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Heterogeneous chemo-, regio- and diastereoselective hydrogenation of steroidic alpha-diketone

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Abstract

Supported catalysts, Rh/SiO_2, Ru/SiO_2, Pd/SiO_2, Pt/SiO_2 and Pd/C reduce methyloate of 3α-acetyl-11,12-dioxo-5β-cholan-24-oic acid **1** into the vicinal hydroxyketone 11-oxo,12β-OH **2** in 100% chemo-, regio- and diastereoselectivity at 100% of conversion.

Keywords: Steroid; Chemo-, regio-, diastereoselective hydrogenation; Heterogeneous catalysis

1. Introduction

Enantioselective heterogeneous catalysis is a subject of intense research at the moment. Few heterogeneous catalysts exhibit enantioselectivity [1]. The two reactions that are well known to proceed with high enantiomeric excess are (i) the hydrogenation of β-ketoesters catalysed by nickel modified by tartaric acids [2] and (ii) the hydrogenation of α-ketoesters catalysed by platinum modified by cinchona alkaloids [3]. In the case of the hydrogenation of α-ketoesters, the modifier increases the rate of the reduction. The latter catalyst can hydrogenate enantioselectively the conjugated diketones butane-2,3-dione and hexane-3,4-dione [4].

Two hypothesis are proposed in order to explain the role of the chiral 'modifier'. Either, this chiral 'modifier' is chemisorbed [5] on the metallic surface and induces one mode of adsorption and (or) reaction of the double bond to be hydrogenated (hypothesis 1, Scheme 1a). Or, the chiral 'modifier', A*, is first associated with the prochiral substrate, B, to form a chiral (A–B)* combination. (A–B)* would then adsorb or react on the metallic surface in a stereoselective manner (hypothesis 2, Scheme 1b) [6]. This modifier–substrate combination (A–B)* could be assimilated to a chiral compound leading therefore to a diastereoselective reduction of an

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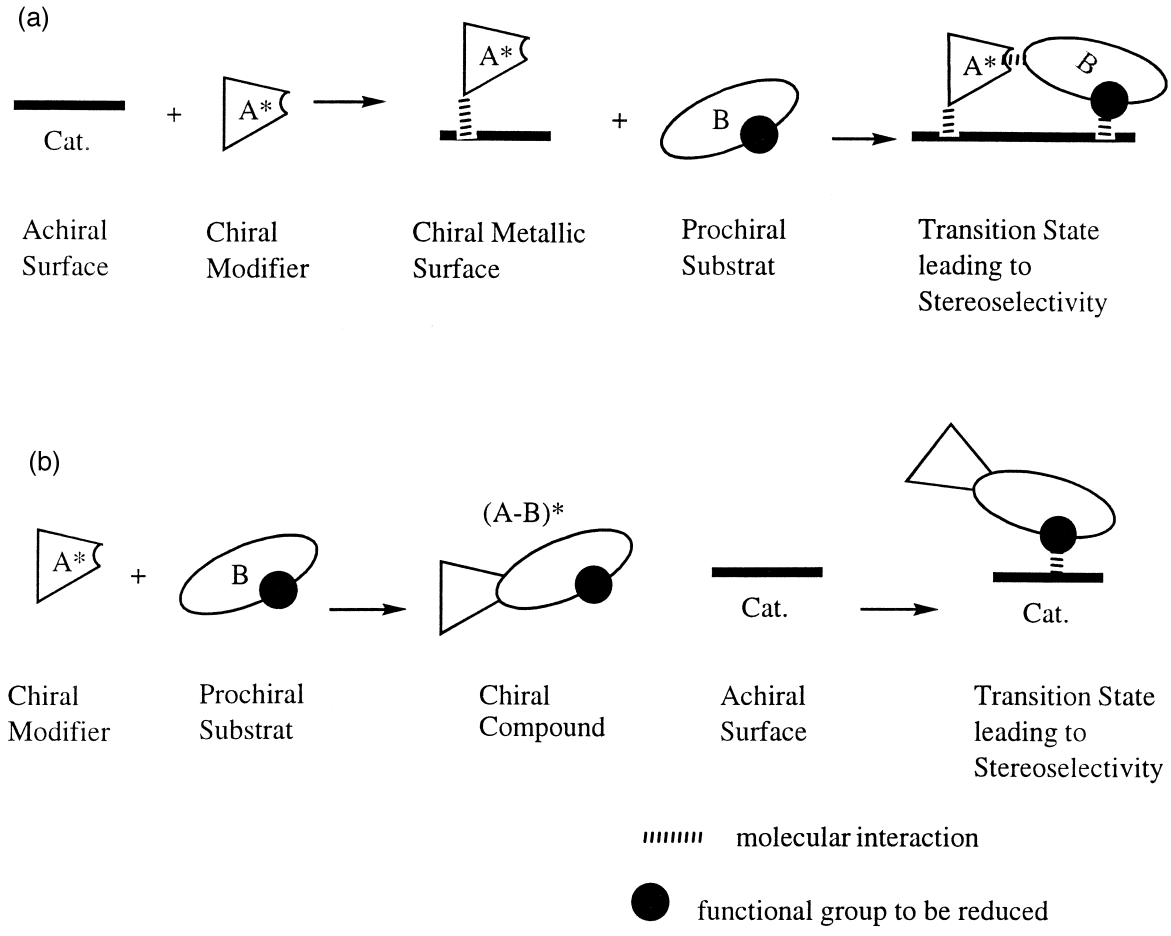
unsaturated chiral species. The difference between these two hypothesis is quite straight forward: in one case the modifier interacts both with the surface and the incoming molecule whereas in the second it is only a single chiral molecule which adsorbs (and or reacts) preferentially on one face of the double bond to be hydrogenated. The consequence in heterogeneous catalysis may be quite different because the choice of the modifiers may be easily governed in the second case by considerations of pure molecular interactions between the prochiral substrate and the modifier.

We wish to report the diastereoselective reduction of a chiral α-diketone with 100% e.d. which supports at least partly the hypothesis 2.

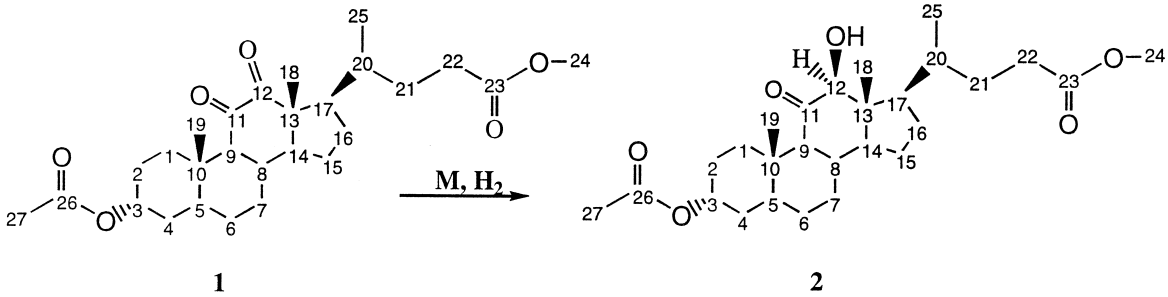
2. Results

With Ru, Rh, Pd, Pt on silica and Pd/C the hydrogenation of methyloate of 3α-acetyl-11,12-dioxo-5β-cholan-24-oic acid **1**, (Scheme 2) a precursor in hydrocortisone synthesis [7] gives a unique compound methyloate of 3α-acetyl-11-oxo-12β-hydroxo-5β-cholan-24-oic acid **2**.

The catalysts have been prepared by classical routes. The results on the catalytic hydrogenation of **1** are given in Table 1 and Fig. 1. Whatever the catalyst, **1** can be hydrogenated with 100% of conversion at 160°C. And **1** was reduced to afford an unique compound **2** isolated in 100% yield (Runs 4–8).



Scheme 1. a: Hypothesis 1. b: Hypothesis 2.



Scheme 2. Hydrogenation of methyloate of 3α-acetyl-11,12-dioxo-5β-cholan-24-oic acid **1** catalysed by supported catalysts.

The structure of this novel steroid **2** was determined by IR analysis and ^{1}H, ^{13}C and bidimensional NMR analysis, .

The comparison of the ^{13}C NMR data of **1** and **2** show a chemoselective hydrogenation of **1** into a α-hydroxyketone **2**. In the ^{13}C NMR spectrum of **2**, the carbonyl carbons C_{11} and C_{12} at δ 208.5 and 205.8 ppm in **1** are replaced by two peaks, one at 211.7 ppm assigned to a carbonyl carbon and other one at 84.1 ppm characteristic of a carbon linked to a hydroxyl group. The presence of a new hydroxyl group is also supported by the appearance in the IR spectrum of a broad band ν(OH) at 3570 cm^{-1}. In the ^{1}H NMR spectrum of **2**, an AB system is found at 3.9 ppm consistent with a CH(OH) either at C_{12} or C_{11}. The methyl proton of **1** in the 18 position are shifted in **2** from 0.9 to 0.5 ppm. The resonance of the ester carbonyl carbons at the C_{23} and C_{26} positions were still present. These data were consistent with the presence in **2** of one ketone group, one hydroxyl group and two esters groups.

2D NMR experiments (^{1}H–^{13}C shift correlation) of **1** indicate a correlation between the resonance at 205.8 ppm and the methyl proton at the 18 position and a correlation between the resonance at 208.4 ppm and the proton at the 9 position. Thus, the signals at δ 208.5 and 205.8 ppm have been assigned to carbonyl carbons C_{11} and C_{12} respectively. The same kind of 2D NMR experiments of **2** indicate that the remaining carbonyl was correlated with the proton at the 9 position. Therefore, there is a regioselective hydrogenation of **1** into a 12-OH,11-one α-hydroxyketone.

A NOESY experiment on **2** indicated a strong through-space interaction between the methyl proton at the 18 position and the AB system centred at 3.9 ppm assigned to the $C_{12}H$(OH)

Table 1
Hydrogenation of **1** catalysed by supported catalysts[a]

Run	Catalysts	Amount of catalyst[b] (mg)	Amount of substrate (mg)	Temperature (°C)	Conversion (%)	Time (h)
1	Rh/SiO_2	74.1	201	25	0	24
2	Rh/SiO_2	74.1	201	60	45	24
3	Rh/SiO_2	74.1	201	120	55	24
4	Rh/SiO_2	74.9	201	160	98	24
5	Pd/SiO_2	45.2	200.7	160	100	15
6	Ru/SiO_2	130.5	199.7	160	100	8
7	Pt/SiO_2	74.9	201	160	100	5
8	Pd/C	61.9	202.4	160	100	6

[a]Reaction conditions: substrate **1** (42 mmol), solvent: ethyl acetate (25 ml), $P_{H_2} = 80$ bar.
[b]The amount of catalyst was always adjusted so that the molar ratio substrate **1**/number of metal surface atoms = 50.

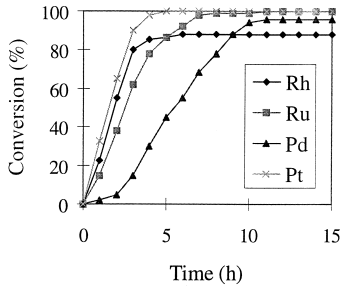


Fig. 1. Effect of the nature of the catalyst on rate of hydrogenation.

protons at the 12 position. When the NOESY experiment was performed in presence of D_2O, the group $C_{12}H(OD)$ gives a singlet; besides the NOESY experiment shows the methyl proton at the 18 position has no interaction through space with the $C_{12}(H)$ proton. The HO–C_{12} and Me–C_{18} are thus located on the same face of the molecule. So, there was a stereoselective hydrogenation of **1** into the 12β-OH,11-one α-hydroxyketone **2**, Scheme 2.

3. Discussion and conclusion

Molecular modelling was used to see if there is a possible correlation between the structure of **1** and the observed regio and stereoselectivities. The more stable conformation of **1** was determined using a semi-empirical method (PM3) [14]. In this low energy conformation, the C_{12}-ketone is on the α face and the C_{11}-ketone on the β face with a dihedral angle of 54° between these two functions. The adsorption via the ketones of this conformer on an idealised Pt(111) face was optimised using the molecular mechanics Tripos force field [15]. In the conformation showing the lowest energy, only the C_{12}-ketone could be in contact with the metallic surface. This is due to the steric repulsive interaction between the two methyl C_{18}, C_{19} and the metallic surface which prevent the adsorption of the C_{11} ketone. Concerning the high stereoselectivity in the hydrogenation of the C_{12}-ketone, the same steric repulsion by the two methyl C_{18}, C_{19} prevent the approach of the ketone by the β face. Thus this molecular modelling approach explains in a very rough manner the regio and stereoselectivity.

1 is therefore quantitatively hydrogenated into a unique compound **2** with 100% of chemo-, regio- and stereoselectivity. This high selectivity which is observed with several metal is likely to be due to steric control during the approach of **1** towards metallic surface.

4. Experimental

Substrate **1** was furnished By Society H.M.R. Ethyl acetate was distilled over CaO degassed and stored over zeolite under argon. HPLC analysis was performed on the following equipment (Water): pump M-45 ultraviolet detector 480, Lichrocart Hypersil ODS column (Roussel Uclaf), acetonitrile/water (7:3 v/v). The NMR spectra were recorded on a Brucker 300 MHz

4.1. Catalysts

The catalysts, Rh/SiO_2, Pd/SiO_2, Pt/SiO_2 grafted onto silica by cationic exchange [8], Ru/SiO_2 obtained from the surface organometallic species $(\equiv Si–O)(H)Ru_3(CO)_{10}$ [9] and commercial Pd/C, were characterised by elementary analysis, chemisorption measurements and CTEM analysis. Ru/SiO_2 {%Ru = 1.37; $\mathscr{D}$ = 60%}; Rh/SiO_2 {%Rh = 1.26; $\mathscr{D}$ = 96%} [10]; Pt/SiO_2 {%Pt = 1.46; $\mathscr{D}$ = 47%} [11]; Pd/SiO_2 {%Pd = 2.3; $\mathscr{D}$ = 90%}; Pd/C {%Pd = 5; $\mathscr{D}$ = 26%} [12,13].

4.2. Catalytic runs

Before use the catalysts are reduced in flowing H_2 at 350°C overnight, and introduced at 25°C under argon flow into the autoclave. The latter was previously loaded with substrate **1** (42 mmol) and ethyl acetate (25 ml). The molar ratio $\mathbf{1}/M_{surface}$ was for all experiments about 50/1. Then the H_2 pressure was increased and

maintained at 80 bar. After reaction time indicated in Table 1, the autoclave was cooled to room temperature and the pressure released. The reactive medium was filtered and analysed by HPLC and NMR spectroscopy.

4.3. Characteristic nmr data ($CDCl_3$)

^{1}H NMR data of **1** ($CDCl_3$, 300 MHz, δ ppm): 0.7 [d, 3H, 7Hz] δMe–C_{25}; 0.9 [s, 3H] δMe–C_{18}; 1.2 [s, 3H] δMe–C_{19}; 1.9 [s, 3H] δMe–C_{27}; 3.6 [s, 3H] δMe–C_{24}; 4.6 [m, 1H] δH–C_3.

^{1}H NMR data of **2** ($CDCl_3$, 300 MHz, δppm): 0.5 [s, 3H] δMe–C_{18}; 1.0, [d, 3H, 7Hz] δMe–C_{25}; 1.2 [s, 3H] δMe–C_{19}; 1.9 [s, 3H] δMe–C_{27}; 3.7 [s, 3H] δMe–C_{24}; 3.9 [AB, 2H] δH–C_{12} and δHO–C_{12}; 4.7 [m, 1H] δH–C_3.

^{13}C NMR data of **1** ($CDCl_3$, 75.5 MHz, δppm): 208.5, δC_{11}; 205.8, δC_{12}; 174.3, δC_{23}; 170.4, δC_{26}.

^{13}C NMR data of **2**($CDCl_3$, 75.5 MHz, δppm): 211.7, δC_{11}; 174.6, δC_{23}; 170.4, δC_{26}; 84.1, δC_{12}.

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