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Catalytic hydrogenation of nitrocyclohexane as an alternative pathway for the synthesis of value-added products

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Catalytic hydrogenation of nitrocyclohexane could be an alternative source of various useful chemicals: cyclohexanone oxime, cyclohexanone, cyclohexanol, cyclohexylamine and dicyclohexylamine. Each one of these compounds found application in the modern chemical industry and has been produced on a large scale in multi-step processes. The possibility of direct synthesis *via* selective hydrogenation of nitrocyclohexane seems to be an excellent alternative. A thorough literature review shows broad research potential in this topic. Herein, we present the state of the art on nitrocyclohexane hydrogenation under batch and flow conditions and indicate possible directions for further studies in this topic.

1. Introduction

As a leading provider of materials for other industrial branches, the chemical industry is crucial to the global economy. Therefore, even a slight change in any chemical process may have a tremendous impact on many areas related to human activity. Hence, there is a strong need to search for novel, environmentally-friendly and inexpensive synthesis methods or modifications of the currently used ones. For instance, switching from batch to flow is one of the most often mentioned priorities for sustainable manufacture in the fine chemical sector.[1]

A significant increase in interest in flow chemistry has been observed since the 2000s.[2] Most of the previously conducted research was focused on batch processes.[3] Wegner *et al.*[4] suggested that the reason for that state of affairs in the past was related to the lack of flow equipment for laboratory-scale research. However, the systems for three-phase catalytic hydrogenation, for example developed by Kobayashi *et al.*,[5] have opened entirely new perspectives for flow reaction studies. Among the many advantages of flow chemistry, easy scale-up and process intensification are the most interesting from the industrial point of view.[6–8] Furthermore, a simple modification of the reaction conditions supports the procedure of the process optimisation, which can be performed even by automatic systems.[9,10]

The transition from batch to flow operation conditions is not the ultimate goal for all industrial syntheses, especially in the case of well-established manufacturing processes. The possibility and profitability of such transformations have been the subject of much research in the past two decades.[11–15] Some researchers approached this issue in a very comprehensive and universal manner. For instance, Calabrese and Pissavini[16] suggested a screening algorithm for batch reactions to determine the feasibility of transition processes. Similar work was performed by Teoh *et al.*[17] by proposing practical assessment technology for converting fine chemicals production from batch to continuous. Nevertheless, the most important conclusion from these studies[11–17] is the need for an in-depth analysis of already performed research and the use of developed solutions.

Nitrocyclohexane hydrogenation products

Catalytic hydrogenation of nitrocyclohexane is a promising source of various value-added chemical compounds. This reaction has been performed in batch reactors since the 1940s,[18] and it has enormous and unfortunately still untapped application potential. The lack of laboratory-scale continuous flow equipment seems to be a reasonable explanation for the underestimation of this reaction.[4] Despite the simplicity of nitrocyclohexane (NC), the process of its hydrogenation could be very challenging due to follow-up hydrogenation and competing reactions, which are presented in Scheme 1. Hence, easy control of reaction conditions and the usage of an appropriate catalyst are essential to achieve desired activity and selectivity to specific products. Among them are cyclohexanone oxime, cyclohexanone, cyclohexylamine, cyclohexanol and dicyclohexylamine. Each one of these compounds found application in modern industry.

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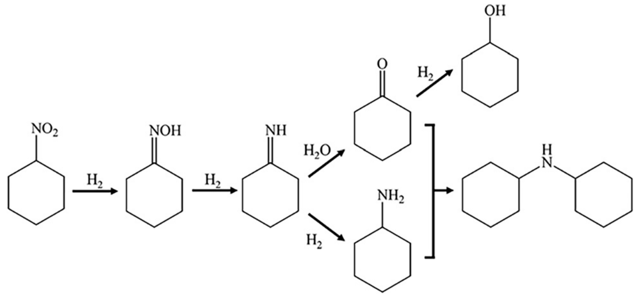


Scheme 1 Mechanism of nitrocyclohexane hydrogenation proposed by Wang *et al.*[19] Reprinted (adapted) with permission from Wang *et al.*[19] Copyright {2013} Elsevier.

Cyclohexylamine – is a colourless aliphatic amine compound in liquid form, which is miscible with water. It is used as a versatile intermediate in the production of herbicides, insecticides, artificial sweeteners (sodium/calcium cyclamate), corrosion inhibitors, rubber vulcanising additives, plasticisers and a lot more.[20,21] Currently, cyclohexylamine is produced on an industrial scale by several different methods. The most commonly used is catalytic hydrogenation of aniline under elevated pressure. In this process, satisfactory efficiency is obtained with Ni and Co catalysts treated with basic oxides,[22–24] *e.g.* RANEY®-Co treated with sodium carbonate and calcium oxide gives more than 96% yield at 503 K and 60 bar.[25] The other method of cyclohexylamine production is based on the synthesis from cyclohexanol and ammonia with a Co catalyst in a continuous reactor. Cyclohexanol reacts with at least 3 mol of ammonia in the presence of circulating hydrogen over a fix-bed catalyst at 493 K and 20 bar.[25] Alternatively, Ni or Co catalysts can be used for the hydrogenation of cyclohexanone in the process carried out at 1–20 bar. Finally, cyclohexylamine can be obtained from the hydrogenation of phenol in the presence of ammonia over a rhodium catalyst.[26] Most of these processes require high temperature and pressure, hydrogen excess and a large amount of ammonia to prevent side reactions, which cause waste formation. The commercially available cyclohexylamine purity is over 99.5%, in which the impurities are ammonia and water.

Dicyclohexylamine – is a colourless liquid secondary amine, sparingly soluble in water. It is used as a valuable chemical intermediate in the production of rubber vulcanisation accelerators, textiles, commercial insecticides, varnishes and corrosion inhibitors.[27] Currently, it is produced by catalytic hydrogenation of aniline at elevated pressure and temperature over a Ru/Pd catalyst.[28] This process leads to the formation of the cyclohexylamine/dicyclohexylamine mixture, which is hard to separate.[27] Dicyclohexylamine as a main product can be formed by the amination of cyclohexanone under hydrogenation conditions[29] or from cyclohexanone and cyclohexylamine at 4 bar with a Pd/C catalyst.[29] Alternatively, it can also be obtained by the reaction of phenol and aniline over Pd/C under hydrogenation conditions at 5 bar.[30–32]

Cyclohexanol – is a secondary alcohol. This colourless substance creates crystalline needles with a camphor-like odour. Mild oxidation or catalytic dehydrogenation leads to cyclohexanone, whereas stronger oxidation gives adipic acid.[33] Cyclohexanol is an essential intermediate in the production of Nylon-6. The mixture of cyclohexanol and cyclohexanone together is called KA oil (ketone-alcohol oil) – necessary for the production of adipic acid. Most of cyclohexanol is produced by liquid phase air oxidation of cyclohexane,[33,34] which gives a cyclohexanone/cyclohexanol mixture. The ratio between these compounds could be modified by changing the production parameters or the application of the specific metal catalyst. The presence of anhydrous boric acid in the process leads to a higher yield of cyclohexanol, thanks to the trapping of the intermediate product.[33] An alternative synthesis procedure involves hydrogenation of phenol over metal catalysts, *e.g.* the RANEY® nickel catalyst under specific conditions gives 99.9% selectivity to cyclohexanol.[35] However, the only remaining large-phenol based plants belong to DSM in Holland and Allied in the Unites States.[36]

Cyclohexanone – is a cyclic ketone in the form of colourless liquid with an acetone-like odour. It can be hydrogenated to cyclohexanol, but also under more reductive conditions, it could be transformed into cyclohexane.[33] The mixture of cyclohexanone and cyclohexanol could be used in the synthesis of adipic acid.[33] It is also used to synthesise pharmaceuticals, plasticisers, herbicides and growth regulators for plants. However, the most important application, from the industrial point of view, is the synthesis of cyclohexanone oxime in the reaction with hydroxylamine. Cyclohexanone is synthesised similarly to cyclohexanol, mainly by the liquid phase air oxidation of cyclohexane.[33] The addition of chromium(III) to the air oxidiser promotes the formation of cyclohexane.[37] Cyclohexanone can be also prepared by dehydrogenation of cyclohexanol.[36]

Cyclohexanone oxime – is a solid colourless compound. The main application of cyclohexanone oxime is the role of an intermediate in the enormous industry of Nylon-6 production. It is transformed into ε-caprolactam *via* Beckman rearrangement. There are several commercial processes for the production of cyclohexanone oxime, which could be categorized into two groups. The first one is based on the most commonly applied process – the reaction of cyclohexanone with hydroxylamine (in the form of sulfate or phosphate[38–40]). The second group involves a more recent technology, in which cyclohexanone reacts with ammonium and a peroxide compound with the presence of a heterogeneous catalyst (known as the ammoximation process). For example, BASF and Inventa produce cyclohexanone oxime in a two-step process: a) formation of hydroxylamine sulfate solution from nitric oxide hydrogenation with a Pt catalyst, and b) oximation of cyclohexanone in weak acidic solution at 353 K.[41,42] However, the main drawback in this solution is the production of a large amount of ammonium sulfate. In general, currently used methods involve multi-step processes, which demand specific conditions to prevent waste formation.[40–44]

As shown above, the production of these compounds is carried out with various technological processes with their advantages and disadvantages. The biggest problem for most of them is waste generation, which affects cost-effectiveness and negatively impacts the environment. Hence, the possibility to synthesise each one of them in one reaction makes catalytic hydrogenation of nitrocyclohexane extremely interesting.

2. Nitrocyclohexane hydrogenation

Despite the enormous versatility of nitrocyclohexane hydrogenation, a thorough literature investigation showed only limited data related to this process. Most of these research studies were focused on batch conditions at elevated pressure and temperature[18,45–52] (Table 1). Nevertheless, these studies can serve as a guide for further experiments carried out in flow reactors (Table 2).

Batch conditions

First attempt to apply nitrocyclohexane hydrogenation. The first attempt to use nitrocyclohexane hydrogenation to obtain value-added products in the heterogeneous process was performed by Grundmann *et al.* at the beginning of the 1950s.[18] These results proved that it is possible to synthesise various beneficial chemical compounds depending on the used catalyst. All of the experiments were conducted in a 250 cm^3 shaking autoclave with 15 g of the catalyst and 50 cm^3 of nitrocyclohexane dissolved in methanol. This reaction solvent was determined in the independent tests. Well known and commercially available hydrogenation catalysts, like RANEY®-Ni, transformed NC into cyclohexylamine at 313 K and 30 bar. A similar selectivity was observed for Cu containing catalysts in reactions performed at a significantly higher temperature and pressure, 413 K and 100 bar. Transition to the multi-component systems changed the selectivity to cyclohexanone oxime, 26% in the case of the Cu–Zn–Mn–Cr–O catalyst.[18] However, harsh conditions were the main drawback for these materials. In order to achieve higher selectivity to cyclohexanone oxime, the researchers moved to silver-containing catalysts. The usage of the complex Ag–Zn–Cr–O material produced cyclohexanone oxime with 64% selectivity at 368 K and 50 bar. Additionally, in these studies, Grundmann *et al.*[18] also analysed the influence of the support, which was recognised as insignificant for catalyst selectivity. In the light of recent studies, the used conditions were relatively high, and some of the observations do not correspond to the current knowledge. Nevertheless, these results were an essential foundation for research on this topic.

Du Pont performed a further investigation on nitrocyclohexane hydrogenation with a Pd catalyst at the beginning of the 1960s.[45,46] The experiments conducted at 35 bar and 413 K with palladium supported on acetylene-black gave selectivity mainly to cyclohexylamine (63%). The other products were cyclohexanone oxime (24%) and cyclohexanone (13%). The introduction of lead to the reaction system completely changed the proportions between products. Interestingly, different results were induced by the mere presence of Pb, irrespective of the method of introduction. For instance, the hydrogenation catalyst may be treated with elemental lead, a catalyst may be supported on a lead-containing material, or the reaction medium may be enriched with the lead compound. Even the reactor lined with lead gave different selectivity than the pure Pd catalyst. In terms of selectivity to cyclohexanone oxime, the best results were obtained in the presence of lead oxide at 35 bar and 433 K – 80% selectivity. These results were quite promising and were patented by Du Pont.[45,46] It should be noted here that the requirement to use Pb-containing compounds entails enormous environmental costs, which could be a possible reason why this process was not implemented on an industrial scale.

Recent studies on nitrocyclohexane hydrogenation

Application of noble metals as catalysts. More recent studies on nitrocyclohexane hydrogenation have changed the strategy of designing catalysts and usually used milder reaction conditions. Serna *et al.*[47] tested various catalytic materials in the experiments performed in ethanol, and in the temperature and pressure range of 373–413 K and 4–15 bar. The typical hydrogenation catalyst – 5 wt% Pd/C – was used as a reference sample. Only 15 mg of it converted NC into cyclohexylamine with 85% selectivity (97% conversion) in the process conducted for 195 min at 15 bar and 413 K. However, the main goal of this research was to investigate the catalytic properties of catalysts with low Pt loading.[47] For instance, under the same reaction conditions, 100 mg of 0.2 wt% Pt/C produced mainly cyclohexylamine (70%, conversion – 85%). On the other hand, Pt nanoparticles supported on TiO_2 contributed to the formation of different products, with emphasis on dicyclohexylamine (41%, conversion – 97%). Additional modification of this catalyst by high-temperature treatment in H_2 flow (723 K, 50 ml min^{-1}) resulted in the formation of TiO_2 decorating the platinum surface. It was followed by the addition of Na – the inhibitor of the hydrolysis of the intermediates. These operations gave the active catalyst (95% conversion), which steered the reaction into the creation of cyclohexanone oxime – 85% selectivity in the process conducted for 880 minutes at 4 bar and 383 K. All of these results indicated the need to reduce the hydrogenolysis properties of the metal nanoparticles to obtain products of partial hydrogenation of nitrocyclohexane.

Serna *et al.*[47] found the Au/Al_2O_3 catalyst to be inactive in this process. However, it was verified by Shimizu *et al.*[46] In their research,[46] they were focused on the Au clusters supported on various metal oxides (Al_2O_3, SiO_2, MgO and TiO_2).[48] Surprisingly, such catalysts turned out to be active and selective in nitrocyclohexane hydrogenation in the experiments performed at 373 K and 6 bar with ethanol as a solvent. For instance, 1.5 wt% Au/TiO_2 was selective to cyclohexylamine, cyclohexanone and cyclohexyl–cyclohexylidene at the beginning

Table 1 Activity and selectivity of the selected catalysts of nitrocyclohexane hydrogenation under batch conditions

Literature	Catalyst	Catalyst amount [mg]	Solvent	NC amount [ml]	T [K]	p [bar]	Time [min]	Conversion [%]	Selectivity [%] Cyclohexylamine	Dicyclohexylamine	Cyclohexanol	Cyclohexanone	Cyclohexanone oxime	Other
18	RANEY®-Ni	1500	MeOH	50	313	30	180	n/a	100	—	—	—	—	—
	$CuCo_3$	1500	MeOH	50	423	100	120	n/a	100	—	—	—	—	—
	Cu–Zn–Mn–Cr–O	1500	MeOH	50	408	100	540	n/a	n/a	n/a	n/a	n/a	26	n/a
	Ag–Zn–Cr–O	1500	MeOH	50	368	50	1080	n/a	n/a	n/a	n/a	n/a	64	n/a
47	5 wt% Pd/C	15	EtOH	0.25^a	413	15	195	97.0	84.9	—	—	4.7	4.9	5.5
	0.2 wt% Pt/C	150	EtOH	0.25^a	413	15	100	85.0	70.0	—	—	5.0	18.0	7.0
	0.2 wt% Pt/TiO_2	150	EtOH	0.25^a	413	15	100	97.0	31.8	40.6	—	14.2	5.4	8.0
	0.2 wt% Pt/TiO_2	200	—	1^a	383	4	880	95.0	3.4	—	—	8.6	84.5	3.5
48	1 wt% Au/Al_2O_3	200	$C_2H_8N_2$	1.2^a	373	6	720	100	—	—	—	—	83	17
	1.5 wt% Au/TiO_2	200	$C_2H_8N_2$	1.2^a	373	6	720	100	—	—	—	—	9	91
49	5 wt% Pd/C	200	$C_2H_8N_2$	1.2^a	323	2	180	100	6.2	—	7.9	—	55.1	—
	5 wt% Pd/CNTs	200	$C_2H_8N_2$	1.2^a	323	2	360	97.6	5	—	2.9	—	85.9	—
53	5 wt% Pd/LAC	200	$C_2H_8N_2$	1.2^a	323	3	360	98.9	5	—	4.6	—	55.0	—
	5 wt% Pd/CAC	200	$C_2H_8N_2$	1.2^a	323	3	360	99.2	5.6	—	3.2	—	60.5	—
	5 wt% Pd/CSAC	200	$C_2H_8N_2$	1.2^a	323	3	360	91.0	4.6	—	2.9	—	38.9	—
	5 wt% Pd/SWCNTs	200	$C_2H_8N_2$	1.2^a	323	3	360	97.3	0.3	—	2.9	—	94.6	—
	5 wt% Pd/DWCNTs	200	$C_2H_8N_2$	1.2^a	323	3	360	98.1	0.2	—	4.5	—	83.5	—
	5 wt% Pd/MWCNTs	200	$C_2H_8N_2$	1.2^a	323	3	360	99.9	3.4	—	4.6	—	87.9	—
54	5 wt% Pd/SWCNTs	100	$C_2H_8N_2$	0.6^a	323	3	360	98.9	6.3	—	—	—	85.9	—
	5 wt% Pd/SWCNTs	100	$C_2H_8N_2$	0.6^a	323	3	360	98.5	4.2	—	—	—	93.5	—
	5 wt% Pd/SWCNTs	100	$C_2H_8N_2$	0.6^a	323	3	360	96.0	3.2	—	—	—	96.4	—
50	5 wt% Pd/HTMC	100	$C_2H_8N_2$	0.53^a	323	3	360	71.4	1.3	—	—	0.3	82.9	—
51	15 wt% Cu/SiO_2	20	$C_2H_8N_2$	6×10^{-6a}	373	10	180	74	3	—	—	5	92	—
	15 wt% Ni/SiO_2	20	$C_2H_8N_2$	6×10^{-6a}	373	10	180	19	20	—	—	21	59	—
	15 wt% Fe/SiO_2	20	$C_2H_8N_2$	6×10^{-6a}	373	10	180	8	—	—	—	75	25	—
	15 wt% Co/SiO_2	20	$C_2H_8N_2$	$6 \times^a 10^{-6}$	373	10	180	4	—	—	—	88	12	
52	1% Cu–20% Ni/AC	120	$C_2H_8N_2$	0.47^a	373	3	480	99.6	n/a	n/a	n/a	n/a	87.8	n/a

[a] Estimated from the data available in the article.

Table 2 Activity and selectivity of the selected catalysts of nitrocyclohexane hydrogenation under flow conditions

Literature	Catalyst	Reaction conditions	TOF [h^{-1}]	Activity [μmol min^{-1}]	Selectivity [%] Cyclohexylamine	Dicyclohexylamine	Cyclohexanol	Cyclohexanone	Cyclohexanone oxime	Other
19	0.8 wt% Au/ZrO_2	Gas flow reactor 353 K	6.1	—	28	—	—	54	18	—
	1.2 wt% Au/TiO_2		9.1	—	34	20	—	40	6	—
	1.1 wt% Au/Al_2O_3		16.4	—	18	—	—	2	80	—
	3.0 wt% Au/CeO_2		1.6	—	2	—	—	98	—	—
56	2.2 wt% Pd@Tentagel-S-NH_2	Liquid flow reactor 20.5 μmol NC min^{-1} 10 bar, 313 K	—	0.1	—	—	—	—	100	—
57	CuZnAl(0.5–1–1)	Liquid flow reactor 20.5 μmol NC min^{-1} 5 bar, 413 K	—	9	—	—	9	89	2	—
	CuZnAl(1–1–1)	Liquid flow reactor 20.5 μmol NC min^{-1} 10 bar, 403 K	—	15	100	—	—	—	—	—

of the process conducted for 12 h (unfortunately specific values were not provided). However, with prolonged reaction time, these products decomposed into undetectable compounds. On the other hand, 1 wt% Au/Al_2O_3 gave selectivity to cyclohexanone oxime (83%) and cyclohexanone (7%) at 100% conversion. Moreover, in other studies, the researchers discovered various correlations between morphology and catalytic parameters, like the influence of the average particle size. Independent from the support material, smaller Au nanoparticles gave higher conversion. For example, in the case of the previously mentioned 1 wt% Au/Al_2O_3, increasing the size of nanoparticles from 2 nm to 6 nm resulted in a significant drop in conversion (from 100% to 4.5%) and changed selectivity to cyclohexanone oxime (from 83% to 0%) in the processes conducted for 6 h at 373 K. Beside the influence of the particle size, the properties of the support materials also have a massive impact on the catalytic behaviour of gold. Basic metal oxides (MgO) and the one with more acidic character (SiO_2) gave worse results than the amphoteric Al_2O_3. Acid–base pair sites seem to be crucial for this reaction. Based on these observations, Shimizu *et al.*[48] proposed a cooperative mechanism, in which dissociative adsorption of H_2 at the gold–support interface produces $H^{\delta-}$ on the low coordinated Au and $H^{\delta+}$ on the support. Both groups are transferred to the polar nitro group, preferably adsorbed on the $Al^{\delta+}$–$O^{\delta-}$ site.[48] This phenomenon could explain the higher activity of the gold nanoparticles supported on Al_2O_3. Hence, the impact of reaction pressure and temperature was investigated for the best catalyst – 1 wt% Au/Al_2O_3 with 2.5 nm nanoparticles. Its activity increased with increasing pressure up to 6 bar, to achieve 100% conversion and 83% selectivity to cyclohexanone oxime. Above this pressure, the selectivity to oxime decreased, and the formation of cyclohexanone was observed up to maximum at 11 bar. After exceeding this value, cyclohexyl–cyclohexylidene amine and dicyclohexylamine appeared among the reaction products. The same compounds were observed for temperatures above 373 K. At this temperature the catalyst achieved its maximum activity and selectivity to cyclohexanone oxime (83%) and cyclohexanone (7%). Serna *et al.*[47] proved that the combination of specific morphology parameters and reaction conditions makes gold catalysts active and selective in nitrocyclohexane hydrogenation.

The research group from Xiangtan University came back to Pd catalysts and thoroughly investigated the catalytic performance of palladium nanoparticles supported on various carbon materials.[49,50,53,54] In general, these catalysts showed high activity and selectivity to cyclohexanone oxime in the processes performed in the temperature and pressure range of 313–353 K and 2–3 bar, respectively. Unlike the other studies, ethylenediamine was chosen as the reaction solvent. The researchers established the optimal temperature for this process – 323 K, but also the minimal time required to achieve satisfactory conversion – 85% after 2 h. The initial experiments were performed with palladium nanoparticles supported on microporous activated carbon and carbon nanotubes, marked respectively as 5 wt% Pd/C and 5 wt%

Pd/CNTs.[49] These tests, conducted at optimal temperature and under 2 bar, showed the superiority of the Pd/CNTs in terms of selectivity to cyclohexanone oxime – 85.9% after 6 h, in comparison to 55.1% obtained after 3 h by Pd/C. Pd/CNTs domination was explained by smaller Pd nanoparticle size and the positive influence of the CNT support.[49]

Despite the satisfying results, Liu *et al.*[53] decided to investigate more carbon derivative materials. Hence, a series of Pd catalysts (5 wt%) supported on activated carbons made from lignin, coal and coconut shell (LAC, CAC and CSAC), but also on carbon nanotubes: single-wall, double-wall and multi-wall (SWCNTs, DWCNTs, MWCNTs) were synthesised.[53] Due to previously performed experiments[49] it was not very surprising that all of these catalysts were active in nitrocyclohexane hydrogenation conducted in batch mode at 3 bar and 323 K. However, the usage of carbon materials with different properties allowed the structure of the support to be established as crucial to catalyst selectivity. The reactant sizes are comparable with the micropore dimension. Hence, the microporous structure is unfavourable for its adsorption and diffusion.[53] The comparison between materials with the lowest and highest pore size, Pd/CAC – 0.95 nm and Pd/SWCNTs – 2.73 nm, showed similar conversion for both catalysts ~100%. However, Pd/CAC gave 55% selectivity to cyclohexanone oxime, and PD/SWCNTs – 94.6%.

The carbon nanotubes generally revealed better catalytic performance, but there were also differences among them. Various structures of CNTs affected the reduction state of palladium. The Pd^+ content increased in the following order: Pd/DWCNTs → Pd/MWCNTs → Pd/SWCNTs. Simultaneously, the selectivity to cyclohexanone oxime also increased for these materials in the same order 83.5% → 87.9% → 94.6%. Therefore, it could be concluded that Pd^+ favours the formation of cyclohexanone oxime.

The studies performed in 2015 (ref. 54) aimed at the optimisation of the synthesis procedure to achieve higher Pd^+ content for Pd/SWCNTs catalysts. The researchers checked various preparation methods: wet impregnation in water, wet impregnation in methanol, ion exchange and chemical reduction, but also different pretreatment conditions. Among the obtained catalysts, the ones gained by wet impregnation in water showed the best catalytic performance. With increasing reduction temperature of the Pd precursor (523 K → 623 K → 723 K), the selectivity to cyclohexanone oxime also increased (85.9% → 93.5% → 96.4%). It was related to the increase in Pd^+ content with the reduction temperature in the following order 33.0% → 33.8% → 38.7%.

Unfortunately, the preparation of carbon nanotubes on a large scale is extremely complicated and expensive.[50] Hence, Yan *et al.*[50] attempted to achieve better results with palladium nanoparticles supported on mesoporous activated carbons. The researchers tested different materials synthesised by soft templating, hard templating and hydrothermal synthesis from various raw materials. The best results were obtained for Pd (5 wt%) supported on mesoporous carbon obtained by the hard template method from mesoporous silica.[55] In the case of this catalyst, the selectivity to cyclohexanone oxime was equal to 82.8% in the experiments performed for 6 h at 323 K and 3 bar. However, its catalytic performance was affected by the small surface area and pore volume, and hence the final conversion was only 71.4%. Nevertheless, due to the cost of activated carbons, it can be an interesting alternative for carbon nanotubes.

In the end, all of the results obtained by the research group from Xiangtan University led to the conclusion that smaller Pd nanoparticles with higher dispersion and greater Pd^+ content (which are supported on carbon materials with adequate pore size) favour the formation of cyclohexanone oxime with high activity.[49,50,53,54]

Application of non-noble metals as catalysts. Despite the attempt performed by Liao *et al.*[49] with the Ni catalyst, hydrogenation of nitrocyclohexane was performed with noble metals. It did not change until 2017, when Zhang *et al.*[51] tested with success low-cost transition metals. Among them were Cu, Ni, Fe and Co supported on silica dioxide with target metal loading – 15 wt%. The experiments were performed for 3 h at 373 K and under 10 bar in ethylenediamine. Dependent on the used metal nanoparticles, the catalysts were selective to different reaction products: Co–cyclohexanone (88%) and cyclohexanone oxime (12%), Fe–cyclohexanone (75%) and cyclohexanone oxime (25%), Ni–cyclohexanone oxime (59%), cyclohexanone (21%) and cyclohexylamine (20%), Cu–cyclohexanone oxime (92%), cyclohexanone (5%) and cyclohexylamine (3%).

Because Zhang *et al.*[51] were focused on the selectivity to cyclohexanone oxime, the copper catalyst was selected for further studies. Modification of various factors, such as the support material, synthesis method and metal loading, led to the catalyst with 92% selectivity to cyclohexanone oxime in combination with 74% conversion. The process of characterisation of these catalysts revealed the coexistence of metallic Cu and Cu_2O. The ratio between these two species seems to be crucial for catalytic performance. Zhang *et al.*[51] postulated that Cu^0 species dissociate H_2 and Cu^{2+} sites function as electrophilic sites to polarise the nitro group. Additionally, the researchers also discovered that with the increase of the pressure from 10 to 40 bar, the time needed to obtain the same conversion shortened proportionally from 4 to 1 h, which can be crucial for designing processes on the industrial scale.

In general, apart from the used catalyst, the combination of time, temperature and pressure is crucial to the catalytic performance in the hydrogenation of nitrocyclohexane in batch reactors. In order to obtain products of partial hydrogenation, the reaction has to be conducted at a lower temperature and pressure. Higher values favour the formation of cyclohexanone, cyclohexanol, cyclohexylamine and dicyclohexylamine. A similar situation is observed for the reaction time, which also affects the selectivity of the catalysts. Prolonged time supports further hydrogenation and even the decomposition of the products into undetectable compounds. For the above reasons, easy control of the reaction conditions provided by flow reactors appears to be very attractive.

Flow conditions

A thorough literature investigation revealed only three papers related to the usage of flow conditions in this reaction, Wang *et al.* in the gas phase[19] and Kowalewski *et al.* in the liquid phase.[56,57]

Gas flow conditions

Inspired by the studies performed by Serna *et al.*,[47] Wang and coworkers[19] proved that gold catalysts could be as active under flow as under batch conditions. A series of Au catalysts were prepared by the deposition–precipitation method with various metal oxides: 0.8 wt% Au/ZrO_2, 1.2 wt% Au/TiO_2, 1.1 wt% Au/Al_2O_3 and 3.0 wt% Au/CeO_2. Different support materials affected nanoparticles' size and their distribution; a decrease in the mean values was observed in the following order: Au/ZrO_2 (7.0 nm) → Au/TiO_2 (4.7 nm) → Au/Al_2O_3 (4.3 nm) → Au/CeO_2 (3 nm). Similar to previous studies,[47] Wang *et al.*[19] observed a strong correlation between Au nanoparticle size and the overall activity of the catalyst; smaller particles are better in the activation of H_2 which is a crucial step in the hydrogenation of nitrocyclohexane. These properties were reflected in the catalytic performance. In the experiments performed at 353 K each one of these catalysts was selective to different products: Au/ZrO_2–cyclohexanone (54%), cyclohexylamine (28%) and cyclohexanone oxime (18%), Au/CeO_2–cyclohexanone (98%) and cyclohexylamine (2%), Au/TiO_2–cyclohexanone (40%), cyclohexylamine (34%), dicyclohexylamine (20%) and cyclohexanone oxime (6%), and Au/Al_2O_3–cyclohexanone oxime (80%), cyclohexylamine (18%) and cyclohexanone (2%). In general, selectivity to cyclohexanone oxime is sensitive to surface hydrogen. The formation of cyclohexanone and cyclohexylamine is favoured at low and high coverage, respectively.

Liquid flow conditions

Kowalewski *et al.*[56,57] also conducted catalytic reactions under flow conditions, but in the liquid phase. This approach allowed them to perform the catalytic process under conditions comparable with batch hydrogenation studies.[48–53] The application of palladium nanoparticles grafted on the polymeric resin ($TSNH_2$) led to the formation of two different products: cyclohexanone oxime and cyclohexylamine. In general, a higher pressure requires a higher temperature to achieve 100% selectivity to cyclohexanone oxime (298 K for 5 bar, 313 K for 10 bar). On the other hand, the selectivity to cyclohexylamine increases with increasing temperature and pressure. In comparison to previous results obtained under batch conditions,[49,53,54] palladium nanoparticles grafted on polymeric resin gave lower conversion.

However, considering that the flow conditions allow for a long-term process, inferior activity was reduced, and selectivity can be easily modified by changing the reaction conditions.[56]

Inspired by Zhang *et al.*,[51] Kowalewski *et al.*[57] applied in nitrocyclohexane hydrogenation catalysts based on low-cost transition metals – CuZnAl hydrotalcite derived materials. The activated catalyst gave an entirely different catalytic performance depending on the different molar ratios between Cu, Zn and Al in the parent hydrotalcite material. The alteration of the copper content completely modified the selectivity of the used materials, which was caused by the modification of catalyst morphology. Lower copper content led to the formation of the CuZn alloy. It steered the reaction into cyclohexanone formation, and higher Cu concentration resulted in the production of cyclohexylamine (thanks to the presence of Cu–ZnO core–shell structure).

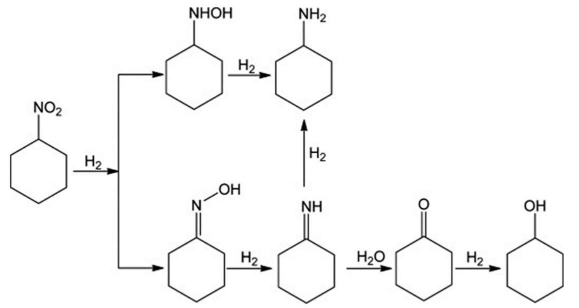
Comparison of batch and flow nitrocyclohexane hydrogenation

The comparison of batch and flow catalytic hydrogenation of nitrocyclohexane is not straightforward (Tables 1 and 2). Reaction conditions applied by the research groups from all around the world are not consistent with each other. Hence, even the comparison of the results obtained in batch reactors could be problematic (Table 1). However, assuming that in the average batch catalytic reaction (performed for 6 h) the amount of the used nitrocyclohexane is 0.6 g (4.37 mmol) per 0.1 g which corresponds to the flow reaction performed for 6 h with the same amount of catalyst with an NC flow rate ~12 μmol min^{-1}, some general conclusions can be made. Catalysts under batch conditions show higher activity. On the other hand, the possibility to perform long-term processes in continuous-flow reactors eliminates to some extent the problem with yield in a short time.

Mechanism of nitrocyclohexane hydrogenation

Most of the research on nitrocyclohexane hydrogenation presents the reaction pathway as it was presented in Scheme 1, which was proposed by Wang *et al.* for the reaction conducted under gas flow conditions. Direct hydrogenation of nitrocyclohexane leads to the formation of cyclohexanone oxime. Further hydrogenation involves only one intermediate product – imine. Its hydrogenation leads to cyclohexylamine. On the other hand, the formation of cyclohexanone requires the participation of water.

The mechanism proposed by Liu *et al.* (Scheme 2) indicates the possibility of the formation of two intermediate products: *N*-cyclohexylhydroxylamine and imine. The former one is obtained directly from nitrocyclohexane and can be hydrogenated to cyclohexylamine. The latter one is produced from cyclohexanone oxime and can be transformed into cyclohexylamine or cyclohexanone. Moreover, further hydrogenation of cyclohexanone leads to cyclohexanol.

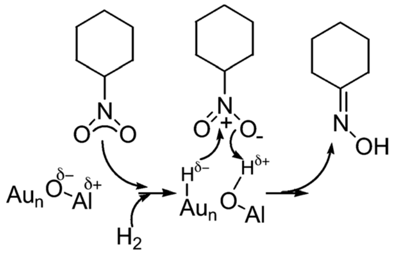


Scheme 2 Nitrocyclohexane hydrogenation mechanism proposed by Liu *et al.*[53] Reprinted (adapted) with permission from Liu *et al.*[53] Copyright {2013} John Willey & Sons.

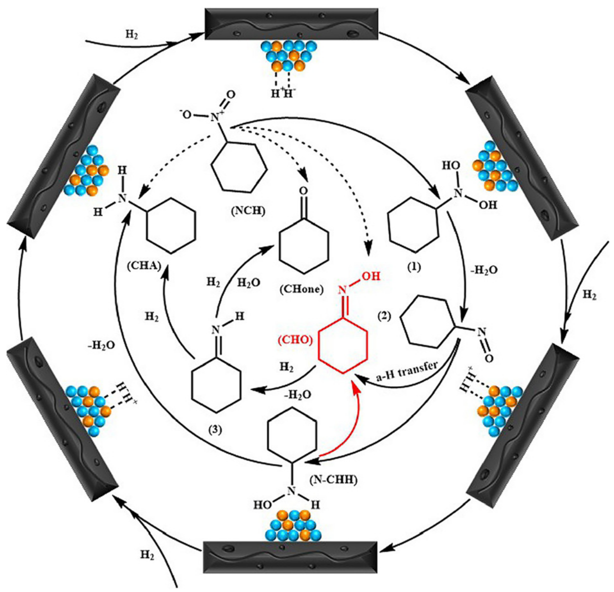
More thorough studies on nitrocyclohexane hydrogenation mechanisms were performed by Shimizu *et al.*[48] and Yao *et al.*[52]

Shimizu *et al.*[48] exposed the beneficial role of coordinatively unsaturated Au atoms and the acid–base pair site ($Al^{\delta+}$–$O^{\delta-}$ site) coexistence (Scheme 3). In accordance with their work, the dissociation of H_2 at the gold–support interface led to the formation of the $H^{\delta-}$ atom on the low coordinated Au atom and an H atom which releases an electron to the Lewis acid site of the support. The latter one is transformed to a proton stabilized at the oxygen atom (Lewis base) near the Lewis acid site. The nucleophilic $H^{\delta-}$ species on Au and electrophilic $H^{\delta+}$ species on the support transfer to the polar nitro group. The $Al^{\delta+}$–$O^{\delta-}$ site also acts as the adsorption site of the nitro group.

Yao *et al.*[52] proposed the nitrocyclohexane hydrogenation mechanism on the Cu–Ni/AC catalyst based on the classical Langmuir–Hinshelwood model (Scheme 4). Nitrocyclohexane and hydrogen molecules are adsorbed on the Cu–Ni catalyst surface, and hydrogen is dissociated to active hydrogen (H*). H* reacts with nitrocyclohexane to produce unstable intermediate *N*,*N*′-dihydroxycyclohexane (Scheme 4, (**1**)), and then it can be further dehydrated to form the intermediate (Scheme 4, (**2**)). Moreover, Knifton *et al.* by exchanging hydrogen for deuterium showed that the hydrogen atom in oxime does not come from hydrogen but from the reactants. It was suggested that the nitroso compound containing α-H can easily tautomerize to form oxime *via* α-H transfer, and the polar solvent environment is more favourable for this reaction.



Scheme 3 Nitrocyclohexane hydrogenation on the acid–base pair site on Au catalysts. Reprinted (adapted) with permission from Shimizu *et al.*[48] Copyright {2011} Elsevier.



Scheme 4 Mechanism involving the formation of cyclohexanone oxime over the Cu–Ni/AC catalyst. Reprinted (adapted) with permission from Yao *et al.*[52] Copyright {2021} American Chemical Society.

Hence, the produced intermediate (Scheme 4, (**2**)) can be isomerized by α-H transfer to form cyclohexanone oxime, which can be further hydrogenated and hydrolyzed to cyclohexylamine and cyclohexanone *via* intermediate cyclohexanimide (Scheme 4, (**3**)).[47] Additionally, the intermediate (Scheme 4, (**2**)) can be hydrogenated to *N*-cyclohexylhydroxylamine, which can be further hydrogenated and deoxidized to cyclohexylamine.[58] The results obtained by Yao *et al.*[52] suggest that *N*-cyclohexylhydroxylamine can be quickly converted to cyclohexanone oxime. Additionally, they postulated that the decrease of cyclohexylamine content may be the effect of the formation of *N*,*N*-dicyclohexylamine by a condensation reaction between cyclohexylamine and *N*-cyclohexylhydroxylamine. Moreover, the reaction under hydrogenation conditions favors the conversion of *N*-cyclohexylhydroxylamine to cyclohexanone oxime as well as the condensation reaction between *N*-cyclohexylhydroxylamine and cyclohexylamine.

3. Conclusions

Based on the presented results, the seemingly simple catalytic hydrogenation of nitrocyclohexane can be very challenging due to the enormous number of crucial factors. However, the possibility to obtain numerous valuable compounds from the same substrate seems to be an exciting topic for further research. Among these chemicals, precursors for the production of pharmaceuticals, artificial sweeteners, insecticides, textiles, and many others can be found. Several very active and selective catalysts have been obtained so far (Table 1). Serna *et al.*[47] synthesised 5 wt% Pd/C which converts nitrocyclohexane (97%) into cyclohexylamine with ~85% selectivity. However, only 0.2 wt% Pt/TiO_2 transforms NC into cyclohexanol (conversion – 97%, selectivity – 40.6%).

Also, cyclohexanone could be efficiently obtained from NC with the 15 wt% Co/SiO_2 catalyst offered by Zhang *et al.*[51] (88% selectivity, but only 4% conversion). Moreover, Liu *et al.*[53] proposed Pd nanoparticles supported on single-wall carbon nanotubes (5 wt% Pd/SWCNTs) which gave ~95% selectivity to cyclohexanone oxime with 97% conversion. Until now, the catalyst for the efficient formation of cyclohexanol has not been proposed. Hence, more advanced studies on the influence of metal active phase support materials and reaction conditions should be carried out in the future. The already obtained results form the basis for future studies.

Noteworthy is the lack of reactions conducted in flow reactors in the liquid phase. The application of the flow technique eliminates many problems of batch conditions and facilitates the performance of the nitrocyclohexane hydrogenation. Flow reactors were successfully applied in the hydrogenation of various nitro compounds,[59–63] also in the hydrogenation of nitrocyclohexane. The thorough analysis of the already obtained results showed that 3 wt% Au/CeO_2 is the best catalyst for the synthesis of cyclohexanone oxime (98% selectivity) under gas flow conditions.[19] On the other hand, under liquid flow conditions, cyclohexanone oxime can be produced efficiently with palladium nanoparticles grafted on polymeric resin (2.2 wt% Pd@Tentagel-S-NH_2, selectivity – 98%).[56] Moreover, Kowalewski *et al.*[57] also proposed catalysts based on hydrotalcite derived materials CuZnAl (0.5–1–1) and CuZnAl(1–1–1), which give possibility to produce cyclohexanone (selectivity – 89%) and cyclohexylamine (selectivity – 100%), respectively. Nevertheless, there are still not many publications concerning flow conditions. Hence, the hydrogenation of nitrocyclohexane under liquid flow conditions with readily available transition metals as catalysts should be a priority for further research on this topic.

Conflicts of interest

There are no conflicts to declare.

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