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LETTERS

Proton/deuterium exchange in cinchonidine and deuteration of ethyl pyruvate using platinum/Al_2O_3 catalysts

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Abstract—A study of deuteration of cinchonidine (CD) under conditions (pressure (40 bar), temperature (25°C) and reaction times (2 h)) used for usual hydrogenation of ethyl pyruvate showed that the vinyl group is totally transformed into an ethyl (deuterated) and that H for D exchanges occur on the quinoline ring and at C9. Deuteration of ethyl pyruvate under the same conditions showed that no deuteration occurs at the chain-methyl, neither in toluene nor in AcOH, indicating that the enol is not the reacting species. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The main feature of the enantioselective hydrogenation of α-keto esters over catalytic amounts of supported platinum in the presence of catalytic amounts of Cinchona alkaloids is, together with high enantioselectivities (up to 95/5 e.r. for hydrogenation of ethyl pyruvate), an important acceleration of the reaction in the presence of the alkaloid (particularly cinchonidine, CD), both in toluene (a nonprotic solvent) and acetic acid (a protic solvent).

Electrophilic assistance of the pyruvate-carbonyl through formation of a strong H-bond between protonated CD and pyruvate,[1] a 'ligand-accelerated reaction'[2] and formation of the enol form of pyruvate H-bonded to CD[3] have been proposed to be at the origin of the acceleration observed.

Deuteration and proton/deuterium exchange in CD using Al_2O_3-supported Pt catalysts has been studied to compare with the results obtained in the literature with SiO_2 supported Pt.[4]

To check the hypothesis concerning the enol H-bonded to CD as a more reactive species, deuteration of ethyl pyruvate has also been studied.

2. H/D exchange

The catalyst (E-4759 from Engelhard) was reduced at 350°C under a D_2 flow for 2 h and kept under argon *prior* to utilization. THF was used as aprotic solvent.[5]

Deuteration and H for D exchange in CD have been studied under the pressure, temperature and time conditions (40 bar, 20°C, 2 h) used for hydrogenation of ethyl pyruvate[6] and it must be noted that the time of reaction (2 h) was shorter and the pressure higher (40 bar) than those used in the literature with SiO_2 supported Pt (500 h and 1 bar).[4] The sites and percentages of deuteration and of H/D exchange have been determined by ^1H NMR (400 MHz) after assignment of all the proton signals of dihydro-CD using the COSY and NOESY techniques, Fig. 1.[7] The multiplets of protons H6e, H6ex and H2c, being well isolated, have been taken as surface reference for 1H.

Total disappearance of the vinyl group[8] was observed in accord with previous results[4] but no hydrogenation of the quinoline ring was detected. As already observed over Pt/SiO_2, H for D exchanges were observed at the quinoline ring and at C9 but no exchange occurred on the quinuclidine ring (Fig. 2a). It thus appears that, although the conditions are quite different and the reaction time very short, H for D exchanges do occur (but of course to a small extent) under the conditions used for hydrogenations. The multiple exchanges observed corroborate the hypothesis of CD adsorption (and/or dihydro-CD adsorption) through multicenter

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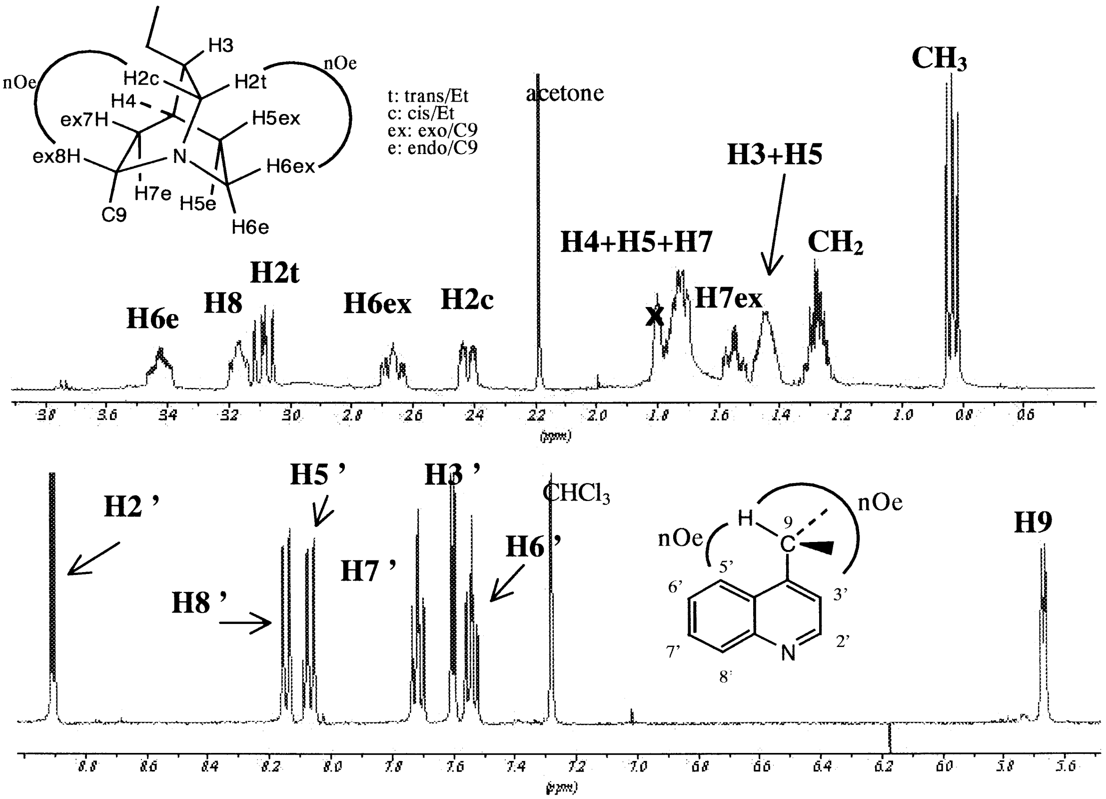
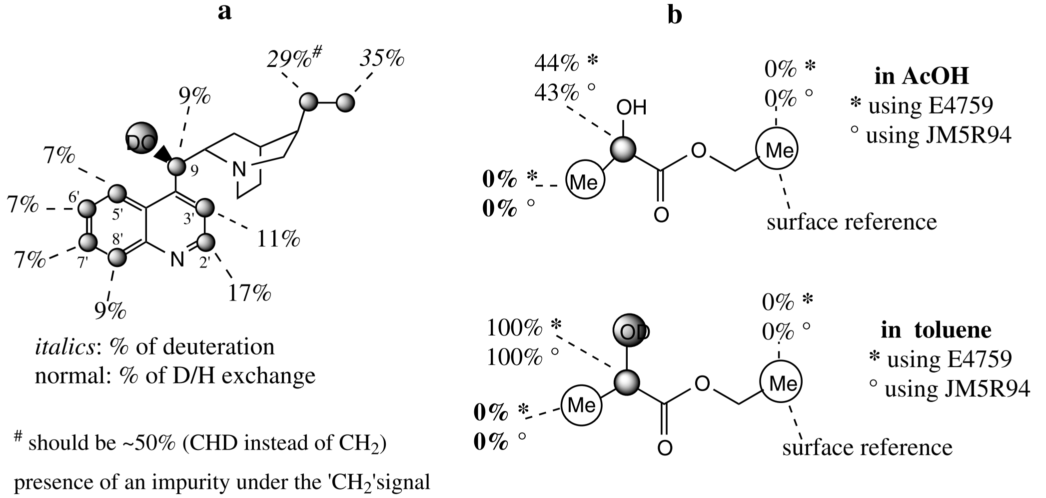


Figure 1. NMR (400 MHz, $CDCl_3$) of dihydro cinchonidine.



italics: % of deuteration
normal: % of D/H exchange

should be ~50% (CHD instead of CH_2)
presence of an impurity under the 'CH_2'signal
increases the observed surface of the signal

Figure 2.

π-bonds between the quinoline ring and the platinum surface, as already proposed.[4,9]

3. Deuteration

Deuteration of ethyl pyruvate was conducted in toluene and in AcOH as was the hydrogenation (40 bar, 20°C, 2 h). The catalysts (E-4759 and JM 5R94) were reduced at 350°C under a D_2 flow during 2 h *prior* to utilization. The CH_3–CH_2 signals (triplet at 1.30 ppm and quadruplet at 4.22 ppm) of the ester group have been used as 3H and 2H surface references to calculate the percentages of deuteration. The results (Fig. 2b) show that, with both catalysts, ***no deuteration of the chain-CH_3 occurred, neither in toluene nor in AcOH, indicating that the enol is not the reacting species in these hydrogenations.***

The lower percentage of deuteration in AcOH is due to H/D exchange between the D_2-saturated catalyst and the mobile OH protons of the solvent as already observed for EtOH.[4]

The enantiomeric ratio was determined to be 84/16 in favor of the *R*-lactate for both catalysts (with a [CD]/[Catal.] ratio of 1.3)[10] using gas chromatography.[11]

As already suggested,[9] the quinoline ring serves as a binding site with a flat adsorption of the ring parallel to the surface of the platinum. Exchange at C9 suggest formation of the transitory species **T** and it is interesting to note that no epimerization occurs at C9 as no *threo* isomer is detected after hydrogenation of CD (*erythro* isomer) under the deuteration conditions. However, the most important conclusion is that the enol is not the reacting species in these hydrogenations.

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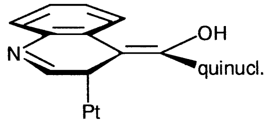

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2. Garland, M.; Blaser, H. U. *J. Am. Chem. Soc.* **1990**, *112*, 7048. For accelerating effect of CD in homogeneous catalytic reactions, cf. Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135.
3. Solladié-Cavallo, A.; Marsol, C.; Hoernel, F.; Garin, F. *Tetrahedron Lett.* **2001**, *42*, 4741.
4. Bond, G.; Wells, P. B. *J. Catal.* **1994**, *150*, 329.
5. Cinchonidine is not soluble in toluene.
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7. ^{1}H NMR ($CDCl_3$); H6e: 3.42 ppm (dddd, $^2J_{66}=13$ Hz, $^3J_{6e5e}=10.5$ Hz, $^3J_{6e5ex}=5.5$ Hz, $^3J_{6e2c}=2.5$ Hz). H2t: 3.08 ppm (dd, $^2J_{22}=13.5$ Hz, $^3J_{2t3}=10$ Hz). H6ex: 2.66 ppm (ddd, $^2J_{66}=13$ Hz, $^3J_{6ex5ex}=10.5$ Hz, $^3J_{6ex5e}=5.5$ Hz). H2c: 2.42 ppm (ddd, $^2J_{22}=13.5$ Hz, $^3J_{2c3}=4.5$ Hz, $^4J_{2c6e}=2.5$ Hz). H7ex: 1.54 ppm (ddt, $^2J_{77}=12.5$ Hz, $^3J_{7ex8}=10.5$ Hz, $^3J_{7ex4}=3$ Hz, $^4J_{7ex5ex}=3$ Hz). Assignment of the two spin system 2c–2t was done through the expected pattern (two large coupling constants for 2t and only one large for 2c) and confirmed by NOESY (a correlation spot is observed between H8 and H2t). H6e and H7e were assigned by NOESY through correlation spots with H9 and H6ex through a correlation spot with H2c.
8. The partially deuterated ethyl group appears at: 1.28 ppm (CH_2) and 0.82 ppm (CH_3).
9. (a) Baiker, A. *J. Mol. Catal. A: Chem.* **2000**, *163*, 205; (b) Smith, G. V.; Notheisz, F. *Heterogeneous Catalysis in Organic Chemistry*; Academic Press, 1999.
10. A lower [CD]/[Catal.]ratio would have led to higher e.r. (cf. C. Marsol: PhD, Strasbourg, 2001; LeBlond, C.; Wang, J.; Liu, J.; Andrews, A. T.; Sun, Y. K. *J. Am. Chem. Soc.* **1999**, *121*, 4920 and Baiker, A. *J. Mol. Catal. A: Chem.* **1997**, *115*, 473), but we were looking for determination of sites of deuteration and not for high e.r.
11. A Cyclodex B (30 m×0.32 mm, film thickness = 0.25 μm) from J. & W. Scientific and a HP 6890 machine were used. Flow rate of He = 2.2 mL/min, 45–230°C (10°C/min).