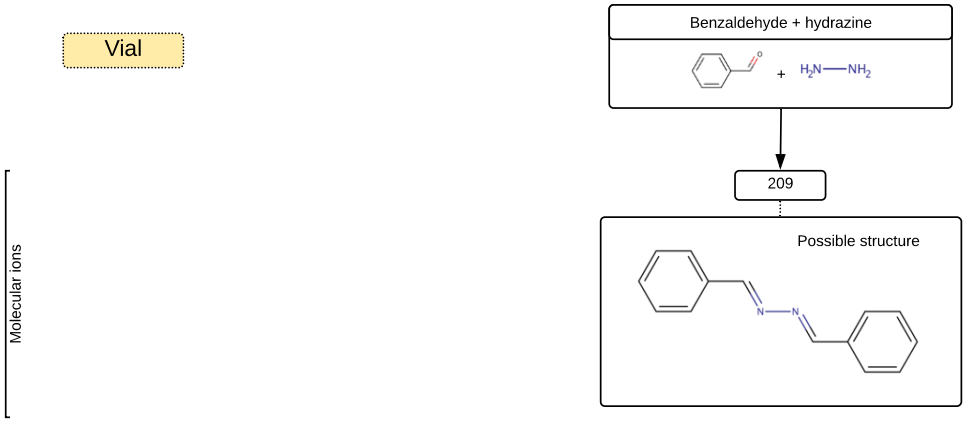


Table SI 2.2. Results for the reaction between hydrazine and benzaldehyde in charged droplets (collected from the beaker).

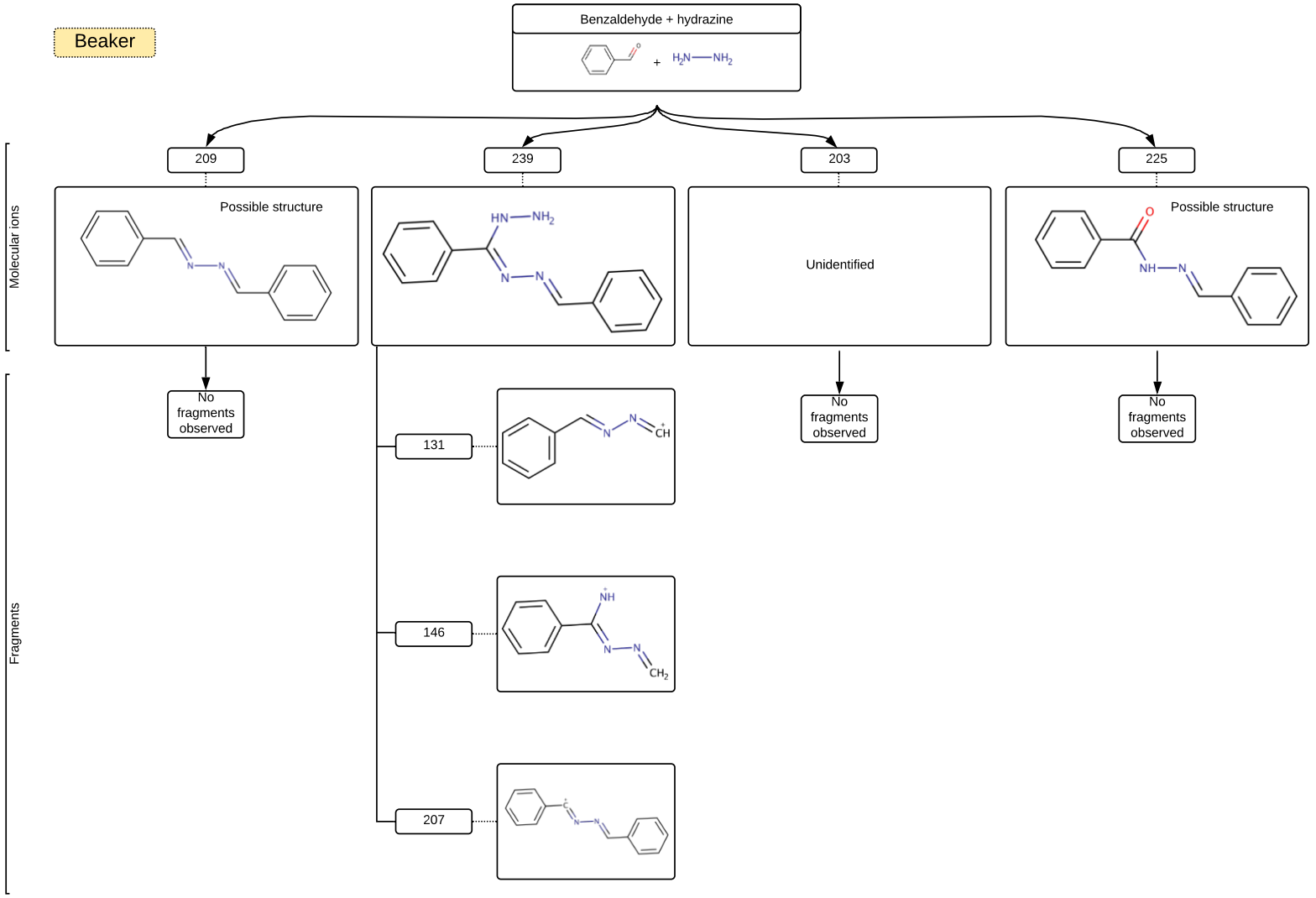


Table SI 2.3. Results for the reaction between hydrazine and benzaldehyde in charged droplets (collected from the counter electrode).

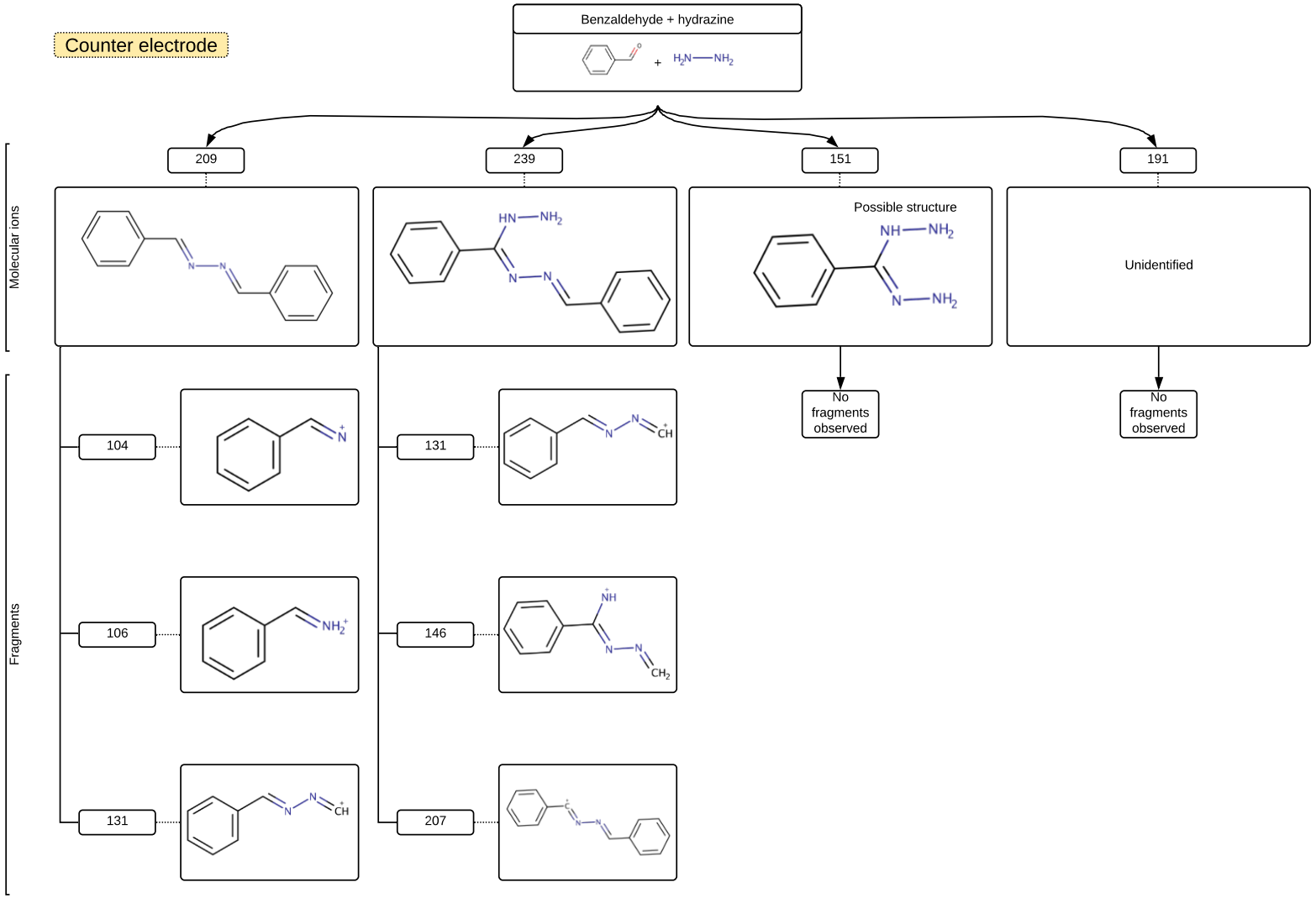


Table SI 2.4. Results for the reaction between hydrazine and 2-methoxybenzaldehyde in bulk phase.

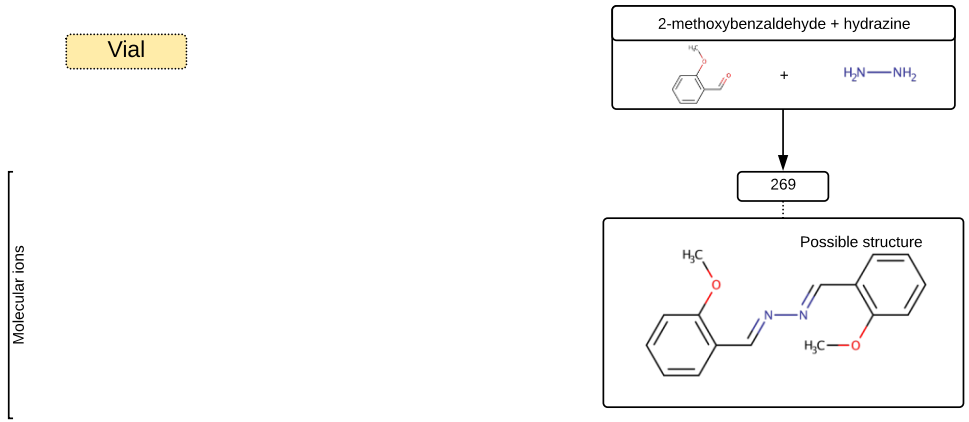


Table SI 2.5. Results for the reaction between hydrazine and 2-methoxybenzaldehyde in charged droplets (collected from the beaker).

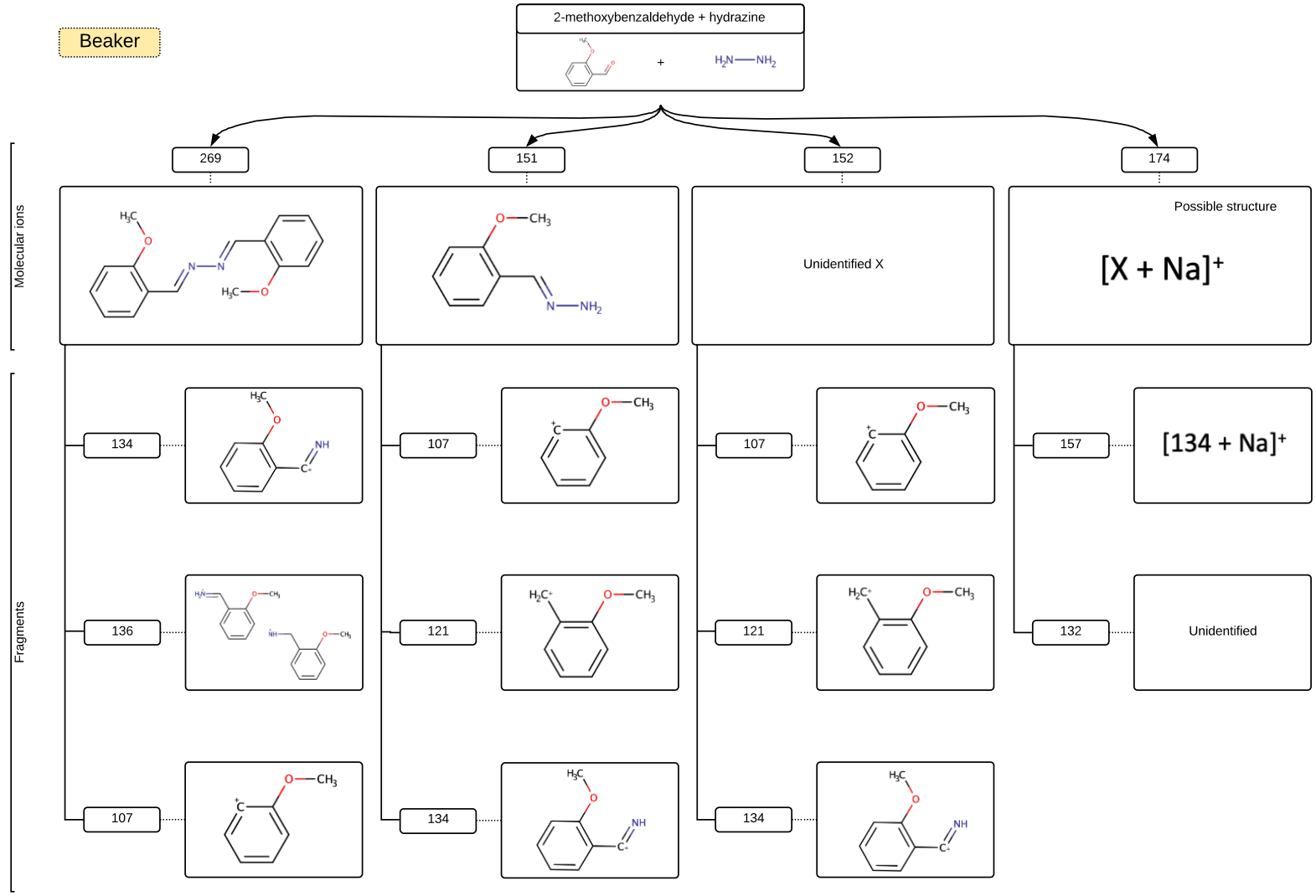


Table SI 2.6. Results for the reaction between hydrazine and 2-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

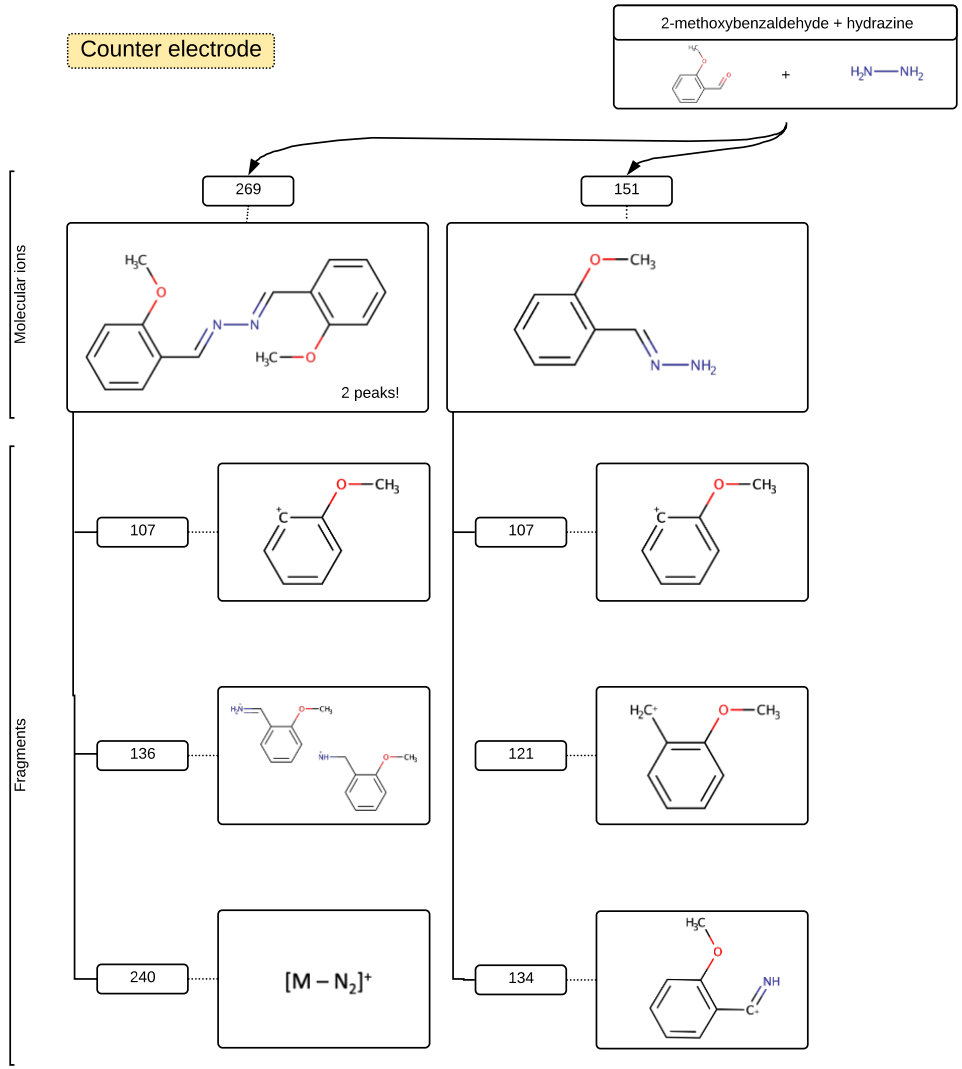


Table SI 2.7. Results for the reaction between hydrazine and 4-methoxybenzaldehyde in bulk phase.

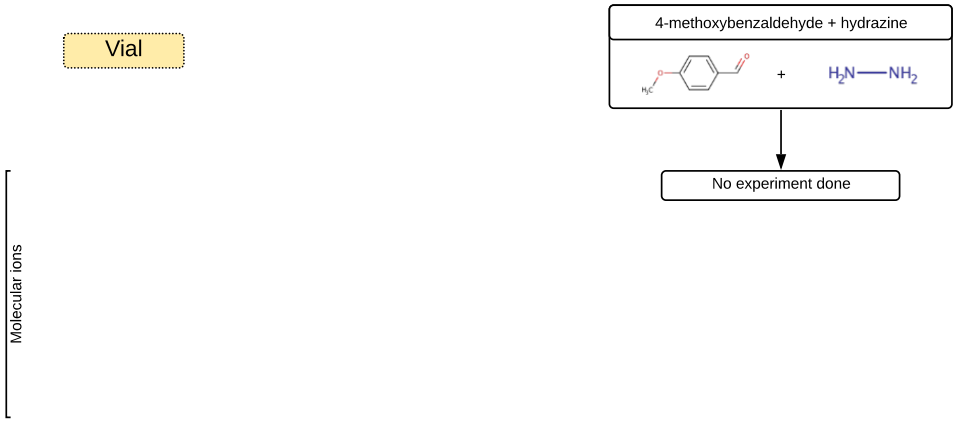


Table SI 2.8. Results for the reaction between hydrazine and 4-methoxybenzaldehyde in charged droplets (collected from the beaker).

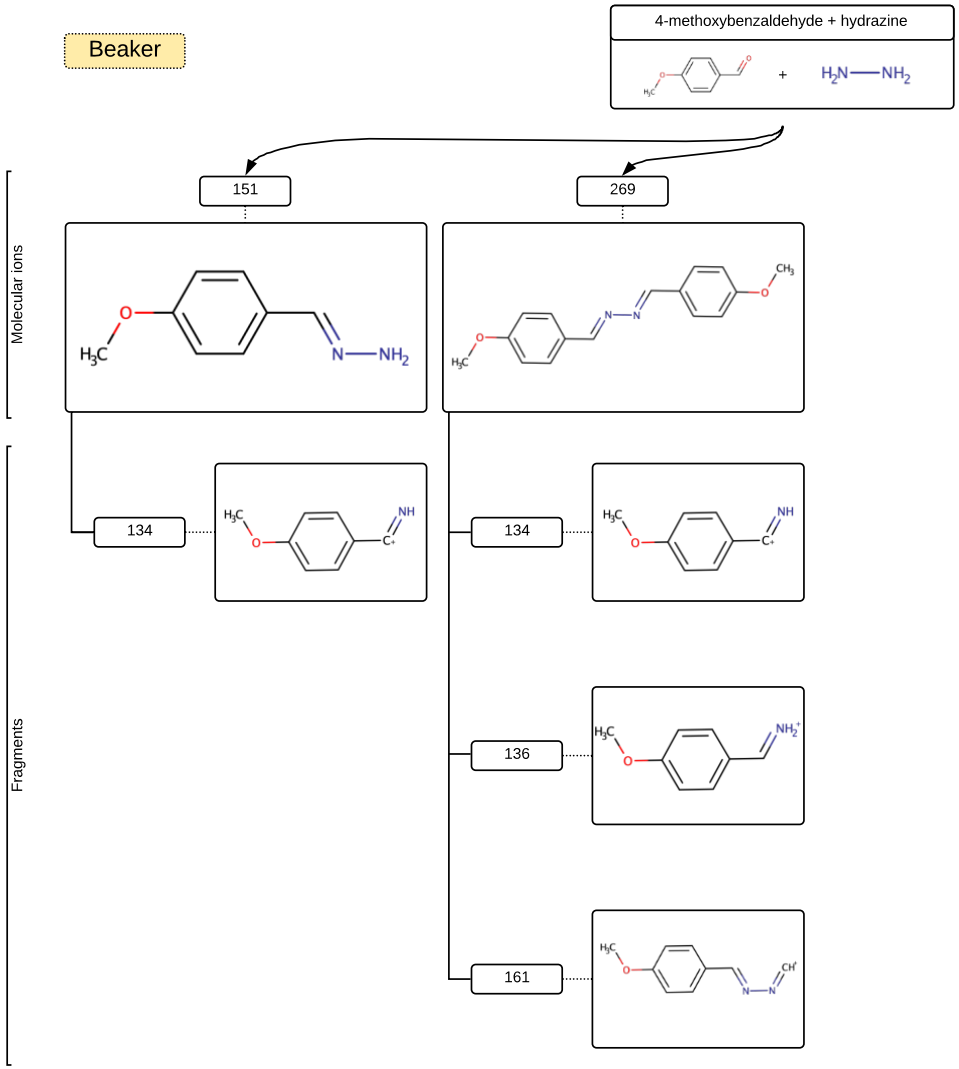


Table SI 2.9. Results for the reaction between hydrazine and 4-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

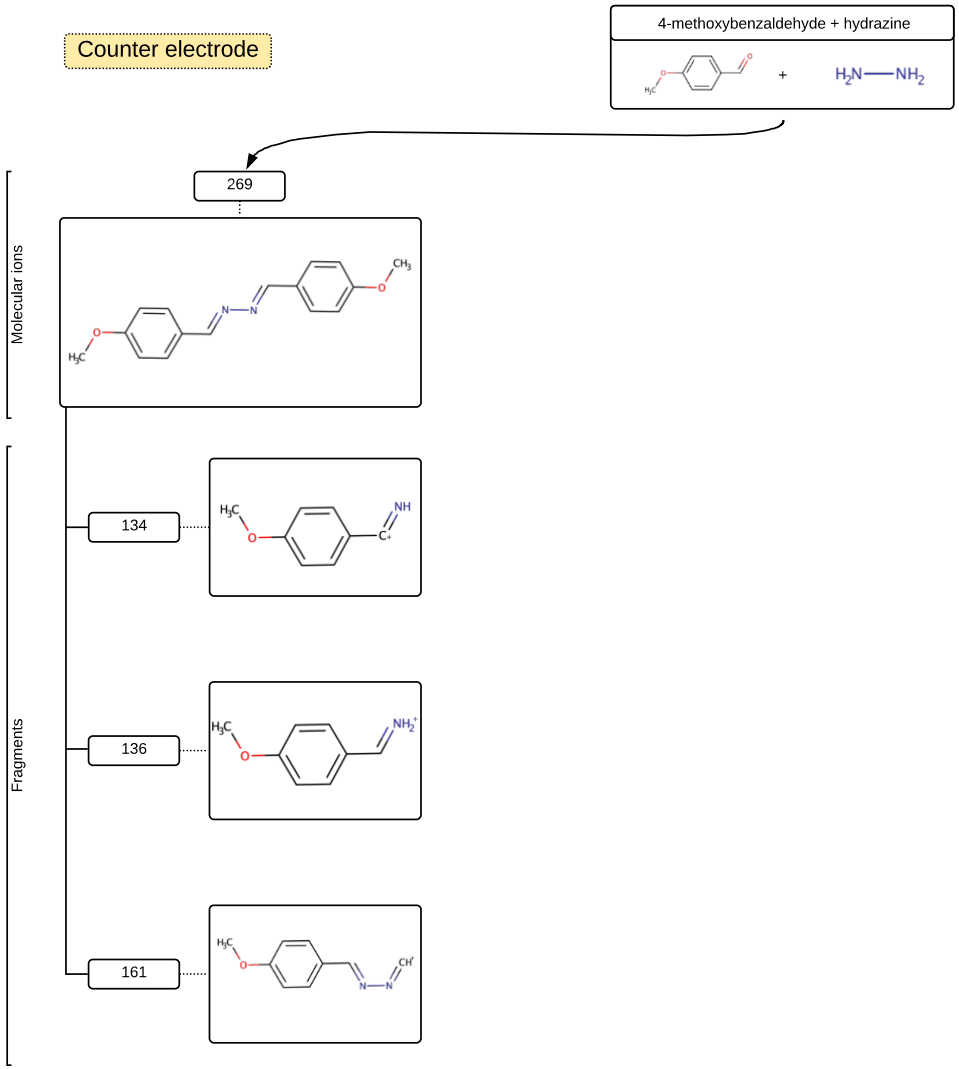


Table SI 2.10. Results for the reaction between hydrazine and 2-hydroxybenzaldehyde in bulk phase.

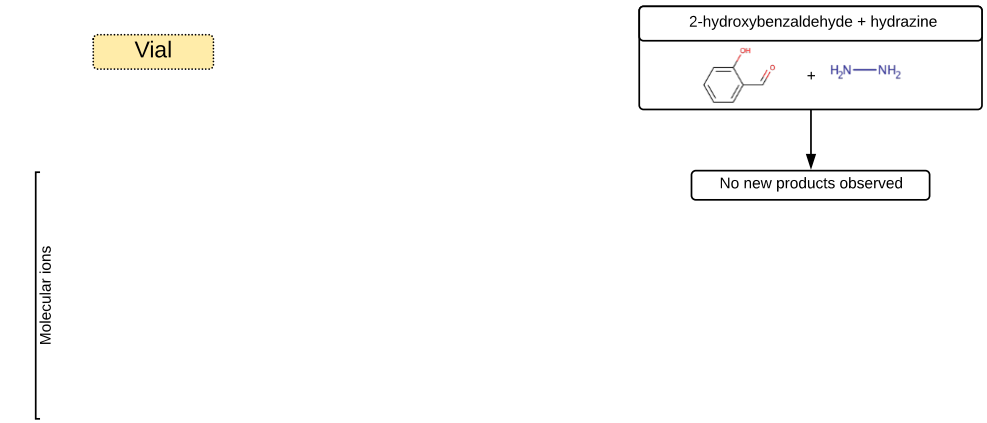


Table SI 2.11. Results for the reaction between hydrazine and 2-hydroxybenzaldehyde in charged droplets (collected from the beaker).

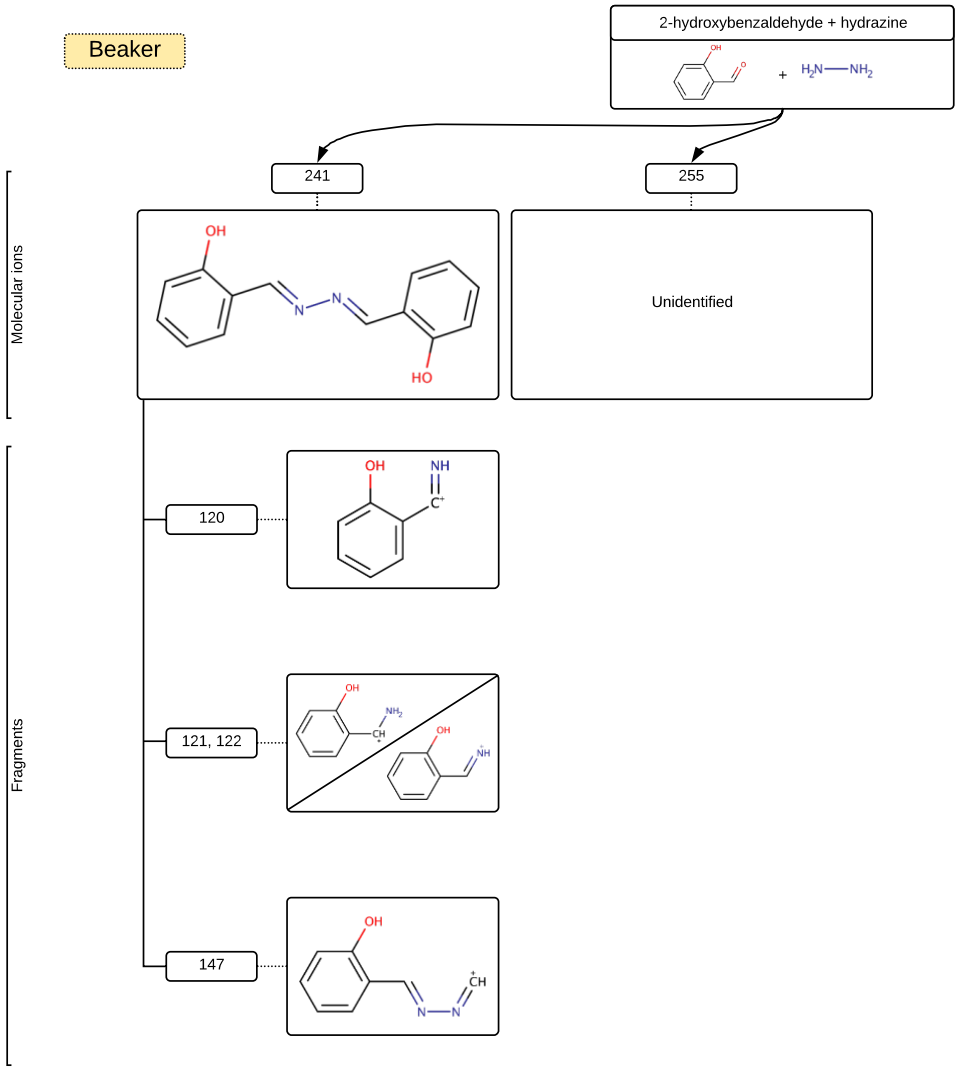


Table SI 2.12. Results for the reaction between hydrazine and 2-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

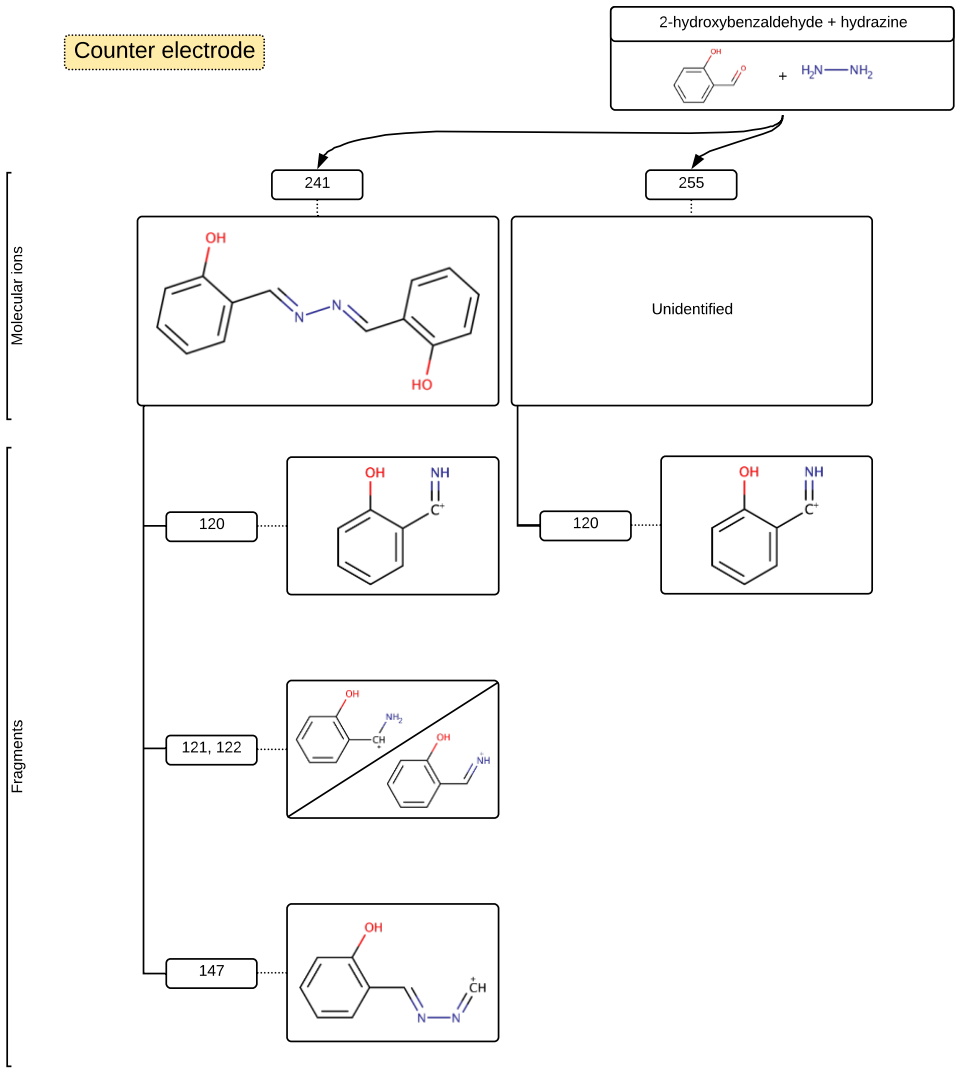


Table SI 2.13. Results for the reaction between hydrazine and 4-hydroxybenzaldehyde in bulk phase.

Table SI 2.14. Results for the reaction between hydrazine and 4-hydroxybenzaldehyde in charged droplets (collected from the beaker).

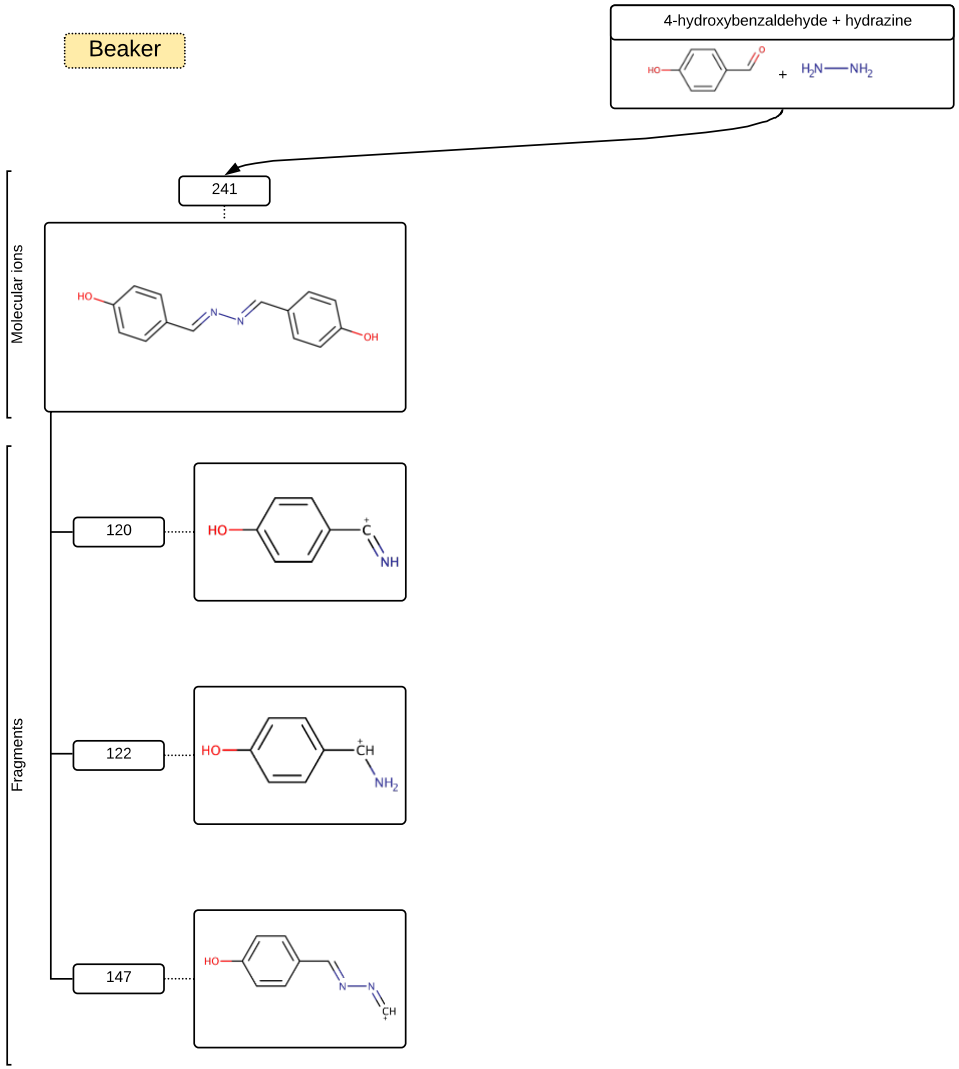


Table SI 2.15. Results for the reaction between hydrazine and 4-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

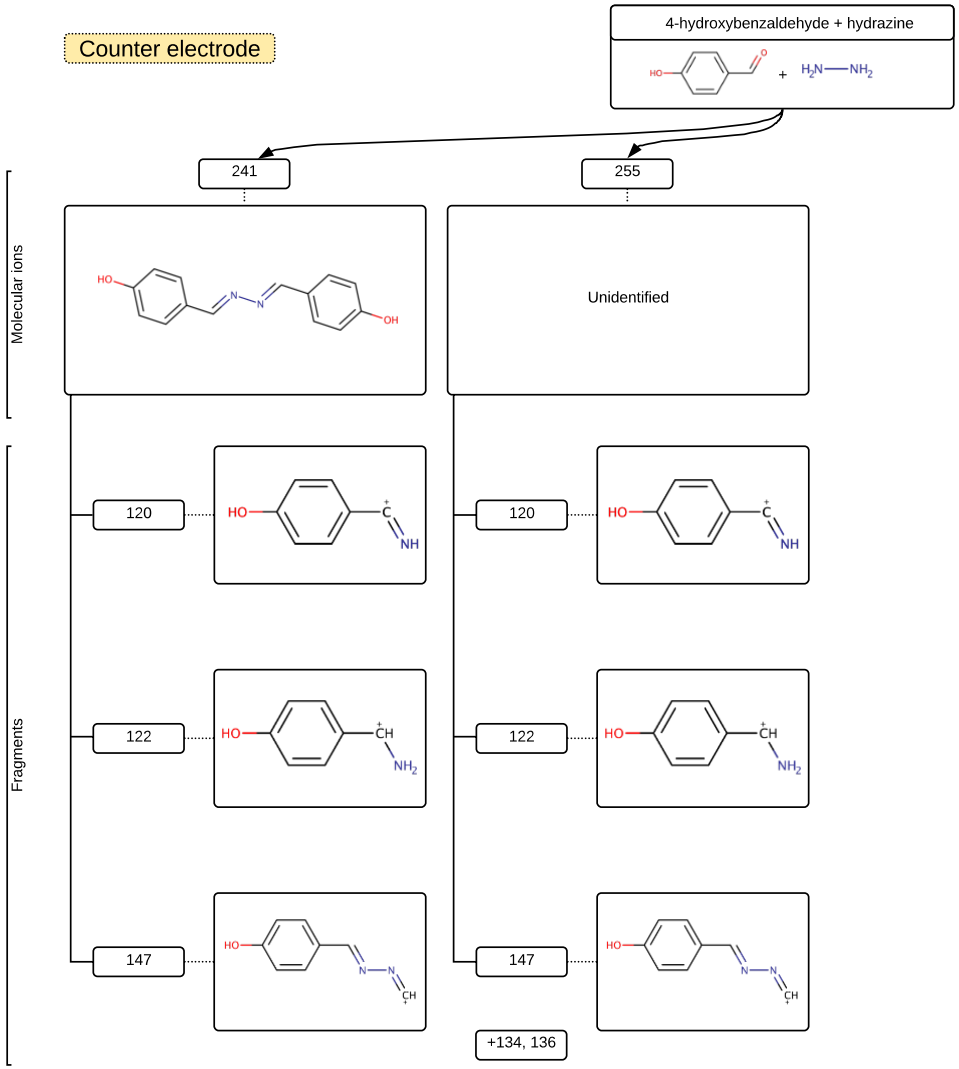


Table SI 2.16. Results for the reaction between hydrazine and 2-nitrobenzaldehyde in bulk phase.

Table SI 2.17. Results for the reaction between hydrazine and 2-nitrobenzaldehyde in charged droplets (collected from the beaker).

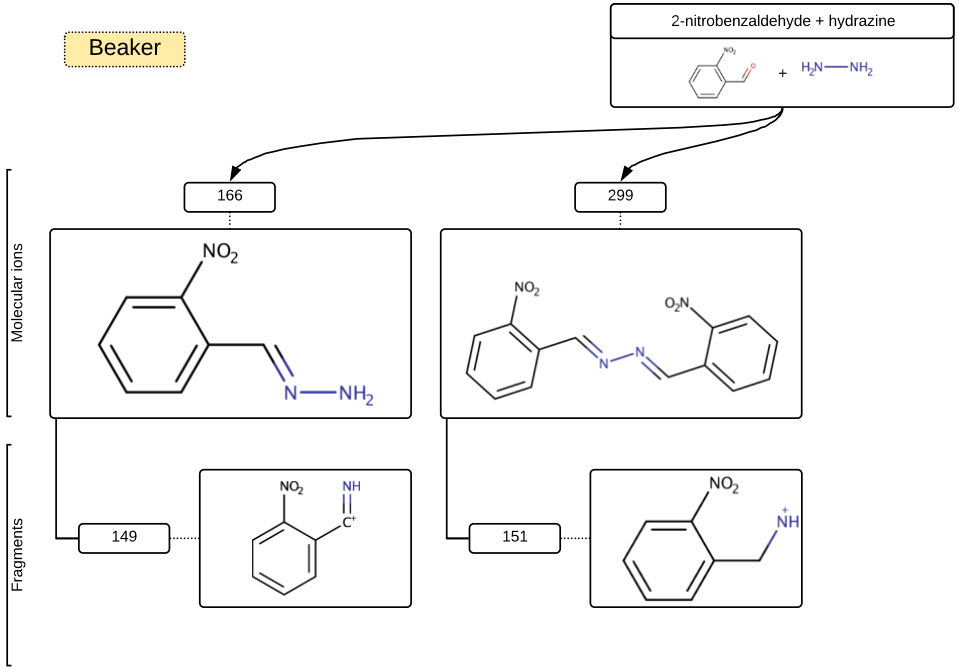


Table SI 2.18. Results for the reaction between hydrazine and 2-nitrobenzaldehyde in charged droplets (collected from the counter electrode).

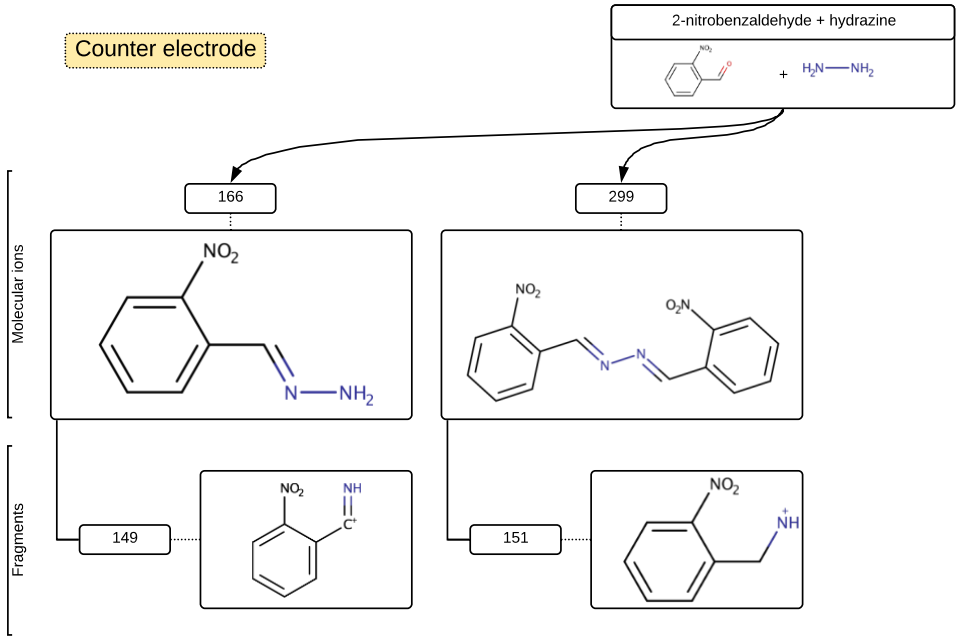


Table SI 2.19. Results for the reaction between hydrazine and 4-nitrobenzaldehyde in bulk phase.

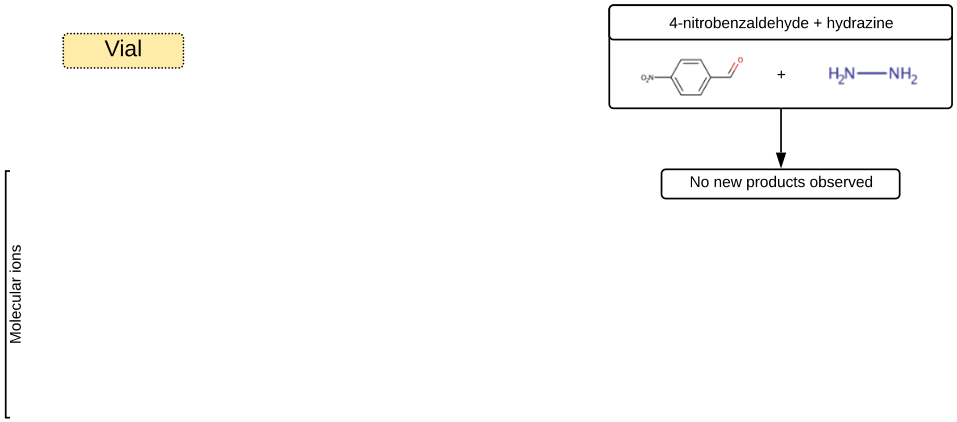


Table SI 2.20. Results for the reaction between hydrazine and 4-nitrobenzaldehyde in charged droplets (collected from the beaker).

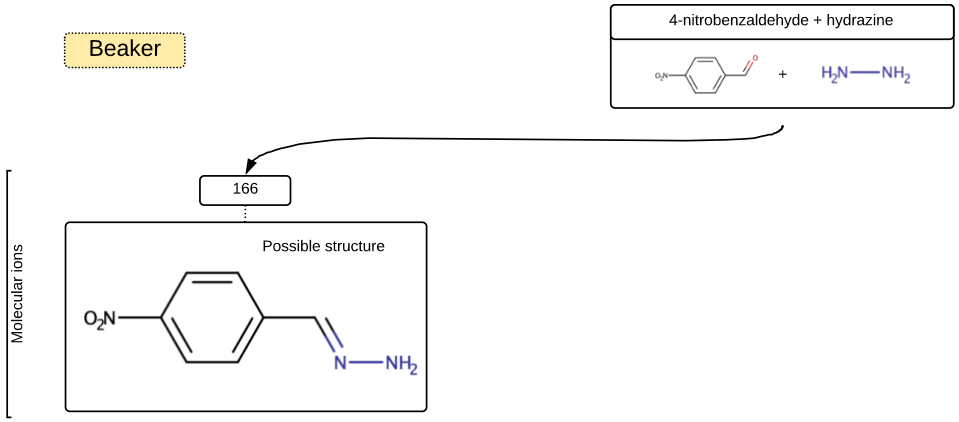
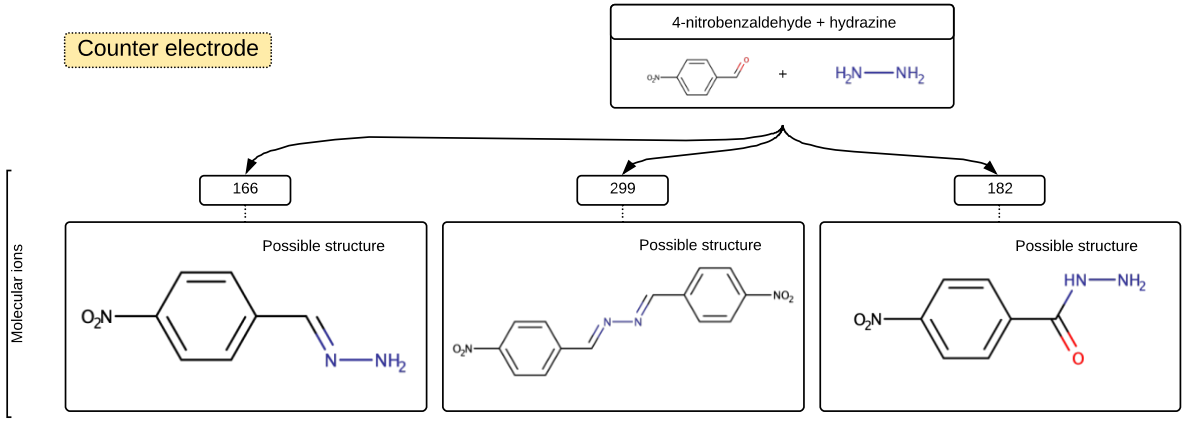


Table SI 2.21. Results for the reaction between hydrazine and 4-nitrobenzaldehyde in charged droplets (collected from the counter electrode).



Reactions with Phenylhydrazine

Table SI 2.22. Results for the reaction between phenylhydrazine and benzaldehyde in bulk phase.

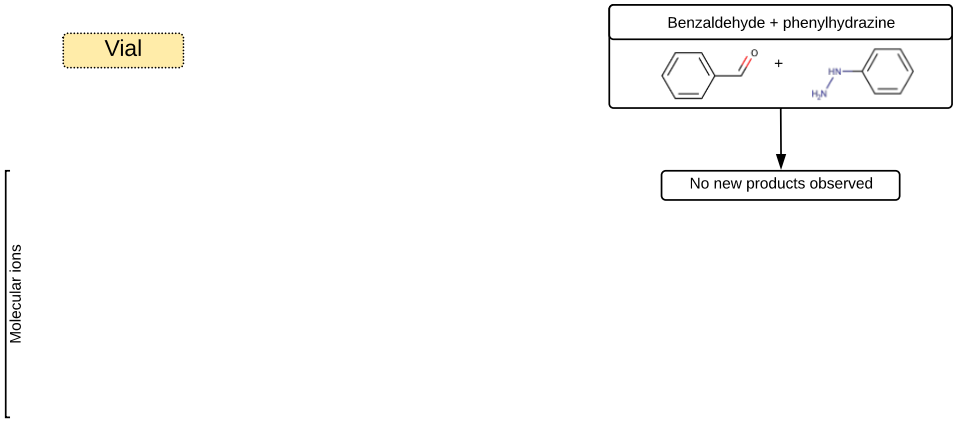


Table SI 2.23. Results for the reaction between phenylhydrazine and benzaldehyde in charged droplets (collected from the beaker).

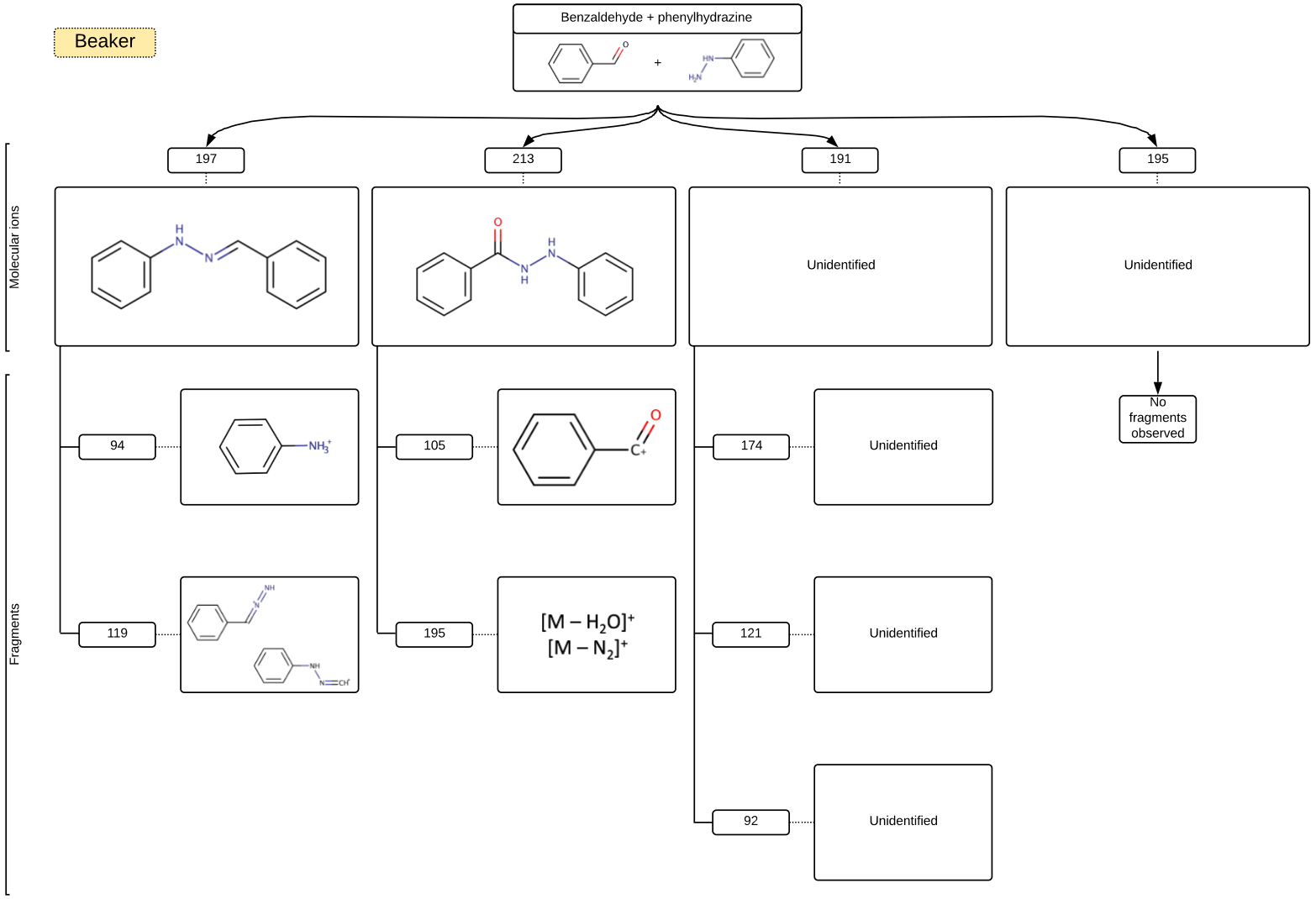


Table SI 2.24. Results for the reaction between phenylhydrazine and benzaldehyde in charged droplets (collected from the counter electrode).

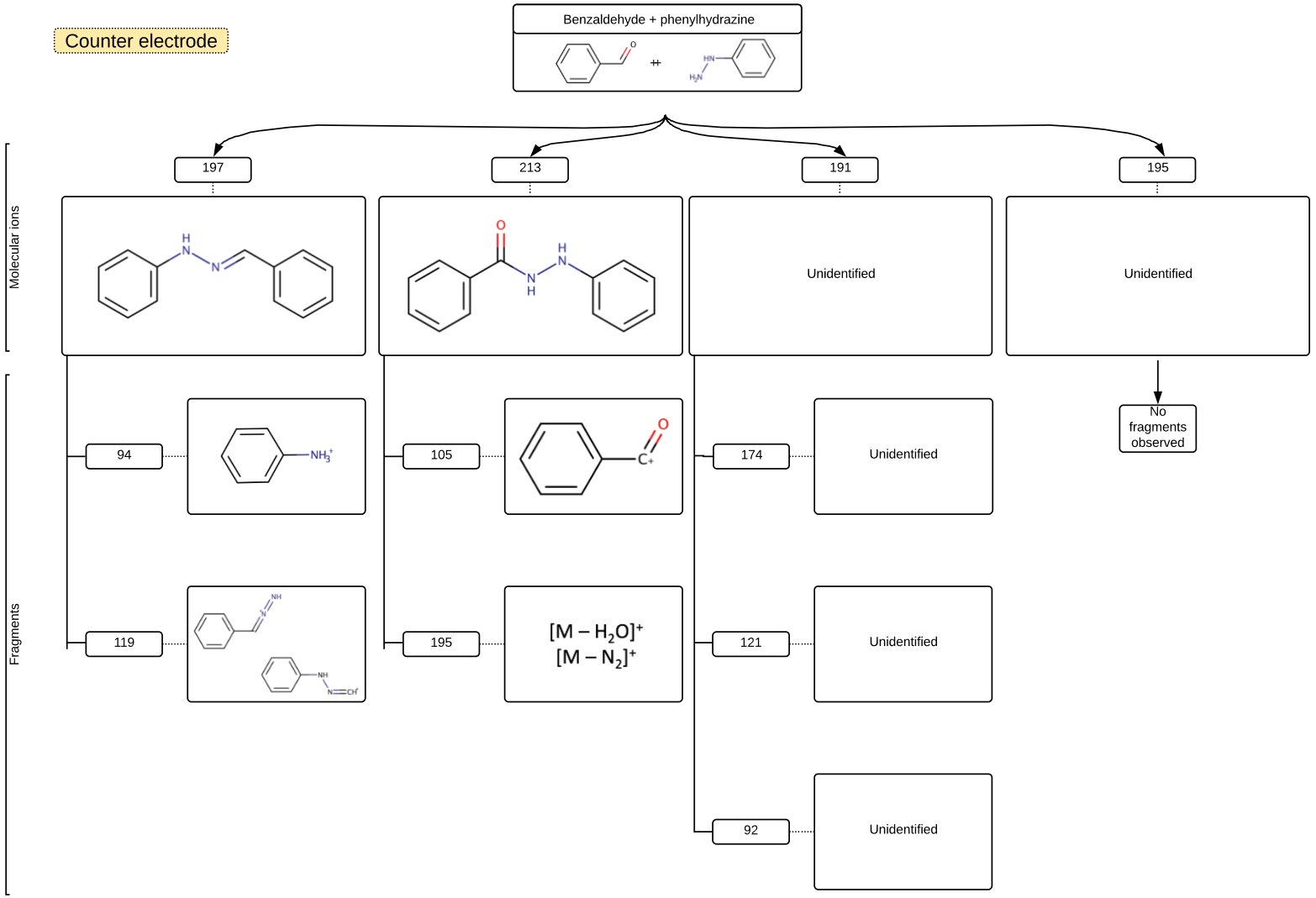


Table SI 2.25. Results for the reaction between phenylhydrazine and 2-methoxybenzaldehyde in bulk phase.

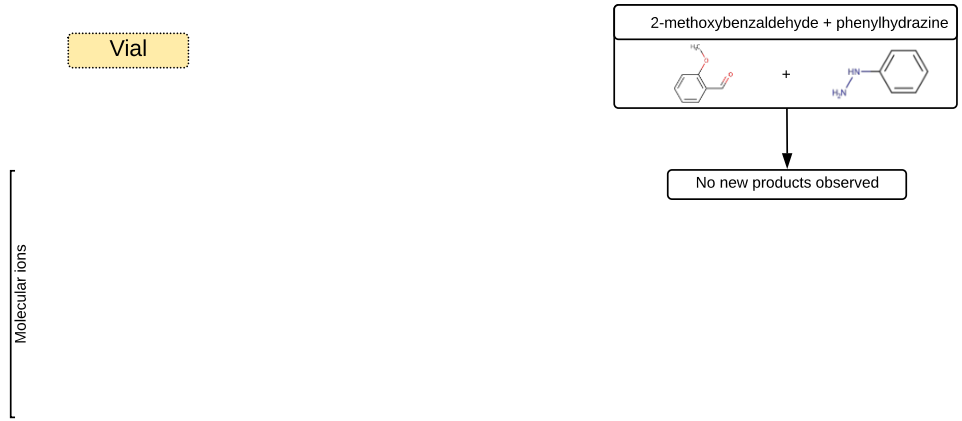


Table SI 2.26. Results for the reaction between phenylhydrazine and 2-methoxybenzaldehyde in charged droplets (collected from the beaker).

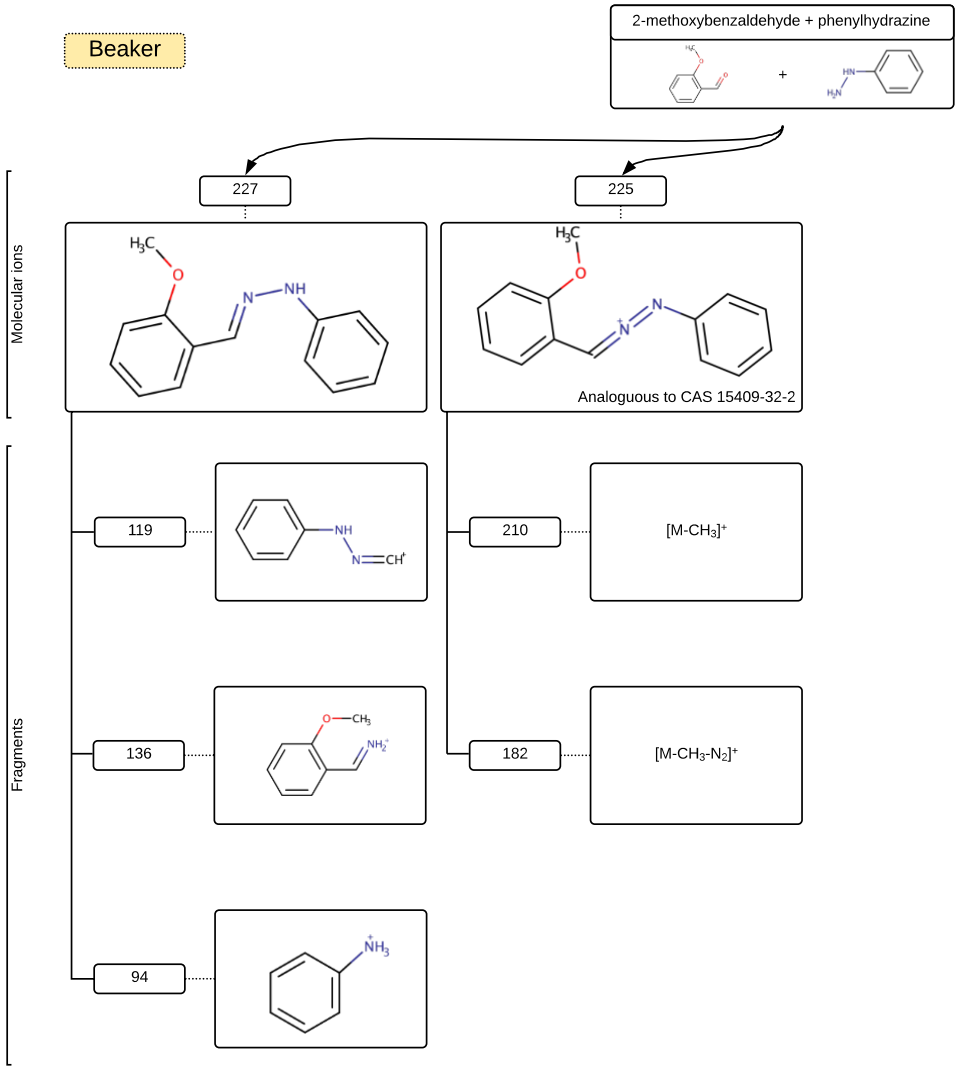


Table SI 2.27. Results for the reaction between phenylhydrazine and 2-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

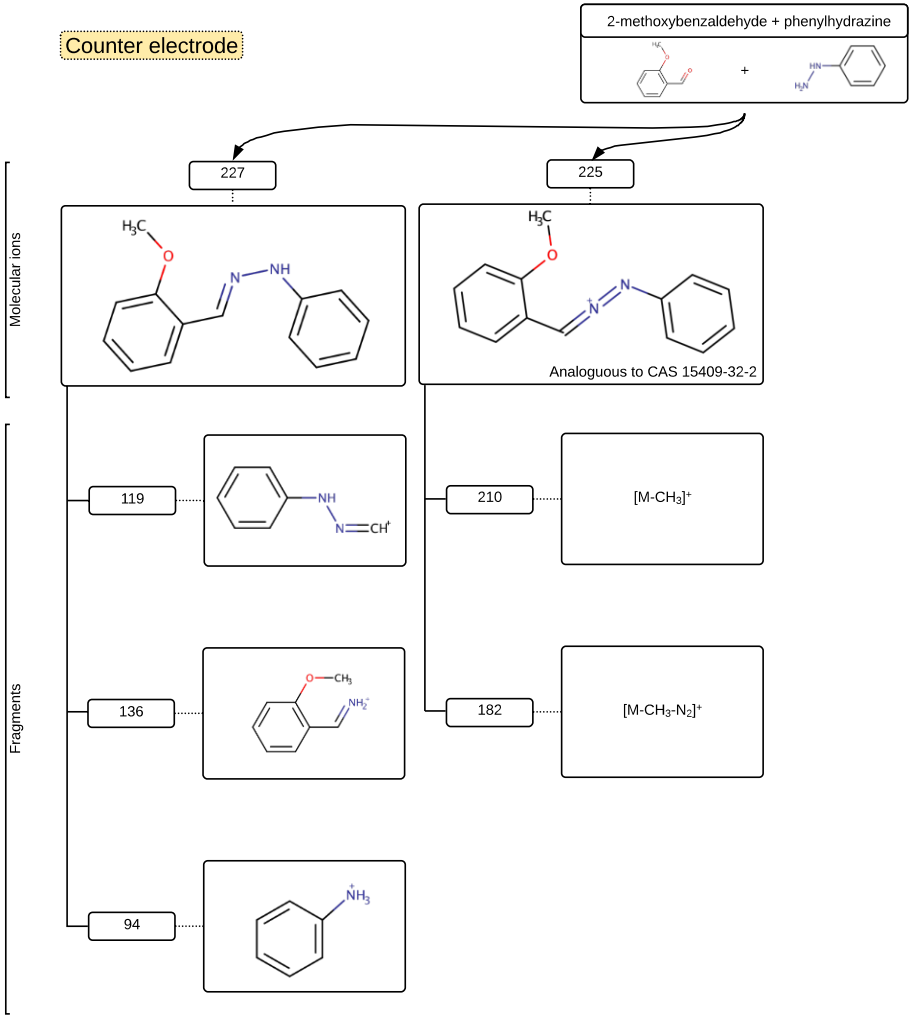


Table SI 2.28. Results for the reaction between phenylhydrazine and 4-methoxybenzaldehyde in bulk phase.

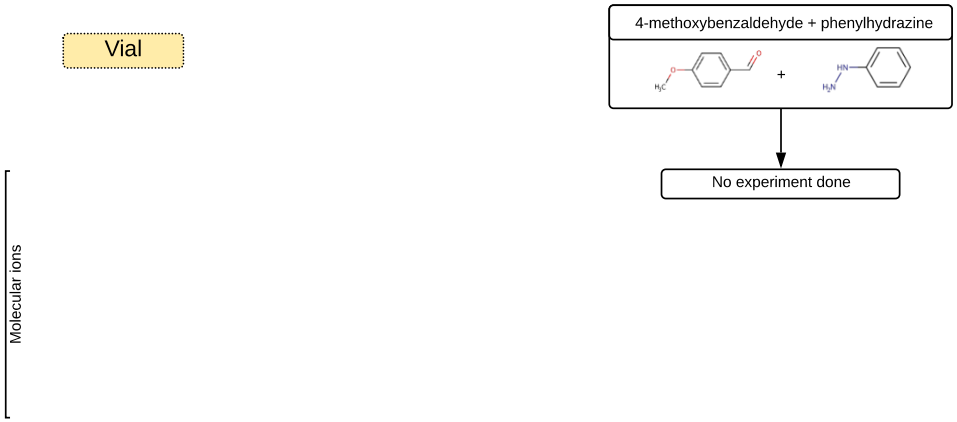


Table SI 2.29. Results for the reaction between phenylhydrazine and 4-methoxybenzaldehyde in charged droplets (collected from the beaker).

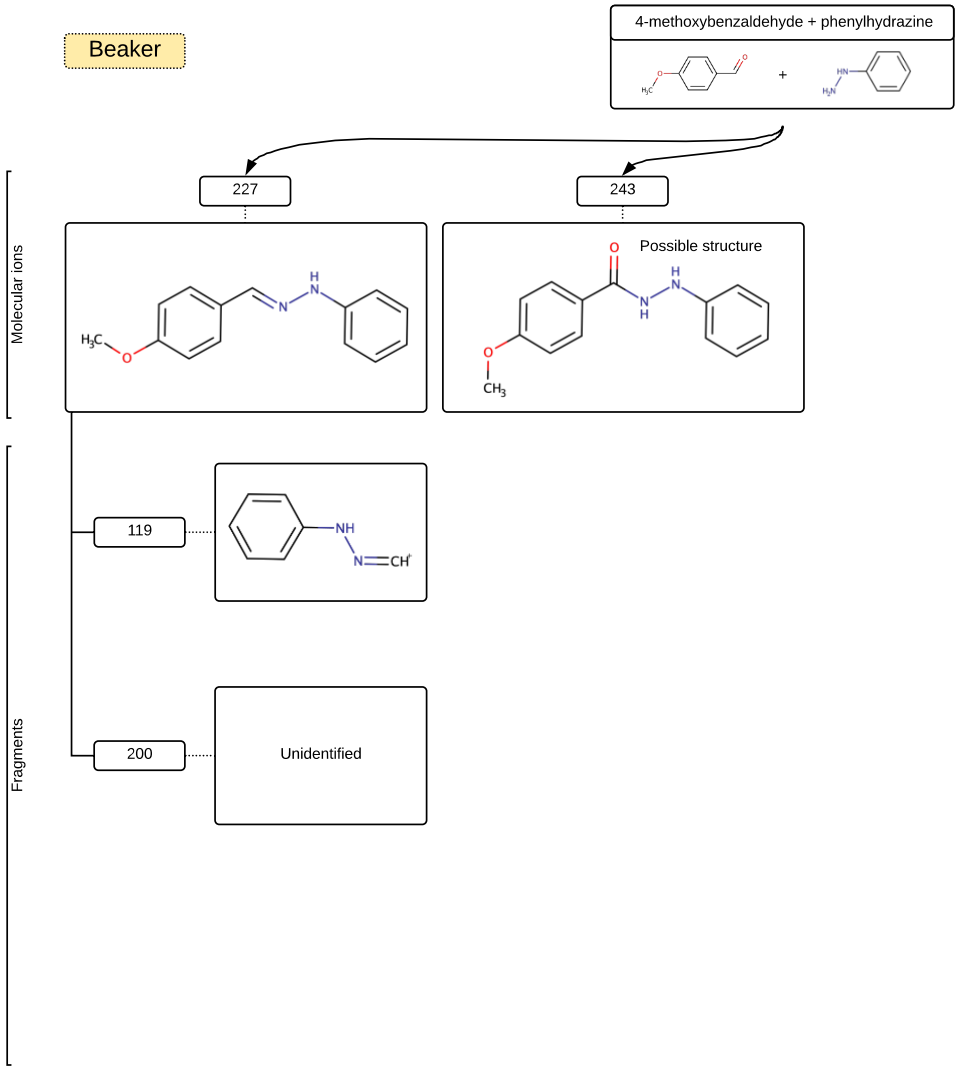


Table SI 2.30. Results for the reaction between phenylhydrazine and 4-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

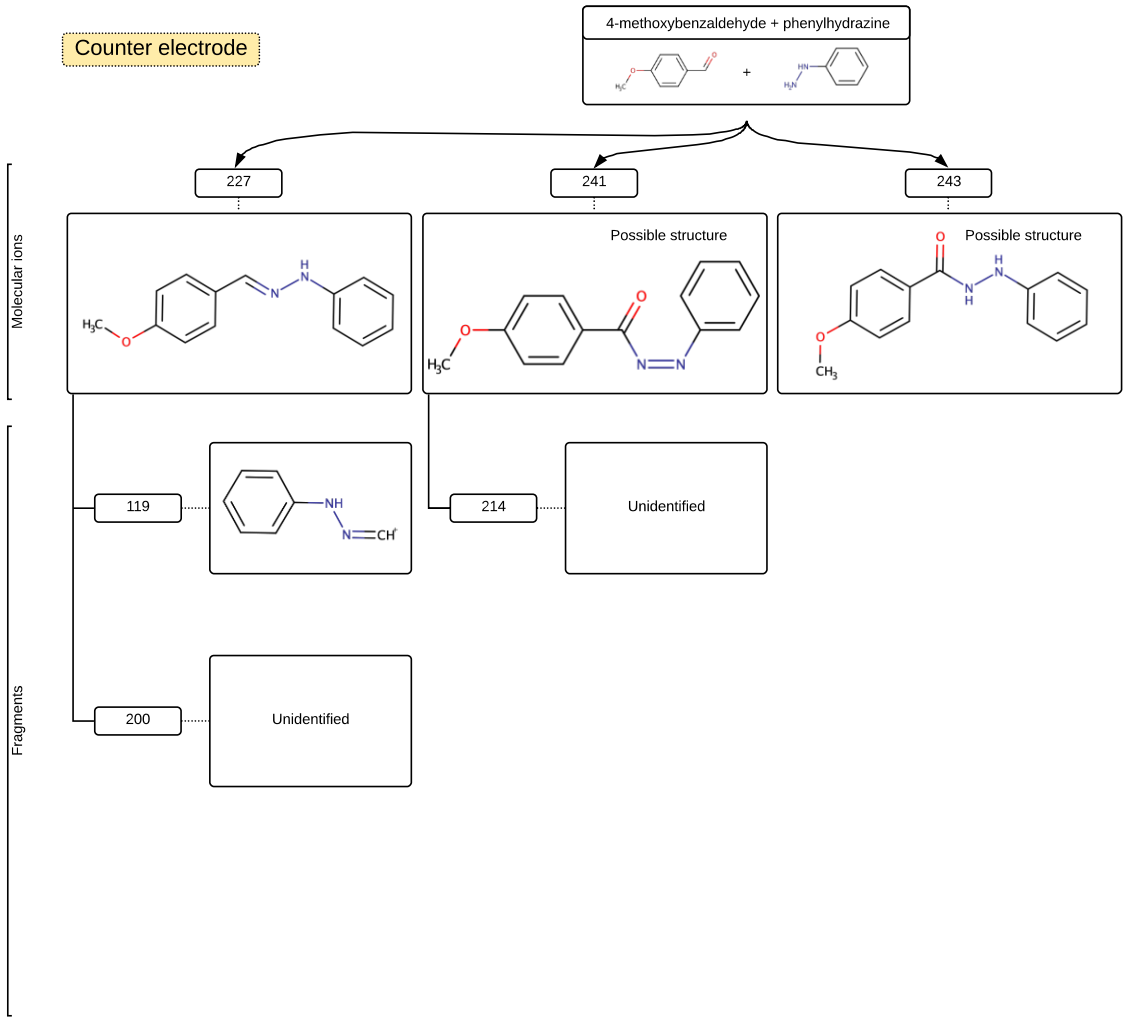


Table SI 2.31. Results for the reaction between phenylhydrazine and 2-hydroxybenzaldehyde in bulk phase.

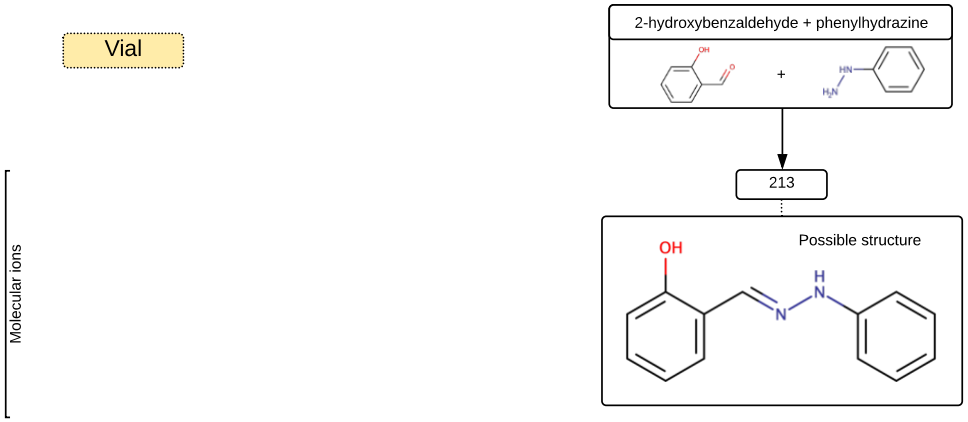


Table SI 2.32. Results for the reaction between phenylhydrazine and 2-hydroxybenzaldehyde in charged droplets (collected from the beaker).

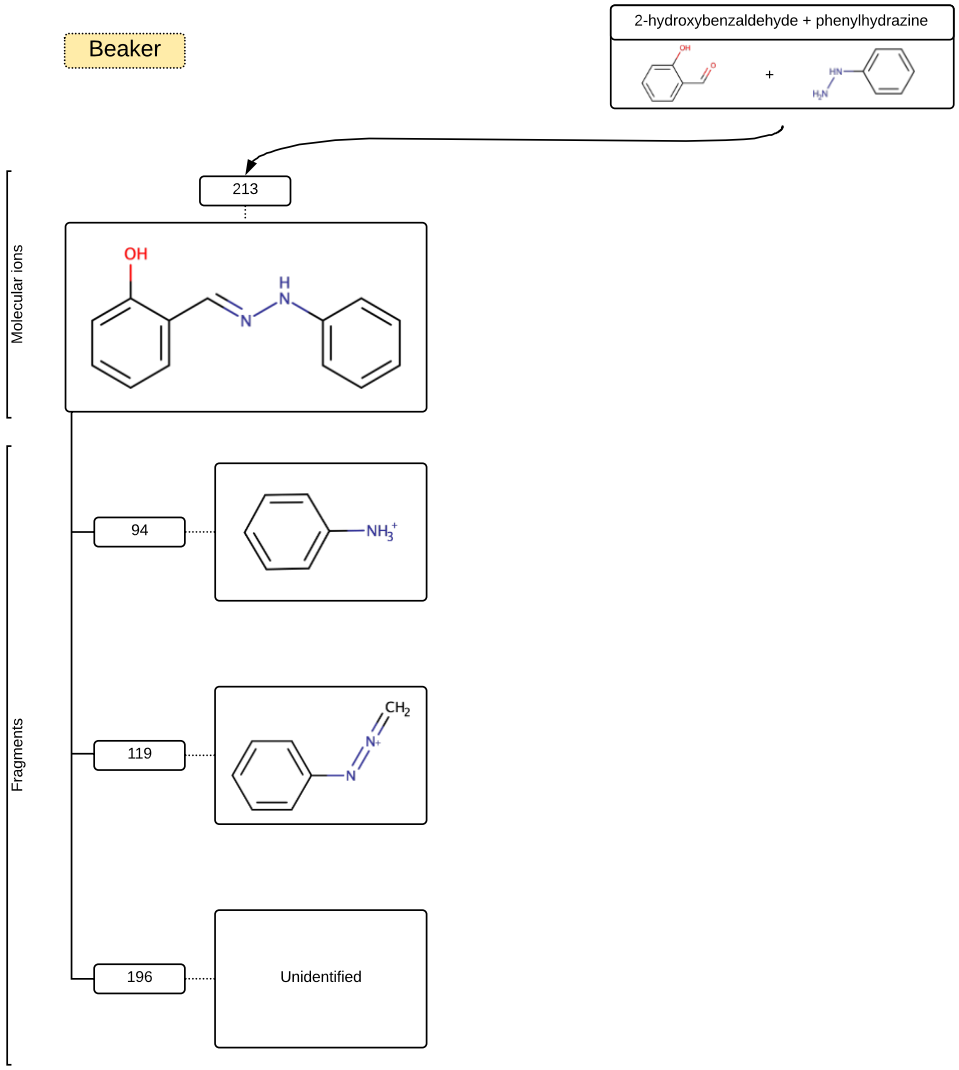


Table SI 2.33. Results for the reaction between phenylhydrazine and 2-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

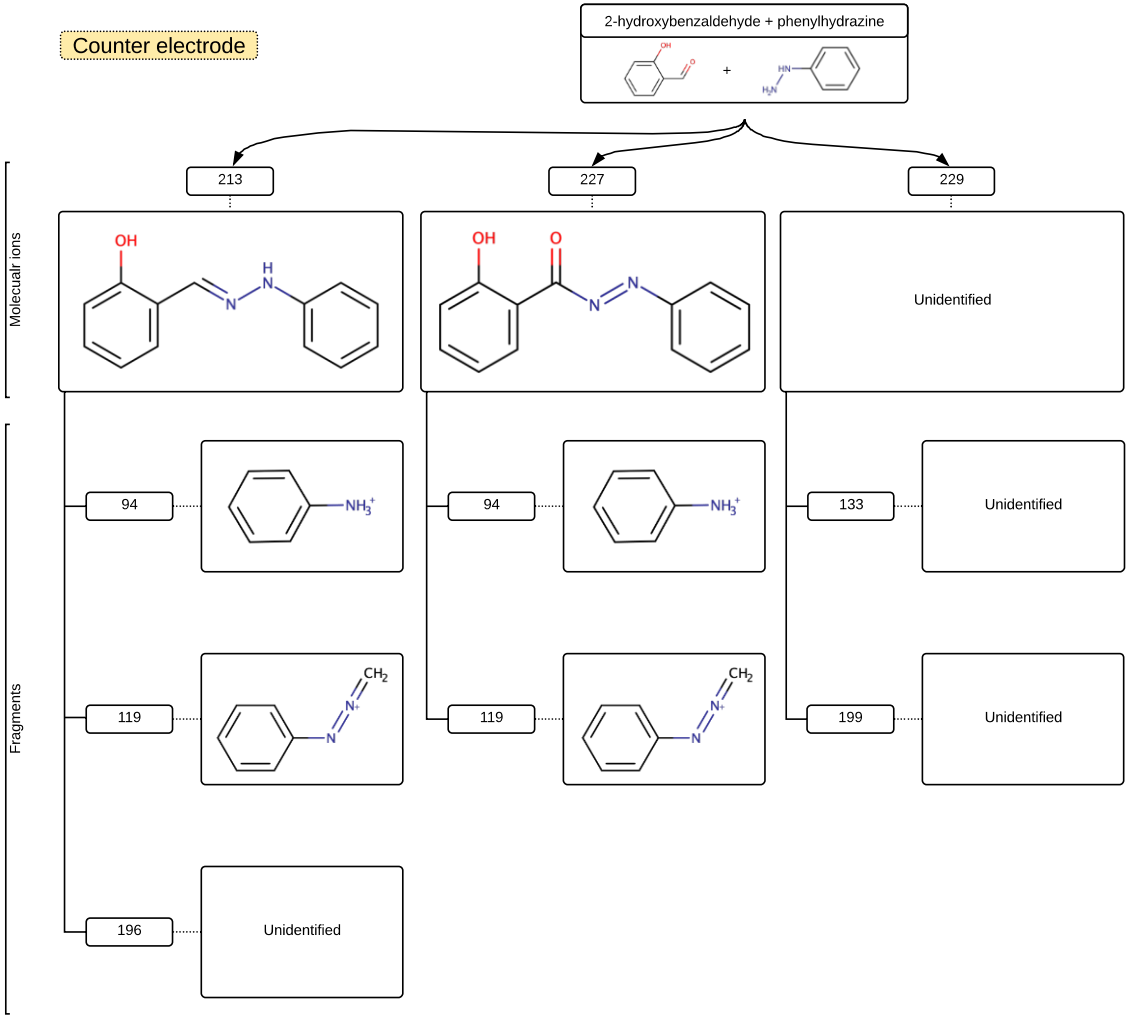


Table SI 2.34. Results for the reaction between phenylhydrazine and 4-hydroxybenzaldehyde in bulk phase.

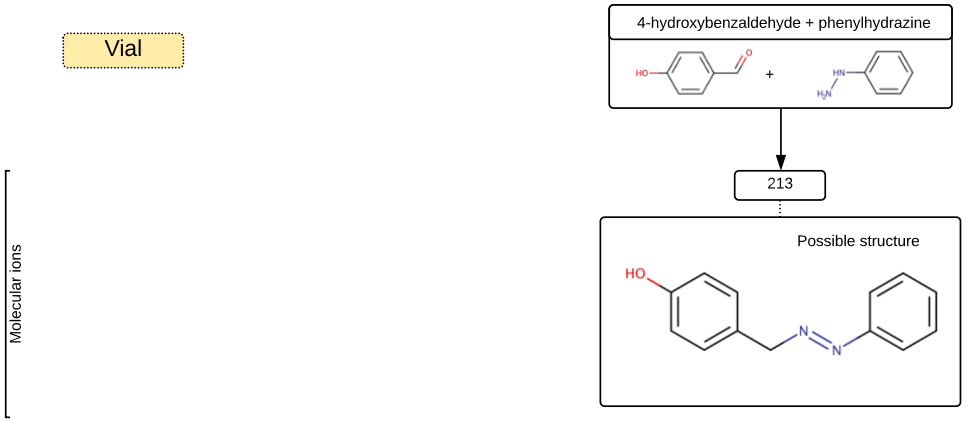


Table SI 2.35. Results for the reaction between phenylhydrazine and 4-hydroxybenzaldehyde in charged droplets (collected from the beaker).

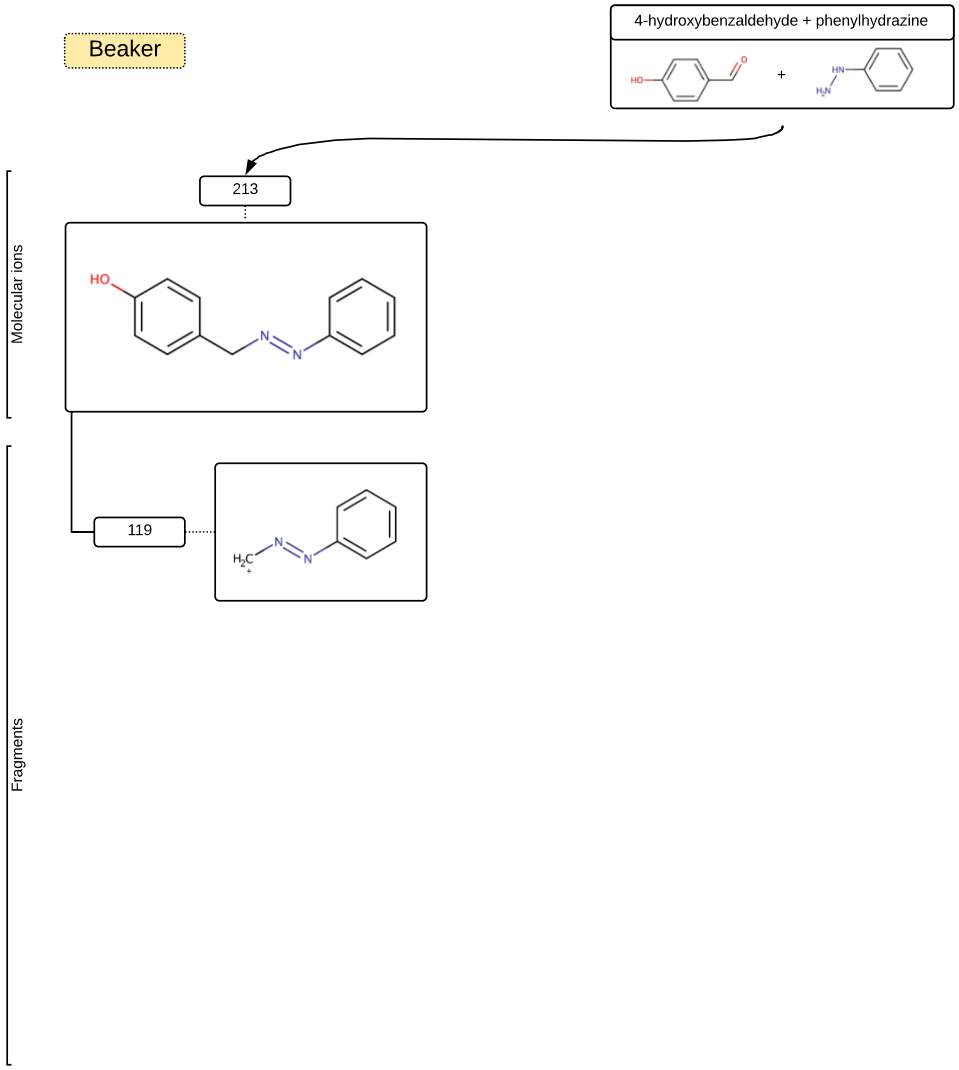


Table SI 2.36. Results for the reaction between phenylhydrazine and 4-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

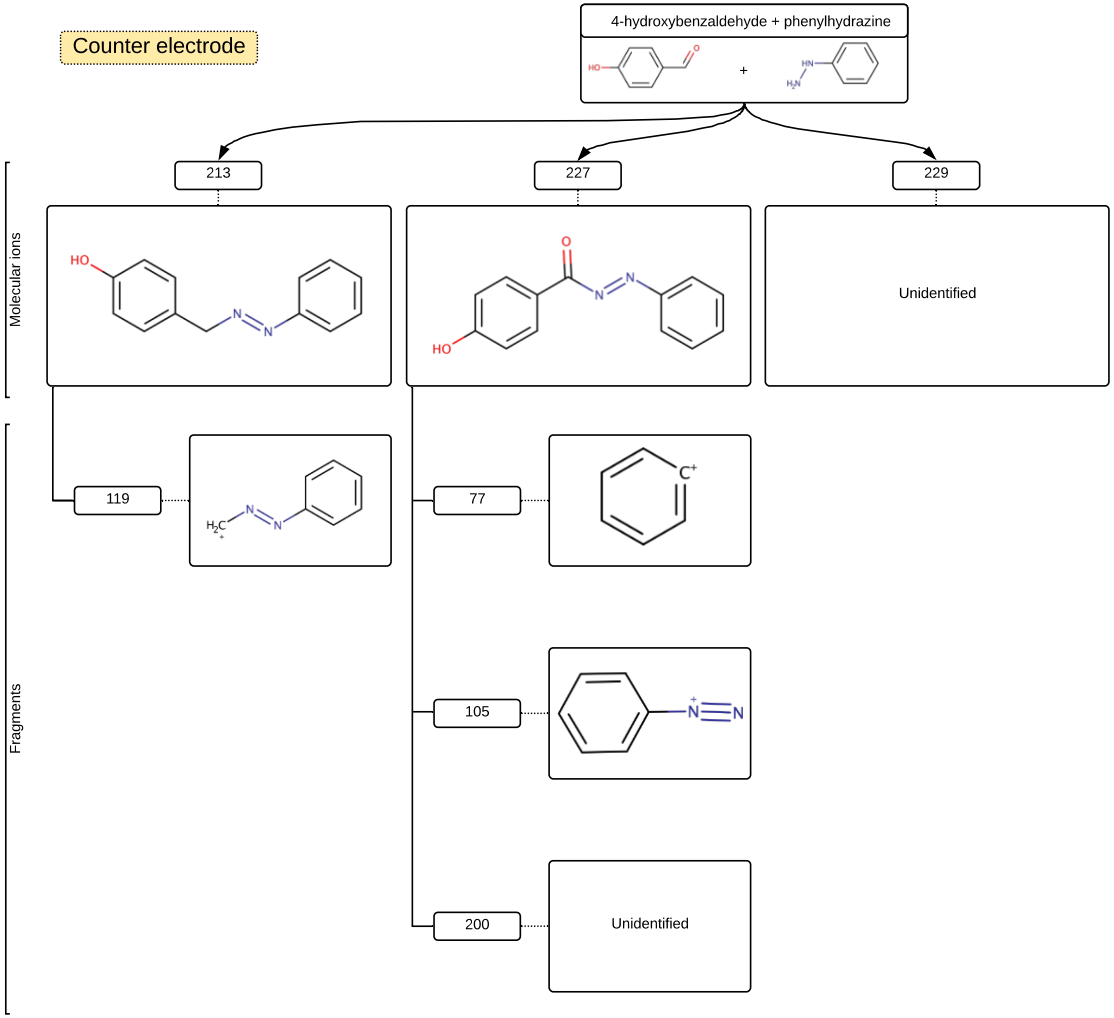


Table SI 2.37. Results for the reaction between phenylhydrazine and 2-nitrobenzaldehyde in bulk phase.

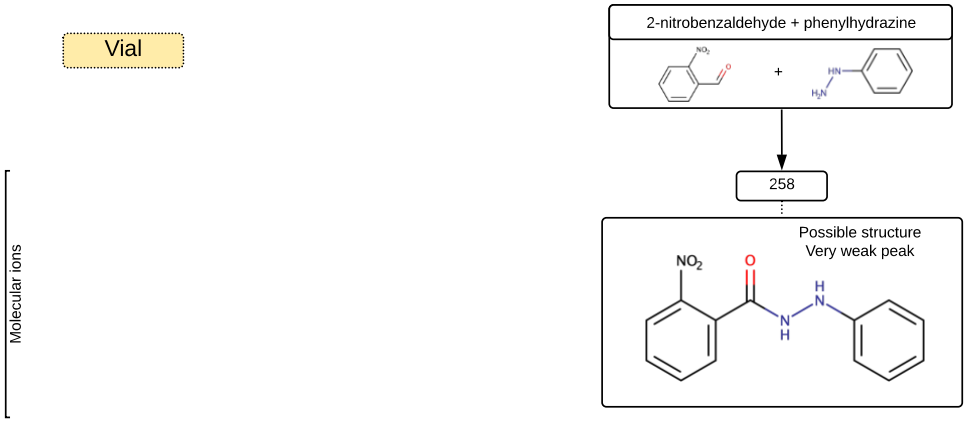


Table SI 2.38. Results for the reaction between phenylhydrazine and 2-nitrobenzaldehyde in charged droplets (collected from the beaker).

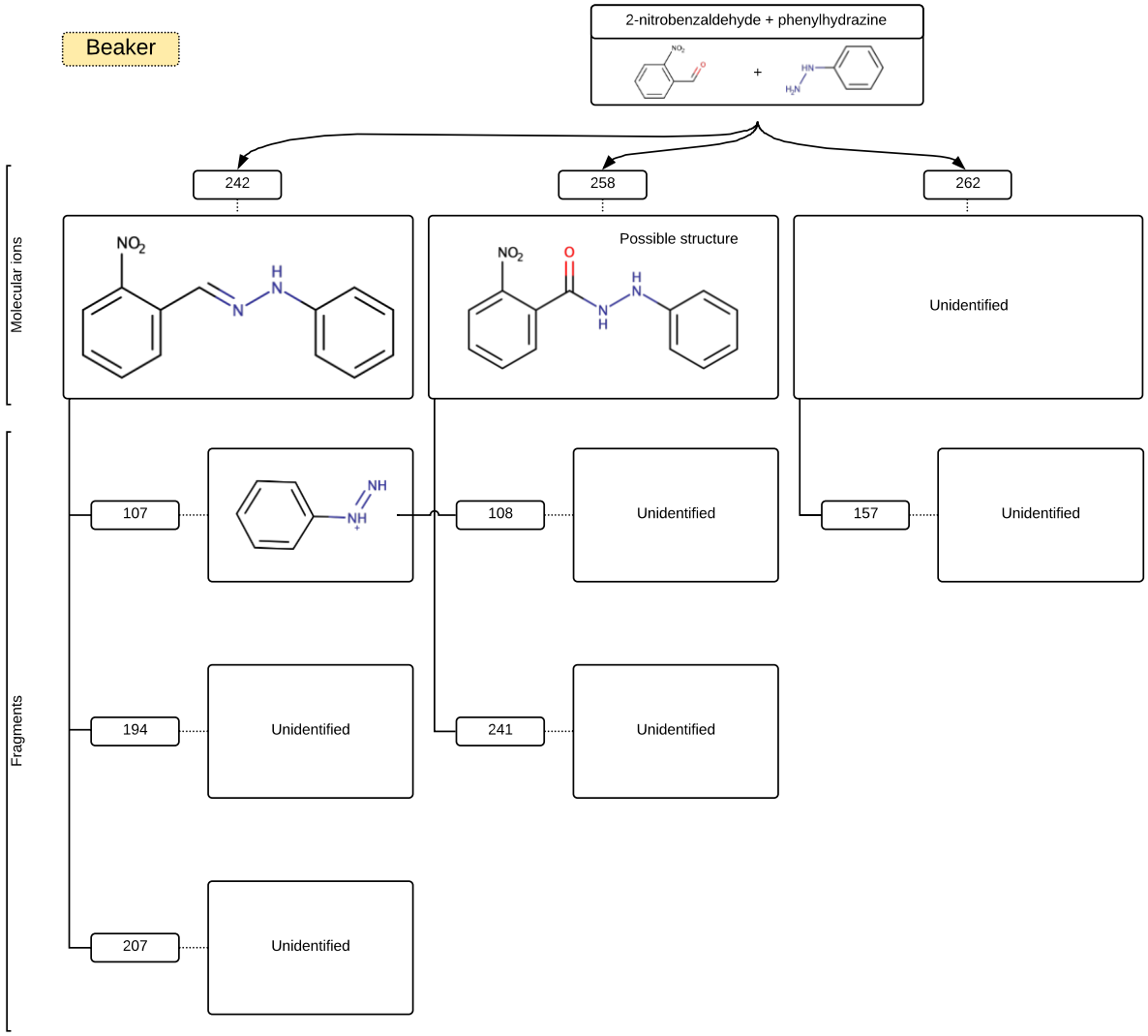


Table SI 2.39. Results for the reaction between phenylhydrazine and 2-nitrobenzaldehyde in charged droplets (collected from the counter electrode).

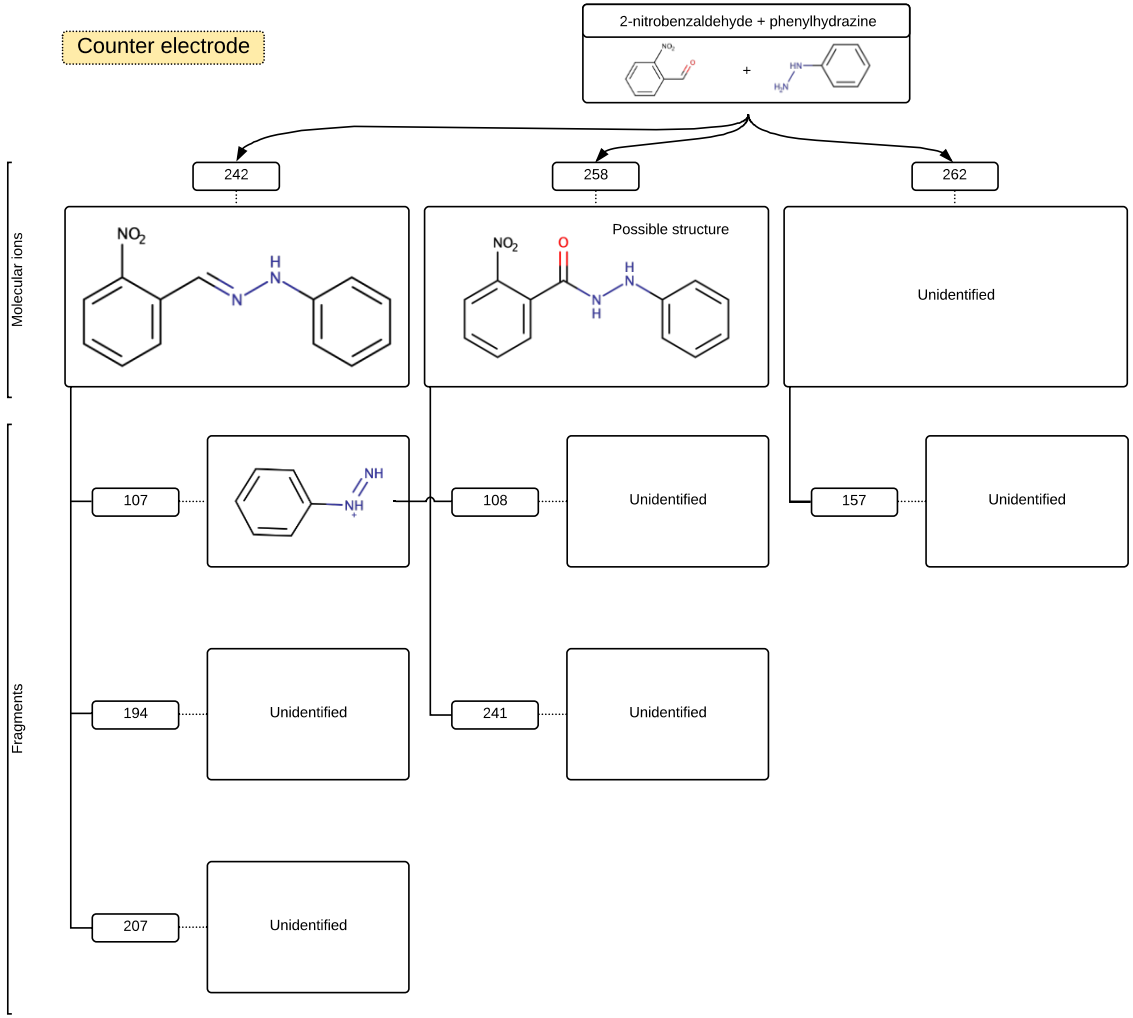


Table SI 2.40. Results for the reaction between phenylhydrazine and 4-nitrobenzaldehyde in bulk phase.

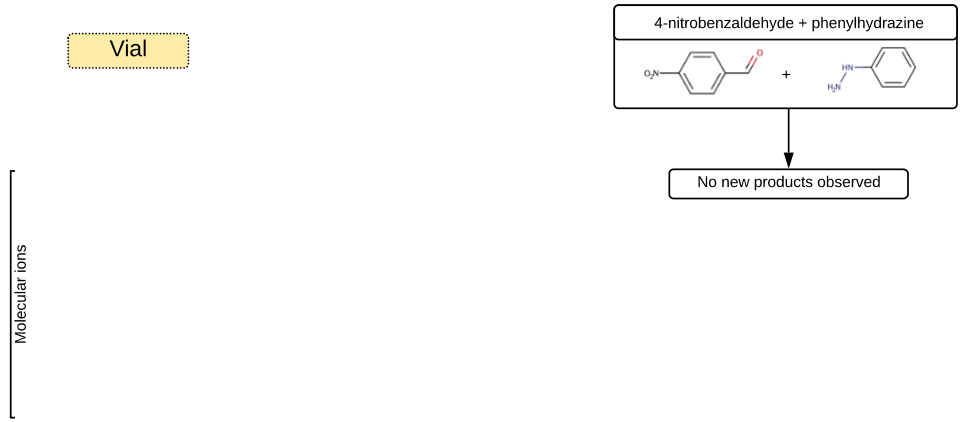


Table SI 2.41. Results for the reaction between phenylhydrazine and 4-nitrobenzaldehyde in charged droplets (collected from the beaker).

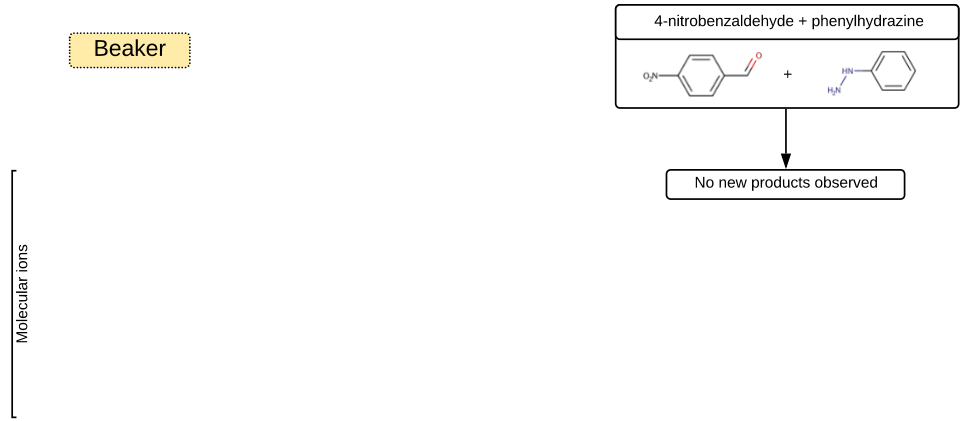
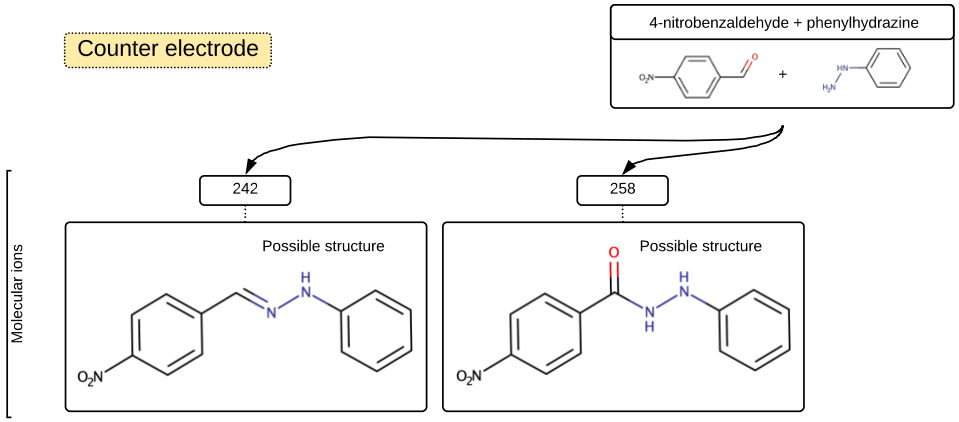


Table SI 2.42. Results for the reaction between phenylhydrazine and 4-nitrobenzaldehyde in charged droplets (collected from the counter electrode).



Reactions with Aniline

Table SI 2.43. Results for the reaction between aniline and benzaldehyde in bulk phase.

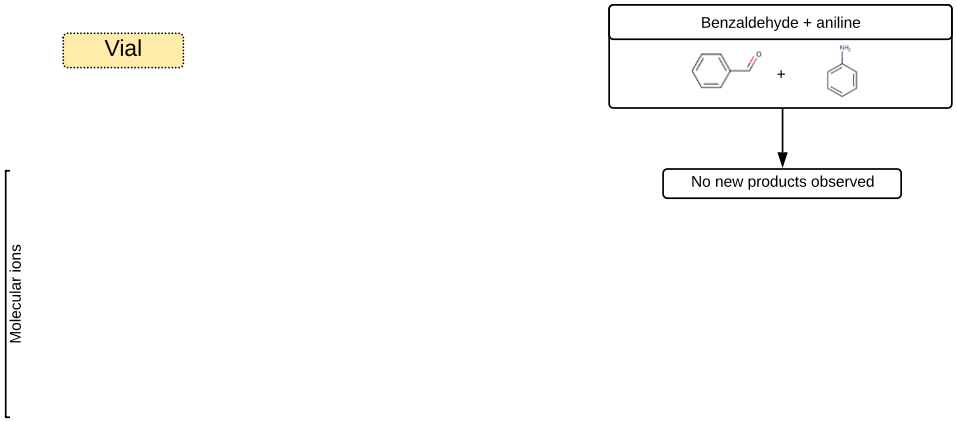


Table SI 2.44. Results for the reaction between aniline and benzaldehyde in charged droplets (collected from the beaker).

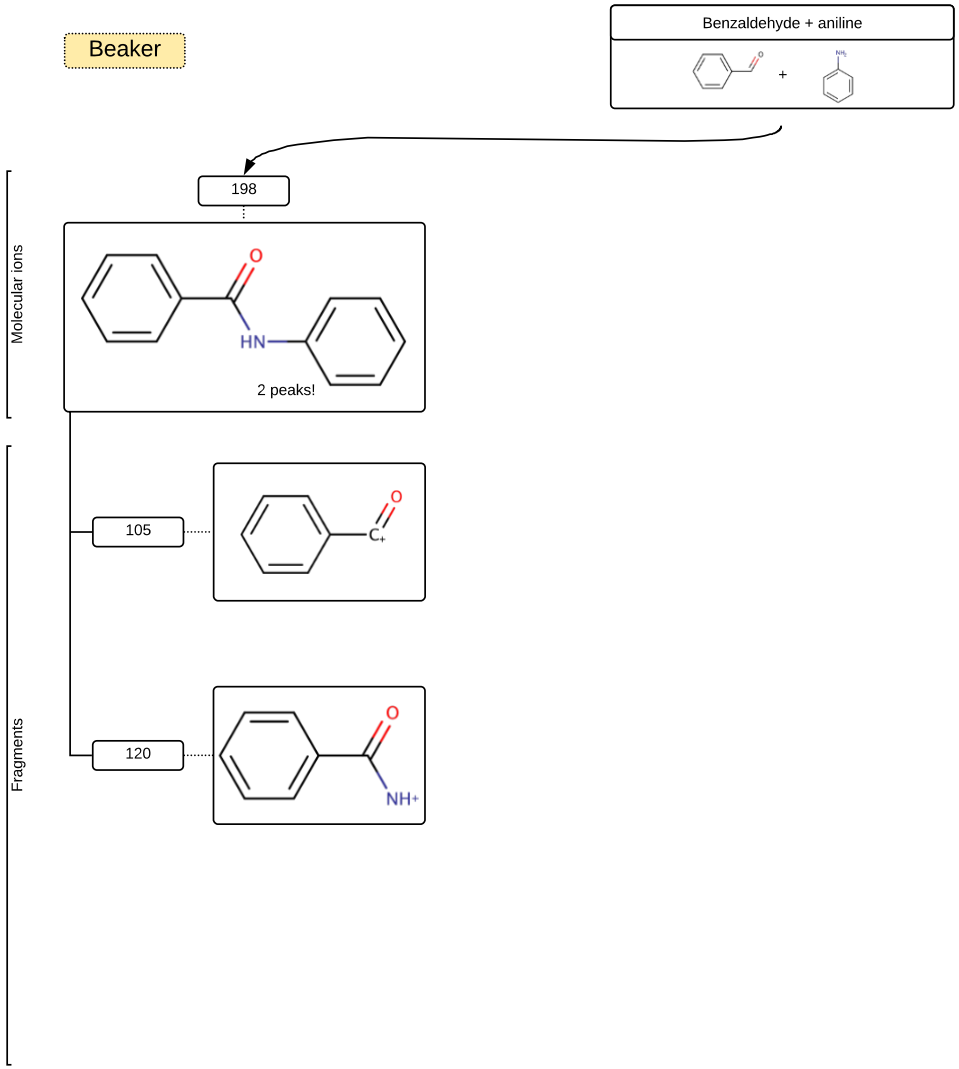


Table SI 2.45. Results for the reaction between aniline and benzaldehyde in charged droplets (collected from the counter electrode).

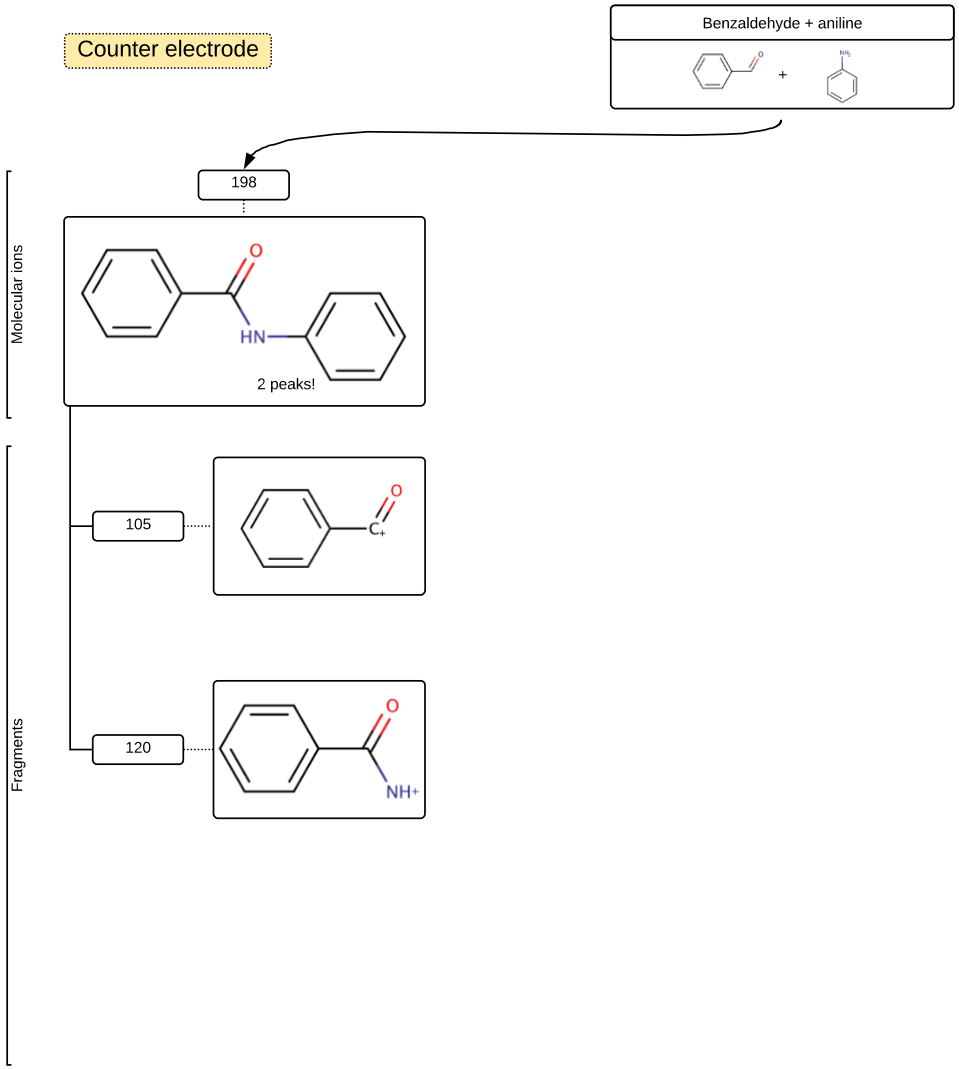


Table SI 2.46. Results for the reaction between aniline and 2-methoxybenzaldehyde in bulk phase.

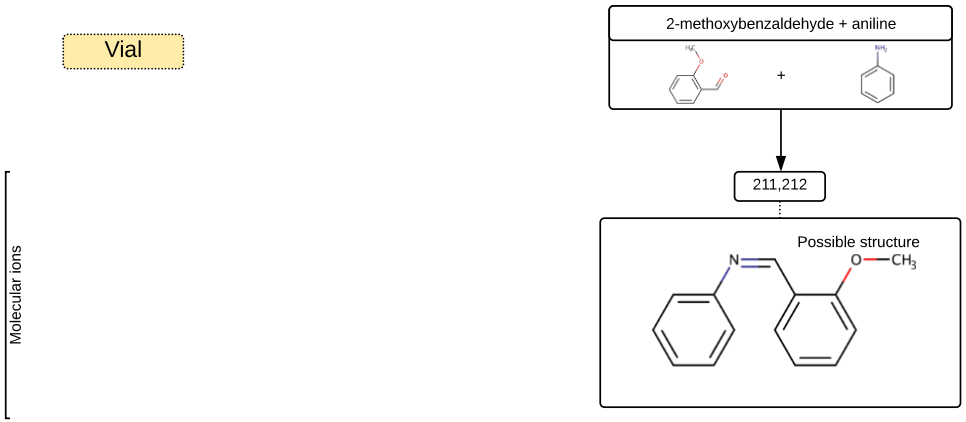


Table SI 2.47. Results for the reaction between aniline and 2-methoxybenzaldehyde in charged droplets (collected from the beaker).

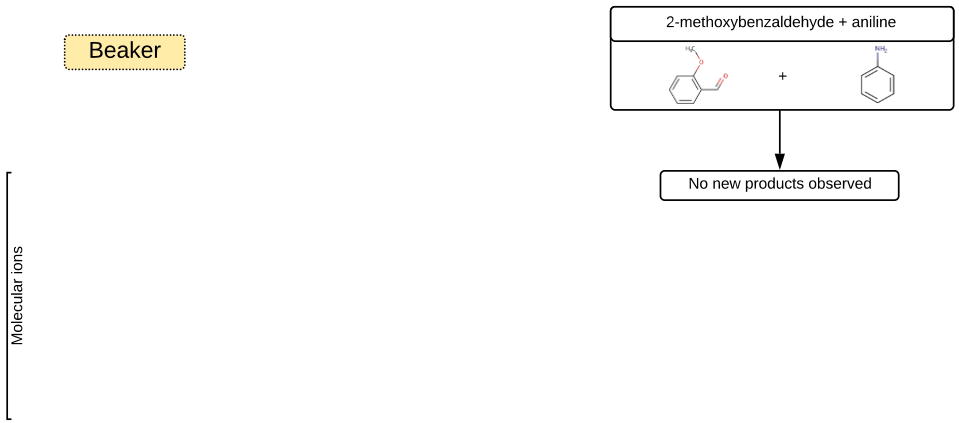


Table SI 2.48. Results for the reaction between aniline and 2-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

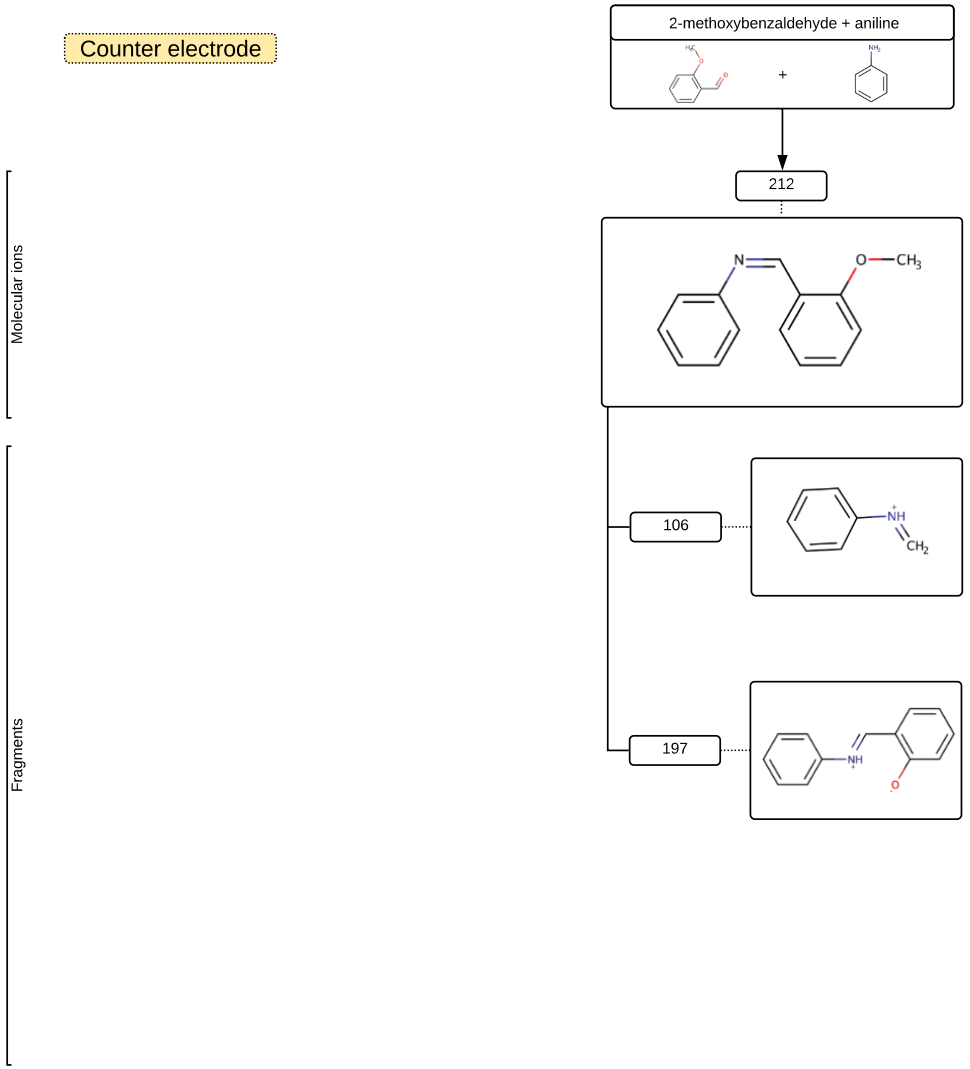


Table SI 2.49. Results for the reaction between aniline and 4-methoxybenzaldehyde in bulk phase.

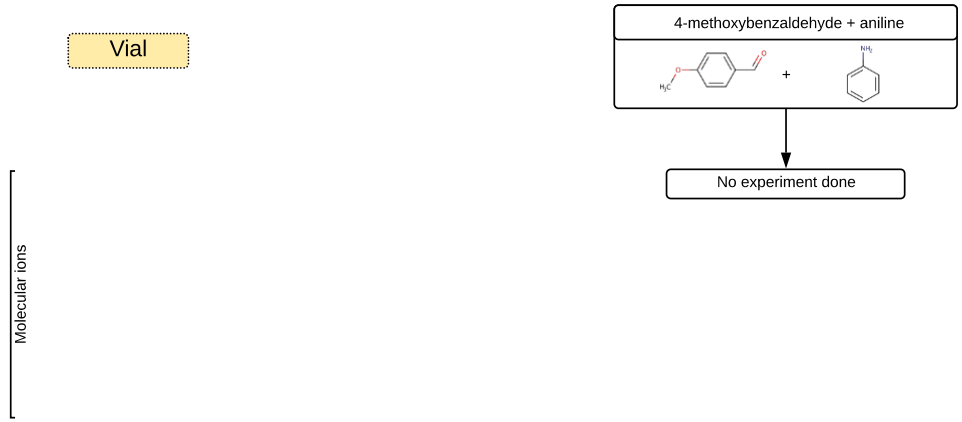


Table SI 2.50. Results for the reaction between aniline and 4-methoxybenzaldehyde in charged droplets (collected from the beaker).

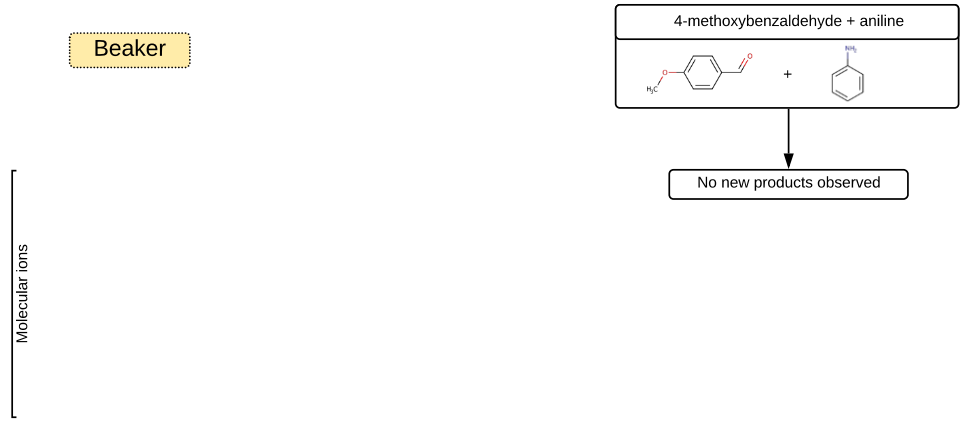


Table SI 2.51. Results for the reaction between aniline and 4-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

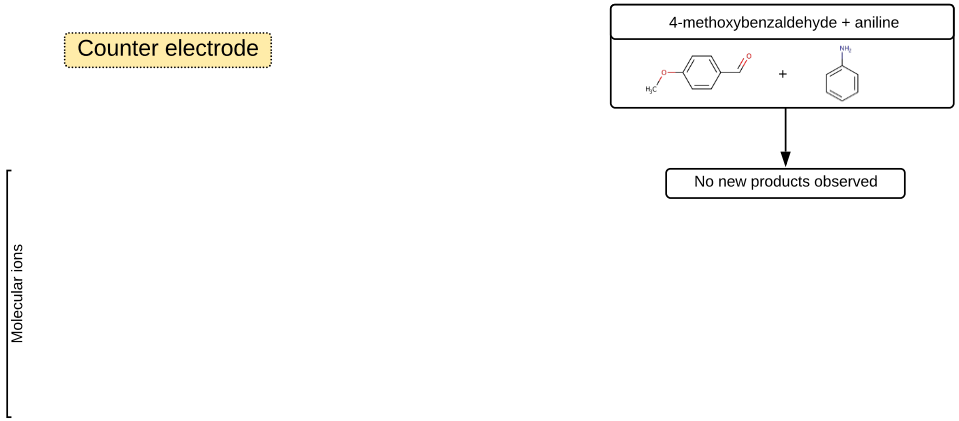


Table SI 2.52. Results for the reaction between aniline and 2-hydroxybenzaldehyde in bulk phase.

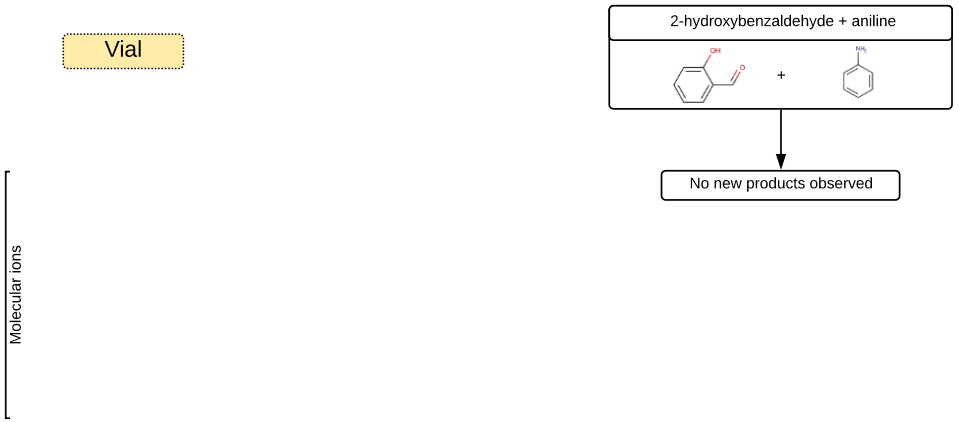


Table SI 2.53. Results for the reaction between aniline and 2-hydroxybenzaldehyde in charged droplets (collected from the beaker).

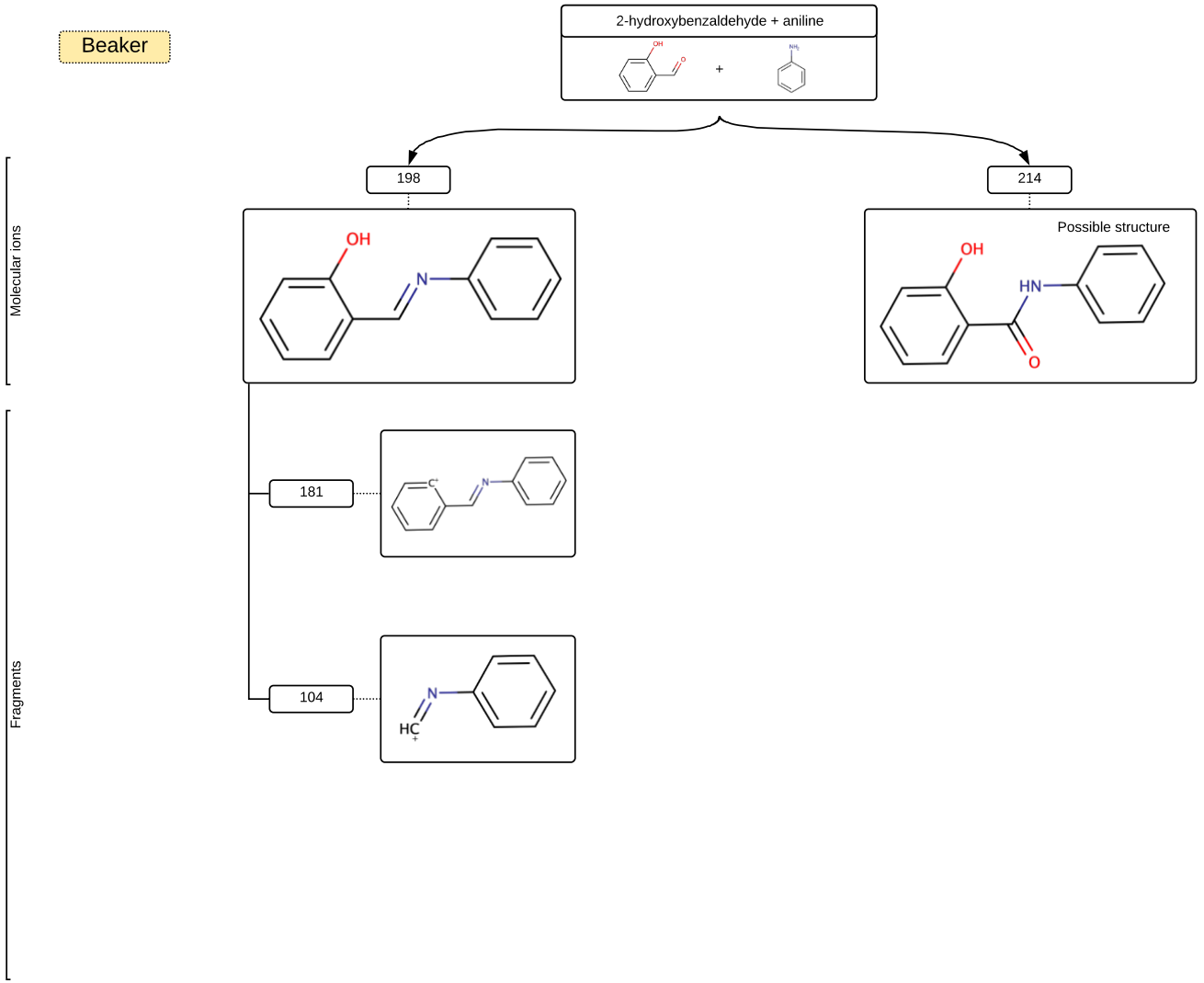


Table SI 2.54. Results for the reaction between aniline and 2-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

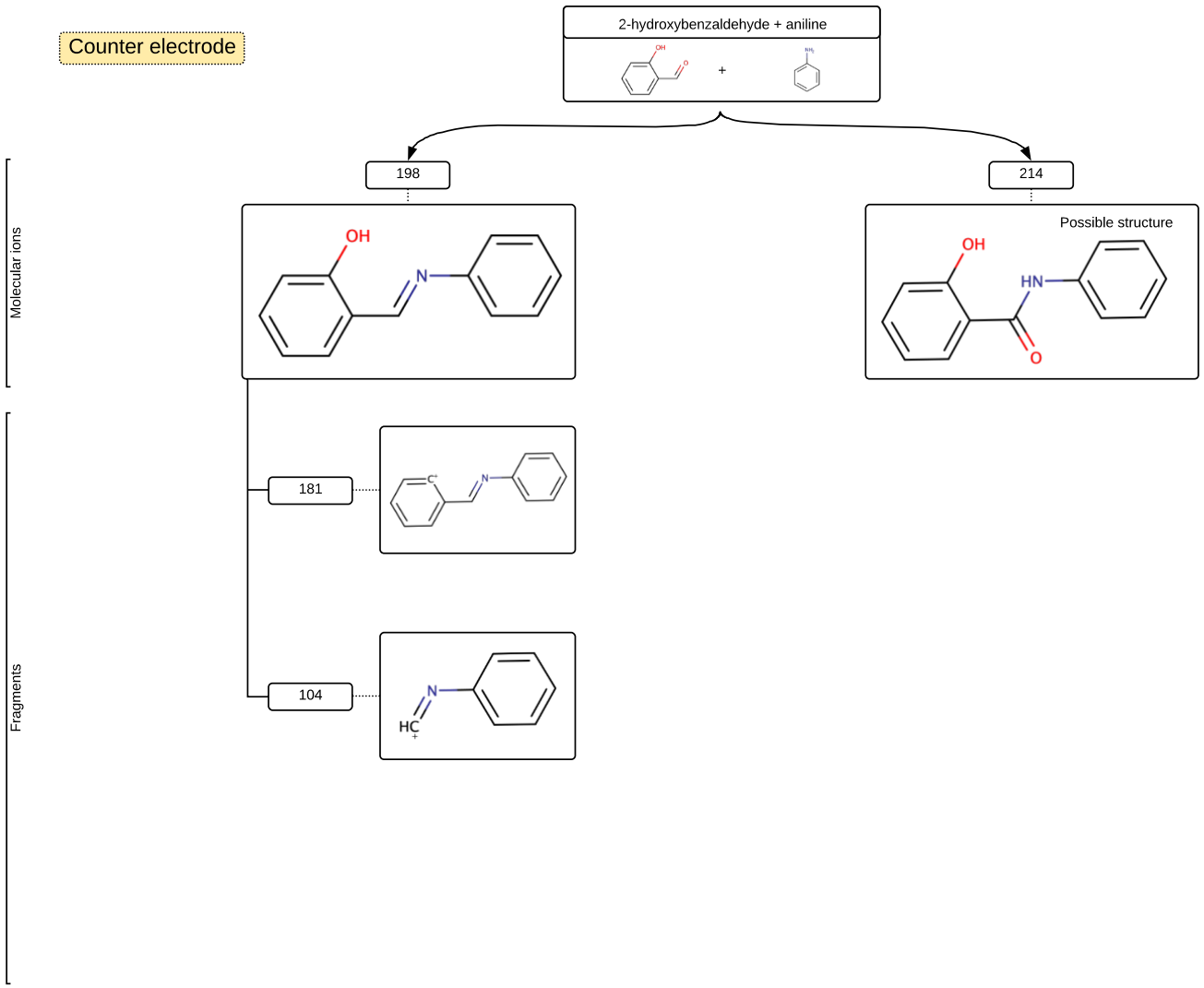


Table SI 2.55. Results for the reaction between aniline and 4-hydroxybenzaldehyde in bulk phase.

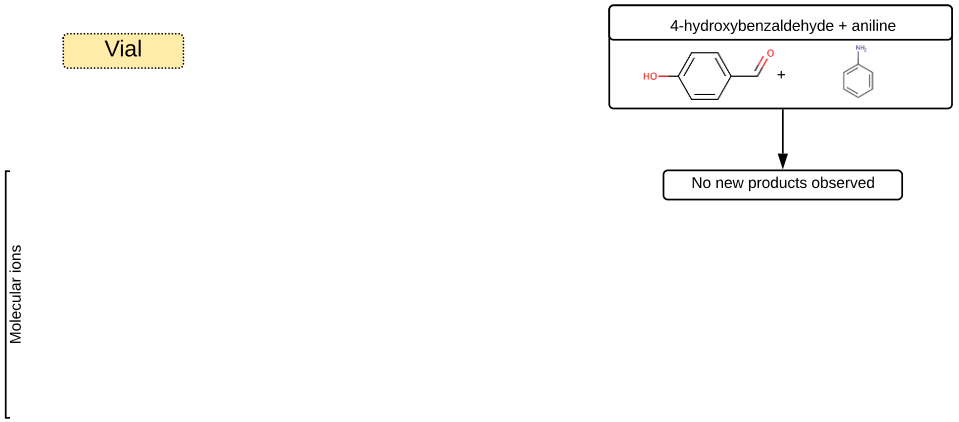


Table SI 2.56. Results for the reaction between aniline and 4-hydroxybenzaldehyde in charged droplets (collected from the beaker).

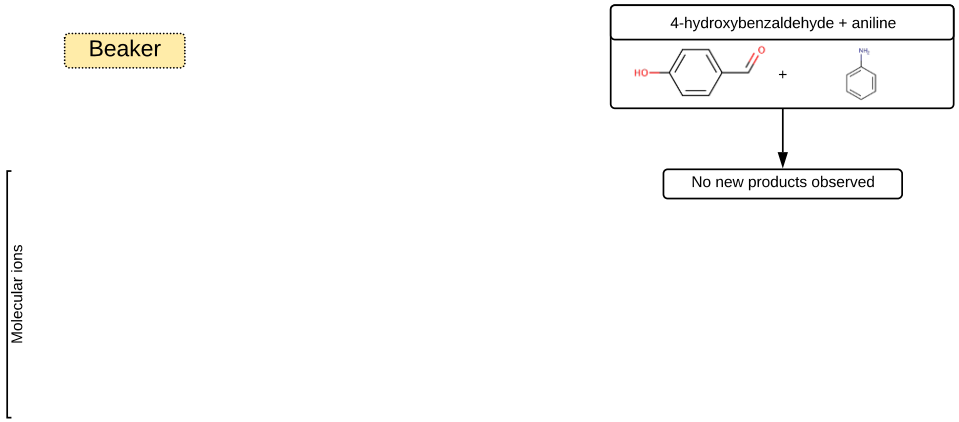


Table SI 2.57. Results for the reaction between aniline and 4-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

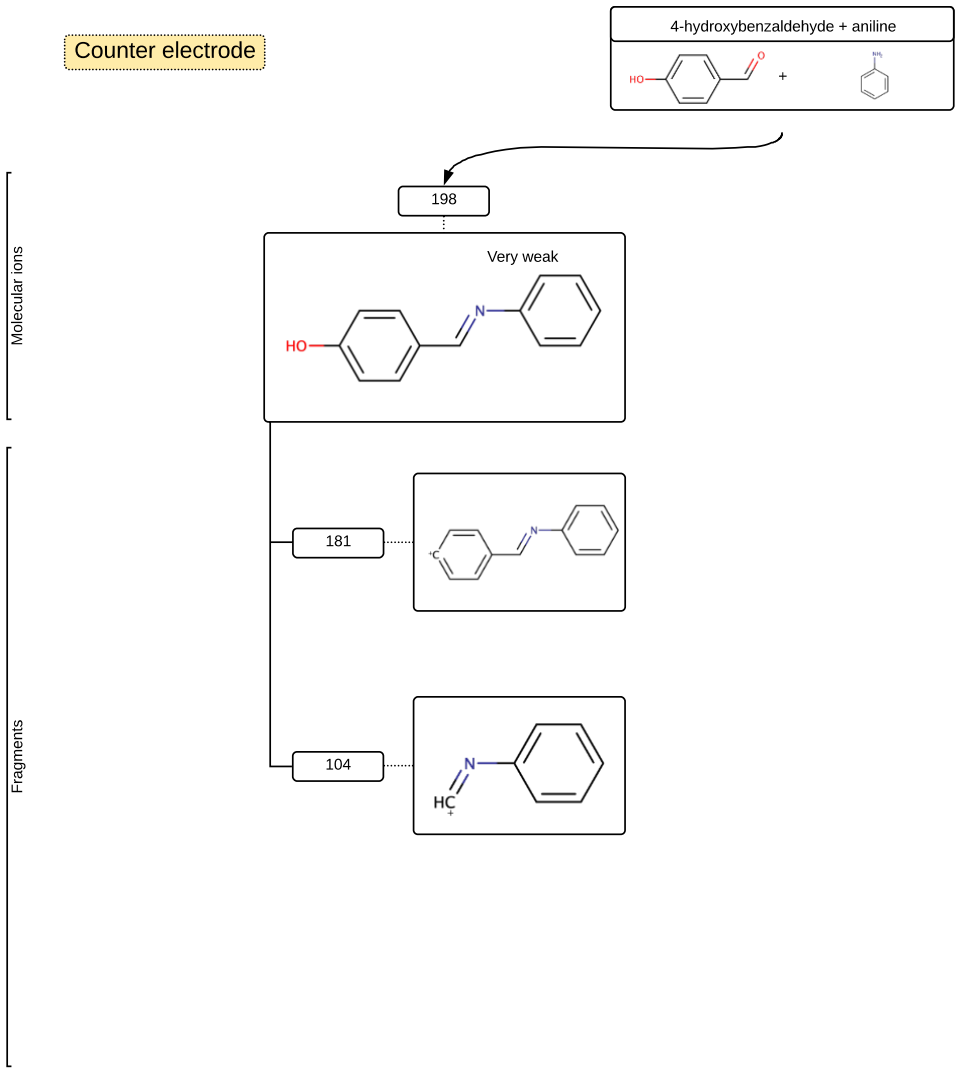


Table SI 2.58. Results for the reaction between aniline and 2-nitrobenzaldehyde in bulk phase.

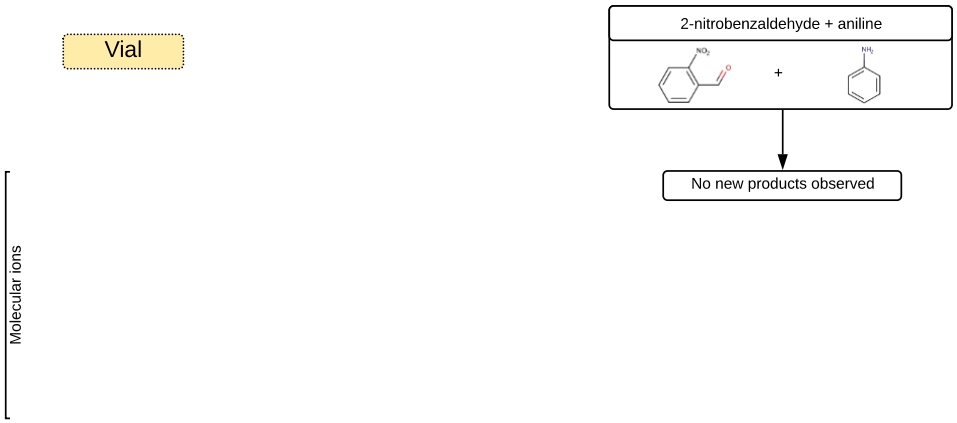


Table SI 2.59. Results for the reaction between aniline and 2-nitrobenzaldehyde in charged droplets (collected from the beaker).

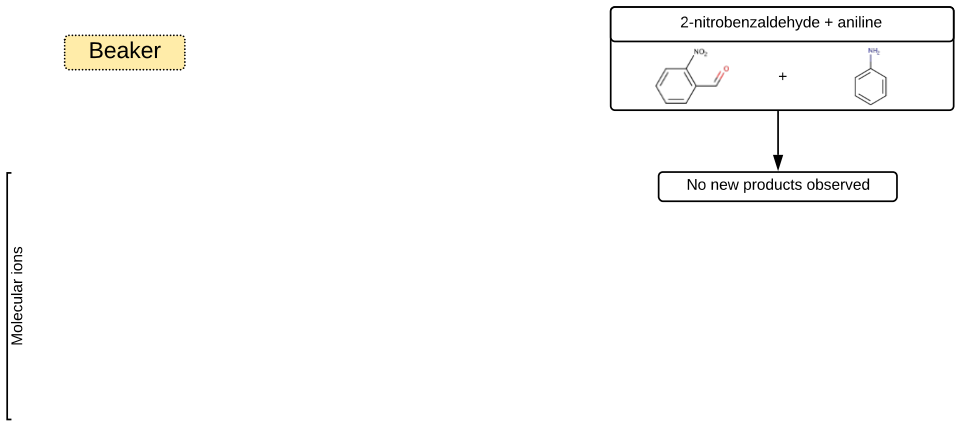


Table SI 2.60. Results for the reaction between aniline and 2-nitrobenzaldehyde in charged droplets (collected from the counter electrode).

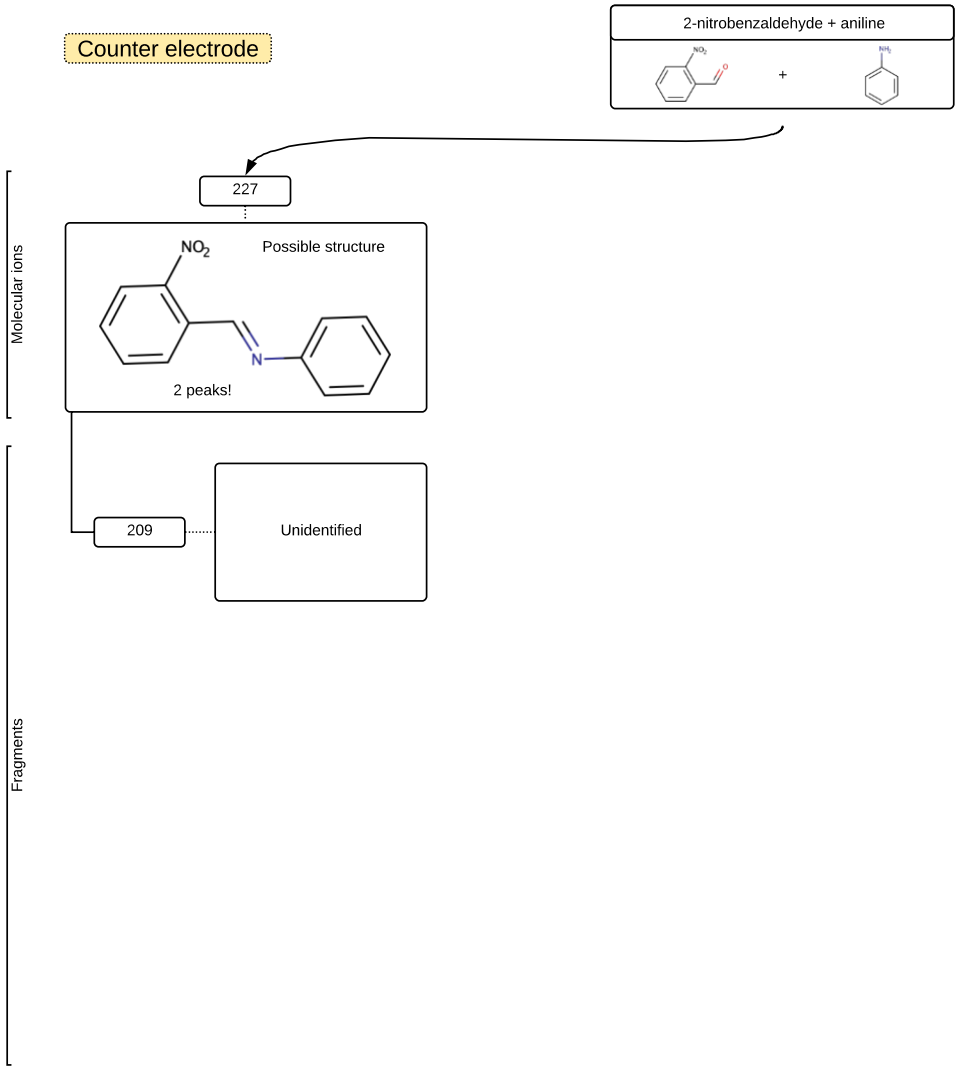


Table SI 2.61. Results for the reaction between aniline and 4-nitrobenzaldehyde in bulk phase.

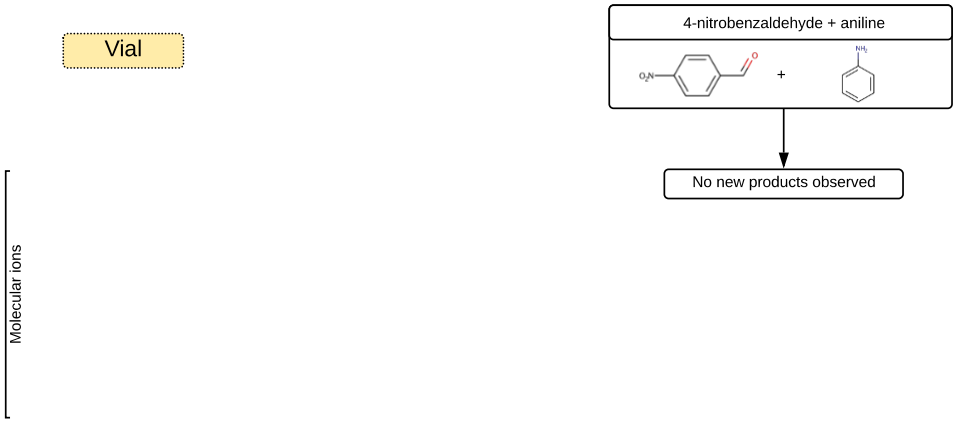


Table SI 2.62. Results for the reaction between aniline and 4-nitrobenzaldehyde in charged droplets (collected from the beaker).

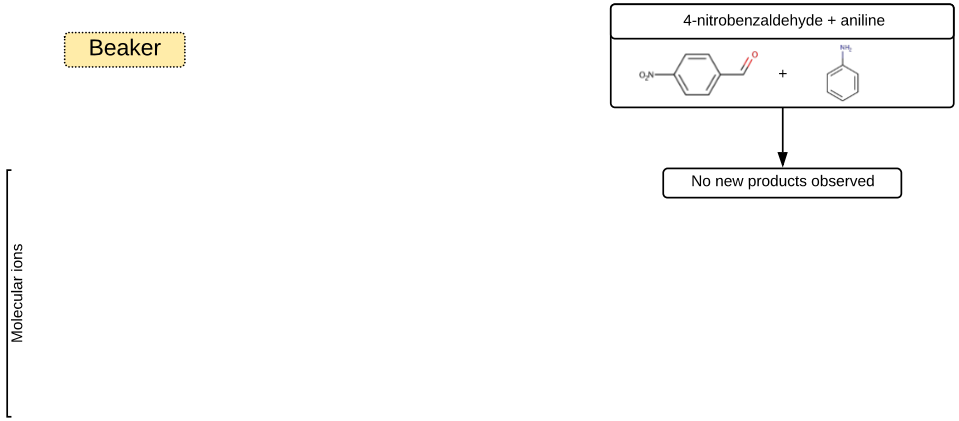
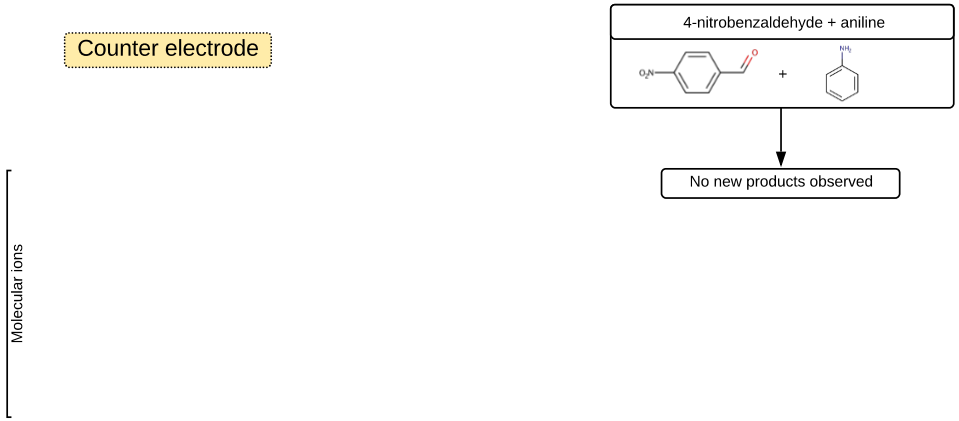


Table SI 2.63. Results for the reaction between aniline and 4-nitrobenzaldehyde in charged droplets (collected from the counter electrode).



Reactions with Hexylamine

Table SI 2.64. Results for the reaction between hexylamine and benzaldehyde in bulk phase.

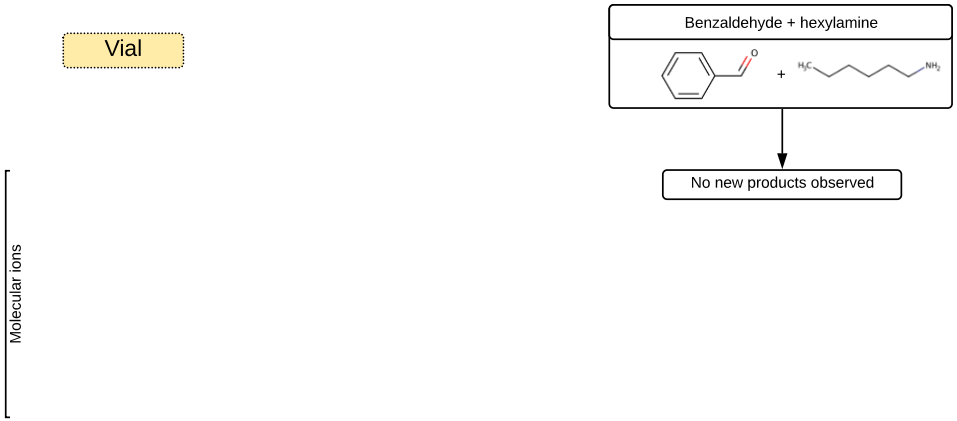


Table SI 2.65. Results for the reaction between hexylamine and benzaldehyde in charged droplets (collected from the beaker).

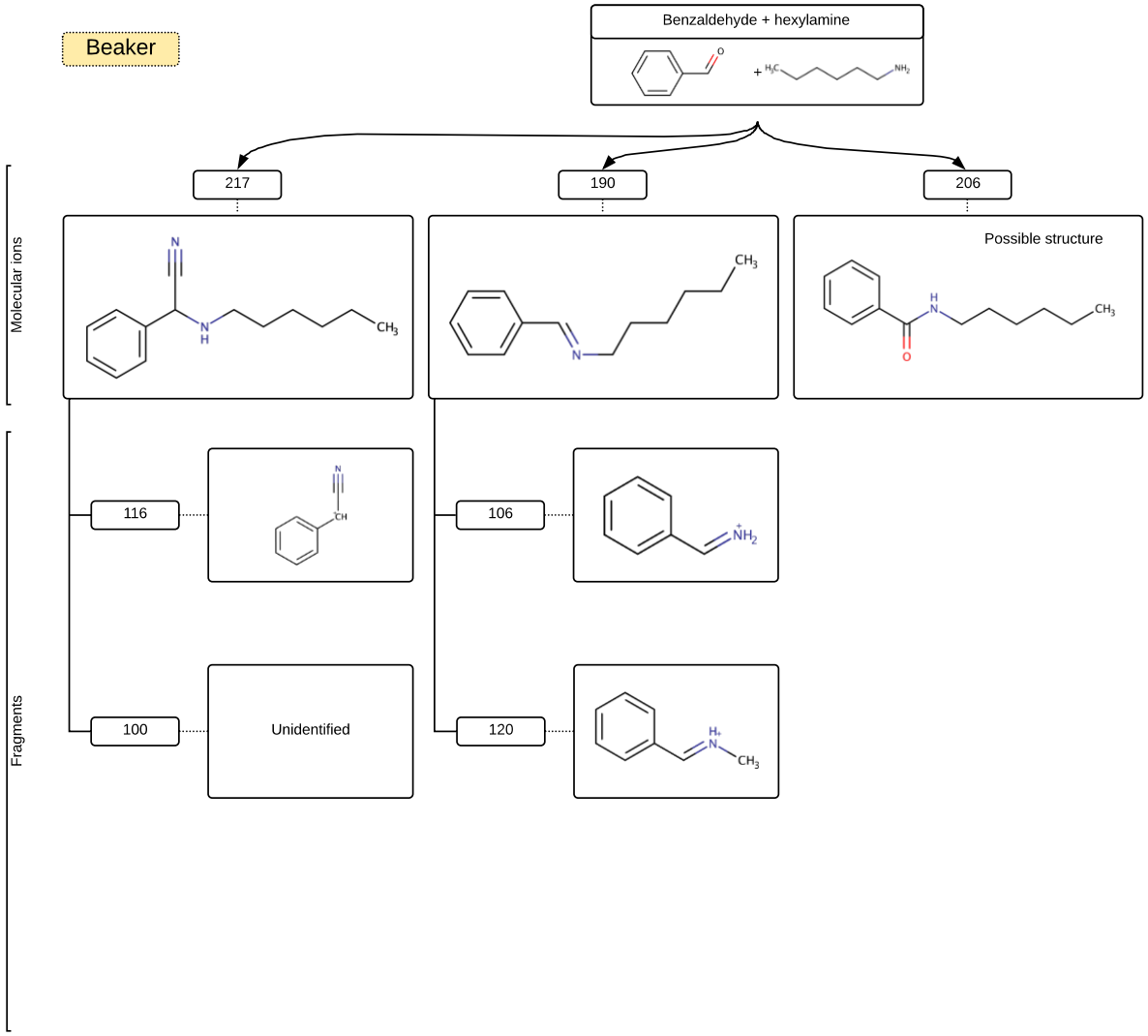


Table SI 2.66. Results for the reaction between hexylamine and benzaldehyde in charged droplets (collected from the counter electrode).

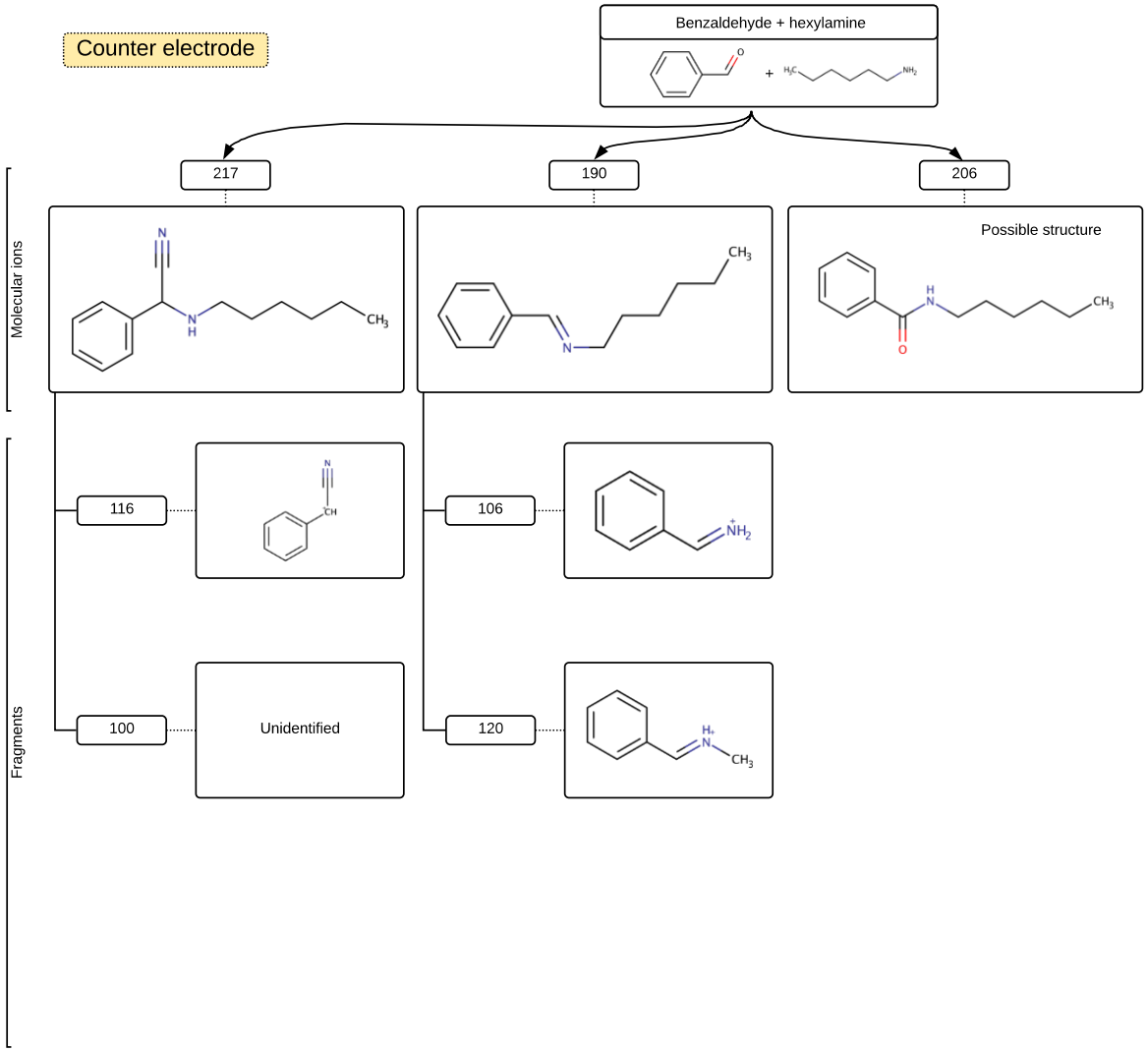


Table SI 2.67. Results for the reaction between hexylamine and 2-methoxybenzaldehyde in bulk phase.

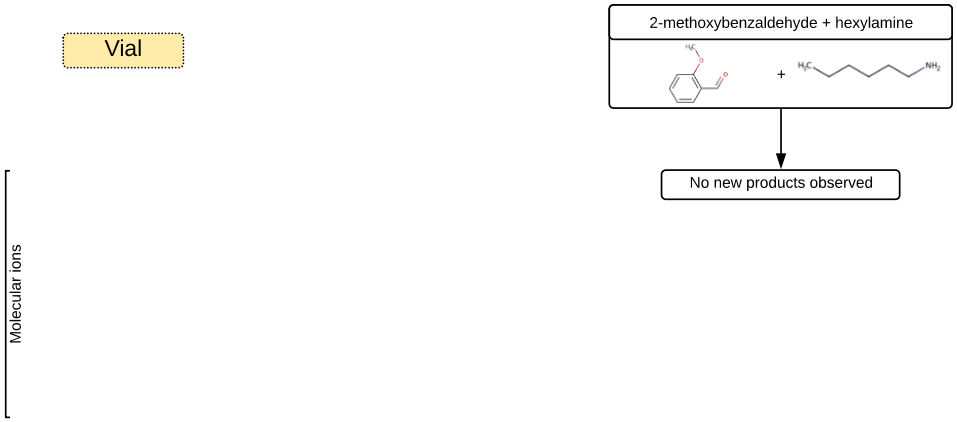


Table SI 2.68. Results for the reaction between hexylamine and 2-methoxybenzaldehyde in charged droplets (collected from the beaker).

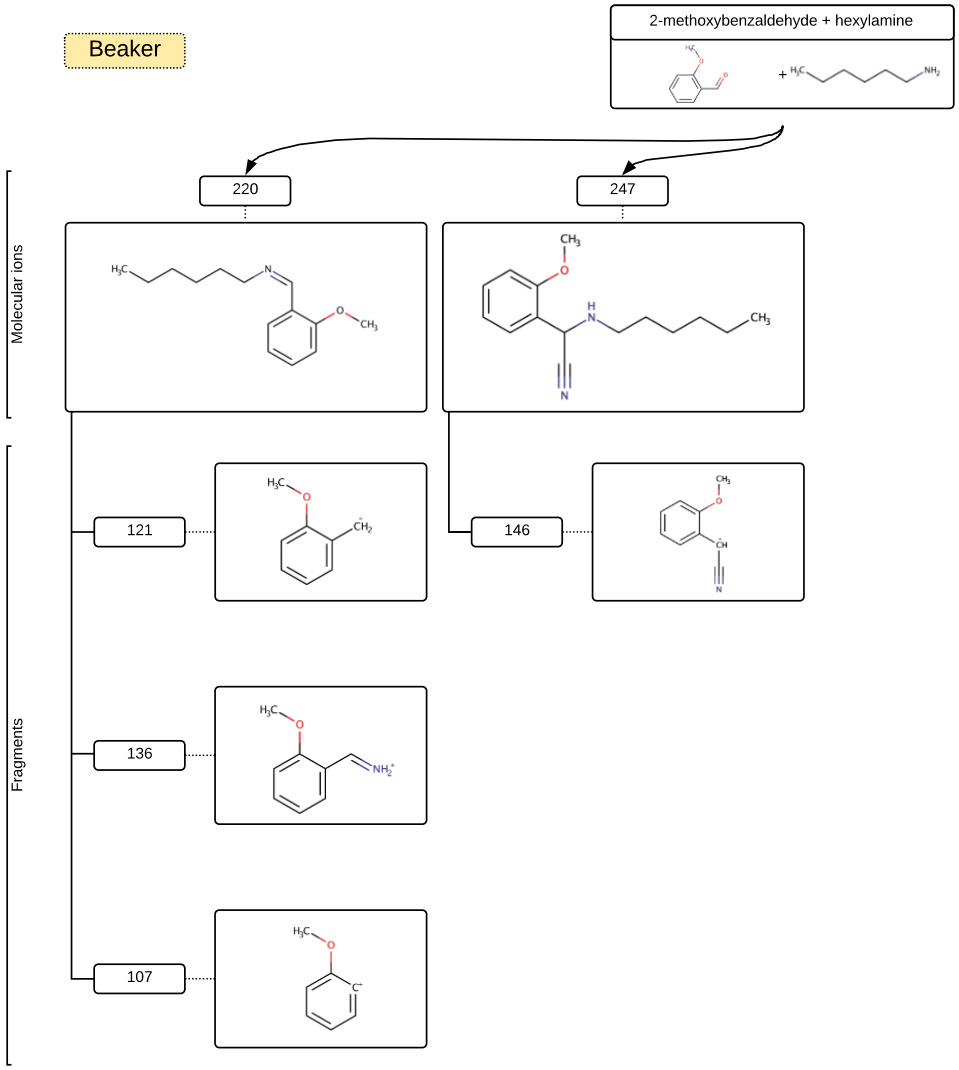


Table SI 2.69. Results for the reaction between hexylamine and 2-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

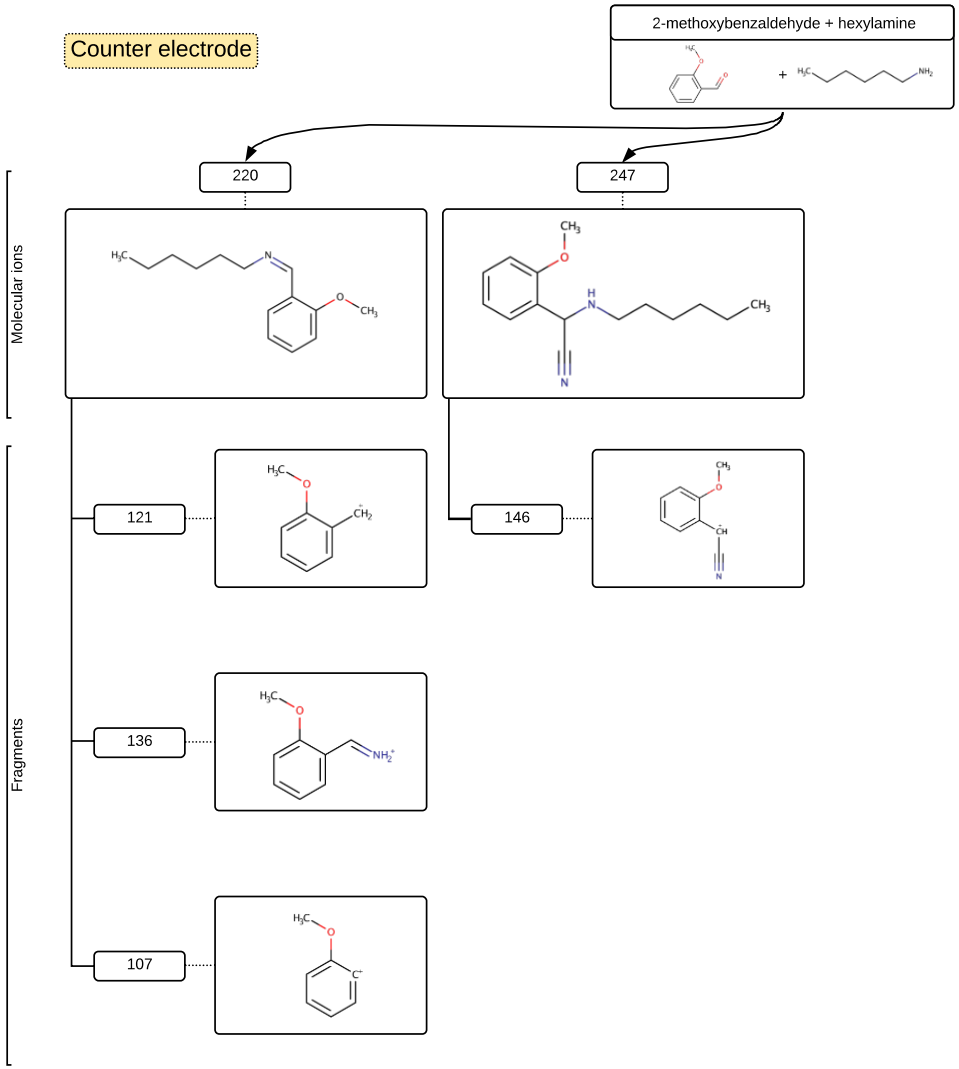


Table SI 2.70. Results for the reaction between hexylamine and 4-methoxybenzaldehyde in bulk phase.

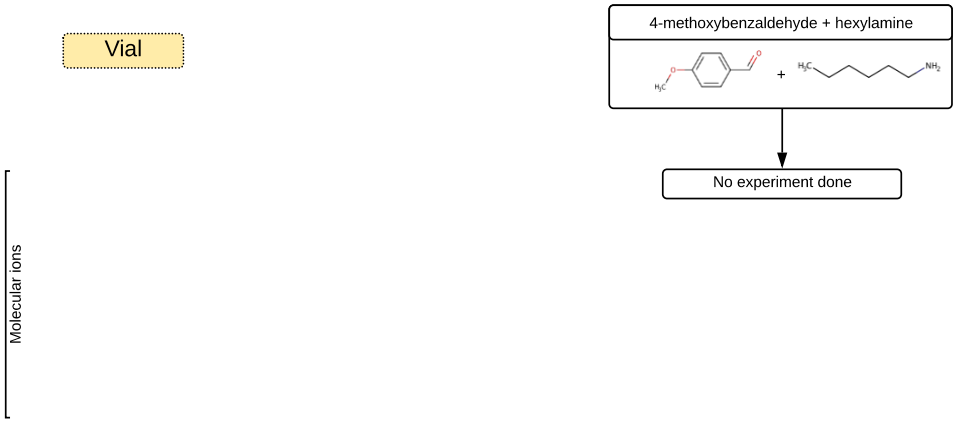


Table SI 2.71. Results for the reaction between hexylamine and 4-methoxybenzaldehyde in charged droplets (collected from the beaker).

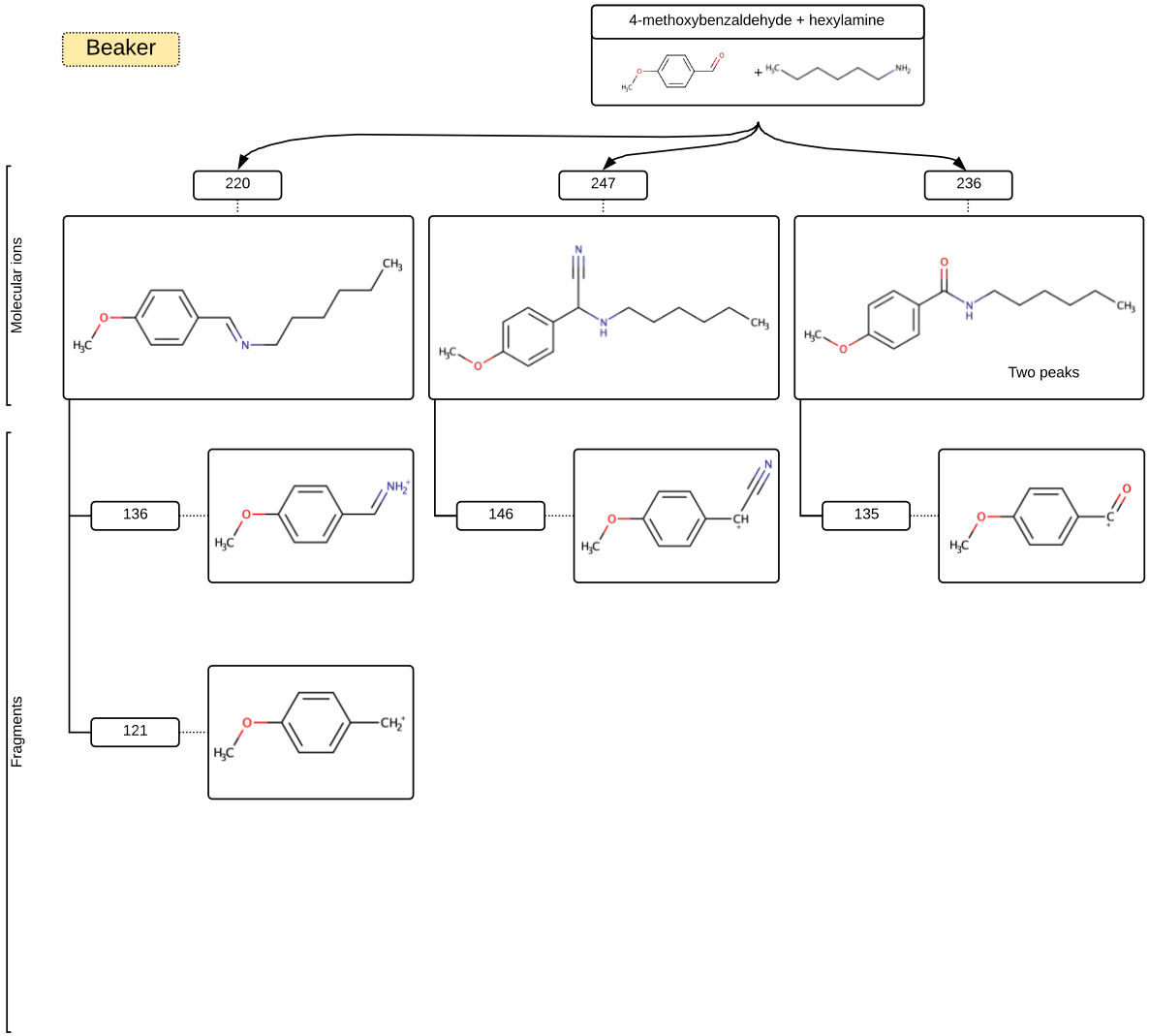


Table SI 2.72. Results for the reaction between hexylamine and 4-methoxybenzaldehyde in charged droplets (collected from the counter electrode).

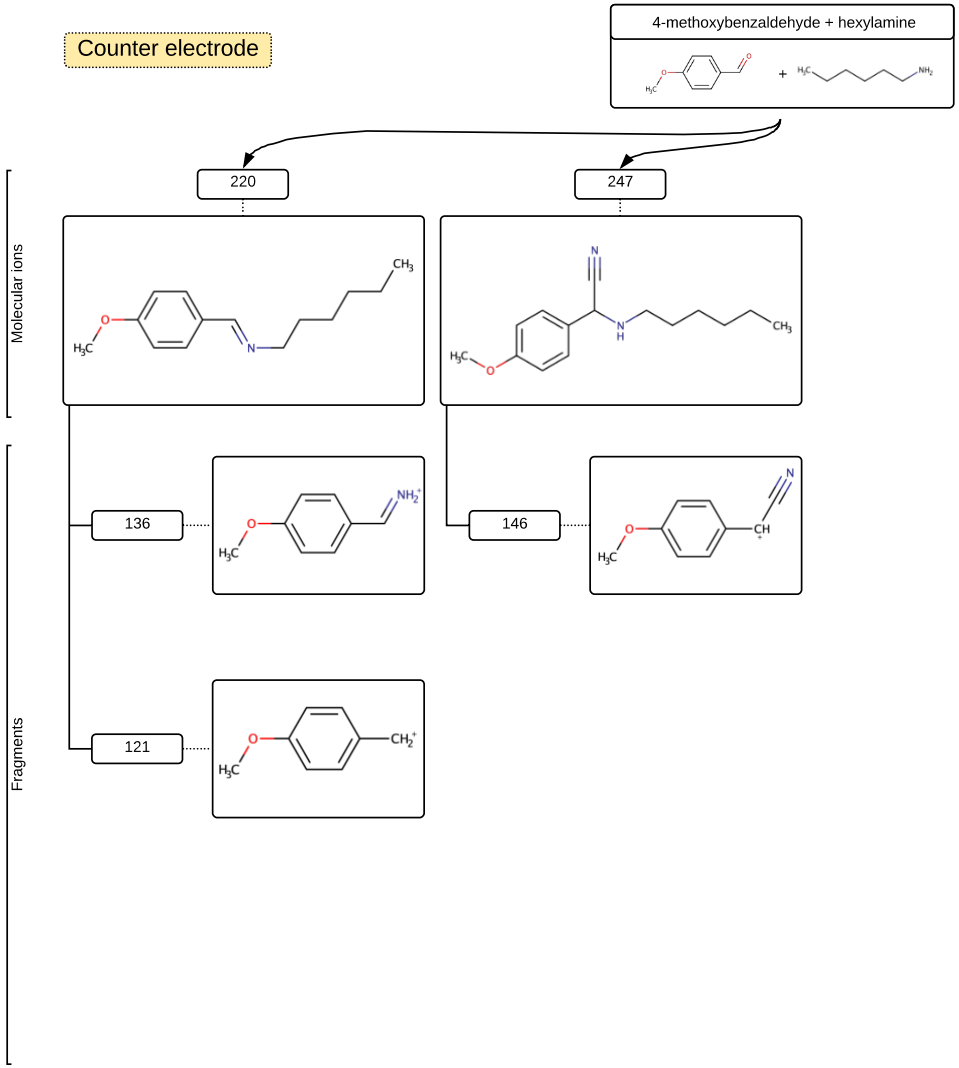


Table SI 2.73. Results for the reaction between hexylamine and 2-hydroxybenzaldehyde in bulk phase.

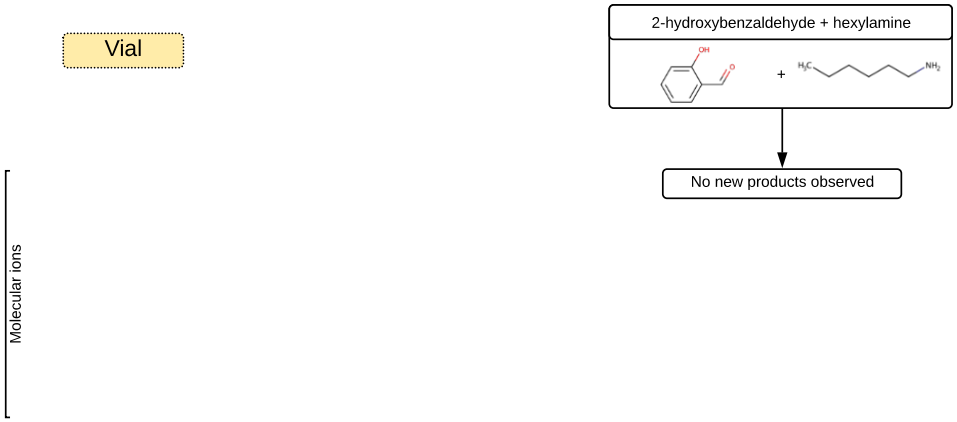


Table SI 2.74. Results for the reaction between hexylamine and 2-hydroxybenzaldehyde in charged droplets (collected from the beaker).

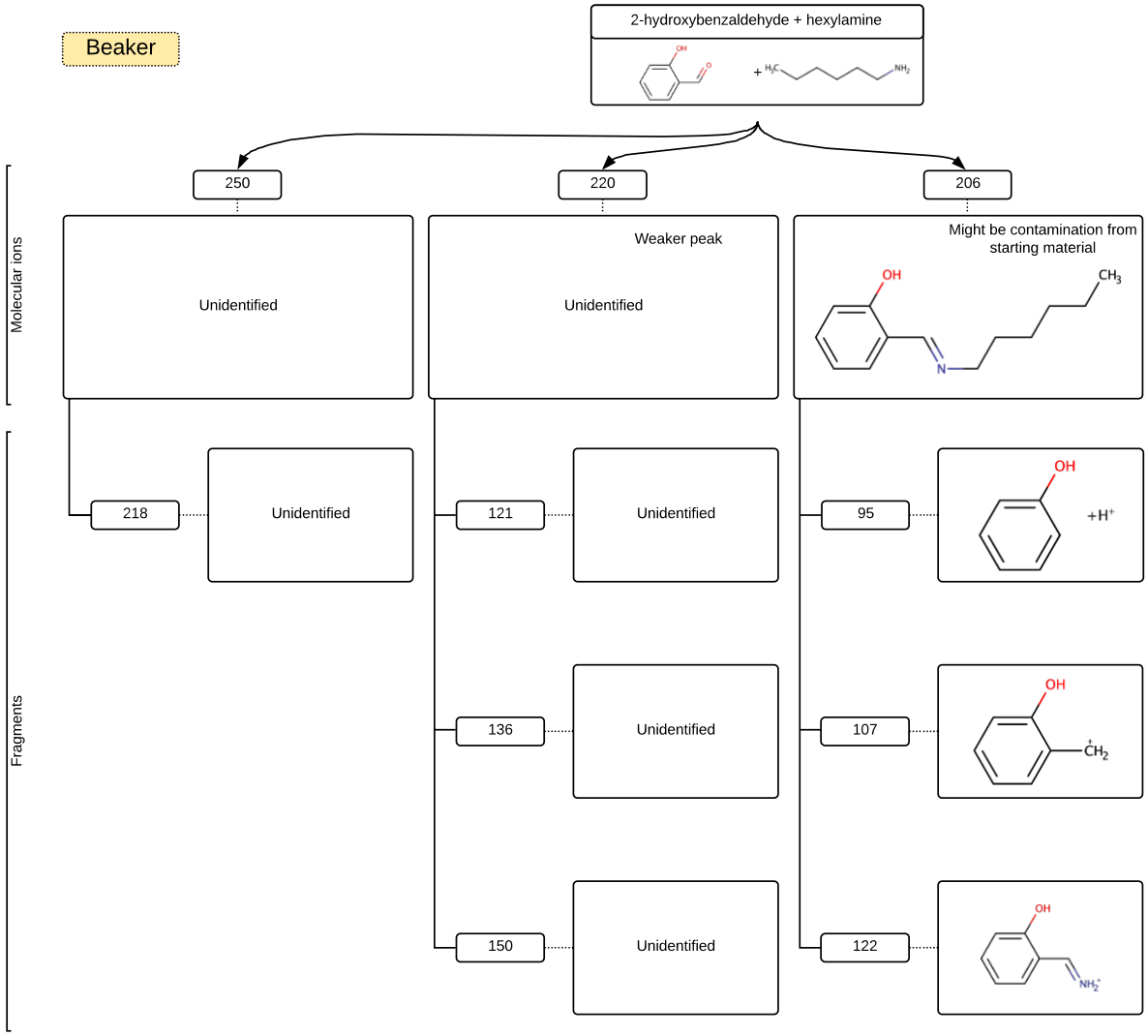


Table SI 2.75. Results for the reaction between hexylamine and 2-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

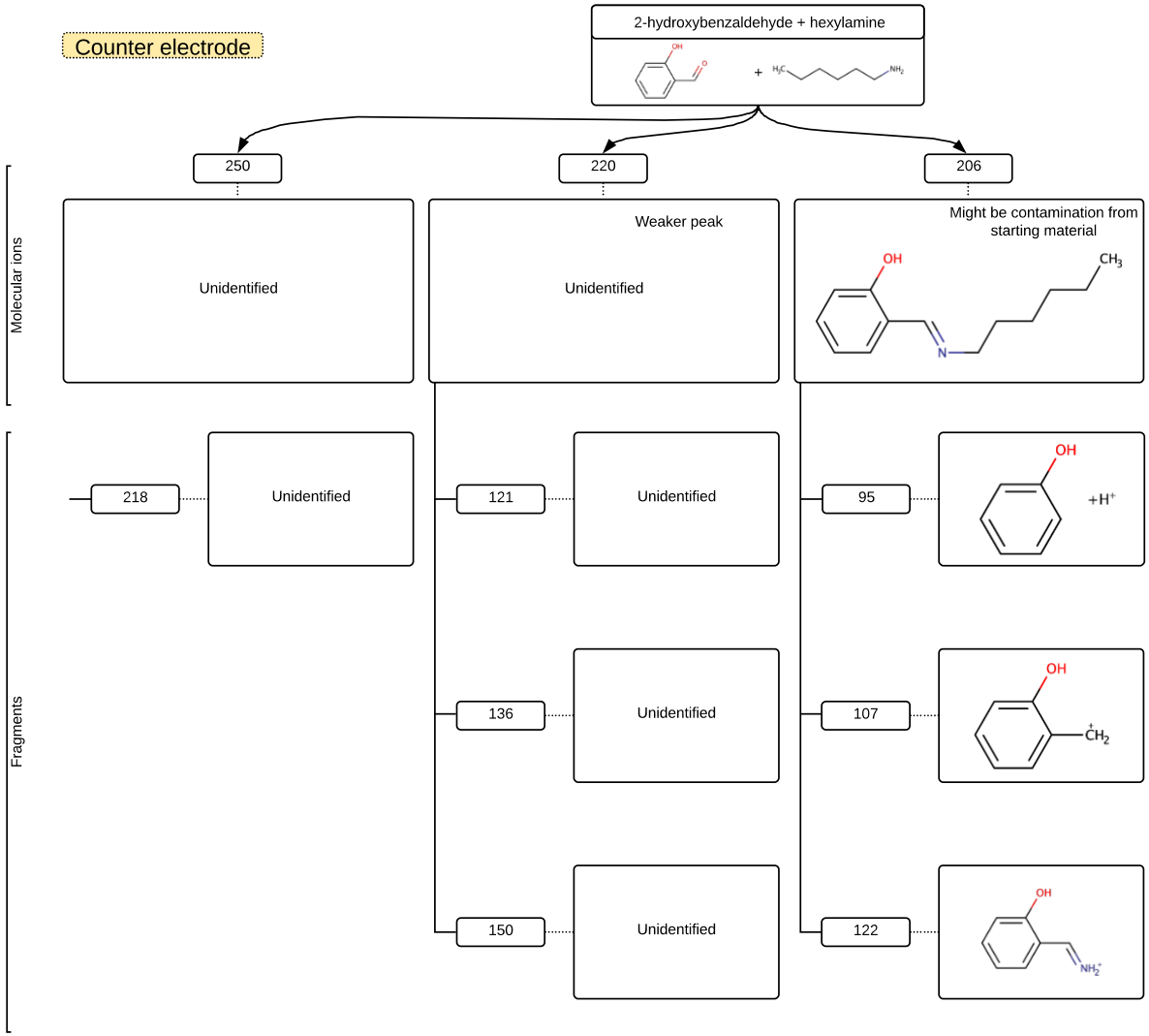


Table SI 2.76. Results for the reaction between hexylamine and 4-hydroxybenzaldehyde in bulk phase.

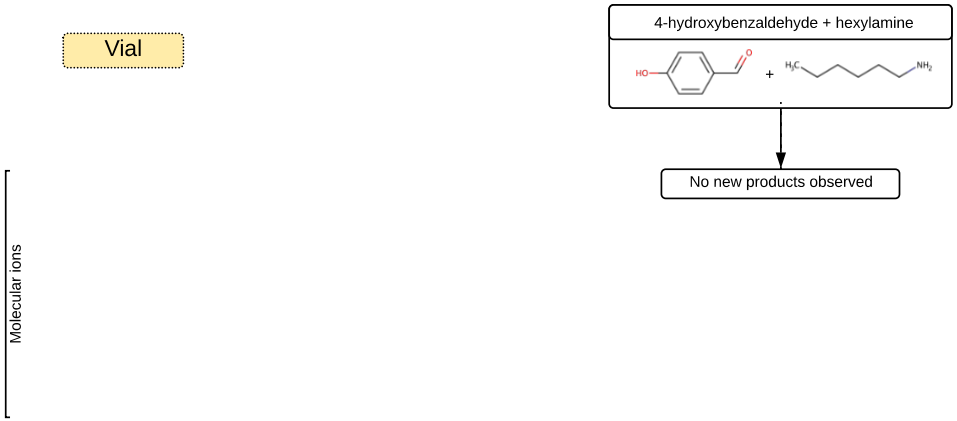


Table SI 2.77. Results for the reaction between hexylamine and 4-hydroxybenzaldehyde in charged droplets (collected from the beaker).

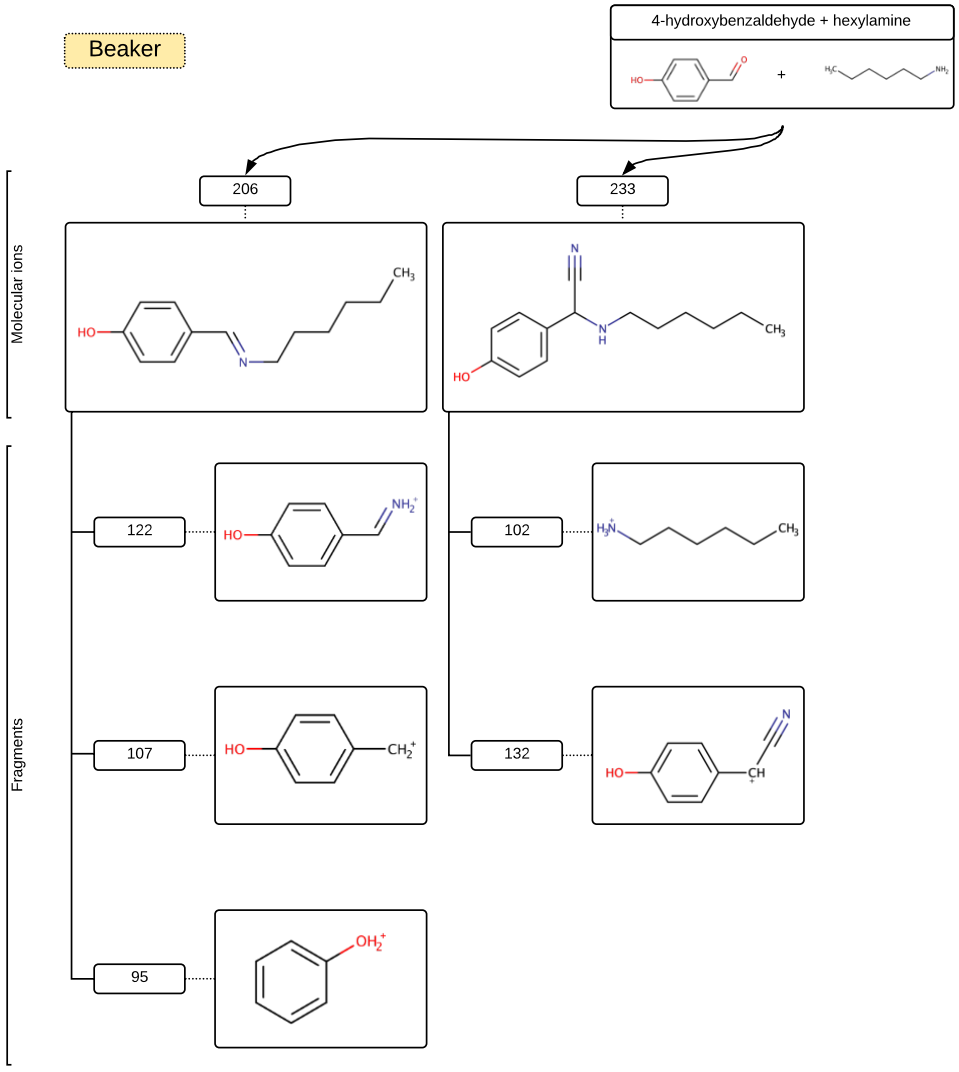


Table SI 2.78. Results for the reaction between hexylamine and 4-hydroxybenzaldehyde in charged droplets (collected from the counter electrode).

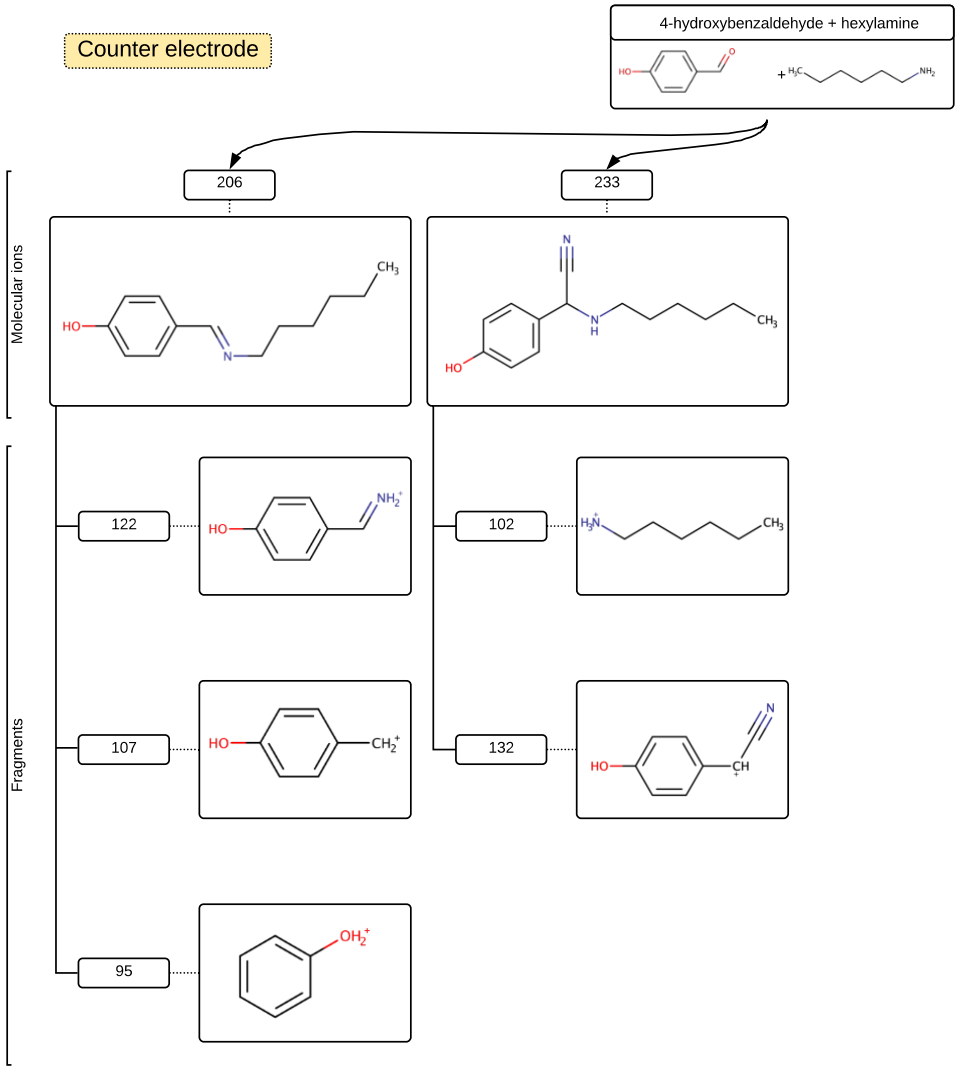


Table SI 2.79. Results for the reaction between hexylamine and 2-nitrobenzaldehyde in bulk phase.

Table SI 2.80. Results for the reaction between hexylamine and 2-nitrobenzaldehyde in charged droplets (collected from the beaker).

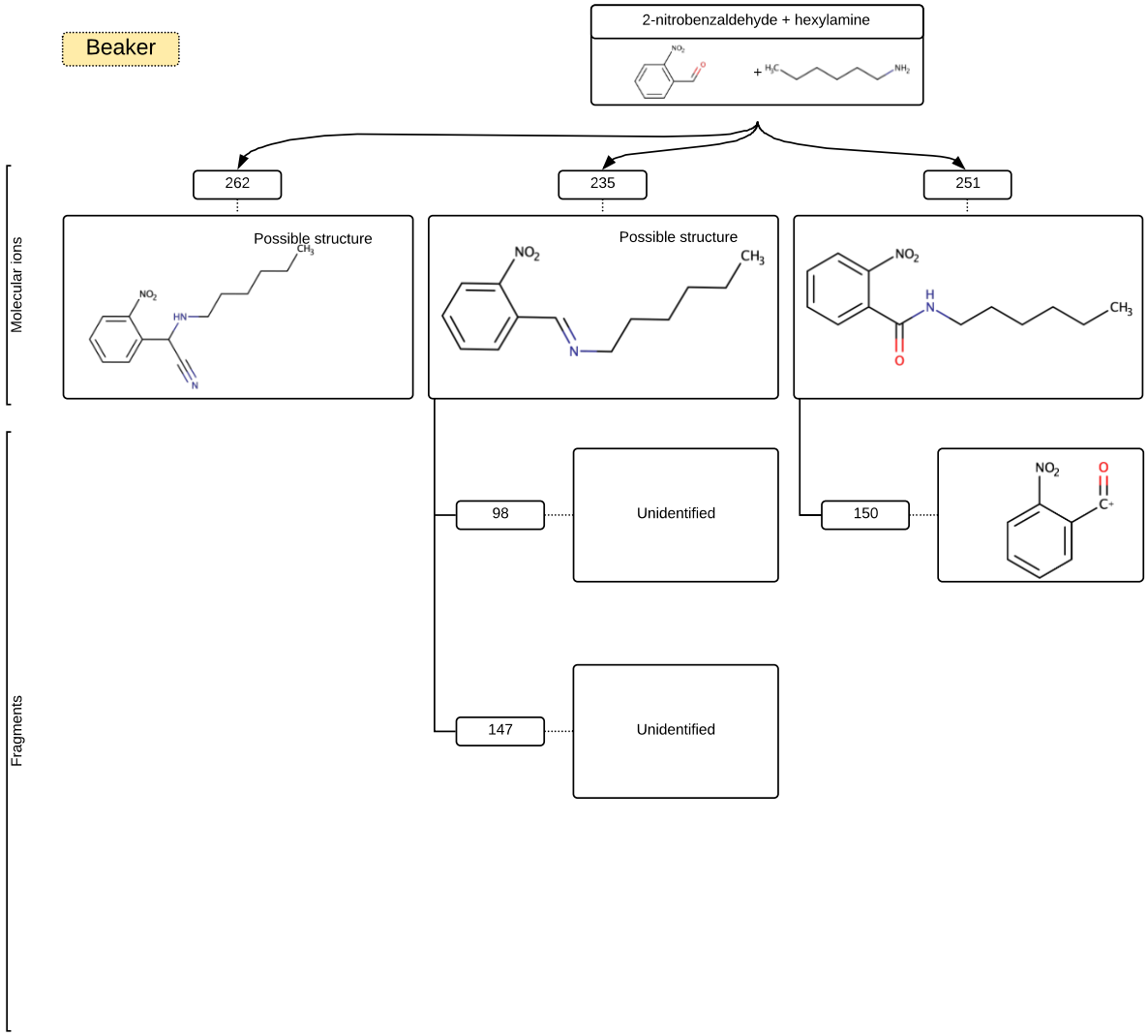


Table SI 2.81. Results for the reaction between hexylamine and 2-nitrobenzaldehyde in charged droplets (collected from the counter electrode).

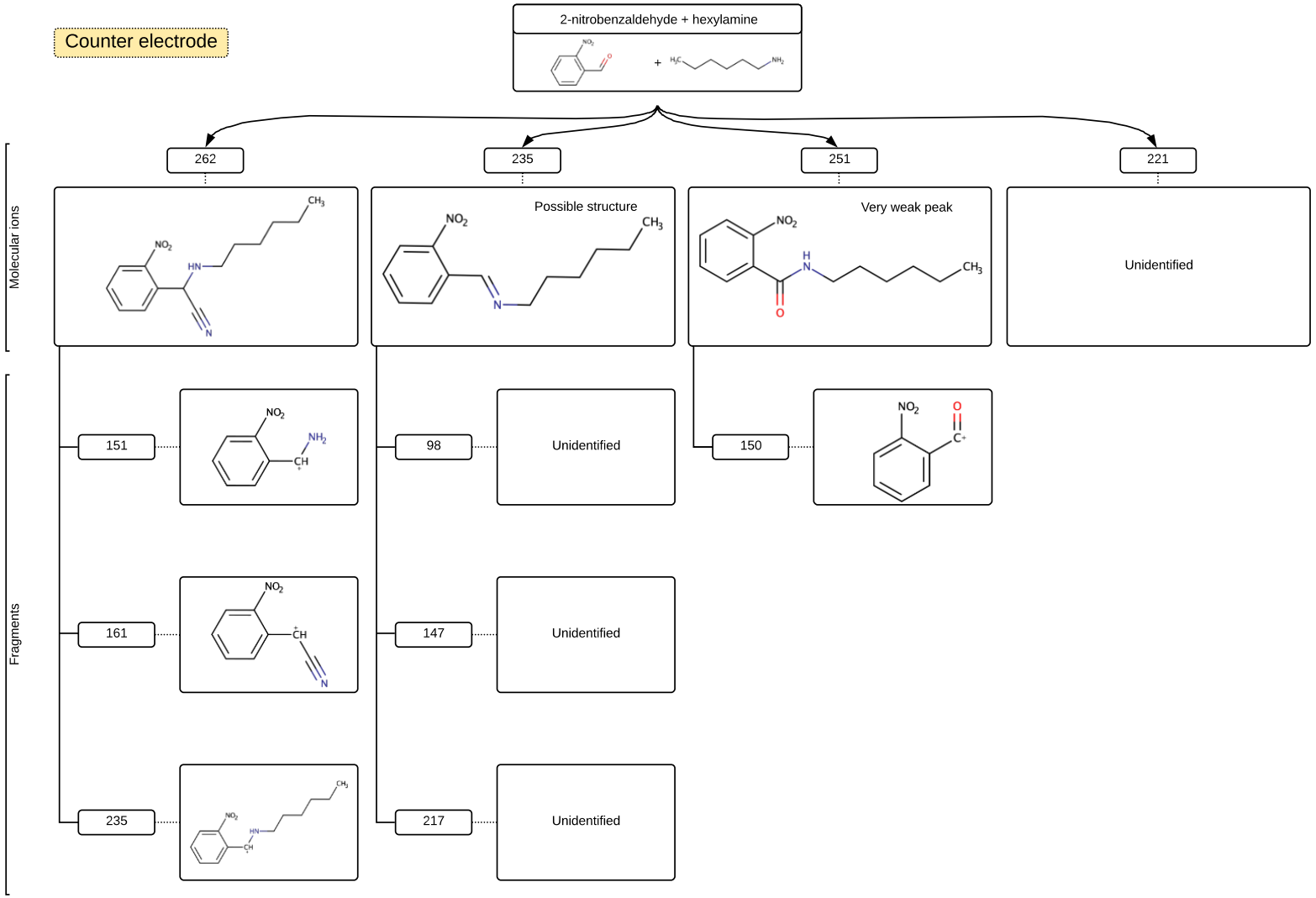
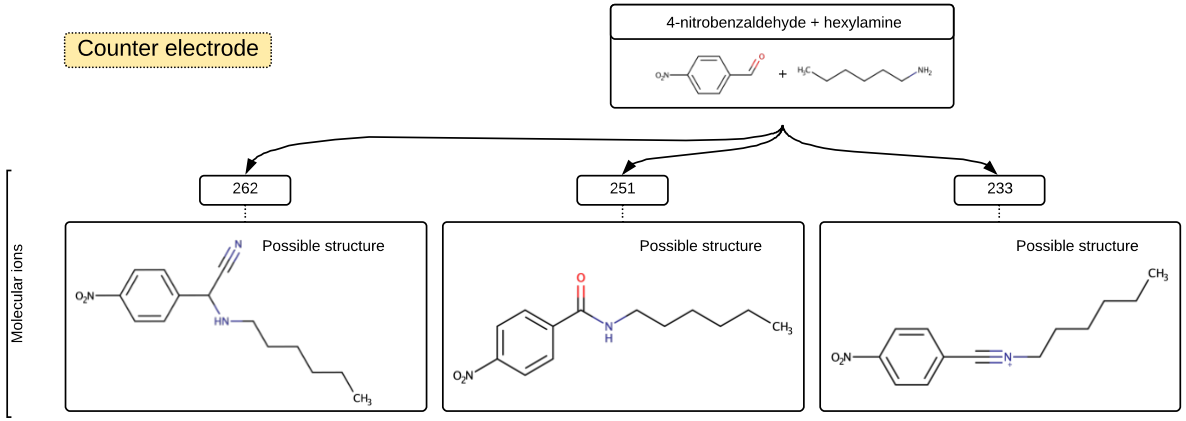


Table SI 2.82. Results for the reaction between hexylamine and 4-nitrobenzaldehyde in bulk phase.

Table SI 2.83. Results for the reaction between hexylamine and 4-nitrobenzaldehyde in charged droplets (collected from the beaker).

Table SI 2.84. Results for the reaction between hexylamine and 4-nitrobenzaldehyde in charged droplets (collected from the counter electrode).

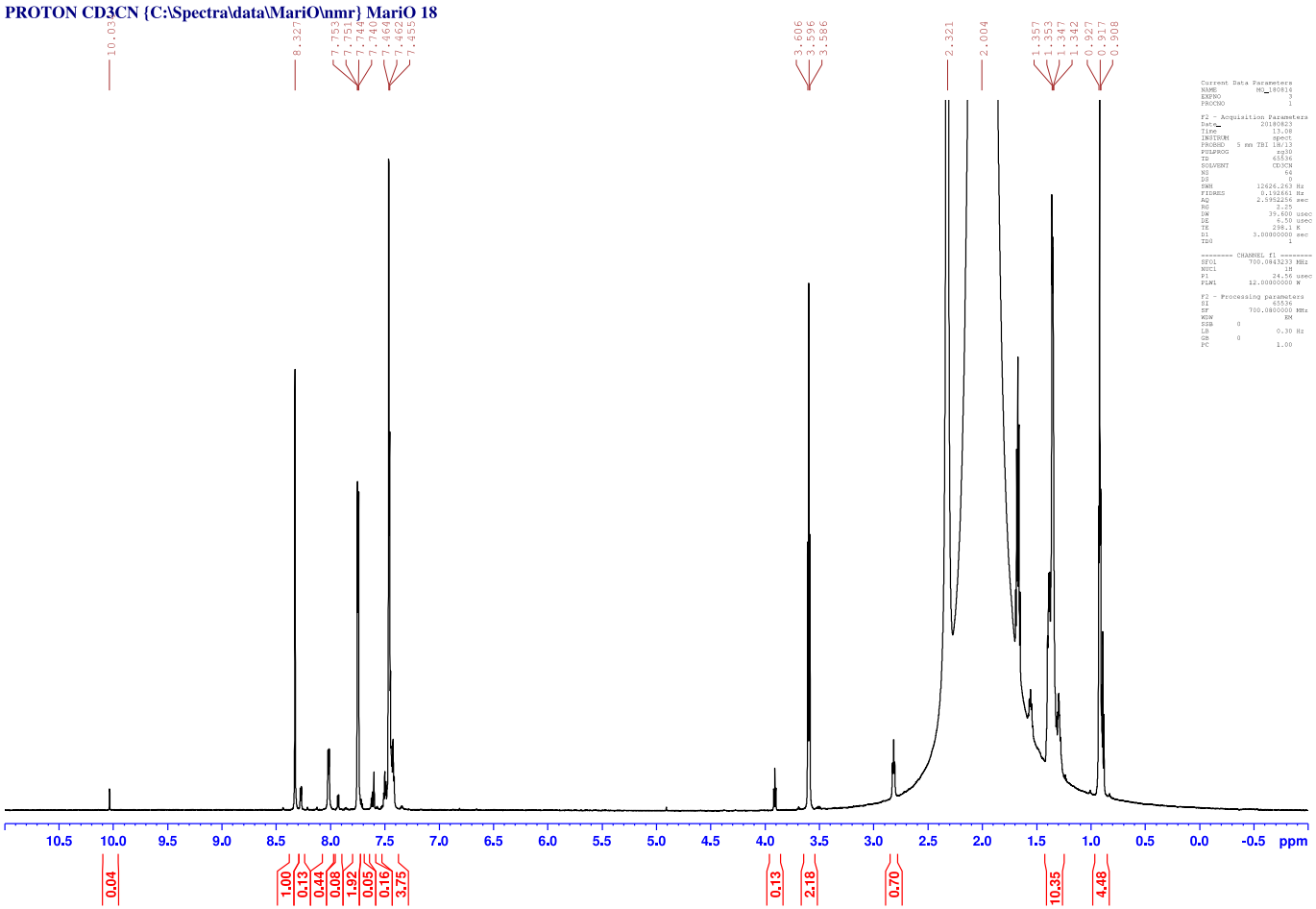


SI 3. NMR spectra

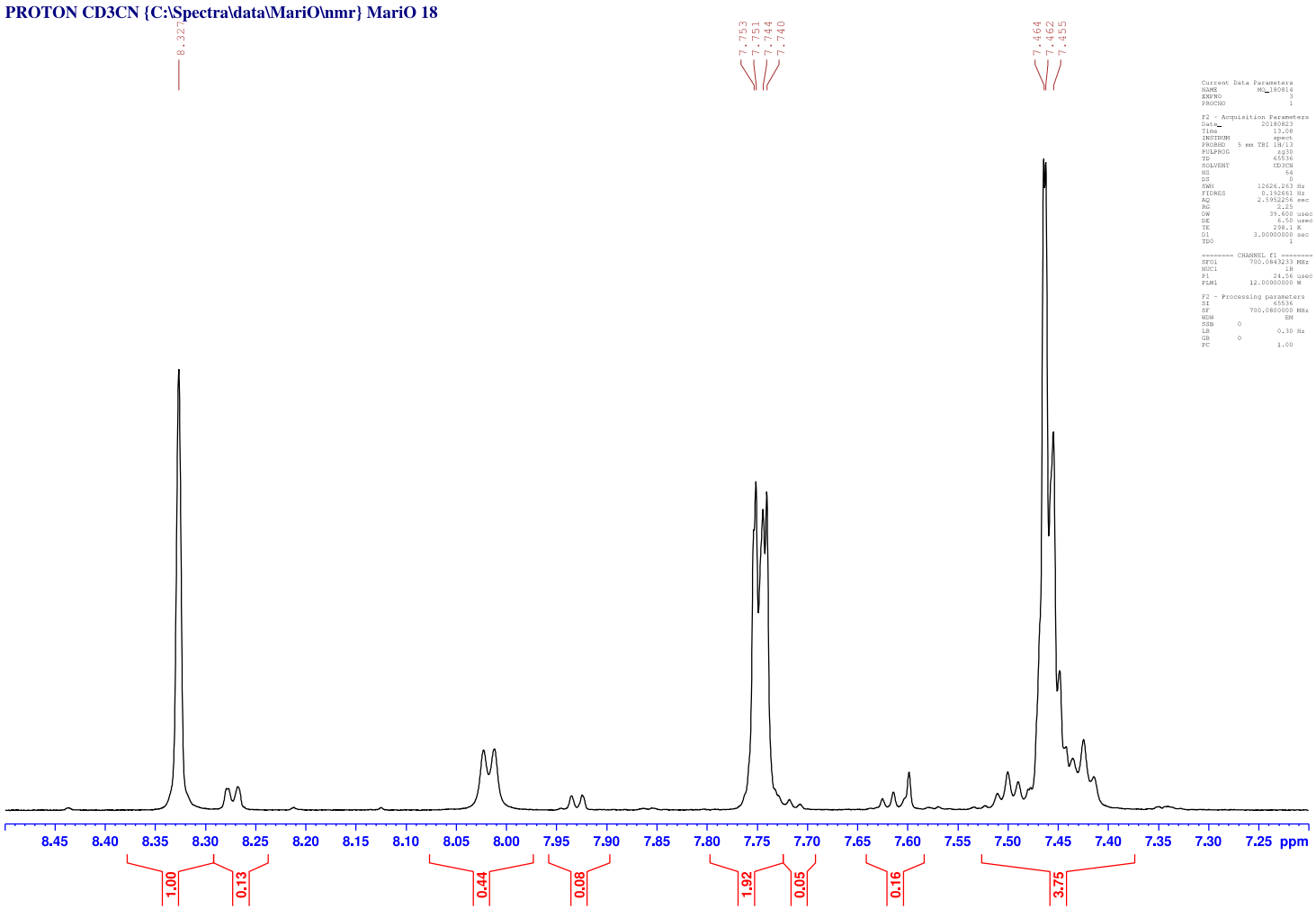
NMR spectra of the reaction mixture of hexylamine and benzaldehyde

Peaks corresponding to the imine product are the ones at 8.35 ppm, 7.45 ppm, 3.6 ppm, 1.70 ppm, 1.30 ppm and 0.90 ppm. Peaks corresponding to the amide product are the ones at 7.75 ppm, 7.60 ppm and 7.50 ppm. Peaks between 8.05 ppm and 7.90 ppm are unidentified.

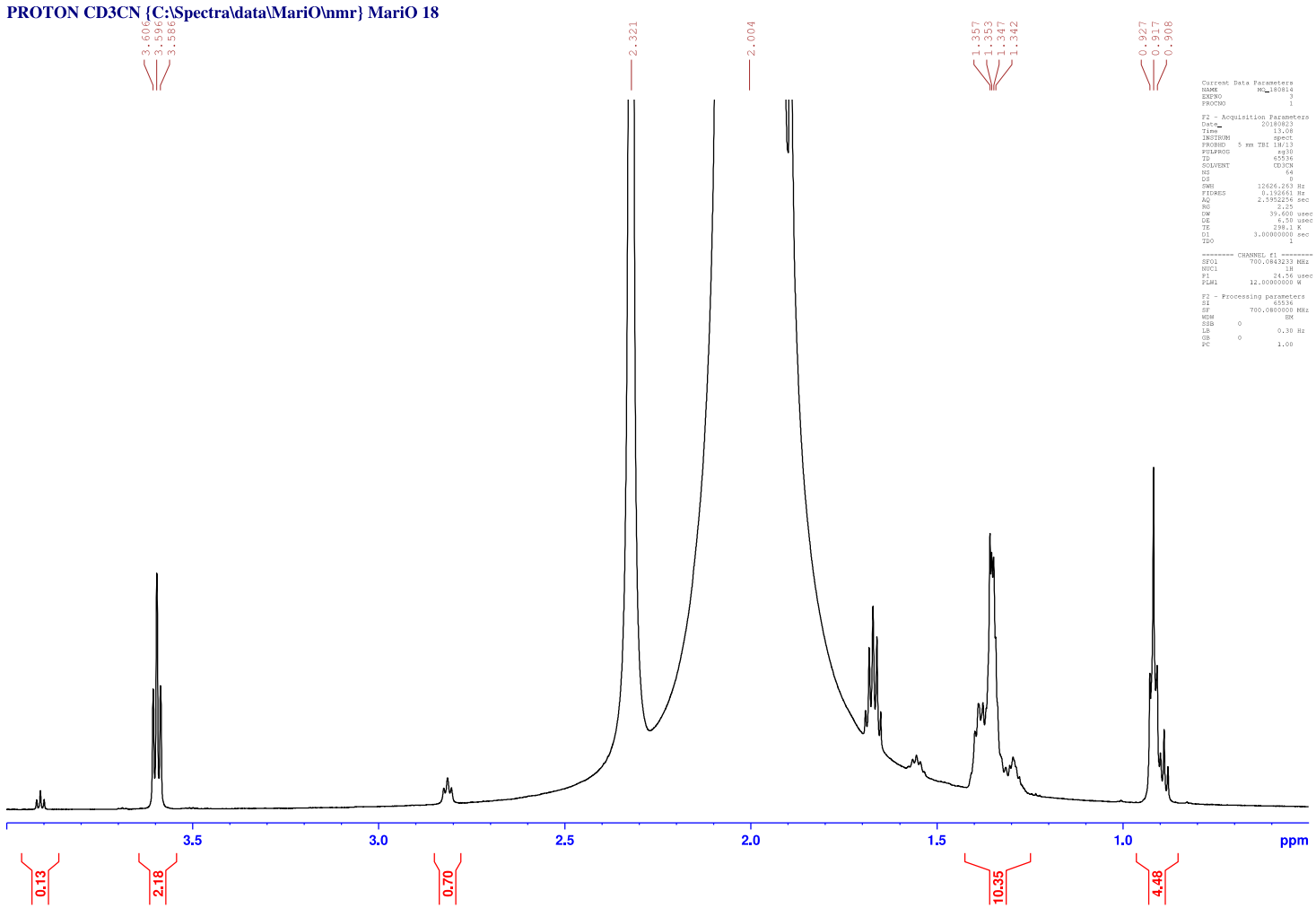
Spectrum SI 3.1. ^{1}H spectrum of hexylamine and benzaldehyde reaction product mixture (whole ppm range).



Spectrum SI 3.2. ^{1}H spectrum of hexylamine and benzaldehyde reaction product mixture (ppm 8.5–7.2).



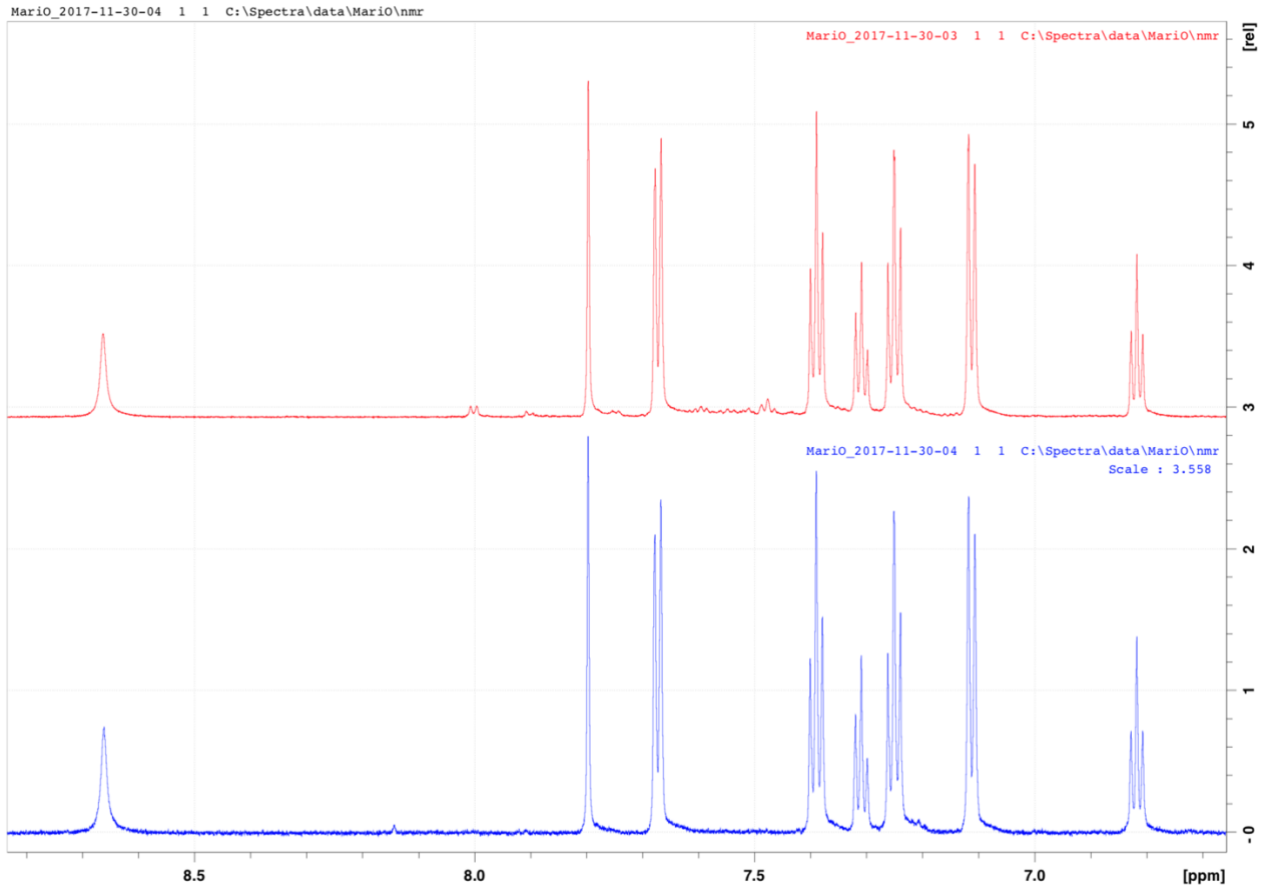
Spectrum SI 3.3. ^{1}H spectrum of hexylamine and benzaldehyde reaction product mixture (ppm 4.0–0.0).



NMR spectra of the reaction mixture of phenylhydrazine and benzaldehyde

All of the peaks correspond to the imine product.

Spectrum SI 3.4. ^{1}H spectrum of phenylhydrazine and benzaldehyde reaction product mixture (whole range) in charged droplets (blue) and in bulk phase (red).



Lihtlitsents lõputöö reprodutseerimiseks ja üldsusele kättesaadavaks tegemiseks

Mina, Mari Ojakivi,

1. annan Tartu Ülikoolile tasuta loa (lihtlitsentsi) minu loodud teose „Charged Droplets – Novel Media for Studying Reactions between Aldehydes and Amines/Hydrazines“, mille juhendaja on Anneli Kruve, reprodutseerimiseks eesmärgiga seda säilitada, sealhulgas lisada digitaalarhiivi DSpace kuni autoriõiguse kehtivuse lõppemiseni.

2. Annan Tartu Ülikoolile loa teha punktis 1 nimetatud teos üldsusele kättesaadavaks Tartu Ülikooli veebikeskkonna, sealhulgas digitaalarhiivi DSpace kaudu Creative Commonsi litsentsiga CC BY NC ND 3.0, mis lubab autorile viidates teost reprodutseerida, levitada ja üldsusele suunata ning keelab luua tuletatud teost ja kasutada teost ärieesmärgil, kuni autoriõiguse kehtivuse lõppemiseni.

3. Olen teadlik, et punktides 1 ja 2 nimetatud õigused jäävad alles ka autorile.

4. Kinnitan, et lihtlitsentsi andmisega ei riku ma teiste isikute intellektuaalomandi ega isikuandmete kaitse õigusaktidest tulenevaid õigusi.

Mari Ojakivi

26.05.2019