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Effect of basic and acidic additives on the (*S*)-proline and Pd mediated kinetic resolution of 3,5,5-trimethyl cyclohexanone and asymmetric hydrogenation of isophorone

Nóra Győrffy*, Antal Tungler

Institute of Isotopes, Hungarian Academy of Sciences, P.O. Box 77, Budapest H-1525, Hungary

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ABSTRACT

The kinetic resolution of 3,5,5-trimethyl cyclohexanone (TMCH) and the asymmetric hydrogenation of isophorone (IP) were investigated both in the presence of (*S*)-proline (Pro) and of basic and acidic additives. The aim was to find out how the bidirectional shift from the zwitterionic form of proline can influence the reaction rates and stereoselectivities of these reactions.

1. Introduction

A more than 20 years old reaction recently attracted renewed attention [1–3], namely the asymmetric hydrogenation of isophorone (3,5,5-trimethyl cyclohex-2-enone, IP) with Pd catalyst in the presence of (*S*)-proline (Pro) as chiral auxiliary (Scheme 1).

Török and co-workers [1,2] regarded Pro as a catalyst modifier, rather than as a chiral auxiliary. They proposed later the participation of kinetic resolution in the formation of optically active 3,5,5-trimethyl cyclohexanone (TMCH). Lambert and co-workers [3] claimed that enantiodifferentiation took only place in solution and that optically active TMCH was exclusively formed *via* kinetic resolution of this compound, i.e., by stereoselective reductive alkylation of Pro. Thus, the metal surface was not involved in the crucial enantiodifferentiation step.

Since the mechanism proposed in our former publications [4] has been disputed, the research has been continued in our laboratory as well [5,6].

We agree that kinetic resolution plays a role in the formation of optically active TMCH, as described by Török and co-workers, and Lambert and co-workers [1–3]. We have only debated two conclusions of Lambert and co-workers [3] namely: (i) no direct asymmetric C═C hydrogenation takes place, the isophorone-proline condensation product is a spectator molecule only, (ii) the catalyst surface plays no role in enantiodifferentiation. It could be verified (i) with material balance data of the asymmetric hydrogenation of isophorone that in the early stage of the reaction the direct asymmetric hydrogenation of C═C takes place, (ii) with the use of different Pd catalysts that their surface is involved in enantiodifferentiation [5,6].

It was pointed out [5] that (i) on Pd/C optically active TMCH was formed in significant amounts even at small conversions (<20%, consumption of 0.12–0.2 mol of hydrogen/mol IP), due, likely to the asymmetric hydrogenation of IP, rather than just by kinetic resolution of the saturated ketone; (ii) at high conversions (>80%) a mixture of the two alkylated proline products could be obtained which shows that Pro reacts also with (*S*)-TMCH and enantiodifferentiation takes place not only in the homogeneous liquid-phase condensation reaction but also on the catalyst surface.

Recently [6] it could be proven with measuring the amount of the starting isophorone and of the enantiomers of the saturated ketone product that in the early stage of the reaction the optically active TMCH was formed in hydrogenation of isophorone through asymmetric C═C saturatation, rather than only by kinetic resolution. On this basis, a new, complete mechanism has been proposed (Schemes 1 and 2 in [6]). The activity and stereoselectivity of different Pd catalysts depended on the support material, preparation method, and reaction conditions as well; serving new arguments on that enantiodifferentiation takes also place on the catalyst surface.

* Corresponding author. Tel.: +36 1 392 2222/3170; fax: +36 1 392 2533.
E-mail address: gyorffy@iki.kfki.hu (N. Győrffy).

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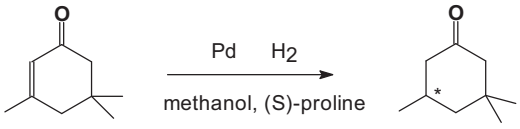
Table 1
Results of TMCH + Pro hydrogenations with basic and acidic additives.

Additive	Additive (mol)	Reaction time (h)	Conv. (%)	*ee* (%)	Missing *S* isomer (%)	Yields (%)			Rate[a]	
						S TMCH	R TMCH	Alkylated proline	Period I	Period II
No	–	10	62	100	23.3	76.7	0	61.6	16,7	3.6
Na-methylate	1	21	61	100	21.4	78.6	0	60.7	8.9	1.9
Triethyl amine	0.5	10	59	92	21.9	78.1	3.1	59.4	20.9	3.3
	1	7	56	98	13.3	86.7	1.1	61.1	20.5	4.6
	1.5	31	60	100	21.9	78.1	0.1	60.9	13.3	0.7
Acetic acid	0.5	33	63	94	30.2	69.8	2.1	64.1	11.4	1.1
	1	8	65	100	29.7	70.3	0	64.9	20.3	4.8
	1.5	7	63	90	30.2	69.8	3.9	63.2	25.2	4.6
Trifluoro-aceticacid	1	7	75	85	35.6	64.4	5.2	65.2	27.2	5.3

[a] Conversion rate (%)/(h).



Scheme 1. Hydrogenation of isophorone in the presence of *S*-proline.

Adding bases or acids in stoichiometric amount to the reaction mixture, the zwitterionic form of Pro changes, the carboxylate or ammonium ion forms will dominate. The aim of the present research was to investigate the effect of a strong and weak base and acid on the kinetic resolution of TMCH and on the asymmetric hydrogenation of IP. In addition to learn about the influence of basic or acidic property of the reaction mixture on the outcome of these hydrogenations, another expected result of this work was a deeper insight into the reaction mechanism.

2. Experimental

2.1. Materials

Pd/C catalyst was Selcat Q with 10% metal content, purchased from Fine Chemical Company. Its support is a high surface area activated carbon (BET surface area 1200 m^2/g). More detailed characterization can be found in [6].

Additives (acetic acid, AA; trifluoroacetic acid, TFAA; Na-methylate, NaOMe; triethylamine, TEA), methanol, n-hexanol, (*S*)-proline and isophorone were supplied by Sigma–Aldrich. The latter was distilled in vacuum before use. Racemic TMCH was prepared in our laboratory, by hydrogenating IP without solvent, using Pd/C catalyst at ambient temperature and 10 bar hydrogen pressure. TMCH content was >99%, as determined with GC.

2.2. Hydrogenation

Hydrogenations were carried out at 25 °C, under hydrogen pressures of 2 and 10 bar in a 250 cm^3 stainless steel autoclave (Technoclave) equipped with a magnetic stirrer. The solvent was methanol, with 3.5 vol% n-hexanol content, which served as internal standard for GC measurements. Before hydrogenation, the reaction mixtures were boiled for 5 min, then cooled, the catalyst was added, finally the solution was stirred under nitrogen for 10 min in the reaction vessel.

2.3. Analysis

Reaction mixtures were analysed with a Chrompack 9001 gas chromatograph equipped with a β-cyclodextrine capillary column (temperature programmed analysis: 90 °C (10 min) – increasing to 160 °C at a rate of 10 °C/min) and FID. Chromatograms were recorded and the peak areas were calculated with Chromatography Station for Windows V1.6 (DataApex Ltd., Prague). n-Hexanol was used as an internal standard. The peak areas of TMCH enantiomers and IP (the FID detector signals for same amount of TMCH and IP are identical) were correlated with that of n-hexanol, in order to determine the amount of ketones converted to alkylated proline, which cannot be detected with GC. The enantiomeric excess was defined as:

$$ee\ \ (\%) = \frac{[R]-[S]}{[R]+[S]}100$$

3. Results and discussion

3.1. Results of hydrogenation of TMCH-proline

According to the results of our previous work [6], Pd/C was the most active supported catalysts in reductive alkylation of TMCH.

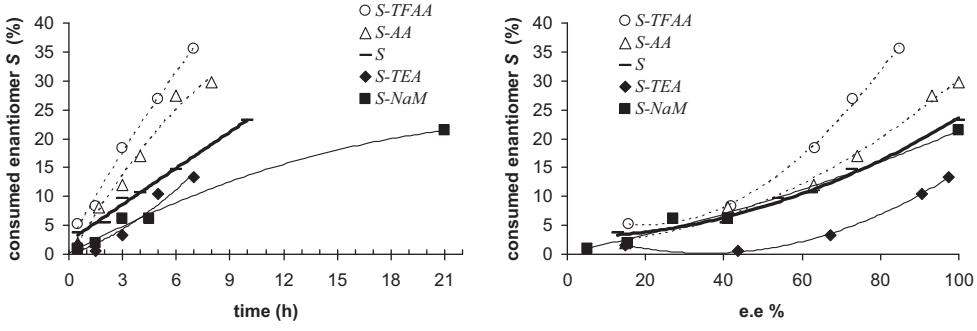


Fig. 1. The amount of consumed *S* enantiomer vs. time (a) and *ee* (b).

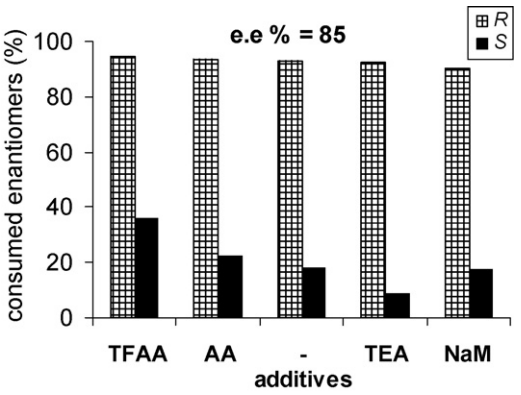


Fig. 2. The amount of the enantiomers consumed at 85% *ee* with the four additives and in the non-doped reaction.

In the present work only this Pd catalyst (10 mg catalyst, 5 mmol of TMCH or IP, Pro and the acidic and basic additives, dissolved in 20 cm^3 methanol–hexanol (3.5 vol%) mixture) was used for the hydrogenations. Two acids (AA, TFAA) and two bases (TEA, NaOMe), a weaker and a stronger one from both types of compounds, were added to the reaction mixtures in stoichiometric amount (and in 0.5 and 1.5 molar ratio for AA and TEA) with respect to Pro. The aim of adding these compounds to the reaction mixture was to find out what happens if the zwitterionic form of Pro changes, how will this change influence the activity and stereoselectivity? In addition to the reactivity change of Pro, the additives probably influence also the substrate reactivity and the catalyst surface. Both basic and acidic compounds, especially TEA adsorb on Pd surface, even the adsorption of Pro was detected by Lambert and co-workers [7]. The protonation of the basic N of Pro by the acidic additives may decrease its adsorption and cause rate increase. The restructuring of Pd among acidic conditions may occur, but leaching is not probable in the presence of hydrogen. For that very reason we tried to characterize the spent catalysts but no useful results were obtained with chemisorption and TEM measurements. The Pd/C catalyst which was used in this series of experiments was prepared on a high surface area (1200 m^2/g) activated carbon with metal loading of 10 wt%, the metal dispersion being relatively low (1.8 m^2/g catalyst active surface area determined by hydrogen adsorption) [6]. Therefore the spent catalyst contained high amounts of adsorbed organic materials, which hindered the structural characterization and the exact comparison with the fresh one. The thermal treatment of the catalyst for removal of the adsorbed materials had to be excluded, as it changed the structure, too.

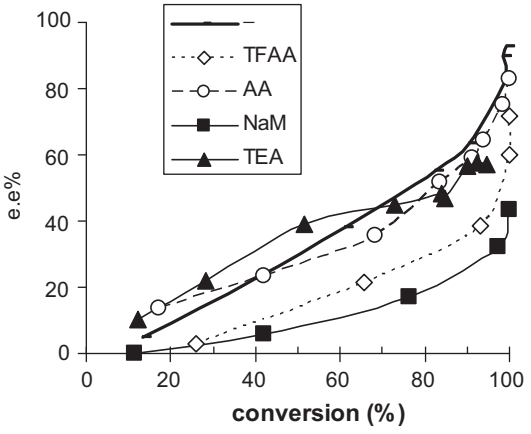


Fig. 3. *ee* values vs. conversion in the hydrogenation of IP + Pro.

Table 2
IP + Pro hydrogenation results with basic and acidic additives, Pd/*C* at 10 and 2 bar.

Additive	Reaction time (h)	IP conv. (%)	*ee* (%)	Yields (%)			Reaction rate[a]		Reaction rate[b] (%)	Reaction rate[c] (%)	Reaction rate[c] at 40% *ee*	t_{50} (h)
				S TMCH	R TMCH	Alkylated proline	Period I	Period II				
–	12.7	99	93	34.6	1.3	63.3	24.4	3.7	0	29.7	3.1	1.8
^{2bar}	125	99.8	88	40.4	2.5	56.5	11.1	0.28	–8.1	19.0	–2.7	4.4
TEA 1 mol	17	95	57	40.5	11.0	42.9	17.2	3.1	0<	13.7	5.3	2.9
TEA 0.5 mol	5	99	88	30.8	2.0	66.4	29.3	5.6	0	37.5	4	1.3
NaOMe	6	100	43	41.3	16.3	42.1	28.1	12.9	0<	17.4	16.2	1.8
AA	14	100	83	37.9	3.5	58.6	28.1	4.6	0<	24.1	9.8	1.9
AA^{2bar}	24	89	41	33.3	14.0	41.0	17.8	1.7	0<	22.1	21.9	2.6
TFAA	4.5	100	60	34.0	5.6	60.3	43.7	11.5	0<	25.1	16	1.1

[a] Conversion (%)/reaction time (h).
[b] The smallest value of [missing (IP + TMCH)] – [S excess]/IP_o.
[c] [missing IP + TMCH] – [S excess]/IP_o measured at the highest *ee* value in the reaction, ^{2bar}hydrogen pressure.

Table 3
Reaction scheme and effect of basic and acidic additives on reaction rate and selectivity.

Reactions	Effect of additives on reaction rate				Effect of additives on selectivity			
	TEA	NaOMe	AA	TFAA	TEA	NaOMe	AA	TFAA
(1) + (2) $\xrightarrow{Pd + H_2}$ **(1) + Rac (7)**	⇓	⇓	0	0	–	–	–	–
(1) + Rac (7) $\underset{}{\overset{-H_2O}{\rightleftharpoons}}$ **(5) or (6)** $\xrightarrow{Pd + H_2}$ **(8) + *S* (7) + (1)**; ***S* (7) >> *R* (7) + (1)**	⇑	⇓⇓	⇑	⇑⇑	⇑⇑	⇑	⇓	⇓⇓
(1) + **(2)** ⇌ **(3)** or **(4)**								
(3) or (4) $\xrightarrow{Pd + H_2}$ **(5)** >> **or** **(6)** $\xrightarrow{H_2O}$ **(7)** + **(1)**; ***S* excess**	⇓	⇑	⇑	⇑⇑	0	⇓	⇓	⇓⇓
(5) or (6) $\xrightarrow{Pd + H_2}$ **(8)**								

(⇓) Decrease; (⇓⇓) significant decrease; (⇑) increase; (⇑⇑) significant increase; (0) no change.

The results of hydrogenation of TMCH + Pro are collected in Tables 1 and 3, second line. Beyond the reactions with acidic and basic additives, a non-doped reaction is also presented for comparison. Beside conversion and *ee*, the yields of the TMCH enantiomers and the alkylated proline, and reaction rate values for the two periods of the process were given. In all hydrogenations with different additives there are two sections with respect to reaction rate. Initially it is faster approximately until 30–40% conversion, this period is followed by a significantly slower one. The reaction rate and stereoselectivity of reductive alkylation of Pro, namely the kinetic resolution of TMCH, significantly changed with the properties of additives. Both acidic additives and TEA, in 0.5 and 1.0 ratio increased the reaction rate, while NaOMe decreased it significantly. The values of the consumed *S* enantiomer in excess vs. time and vs. *ee* are shown in Fig. 1a and b.

The continuous thick line represents the non-doped reaction. Reactions in the presence of basic additives, with higher selectivity appear below this line. NaOMe influenced slightly and TEA significantly the selectivity, with less consumed *S* enantiomer in excess. Acidic additives decreased the selectivity significantly, which can be seen also in Fig. 2, where the influence of additives on selectivity at a given *ee* is compared.

The increase of the molar ratio of AA did not, but that of TEA changed the selectivity (Table 1). In the case of the latter this can be due to its strong adsorption on Pd. The selectivity change can be attributed rather to the surface change of the catalyst than to the change of ratio of the two condensation product diastereoisomers upon adding the acidic and basic additives.

The effect of acidic additives on the activity can also be explained by the sequence of the strengths of the added acids.

TEA acts not only as a base but as a catalyst modifier, which increases both activity and selectivity, due to its strong adsorption on Pd. TEA is the best additive, at almost 100% *ee* the amount of missing TMCH *S* enantiomer is only 13%, which is less by 10% than that of the non-doped reaction. The optimum ratio of TEA is 1:1 mole, both less and more added modifier is less beneficial.

3.2. Hydrogenation of IP in the presence of Pro

On the basis of the results of TMCH + Pro hydrogenation and of the asymmetric reduction of benzylidene benzosuberone [8] our expectation was that basic additives will improve enantioselectivity in the hydrogenation of IP, too. But according to the results in Table 2, the additives with the exception of TEA all increased the reaction rate (conversion rate and reaction time until 50% conversion (t_{50})), but decreased the enantioselectivity (yields and values of missing *S* isomer). The majority of the *ee* values in Fig. 3 are located below the curve of the non-doped reaction (continuous thick line), meaning that the additives deteriorate enantioselectivity. This is surprising in the light of the results of TMCH + Pro hydrogenation, where both basic additives improved the yield of kinetic resolution. The reason of enantioselectivity decrease can only be the partial elimination of the direct enantioselective hydrogenation of the C=C bond.

Beside the trend in enantioselectivity and rate (Table 3) upon adding bases and acids to the reaction mixture, it was also questionable whether direct asymmetric C=C hydrogenation could be verified in the doped reactions. Data of Table 3, third line and Fig. 4 indicates that the answer is no, all missing ketones minus *S ee* values are positive, located above the line of the non-doped reaction. In previous investigations [6] significant negative values could be detected with Pd catalysts on basic supports ($BaCO_3$, MgO) and with Pd/C catalyst in hydrogenation at 2 bar pressure. Therefore hydrogenation with Pd/C and AA additive (the other additives decreased *ee* significantly, see Table 2) was carried out at 2 bar pressure and its

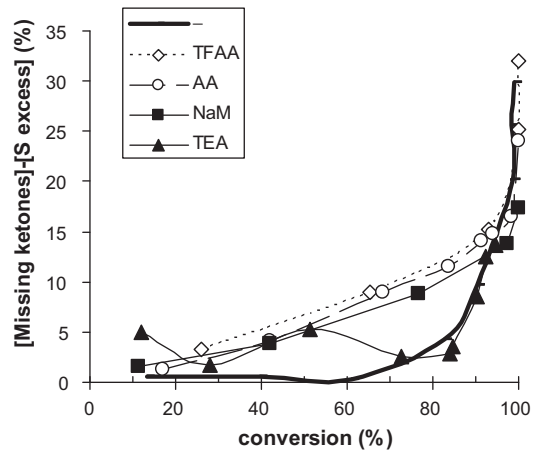


Fig. 4. The amount of missing ketones minus *S ee* vs. conversion in the reaction carried out at 10 bar hydrogen pressure.

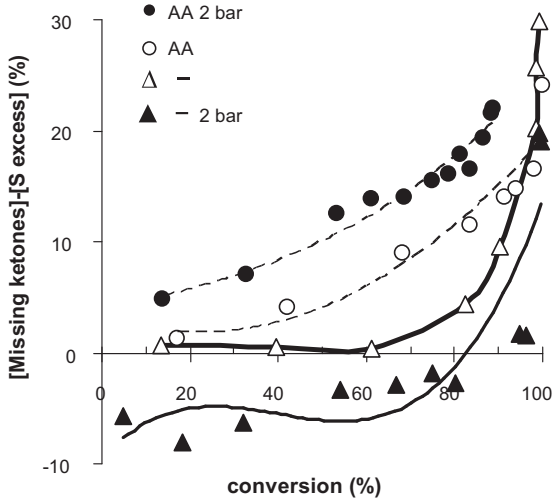


Fig. 5. The amount of missing ketones minus *S ee* vs. conversion in the reactions carried out at 2 and 10 bar hydrogen pressure with and without AA additive.

result compared with those measured at 10 bar and 2 bar with and without the same additive (Fig. 5). The values of missing ketones minus *S ee* for the doped reactions were positive at both pressures, this indicated that the direct C=C hydrogenation could not be confirmed.

The suggested explanation is that both basic and acidic additives inhibit the direct asymmetric C=C hydrogenation of IP (see Table 3, third line) which takes place through the chemoselective and diastereoselective hydrogenation of the condensation product of IP and Pro (see Schemes 1 and 2 in [6]). The neutral reaction mixture seems to be beneficial for the condensation product of IP and Pro being not only a spectator molecule [3], but to be hydrogenated at the C=C bond through the asymmetric reaction route.

4. Conclusions

Basic (TEA, NaOMe) and acidic (AA, TFAA) additives were tested in the asymmetric hydrogenation of TMCH + Pro and IP + Pro. In the kinetic resolution of TMCH with Pro the effect of these additives can be summarized in the following (Table 3, second line):

1. Basic additives increased, acidic ones decreased selectivity.
2. Acidic additives increased the reaction rate.

3. NaOMe decreased the reaction rate significantly due to its effect that Na salt of Pro behaved as a catalyst poison, a secondary amine.
4. Most advantageous additive was TEA, especially in 1:1 molar ratio, since it increased both reaction rate and selectivity.

In the hydrogenation of IP + Pro the effect of the additives was in some respect different and unexpected (Table 3, first and third line):

1. Acidic additives increased the reaction rate.
2. Both acidic and basic additives decreased the enantioselectivity; there was no proof for direct asymmetric C=C hydrogenation.
3. The neutral pH, the zwitterionic character of (S)-proline was necessary for the asymmetric C=C hydrogenation of the intermediate condensated compound.

The comparison of reactions using TEA additive with the non-doped reactions served as an indirect proof for the disputed direct asymmetric hydrogenation of the C=C double bond. TEA improved the yield of the kinetic resolution of TMCH. In spite of this effect the enantioselectivity in the hydrogenation of IP + Pro + TEA was less than in the non-doped reaction. The explanation can be the inhibition of the direct asymmetric C=C hydrogenation, which can take place only in neutral reaction mixture.

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