

REDUCTION OF α , β -UNSATURATED ACIDS WITH Ni-Al ALLOY IN ALKALINE AQUEOUS MEDIUM – MECHANISTICAL ASPECTS

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Abstract: The results described in the literature and our previous research confirms the efficiency of the reduction reactions of α , β -unsaturated compounds and carbonyl compounds mediated by the Ni-Al alloy in alkaline (NaOH) aqueous solution. Some particularly experiments for reduction of crotonic and cinnamic acid, was designed to bring information on the mechanism of reduction reaction with Ni-Al alloys in alkaline aqueous media. Also it was developed several deuteration reaction of this α , β -unsaturated acids. The analysis of the isotopic distribution shows a significant and reproducible difference between C α and C β that help us to draw some conclusions. In addition, recent researches give us additional arguments concerning the existence of anionic aluminum clusters with water. All this information contributes to propose a mechanism of reduction reaction and could provide new possibilities for development of this reaction: improving yield and selectivity, promoting a new synthesis etc.

Keywords: 1,4-addition, cinnamic acid, crotonic acid, deuteration, isotopic labeling, Ni-Al alloy, reduction, water

INTRODUCTION

At the present there are numerous studies published on the reduction reactions mediated by a reducing system composed of Ni-Al alloy in an aqueous alkaline. Both the results described in the literature and our previous research confirms the efficiency of the reduction reactions of α , β -unsaturated acids [1 – 3], carbonyl compounds [4 – 9], halogenated derivatives [10 – 12] etc. mediated by the Ni-Al alloy in alkaline (NaOH) aqueous solution. This type of reaction shows multiple advantages, such as: simplicity, mild reaction conditions, aqueous media, high conversions and selectivities [2, 5, 7]. Nevertheless, until now it was not given an explicit answer to the question "what is the specific mechanism of investigated reactions and what the degree of generality is?" In addition, contradictory observations in the literature require an explanation. For example, the reducing of cyclooctatetraene with Ni-Al alloy in NaOH solution, give the cyclooctene, while by it catalytic hydrogenation with H₂ and Raney nickel, cyclooctane is obtained [2], suggesting a different mechanism between the two types of hydrogenation. Similarly, unsaturated fatty acids show an advanced inertia of C=C double bonds reduction with Ni-Al/NaOH system, in contrast to easy hydrogenation under heterogeneous catalysis conditions with H₂ and Raney Ni [2, 13].

Our research has started from the idea of choosing the reaction conditions (using an excess of Ni-Al alloy as a reducing agent), it was intended to favor a process type in which the reduction originates directly from the reactive metal (aluminum) [14]. Therefore, it is suggested a separation from the mechanism of a catalytic reduction by hydrogen and nickel catalyst, both generated *in situ* by an attack with alkaline aqueous solution of the Ni-Al alloy. It is also suggested that the reactions do not occur either by "active hydrogen forms", for example aluminum hydrides, there is also generated intermediately. In our experiments, it was chosen a molar ratio of reactants such that provide a large excess of reducing agent (given in aluminum equivalents). The amount of Ni-Al alloy used provided an excess of 5-10 times to the required stoichiometric amount. The choice for this large excess of reducing agent was done both to ensure a relatively constant composition and morphology of the solid phase reagent during the reaction and also to place the entire study of reactivity taken herein to the favorable type of mechanism in which the key reduction reagent is aluminum (reactive metal). The arguments which have led to the assumption that the main source of reduction in Ni-Al/NaOH system comes from aluminum atoms were provided from the experiments carried out using Ni-Al alloys with controlled aluminum content [15]. The experimental data was supplemented with a reduction test using NaOD-D₂O as the reaction medium. Examination of the isotopic distribution in the reaction product gave us essential information on the progress of the reaction and the nature of the intermediates [16, 17].

MATERIALS AND METHODS

Reduction reactions

Crotonic and cinnamic acids (analytical purity reagents from Merck) were used as reducing substrates. The reduction reactions were carried out with 50 %-50 % Ni-Al alloy powder (Merck) and 20 % NaOH (Sigma-Aldrich) aqueous solution at 50 °C. The

progress of the reaction was monitored by TLC. The mixture was cooled at room temperature, and then was acidulated with HCl 37 % aq. until pH 2, extracted with diethyl ether and evaporated at normal pressure. The analyses were performed by GC-MS and ^1H -NMR. The reduction reaction conditions were presented in Table 1, reactions (a, b).

Deuteriation reactions

Deuteriation reactions were performed similarly to the reduction, but replacing completely the aqueous system with D_2O -NaOD. The NaOD reagent was prepared by dissolving the required amount of CH_3ONa in D_2O , the latter being prepared by solving of sodium (Merck) in methanol, followed by evaporation and thoroughly removing the traces of methanol under long heating under reduced pressure. Working with a reagent with a minimum content 99 % of D_2O (Sigma-Aldrich) and a molar substrate: D_2O ratio not more than 5 : 100, an isotopic content of at least 95 % atom D : 5 % atom H of the reaction medium is estimated. The deuteriation reaction conditions were presented in Table 1, reactions (c-g).

Table 1. Reaction conditions for the reduction and deuteriation of crotonic and cinnamic acids

Substrate	Weight of substrate [mmoles]	Ni-Al alloy [mg]	NaOH 20 % aq. [mL]	D_2O / MeONa [mL/mmoles]	Solvent	Temp. [$^{\circ}\text{C}$]	Time [hours]	Rct. No.
Crotonic acid	5	360	5	-	-	50	5	(a)
Cinnamic acid	5	360	5	-	-	50	9	(b)
Crotonic acid	5	180	-	2 / 15	-	70	5	(c)
Crotonic acid	2.5	900	-	2 / 15	-	70	5	(d)
Cinnamic acid	5	180	-	2 / 15	DMSO	70	5	(e)
Cinnamic acid	0,67	180	-	2 / 15	Dioxane	70	5	(f)
Cinnamic acid	5	900	-	2 / 15	DMSO	80	10	(g)

Structural and compositional analysis of the reduction and deuteriation products

Structure determination was done by spectroscopic methods (^1H NMR) using an instrument Varian INOVA 400 and by gas-chromatographic coupling with mass spectrometry detection (GC-SM) using an Agilent 6890N gas chromatograph coupled with Agilent 5975 mass spectrometer. The composition analysis was performed by chromatographic methods (GC) and by quantitative analysis based on the integral values of the pertinent signals from the ^1H NMR spectrum of the crude reaction product.

RESULTS AND DISCUSSION

Figure 1 shows that after reduction of crotonic acid and cinnamic acid under mild reaction conditions (**a**, **b**) the butyric acid and 3-phenylpropionic acid, respectively, are achieved in high yields (85-90 %).

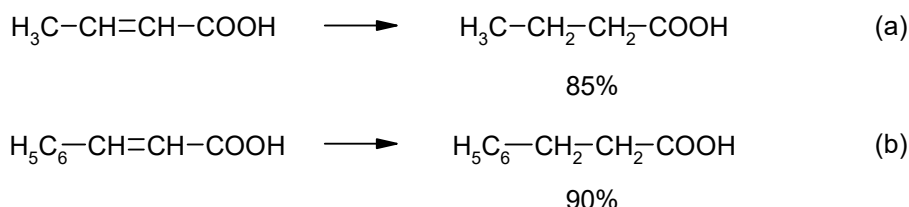


Figure 1. Reduction reactions of crotonic and cinamic acid with Ni-Al/NaOH/H₂O

Similar reductions and high conversion in the presence of the Ni-Al/NaOH system have been reported in the literature for other α , β -unsaturated compounds: derivatives of cinnamic acid substituted at the aromatic ring, cyclohexylidene acetic acid or benzylideneacetone. It is certain that C=C double bonds in conjugated systems (particularly α , β -unsaturated carboxylic and α , β -carbonyl compounds) have a much higher reactivity than isolated alkenes. The most likely explanation of this behavior has to be sought in the much higher polarity of the above-mentioned systems which allows better accommodating the intake of electrons from the Al atoms acting as reducing agents.

The main procedure of monitoring both the conversion and the distribution of deuteration at α and β positions of the substrates was based on ¹H NMR analysis of the crude reaction product. This method is perfectly ensured by the chemical shift differences ¹H NMR as shown in Figures 2a, 2b.

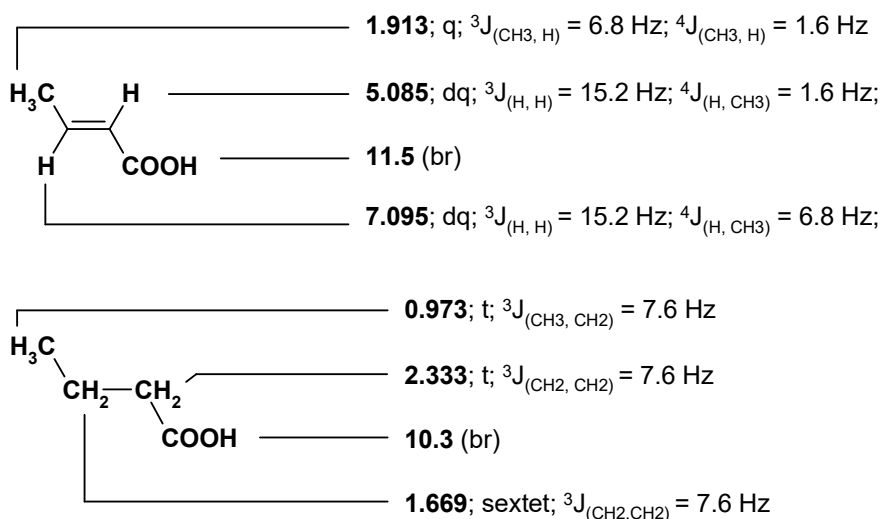


Figure 2a. Chemical shifts and coupling constants of crotonic acid and butyric acid

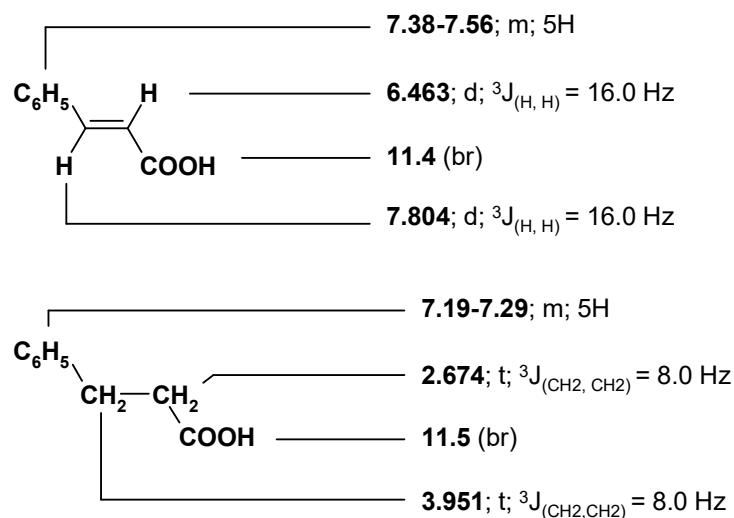


Figure 2b. Chemical shifts and coupling constants of cinnamic acid and 3-phenylacetic acid

A specific example of the procedure followed is illustrated in Figures 3-5 concerning the cinnamic acid deuteration. Figure 3 shows the ^1H NMR spectrum of the starting material (cinnamic acid) and in Figure 4 is presented the ^1H NMR spectrum of the reducing product (3-phenylpropionic acid). The information provided by this spectrum allows analysis of the results of the cinnamic acid reduction reaction in the Ni-Al/NaOD- D_2O system (Table 1, f), as shown in Figure 5.

Comparison of the spectrum from Figure 5 with those of Figures 3 and 4 indicates a total conversion of cinnamic acid (absence of the signal from $\delta = 6.463$ ppm and $\delta = 7.804$ ppm, and allure of the aromatic region). The quantitative distribution of deuterium in α and β positions of the product is deduced from signal intensities from $\delta = 2.674$ ppm (α) and 2.951 ppm (β) relative to the signal in benzene nucleus adopted as internal standard (5H).

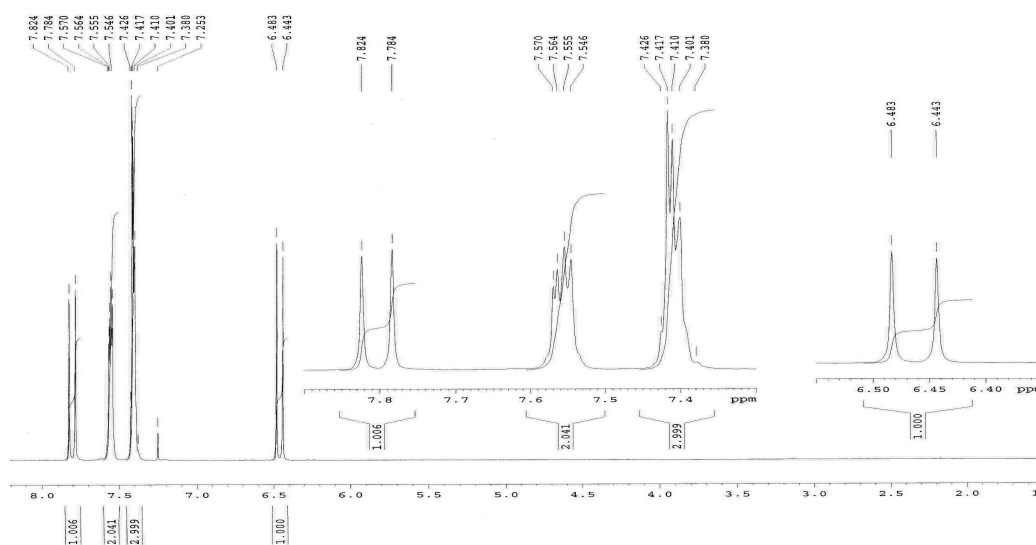


Figure 3. ^1H NMR spectrum of cinnamic acid

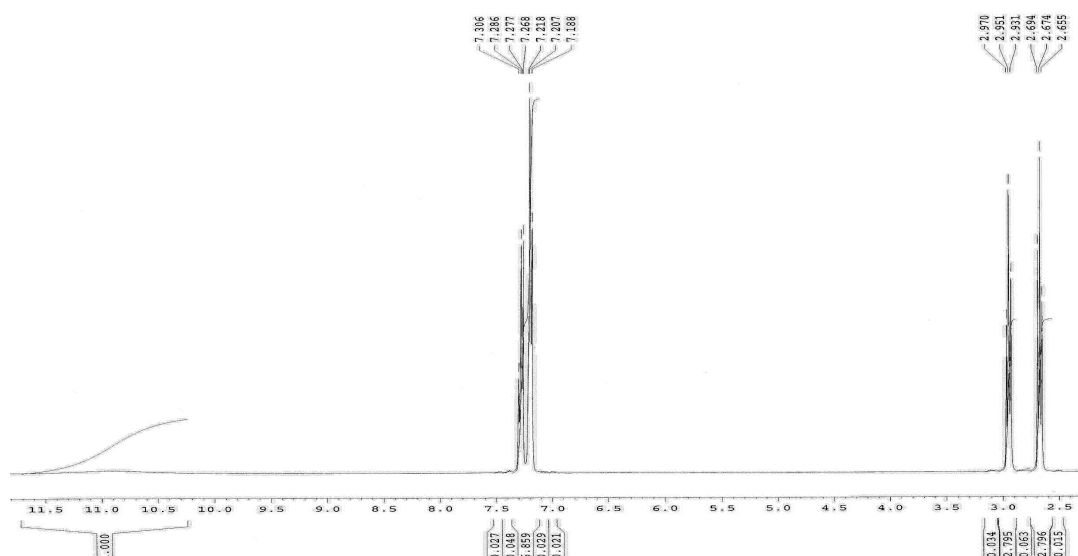


Figure 4. ^1H NMR spectrum of 3-phenylpropionic acid

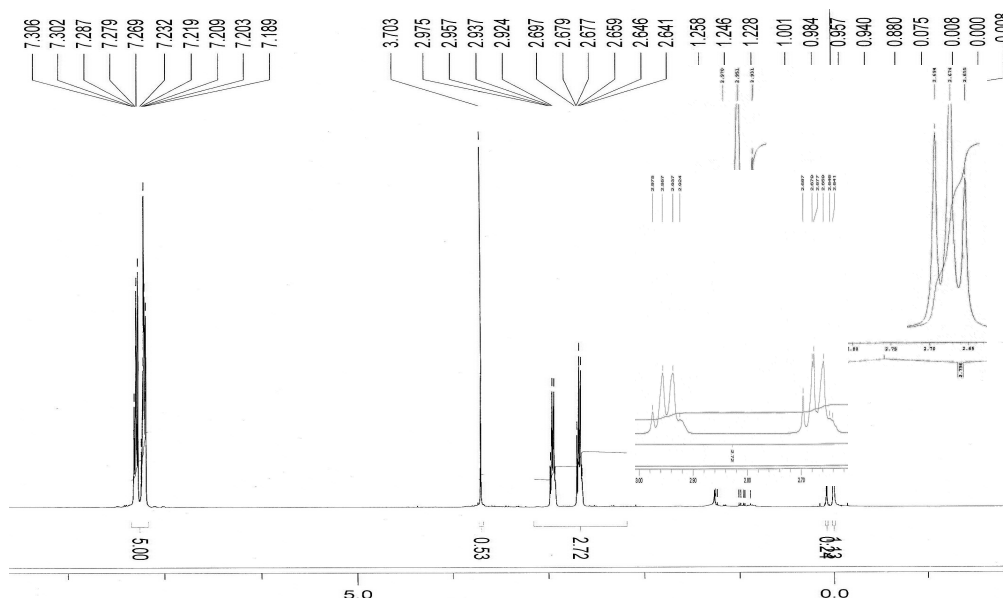


Figure 5. ^1H NMR spectrum of deuteration product of cinnamic acid (f)

In these conditions the signal intensities in position α (1.58 protons) and β (1.39 protons, see detail in Figure 5) lead to the indicated deuteration ratios (as number of atoms per molecule) in Figure 6.

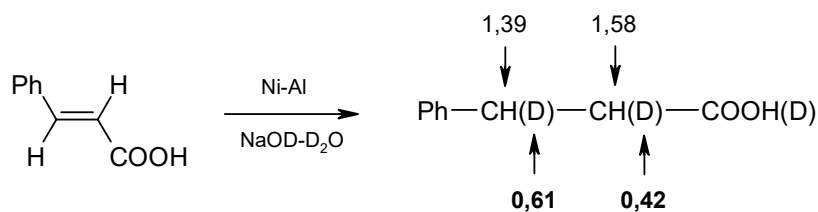


Figure 6. The quantitative distribution of deuterium in α and β positions of the reduction product of reaction (f)

Similarly, the analysis of data provided by the ^1H RMN spectrum in Figure 7 leads to another distribution of deuterium considering the different conditions of the deuteriation reactions, according to the reaction conditions (g) from Table 1.

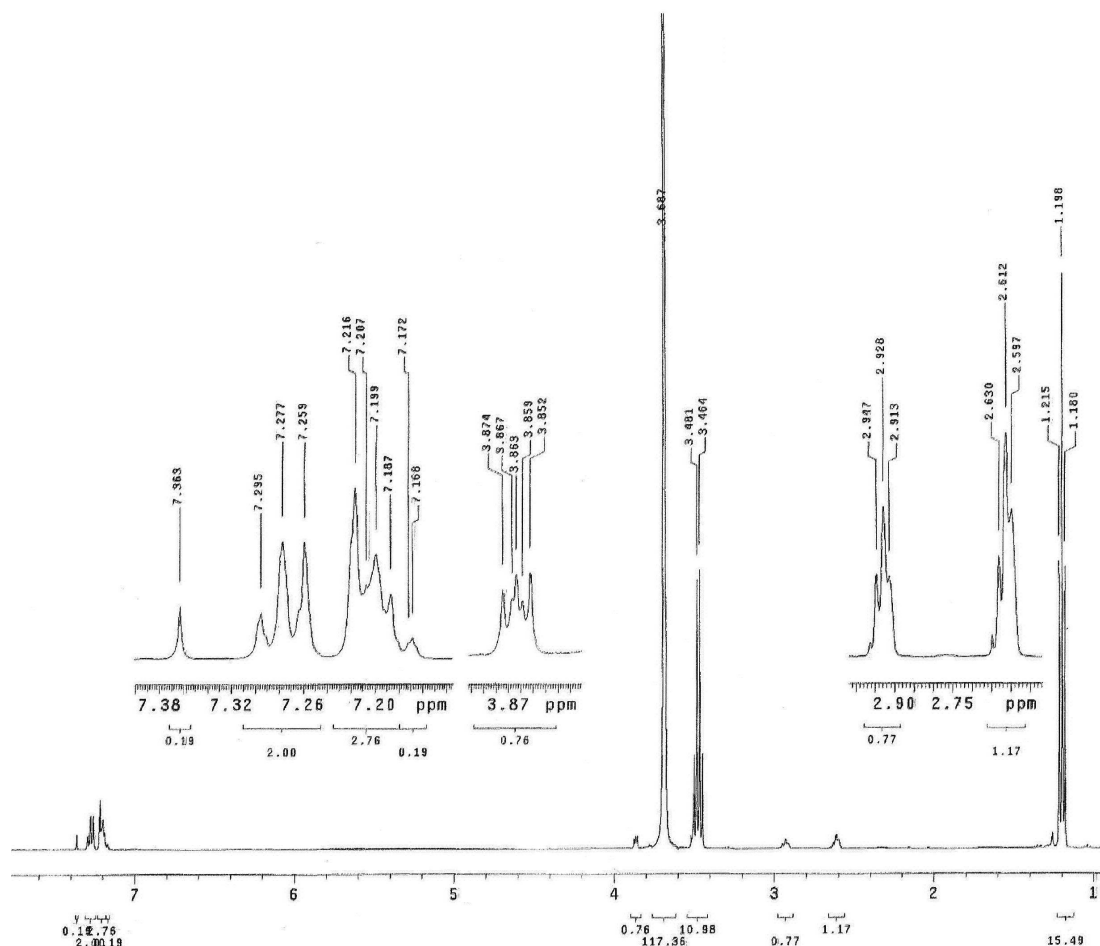
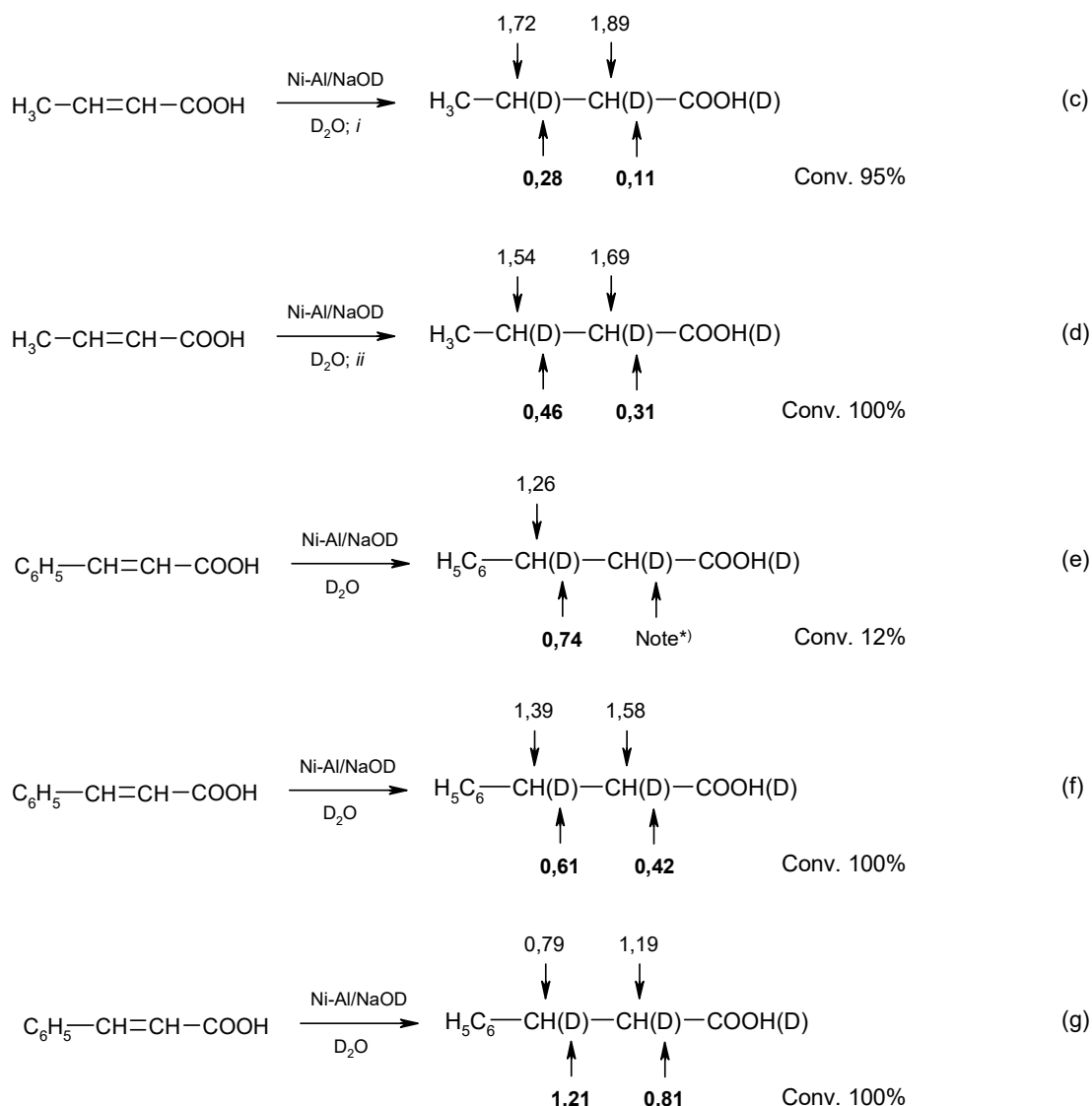


Figure 7. ^1H NMR spectrum of deuteriation product of cinnamic acid (g)

The results of the deuteriation experiments are shown in Figure 8, where the isotopic distribution of each product was indicated by the numbers representing the mean number of deuterium atoms (**bold**) and hydrogen per molecule, respectively, under the reaction conditions specified in Table 1.



^{*)} Note: The isotopic ratio H/D in this position could not be determined because of the superposition of the signal from β -position in 3-phenylpropionic acid with the residual signal from dimethylsulfoxide

Figure 8. The quantitative distribution of deuterium in α and β positions in the reduction product of reaction (c-g)

The data presented in Figure 8 provides some remarks:

- In all cases, there is a difference in the deuteriation ratio between α and β positions of the same substrate. This is an argument against a catalyst mechanism of addition and favors a mechanism in which the incorporation of deuterium occurs in distinct stages in α and β respectively. Adding to this that the C=C double bond in conjugated systems is incomparably more reactive than in isolated systems, the conclusion of an mechanism for 1,4-addition can be deduced in the case of α , β -unsaturated acids reduction using Ni-Al alloys in alkaline media;
- Also, in all cases (except the reaction g from Figure 8), the proportion of deuterium incorporated in the product is less than expected: at a ratio of D : H in the reaction medium evaluated at minimum 95 : 5, a similar proportion of deuterium is expected

to be incorporate. In fact, the proportion is much lower because hydrogen was incorporating instead of deuterium. The deuterium content in position β is 0.28÷0.74 D atoms instead of about 0.95 D atoms per molecule that corresponding to the isotopic composition of the reducing medium. The explanation could be partially due to the formation of the new C-D, respectively C-H bonds by acidification in protonic medium (HCl-H₂O). This fact proves that by the action of the Ni-Al alloy on the organic substrate is formed an organoaluminium compound with unusual stability in a relatively acidic medium (D₂O);

- The exception represented by the reaction performed at a higher temperature and long contact time (Figure 8 - g) shows a "supra-deuteriation" (1.21 D atoms) which is obviously obtained by an isotopic H-D exchange. There are numerous cases of deuteriation in the Ni-Al/NaOD-D₂O medium, especially for benzylic compounds and even for aromatic nucleus.

Another important support in the elaboration of the reaction mechanism are some recently published results [17, 18] on the mechanism and reactivity of anionic aluminum clusters with water. It is demonstrated experimentally and by mass spectrometry that in the above mentioned reaction the process starts by bonding the water molecules on the surface of the cluster by implication of two complementary centers: one is a Lewis acid which generates an Al-O bond and the other being a Lewis base that accepts a proton. In this way (by a Langmuir-Hinshelwood type mechanism) after the dissociation of water molecules and the formation of Al-OH and Al-H bonds, the H₂ molecules resulted are released [18].

Taking into account the literature proofs regarding the fixation of water molecules on pairs of active centers of aluminum and exploiting the experimental information from the present research, the mechanism of reduction and deuteriation of α , β -unsaturated acids of the Ni-Al/NaOD-D₂O system is formulated below:

1 - Formation of the active aluminum species **III** by basic deprotonation of only one water molecule coordinated by the pair of active aluminum centers (Figure 9).

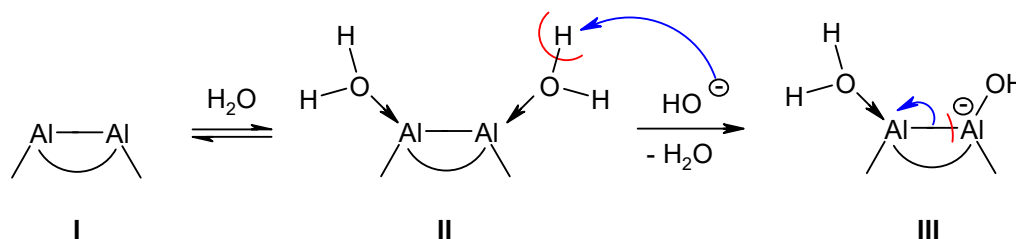


Figure 9. Formation of the active aluminum species **III**

The active centers are generated on the surface of the solid phase of Ni-Al alloy from pairs of aluminum atoms **I** that functions as the Lewis acids and fixes consecutively two molecules of water to generate a precursor of the active species **II**. A deprotonation of one coordinated water molecules follows with a strong polarization of the Al-Al bond, that create the premise of a heterolytic cleavage with the formation of nucleophilic species **III**. In the presence of an electrophilic reagent, this process is increased. The curved bond between the aluminum atoms signifies that the aluminum atoms belonging to the metallic, network and then the reaction occurs on the surface of the solid phase.

2 - The deuteration mechanism begins by a nucleophilic attack of a type **III** species (formed by the coordination of D₂O molecules instead the general case, with H₂O) on α , β -unsaturated acid anion. This is a nucleophilic attack on C β associated with an electrophilic assistance provided by the other aluminum atom that becomes a Lewis acid after the Al-Al heterolytical cleavage. We consider that the process is a 1, 4-addition of α , β -unsaturated system, where active species **III** acting as a reactant push-pull (Figure 10).

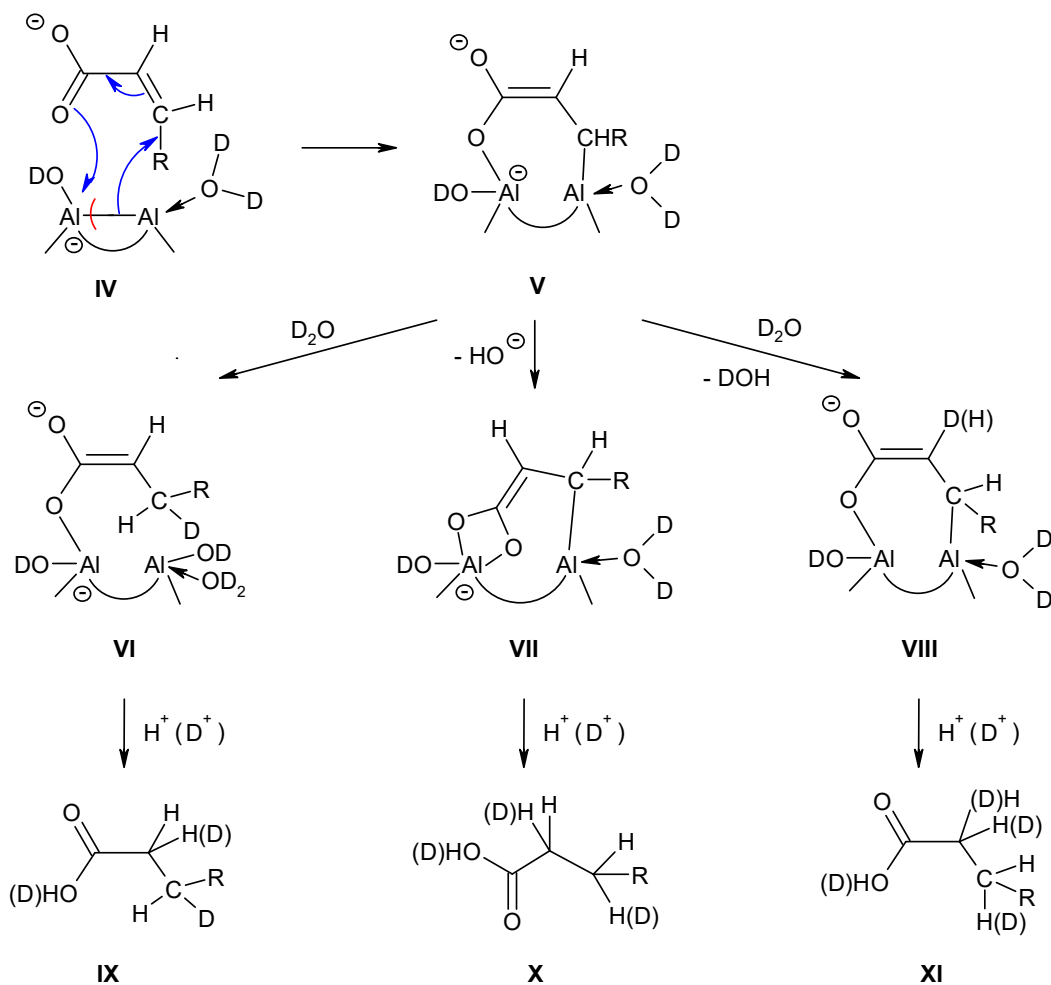


Figure 10. Mechanism of reduction reaction with Ni-Al/NaOH/D₂O

The intermediate **V** is a compound with an organoaluminum structure. The normal reaction of **V** involves the transfer of deuterium (D⁺) from a D₂O molecule to obtaining of enolate **VI** that after the final acidification (HCl-H₂O-D₂O), leads to the final product **IX**. The distribution D : H in the product **IX** in position β is 1 : 1. If intermediate **V** or rather enol carboxylate **VII** has certain stability in the D₂O-NaOD medium, it will last partially until the final acidification. Any of intermediates **V**, **VII** or **VIII** will transform in a product type **X** or **XI** with less than 1 D atom in position β , as has been shown experimentally.

For a long contact time of cinnamic acid with the Ni-Al/NaOD-D₂O system an advanced deuteration degree occurs (Figure 8 - g). The final content of more than 1 D atom / molecule indicates that there has been an isotopic exchange H-D promoted by the Ni-Al system. The explanation we propose for the particular case of H-D isotopic exchange reaction (Figure 8 - g) involves the active species **III** also.

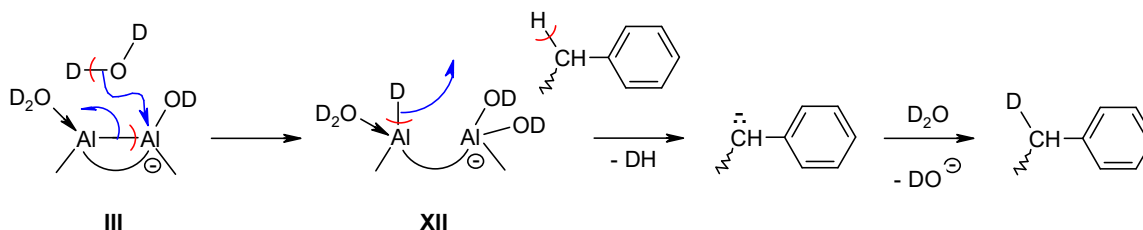


Figure 11. Mechanism of the deuteration reaction in the benzylic position by Ni-Al/NaOH/D₂O system

As we can see from Figure 11 in the nucleophilic reaction with a D₂O molecule it is generated a bond aluminum hydride type **XII**. The high basicity of **XII** allows the extraction of a proton (especially from the acidic benzylic position) of the formed carbanion, which then suffers a deuteration.

CONCLUSIONS

The deuterium isotopic labeling of α , β -unsaturated acids with Ni-Al/NaOD-D₂O system shows a deuterium content in the β position lower than the normal one. This proves the existence of an organoaluminium intermediate sufficiently stable to exist at least partially up to decomposition in the acidic medium.

The proposed mechanism contains unitary valid elements for the reduction reaction of other reducible compounds (aldehydes, ketones, α , β -unsaturated carbonyl compounds and halogenated derivatives) with Ni-Al/NaOH-H₂O.

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