

Article

Chemoselective Reduction of 3-Methylcyclohex-2-enone into *rac* 3-Methylcyclohex-2-enol (Seudenol) by NaBH₄ Alone, with Modifiers or via Catalytic Transfer Hydrogenation

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Abstract

A systematic study of the chemoselectivity of the reduction of 3-methylcyclohex-2-enone (seudenone) to 3-methylcyclohex-2-enol (seudenol) was performed. Two approaches were investigated, namely the reduction of this ketone using NaBH₄ with modifiers and Catalytic Transfer Hydrogenation (CTH). The former resulted in higher conversions (95–99%) and high selectivity (up to 95%), whereas with CTH, a selectivity of 100% was achieved, albeit with a low conversion. The study therefore demonstrated that it is possible to chemoselectively reduce an α,β -unsaturated ketone in the liquid phase CTH using MgO as the catalyst and 2-pentanol as the hydrogen donor. The application of modifiers such as CeCl₃ · 7H₂O and MCl₂, where M = Be, Mg, Ca, Sr, and Ba, resulted in a significant improvement of the chemoselectivity (up to 95%) of the reduction with NaBH₄. The effect of parameters such as the solvent mixture composition, reaction temperature and modifier:NaBH₄ molar ratio was also investigated. In CTH, although high conversions of the ketone were observed for Al₂O₃, ZrO₂ and MgO in the vapor phase, the first two did not yield 3-methylcyclohex-2-enol among the obtained products. It was shown that 3-methylcyclohex-3-enol was the main product of the transformations of 3-methylcyclohex-2-enone in the presence of MgO, with yields of 25–33%. In a series of experiments, it was shown that 3-methylcyclohex-3-enol is formed as a result of the transformation of 3-methylcyclohex-2-enol in the presence of MgO as a catalyst.

Keywords: seudenol; seudenone; metal oxides; NaBH₄ modifiers; Catalytic Transfer Hydrogenation; high chemoselectivity



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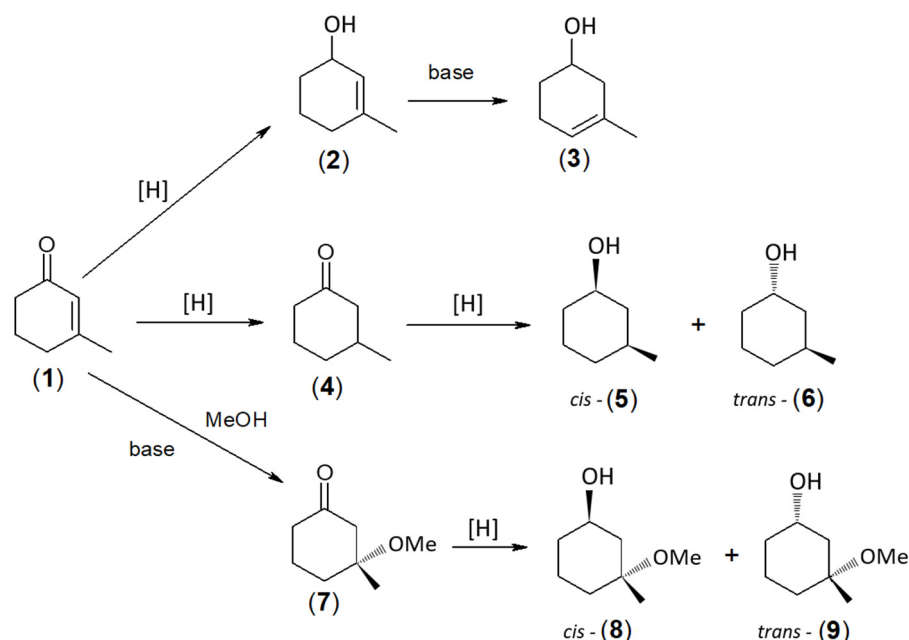
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1. Introduction

Racemic 3-methylcyclohex-2-enol, called seudenol, is an aggregation pheromone for the Douglas-fir beetle (*Dendroctonus pseudotsugae* Hopkins) [1], which is currently in high demand due to its application as the active substance in traps for these insects. They are known as a very destructive pest for the Douglas-fir trees [2,3]. This unsaturated alcohol is obtained by various methods [4–9], of which the most frequently used is the reduction of 3-methylcyclohex-2-enone [3–5,7]. The synthesis of both (*R*) and (*S*)-3-methylcyclohex-2-enols was first reported by Mori [6]. The enantiomers were found to exhibit nearly equal bioactivities [10]. In contrast to the alcohol, the corresponding ketone (3-methylcyclohex-2-enone, i.e., seudenone) is an antiaggregation pheromone of the same beetle [11]. The ketone was obtained from different starting materials: formaldehyde and ethyl acetoacetate [12,13],

δ -ketocarboxylic acids and their derivatives through Wittig reactions [14], as well as via copper-catalysed addition of methyl manganese chloride to cyclohexanone [15] and from 1,8-cyneole [16]. The molecule of this ketone contains two functional groups: a carbonyl and a vinyl. Since they are in a conjugated position relative to each other and, equally importantly, they are incorporated into a rigid fragment of the cyclohexene ring, the transformations in the presence of reducing agents can lead to several products (Scheme 1).



Scheme 1. Products formed during reduction of 3-methylcyclohex-2-enone (1): 3-methylcyclohex-2-enol (2); 3-methylcyclohex-3-enol (3); 3-methylcyclohexanone (4); *cis* and *trans* 3-methylcyclohexanols (5) and (6); 3-methoxy-3-methylcyclohexanone (7); *cis* and *trans* 3-methoxy-3-methylcyclohexanols (8) and (9).

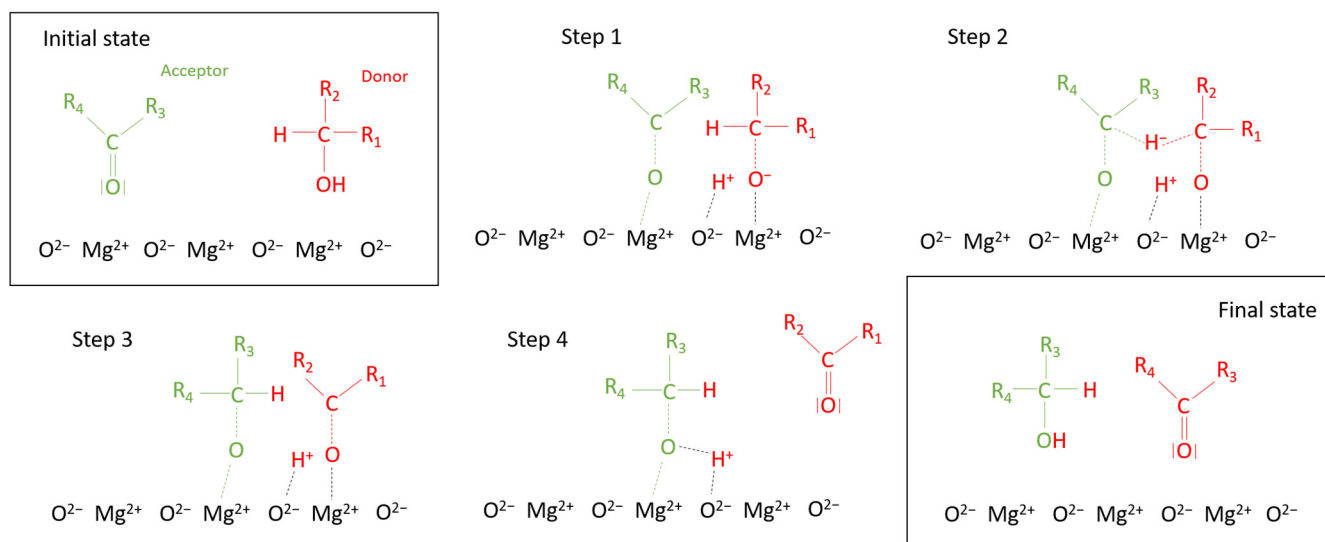
The attack of a reducing agent on the carbonyl group produces the unsaturated alcohol 3-methylcyclohex-2-enol (2), common name seudenol, which may undergo an isomerization reaction of the carbon-carbon double bond to produce 3-methylcyclohex-3-enol (3). In contrast, the reduction of the vinyl group results in the formation of the saturated ketone 3-methylcyclohexanone (4), which is a sought-after starting material in organic synthesis [17]. The reduction of both functional groups in the substrate molecule leads to the formation of two saturated alcohols in the form of a mixture of *cis* (5) and *trans* (6) diastereomers of 3-methylcyclohexanols [18]. In theory, 3-methylcyclohex-2-enone (1) as an α,β -unsaturated ketone can undergo the addition of methanol in the presence of a base as catalyst in the Michael reaction to form 3-methoxy-3-methylcyclohexanone (7), which in turn is reduced by $NaBH_4$ to two diastereoisomers of 3-methoxy-3-methylcyclohexanols (8) and (9); however, a study by Johnson et al. showed that the addition of 2-propanol to 3-methylcyclohex-2-enone (1) does not take place [19]. In our studies, the Michael addition reaction of methanol to 3-methylcyclohex-2-enone (1) was not observed, and therefore neither compound (7) nor its reduction products (8) and (9) were formed. This diversity of substrate transformations makes the chemoselectivity of reduction a key issue. The only desired reduction product is 3-methylcyclohex-2-enol (2). Our analysis of the reduction of other α,β -unsaturated carbonyl compounds clearly indicates that the formation of the saturated ketones and saturated alcohols is thermodynamically favored compared to the formation of the unsaturated alcohol [20]. It can therefore be concluded that of the eight products of the transformations of 3-methylcyclohex-2-enone (1), including two pairs of diastereoisomers of saturated alcohols, the formation of 3-methylcyclohex-2-enol (2) is the

least thermodynamically favored reaction, and its preferential formation requires the use of a chemoselective reducing agent or chemoselective hydrogenation catalyst.

NaBH_4 is the most commonly used reducing agent in organic synthesis as a mild, inexpensive, and invaluable reagent for applications in a wide range of reductions, including aliphatic and cyclic α,β -unsaturated compounds. Its main advantage, as shown by, e.g., Johnson and Rickborn, was a high conversion of the ketone [19]. However, the chemoselectivity was low, such as that noted for 3-methylcyclohex-2-enone (**1**) (50%). The application of modifiers with NaBH_4 was first postulated by Luche, who studied a series of modifiers (lanthanoid halides: LnCl_3 , where $\text{Ln} = \text{La}, \text{Ce}, \text{Sm}, \text{Eu}$ and Yb) for the chemoselective reduction of α,β -unsaturated ketones [21,22]. The Luche reduction was found to yield the best results for $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in methanol, achieving quantitative conversion of the ketone and 100% yield of 3-methylcyclohex-2-enol (**2**) when the NaBH_4 to $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ratio is 1:1 [22]. However, cerium is a critical raw material, which is why in the current paper, the attempt was made to reduce the amount of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ used without loss of chemoselectivity. Moreover, due to this fact, the halides of alkaline earth metals, which are more readily available, were also used as modifiers of NaBH_4 in the reduction of cyclic and acyclic α,β -unsaturated ketones [23]. For cyclohex-2-enone, very high conversions, i.e., from 85 up to 92%, and yields of cyclohex-2-enol in the range of 81 to 97% were noted. The chemoselectivity of other $\text{NaBH}_4\text{-MX}_n$ systems can be substantially higher than that of NaBH_4 alone [24–26]. For example, the $\text{NaBH}_4\text{-ZnCl}_2$, $\text{NaBH}_4\text{-CuSO}_4$ and anhydrous AlCl_3 have been applied.

CTH of various unsaturated organic compounds has been known since 1903, in which hydrogenation occurs under normal pressure at moderate temperatures [27,28]. Various functional groups in organic compounds can be hydrogenated using this method, either with homogeneous or heterogeneous catalysts. Homogeneous catalytic systems in the form of organometallic complexes of, e.g., Fe(II) , Ru(II) and Os(II) , constitute a group of catalysts with demonstrated high chemoselectivity for the reduction of compounds containing multiple functional groups, such as α,β -unsaturated carbonyl compounds. The major disadvantage of this group of catalysts is their high cost. Moreover, these compounds require handling under oxygen-free and anhydrous conditions. In the case of heterogeneous catalysts used for the reduction of carbonyl compounds using metal oxide systems, MgO is particularly active [20,29–31]. It is commonly known that CTH on MgO proceeds via the Meerwein–Ponndorf–Verley mechanism shown in Scheme 2. The first step consists of the dissociative adsorption of the hydrogen donor (alcohol) along with the associative adsorption of the hydrogen acceptor (ketone). Next, the hydride ion is transferred from the donor to the carbonyl group of the adsorbed acceptor molecule (Step 2), and the proton migrates towards the acceptor molecule (Step 3). Finally, the newly formed alcohol (Step 4) and ketone desorb from the MgO surface. Significant activity of metal oxides in CTH of carbonyl groups of a number of aldehydes and ketones has been observed, and differently structured molecules have been reduced by this method [20,30–32]. Catalytic hydrogenation of α,β -unsaturated carbonyl compounds with gaseous hydrogen in the presence of metallic catalysts leads to preferential hydrogenation of the carbon-carbon double bond [33–35]. This occurs for two reasons: first, it is thermodynamically favored over the hydrogenation of the carbonyl group, and secondly, because under these conditions (metal catalyst), it proceeds faster (reaction kinetics) [36,37]. As such, Fe^{2+} can substantially enhance its chemoselectivity towards the unsaturated alcohols [38]. Due to the lack of comparable data from the literature regarding this reaction, a systematic study comprising the investigation of several key parameters was performed. The aim of these measurements was to obtain a general outlook on the chemoselectivity of the reduction of

3-methylcyclohex-2-enone (1) to 3-methylcyclohex-2-enol (2) with NaBH_4 (used with and without modifiers) and via CTH using several metal oxides as catalysts.



Scheme 2. The mechanism of the Meerwein–Ponndorf–Verley reaction over MgO .

2. Materials and Methods

2.1. Reagents

2.1.1. 3-Methylcyclohex-2-enone (1)

This compound was obtained by the reaction of formaldehyde with ethyl acetoacetate according to the procedure described in the literature [39], which was subjected to significant modifications in our laboratory. In the first stage of the synthesis, 15.0 g (0.5 mol) of paraformaldehyde $(\text{CH}_2\text{O})_n$ (95%, powder, Aldrich, Poznań, Poland) was placed in a 1 dm³ flask equipped with a reflux condenser, 162.5 g (1.25 mol) of ethyl acetoacetate (>99%, Fluka, Buchs, Switzerland) was poured in and 1.52 g (2.1 cm³, 0.015 mol) of freshly distilled triethylamine (99%, Aldrich, Poznań, Poland) was added dropwise. Within a few minutes, an exothermic reaction began, and the mixture reached the boiling point (external cooling of the flask was required). When the ebullition ceased, the flask was heated in an electric mantle to maintain boiling, which was continued for 1 h. To 300 cm³ of acetic acid (pure, POCh, Gliwice, Poland), a cold solution of concentrated sulfuric acid (98.5%, p.a., POCh, Gliwice, Poland), 30 cm³ of acid in 200 cm³ of water, was added, and the resulting solution was poured slowly into the cooled reaction mixture. The content of the flask was heated to a gentle boil for 4 h. After the flask had cooled, its content was poured into a 3 dm³ Erlenmeyer flask, which was placed in an ice bath. The liquid in the flask was neutralized by slow addition of a solution of 254 g (6.35 mol) of NaOH (pure, POCh, Gliwice, Poland) in 700 cm³ of water. The crude reaction product was extracted with ethyl ether (4 × 100 cm³), the extracts were combined, washed with brine, and dried over anhydrous MgSO_4 . The ethereal solution was evaporated on a rotary evaporator (Büchi AG, Uster, Switzerland) and the concentrate was distilled under reduced pressure. The fraction with a boiling range of 357–9 K/15 hPa weighing 42.90 g was collected, yield 77.9%. The repeated distillation yielded a colorless ketone with a purity of 99.7% (GC).

2.1.2. NaBH_4 and the Modifiers

NaBH_4 (98%, granules, Aldrich, Poznań, Poland) was used as received. The following set of commercial reagents in the form of metal chlorides of standard purity was purchased at POCh, Gliwice, Poland: BiCl_3 , $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CdCl}_2 \cdot 2.5\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, CuCl , $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and

$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$. The second group of modifiers was those ordered from Aldrich, Poznań, Poland: HgCl_2 (>99.5%), $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (99%), $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (puriss. p.a.), $\text{Mg}(\text{CH}_3\text{COO})_2 \cdot 3\text{H}_2\text{O}$ (>98%) and $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (>99%). The last group of compounds derived from different companies: $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (puriss. p.a., 99%, Fluka, Buchs, Switzerland), CeCl_3 (anhydrous, 99.9%, Fluka, Buchs, Switzerland), SbCl_3 (99.999%, ampoule, Koch Light Lab. Ltd., Colnbrook, Bucks, UK), $\text{SrCl}_2 \cdot 6\text{H}_2\text{O}$ (p.a., Reachim, Chişinău, Moldova), SrBr_2 (anhydrous, Serva, Heidelberg, Germany) and $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (pure, Fluka, Buchs, Switzerland). All modifiers indicated above were used as received. $\text{BeCl}_2 \cdot x\text{H}_2\text{O}$ was prepared in our laboratory from BeO (pure, Reachim, Chişinău, Moldova). In total, 5.0 g of the oxide was calcined at 873 K for 6 h in an open quartz vessel. After cooling, the sample was suspended in water containing oxalic acid (>99.0%, Aldrich, Poznań, Poland), used in 20% excess. The suspension was heated to 343 K for 20 h until the total dissolution of BeO had occurred. The resulting solution of beryllium oxalate was filtered in order to remove small amounts of insoluble oxalates of heavier alkaline earth metals. The filtrate was evaporated to dryness, and the solid oxalate was decomposed at 873 K in air. To 0.125 g (5 mmol) of the purified BeO and 1 cm^3 of water, a concentrated HCl (35–38%, pure, POCh, Gliwice, Poland) was added drop by drop to dissolve the oxide. The resulting solution was concentrated by heating it to 363 K for 2 h, and the semi-solid residue was used as a modifier. Anhydrous MgCO_3 (Upsalite) was prepared according to the procedure described in our previous work [40].

2.1.3. Metal Oxide Catalysts

Commercial SiO_2 (Aerosil 250), Al_2O_3 (Alumina C) and TiO_2 (P-25), all from Degussa (Frankfurt, Germany), and ZnO (purum p.a. Fluka AG, Buchs, Switzerland) in powder form were used for the preparation of catalysts [29]. $\text{ZrOCl}_2 \cdot 6\text{H}_2\text{O}$ (puriss. p.a. Fluka AG, Buchs, Switzerland) was used as the zirconia precursor. MgO was obtained by digestion of MgO (purum p.a., Reachim, Chişinău, Moldova) in nitric acid, followed by precipitation of the hydroxide, drying and calcination. The preparation of ZrO_2 and MgO catalysts was exhaustively described previously [29].

2.1.4. Hydrogen Donors

Three aliphatic alcohols, ethanol (anhydrous 99.8%, POCh, Gliwice, Poland), 2-propanol (puriss., POCh, Gliwice, Poland), and 2-pentanol (98%, Aldrich, Poznań, Poland), were purchased. The purification of the alcohols was described in our previous work [41]. The final purities (GC) of the distilled reagents were as follows: EtOH (99.9%), 2-PrOH (99.8%) and 2-PeOH (99.0%). The alcohols were stored over freshly dehydrated 4 Å molecular sieves in tightly closed containers.

2.1.5. Other Reagents

The following reagents were purchased and used as received:

- 3-methylcyclohexanone (**4**) (pure, Fluka, Buchs, Switzerland).
- 3-methylcyclohexanol (**5**) and (**6**) (mixture of *cis* and *trans* diastereoisomers, Koch-Light Lab. Ltd., Colnbrook, Bucks, UK).

The following reagents were synthesized with the procedures given below:

- *t*-butylbenzene was prepared in our laboratory by alkylation of benzene with isobutylene in the presence of concentrated H_2SO_4 (98%, p.a., POCh, Gliwice, Poland). The organic fraction was washed, dried and distilled twice over metallic sodium under normal pressure. Purity 99.8% (GC).
- (*rac*) 3-methylcyclohex-2-enol (**2**). In an Erlenmeyer flask (250 cm^3) equipped with a magnetic bar and immersed in an ice bath, 7.46 g (20 mmol) of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$

(puriss. p.a., 99.0%, Fluka, Buchs, Switzerland) was dissolved in 50 cm³ of methanol (p.a., POCh, Gliwice, Poland). To this clear solution, 2.2 g, 2.30 cm³ (20 mmol) of 3-methylcyclohex-2-enone (**1**) (see Section 2.1.1) was added in one portion. Solid NaBH₄ 1.52 g (40 mmol) (98%, Aldrich, Poznań, Poland) was added portion by portion over 40 min. After the addition of the last portion of the NaBH₄, the resulting mixture was stirred for the next 40 min. The reaction mixture was diluted with 150 cm³ of water and extracted with diethyl ether (3 × 40 cm³). The extracts were collected, washed with brine and dried over anhydrous MgSO₄ (pure, POCh, Gliwice, Poland). Volatiles were distilled off in a rotary evaporator, leaving 1.81 g (16.1 mmol) of 3-methylcyclohex-2-enol (**2**) as a colorless liquid, with a yield of 80.5%.

- 3-methylcyclohex-3-enone (**11**) (solution of the ketone in 3-methylcyclohex-2-enone). To an 11.02 g (100 mmol) of 3-methylcyclohex-2-enone, placed in a round-bottomed flask equipped with a 30 cm long Vigreux column and a total condensation head, 1.461 g (10 mmol) of adipic acid (99%, Aldrich, Poznań, Poland) was added in one portion and a mixture was heated to boiling for 4 h [42]. The resulting solution was distilled under normal pressure, collecting a fraction (5.54 g) boiling at the temperature range of 449–453 K. The fraction contains two compounds according to GC-MS analysis, a starting ketone and the product of its deconjugation, 3-methylcyclohex-3-enone (**11**), in a ratio of 96.6:3.4.

2.2. Reduction Studies

The post-reaction products were analyzed using an HRGC KONIK (Barcelona, Spain) gas chromatograph equipped with a TRACER WAX capillary column (length 30 m, 0.25 mm i.d.) and a flame ionization detector. The compounds were identified by GC-MS (HP-6890 N with a 5973 N mass detector (Agilent, Santa Clara, CA, USA)).

2.2.1. Reduction of 3-Methylcyclohex-2-enone (**1**) by NaBH₄ Alone

In an Erlenmeyer flask (100 cm³) equipped with a magnetic bar, 1.10 g (1.13 cm³, 10 mmol) of 3-methylcyclohex-2-enone (**1**) was dissolved in 30 cm³ of methanol (p.a., POCh, Gliwice, Poland). A clear solution of 0.378 g (10 mmol) of NaBH₄ (98%, Aldrich, Poznań, Poland) and 0.040 g (1 mmol) of NaOH (pure, POCh, Gliwice, Poland) in 5 cm³ of water was dropped (20 min) into the methanolic solution of ketone with stirring. After the addition of the NaBH₄, the reaction mixture was stirred for 2 h. The post-reaction mixture was diluted with 100 cm³ of water and extracted with CH₂Cl₂ (pure, POCh, Gliwice, Poland) (4 times 10 cm³). The extracts were collected, washed with brine and dried over anhydrous MgSO₄ (pure, POCh, Gliwice, Poland). Volatiles were distilled off in a rotary evaporator and a crude product was weighed, and its composition was analysed using gas chromatography.

2.2.2. Reduction of 3-Methylcyclohex-2-enone (**1**) by NaBH₄ in the Presence of Modifiers

The reactions were carried out analogously to those in Section 2.2.1, with the difference that 1.10 g (1.13 cm³, 10 mmol) of 3-methylcyclohex-2-enone (**1**) was added to the mixed solution/suspension of the modifier, usually in the amount of 5 mmol, in 25 cm³ of methanol (p.a., POCh, Gliwice, Poland). To the obtained solution/suspension, 0.378 g (10 mmol) of solid NaBH₄ (98%, Aldrich, Poznań, Poland) was added portion by portion within 20 min. After the addition of the NaBH₄, the reaction mixture was stirred for 30 min. The post-reaction mixture was diluted with 150 cm³ of water and extracted with CH₂Cl₂ (p.a., POCh, Gliwice, Poland) (4 times 30 cm³). The extracts were collected, washed with brine and dried over anhydrous MgSO₄ (pure, POCh, Gliwice, Poland). Volatiles were distilled off in a rotary evaporator, and a crude product was weighed; its composition was analysed using gas chromatography.

2.2.3. Reduction of 3-Methylcyclohex-2-enone (**1**) via CTH

CTH tests were carried out either in the liquid or vapor-phase modes of reaction:

- Liquid-phase catalytic activity measurements. A weighed sample of a metal oxide (250 ± 2 mg) was introduced into a one-piece cylindrical glass reactor, equipped with a condenser, followed by a magnetic bar, the hydrogen donor, hydrogen acceptor, usually 5 mmol, and *t*-butylbenzene (400 μ L) as an internal standard. The reactor was heated by silicon oil to a temperature 20 degrees higher than the boiling point of the donor to ensure ebullition of the solution. Samples of post-reaction mixtures were first centrifuged in order to separate the catalyst and then analyzed by GC.
- Vapor-phase catalytic activity measurements. A weighed sample of a metal oxide (250 ± 2 mg) was placed in a fixed-bed tubular glass reactor in a stream of nitrogen (50 cm³ min⁻¹). After heating the reactor in the electric furnace to the set temperature, the reactant mixture containing 1.10 g (1.13 cm³, 10 mmol) of 3-methylcyclohex-2-enone (**1**), 3.61 g (4.60 cm³, 60 mmol) of 2-propanol and 400 μ L of *t*-butylbenzene as the internal standard was dosed using a microdosing pump with the Liquid Hourly Space Velocity (LHSV) of 3 cm³ per 1 g of catalyst per hour. The resulting residence time of the gaseous reactants was 9000 h⁻¹ (GHSV). The reaction products were collected in a receiver cooled to 273 K in an ice-water bath. The post-reaction mixture obtained during the first 60 min of the reaction was discarded. Samples were taken within 30 min of the reaction and their composition was determined by gas chromatography.

2.3. Characterization Studies

The catalysts used in CTH were characterized with several techniques, such as nitrogen physisorption (Micromeritics, Norcross, GA, USA), Hammett indicator tests, X-Ray diffraction studies (Brucker, Billerica, MA, USA) and SEM-Energy Dispersive X-Ray spectroscopy (SEM-EDX, Prisma E, ThermoFisher, Waltham, MA, USA). Since these are the same catalysts used in our previously published studies [29], the procedures and results have already been thoroughly discussed. Additionally, the surface composition of spent catalysts was investigated using SEM-EDX. The spent catalysts were imaged with a Prisma E microscope. The elemental maps were collected with a beam voltage of 15 kV, a working distance of 10 mm and a spot size of 5.

3. Results and Discussion

3.1. Reduction of 3-Methylcyclohex-2-enone (**1**) by NaBH₄ (Without Modifiers)

NaBH₄ is a mild reducing agent that selectively reduces formyl and carbonyl groups that are present in aldehyde and ketone molecules to the corresponding alcohols. The presence of other functional groups in the molecule of the reduced compound, e.g., a vinyl group in an isolated position, does not usually interfere with the selective reduction of the carbonyl group. The situation is different when there is a conjugation between the two groups, as is the case with α,β -unsaturated carbonyl compounds. In such a case, the composition of the post-reaction mixture strongly depends on a number of parameters, such as: the structure of the carbonyl compound, the molar ratio of reducing agent to carbonyl compound, reaction temperature, reaction time, solution pH, and type of solvent, etc. The first part of our research was devoted to the attempt of reducing 3-methylcyclohex-2-en- one (**1**) using a solution of NaBH₄ in various solvents, i.e., water, tetrahydrofuran or alcohols: methanol, ethanol, 2-propanol and *t*-butyl alcohol. The results are summarized in Table 1.

Table 1. Reduction of 3-methylcyclohex-2-enone (10 mmol) dissolved in various solvents (30 cm³) by NaBH₄ (10 mmol) dissolved in 5 cm³ of a water solution of NaOH (40 mg, 1 mmol). The solution of the reducing agent was added dropwise over 1 h at room temperature. After the addition of the reducing agent, the mixture was stirred for 2 h.

NaBH ₄ Ketone Molar Ratio	Solvent	Conversion [%]	Moles from 100 mol of (1)				
			(2) ¹	(3) ¹	(5) ¹	(6) ¹	Others
1:1	H ₂ O	91	53	2	29	5	2
2:1	MeOH	100	50	7	31	6	6
1:1	MeOH	99	49	8	29	6	7
	MeOH ²	94	44	7	31	6	6
1:2	MeOH	86	42	9	24	5	6
1:4	MeOH	49	23	5	13	3	5
1:2	MeOH ³	90	38	9	29	6	8
	EtOH	100	50	9	33	5	3
	EtOH ⁴	99	49	8	34	5	3
	EtOH ^{4,5}	100	53	6	34	5	2
	EtOH ^{4,6}	100	49	10	33	5	3
1:1	EtOH ^{4,7}	74	44	5	20	3	1
	2-PrOH	100	51	5	37	5	3
	<i>t</i> -BuOH	89	51	0	32	4	2
	⁸	72	48	0	21	2	1
	⁹	100	51	0	42	5	2

¹—3-methyl-cyclohex-2-enol (2), 3-methyl-cyclohex-3-enol (3), *cis* 3-methylcyclohexanol (5), *trans* 3-methylcyclohexanol (6); ²—stirred 1 h after addition of NaBH₄; ³—stirred 4 h after addition of NaBH₄; ⁴—96% EtOH; ⁵—without addition of NaOH to NaBH₄; ⁶—100 mg of NaOH; ⁷—T = 273 K; ⁸—(57 cm³ THF + 5.7 cm³ H₂O) as a solvent, T = 273 K [43]; ⁹—(30 cm³ THF + 1 cm³ H₂O) as a solvent, reflux 8 min [43].

The reduction was carried out at room temperature with an alkalized NaBH₄ solution at a constant NaBH₄—ketone molar ratio of 1:1 and a constant stirring period after the addition of the reducing agent of 2 h. Under these conditions, when MeOH, EtOH or 2-PrOH were used as the solvent (but not *t*-BuOH), 3-methylcyclohex-2-enone (1) conversions of 99–100% and 3-methylcyclohex-2-enol (2) yields of 49–51% were recorded. The highest chemoselectivity value of the reaction towards 3-methylcyclohex-2-enol (2) was 58%. The remaining reaction products were: *trans* and *cis* 3-methylcyclohexanols (6) and (5) and 3-methylcyclohex-3-enol (3). *cis* 3-Methylcyclohexanol (5) is the main by-product generated in this reaction. Its yield ranged from 27–34%. The yield of *trans* 3-methylcyclohexanol (6) was practically constant and amounted to 5–6%. The relative fractions of 3-methylcyclohexanol diastereomers in the post-reaction mixtures were consistent with the greater stability of the *cis* diastereomer, which is known from the literature [44]. Diminished conversions (between 89 and 91%) were observed when water and *t*-butyl alcohol were used as solvents, with retained 3-methylcyclohex-2-enol (2) yields of 51 and 53%, respectively. However, in contrast to water, in the presence of *t*-butyl alcohol, no 3-methylcyclohex-3-enol (3) formation was observed. It was also found that the use of anhydrous ethanol and its solution containing 96% ethanol and water as solvents had no effect on the reaction course and the yield of 3-methylcyclohex-2-enol (2). However, a strong influence of temperature on the reaction course was noted; at 273 K using 96% ethanol as a solvent, a conversion of 74% and a lower yield (44%) of 3-methylcyclohex-2-enol (2) were measured compared to the values obtained at room temperature (298 K), i.e., 99% and 49%, respectively. The use of tetrahydrofuran with added water as a solvent had no effect on the 3-methylcyclohex-2-enol (2) yield despite carrying out the reaction at 273 and 340 K [43].

We also examined the effect of the NaBH_4 –3-methylcyclohex-2-enone (**1**) molar ratio on the composition of the post-reaction mixture, especially the chemoselectivity to 3-methylcyclohex-2-enol (**2**). Quantitative conversion of 3-methylcyclohex-2-enone (**1**) was obtained for reducing agent–3-methylcyclohex-2-enone (**1**) molar ratios of 2 and 1. Further lowering of this ratio (1:2 and 1:4) resulted in lower conversion and 3-methylcyclohex-2-enol (**2**) yield. For the lowest reducing agent–3-methylcyclohex-2-enone (**1**) ratio (1:4), the conversion and yield of 3-methylcyclohex-2-enol (**2**) values were 49 and 23%, respectively.

3.2. Reduction of 3-Methylcyclohex-2-enone by NaBH_4 in the Presence of Various Modifiers

In the studies carried out in the previous section, it was found that NaBH_4 , used for the reduction of a cyclic α,β -unsaturated ketone such as 3-methylcyclohex-2-enone (**1**), showed only a moderate chemoselectivity towards the unsaturated alcohol along with high reactivity. Therefore, a method was sought to decrease the reactivity of the reducing agent and hence increase the chemoselectivity of the reaction to 3-methylcyclohex-2-enol (**2**). At the end of the 1970s, Luche's work showed that the use of rare earth halides and NaBH_4 led to very high yields of enols in the reduction of the corresponding α,β -unsaturated ketones [21,22]. Japanese chemists reported the effective use of alkaline earth metal chlorides as modifiers of NaBH_4 [23]. Due to the rather modest amount of experimental material from the literature regarding the use of modifiers in the reduction of α,β -unsaturated ketones by NaBH_4 , it was decided to conduct studies of various metal halides as modifiers in the reduction of 3-methylcyclohex-2-enone (**1**) with NaBH_4 . Seventeen metal halides were selected for testing, some in their anhydrous form and others as hydrates. Modifiers that are reduced to metal, metal hydride or metal boride under the reaction conditions have a strong deactivating effect on the NaBH_4 , e.g., HgCl_2 , SbCl_3 , BiCl_3 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ and CuCl . Alkaline earth metal halides and lanthanoid (III) halides are not subject to NaBH_4 reduction, but they react with NaBH_4 to form borohydrides or their derivatives of these metals, which in turn increase the chemoselectivity of reduction to 3-methylcyclohex-2-enol (**2**). It is postulated that the Ce^{3+} ions increase the acidity of the hydroxyl proton in the methanol molecule and hence enable its attack on the carbonyl oxygen atom [45].

To compare the performance of the modifiers, all tests were conducted at a constant NaBH_4 –ketone molar ratio of 1:1 and at a molar ratio of NaBH_4 to modifier equal to 2 in methanol as the solvent. The results are summarized in Figure 1. It can be seen that only in the case of two metal halides, namely $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, a quantitative conversion of 3-methylcyclohex-2-enone (**1**) was noted. This was also the case in the studies focused on rare earth metal chlorides carried out by Gemal and Luche [21]. What is more, 100% yield of the unsaturated alcohol was noted. In the case of benzylidene acetone, dibenzylidene acetone and benzylidene acetophenone, the yields observed by Sande et al. were 90%, 90% and 89%, although the first two were reduced for 4 h, whereas the last was reduced for 28 h [46]. Moreover, the quantitative conversion was accompanied by very high yields of 3-methylcyclohex-2-enol (**2**), 95 and 94% for $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, respectively. It is noteworthy that the latter is an abundant metal, whose effect of NaBH_4 modification is substantially equal to that of the Ce modifier in terms of conversion and selectivity. Therefore, it exhibits a significant advantage in applicability. Conversions of 3-methylcyclohex-2-enone (**1**) above 50% were observed only in the presence of two further halides (CuCl and $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$), which were 73 and 71%, respectively, and only in the presence of the latter halide was a 64% yield of 3-methylcyclohex-2-enol (**2**) obtained. The NaBH_4 – CuCl system was highly active in reducing 3-methylcyclohex-2-enone (**1**) to a mixture of *cis* and *trans* 3-methylcyclohexanols (**5**) and (**6**). In this case, (**5**) and (**6**) reportedly yielded 52% and 11%, respectively, with a very low (4%) yield of

3-methylcyclohex-2-enol (2). In the presence of the other metal halides, varying conversions of 3-methylcyclohex-2-enone (1) were observed, ranging from 33 to 1%. For these halides, the highest yields of 3-methylcyclohex-2-enol (6–7%) were obtained in the case of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{CdCl}_2 \cdot 2.5\text{H}_2\text{O}$. In the case of all metal halides used as modifiers of NaBH_4 , no 3-methylcyclohex-3-enol (3) was found as a reaction product.

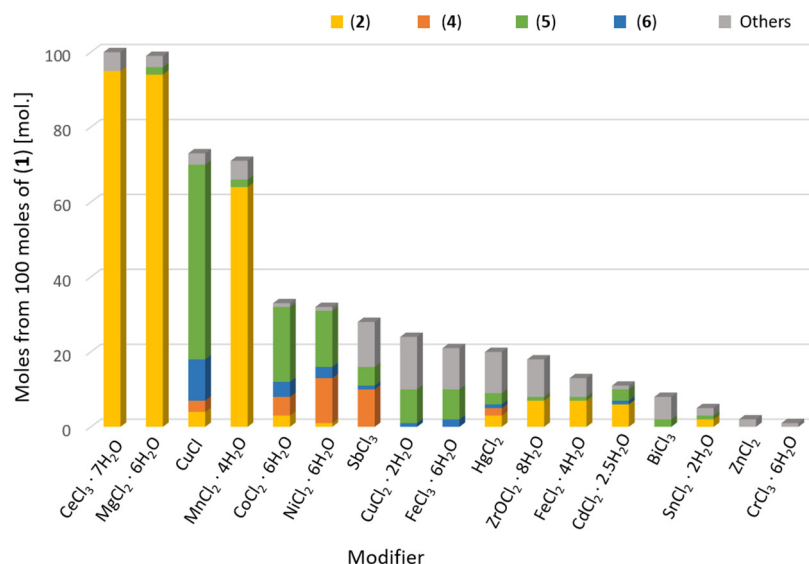


Figure 1. Results of the reduction of 3-methylcyclohex-2-enone (1) (10 mmol) dissolved in methanol (25 cm³) to which various modifiers (5 mmol) and a solid NaBH_4 (10 mmol) were added at room temperature. The reaction mixture was stirred for 30 min after the addition of the reducing agent.

In the next stage of the research, our activities were focused on detailed studies of the two types of the most promising systems, i.e., $\text{NaBH}_4\text{--MCl}_2$, where $\text{M} = \text{Be, Mg, Ca, Sr}$ and Ba , and $\text{NaBH}_4\text{--CeCl}_3 \cdot 7\text{H}_2\text{O}$. The results for this first system are summarized in Figure 2. It was found that the use of all alkaline earth metal halides as modifiers significantly increases the chemoselectivity of the reduction of 3-methylcyclohex-2-enone (1) by NaBH_4 towards the unsaturated alcohol, with the effect depending on the type of metal. The highest yield of 3-methylcyclohex-2-enol (2) (94%) was noted for $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ as the modifier. The $\text{NaBH}_4\text{--BeCl}_2 \cdot x\text{H}_2\text{O}$ system showed the least reactivity to afford 76% yield of 3-methylcyclohex-2-enol (2). It was also noted that when bromides are applied as the modifier, the reactivity and chemoselectivity of the system do not change, as seen in the case of $\text{NaBH}_4\text{--SrCl}_2 \cdot 6\text{H}_2\text{O}$ and $\text{NaBH}_4\text{--SrBr}_2$ systems.

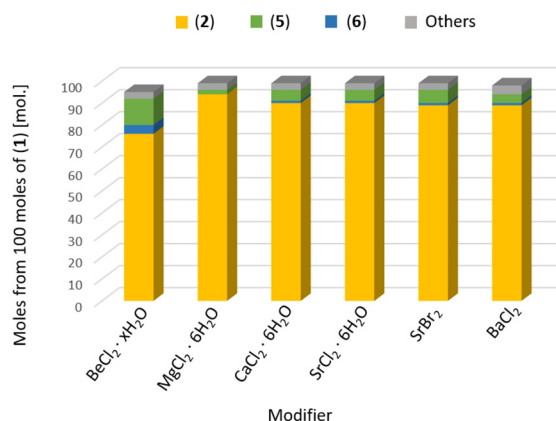


Figure 2. Results of the reduction of 3-methylcyclohex-2-enone (1) with NaBH_4 and alkaline earth metal halides as modifiers.

The $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ – NaBH_4 system was tested in the reduction of 3-methylcyclohex-2-enone (**1**) with a variable modifier to NaBH_4 molar ratio. The results of these experiments are provided in Figure 3a. A series of measurements was carried out, starting from the value of this ratio equal to 1, and in each subsequent step, its value was reduced by half, ending the series with a value of 0.031. Quantitative conversion (99–100%) was found in the entire range of molar ratios tested. In the range between 1.0 and 0.063, the yield of 3-methylcyclohex-2-enol (**2**) was practically constant and equal to 94–95%. Further lowering of the ratio resulted in a slight reduction in the 3-methylcyclohex-2-enol (**2**) yield to 90%. Within the entire range of modifier to NaBH_4 ratio values, 3-methylcyclohexanone (**4**) and 3-methylcyclohex-3-enol (**3**) were absent in the post-reaction mixture. Regioisomeric 3-methylcyclohexanols (**5**) and (**6**) only appeared in the post-reaction mixture when the test was carried out at the lowest modifier to NaBH_4 ratios, namely 0.063 and 0.031. Their yields did not exceed 3%. As part of this stage of the research, it was also checked how the reduction of 3-methylcyclohex-2-enone (**1**) took place when the solvent was a mixture of methanol and water (Figure 3b). Replacing methanol with water resulted in a very slight decrease in conversion (from 100 to 97%) as well as a slight decrease in the 3-methylcyclohex-2-enol (**2**) yield (from 93 to 91%). Lowering the reduction temperature in pure water as a solvent to 273 K allowed for higher conversion and yield of 3-methylcyclohex-2-enol (**2**) compared to those values obtained at room temperature. Reduction at a temperature of 313 K had a negative impact on the conversion (93%) and the yield of the main product (85%). The use of anhydrous CeCl_3 as the modifier resulted in a higher yield of *cis* 3-methylcyclohexanol (**5**) (8%) at the expense of the 3-methylcyclohex-2-enol (**2**) yield (84%).

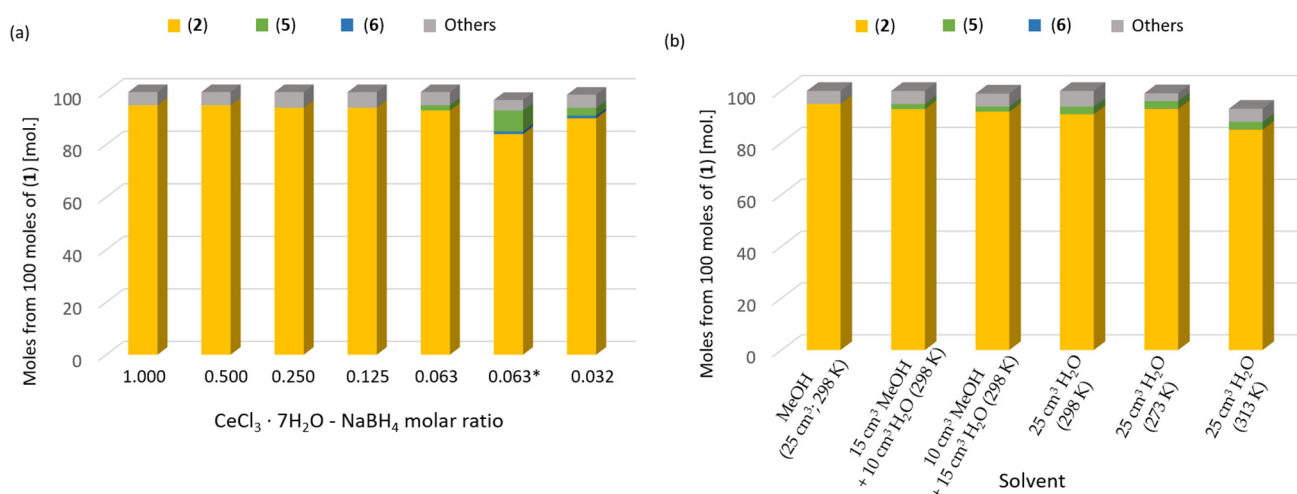


Figure 3. Results of reduction studies: (a) influence of the $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ – NaBH_4 molar ratio and (b) influence of the solvent mixture and reaction temperature on the reactivity and chemoselectivity of the reduction of 3-methylcyclohex-2-enone (**1**); * anhydrous CeCl_3 in methanol.

In the last part of this stage of the research, it was examined how the type of anion in the magnesium salt used as a modifier influences the composition of the post-reaction mixture. Results of tests using five different magnesium salts, namely acetate, carbonate, chloride, nitrate and sulfate, are presented in Figure 4a. It was found that in the reduction of 3-methylcyclohex-2-enone (**1**) with NaBH_4 , with the presence of magnesium salts, an increase in the chemoselectivity towards 3-methylcyclohex-2-enol (**2**) compared to that noted for the reduction with NaBH_4 alone was observed. However, this increase is dependent on the type of anion. In the presence of three magnesium salts, acetate, carbonate and sulfate, conversions of 66, 73 and 93%, respectively, were recorded, which are lower than those observed in the reduction with NaBH_4 alone. The two most reactive systems were NaBH_4 – $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and NaBH_4 – $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, in the presence of which

the conversion was 99% and the yield of 3-methylcyclohex-2-enol (**2**) was 92 and 94%, respectively. The latter system was subjected to detailed studies taking into account the change of the $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ – NaBH_4 molar ratio for values of this ratio of 0.1, 0.25, 0.5 and 0.75 (Figure 4b). The highest values of 3-methylcyclohex-2-enol (**2**) yield of 94% at 99% conversion were found for values of this ratio of 0.50 and 0.75.

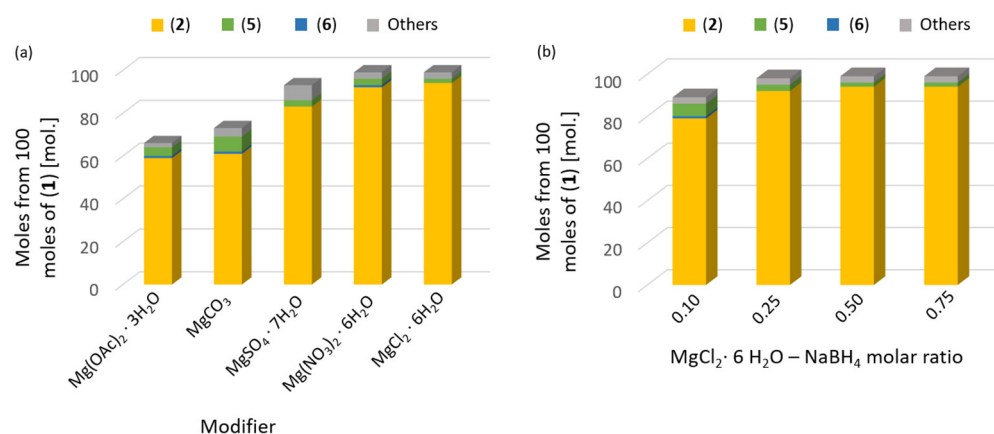


Figure 4. Results of the reduction of 3-methylcyclohex-2-enone with NaBH_4 and (a) various magnesium salts as modifiers as well as (b) different $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ – NaBH_4 molar ratios.

3.3. Characterization of Metal Oxide Catalysts

All oxide catalysts used in this work (Al_2O_3 , SiO_2 , TiO_2 , ZrO_2 , ZnO and MgO) were studied in our recent publication and were comprehensively characterized there [29]. Hence, in the present work, only the key parameters characterizing the catalysts used in the study are given in a short form. The specific surface area (S_{BET}), crystallite size of metal oxides used as catalysts, and their acid–base properties are collected in Table 2. The Al_2O_3 surface is characterized by the presence of acidic sites with the highest strength compared to the strengths of acidic sites present on the surfaces of other studied oxides, and by the lowest strength of basic sites. MgO is an oxide whose surface is characterized by the presence of only basic sites with very diverse strengths, including some that exhibit the properties of superbasic sites ($\text{H}_- < 33.0$). In contrast, silica is an oxide with only the weakest acidic and basic sites on its surface. In the case of other oxides, acidic sites are prevalent on their surfaces along with weak basic sites.

Table 2. Results of characterization studies of metal oxide catalysts.

Catalyst	2θ [°]/(hkl)	Crystallite Size [nm]	S_{BET} [$\text{m}^2 \cdot \text{g}^{-1}$]	Acid–Base Properties	
				Acidic	Basic
SiO_2	--	-- ¹	253	$0.8 < \text{H}_0 \leq 4.8$	$7.2 \leq \text{H}_- < 9.3$
Al_2O_3	67.1/(042)	12	103	$-5.6 < \text{H}_0 \leq 4.8$	$7.2 \leq \text{H}_- < 9.3$
MgO	42.9/(200)	12	100	n.a.	$7.2 \leq \text{H}_- < 33.0$
TiO_2	25.3/(101)	23 ²	35	$-3.0 < \text{H}_0 \leq 4.8$	$7.2 \leq \text{H}_- < 9.3$
	27.4/(110)	31 ³			
ZrO_2	28.2/(111)	18	32	$-3.0 < \text{H}_0 \leq 4.8$	$7.2 \leq \text{H}_- < 18.4$
ZnO	36.2/(101)	33	4	$0.8 < \text{H}_0 \leq 4.8$	$7.2 \leq \text{H}_- < 15.0$

¹—amorphous phase; ²—anatase; ³—rutile.

3.4. Vapor- and Liquid-Phase CTH of 3-Methylcyclohex-2-enone with Alcohols in the Presence of Various Metal Oxides as Catalysts

Very high yields of 3-methylcyclohex-2-enol (**2**) obtained in the liquid-phase reduction of 3-methylcyclohex-2-enone (**1**) by NaBH_4 with the addition of some modifiers, encouraged us to attempt to synthesize 3-methylcyclohex-2-enol (**2**) in the vapor phase by CTH. Six

metal oxides were used as catalysts, namely SiO_2 , TiO_2 , Al_2O_3 , ZrO_2 , ZnO and MgO . Catalytic tests were carried out at a temperature range of 523–623 K. The results are presented in Figure 5. It was observed that the 3-methylcyclohex-2-enone (**1**) conversions, depending on the type of catalyst used, varied from 2% (SiO_2) to 98% (Al_2O_3 and ZrO_2). In the presence of four catalysts (SiO_2 , TiO_2 , ZrO_2 and Al_2O_3), no 3-methylcyclohex-2-enol (**2**) formation was observed in the reaction within the tested temperature range. Its formation was observed only in the case of two catalysts, i.e., MgO and ZnO , with the yields of 22% and 2%, respectively. High conversions of 3-methylcyclohex-2-enone (**1**) (of the order of 90–98%) noted in the presence of Al_2O_3 and ZrO_2 were accompanied by the formation of heavy condensation products and alkenes formed in the dehydration reaction of the intermediate alcohols. Among the catalysts used, MgO exhibited the highest selectivity to 3-methylcyclohex-2-enol (**2**). In its presence, the yields of this product ranged from 18 to 22%. It is noteworthy that the main reaction product was 3-methylcyclohex-3-enol, whose yield (25 to 33%) exceeded that of 3-methylcyclohex-2-enol (**2**) across the entire reaction temperature range. A similar pattern of 3-methylcyclohex-2-enone (**1**) transformations was observed when another hydrogen donor, ethanol, was used, or when the 2-propanol-3-methylcyclohex-2-enone (**1**) molar ratio was changed to 3.

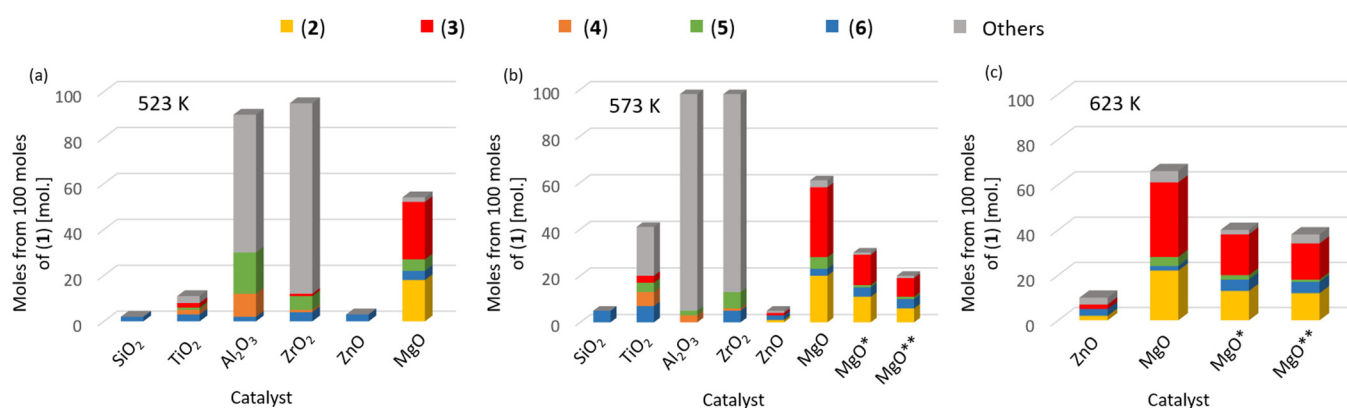


Figure 5. Results of the vapor-phase CTH of 3-methylcyclohex-2-enone with 2-propanol in the presence of metal oxides as catalysts carried out at three different temperatures: (a) 523 K, (b) 573 K and (c) 623 K. D/A = 6, LHSV = 3.0 h^{-1} . Anone = 3-methylcyclohexanone, *t*-Anol = *trans* 3-methylcyclohexanol, *c*-Anol = *cis* 3-methylcyclohexanol, Enol = 3-methylcyclohex-2-enol; *i*-Enol = 3-methylcyclohex-3-enol; *—2-PrOH, D/A = 3; **—EtOH, D/A = 6.

The two oxides with the highest yields of condensation products, namely Al_2O_3 and ZrO_2 , as well as MgO , were tested with SEM-EDX to determine if any carbonaceous deposits form on their surface. Although the grains were orange/brown after 6 h of CTH, the elemental maps of their surfaces did not reveal any patches or particles of char on their surface, as shown in Figure 6. The distribution of carbon on the surface is uniform. Its relative abundance is much lower than on the graphite tape onto which the grains were placed for analysis. The EDX analysis (Figure 7) revealed that all three oxides have a substantial carbon content, but contain no other elements, as in the case of the fresh grains. The carbon deposit can be easily burnt off at 873 K (30 min), which means that it is possible to reuse the spent catalyst after thermal treatment.

A time-on-stream test was carried out in order to check if the yields of 3-methylcyclohex-2-enol (**2**) and 3-methylcyclohex-3-enol (**3**) changed over time on MgO , i.e., the most active catalyst. The test was performed at a constant temperature of 573 K. The results are given in Table 3. The catalyst remained active throughout the entire reaction time (30–360 min), and the 3-methylcyclohex-2-enone (**1**) conversion decreased from 58% (30 min) to 27% (360 min). The 3-methylcyclohex-2-enol (**2**) yield decreased from 14 to 8%. The main

product, over the entire reaction time range, was 3-methylcyclohex-3-enol (**3**); its yield was 23–15%. The presence of both *cis* (**5**) and *trans* (**6**) diastereomers of 3-methylcyclohexanol in the post-reaction mixtures was recorded; their fractions decreased rapidly over time, and after 120 min of reaction, this value dropped to 2%. There was no formation of 3-methylcyclohexanone (**4**) during the entire reaction time.

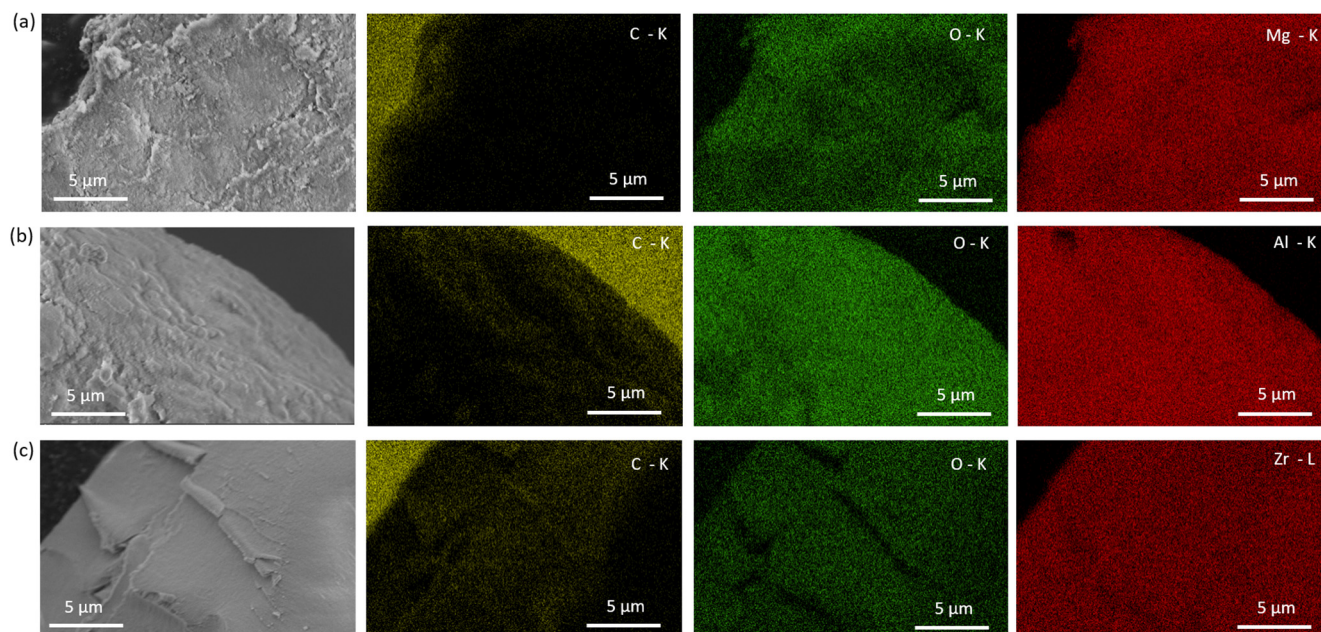


Figure 6. SEM images and elemental maps of (a) Al_2O_3 , (b) MgO , and (c) ZrO_2 after 6 h of catalytic tests.

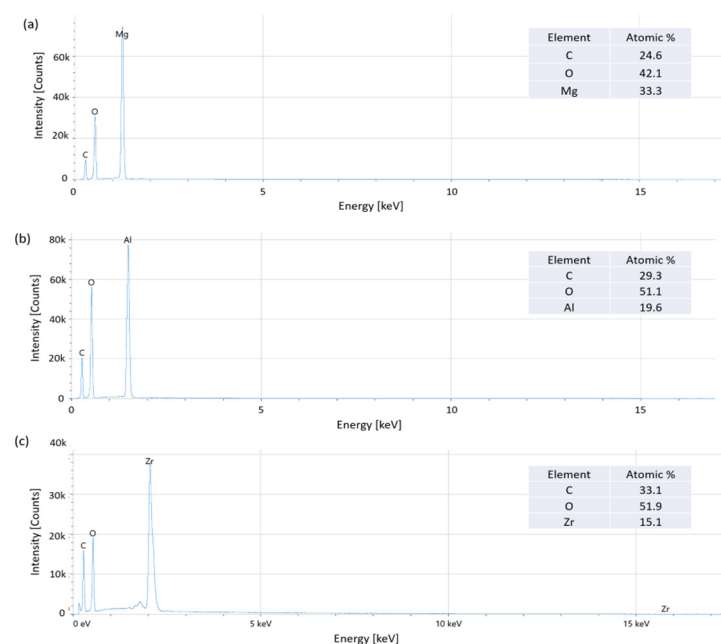


Figure 7. EDX spectra and relative atomic compositions of (a) MgO , (b) Al_2O_3 , and (c) ZrO_2 after 6 h of catalytic tests.

Studies on the CTH of 3-methylcyclohex-2-enone (**1**) by alcohols were carried out in the liquid phase only with MgO as the catalyst. Two secondary alcohols were used as hydrogen donors: 2-propanol and 2-pentanol (Table 4). Only a trace conversion of 3-methylcyclohex-2-enone (**1**) (2%) was found after 360 min of reaction with 2-propanol, and the only conversion product of this ketone was 3-methylcyclohex-2-enol (**2**). After 360 min of reaction with 2-pentanol as the hydrogen donor, the ketone conversion was

equal to 12%, and a 100% chemoselectivity of its reduction to 3-methylcyclohex-2-enol (2) was observed.

Table 3. Time-on-stream test of MgO activity in vapor-phase CTH of 3-methylcyclohex-2-enone (1) with 2-propanol at 573 K. D/A = 6, LHSV = 3.0 h^{−1}.

Time [min]	Conversion [%]	Moles from 100 mol of (1)				Others
		(2) ¹	(3) ¹	(5) ¹	(6) ¹	
30	58	14	23	12	7	2
60	43	13	21	5	3	1
120	33	10	18	2	2	1
180	30	9	16	2	2	1
240	28	8	15	2	2	1
300	27	8	15	1	2	1

¹—3-methylcyclohex-2-enol (2); 3-methylcyclohex-3-enol (3); *cis* 3-methylcyclohexanol (5); *trans* 3-methylcyclohexanol (6).

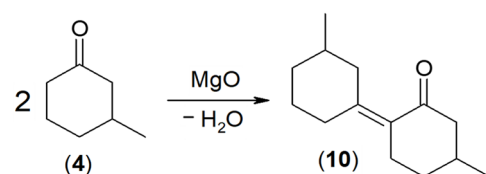
Table 4. Results of the liquid-phase CTH of 3-methylcyclohex-2-enone (1) with alcohols in the presence of MgO. D/A = 6.

Hydrogen Donor	Time [min]	Conv. [%]	Moles from 100 mol of (1)	
			(2) ¹	Others
2-PrOH ²	30	0	0	0
	360	2	2	0
	30	3	3	0
2-PeOH ³	60	5	5	0
	360	12	12	0

¹—3-methylcyclohex-2-enol (2); ²—reaction temperature was 355 K; ³—reaction temperature was 392 K.

3.5. Transformations of the CTH Products Derived from 3-Methylcyclohex-2-enone (1) in the Presence of MgO as the Catalyst

The last part of the research in this work was devoted to an attempt to determine the sources of 3-methylcyclohex-3-enol (3) formation in the transformations of 3-methylcyclohex-2-enone (1) and derivatives obtained from it in CTH. In the first step of these studies, it was shown that the compound in question was not formed from 3-methylcyclohexanone (4) in its 10 wt.% solution in boiling cyclohexane (b.p. 353 K) in the presence of MgO within 6 h of heating to reflux. In this system, the homoaldol condensation of 3-methylcyclohexanone (4) proceeded (Scheme 3), forming 5-methyl-2-(3-methylcyclohexylidene)cyclohexanone (10) as the only product. After 6 h of reaction, the product yield was 85%.



Scheme 3. Aldol condensation of 3-methylcyclohexanone (4) to 5-methyl-2-(3-methylcyclohexylidene)cyclohexanone (10).

The second point of the study showed that the mixture of regioisomeric 3-methylcyclohexanols (5) and (6) dissolved in cyclohexane (10 wt.% solution) in the presence of MgO at 353 K (boiling) did not undergo any transformations during the 6 h of reaction. A similar lack of reaction in the liquid phase was reported for 3-methylcyclohex-2-enol (2) dissolved in 2-propanol or cyclohexane (15 wt.% solutions) in the presence of MgO at temperatures of 355 and 353 K, respectively. Due to the lack of conversion of the alcohol

substrates under these conditions, it was decided to perform catalytic tests at higher temperatures than those used previously. Hence, *n*-decane, with a boiling point of 446 K, was used as the solvent for 3-methylcyclohex-2-enol (2). The results are presented in Table 5. It was shown that at the temperature of 446 K, the isomerization of 3-methylcyclohex-2-enol (2) occurs in the presence of MgO and primarily proceeds to 3-methylcyclohex-3-enol (3). After 6 h of heating to boiling, the yield was 19%. Moreover, it was found that 3-methylcyclohexanone (4) is also formed in the reaction with a small yield (3%). In contrast, 3-methylcyclohexanols (5) and (6) were not found in the reaction products.

Table 5. Liquid-phase transformations of 3-methylcyclohex-2-enol (2) (10 wt.%) dissolved in *n*-decane in the presence of MgO at 446 K.

Time [min]	Conversion [%]	Moles from 100 mol of (2)		
		(3) ¹	(4) ¹	Others
60	6	5	1	0
180	16	12	3	1
360	24	19	3	2

¹—3-methylcyclohex-3-enol (3), 3-methylcyclohexanone (4).

Attempts were made to synthesize 3-methylcyclohex-3-enol (3) in the vapor phase by the transformation of 3-methylcyclohex-2-enol (2) dissolved in cyclohexane (1:6 molar ratio) in the presence of MgO. The results are compiled in Figure 8. It was found that in the entire reaction temperature range (473–623 K), the main product of 3-methylcyclohex-2-enol (2) transformation was 3-methylcyclohex-3-enol (3) (yield 23–39%), accompanied by both regioisomeric 3-methylcyclohexanols (5) and (6) in low yields (up to 5 and 8%, respectively). No 3-methylcyclohexanone (4) was detected among the reaction products, but 3-methylcyclohex-2-enone (1) was present, the maximum yield of which was 15% at 623 K.

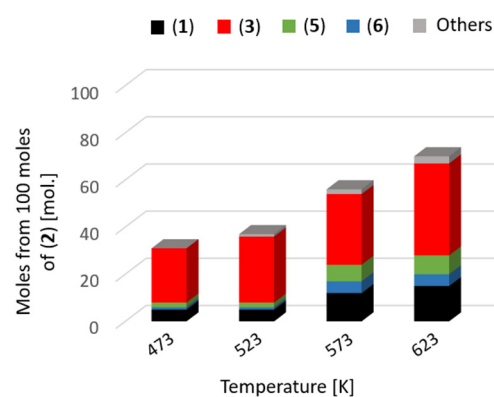


Figure 8. Results of vapor-phase transformations of 3-methylcyclohex-2-enol (2) dissolved in cyclohexane (1:6 molar ratio) in the presence of MgO.

4. Conclusions

Reduction of 3-methylcyclohex-2-enone (1) by NaBH₄ in methanolic solution was investigated. It was noted that the reaction leads to 3-methylcyclohex-2-enol (2) as a main product with a maximum yield of 53% at 91–100% conversion. 3-Methylcyclohex-2-enol (2) was accompanied by both 3-methylcyclohexanols (5) and (6) (6 and up to 42%, respectively) and 3-methylcyclohex-3-enol (3) (up to 10%). Various metal halides were used as modifiers for NaBH₄, significantly influencing its reactivity and the chemoselectivity of 3-methylcyclohex-2-enone (1) reduction. The results of screening studies using seventeen NaBH₄ modifiers clearly indicate that two types of systems, namely NaBH₄–CeCl₃ · 7H₂O and NaBH₄–MCl₂ · 6H₂O, where M = Be, Mg, Ca, Sr, and Ba, yield the highest chemos-

electivity in the reduction of 3-methylcyclohex-2-enone (**1**) among the modifiers studied in this work. Moreover, we disclosed the possibility of the reduction of the modifier fraction to the value of this ratio of 0.25 with only a slight change in the conversion and the 3-methylcyclohex-2-enol (**2**) yield. Since among the various modifiers tested with NaBH₄ in the reduction of 3-methylcyclohex-2-enone (**1**), only systems containing CeCl₃ · 7H₂O and MgCl₂ · 6H₂O were characterized by very high chemoselectivity towards 3-methylcyclohex-2-enol (**2**) with almost quantitative conversion, a detailed study of the NaBH₄–CeCl₃ · 7H₂O system was carried out. In the case of the second modifier (MgCl₂ · 6H₂O), the high chemoselectivity and 98% conversion were a signal for testing other alkaline earth metal halides, which was also performed. It was expected that halides of the two most common alkaline earth metals (Mg and Ca) would also be the best modifiers of NaBH₄. The best results were obtained for the system with Mg, which is a cheap and abundant metal. Since the conversion of 3-methylcyclohex-2-enone (**1**) and selectivity to 3-methylcyclohex-2-enol (**2**), it is more advantageous for implementation on a larger scale. The fact that it showed such beneficial properties led to the use of other magnesium-containing salts as modifiers. However, chloride was the most effective one.

In the case of CTH studies, a 100% chemoselectivity was obtained in the liquid phase with MgO as the catalyst, though with a moderate conversion. In the vapor phase of the 6 selected metal oxides as catalysts, only two, namely MgO and ZnO, led to the formation of 3-methylcyclohex-2-enol (**2**). The remaining catalysts, even very active ones, were characterized by negligible chemoselectivity towards 3-methylcyclohex-2-enol (**2**). As a result of the studies undertaken to clarify the source of origin of 3-methylcyclohex-3-enol (**3**), it was found that it is a product of the subsequent transformation of 3-methylcyclohex-2-enol (**2**) formed in the reaction in the presence of a strongly basic catalyst, i.e., magnesium oxide. This also explains the presence of this compound after the reduction of 3-methylcyclohex-2-enone (**1**) with NaBH₄ alone, because of the basicity of NaBH₄ itself, and the addition of small amounts of a strong base, NaOH, to methanol in order to stabilize the NaBH₄ solution prepared for the reaction is responsible for its formation.

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