Electrospray ionization mass spectrometry in the heterogeneous catalyzed organic reactions: unknown compounds in the pyruvate hydrogenation *

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The transformation of cinchonidine was studied in the presence of hydrogen on Pt/alumina by electrospray ionization mass spectrometry using in-source CID. So far unknown compounds were identified. Further studies on the basis of these new observations may permit to establish a more comprehensive mechanism of enantioselective hydrogenation of α-ketoesters.

Keywords: enantioselective, hydrogenation, ethyl pyruvate, electrospray ionization, MS, mechanism

1. Introduction

Measuring techniques developed as a result of new discoveries have played a significant role in the elucidation of the mechanism of chemical processes. The extremely high-volume industrial application of heterogeneous catalytic reactions has been made possible, among other factors, by the continuous modernization of analytical procedures. The work of Somorjai et al. [1] in this field has been of outstanding importance in the past two decades. One of these important analytical methods is mass spectrometry, utilizing various ionization techniques. Significant results have lately been produced by electrospray ionization mass spectrometry (ESI-MS) that has been used extensively in the characterization of proteins, nucleic acids and in the analysis of other high-mass polymers [2]. A great advantage of ESI-MS compared to other ionization methods is that the mildness of the ionization process ensures less severe sample fragmentation. In most cases, it is possible to observe intact molecular ions of the sample. Less well developed are applications of ESI to smaller molecules (for some examples, see [3]), although it has been applied increasingly in studies on homogeneous liquid-phase catalytic reactions (see, e.g., [4]).

The aim of this work is to demonstrate the importance of the ESI-MS technique in studies on heterogeneous catalytic reactions. The example chosen is the Orito reaction (scheme 1) [5].

Since pyruvate hydrogenation is one of the two heterogeneous enantioselective hydrogenations producing the best ee values [6], extensive efforts have been made to gain insight into its mechanism. Although many mechanistic details of pyruvate hydrogenation have been elucidated, no agreement has been reached concerning the structure of the intermediate (cinchonidine (CD)–pyruvate 1 : 1 complex) responsible for chirality. In the course of studies on the mechanism of chiral hydrogenation, identification of the intermediate complex as well as the effect of secondary reactions and the products of the hydrogenation of CD on optical selectivity have been addressed using TLC, HPLC and NMR [7]. These methods, however, did not permit either the identification of the majority of intermediates and secondary products or their effect in the catalytic reaction.

2. Experimental

2.1. Materials

CD, AcOH (99.5%) and HPLC-grade methanol were purchased from Fluka and were used as received. Ethyl pyruvate (EtPy, Fluka) was distilled immediately before use to attain 99.8% purity. The 5% (w/w) Pt/Al_2O_3 catalyst (Engelhard 4759) was pretreated before use in a fixed-bed reactor by flushing with 30 ml min^{-1} helium at 300–673 K for 30 min and 30 ml min^{-1} hydrogen at 673 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium at this temperature for 30 min and stored before use.

2.2. Hydrogenation

Hydrogenation was performed in an atmospheric batch reactor at room temperature. After flushing with hydrogen the catalytic system including catalyst, AcOH and modifier

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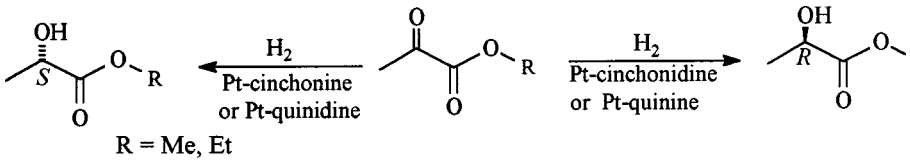

Scheme 1.

(50 mg of 5% Pt/Al_2O_3, 1 mg of CD, H_2 pressure 1 bar and 5 ml of AcOH) the reactant (0.25 ml of EtPy) was introduced and stirred (800 rpm) for the required reaction time (usually 40–80 min). After the hydrogenation, the liquid was removed and the solid catalyst was re-used for new experiments (table 1).

Products were identified and the enantiomeric excess (ee (%) $= ([R] - [S]$ (or $[S] - [R]))/([R] + [S]) \times 100$) was monitored by gas chromatography (HP 5890 GC-FID, 30 m long Cyclodex-B capillary column).

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

	EtPy (ml)	CD (mg)	Catalyst	Conversion (%)	ee[b] (%)
A	0.25	1	50 mg Pt/Al_2O_3	100	68
B	0.25	1	reuse after A	100	81
C	0.25	1	reuse after B	100	82
D	0.25	1	reuse after C	100	82

[a] 50 mg of catalyst (pretreated), 1 mg of modifier, H_2 pressure 1 bar, 5 ml of AcOH and 0.25 ml of EtPy, CD = cinchonidine.
[b] Uncertainty ±2%.

2.3. Equipment

A Hewlett–Packard HP 5989B MS Engine mass spectrometer equipped with an extended mass range (2000 u), a high-energy dynode detector and an atmospheric pressure ionization ES (API-ES) interface (HP 59987A) with in-source CID (collision-induced dissociation) was used. A Harvard type 22 syringe pump (Harvard Apparatus, South Natick, MA, USA) was applied at a flow rate of 20 μl min^{-1} to infuse the samples into the electrospray ion source. Nebulizing gas (N_2) was introduced into the solvent/sample stream at a pressure of 50 psi. The fine spray formed was focused off axis onto the spray shield (heated with N_2 drying gas to 250 °C) at a flow rate of 8 l min^{-1} in order to facilitate solvent evaporation from the droplets in the spray chamber. The mass spectrometer and ES parameters were optimized with a standard solution of benzylaminopurine riboside (100 ng μl^{-1} MeOH–H_2O–AcOH (48.5 : 48.5 : 3, v/v)) to give molecular adduct ions ($[M + H]^+$) in the highest possible abundance and with minimum CID.

3. Results and discussion

The highest ee in the enantioselective hydrogenation of pyruvates was attained in the presence of AcOH as a solvent. This is explained by the protonation [6] of dihydro-CD (DHCD) (CD is converted to DHCD in the course of prehydrogenation). DHCD·H^+ with EtPy forms a 1 : 1 complex having the conformation necessary for chiral hydrogenation. Accordingly, EtPy was hydrogenated in the presence of DHCD on Pt/Al_2O_3 catalyst in AcOH.

The results of hydrogenation and of some representative ESI-MS measurements are presented in table 1 and in figure 1.

The mass spectra yielded surprising results. Depending on DHCD concentration, in addition to tetrahydro-CD (THCD, $[M + H]^+ = 299$), hexahydro-CD (HHCD, $[M + H]^+ = 301$) and dodecahydro-CD (DDHCD, $[M + H]^+ = 307$) (figure 2), the formation of identified and as yet unidentified molecules with considerably higher m/z, furthermore products with lower and much higher m/z not appearing in the figures shown (among them, probably, platinum complexes) were also observed. When ESI-MS was coupled with HPLC, two products each with m/z values of 299, 301 and 307 were detected, indicating hydrogenation of the pyridine ring, since in the course of hydrogenation a new center of asymmetry is formed (C4′). The probable structure of the product with $m/z = [451]^+$ is shown in figure 2 (**A** or **B**), while product $[469]^+$ is the adduct of the same molecule with water. This at the same time raises the question of the role of N → O acyl migration in the entire process [8]. The identification of the other, so far unknown molecular ions (at m/z = 321, 335, 353, 395, 480, 509 and others) is in progress.

The results of the extensive investigations concerning the mechanism of pyruvate hydrogenation published up to now, supplemented with experimental data obtained by ESI-MS made possible the formulation of the simplified reaction scheme outlined in figure 3. The reaction pathway envisaged comprises the following steps: (i) protonated DHCD associated with acetic acid is adsorbed on the surface of the Pt/Al_2O_3 catalyst (complete surface coverage); (ii) in the course of the addition of EtPy, a complex consisting of protonated DHCD·EtPy·AcOH is formed, in which DHCD·H^+, in our view, is present in the "anti-open" conformation; (iii) due to its higher tendency for adsorption, this latter complex displaces DHCD·H^+·AcOH on the platinum catalyst; (iv) hydrogenation is completed on the surface; (v) after rapid desorption of (R)-EtLt·AcOH, the cycle is repeated.

In addition to the molecules and molecule complexes participating in the reaction pathway presented in figure 3, HHCD and DDHCD formed in the course of the hydrogenation of CD and products formed in their further reac-

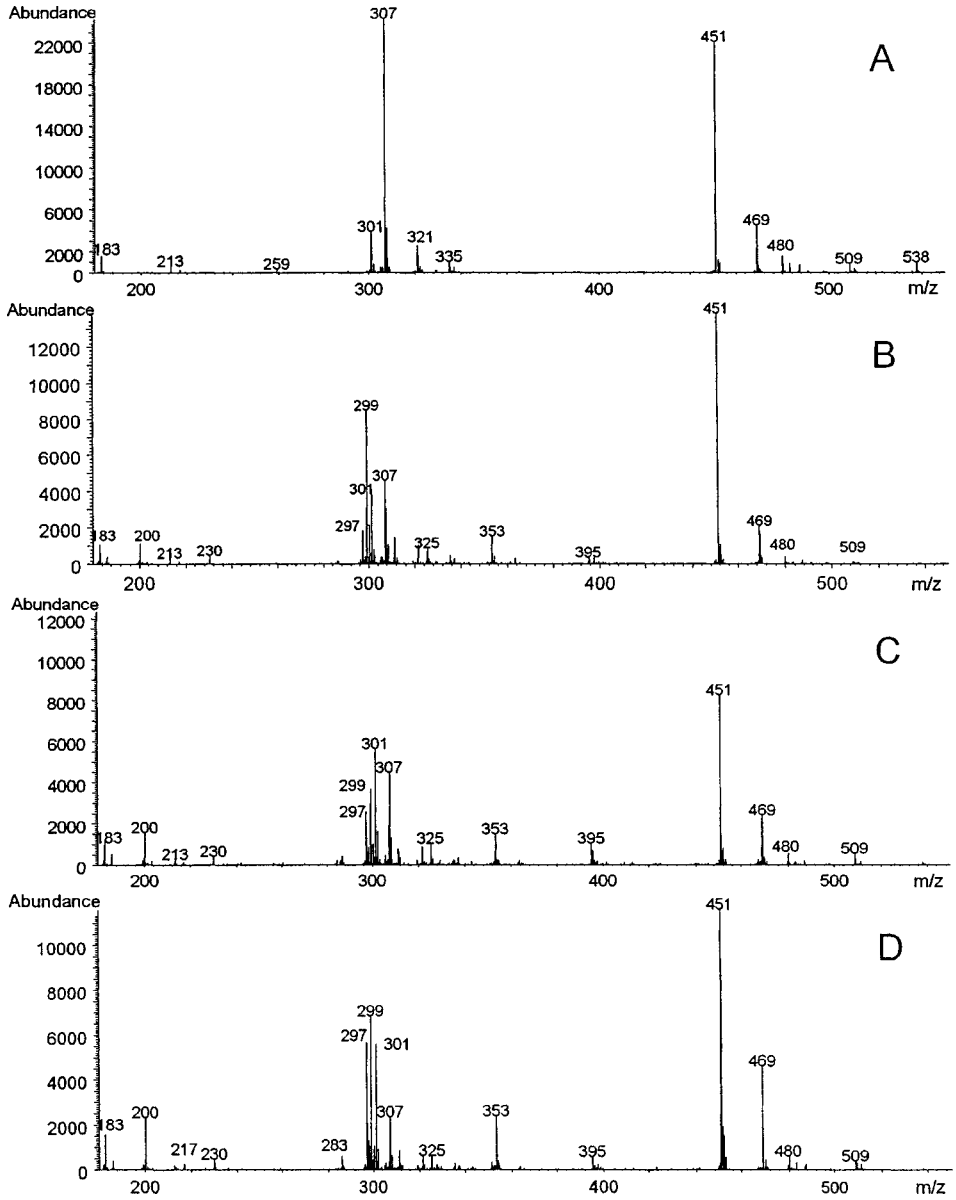

Figure 1. Positive-ion electrospray mass spectra (CapEx 80 V) of cinchonidine in the EtPy hydrogenation (for abbreviations, see table 1).

tions are also observed (see figure 1). The concentration of these compounds depends on the experimental conditions and they affect the achievement of high optical selectivities.

Since reaction conditions (especially solvents and the concentration of CD and EtPy) have a fundamental effect on optical yield [6] which is closely correlated with the composition of the entire system, detailed systematic studies have to be carried out using ESI-MS and ESI-MS-MS techniques [9] as well as their combinations with HPLC. These studies may help to determine which intermediates hinder and which ones promote the realization of high optical yields.

On the basis of the results available up to now [6], this heterogeneous reaction is the so-called "ligand-accelerated" catalysis [10] proceeding via a pyruvate–DHCD 1 : 1 complex. Considering, however, that in the presence of AcOH the interaction between the catalyst and the reaction partners is of the electrostatic type, i.e., it is mediated by polar molecules (ions), the so-called "electrostatic catalysis" [11] based on "electrostatic acceleration" [12] may play a decisive role in the acceleration of the catalytic reaction. Consequently, for the interpretation of studies on solvent polarity not only should the solubilities of substrates and products be considered, but the possibility that the reaction mechanism may be affected by solvent polarity through electrostatic catalysis should also be taken into account.

4. Conclusion

The Orito reaction was studied by the ESI-MS technique. The results obtained demonstrate the complexity of this chiral hydrogenation process and urge further investigations. At the same time these experimental data also

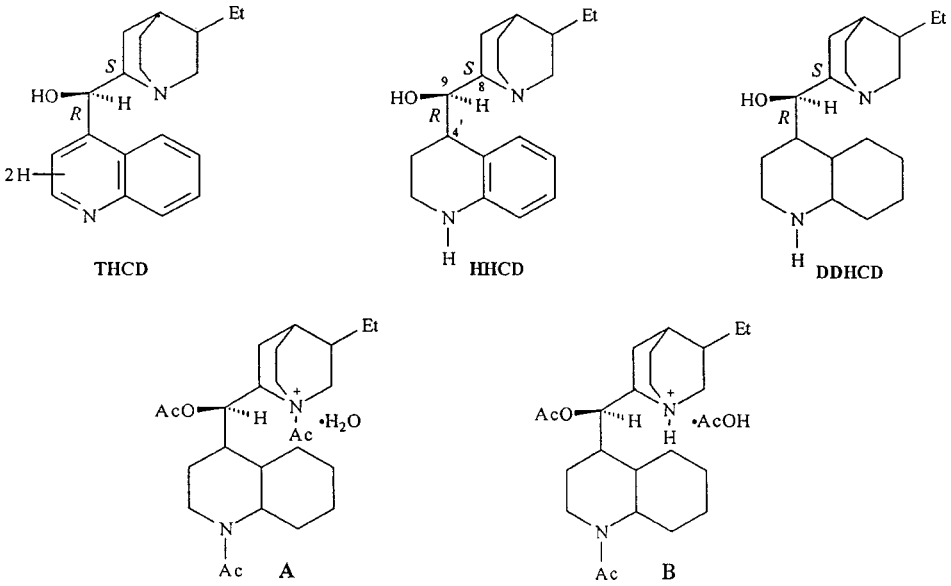

Figure 2. The structure of compounds formed from cinchonidine in the EtPy hydrogenation (THCD = tetrahydrocinchonidine, HHCD = hexahydrocinchonidine, DDHCD = dodecahydrocinchonidine).

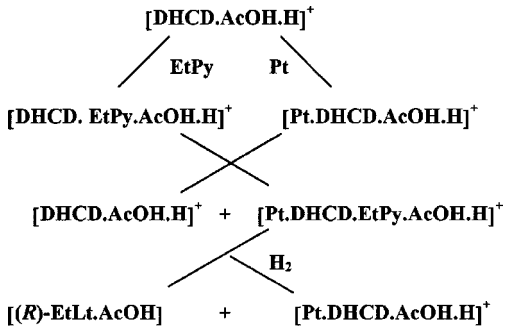

Figure 3. Reaction pathway of enantioselective ethyl pyruvate hydrogenation (for abbreviations, see table 1 and figure 2; EtLt = ethyl lactate).

call attention to the significance of the application of the ESI-MS technique in studies on the reaction mechanism of heterogeneous liquid-phase catalytic reactions.

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