Heterogeneous asymmetric reactions. 23. Enantioselective hydrogenation of ethyl pyruvate over cinchonine- and α-isocinchonine-modified platinum catalysts

Mihály Bartók [a],*, Béla Török [a],*, Katalin Balázsik [a] and Tibor Bartók [b]

[a] *Organic Catalysis Research Group of the Hungarian Academy of Sciences and Department of Organic Chemistry, University of Szeged,*
H-6720 Szeged, Dóm tér 8, Hungary
E-mail: btorok@chem1.usc.edu
[b] *Analytical Laboratory of Cereal Research Institute, PO Box 391, H-6701 Szeged, Hungary*

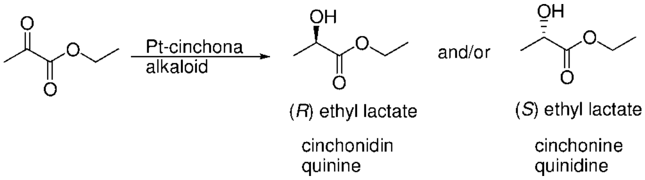
Received 30 November 2000; accepted 21 February 2001

The enantioselective hydrogenation of ethyl pyruvate to (*S*)-ethyl lactate over cinchonine- and α-isocinchonine-modified Pt/Al_2O_3 catalysts was studied as a function of modifier concentration and reaction temperature. The maximum enantioselectivities obtained under the applied mild conditions were 89% ee using cinchonine (0.014 mmol dm^{-3}, 1 bar H_2, 23 °C, 6% AcOH in toluene), and 76% ee in the case of α-isocinchonine (0.14 mmol dm^{-3}, 1 bar H_2, -10 °C, 6% AcOH in toluene). Since α-isocinchonine of rigid structure exists only in "anti-open" conformation these data provide additional experimental evidence to support the former suggestion concerning the dominating role of "anti-open" conformation in these cinchona-modified enantioselective hydrogenations.

KEY WORDS: hydrogenation; enantioselective; Pt/Al_2O_3; α-isocinchonine; ethyl pyruvate

1. Introduction

The preparation of chiral pharmaceuticals and agrochemicals by direct asymmetric synthesis is one of the most fascinating areas in contemporary chemical research [1]. Although most remarkable results are obtained by homogeneous reactions, however, due to the recent trends in regulation of safety and environmental issues, the heterogeneous processes are much more preferable [2]. In this field, the enantioselective hydrogenation of activated ketones has received significant attention [3,4]. Despite its twenty-two years old history [5], the research activity in the asymmetric hydrogenation of α-ketoesters over cinchona-alkaloid-modified platinum catalysts still increases.



New methods were developed to increase the performance of the system (up to 98% ee) such as ultrasonic activation [6] or platinum colloid catalyst systems [7]. More and more successful applications with ee values usually higher than 95% ee were recently reported including a cyclic ketoester [8], α-ketoesters [9], α-ketoacetals [10,11], α-ketodicarboxylic acid esters [12] and 2,4-diketoesters [13]. Besides improving the cinchonidine/platinum catalyst system, extensive efforts have been made in developing a reliable mechanistic interpretation. Though this topic was extensively reviewed [3,14] in recent years, since then significant new details were published concerning the mechanism. Different groups contributed to the development of the present mechanistic representation. The different viewpoints from the alkaloid [15,16] or the ketoester [17,18] sides both provided important new details to refine the mechanistic explanations. In a preliminary communication [19] using α-isocinchonine as modifier we disclosed experimental evidence which indicated that the open conformer of the alkaloid, at least in relatively high concentration, is an effective modifier for the reaction. However, the effect of modifier concentration, especially in the very low regions, simultaneously with the possible transformation or stability of the modifier in the reaction mixture was not fully characterized. The same features of cinchonine-modified hydrogenations, according to the lack of experimental data, are also not yet known.

Here, we describe a detailed study concerning the effect of cinchonine and α-isocinchonine concentration on the enantioselective hydrogenation of ethyl pyruvate, and their stability or transformation in the reaction mixture by electrospray ionization mass spectrometry (ESI-MS) recently described as a useful tool in similar investigations [20].

---

* To whom correspondence should be addressed. Present address: Loker Hydrocarbon Research Institute, University of Southern California, University Park, Los Angeles, CA 90089-1661, USA.

2. Experimental

2.1. Materials

The ethyl pyruvate (EtPy) used was of analytical grade and purchased from Fluka, while the solvents with minimum purity of 99.5% were also Fluka products. Cinchonine (CN) (minimum purity $>98\%$) was purchased from Fluka, while α-isocinchonine (α-ICN) was synthesized according to the literature [21] and isolated from the product mixture by preparative HPLC. The α-isocinchonine thus prepared contained 3% impurities (0.81% β-isocinchonine, 0.36% dihydrocinchonine, 1.83% unknown) detected by HPLC and ESI-MS. The organic compounds including the reactant and the solvents were freshly distilled prior to use. The catalyst used in the hydrogenations was a well-known reference catalyst 5% Pt/Al_2O_3 (Engelhard 4759). It was subjected to a reductive heat treatment (400 °C, H_2 flow, cooling in flowing He) before reactions.

2.2. Enantioselective hydrogenations

The hydrogenations were performed in an atmospheric glass batch reactor at room temperature (23 °C), at 0 and at -10 °C. The catalytic system including the catalyst and solvent (standard conditions: 25 mg of catalyst, 1.8 ml of solvent) was activated (1 bar hydrogen pressure), then the modifier solution and the reactant (usually 0.5 ml of ethyl pyruvate) were introduced via a syringe and the reaction mixture was stirred (1300 rpm) for the required reaction time. The product identification and the determination of enantiomeric excesses ($ee\% = (|[S] - [R]|) \times 100/([R]+[S])$) were made by gas chromatography (HP-5890 GC-HP 5970 MSD and HP 5890 GC-FID, 30 m long Cyclodex-B (J&W Scientific) and Lipodex-A (Macherey-Nagel) capillary columns). The ee values were reproducible within 2%.

2.3. Electrospray ionization mass spectrometry (ESI-MS)

A Hewlett–Packard HP 5989 B MS Engine quadrupole mass spectrometer equipped with a high energy dinode detector and an atmospheric pressure ionization electrospray (API-MS) interface (HP 59987 A) were used. For ES experiments, samples were dissolved separately in a mixture of MeOH/AcOH = 98/2 (v/v) and introduced into the ES ion source with a syringe pump at a flow rate of 20 $\mu l\,min^{-1}$. A fine spray was formed by nitrogen as nebulizer gas at 135 kPa pressure. Nitrogen drying gas (heated up to 563 K) was used at a flow rate of 8 $dm^3\,min^{-1}$ to facilitate solvent evaporation from the droplets. After tuning, the fragmentation pattern of cinchonas was studied by in-source collision-induced dissociation (CID). During the CID experiment the capillary exit voltage (CapEx) was increased from 80 to 400 V in 20 V steps and spectra were recorded for 0.5 min at each CapEx setting.

3. Results and discussion

First of all, the effect of modifier concentration was studied on the enantioselective hydrogenation of ethyl pyruvate in order to observe the actual changes in the reaction rates and enantioselectivities. After the catalytic studies reaction mixtures were analyzed in extended ESI-MS measurements to learn more about the stability of modifier under the reaction conditions.

In order to reveal the effect of the modifier concentration on hydrogenation of ethyl pyruvate, CN and α-ICN solutions in a wide concentration range (0.0014–2.85 $mmol\,dm^{-3}$) have been prepared and used. As we pointed out recently, the use of neat acetic acid as solvent in these hydrogenations is not necessary [22]; a small amount of acid additive (approximately 5–6%) in toluene results in the same enantioselectivity as neat acid. In order to avoid any structural changes of the modifier such as the ring opening of the O-containing ring we applied as mild experimental conditions as possible. As a result, the hydrogenation reactions were carried out in neat toluene and toluene–acetic acid mixture. The experimental conditions and the enantioselectivity data are collected in table 1, while the conversion vs. reaction time curves of the catalytic systems are displayed in figures 1 and 2.

As the results show, cinchonine and α-isocinchonine produced comparable results in the hydrogenation reactions in the case of 0.014 $mmol\,dm^{-3}$ modifier concentrations concerning both the hydrogen uptake rates and enantioselectivities. Although these enantioselectivity values (86% ee for CN and 76% ee for α-ICN) are not close to those obtained by cinchonidine or 9-O-methoxy-cinchonidine [6,7], they still indicate effective enantiodifferentiation. According to the experimental data, however, the effect of different

Table 1

Enantioselective hydrogenation of ethyl pyruvate to (*S*)-ethyl lactate over cinchona-alkaloid-modified platinum catalyst (25 mg pretreated 5% Pt/Al_2O_3 (E4759), 0.5 ml ethyl pyruvate, 2 ml solvent, 1 atm H_2 pressure).

Entry	Modifier[a]	$c_{modifier}$ ($mmol\,dm^{-3}$)	T (°C)	Solvent	ee (%)
1[b]	α-ICN	1.71	23	EtOH	–
2	α-ICN	0.014	24	Toluene	0
3	α-ICN	0.14	23	Toluene	10
4	α-ICN	1.14	24	Toluene	8
5	α-ICN	0.0014	24	6% AcOH in toluene	0
6	α-ICN	0.014	−10	6% AcOH in toluene	74
7	α-ICN	0.14	24	6% AcOH in toluene	60
8	α-ICN	0.14	−10	6% AcOH in toluene	76
9	α-ICN	2.85	24	AcOH	67
10	CN	0.0014	23	6% AcOH in toluene	13
11	CN	0.014	23	6% AcOH in toluene	54
12	CN	0.14	23	6% AcOH in toluene	86
13	CN	0.0014	23	AcOH	36
14	CN	0.014	23	AcOH	89
15	CN	0.14	23	6% AcOH in toluene	87
16	CN	0.0014	0	6% AcOH in toluene	16
17	CN	0.014	0	6% AcOH in toluene	78

[a] α-ICN = α-isocinchonine, CN = cinchonine.

[b] No ethyl pyruvate was added.

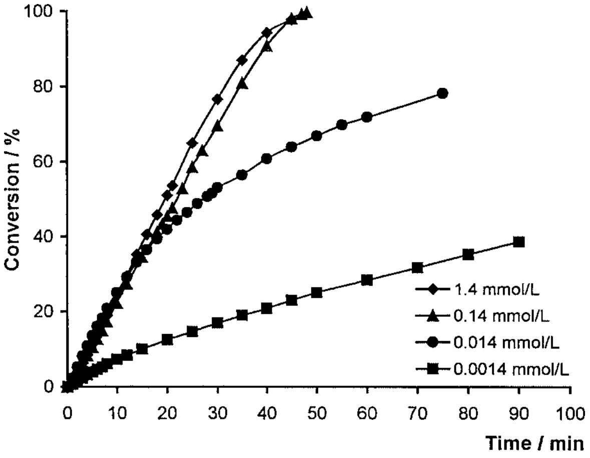


Figure 1. Conversion vs. reaction time curves of enantioselective hydrogenation of ethyl pyruvate over cinchonine-modified platinum catalyst (E4759 5% Pt/Al_2O_3) in 6% acetic acid–toluene solvent mixture under 1 atm hydrogen pressure (25 mg pretreated 5% Pt/Al_2O_3 (E4759), 0.5 ml ethyl pyruvate, 2 ml solvent).

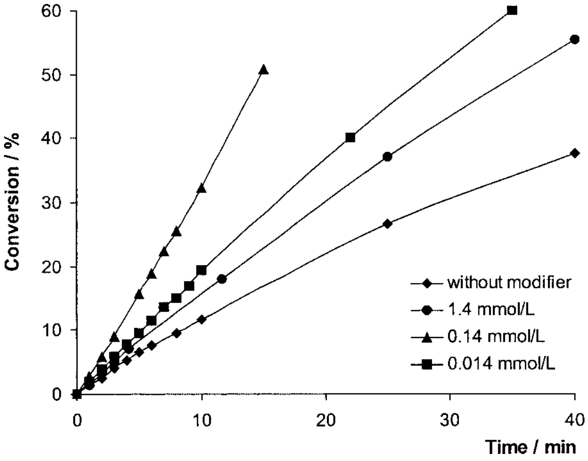


Figure 2. Conversion vs. reaction time curves of enantioselective hydrogenation of ethyl pyruvate over α-isocinchonine-modified platinum catalyst (E4759 5% Pt/Al_2O_3) in 6% acetic acid–toluene solvent mixture under 1 atm hydrogen pressure (25 mg pretreated 5% Pt/Al_2O_3 (E4759), 0.5 ml ethyl pyruvate, 2 ml solvent).

modifiers on the ee values under 0.0014 mmol dm^{-3} concentrations indicates significant alteration. Namely, while in the case of α-isocinchonine no chiral induction was observed at 0.0014 mmol dm^{-3} concentration, cinchonine could still induce enantiodifferentiation (13% ee) even in this concentration. These observations led us to a consideration, that the possible previous assumption regarding the major role of 1–2% cinchonine (or dihydrocinchonine formed under the reaction conditions) impurities in the α-isocinchonine sample can be excluded. It is worth noting that the decrease in temperature has a significant beneficial effect on chiral induction; at lower temperatures (0 or −10 °C) higher ee values are observed than at room temperature (23 °C).

As also shown, an optimum concentration of the modifier exists regarding the reaction rates. Using α-isocinchonine the rate increases with increasing modifier concentration, however, a decrease in reaction rate is observed at high concentration range, which is in accordance with the literature findings and explanations [16].

Therefore, after the catalytic measurements the reaction mixtures obtained were subjected to electrospray mass spectrometric measurements. Recently, this technique is very popular in the analysis of metal-containing species [23] as well as biological samples [24] and has been pointed out to be useful in catalytic studies, too [20]. The cinchona alkaloids are of low volatility in itself, and the formation of even larger complexes requires the use of ESI-MS technique. In this way we can point out most transformations occurred with the modifier (table 2).

In our earlier studies the identification of the relevant peaks was already described [20,25]; here, only the most characteristic peaks regarding the goal of the study will be analyzed. These peaks are m/z = 295 ($[\alpha\text{-ICNH}]^+$), 297 ($[\text{dihydro-CNH}]^+$), 299 ($[\text{tetrahydro-}\alpha\text{-ICNH}]^+$), 305 ($[\text{decahydro-}\alpha\text{-ICNH}]^+$) and 307 ($[\text{dodecahydro-CNH}]^+$). The present ESI-MS measurements revealed important information concerning the transformation of the modifiers during these hydrogenation reactions. First of all, it was observed that the hydrogenation rate of the cinchona alkaloids

Table 2

Relative abundances of ESI-MS spectra of the product mixtures obtained from enantioselective hydrogenation of ethyl pyruvate to (S)-ethyl lactate over cinchona-alkaloid-modified platinum catalyst (25 mg pretreated 5% Pt/Al_2O_3 (E4759), 0.5 ml ethyl pyruvate, 2 ml solvent, 1 atm H_2 pressure).

Entry	Modifier[a]	c_{modifier} (mmol ml^{-1})	Solvent[b]	T (°C)	m/z (%)							
					141	257	259	295	297	299	301	305
1[c]	α-ICN	1.71	T	23	0	0	0	1	2	100	3	0
2	α-ICN	0.014	T	24	0	100	0	0	0	0	0	0
3	α-ICN	0.14	T	23	4	100	0	Traces	0	Traces	0	0
4	α-ICN	1.14	A-T	24	2	100	0	19	Traces	14	0	0
5	α-ICN	0.0014	A-T	24	0	0	100	0	0	0	0	0
6	α-ICN	0.014	A-T	−10	0	0	100	0	0	0	0	0
7	α-ICN	0.14	A-T	24	100	66	0	4	0	2	0	29
8	α-ICN	0.14	A-T	−10	0	1	100	0	0	1	Traces	2
9	α-ICN	2.85	A	24	15	69	0	100	2	60	2	9
10	CN	0.14	A-T	23	100	50	10	0	2	7	25	0

[a] α-ICN = α-isocinchonine, CN = cinchonine.
[b] T = toluene, A = acetic acid, A-T = 6% acetic acid in toluene.
[c] No ethyl pyruvate was added.

is lower in toluene than in AcOH-containing mixtures. Further major difference was found in the hydrogenation rate and product selectivity of the different modifiers. Namely, the N-containing part of the quinoline ring in α-ICN is hydrogenated in a faster reaction and forms tetrahydro-α-ICN, while the CN is transformed to hexahydro-CN. In the case of very low concentrations (0.014 mmol dm^{-3} and below) none of the cinchona alkaloids could be identified under the experimental conditions applied. The ESI-MS data indicated (entries 7 and 8) that the cyclic ether structure remains stable during the hydrogenation reaction, no C–O hydrogenolysis was observed. Moreover, the hydrogenation of the quinoline skeleton is extensively suppressed at −10 °C, even in the presence of acetic acid. Only peaks related to the step-by-step saturation of the quinoline ring could be detected (m/z = 295 ([α-ICNH]$^+$), 299 ([tetrahydro-α-ICNH]$^+$) and 305 ([decahydro-α-ICNH]$^+$)). Since the relevant peaks, thought to be characteristic in detection of C–O hydrogenolysis (m/z = 297 ([dihydro-CNH]$^+$) and 307 ([dodecahydro-CNH]$^+$)) are completely missing we can exclude the formation of reasonable amount of dihydrocinchonine. This statement has been confirmed by HPLC analysis as well. On the basis of the literature [3,14] we can assume that the mechanistic interpretation of the enantiodifferentiation is similar using different cinchona alkaloids. Since their structure is basically the same except the absolute configurations in the stereogenic region, there is no reason to distinguish concerning adsorption properties and complex formation with the ligand (EtPy). Several structural studies described the most probable structure of isocinchona alkaloids including α-isocinchonine. NMR and X-ray structure studies as well as molecular mechanics calculations described its conformation to be fixed in *anti*-open state, while the closed conformations were excluded [26]. Unlike cinchonine, α-isocinchonine has a rigid structure and the quinuclidine part cannot rotate around the C(8)–C(9) bond. As a result, in the present paper we confirm our former statement [19], namely the presence of cinchona alkaloid in closed conformation [27] is not a precondition for chiral induction. The actual conformations of cinchonine and α-isocinchonine are illustrated in figure 3.

Our data show, that the enantioselectivities obtained in the reactions modified with α-ICN are the results of the complex formation between the modifier and the alkaloid (figure 3). The formation of cinchonine under the experimental conditions was excluded by ESI-MS and HPLC measurements. The decrease in enantioselectivities as a function of diminishing modifier concentration can be explained by the simultaneous hydrogenation of the N-containing part of the quinoline ring in the modifier, which occurs in a considerably faster reaction in the case of α-ICN than with CN. This significant structural change results in the loss of adsorption capabilities of the compounds and makes them inefficient for inducing enantiodifferentiation. However, working in higher concentration regions the effect does not entirely determine the outcome of the hydrogenations.

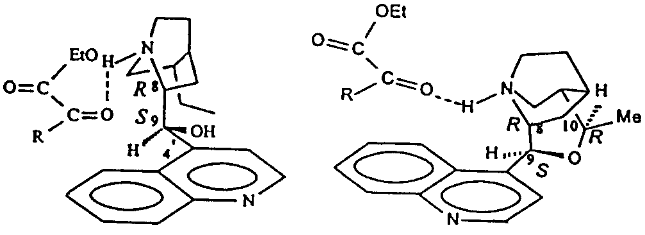


Figure 3. The schematic representations of the structures of 1 : 1 dihydrocinchonine– and α-isocinchonine–α-ketoester intermediate complexes.

4. Conclusions

On the basis of the above detailed results we can conclude that the cinchona alkaloids most likely took part in the process of enantiodifferentiation in their "anti-open" conformation in the case of enantioselective hydrogenation of α-ketoesters. The experimental data also revealed that the effect of cinchonine and α-isocinchonine as chiral modifiers on the rate of these hydrogenations is different.

Acknowledgement

Financial support by the Hungarian National Science Foundation (OTKA Grant T031707) and the Hungarian Academy of Sciences is highly appreciated.

References

[1] H. Brunner and W. Zettlemeyer, *Handbook of Enantioselective Catalysis with Transition Metals* (VCH, Weinheim, 1993);
I. Ojima, *Catalytic Asymmetric Synthesis* (VCH, Weinheim, 1993);
R. Noyori, *Asymmetric Catalysis in Organic Synthesis* (Wiley, New York, 1994).
[2] M. Bartók and Gy. Wittman, in: *Stereochemistry of Heterogeneous Metal Catalysis*, ed. M. Bartók (Wiley, Chichester, 1985) ch. XI, p. 511;
H.-U. Blaser and M. Müller, Stud. Surf. Sci. Catal. 59 (1991) 73;
G. Jannes and V. Dubois, *Chiral Reactions in Heterogeneous Catalysis* (Plenum, New York, 1995);
G.V. Smith and F. Notheisz, *Heterogeneous Catalysis in Organic Chemistry* (Academic Press, San Diego, 1999).
[3] A. Baiker and H.-U. Blaser, in: *Handbook of Heterogeneous Catalysis*, Vol. 5, eds. G. Ertl, H. Knözinger and J. Weitkamp (Wiley/VCH, New York/Weinheim, 1997) p. 2422.
[4] T. Osawa, T. Harada and O. Takayasu, Topics Catal. 13 (2000) 155;
S. Nakagawa, A. Tai, T. Okuyama and T. Sugimura, Topics Catal. 13 (2000) 187.
[5] Y. Orito, S. Imai and S. Niwa, J. Chem. Soc. Jpn. (1979) 1118; Chem. Abstr. 91 (1979) 192483h.
[6] B. Török, K. Felföldi, G. Szakonyi, K. Balázsik and M. Bartók, Catal. Lett. 52 (1998) 81.
[7] X.B. Zuo, H.F. Liu, D.W. Guo and X.Y. Yang, Tetrahedron 55 (1999) 7787.
[8] M. Shurch, N. Kunzle, T. Mallat and A. Baiker, J. Catal. 176 (1998) 569.
[9] B. Török, K. Balázsik, Gy. Szöllösi, K. Felföldi and M. Bartók, Chirality 11 (1999) 470.
[10] B. Török, K. Felföldi, K. Balázsik and M. Bartók, J. Chem. Soc. Chem. Commun. (1999) 1725.
[11] M. Studer, S. Burkhardt and H.-U. Blaser, J. Chem. Soc. Chem. Commun. (1999) 1727.

[12] K. Balázsik, K. Szöri, K. Felföldi, B. Török and M. Bartók, J. Chem. Soc. Chem. Commun. (2000) 555.

[13] M. Studer, S. Burkhardt, A.F. Indolese and H.-U. Blaser, J. Chem. Soc. Chem. Commun. (2000) 1327.

[14] H.-U. Blaser, H.-P. Jalett, M. Müller and M. Studer, Catal. Today 37 (1997) 441.

[15] M. Bartók, K. Felföldi, Gy. Szöllösi and T. Bartók, Catal. Lett. 61 (1999) 1.

[16] C. Leblond, J. Wang, J. Liu, T. Andrews and Y.-K. Sun, J. Am. Chem. Soc. 121 (1999) 4920.

[17] D. Ferri, T. Bürgi and A. Baiker, J. Chem. Soc. Perkin Trans. 2 (2000) 221.

[18] D. Ferri, T. Bürgi, K. Borszéky, T. Mallat and A. Baiker, J. Catal. 193 (2000) 139.

[19] M. Bartók, K. Felföldi, B. Török and T. Bartók, J. Chem. Soc. Chem. Commun. (1998) 2605.

[20] M. Bartók, T. Bartók, Gy. Szöllösi and K. Felföldi, Catal. Lett. 61 (1999) 57.

[21] A. Konopnicki, J. Szuszko and R. Ludwiczakowna, Roczniki Chem. 9 (1929); 13 (1933) 360.

[22] B. Török, K. Balázsik, K. Felföldi and M. Bartók, Stud. Surf. Sci. Catal. 130 (2000) 3381.

[23] A.R.S. Ross, M.G. Ikonomou and K.J. Orians, J. Mass Spectrom. 35 (2000) 981.

[24] H. Sato, N. Yamada, N. Shimba and Y. Takahara, Anal. Biochem. 281 (2000) 68.

[25] M. Bartók, T. Szabó, T. Bartók and Gy. Szöllösi, Rapid Commun. Mass Spectrom. 14 (2000) 509.

[26] J. Thiel and P. Fiedorow, J. Mol. Struct. 405 (1997) 219.

[27] J.L. Margitfalvi, M. Hegedus and E. Tfirst, Stud. Surf. Sci. Catal. 101 (1996) 24.