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Direct Amination of Benzene with Ammonia by Flow Plasma Chemistry

Victor Dupont,^[a] Stéphanie Ognier,^[a] Gabriel Morand,^{*,[a]} Cyril Ollivier,^{*,[b]} Louis Fensterbank,^[b] and Michael Tatouliau^[a]

Amine derivatives, including aniline and allylic amines, can be formed in a single-step process from benzene and an ammonia plasma in a microreactor. Different process parameters such as temperature, residence time, and plasma power were evaluated to improve the reaction yield and its selectivity toward aminated products and avoid hydrogenated or oligomerized products. In parallel, simulation studies of the process have been carried out to propose a global mechanism and gain a

better understanding of the influence of the different process parameters. The exploration of diverse related alkenes showed that the double bonds, conjugation, and aromatization influenced the amination mechanism. Benzene was the best reactant for amination based on the lifetime of radical intermediates. Under optimized conditions, benzene was aminated in the absence of catalyst with a yield of 3.8% and a selectivity of 49% in various amino compounds.

Introduction

The development of an efficient method for direct amination remains a considerable challenge in industrial agrochemistry and medicinal synthesis. Indeed, current reaction pathways do not meet new environmental objectives of green chemistry and require milder conditions. For example, the industrial synthesis of a common amine as aniline^[1] involves harsh and dangerous conditions such as the use of toxic compounds and high pressure and temperature^[4] which are in discord with sustainable chemistry.^[5]

Alternatively, plasma technology has become increasingly attractive as an original, more economical and environmental-friendly activation method.^[6,7] It consists of a gaseous source of reactive species such as electrons, radicals, ions as well as neutrals in different excited electronic states. It has already been widely explored for material surface treatment,^[8] gas and liquid depollution,^[9] and gas conversion.^[10] Recently, plasma has

also emerged as a promising tool to induce organic radical-based reactions. Indeed, it allows new synthesis pathway, limits the use of solvent, and can substitute conventional catalysts. Also, it can be easily generated in a safe way with electrical fields.^[11]

Most plasma applications consist in gas/gas^[12] or gas/solid reactions.^[13] However, such methods are not suitable for organic chemistry, which usually involves liquid phases. Only few technologies rely on plasma/liquid interaction due to the difficulty of stabilizing the interface. To date, different approaches have been developed; the most widely used methods consist of (i) a plasma jet on top of or in a liquid and (ii) the introduction of a liquid aerosol or a saturated gaseous phase in a plasma.^[14] Using the first approach (Figure 1a), X. Xu et al. aminated benzene with a nitrogen plasma^[2] and obtained a yield of 44% in arylamine adducts. However, the process was not selective for aniline synthesis and showed a broad diversity of aminated products, with the formation of diphenylamine, triphenylamine, and aminobiphenyl isomers. Moreover, it required the use of catalyst (MgO). Using the second approach (Figure 1b), J. Dieu et al. studied the amination of alkenes such as ethylene (to form ethylamine, yield of 17%, selectivity of 30%) and 1-octene (to form 1-octylamine, yield of 14%, selectivity of 18%) with an ammonia/helium plasma in a continuous reactor.^[3] This study showed promising results, but the reactant had to be a gas or diluted in a gaseous phase, which severely limits the process.

In parallel, the use of microfluidic system for plasma generation has progressively gained popularity to obtain an improved and controlled liquid/gas interface allowing mass and heat transfer in a continuous process.^[15,16,17] Moreover, sub-millimetric distance between the two electrodes facilitates the generation of homogeneous plasma (Paschen law). Using this approach, a microfluidic chip was developed^[18] permitting to maximize the interface between the liquid and plasma, which flows in two parallel canals. This diphasic plasma/liquid micro-reactor has already been used for organic chemistry and

[a] V. Dupont, Dr. S. Ognier, Dr. G. Morand, Prof. M. Tatouliau
Institut de Recherche de Chimie Paris, UMR 8247, 2PM group
Chimie ParisTech-PSL, PSL Université Paris, CNRS
11 rue Pierre et Marie Curie, 75005 Paris (France)
E-mail: gabriel.morand@chimieparistech.psl.eu

[b] Dr. C. Ollivier, Prof. L. Fensterbank
Institut Parisien de Chimie Moléculaire, UMR 8232, MACO group
Sorbonne Université, CNRS
4 place Jussieu, 75005, Paris (France)
E-mail: cyril.ollivier@sorbonne-universite.fr

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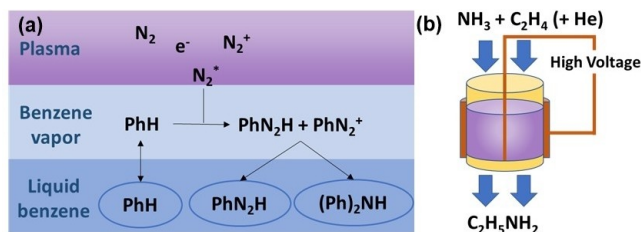


Figure 1. (a) Scheme of amination of liquid benzene with N_2 plasma by X. Xu *et al.*^[2]. (b) Scheme of amination of gaseous ethylene with NH_3 plasma by Dieu *et al.*^[3].

depending on the gas it is possible to select the reactive species and trigger specific chemical reactions. For example, our group has shown that argon plasma can promote olefin oligomerization^[15] and amidation reactions.^[19] On the other hand, gases such as dioxygen or carbon dioxide can directly functionalize molecules and induce oxidation^[16] or carbonylation.^[20] These microreactors have also been used to explore amination of cyclohexane with ammonia plasma.^[21] A promising yield of 3.2% in cyclohexylamine was obtained but various side products from the fragmentation of cyclohexane due to plasma activation were observed.

In this work, we explore the feasibility of using plasma in a microfluidic gas/liquid reactor to perform amination of benzene in a single step, without catalyst. This reaction is based on the plasma dissociation of ammonia to form NH_2° and H° (Eq. (1)).^[21] In this paper, the activation of benzene in contact of ammonia plasma was investigated using both experimental and theoretical (kinetic simulation studies with COMSOL Multiphysics software) approaches. The influence of key parameters was assessed to optimize the yield and the selectivity of the amination reaction. Finally, a series of related alkenes was investigated to evaluate the influence of the physicochemical properties of liquid reactants.



Results and Discussions

Characterization of the plasma

A pure NH_3 plasma was generated and characterized by optical emission spectroscopy (OES). Emission peaks could be observed in the range 200–1000 nm, which allowed to identify excited species contained in the gas phase (Figure 2a). The different identified peaks are located at 315 nm ($N_2^* C^3\Pi_u \rightarrow B^3\Pi_g 1-0$),^[22] 336 nm and 337 nm (NH° biradicals and $N_2^* C^3\Pi_u \rightarrow B^3\Pi_g 0-0$, respectively),^[22–26] at 357 nm ($N_2^* C^3\Pi_u \rightarrow B^3\Pi_g 0-1$)^[22,23,25,26] and 380 nm ($N_2^* C^3\Pi_u \rightarrow B^3\Pi_g 0-2$).^[22] This analysis confirmed the dissociation of ammonia in the plasma with the formation of NH° and excited neutrals N_2^* . Although it cannot be observed by OES, NH_2° is expected to be the major radical formed by ammonia dissociation.^[21,27]

Characterization of liquid products

Benzene was treated with the NH_3 plasma under the following conditions: a liquid flowrate of 12 $\mu\text{L}/\text{min}$ (corresponding to a residence time of 50 s in the reactor), a gas flowrate of 4 mL/min, an electrical sinusoidal signal of 20 kV at 2 kHz and a temperature of 20 °C. As shown by the chromatogram (Figure 2b), obtained by gas chromatography with flame ionization detection, the solution exiting the microreactor contained several products (identified by their mass spectrum using the data base of National Institute of Standards and Technology (NIST)). These products were classified into three categories: (i) unsaturated products (cyclohexadiene and cyclohexene), (ii) aminated products (aniline, two distinct cyclohexadienamines, and one cyclohexenamine), and (iii) dimers. The chromatogram revealed that 49% of products were aminated. Among these products, 35% are associated to aniline, giving a global selectivity for aniline of 17%. In this chromatogram, no poly-aminated products were visible and dimeric ones did not contain any nitrogen.

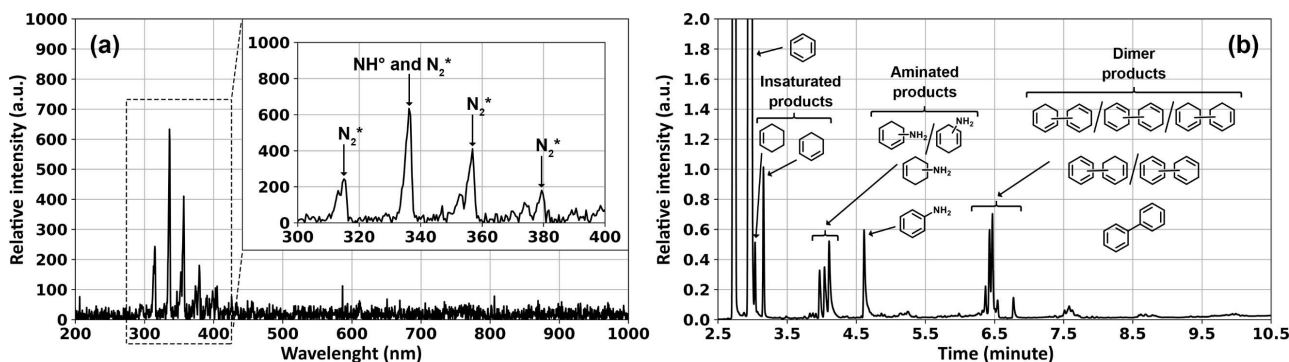


Figure 2. (a) Optical Emission Spectrum of the NH_3 plasma (12 kV, 2 kHz, 10 mL/min, atmospheric pressure, and ambient temperature). (b) Chromatogram (2.5–7 min) of benzene treated with a NH_3 plasma (benzene 6 $\mu\text{L}/\text{min}$, NH_3 2 mL/min, 20 kV, 2 kHz, 20 °C) obtained by gas chromatography with flame ionization detection.

Rationalization of results

In an ammonia plasma, the benzene could be activated in different ways. It would react with primary radicals formed from NH_3 dissociation (Eq. (1)) in three different ways (Eqs. (2), (3), and (4)) or with the plasma generated electrons (Eq. (5)). According to literature, reactions (3) and (4) have kinetic constants around 4 orders of magnitude lower than the reaction 2 (Supporting Information). Therefore, reaction of benzene with primary radicals would give almost exclusively the cyclohexadienyl radical $\text{C}_6\text{H}_7^\bullet$. By assuming that aniline is formed from the recombination of phenyl radical $\text{C}_6\text{H}_5^\bullet$ and amino radicals (Eq. (6)), benzene should also be directly activated by electron impacts and breaking of a C–H bond (Eq. (5)).



Therefore, activation of benzene in an ammonia plasma would lead to the formation of $\text{C}_6\text{H}_7^\bullet$ and $\text{C}_6\text{H}_5^\bullet$ (Eqs. (2) and (5)). Once the phenyl radical is formed, it can react with $\text{NH}_2^\bullet$ to produce aniline (radical termination reaction, Equation (6)). It can also react with another $\text{C}_6\text{H}_5^\bullet$ (Eq. (7)) or $\text{C}_6\text{H}_7^\bullet$ (Eq. (8)) to form dimers. In the same way, $\text{C}_6\text{H}_7^\bullet$ radicals formed by the reaction (2) can react with $\text{NH}_2^\bullet$ to produce cyclohexadienamine (Eq. (9)). It can also react with $\text{H}^\bullet$ to form cyclohexadiene (Eq. (10)) or with another $\text{C}_6\text{H}_7^\bullet$ radical to obtain dimers (Eq. (11)).



Finally, formed cyclohexadienes could be activated, in the same way as benzene to form $\text{C}_6\text{H}_7^\bullet$ (Eq. (12)) and cyclohexenyl radical $\text{C}_6\text{H}_9^\bullet$ (Eq. (13)). Further reactions of these radicals would produce cyclohexenamine (Eq. (14)), cyclohexene (Eq. (15)) and dimers (Eqs. (16–18)). All those reactions could explain the formation of all the compounds identified in the chromatogram.



As mentioned above, no poly-aminated products or aminated dimers were formed in the plasma/liquid micro-reactor. Those results would indicate that the dimers and the mono-aminated products cannot react again once formed, contrary to the cyclohexadiene substrates, which could undergo multiple reactions as previously proposed. This observation highlights the importance of the volatility of products (Table 1, the vapor pressure of cyclohexadienamine and cyclohexenamine are not known but can be supposed to be between aniline and cyclohexylamine). Given their low vapor pressure, it is likely that aminated products and dimers readily condense once created and remain in the liquid phase where they are less exposed to reactive plasma species. On the other hand, due to their high volatility, substantial amounts of cyclohexadienes and cyclohexene are still present in the gas phase where they can react again with plasma-generated active species. This

Table 1. Explored substrates and their vapour pressure.

Name	Type of compound	Vapor pressure at 20 °C (bar)
Benzene	reactant	0.1001 ^[29]
1,3-cyclohexadiene	Hydrogenated product	0.1031 ^[30]
1,4-cyclohexadiene	Hydrogenated product	–
Cyclohexene	Hydrogenated product	0.0938 ^[30]
Aniline	aminated product	0.00058 ^[31]
Cyclohexadienamine	Aminated product	–
Cyclohexenamine	Aminated product	–
Cyclohexylamine	Example for the amines	0.00908 ^[32]
Biphenyl	Dimer	0.00002 ^[33]

confirms the previously emitted hypothesis^[16] that plasma/liquid reactions mainly occur in the gas phase or at the gas/liquid interface. Therefore, the equilibrium between the two phases exerts a crucial influence on the performance of chemical reactions in terms of conversion and selectivity. Thus, the influence of the vapor pressure will be further evaluated in this publication. Finally, excited species observed by OES (such as N_2^* and NH^+) did not seem to take part in the mechanism of reactions. This could be explained by a low reactivity or low concentration of those species.

Simulation study

The amination reaction of benzene and all previously mentioned reactions were simulated using the software COMSOL Multiphysics. The kinetic model was constituted of 22 reactions and is detailed in Supporting Information. Due to their low volatility, no reaction between dimers or aminated products and reactive species were considered. From the results of Lepoetre et al.,^[21] the plasma was simulated by dissociating 1 mmol/m³ of NH_3 into NH_2^+ and 0.01% of the evaporated benzene for each plasma discharge, every 1 ms (plasma generated at 1 kHz based on Lepoetre et al. results^[21] (benzene dissociation is based on its concentration, detailed are in Supporting Information). Kinetic constants were obtained from NIST^[28] except for reactions (6), (9–11), and (13–19). As the kinetic of those reactions remains unknown, it was fixed to $4E-11$ m³/(s.mol) (average of all the kinetics known) or fixed to the constant of similar reactions (Supporting Information). Finally, owing to the mass transfer efficiency in microreactors, gas and liquid were assumed in thermodynamic equilibrium at any time. The simulation outputted selectivities of 11% for aniline, 35% for aminated-hydrogenated products, 11% for hydrogenated products, and 43% for dimers. In comparison, experiments showed selectivities of 16%, 31%, 20%, and 33%, respectively. The simulation also gave a total yield of 2% in aminated products, whereas it was estimated to 1.4% experimentally. Differences can be explained by the uncertainties on the values used in the kinetic model, namely the kinetic constants and the source terms of the plasma dissociation of NH_3 and benzene. Despite these differences, the model reproduces the observed results quite faithfully and can be therefore useful to evaluate and understand the influence of various process parameters.

Optimization of the process parameters

To improve the efficiency of the process in terms of yield and selectivity, three parameters were studied: (i) the residence time (controlled by the liquid flowrate), (ii) the temperature (controlled with a thermostatic bath), and (iii) the plasma power (changed by varying the voltage and frequency of the electric signal). Those parameters were investigated both experimentally and theoretically using the COMSOL model.

Experimentally, the residence time was increased from 25 to 100 s by varying the liquid flowrate from 24 μ L/min to 6 μ L/min

(gas flowrate between 2 and 10 mL/min, temperature set to 20°C). According to the simulation, an increase of the residence time from 25 to 100 s improved the yield in aminated products (Figure 3a) with no variation of the selectivity. In the experiences, selectivity changed for hydrogenated products and aniline between 25 and 100 s (from 21% to 11% for hydrogenated and 13% to 21% in aniline) and yield in aminated products increased from 0.6% to 2.6%. Increasing residence time promotes activation of benzene, which should increase the conversion, thus the yield of all products. The decrease in the selectivity of hydrogenated products with residence time can be explained by their reactivity with plasma active species combined with their relative high volatility as explained previously (they stay longer in the gaseous phase and have more time to react). The increase of the selectivity in aniline could be explained by (i) the reactivity of C_6H_8 being able to form benzene which could then produce aniline and (ii) the increase of the pressure when the residence time decreases (by increasing the gas flow) which plays a role on the energy of the plasma and thus the activation of the benzene by electrons (Eq. (5)). The yield in amino compounds increased with residence time in the simulation results. Finally, the best yield in amino compounds is 2.6% with the highest residence time (100 seconds).

Both experimentally and theoretically, rising temperature increased the selectivity of dimers (Figure 3b) (from 33% at 20°C to 47% at 45°C) and the maximum yield obtained in amino compound was 1.8% at 35°C (linked to the maximum of selectivity in amino compounds at 35°C). In the simulation, results are similar but the yield in aminated products still increases. These results could be related to a promotion of the formation of phenyl radicals due to higher benzene concentration in the gas phase. Indeed, when increasing the temperature, benzene vapor pressure increases (0.1 bar at 20°C, 0.2 bar at 35°C, and 0.3 bar at 45°C). This explains the improved yield of all products such as aminated compounds (Figure 3b). Indeed, Increasing the temperature promotes the formation of phenyl radicals but not of NH_2^+ . As a result, dimerization reactions, involving two phenyl radicals, are favoured. In the simulation, selectivity in amino compounds decreased with temperature as with experimental results where it decreases after 35°C. Moreover, the experimental yield at 45°C was not as high as expected. Both observations could be explained by the formation of some oligomers, which were not visible in the chromatogram (too heavy to be analysed on the gas chromatography), and thus, not included in the calculation of experimental selectivity. This is corroborated by the fact that it was not possible to test higher temperatures experimentally because of clogging in the reactor due to benzene polymerization. Also, it was not possible to test lower temperature as benzene becomes solid below 5°C.

The impact of the plasma power (directly related to frequency and voltage) was also evaluated. Concerning frequency, simulation studies showed that the characteristic time of the consumption of all radical after an ammonia plasma discharge was around 0.03 ms. Therefore, each discharge of plasma under 33 kHz should be independent from others and

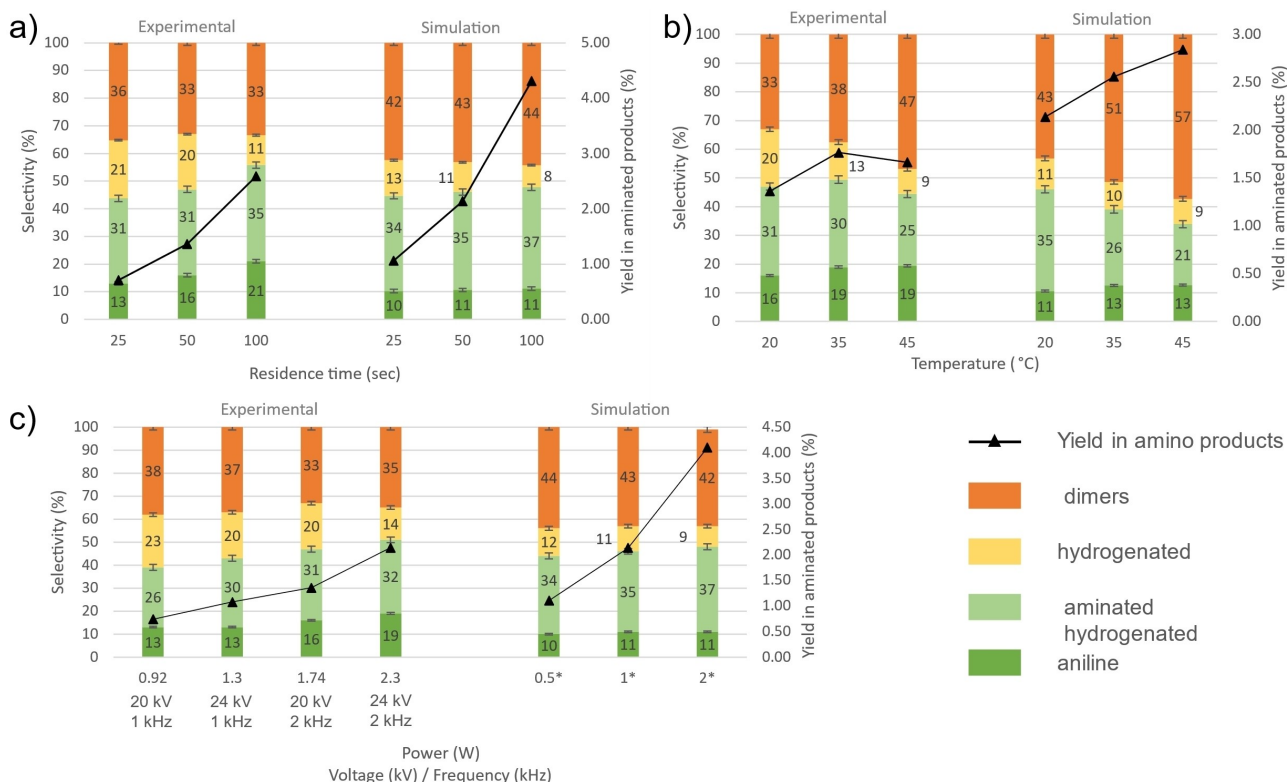


Figure 3. (a) Evolution of selectivity and yield in amino compounds with different residence time (100, 50 and 10 seconds) with benzene and ammonia plasma experimentally (liquid flowrate variable, gas flowrate variable, 20 kV, 2 kHz, 20 °C) and in simulation. (b) Evolution of selectivity and yield in aminated products with different temperature (20, 35 and 45 °C) with benzene and ammonia plasma experimentally (liquid 12 μ L/min, gas flowrate 4 mL/min, 20 kV, 2 kHz, temperature variable) and in simulation. (c) Evolution of selectivity, yield in amino compounds and measured power with different plasma parameters (20 kV 1 kHz, 20 kV 2 kHz, 24 kV 1 kHz, 24 kV 2 kHz) with benzene and ammonia plasma experimentally (liquid 12 μ L/min, gas flowrate 4 mL/min, voltage, and frequency variable, 20 °C) and in simulation (*arbitrary value for frequency).

increasing the frequency should linearly increase the number of activated species (radicals such as $\text{NH}_2^\bullet$ and $\text{C}_6\text{H}_5^\bullet$). Indeed, simulation showed that the yield in amino compounds was proportional to the frequency (from 0.5 kHz to 2 kHz, $R^2 = 0.9999$), without affecting selectivity (Figure 3c). Experimentally, when frequency was doubled, the yield in aminated products doubled as expected (from 0.7% to 1.4% with 20 kV and from 1.1% to 2.1% with 24 kV), and the selectivity did not change. Similarly, the voltage was expected to increase the electronic density as described in literature.^[6] Experimentally, when voltage increased (from 20 to 24 kV), yield in amino compounds increased from 0.7% to 1.1% at 1 kHz, and from 1.4% to 2.1% at 2 kHz. Finally, increasing plasma power by varying frequency and voltage permitted to increase the yield in aminated products; the best yield obtained being 2.1% with 2.3 W (24 kV–2 kHz) (Figure 3c), whereas no variation of the selectivity was observed. Yield in amino compounds was linearly linked to the measured power of plasma ($R^2 = 0.98$).

Optimized process parameters

Finally, under optimized conditions (24 kV, 2 kHz, 35 °C, residence time 100 s, liquid flowrate 6 μ L/min, gas flowrate 2 mL/min) with benzene under ammonia plasma, the yield in

aminated products reached $3.8\% \pm 0.2\%$ (1.7% for aniline and 2.1% for aminated and hydrogenated products).

Other reactants

In addition to benzene, other substrates were tested to evaluate the influence of the double bonds conjugation, aromaticity, and vapor pressure on the amination selectivity. The list of starting materials and resulting selectivities are presented in Table 2. Respective chromatograms can be found in the Supporting Information.

Using cyclohexane, many side products were obtained due to fragmentation. As a result, the selectivity of aminated products and dimers was lower (16% and 33%, respectively) than for cyclohexene (28% and 58%, respectively). Of note, the selectivity in aminated products with cyclohexane is close to the results obtained by Lepoetres et al.^[21] (13%). Fragmentation of cyclohexane could be explained by the lower energy bond dissociation of the C–C (350 kJ/mol) in comparison with the C–H one (> 400 kJ/mol). Also C=C requires more energy to be broken (614 kJ/mol) against C=C–H bond (427 kJ/mol).

Selectivity in aminated products with cyclohexadienes was lower than with cyclohexene (16% and 18% for 1,3- and 1,4-cyclohexadiene) but increased with benzene (49%). The

Table 2. Explored substrates and results.

Name	Vapor pressure (bar)	Selectivity		
		Hydrogenated	Aminated	Dimers
Cyclohexane	0,1033	51 ^[a]	16	33
Cyclohexene	0,0938	14	28	58
1,3-cyclohexadiene	0,1031	8	16	76 ^[b]
1,4-cyclohexadiene	–	38	18	44
Benzene	0,1001	17	49 ^[c]	34
Octene	0,0175	– ^[d]	32	68
Dodecene	0,0001	– ^[e]	4	96

[a] Includes cyclohexene, fragmentation products from cyclohexane (toluene, ethyl cyclohexane, iso cyclohexane) and phenol. [b] Presence of non-identified heavier products which are placed in the dimers area for the selectivity calculation. [c] In the amino product, hydrogenated aminated product 65% and aniline 35%. [d] Formation of octane but impossible to separate it from the octene peak. [e] Formation of dodecane but impossible to separate it from the dodecene peak.

opposite trend was observed with dimerization (Table 2). Dimerization requires a collision between two intermediates. It can be noticed that a radical formed has more probability to react with $\text{NH}_2^\bullet$ or $\text{H}^\bullet$ than with another activated radical (based on the concentration of the various radicals in the plasma obtained with simulation). Therefore, it may be expected that species stabilized by resonance (Supporting Information) should have more probability to encounter another activated substrate and to form dimers. This could explain higher dimerization with cyclohexadienes. This marks a contrast with the unstabilized $\text{C}_6\text{H}_5^\bullet$ which should react more with $\text{NH}_2^\bullet$.

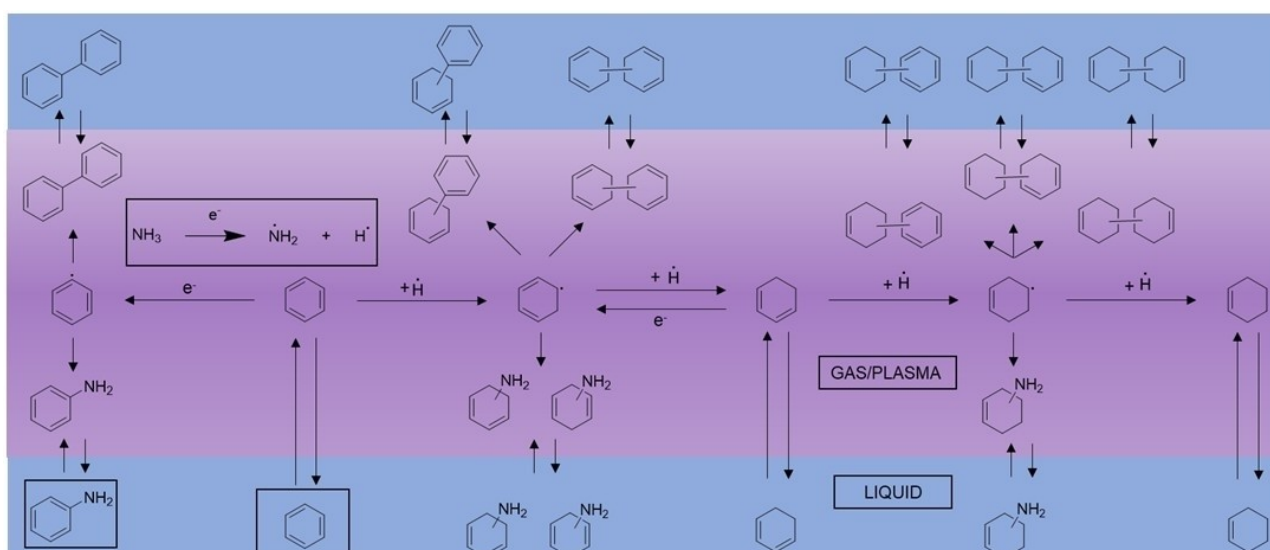
The reaction was also performed with two linear alkenes: octene and dodecene. The resulting selectivities in aminated products were 32% and 4% respectively. The difference in

reactivity could be explained by the volatility (Table 2). Indeed, dodecene is present in a smaller amount than octene in the gas phase explaining that it is less inclined to react with the $\text{NH}_2^\bullet$. It is important to underline that the product obtained is not a terminal amine but a Markovnikov amination in opposition with the work of Dieu et al.^[3]

Conclusions

Benzene has been directly aminated by ammonia plasma in a flow microreactor without catalyst. The mechanism was proposed by investigating related molecules, parameters of the process and kinetic simulations on COMSOL Multiphysics (Figure 4). It was shown that benzene can be activated by electrons or $\text{H}^\bullet$. The three main type of products obtained were (i) hydrogenated, (ii) aminated, and (iii) dimers. The yield can be improved by increasing the residence time, temperature and plasma power as they enhance the contact between benzene and reactive species in the plasma. Under optimized conditions, a selectivity of around 50% in amino compounds was obtained giving a yield of $3.8\% \pm 0.2\%$ (1.7% for aniline and 2.1% for aminated and hydrogenated). The reaction selectivity was influenced by the stability of the radical intermediates, and it has been suggested that amination was favoured on intermediates not stabilized by resonance. Furthermore, all results tend to confirm that all reactions occurred in the gas phase or at the gas/liquid interface. Once formed, aminated compounds condense in the liquid phase and do not react anymore, leading to mono-amination.

This original process has a potential to perform organic amination on other molecules such as heterocycles or various alkenes. Hydrogenation of aromatic compounds (Birch reduction) or controlled polymerization could be interesting to consider. This plasma process clearly establishes the feasibility of direct amination without catalyst and unveils a promising

**Figure 4.** Supposed mechanism proposed.

alternative to produce amino compounds in mild conditions in accordance with green chemistry.

Experimental section

Reactions were performed in an original homemade microreactor Biflow 2.7 designed to obtain an enhanced stable interface between the NH_3 plasma and the liquid reactant.^[18] Except when it was specified, the flowrate of liquid benzene (VWR, AnalaR NORMAPUR®, France) was set to 12 $\mu\text{L}/\text{min}$ (retention time of 50 s). The flowrate of NH_3 (Alpha gas) was set to 4 mL/min . To explore the mechanism of amination, different liquid substrates have been investigated. As each reactant has a different viscosity, the gas flowrate of ammonia was varied between 2 and 10 mL/min to keep the liquid phase confined in its channel (Supporting Information).

Once the biphasic flow was controlled, the discharge was produced by applying a sinusoidal high-voltage signal (20 kV peak-to-peak at 2 kHz, except when specified) between the electrodes on each side of the microreactor. After the steady state was reached (3 residence time), the liquid phase was collected in a vial for 6 min and injected in a gas chromatography to be analysed.

All selectivities were calculated based on the area of all the compounds obtained by a flame ionization detector and supposing that they own the same response factor (compounds are very close with the same proportion of each element). The yield in amino compound was calculated by using an external etalon and calibration curves (detailed in Supporting Information).

To evaluate the amination of benzene, a simulation was made using the software COMSOL Multiphysics. Detailed conditions can be found in the Supporting Information.

Supporting Information

Additional references cited within the Supporting Information^[34]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: ammonia plasma · aniline synthesis · dielectric barrier discharge · microreactor · radicals

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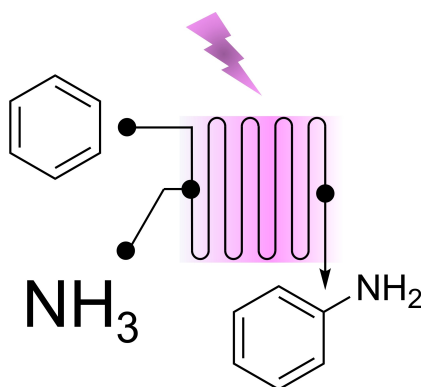
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RESEARCH ARTICLE

Direct amination of benzene is demonstrated with a plasma microreactor. Using ammonia plasma, this process was optimized by studying the influence of temperature, residence time and power of the plasma. Various compounds were evaluated to study influence of double bond, conjugation, and aromaticity. Under optimized conditions, direct amination of benzene gave a total yield of 3.8%.



V. Dupont, Dr. S. Ognier, Dr. G. Morand, Dr. C. Ollivier*, Prof. L. Fensterbank, Prof. M. Tatouliau*

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Direct Amination of Benzene with Ammonia by Flow Plasma Chemistry

