Rigid cinchona conformers in enantioselective catalytic reactions: new cinchona-modified platinum catalysts in the Orito reaction *

Mihály Bartók [a,b,**], Károly Felföldi [a], György Szöllösi [b] and Tibor Bartók [***]

[a] *Department of Organic Chemistry, József Attila University, Dóm tér 8, H-6720 Szeged, Hungary*
E-mail: bartok@chem.u-szeged.hu

[b] *Organic Catalysis Research Group of the Hungarian Academy of Sciences, József Attila University, Dóm tér 8, H-6720 Szeged, Hungary*

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The use of cinchona alkaloids (cinchonidine, cinchonine, quinine, quinidine, α-isocinchonine, α-isoquinidine, γ-isoquinidine) in the Orito reaction (hydrogenation of ethyl pyruvate and ethyl benzoylformate) strongly supports the structure of the intermediate complex (cinchona alkaloid "anti-open" conformer–pyruvate 1 : 1 complex); in addition, so far unknown stereochemical conditions have been identified and the utilization of rigid cinchona conformers in the study of asymmetric syntheses have been generalized.

Keywords: chiral, hydrogenation, ethyl pyruvate, ethyl benzoylformate, cinchona alkaloids, rigid conformers

1. Introduction

The preparation of chiral compounds is widely recognized as one of the most important fields in contemporary chemical research [1–3]. In response to industrial and economic needs, the major aim is the development of heterogeneous catalysts for asymmetric syntheses [4–7]. Within this domain, the Orito reaction (scheme 1) [8] is one of the most frequently studied reactions [6,7,9]. After optimization, 95% [10a] to 97% [10b,c] ee was achieved over Pt/Al_2O_3 catalyst using cinchonidine (CD) as modifier for the preparation of (R)-ethyl lactate or 90% [11] using cinchonine (CN) for (S)-ethyl lactate (R = Me). Since the time of the discovery [8] the CN, quinine (Q) and quinidine (QD) modifiers have been rarely used in hydrogenation [12–17].

Although numerous mechanistic details of pyruvate hydrogenation have been described (recently summarized in [6,7,9]), there is no consensus concerning the structure of the intermediate (CD–pyruvate 1 : 1 complex) responsible for chirality. Knowledge of the exact structure of the intermediate complex may open the way for the development of similar reactions. The intermediate complexes, published recently are summarized in figure 1. CD in **A** [18], **B** [6,12] and **C** [19] is in "open", while in **D** [20] in "closed" conformation. The intermediates **A**–**C** are anchored on the surface of the platinum by a multicenter π-bond of the quinoline skeleton and the conjugated $\delta\pi$ systems of pyruvate. In contrast, structure **D** is already formed in solution and this complex is hydrogenated. The preliminary experimental observations [21] allowed us to conclude that, in the case of the Pt–CD catalyst system, it is not necessary to postulate the presence of the "closed" conformer for chiral induction and the most likely structures of modifier are "anti-open" or "syn-open" conformations.

2. Experimental

2.1. Enantioselective hydrogenation of pyruvate

Hydrogenation was performed in an atmospheric batch reactor at room temperature (25 °C). The catalyst was first pretreated with hydrogen (400 °C, 1.5 h). The catalyst, solvent and modifier (50 mg of 5% Pt/Al_2O_3 (Engelhard 4759), 5 mg of chiral modifier and 5 ml of AcOH) were transferred into the reactor, flushed with hydrogen several times and the reactant (0.25 ml) was introduced. The reactor was filled to the desired pressure and stirred (1300 rpm) for the required reaction time (usually 1–4 h). Product identification was performed and enantiomeric excess (ee (%) = $([R] - [S]$ (or $[S] - [R]))/([R] + [S]) \times 100$) was monitored by gas chromatography (HP 5890 GC-FID, 30 m Cyclodex-B capillary column) (table 1).

2.2. H–D exchange measurements of alkaloids

These measurements were carried out in an atmospheric batch reactor under the experimental conditions described for hydrogenation, using ethanol as a solvent but in the absence of reactant (pyruvate). The assembled system was first deaerated and then prehydrogenated for 2 h. After flushing with deuterium the mixture was kept in deuterium atmosphere for 20 h, stirred as usual during hydrogenation. Both the prehydrogenated and the deuterated mixtures were subjected to MS analysis (table 2). HPLC-MS examinations were performed by using a HP 1090 ser. II liquid chromatograph–HP 5989B MS Engine mass spectrometer.

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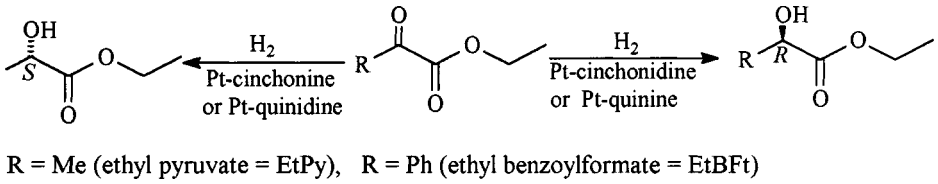
** To whom correspondence should be addressed.
*** Analytical Laboratory of Cereal Research Institute, PO Box 391, H-6701 Szeged, Hungary.



R = Me (ethyl pyruvate = EtPy), R = Ph (ethyl benzoylformate = EtBFt)

Scheme 1.

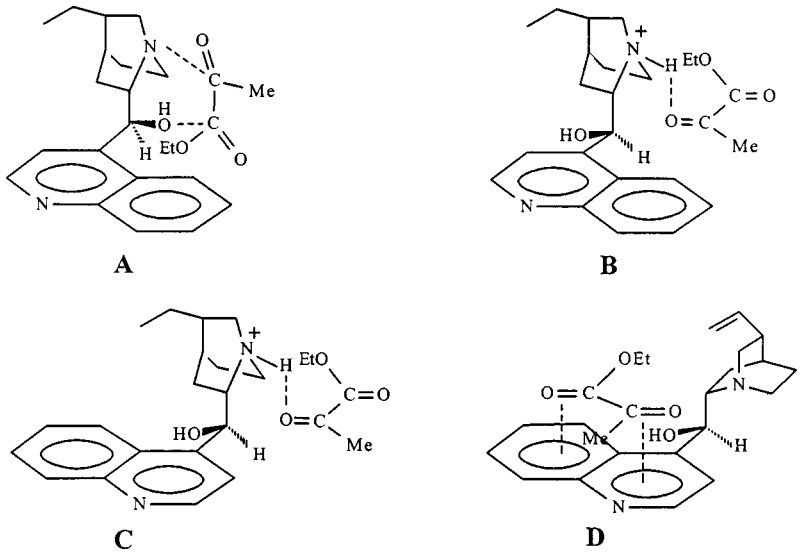


Figure 1. The structures of the cinchonidine–ethyl pyruvate intermediate complexes (**A** and **B**: CD "anti-open", **C**: "syn-open", **D**: "closed" conformation).

Table 1
Enantioselective hydrogenation of ethyl pyruvate (EtPy) and ethyl benzoylformate (EtBFt) over a 5% Pt/Al_2O_3 catalyst (Engelhard 4759) in acetic acid at room temperature.[a]

Entry	Reactant	Modifier	Conversion (%)	ee[b] (%) (configuration)
1	EtPy	CD	100	90 (R)
2	EtPy	CN	100	88 (S)
3	EtPy	Q	100	90 (R)
4	EtPy	QD	100	89 (S)
5	EtPy	α-ICN	100	88 (S)
6	EtPy	α-IQD	100	85 (S)
7	EtPy	γ-IQD	98	22 (S)
8	EtBFt	CD	100	75 (R)
9	EtBFt	CN	94	34 (S)
10	EtBFt	Q	95	50 (R)
11	EtBFt	QD	90	12 (S)
12	EtBFt	α-ICN	100	76 (S)
13	EtBFt	α-IQD	95	45 (S)
14	EtBFt	γ-IQD	84	9 (S)

[a] 50 mg of catalyst (pretreated in H_2 at 400 °C), 5 mg of modifier, H_2 pressure 1 bar, 5 ml of solvent and 0.25 ml of reactant; CD = cinchonidine, CN = cinchonine, Q = quinine, QD = quinidine, α-ICN = α-isocinchonine, α-IQD = α-isoquinidine, γ-IQD = γ-isoquinidine.
[b] Uncertainty ±2%.

Table 2
Several characteristic data of mass spectrometry.[a]

Entry	Modifier		m/z (%)		
	Alkaloid	M	138	139	140
1	DHCD[b]	296	57	18	5
2	DHCD[c]	296	86	28	12
3	DHCN[b]	296	84	26	8
4	DHCN[c]	296	24	19	10
5	α-ICN[b]	294	51	7	4
6	α-ICN[c]	294	84	26	12

[a] For abbreviations, see table 1; DH = dihydro.
[b] Pretreated in H_2.
[c] Pretreated in D_2.

3. Results and discussion

In order to gain knowledge of the structure of the intermediate complex, the enantioselectivity of hydrogenation has to be studied as a function of the structure of the reactant and the modifier. The realization of this research program was made possible by the application of the methods of modern conformational analysis (NMR combined with X-ray crystallography and molecular mechanical calculations) to the determination of the structure of cinchona alkaloids [22–24]. It is concluded that CD, CN, Q, QD must exist in an "anti-open" conformation. Conformational changes in these alkaloids are possible by rotation along the C4′–C9 and C8–C9 bonds in the solution phase. In the case of adsorption on the solid surfaces, the C4′–C9 rotation is hindered. Etheral isomers of cinchona alkaloids (isoalkaloids: α-isocinchonine (α-ICN), α-isoquinidine (α-IQD), γ-isoquinidine (γ-IQD)), which exist in the "anti-open" conformation [24] too, were selected for investigation since there is no C8–C9 rotation:

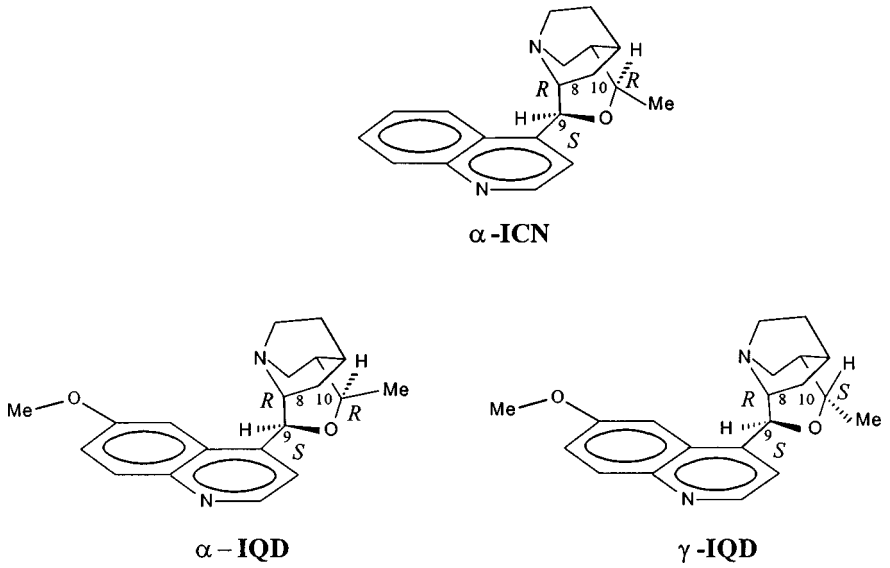


Figure 2. The conformations of isocinchona alkaloids (for abbreviations, see table 1).

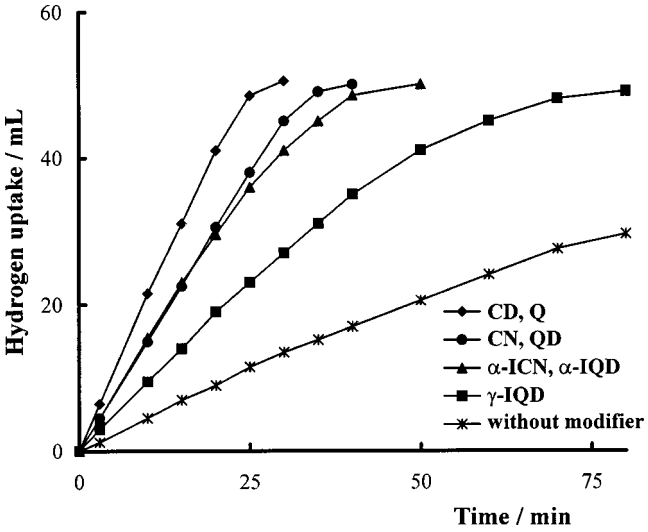


Figure 3. Hydrogenation of ethyl pyruvate (EtPy) on cinchona-alkaloid-modified platinum (50 mg Engelhard 4759 catalyst, H_2 pressure 1 bar, 5 ml AcOH, 0.25 ml EtPy, 5 mg modifier, 25 °C; for abbreviations, see table 1).

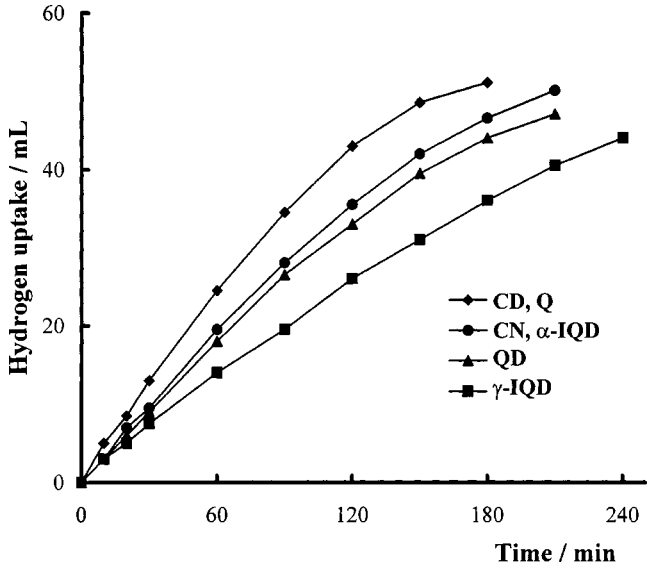


Figure 4. Hydrogenation of ethyl benzoylformate (EtBFt) on cinchona-alkaloid-modified platinum (50 mg Engelhard 4759 catalyst, H_2 pressure 1 bar, 5 ml AcOH, 0.25 ml EtBFt, 5 mg modifier, 25 °C; for abbreviations, see table 1).

these alkaloids are conformationally rigid chiral ligands on the surface. Figure 2 illustrates the most stable conformations of isoalkaloids.

The enantioselective hydrogenation of EtPy and EtBFt was performed in a conventional atmospheric hydrogenation apparatus at room temperature (23 °C). The hydrogenation was studied in the presence of four parent cinchona alkaloids as well as three isoalkaloids not yet tested as chiral modifiers, under conditions previously [6,9] optimised for CD (table 1, figures 3 and 4). The H–D exchange reaction of the above alkaloids was also studied under identical experimental conditions (table 2).

These experimental results can be summarized as follows: (i) Very high (90–92%) ee can be achieved with all four hydroxy cinchona alkaloids in hydrogenation of EtPy to R- or S-ethyl-lactate; (ii) α-ICN and α-IQD also proved to function as effective modifiers, while in the case of γ-IQD ee is only 22%; (iii) in chiral hydrogenation of EtBFt, outstanding ee was obtained with CD and γ-ICN, moderate ee was achieved with CN, Q and α-IQD, while QD and γ-IQD gave poor ee; (iv) as revealed by HPLC measurements, isoalkaloids are not converted back to CN or QD; (v) in all alkaloids studied, H–D exchange takes place on the quinoline skeleton as well as on carbon atom C9; (vi) H–D exchange on the quinuclidine skeleton appears significant only in the case of CN and α-ICN (see the characteristic fragments of [25] in table 2).

Based on our experimental results, chiral hydrogenation of α-ketoesters in the AcOH can be interpreted by the for-

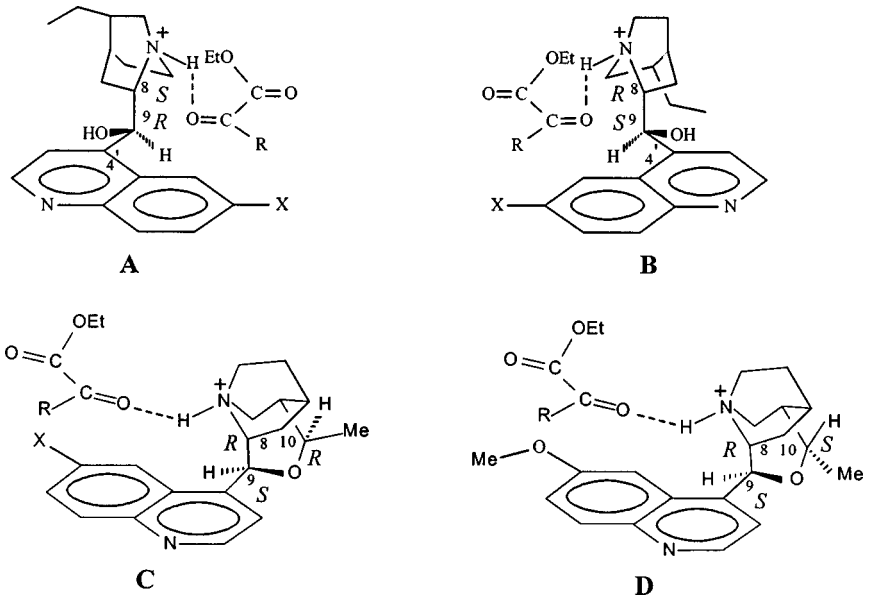


Figure 5. The structures of 1 : 1 cinchona alkaloid–reactant intermediate complexes (R = Me, Ph; for abbreviations, see table 1). **A**: CD (X = H) and Q (X = OMe) "anti-open" complex; **B**: CN (X = H) and QD (X = OMe) "anti-open" complex; **C**: α-ICN (X = H) and α-IQD (X = OMe) "anti-open" complex; **D**: γ-IQD "anti-open" complex.

mation of the reactant–intermediate complexes (1 : 1) proposed by Baiker et al. [6,7] (figure 5). In neutral solvents, the mechanistic proposal by Simons et al. [12] seems most likely.

The starting point of the interpretation of the experimental results must be the fact that all factors stereochemically hindering the formation of the 1 : 1 surface complex of cinchona alkaloid and reactant do not favour high optical yields either. The most important factors to be considered in this respect are: rotation along the C8–C9 axis of cinchona alkaloids, planar adsorption of the quinoline skeleton via multicenter π-bond, the bulk of the R group of α-ketoesters, possibilities of surface adsorption of the methoxy group of the quinoline skeleton and the ethyl group of the quinuclidine skeleton (in the case of CN, QD and isoalkaloids).

It follows from these statements in hydrogenation of EtPy high ee can be attained with all alkaloids except γ-IQD, as no unfavourable factors act to hinder the formation of the 1 : 1 complex (figure 5 **A**–**C**, R = Me, X = H, OMe). In the case of γ-IQD, the Me group on C10 exerts steric hindrance (figure 5 **D**, R = Me).

Experimental results of chiral hydrogenation of EtBFt allowed important conclusions to be drawn, because rotation around the C8–C9 axis in the four parent alkaloids permits the development of different varieties of the "open" conformation on the surface. Owing to changes in dihedral angles, i.e., depending on the size of the reactant, the chiral modifier may spatially fit to the 1 : 1 complex. Thus, in chiral hydrogenation of EtBFt high ee may be achieved in spite of the presence in this molecule of the bulky Ph group in contrast to the Me group of EtPy (figure 5 **A**, X = H, R = Ph). This statement is also supported by the fact that in hydrogenation of EtBFt using Q, considerable ee is achieved in spite of steric hindrance by the OMe group (figure 5 **A**, X = OMe, R = Ph).

In the case of CN (figure 5 **B**, X = H, R = Ph), rotation around the C8–C9 axis is hindered due to surface binding of the ethyl group attached to the quinuclidine skeleton. Consequently, ee is reduced for EtBFt. In QD (figure 5 **B**, X = OMe, R = Ph) and α-IQD (figure 5 **C**, X = OMe, R = Ph), the additional inhibitory effect of the OMe group also manifests itself, while in the case of γ-IQD (figure 5 **D**, R = Ph) the formation of the 1 : 1 complex is hindered by as many as three unfavourable effects (inhibition of rotation, OMe, C10–Me group).

4. Conclusion

The application of cinchona alkaloids newly tested in chiral syntheses (α-ICN, α-IQD, γ-IQD) as chiral modifiers in the Orito reaction for the hydrogenation of EtPy and EtBFt led to the following important conclusions: (i) The presence of 1 : 1 chiral modifier–reactant complexes proposed in the literature [6,7,9,12,18–20] made up of the "anti-open" conformer of the cinchona alkaloid and of the reactant has gained experimental proof; (ii) several, so far unknown stereochemical conditions of the formation of the surface intermediate complex have been identified; (iii) on this basis, the existence of the intermediates proposed by Baiker et al. [6,7] and Simons et al. [12] has been experimentally verified; (iv) chiral induction is not affected by the new chiral centrum (C10) in isoalkaloids; (v) the reaction mechanism established for CD as chiral modifier in the Orito reaction may be generalized for several types of cinchona alkaloids; (vi) the isoalkaloids having rigid structure may be utilized in the interpretation of chiral induction in asymmetric syntheses.

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