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Substrate-modifier but not catalyst-modifier: heterogeneous hydrogenation of C=O and C=C using cinchonidine

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Abstract—Literature results and our own, concerning hydrogenation of ethyl pyruvate and 2-methyl pentenoic acid over Al_2O_3-supported platinum and palladium using cinchonidine (CD), indicate that CD activates pyruvate (through enol formation) and modifies the unsaturated acid (salt formation), but not the catalyst, and that CD may even poison the catalyst (palladium more than platinum). Therefore, the modifier's properties must fit the substrate's properties and not be a catalyst poison, the best sequence for addition of the reactants being: first a mixture of substrate/CD and then the supported Pt and/or Pd catalyst.

Since the early work by Orito et al.[1] and by Lipkin et al.,[2] catalytic amounts ($\sim 10^{-3}$ equiv. versus the substrate to be hydrogenated) of cinchonidine (CD) have been widely used for the hydrogenation of α-ketoesters and conjugated double bonds catalyzed by Al_2O_3 supported platinum and palladium.[3] The origin of the observed enantioselectivity has been widely studied and various chiral modifiers, different from CD, have been proposed.[4,5]

From literature results, it appears that acceleration of the hydrogenation of α-ketoesters in the presence of CD is always observed with Pt/Al_2O_3,[6a,7] and has been rationalized as a 'two-cycle mechanism'.[6b] However, a decrease of the rate of the reaction is observed in the presence of CD with Pd/Al_2O_3.[7] In the case of hydrogenation of α,β-unsaturated esters with Pd/Al_2O_3, a decrease of the rate of the reaction has always been observed in the presence of CD.[8]

Although it was shown by Wells et al. in 1996, through deuteration experiments, that, in the case of hydrogenation of α-ketoesters with Pd/Al_2O_3, the major route to product was conversion to *adsorbed*-enol,[7] the concept of CD being a modifier of the catalyst remains unchanged and the concept of CD being chemisorbed on the metallic surface *before attachment of the substrate* to be hydrogenated (**M**odified-**Cat**alyst **H**ydrogenation: **MCatH**) still dominates the field although, for statistical reasons, one should expect CD to have better chance of reaction with the substrate **1** than with the catalyst (ratio CD/**1** or **5**/cat. = $1/10^3$–$10^2/1$). However, it is worth noting that it has been proposed recently that the 'modifier' could associate with the substrate forming a 'combination' (complex) *before* being adsorbed onto the metallic surface (**C**omplex **H**ydrogenation: **CH**).[9]

We present here some results which, together with literature results, suggest that for hydrogenations of α-ketoesters with Pt/Al_2O_3 and α,β-unsaturated esters with Pd/Al_2O_3 the **CH** mechanism is more efficient than the **MCatH** mechanism which, as already mentioned above and for statistical reasons, can only occur when the catalyst is impregnated with CD before use, and that CD activates α-ketoesters but modifies α,β-unsaturated esters and may poison the catalyst (palladium more than platinum).

Hydrogenation of ethyl pyruvate **1** using 5% Pt/Al_2O_3 (Johnson Matthey 5R94) was conducted in toluene or AcOH (Scheme 1),[11] while acid **5** and ester **8** were hydrogenated in hexane on 5% Pd/Al_2O_3 prepared from γ-alumina and $PdCl_2(NH_3)_4$ following the usual procedure[10] (Scheme 2).[19]

Keywords: heterogeneous hydrogenation; cinchonidine; palladium; platinum.

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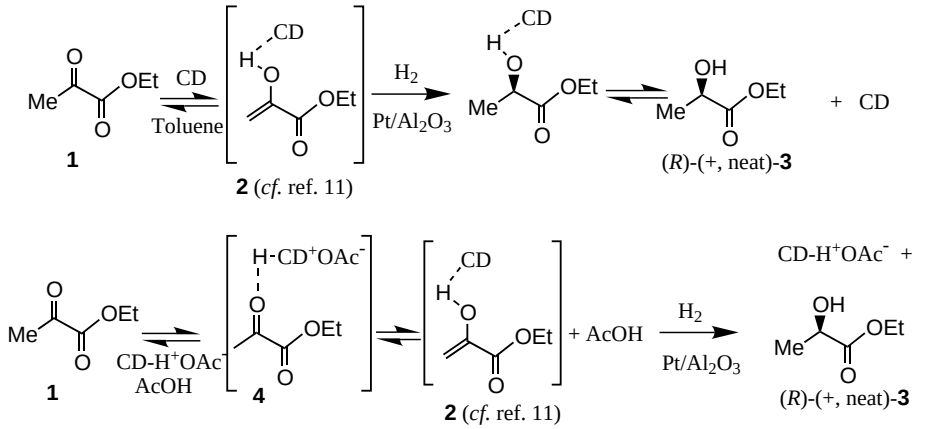
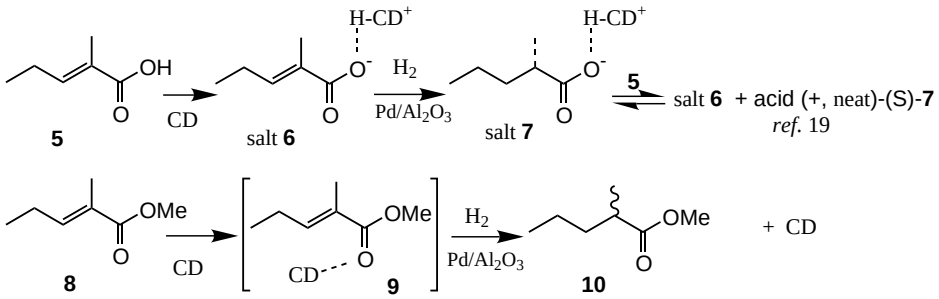


Scheme 1.



Scheme 2.

Concerning hydrogenation of ethyl pyruvate **1**, acceleration of the hydrogenation in the presence of CD is clearly observed (Table 1, compare lines 1 and 2 with 3–6), in accord with literature results.[6a,7]

This acceleration can be explained by formation of the enol **2** as *a faster reacting species* (Scheme 1). The propensity of pyruvates for autocondensation through enolization in the presence of a base is well known in organic chemistry.[12] It has recently been shown that, as expected, CD can act as base promoting autocondensation of pyruvate.[13] Moreover, even in the absence of CD, methyl pyruvate undergoes polymerization on a platinum surface.[14] In AcOH, cinchonidine ammonium acetate ($CD\text{-}H^+/OAc^-$) is formed and associates, through H-bonding, to ethyl pyruvate to give **4** which is in equilibrium with **2** (Scheme 1), which is responsible for the higher reactivity.

Table 1. Hydrogenation of **1**: Pt/Al_2O_3 (JM 5R94), H_2 (40 bar), 2 h

Conditions[a]	Solvent	Conv. (%)	ee (%)
Without CD	Toluene	11	–
Without CD	AcOH	18	–
3×10^{-4} equiv. CD: **A**	Toluene	80	76
3×10^{-4} equiv. CD: **B**	Toluene	100	76
3×10^{-4} equiv. CD: **A**	AcOH	91	85
3×10^{-4} equiv. CD: **B**	AcOH	100	86

[a] Pyruvate concentration = 4.5 M. Pyruvate/CD = 3500. Pyruvate/catalyst = 3500.

The enol form can be considered more reactive towards hydrogenation because the π-electrons (of the *trans* and *cis* enols) are higher in energy (−10.03 and −10.02 eV, respectively),[15a] more polarizable and, therefore, more inclined to complex to platinum than the π-electrons of the pyruvate carbonyl which are significantly lower in energy (−13.38, −13.34 and −13.33 eV)[15a] for the twisted ($\theta = \sim 95°$), *trans* and *cis* coplanar conformations, respectively, which are the three most stable conformations.[15b]

Moreover, when the catalyst (Pt/Al_2O_3) is added into an already formed mixture of pyruvate **1** and CD (method **B**), the reaction proceeds faster than when the catalyst is impregnated with CD before addition of **1** (method **A**), although the reaction remains faster than without CD (Table 1, lines 3 and 4). This suggests that CD slightly poisons the catalyst. However activation of pyruvate **1** by CD is still dominant leading to an overall acceleration of the hydrogenation. It thus appears that the **CH** mechanism is more efficient than the **MCatH** mechanism in the case of Pt/Al_2O_3.

Concerning hydrogenation of acid **5** and ester **8** in hexane, the reaction proceeds much more slowly in the presence of CD (Table 2) as already observed.[8] When the catalyst is impregnated with CD *before* addition of acid **5** (method **A**) no conversion is observed which

Table 2. Hydrogenation of acid **5** and ester **8**: Pd/Al_2O_3, H_2 (40 bar), 24 h

Conditions[a]	5		8	
	Conv. (%)	ee (%)	Conv. (%)	ee (%)
Without CD	100	–	100	–
5×10^{-3} equiv. CD: **A**	0	–	0	–
5×10^{-3} equiv. CD: **B**	30	21	10	0

[a] [**5**] = [**8**] = 0.3 M. Ester or acid/CD = 100. Ester or acid/catalyst = 100.

indicates that CD strongly poisons the Pd catalyst while it does not activate the substrate. The energy of the double-bond π-electrons in salt **6** is only slightly modified compared to the starting acid **5**, as is the energy of the π-electrons of complex **9** compared to **8**.[16] However, some conversion (30%) is obtained when a mixture of **5** and CD is made *before* addition of the catalyst (method **B**): that is when the salt **6** is formed (as already proposed[8,17]) and prevents the free CD from totally poisoning the catalyst.

A conversion of 10% is obtained in the case of the ester **8** when the ester is mixed with CD *before* addition of the catalyst supporting the presence of a weak association (through an OH···O=C bond between the CD's OH and the carbonyl of ester **8**) as already proposed[18] which only partly prevents CD from poisoning the catalyst. That CD strongly poisons palladium is consistent with the observed decrease in the rate of hydrogenation of pyruvate with Pd/Al_2O_3.[7]

In conclusion, it is reasonable to envisage that, in the case of Pt/hydrogenation of pyruvate, the modifier (CD) is a substrate–catalyst (through formation of the more reactive enol form), accelerates the reaction and poisons only slightly the Pt/catalyst. The possible presence of ee is a consequence of formation of the modifier/enol complex and of the chirality of the modifier.

In the case of Pd/hydrogenation of α,β-unsaturated acid/ester, the modifier (CD) does not activate the substrate but provides the chirality and slows down the reaction by poisoning the Pd/catalyst.

For the design of new modifiers it should be kept in mind that to activate enolizable ketoesters (pyruvate and others) and accelerate the hydrogenation in aprotic solvents, the modifier should have a pKa suitable to provide enough enol and then to liberate the corresponding hydroxy-ester once hydrogenation is over.[20] From the above reasoning, it can also be deducted that acceleration of hydrogenation of α,β-unsaturated acids-(esters), which would imply modification of the energy level of the C=C/π-electrons through association with another molecule, will be most difficult.

Of course, a satisfying modifier must not poison the H_2 catalyst and it is worth noting that CD happens to poison the palladium catalyst more than the platinum catalyst. The last requirement for a good modifier will be, of course, to have 'enough' chirality to induce high enantiomeric excess.

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References

1. Orito, Y.; Imai, S.; Niwa, S.; Nguyen, G. H. *Synth. Org. Chem. Jpn.* **1979**, *37*, 173.
2. Lipkin, D.; Stewart, T. D. *J. Am. Chem. Soc.* **1939**, *61*, 3295.
3. For reviews, see: (a) Izumi, Y. *Adv. Catal.* **1983**, *32*, 215; (b) Blaser, H. U. *Tetrahedron: Asymmetry* **1991**, *2*, 843; (c) Baiker, A. *J. Mol. Catal.* **1997**, *115*, 473; (d) Wells, P. B.; Wilkinson, A. G. *Top. Catal.* **1998**, *5*, 39; (e) Baiker, A. *J. Mol. Catal.* **2000**, *163*, 205.
4. (a) Simons, K. E.; Wang, G.; Heinz, T.; Giger, T.; Mallat, T.; Pfaltz, A.; Baiker, A. *Tetrahedron: Asymmetry* **1995**, *6*, 505; (b) Minder, B.; Schürch, M.; Mallat, T.; Baiker, A.; Heintz, T.; Pfaltz, A. *J. Catal.* **1996**, *160*, 261; (c) Schürch, M.; Heintz, T.; Aeschimann, R.; Mallat, T.; Pfaltz, A.; Baiker, A. *J. Catal.* **1998**, *173*, 187.
5. Blaser, H. U.; Jallet, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675.
6. (a) Blaser, H. U.; Jalett, H. P.; Monti, D. M.; Reber, J. F.; Wehrli, J. T. *Stud. Surf. Sci. Catal.* **1988**, *41*, 153; (b) Garland, M.; Blaser, H. U. *J. Am. Chem. Soc.* **1990**, *112*, 7048.
7. Hall, T. J.; Johnston, P.; Vermeer, W. A. H.; Watson, S. R.; Wells, P. B. *Stud. Surf. Sci. Catal.* **1996**, *101*, 221.
8. Kun, I.; Török, B.; Felföldi, K.; Bartok, M. *Appl. Catal. A* **2000**, *203*, 71.
9. Gertosio, V.; Santini, C. C.; Basset, J. M.; Bayard, F.; Buendia, J.; Vivat, M. *J. Mol. Catal.* **1999**, *142*, 141.
10. Marcilly, C.; Franck, J. P. *Revue de l'IFP* **1984**, *39*, 337–364.
11. The CD-OH group is not considered for anchoring of enolate to CD because it has been shown that replacement of the OH by OMe or OAc does not change the reactivity nor the % ee. See: Blaser, H. U.; Jalett, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675.
12. Because of enolization, the carbonyl of pyruvate esters can only undergo reduction, hydrogenation and addition of phenyl or vinyl Grignards.
13. Ferri, D.; Bürgi, T.; Borszeky, K.; Mallat, T.; Baiker, A. *J. Catal.* **2000**, *193*, 139.
14. Bonello, J. M.; Lambert, R. M.; Künzle, N.; Baiker, A. *J. Am. Chem. Soc.* **2000**, *122*, 9864.
15. (a) Calculations have been carried out using PM3 on a CAChe WorkSystem; (b) Partasarathy, R.; Ohrt, J.; Horeau, A.; Vigneron, J. P.; Kagan, H. *Tetrahedron* **1970**, *26*, 4705.

16. HOMO on C=C (PM3 calculations): salt **6** (CD replaced by Me_3N) = −10.0 eV versus **5** = −10.1 eV and **9** (CD replaced by MeOH) = −10.2 eV versus **8** = −10.0 eV.
17. (a) Borszeky, K.; Mallat, T.; Baiker, A. *Catal. Lett*. **1996**, *41*, 199; (b) Borszeky, K.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3745.
18. Although anchoring by the OH group alone is not sufficient to provide enantioselectivity, it has been shown that OH is probably involved in the substrate/CD interaction. See: Ref. 8.
19. For the absolute configuration of (+)-acid **7**, see: Goering, H. L.; Kimoto, W. I. *J. Am. Chem. Soc*. **1965**, *87*, 1748.
20. Acid-catalyzed enol–keto equilibration of enolizable ketoesters is also well known, as well as deuterium exchange under basic and acidic conditions. See: Vollhardt, K. P. C. *Organic Chemistry*; WH Freeman and Company: New York, 1987.