A new cinchona-modified platinum catalyst for the enantioselective hydrogenation of pyruvate: the structure of the 1:1 alkaloid–reactant complex

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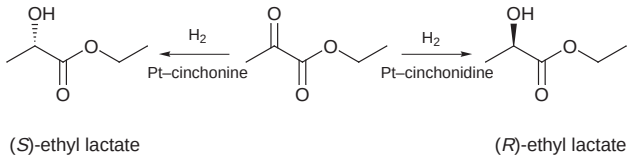
The hydrogenation of ethyl pyruvate to (*S*)-ethyl lactate (up to 70% ee) over a Pt/Al_2O_3 catalyst using α-isocinchonine as a modifier strongly supports the structure of the intermediate complex [cinchona alkaloid (open conformer)–pyruvate 1:1 complex] of this type of reactions.

As is well known, one of the most important fields in contemporary chemical research is the preparation of chiral compounds. The potential of asymmetric catalytic processes is especially high, since in this way large amounts of chiral products can be prepared using catalytic amounts of chiral modifier.[1,2] As a result of industrial and economical requirements the major aim is to develop heterogeneous catalytic asymmetric syntheses.[3–6] In this respect, the hydrogenation of pyruvates is one of the most frequently studied reactions.[7,8] After optimization 95[9]–97% ee[10] was achieved over Pt/Al_2O_3 catalyst using cinchonidine (CD) as the modifier in the preparation of (*R*)-ethyl lactate and 90%[11] ee using cinchonine (CN) for (*S*)-ethyl lactate (Scheme 1).



Scheme 1

Since pyruvate hydrogenation is one of the two[12,13] good ee producing heterogeneous chiral hydrogenations (α-keto esters,[12] β-keto esters and 1,3-diketones[13]), extensive efforts have been made to gain insight into the mechanism. Many mechanistic details of the pyruvate hydrogenation are known, however, there is no agreement concerning the structure of the intermediate (CD–pyruvate 1:1 complex) responsible for chirality. The intermediate complexes (depending on the reaction conditions) published recently are summarized in Fig. 1.

As shown, there is no significant conceptional difference between the structures in each groups [group I: Fig. 1(*a*),[14] (*b*),[15] (*c*),[16] (*f*);[17] group II: (*d*),[18] (*e*)[19]]. The CD in all intermediates in group I is in the 'open' conformation, while in group II it is in the 'closed'conformation. Between the two groups, however, there is a huge difference. The intermediates belonging to group I are anchored to the surface of the platinum catalyst by a multicenter π-bond from the quinoline skeleton and the conjugated σπ systems of pyruvate. In contrast, the structures belonging to group II are already formed in the solution and the complex most likely adsorbs through the conjugated σπ system of the substrate and the non-bonding electron pairs of the quinoline nitrogen due to the so-called 'shielding effect'. It has been clearly proven[7,8,15] that the conformation of the modifier plays a determining role in the chiral induction.

Here we provide new information about the structure of the intermediate complex and experimental proof of whether the 'closed' conformation of the cinchona alkaloids is necessary for chiral induction. For this reason, two cinchona alkaloids, CN and α-isocinchonine (ICN) were selected as chiral modifiers.

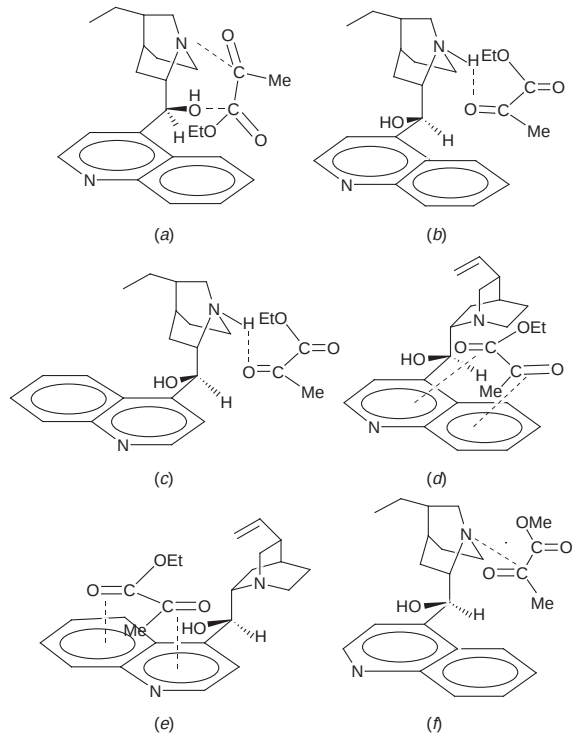


Fig. 1 The structures of the cinchonidine–ethyl pyruvate intermediate complexes.

Although the mechanistic proposals mentioned above are related to the platinum–CD system,[7,8,14,17,18] there is no reason to assume that when using CN the mechanism should be basically different.[11,12,15] Fig. 2 illustrates the most stable

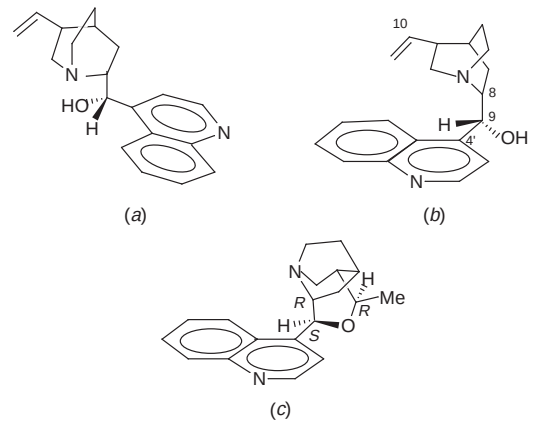


Fig. 2 The conformations of cinchonine [(*a*) 'open' conformer, (*b*) 'closed' conformer] and (*c*) α-isocinchonine.

Table 1 Enantioselective hydrogenation of ethyl pyruvate over a 5% Pt/Al_2O_3 catalyst (Engelhard 4759) in AcOH at room temperature [50 mg of catalyst (as received), 5 mg of modifier, 5 ml of solvent and 0.25 ml of ethyl pyruvate][a]

Modifier	H_2 pressure/bar	Conversion (%)	Ee (%) (configuration)
CD	1	100	80 (*R*)
CD	50	100	90 (*R*)
CN	1	95	72 (*S*)
CN	50	98	67 (*S*)
ICN	1	94	67 (*S*)
ICN	50	98	69 (*S*)

[a] Analysis: ee (%) = 100{[*R*] − [*S*] (or [*S*] − [*R*])}/([*R*] + [*S*]), chiral GC (HP 5890 GC-FID, 30 m long Lipodex-A column), HPLC-MS (HP1090 Ser.II HPLC-HP5989B MS with an HP5987A ES interface).

conformations of CN [Fig 2(*a*)] and ICN [Fig. 2(*c*)] alkaloids suggested and verified by combined NMR and X-ray analysis and molecular mechanical calculations.[20–22] Conformational changes in CN are possible by rotation along the C(4′)–C(9) and C(8)–C(9) bonds. [It should be noted that in the case of flat adsorption of the quinoline skeleton on platinum, as already pointed out,[17,23] the C(4′)–C(9) rotation is hindered.] To realize our aim mentioned above, ICN was selected because it cannot rotate around C(8)–C(9). It is also known that ICN exists only in '*anti*-open' conformation.[22]

The enantioselective hydrogenation of ethyl pyruvate (EtPy) was performed either in a conventional atmospheric hydrogenation apparatus or in a Berghof Bar 45 autoclave at room temperature (25 °C). The results are shown in Table 1.

As the HPLC–ESMS measurements revealed, the ICN modifier did not revert back to CN, *i.e*. the cyclic ether structure remained stable during the hydrogenations. As the results clearly show the ICN modifier of fixed conformation showed practically the same performance (conversion, ee) as CN during the hydrogenations.

The proposed intermediate complex of the chiral hydrogenation carried out in the presence of ICN is illustrated in Fig. 3. It should be mentioned that only the existence of the '*anti*-open' conformer was proven in solution;[22] the formation of the '*syn*-open' conformer during the adsorption cannot be excluded.

These experimental data strongly support the existence of the structures in Fig.1(*b*) and (*c*) when working under acidic conditions. Further measurements are necessary, however, to distinguish between the two structures. Although the reaction conditions are not fully optimized in the case of CN and ICN it is unambiguously proven that the formation of a cinchona alkaloids(closed)–EtPy complex is not a precondition for chiral induction. On the other hand, extensive studies with respect to cinchona-modified pyruvate hydrogenation in AcOH, accompanied by the present results, strongly supports the 1:1 adsorptive interaction model[7,8] of Baiker, Blaser and co-workers. In neutral solvents, the recently revised mechanistic proposal by Wells[17] and co-workers seems most likely.

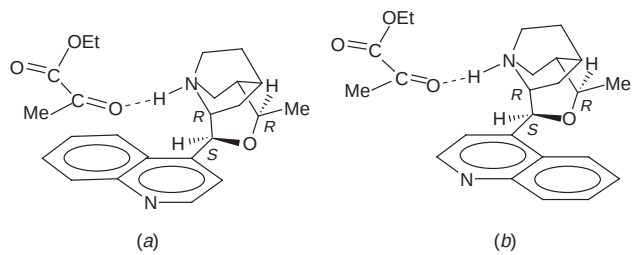


Fig. 3 The structures of α-isocinchonine–ethyl pyruvate intermediate complexes [(*a*) '*anti*-open' complex, (*b*) '*syn*-open' complex].

Our results obtained with ICN suggest further mechanistic studies of cinchona-modified asymmetric syntheses utilising other cinchona alkaloids of rigid conformation. The results of this work provide further proof of our earlier statement[24] that the conformation of the reactants is of crucial importance in determining the selectivity of metal-catalyzed transformations.

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