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Chemo-, Regio-, and Diastereoselective Hydrogenation of Oxopromegestone into Trimegestone over Supported Platinoids: Effects of the Transition Metal, Support Nature, Tin Additives, and Modifiers

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The selective hydrogenation of oxopromegestone (17α-methyl-17β-(1,2-dioxopropyl)-estra-4,9-dien-3-one), 1, into Trimegestone (17α-methyl-17β-(2(*S*)-hydroxy-1-oxopropyl)-estra-4,9-dien-3-one), 2, was carried out on various monometallic catalysts. The order of activity, Pd > Rh > Pt > Ir > Os, was almost opposite that of the chemoselectivity (selective hydrogenation of the carbonyl versus the internal olefinic double bond), Os > Ir > Pt = Pd > Rh. No metal gave any required diastereoselectivity (selective formation of the 21(*S*)-OH alcohol). However, silica-supported rhodium, palladium, and platinum exhibited 100% diastereomer excess (d.e.) for the hydrogenation of the C_3 carbonyl group. Pt/SiO_2 catalyst exhibited a low chemoselectivity (24%), but its TON activity was relatively high (42×10^{-3} s^{-1}). $Pt_s\{Sn\}_n/SiO_2$ catalysts, prepared by the interaction of $Sn(CH_3)_4$ with reduced Pt/SiO_2 under H_2 at room temperature, exhibited a significant increase of chemoselectivity compared to Pt/SiO_2, but still a low diastereoselectivity to the desired 21(*S*)-OH unsaturated ketoalcohol, 2. In parallel, the d.e. for the hydrogenation of the C_3 carbonyl group decreased from 100% to 34%. The addition of (−)cinchonidine and hydrocinchonidine on the platinum–tin catalysts sharply increased the d.e. in favor of the 21(*S*)-OH unsaturated ketoalcohol to 70% without changing the chemoselectivity.

Key Words: **oxopromegestone; Trimegestone; diastereoselective hydrogenation; chemoselective hydrogenation; platinum–tin catalyst; hydro(−)cinchonidine modifier.**

1. INTRODUCTION

Trimegestone, **2** (17α-methyl-17β-(2(*S*)-hydroxy-1-oxopropyl)-estra-4,9-dien-3-one), is a new progestomimetic molecule developed for the treatment of postmenopausal diseases. On an industrial scale, **2** is obtained by a bioreduction process developed by Hoechst Marion Roussel (HMR) with almost 100% chemo-, regio-, and diastereoselectivity from oxopromegestone (17α-methyl-17β-(1,2-dioxopropyl)-estra-4,9-dien-3-one), **1** (1, 2). The main drawback of this bioreduction is the high dilution which requires the use of rather huge reactors. This difficulty opens the field for alternative processes. We report here the preparation and use of supported mono- or bimetallic catalysts in the selective hydrogenation of oxopromegestone, **1**, into Trimegestone, **2** (Scheme 1).

To achieve this aim it was necessary to solve simultaneously three problems of chemo-, regio-, and diastereoselectivity in the hydrogenation of **1** by supported metals catalysts. Selective hydrogenation of α,β unsaturated ketones by supported group VIII metals into the corresponding unsaturated alcohols was considered in a recent review (3). There is no example in the literature of selective hydrogenation of an **unsaturated polyketone** into the corresponding **unsaturated ketoalcohols**. We report here the first example of such a selective reduction.

2. EXPERIMENTAL

2.1. Origin of the Organic Compounds

Oxopromegestone and isomerically pure hydrogenated products **2–7** (Scheme 2) were provided by HMR. (−)Cinchonidine (CD), (+)cinchonine (CN), hydro(−) cinchonidine (HCD), quinuclidine, quinoline, quinidine (QD), quinine (QN), and tetramethylstannane purchased from Aldrich were used without further purification. Ethyl acetate was purified by distillation as described in the literature (4).

2.2. Catalyst Preparation and Characterisation

2.2.1. Monometallic catalysts. The commercial Pd/C (5.0%) catalyst was purchased from Aldrich. Degussa Aerosil 200 silica with a surface area of about 200 m^2/g was

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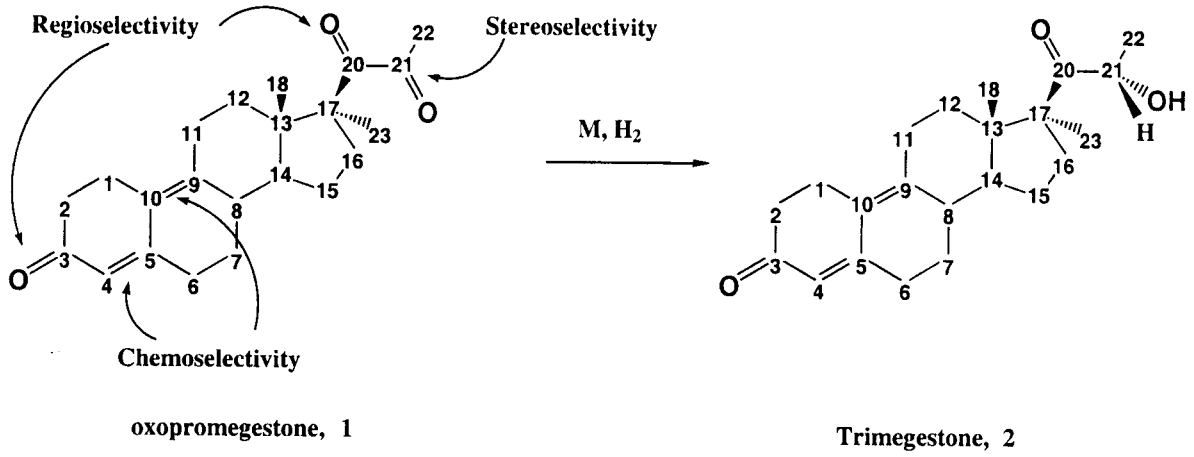


oxopromegestone, 1 Trimegestone, 2

SCHEME 1

used as the support for Rh, Os, Ir, and Pt. It was calcined under an air flow at 500°C before impregnation. Al_2O_3, with a surface area of 100 m^2/g, ZrO_2 with a surface area of 49 m^2/g, and TiO_2, P25™, with a surface area of 50 m^2/g were obtained from Degussa.

The Os/SiO_2 (1.0%) catalyst was prepared by treatment of the dehydroxylated silica with $Os_3(CO)_{12}$ in dichloromethane solution under an argon atmosphere (5). The Rh/SiO_2 (1.4%) and Pt/SiO_2 (1.3%) catalysts were obtained by ionic exchange from $[Rh(NH_3)_5]^+(Cl^-)$ and $[Pt(NH_3)_4]^{2+}(OH^-)_2$ respectively, by surface protons of silica (6, 7). The Ir/SiO_2 (1.5%) catalyst was obtained by impregnation of silica with $Ir(acac)_3$ in toluene. The Pt/ZrO_2 (2.0%) catalyst was obtained by impregnation of zirconia with $Pt(acac)_2$. The Rh/Al_2O_3 (1.8%) and Rh/TiO_2 (1.4%) catalysts were obtained by reduction with H_2 of $(M–O)Rh(\eta^3\text{-}C_3H_5)_2$ (M = Al, Ti) (8).

All the supported metallic precursors described above were washed, dried, and decomposed by calcination at 400°C under a stream of nitrogen/oxygen mixture (5/1). All monometallic catalysts except Pd/C were reduced under flowing H_2 at 350°C overnight before the hydrogenation reaction took place.

The dispersion of the supported metals, expressed as the fraction of surface atoms (M_s/M_t), was calculated from H_2 chemisorption data, obtained in a volumetric apparatus, Pd (9, 10), Pt (11–14), and Rh (6). According to transmission electron microscopy the average surface metal particle size in Rh/SiO_2 and Ir/SiO_2 catalysts was 1 and 3 nm, respectively; this calculation was in good agreement with chemisorption data.

2.2.2. Bimetallic catalyst $Pt_s\{Sn\}_n/SiO_2$. The preparation of the bimetallic catalysts has already been described (7). Pt/SiO_2 was reduced at 350°C under hydrogen for 4 h. At room temperature, the hydrogen flow was replaced by argon, and then the catalyst was introduced into a Schlenk tube. The desired amount of tetramethylstannane and 10 ml of *n*-heptane were added. The reaction medium was stirred at room temperature for 22 h under hydrogen. The complete hydrogenolysis reaction was proved by GC analysis of evolved methane (capillary column, KCl/Al_2O_3, 130°C). After several washings with *n*-heptane, the solid was kept under dynamic vacuum and 10^{-4} Torr (1 Torr = 1.33 N/m^2) at 50°C for 1 h to eliminate all physisorbed tetramethylstannane. The catalyst was then covered with 10 ml of ethyl acetate and this suspension was introduced into the autoclave under argon.

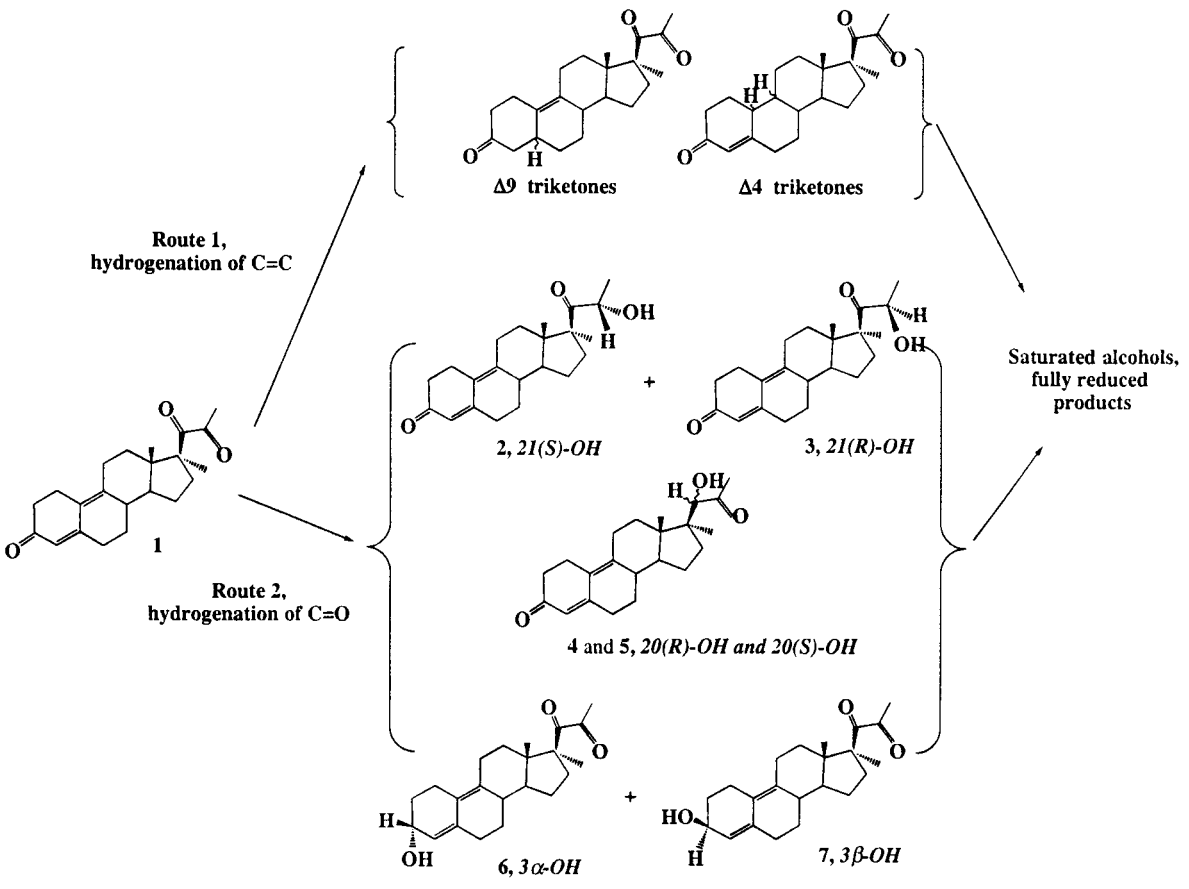
Elemental analysis performed on the bimetallic catalyst before and after the catalytic run showed no decrease in the Sn% and gave the number, n, of fixed tin atoms by surface platinum atoms, $n = Sn/Pt_s$. These catalysts are described as $Pt_s\{Sn\}_n/SiO_2$.

2.3. Catalytic Tests of Oxopromegestone Hydrogenation

The hydrogenation was carried out either under 1 atm of H_2 in a Schlenk tube, or at 80 atm (1 atm = 0.1 MPa) in a Parr 4560 minireactor, fitted with a mechanical stirred. In a usual run, 0.4 g of oxopromegestone, **1**, were dissolved into 50 ml of ethyl acetate under argon. The thin powder of reduced monometallic or dried platinum–tin catalyst was then introduced into the Schlenk tube or autoclave under an argon flow.

Monitoring of the reaction and analysis were carried out by HPLC {column: symmetry C18, 5 μm, l = 25 cm; d = 4.6 mm; eluent: acetonitrile–water 70/30 (v/v), flow rate: 1 ml/mn; detection: UV 210 nm}.

The selectivities were calculated at 50% conversion, a value at which the overreduction products could be neglected (i.e., products in which more than one keto or olefin group is reduced). The numbers in Tables 1–5 are the percentages of each product in the crude reaction mixture calculated by HPLC assay with respect to a pure sample; e.g.,



SCHEME 2

in Table 1, the Os-catalysed reduction gave at 50% conversion 12% Trimegestone, **2**, 12% 21(*R*)-OH, **3**, 4% 20-OH, **4** and **5**, and 66% 3-OH, **6** and **7**. The missing 6% is compatible with the overall experimental error and not identified, fully reduced products. The Rh-catalysed reaction gave only 12% alcohols; the main pathway was in this case the hydrogenation of the olefinic double bonds.

3. RESULTS AND DISCUSSION

Hydrogenation of the initial unsaturated triketone, **1**, can take place at five different sites, two olefins and three ketones at C_3[2], C_{20}, and C_{21} and in each case from two sides, α/β (α = cis to methyl group at C_{17}) for bonds located on the steroid skeleton, or Si/Re for the two ketones C_{20} and C_{21} on the side chain. If the carbon–carbon double bonds are reduced first (Scheme 2, route 1), partially saturated triketones are formed. If the ketone groups are reduced first (Scheme 2, route 2), the unsaturated hydroxyketones, **2**–**7**, are obtained. Then, both kinds of compounds can be further reduced into partially or fully saturated hydroxyketones, and even fully reduced into the saturated alcohols (Scheme 2).

The initial unsaturated ketoalcohols, which can be produced by route 2, are the three pairs of diastereomers: 21(*S*)-OH, **2** (Trimegestone), and 21(*R*)-OH, **3**, 20(*S*)-OH and 20(*R*)-OH, **4** and **5**, 3α-OH, **6**, and 3β-OH, **7** (Scheme 2).

In this work chemoselectivity refers to the reduction of keto groups vs all possible reduced products, regioselectivity to the reduction of the ketone at C_{21} vs all possible reduced products, and diastereoselectivity to the Si/Re reduction at C_{21} and α/β reduction at C_3.

If S(**i**) is the selectivity in the compound **i**, i.e., the ratio between the amount of desired product and the amount of substrate consumed, the chemoselectivity ($S_{C=O}$), regioselectivity (RS), and diastereomer excess (d.e.) will be defined by the following equations:

$$(S_{C=O}) = S(\mathbf{2}) + S(\mathbf{3}) + S(\mathbf{4}) + S(\mathbf{5}) + S(\mathbf{6}) + S(\mathbf{7}); \quad [1]$$

$$RS = S(\mathbf{2}) + S(\mathbf{3}); \quad [2]$$

$$\text{d.e. } C_{21} = 100[S(\mathbf{2}) - S(\mathbf{3})]/[S(\mathbf{2}) + S(\mathbf{3})]; \quad [3]$$

$$\text{d.e. } C_3 = 100[S(\mathbf{7}) - S(\mathbf{6})]/[S(\mathbf{7}) + S(\mathbf{6})]. \quad [4]$$

[2] Ketone at C_3 is more reactive than the other keto groups at any position on steroid (15).

TABLE 1

Monometallic Catalysts: Influence of the Metal Nature on the Catalytic Properties in the Hydrogenation of Oxopromegestone at Room Temperature, $S(\mathbf{i})$ = Selectivity, mol% for Compound i

Cat.	M, wt%	P, atm	Dispertion, M_s/M_t	TON, $\times 10^3$, s^{-1}	$S(\mathbf{2})$	$S(\mathbf{3})$	$S(\mathbf{4},\mathbf{5})$	$S(\mathbf{6})$	$S(\mathbf{7})$	$S_{C=O}$	d.e. C_{21}	d.e. C_3
Pd[a]	5.0	1	0.25	252	0	0	0	0	26	26	—	100
Rh	1.6	1	0.80	58	0	0	0	0	12	12	—	100
Pt	1.3	1	0.55	42	<1	3	0	0	21	24	?	100
Ir	1.5	80	0.30	1.2	4	4	4	13	25	50	0	32
Os	1.0	80	0.90	0.2	12	12	4	22	44	94	0	33

[a] Pd on carbon, all others metals are supported on silica.

3.1. Oxopromegestone Hydrogenation on Different Metals

The activities and the selectivities of different metals in the hydrogenation of oxopromegestone, **1**, are reported in Table 1. Regarding the activity, the most active metals were the supported Rh and Pd catalysts, the less active being Ir and Os. The difference of TON between the most active Pd/C catalyst and the least active Os/SiO_2 catalyst is more than 3 orders of magnitude. The most active metals were tested at 1 atm. The order of TON activity of supported platinum metals is Pd > Rh > Pt > Ir > Os.

Regarding the chemoselectivity, the monometallic catalysts could be divided into two groups: (i) With the Pt, Pd, and Rh catalysts, the hydrogenation of the carbon–carbon double bonds was favoured (route 1), affording mainly the $\Delta 9,\Delta 4$ triketones and/or full reduction products (Scheme 2). As no sample of these products of C=C reduction was available, their actual structure is unknown and their amount was deduced from the value of the chemoselectivity ($S_{C=O}$). With these catalysts, the 3β-OH, **7**, was the only known alcohol formed. Besides **7**, a small quantity of Trimegestone, **2**, was produced over Pt/SiO_2, preventing d.e. C_{21} calculation. (ii) With Ir and Os catalysts, the reduction of keto groups was favoured (route 2). In particular, Os exhibited a total chemoselectivity, but a low regio- and stereoselectivity in C_{21} (d.e. = 0%) and in C_3 (d.e. = 33%) reduction. With these catalysts, the diastereoselectivity in C_3 did not change with conversion.

The order of chemoselectivity ($S_{C=O}$) of supported metals was almost opposite to their order of activities: Os > Ir > Pt ≅ Pd > Rh. This result is close to the literature data for the hydrogenation of α,β unsaturated aldehydes and ketones into the corresponding unsaturated alcohols (3). The trends are the following: Os and Ir are selective, Rh and Pd unselective, and Ru and Pt moderately selective (16–18).

The order of activity and selectivities can be explained (i) by a steric control governed by the geometry of the steroid and (ii) by the intrinsic properties of the catalyst.

(i) The carbonyl group at C_3 of oxopromegestone, **1**, and the C_4=C_5 and C_{10}=C_9 double bonds of the steroid skeleton are conjugated, leading to a flat part of the molecule, **1**. The 100% diastereoselectivity of supported Rh, Pd, and Pt with respect to 3β-OH, **7**, may be explained by the chirality of oxopromegestone and the preferable α-side multicenter chemisorption of this flat part on the several neighbouring surface atoms of these metals. In this case, as proposed in the diastereoselective hydrogenation of a steroidic α-diketone (19), the order of activities and selectivities are also governed by the geometry of the steroid.

(ii) According to theoretical calculations (20), activities and selectivities can be explained by the value of the band width of *d* bands of metal catalysts. The larger this band width, the stronger the repulsive interaction of the metal with the C=C bond and thus the lower the probability of chemisorption. The bandwidth of *d* bands of the metals increases in the series Pd < Pt < Ir ≅ Os, which accounts for the observed selectivities (21). In this case, the nature of the catalyst seems to be the crucial factor in the observed activity and selectivities.

According to this hypothesis, with Os and Ir, the chemisorption via the C=C bond is expected to be weak. Consequently, the substrate was chemisorpted by keto groups. So the less sterically hindered ketones are reduced preferentially C_3 (66%) > C_{21} (24%) > C_{20} (4%) with a low stereoselectivity.

The effect of the support nature is given in Table 2. The best activity and diastereoselectivity at C_3 were obtained for supported Rh and Pt metals on silica. With TiO_2- and ZrO_2-supported metals, low activity and low diastereoselectivity at C_3 were observed. Morever, at a high reduction temperature (HRT) of Pt/ ZrO_2 these effects were increased. In contrast, the chemoselectivity is increased ($S_{C=O}$ = 51%). All these results can be explained by strong metal-supported interaction (SMSI) which is the decoration of the metals surface by carrier suboxides (22). These ZrO_x species decrease the multiplicity of active sites (the number of neighbouring surfaces atoms) and the probability of the

TABLE 2

Effect of the Support on Catalytic Properties of Rh and Pt at $P(H_2) = 1$ atm and Room Temperature, S(i) = Selectivity, mol% for Compound i

Cat.	M, wt%	Dispertion, M_s/M_t	TON, $\times 10^3$, s^{-1}	S(**2**)	S(**3**)	S(**4**, **5**)	S(**6**)	S(**7**)	d.e. C_3
Rh/Al_2O_3	1.8	0.9	21	0	0	0	0	30	100
Rh/SiO_2	1.6	0.8	58	0	0	0	0	12	100
Rh/TiO_2	1.4	0.9	23	0	0	0	8	10	11
Pt/SiO_2	1.3	0.55	42	<1	3	0	0	21	100
Pt/Al_2O_3	0.5	0.9	9	0	0	0	0	7	100
Pt/ZrO_2	2.0	0.2	12	2	3	2	3	13	62
Pt/ZrO_2^*	2.0	0.2	2	10	10	2	7	22	52

[a] Catalyst reduced at 800°C.

α-side multicenter chemisorption of oxopromegestone. Sequentially, the activity and 3β-OH diastereoselectivity is decreased.

3.2. *Effect of Sn on Pt/SiO_2 Properties*

The selectivity and activity of several metals such as Ni, Ru, Rh, Pd, Ir, and Pt can be strongly modified by interaction with organometallic compounds such as R_4Sn (23). In particular, the presence of Sn alkyl fragments or Sn adatoms on the surface of Rh completely reversed the chemoselectivity of this metal in the hydrogenation of α,β unsaturated aldehydes (24) and of aromatic ketones (25).

Various $Pt_s\{Sn\}_n/SiO_2$ catalysts were prepared by selective hydrogenolysis of $Sn(CH_3)_4$ in *n*-heptane solution with a reduced Pt/SiO_2 catalyst. The TON activity was calculated in the hypothesis that the platinum dispersion does not change after tin modification at room temperature. The activities and selectivities of these $Pt_s\{Sn\}_n/SiO_2$ catalysts of different compositions are reported in Table 3.

Formation of Pt–Sn bonds induced a decrease in the catalytic activity of platinum, but increased its chemoselectivity. This is a general observation made with several catalytic reactions carried out with $Pt_s\{Sn\}_n$ catalysts (23, 25). Tin additives reduced the TON activity of Pt/SiO_2 by ≈1 order of magnitude, but increased its chemoselectivity ($S_{C=O}$) from 24% to 60–90%. Besides, as the percentage of hydrogenation at C_{20} and C_3 was almost constant (**4** and **5** and **6** and **7**), the presence of Sn adatoms favours the hydrogenation of **1** into **2** and **3** and the regioselectivity (*RS*) reaches 60%. At the same time, the stereoselectivity at C_3 decreased and remained very low at C_{21}; the variation of the latter is comparable to the accuracy of HPLC analysis (Table 3). Note that the catalyst $Pt_s\{Sn\}_{0.5}/SiO_2$ represents the best compromise between chemoselectivity ($S_{C=O} = 89\%$), regioselectivity ($RS = 53\%$), stereoselectivity (d.e. $C_{21} = 14\%$), and activity.

All these results were obtained at 50% conversion. More precise data could be obtained by following the kinetics of the reaction and the evolution of conversion and selectivity with time. Typical data are given in Fig. 1. These kinetic data can tell us what the primary and secondary products are. With $Pt_s\{Sn\}_n/SiO_2$ ($n = 0.35$–0.63), the diastereoselectivity at C_3 and at C_{21} did not vary with time and conversion, but the chemoselectivity decreased after 40% conversion (Fig. 1). This decrease of chemoselectivity is due to the secondary reduction of unsaturated hydroxyketones, as proposed in Scheme 2. The fact that the diastereoselectivity at C_3 and at C_{21} did not change with conversion means that there was no difference in the rate of further reduction of the two diastereomers, **2** and **3**, in contrast with results obtained with butane-2,3-dione (26).

The ratio of tin introduced by the surface atom of Pt varied from 0 to 0.63. At these values we have already shown

TABLE 3

Influence of the Sn/Pt_s Atomic Ratio (n) on the Catalytic Properties of $Pt_s\{Sn^0\}_n/SiO_2$ Catalysts in the Hydrogenation of Oxopromegestone at 25°C and $P(H_2) = 1$ atm, S(i) = Selectivity, mol% for Compound i

$\{Sn\}_n/Pt_s$, n	TON, $\times 10^3$, s^{-1}	S(**2**)	S(**3**)	S(**4**, **5**)	S(**6**)	S(**7**)	d.e. C_3	$S_{C=O}$	*RS*	d.e. C_{21}
0	42.0	<1	3	0	0	21	100	24	<4	?
0.35	6.8	16	14	8	5	22	63	65	30	8
0.44	6	21	19	10	6	17	62	73	40	5
0.5	4.2	30	23	11	6	19	52	89	53	13
0.56	2.3	28	28	10	7	15	36	88	56	0
0.63	1.2	28	33	11	7	14	34	93	61	−8

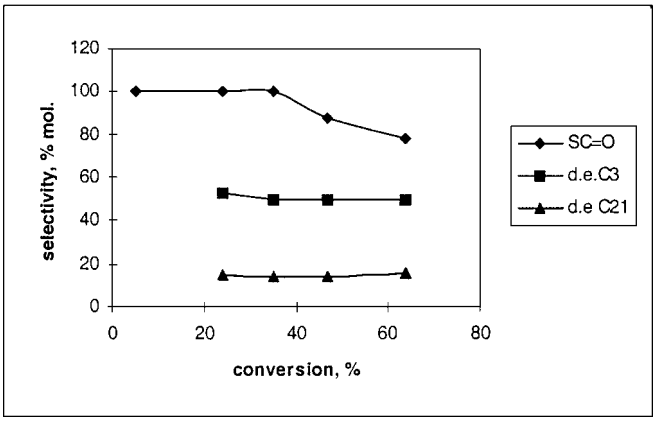
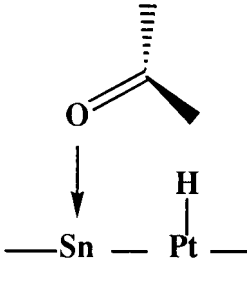


FIG. 1. Variation of the chemoselectivity and diastereoselectivity at C_3 and at C_{21} with the conversion in the hydrogenation of oxopromegestone at 25°C and $P(H_2) = 1$ atm on catalyst $Pt_s\{Sn\}_{0.5}/SiO_2$.

that all tin–carbon bonds of $SnMe_4$ were hydrogenolysed (27). So, the surface of platinum is modified by zerovalent tin adatoms (28, 29) which are likely located on specific crystallographic sites at the surface of the metallic particle.

As already reported in the literature (3), the chemoselectivity of Pt in the hydrogenation of unsaturated aldehydes into unsaturated alcohol is improved by modification with tin adatoms. The enhancement of chemoselectivity could be due to two kinds of electronic modifications of the surface: (i) The oxophilic tin could favour the coordination of the keto group in an η^1 mode (Scheme 3). (ii) The formation of Pt–Sn bonds change the charge on Pt and thus induce a weaker adsorption of the C=C bond on platinum (less back donation) (20, 30, 32). For instance, the heat of adsorption of the ethylene decreases from 23.3 kcal/mol with Pt/SiO_2 to 16.6 kcal/mol with $PtSn/SiO_2$ (31).

Another explanation can be proposed by considering that tin adatoms are inactive. Their presence on the surface could just prevent the adsorption of the multifunctional molecule to Pt via its π-electrons system, as proposed for Pt modified with bismuth adatoms (33, 34). Bismuth has a very small electronic effect on Pt and with a ratio of $Bi/Pt_s = 0.25$, ethylene and benzene adsorption and hydrogenation were suppressed, which require respectively an ensemble of four and six free adjacent Pt atoms. The same was observed with $Sn/Pt_s = 0.25$. In the selective reduction of aromatic ketones, the hydrogenation of the aromatic ring could be suppressed, when $Rh_s\{Sn\}_{0.3}/SiO_2$ was used as the catalyst instead of Rh_s/SiO_2 (25). So it is very reasonable to conclude that Sn can acts as a site blocker in the adsorption of the conjugated C=C bonds. The hydrogenation of a carbonyl function via a η^1 mode is less sterically demanding than that of an olefinic compound.



SCHEME 3

Consequently, (i) the low diastereoselectivity at C_3 can be explained, again, in this case by a less strong chemisorption of the α side, like in the case of Pt/ZrO_2, Rh/TiO_2, and Os/SiO_2, and (ii) the hydrogenation of a carbonyl function via an η^1 mode, less sterically demanding than that of an olefinic compound, is favoured. But the high C_3 regioselectivity is not observed, as in the case of Ir and Os catalysts. This means that the C=O reduction is controlled not only by the sterical factor but also by the different chemical nature of the three carbonyl groups and different electronic properties of modified Pt.

3.3. Influence of Modifiers on the Properties of $Pt_s\{Sn\}_{0.5}/SiO_2$

As both the chemoselectivity and regioselectivity could be improved, but not sufficiently, by the use of $Pt_s\{Sn\}_{0.5}/SiO_2$ catalyst, various factors which could enhance the stereoselectivity at C_{21} were studied. With supported Pt/Al_2O_3, enantioselective hydrogenation of α-diketones is possible with chiral modifiers such as (−)cinchonidine and hydro(−)cinchonidine (26, 35). As oxopromegestone is itself a chiral substrate, a chiral modifier could enhance the diastereoselectivity of the reduction, a concept already known as double asymmetric induction (36). We first used the alkaloid (−)cinchonidine (CD) for the modification of the $Pt_s\{Sn\}_{0.5}/SiO_2$ catalyst.

3.3.1. (−)Cinchonidine(CD). In the presence of CD and independent of the reaction conditions, the TON activity was lower than that in the absence of CD (Fig. 2). This result is opposite to the strong increase in the reaction rate usually observed with cinchona alkaloid modified supported platinum (37). Selectivity to **6** and **7** was decreased. The diastereomer excess at C_{21} and the chemoselectivity were improved when the CD/Pt_s ratio was increased (Fig. 2). This effect was enhanced at high H_2 pressure and low reaction temperature (Table 4).

As with the unmodified $Pt_s\{Sn\}_{0.5}/SiO_2$ catalyst, in the presence of CD the diastereoselectivity at C_{21} did not depend on the conversion, and the chemoselectivity decreased with conversion (Fig. 3). Also in this case, there was no difference in the rate of further reduction of the different diastereomers, **2** and **3**.

At room temperature, in the presence of cinchonidine, the highest diastereomeric excess (d.e.) of 63% for the 21(*S*)-OH, **2**, was obtained with the $Pt_s\{Sn\}_{0.5}/SiO_2$ catalyst (Table 4).

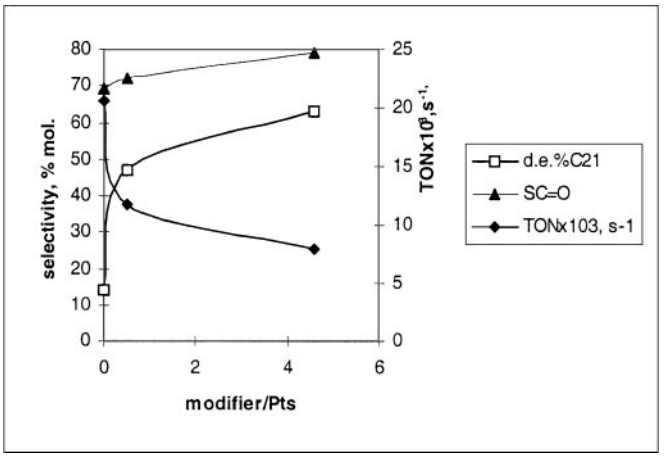


FIG. 2. Influence of the ratio modifier/Pt_s on chemoselectivity and diastereoselectivity at C_{21}, and activity in the oxopromegestone, **1**, hydrogenation at room temperature, $P(H_2) = 80$ atm on catalyst $Pt_s\{Sn\}_{0.5}/SiO_2$ modified by (−)cinchonidine (CD).

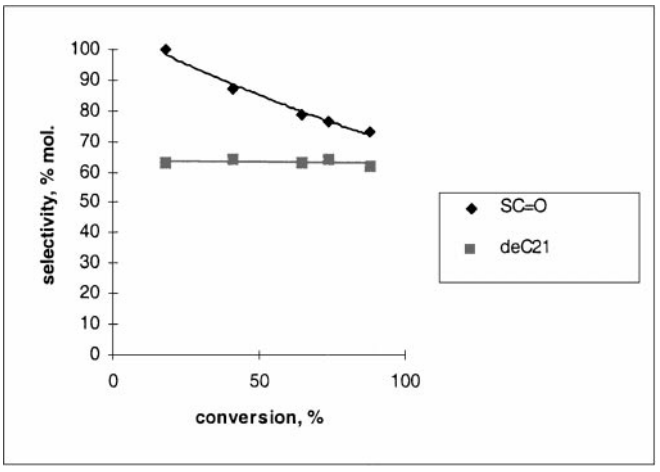


FIG. 3. Dependence of the chemoselectivity and diastereoselectivity at C_{21} from the conversion in the oxopromegestone, **1**, hydrogenation at 25°C, $P(H_2) = 80$ atm with catalyst $Pt_s\{Sn\}_{0.5}/SiO_2$ modified by (−)cinchonidine (CD), CD/$Pt_s = 4.6$, and CD/(**1**) = 0.028.

3.3.2. Influence of other modifiers. The effects of the nature of other modifiers, such as (+)-cinchonine, hydro(−) cinchonidine, quinuclidine, quinoline, quinidine, and quinine on the catalytic properties of $Pt_s\{Sn\}_{0.5}/SiO_2$ catalysts in the oxopromegestone hydrogenation were studied as well (Scheme 4).

Compared to the $Pt_s\{Sn\}_{0.5}/SiO_2$, these modifiers improved simultaneously, but at different levels, the chemo-, regio-, and diastereoselectivity at C_{21} (Table 5).

The TON activity decreases in the order no ligand > hydro(−)cinchonidine, quinuclidine > quinoline > (−)cinchonidine, cinchonine ≫ quinine, quinidine. In any case, no ligand acceleration was observed. Clearly, the observed activity cannot be related to the basicity of the modifier.

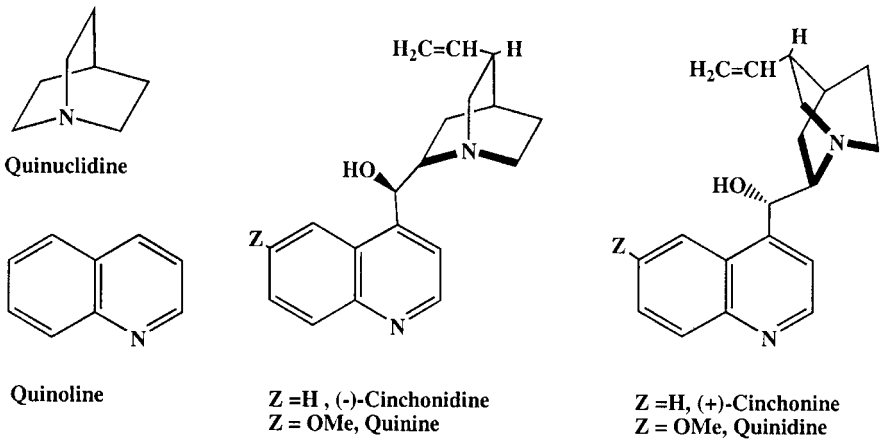
The diastereoselectivity of the hydrogenation at C_{21} was improved by additional ligands, even nonchiral: no ligand ≪ quinoline < quinine, quinidine, (+)cinchonine ≪ quinuclidine < (−)cinchonidine, hydrocinchonidine. Improvement of activity and diastereoselectivity with hydrocinchonidine instead of (−)cinchonidine is generally reported (38). When (+)cinchonine is used instead of (−)cinchonidine, the diastereoisomeric excess at C_{21} was lower, but still higher, than the one obtained with no modifier (respectively, 32%, 63%, and 14%). Quinidine and quinine gave roughly the same chemo-, regio-, and stereoselectivities. These modifiers double the d.e. of the reduction at C_{21}, but inhibit the reaction strongly. This inhibition has already been reported in the enantioselective hydrogenation of an α-ketoacid, though to a lower extent (39). It is clear that the methoxy group of these modifiers plays a major role, either by simple coordination to the catalyst or because this group is hydrogenolysed with the formation of phenol (17).

Many studies indicate that the three crucial structural elements of cinchona alkaloids are (1) the quinoline ring, acting as an *anchoring part*, (2) the *stereogenic region*, which

TABLE 4

Influence of CD/Pt_s Ratio and of Catalytic Conditions on Catalytic Properties $Pt_s\{Sn\}_{0.5}/SiO_2$ in the Hydrogenation of Oxopromegestone, 1, CD = (−)Cinchonidine, CD/(1) = 0.057 for $P(H_2) = 1$ atm and 0.028 for $P(H_2) = 80$ atm, S(i) = Selectivity, mol% for Compound i

CD/Pt_s	P, atm	T, °C	TON, $\times 10^3$, s^{-1}	S(**2**)	S(**3**)	S(**4**, **5**)	S(**6**, **7**)	$S_{C=O}$	RS	d.e. C_{21}
0	1	22	4.2	30	23	11	25	89	53	13
0.5	1	26	2.3	27	13	10	>20	>70	40	35
4.6	1	22	1.1	31	15	12	6	64	46	35
0	80	22	20.6	12	9	6	42	69	21	14
0.5	80	23	11.8	28	10	13	21	72	38	47
4.6	80	22	7.9	49	11	12	7	79	60	63
0.5	80	0	3.8	31	9	10	18	68	40	55
4.6	80	0	3.0	39	7	10	6	62	46	70



SCHEME 4

determines the chirality of the product when the substrate is prochiral, and (3) the *quinuclidine* moiety, which when protonated, is directly linked to the substrate by a hydrogen bond (38, 40). First our results clearly show that tin adatoms prevent adsorption via the π-bonding system, so the quinoline ring cannot be bound to the catalyst by this way. As a matter of fact, the effects of quinoline on the reactivity and the chemoselectivity are the same as those of the nonaromatic quinuclidine (30–50% inhibition, high chemoselectivity). Second, in our case, the chirality of the modifier plays a secondary role in the diastereoselectivity; the main factor is the chirality of the substrate itself. Each pair of pseudo-enantiomers (cinchonidine, cinchonine), (quinuclidine, quinidine) and the nonchiral quinoline and quinuclidine gave in majority the 21(*S*)-OH alcohol, **2**, and with a better selectivity than the nonmodified catalyst.

Finally, in the presence of acetic acid the hydrogenation was nonstereoselective (d.e. $C_{21} = 0$). Generally, the highest optical yields reported so far were achieved in acetic acid which protonates the quiniclidine-*N* of cinchonidine and so favours the interaction between the modifier and reactant by hydrogen bonding (38). Our results indicate that the quiniclidine moiety is not directly bound to the substrate during the hydrogenation. More likely, quinuclidine is absorbed on the catalyst and hinders in some way the approach of the substrate, thus slowing down the reaction and enhancing the steric control, which favours the formation of the 21(*S*)-OH alcohol, **2**.

TABLE 5

Effects of the Nature of the Modifier (*M*) on the Catalytic Properties of $Pt_s\{Sn\}_{0.5}/SiO_2$ Catalysts in the Hydrogenation of Oxopromegestone, 1, at $P(H_2) = 80$ atm, $T = 25°C$, *S*(i) = Selectivity, mol% for Compound i

Modifier $M/Pt_s = 4.6$	TON, $\times 10^3$, s^{-1}	*S*(**2**)	*S*(**3**)	*S*(**4**, **5**)	*S*(**6**, **7**)	p*K*	($S_{C=O}$)	*RS*	d.e. C_{21}
0	20.6	12	9	6	42		69	21	14
Hydrocinchonidine	15.1	46	10	18	6	5.8 10.0	80	56	64
(−)Cinchonidine[a]	7.9	49	11	12	7	5.8 10.0	79	60	63
(+)Cinchonine	6.8	25	13	11	16	5.8 10.0	65	38	32
Quinine	1.0	43	22	14	15	5.1 9.7	94	65	32
Quinidine	0.8	40	22	13	10	5.4 10.0	85	62	29
Quinoline	10.5	29	19	12	38	4.9	98	48	21
Quinuclidine	13.7	45	16	20	12	11	93	61	48
(−)Cinchonidine + acetic acid	13	24	24	12	23		83	48	0
(−)Cinchonidine[b]	3	39	7	10	6		62	46	70
Hydrocinchonidine[b]	8.7	55	9	21	6		91	64	72

[a] CD/(**1**) = 0.028.
[b] T = 0°C.

The selectivity could probably be improved by changing the experimental conditions. This is especially true if the activity is not too low. So with hydrocinchonidine at 0°C, oxopromegestone was hydrogenated with 91% chemoselectivity, 64% regioselectivity, and 72% d.e. at C_{21}.

CONCLUSION

The selective hydrogenation of oxopromegestone (17α-methyl-17β-(1,2-dioxopropyl)-estra-4,9-dien-3-one), **1**, into Trimegestone, (17α-methyl-17β-(2(*S*)-hydroxy-1-oxopropyl)-estra-4,9-dien-3-one), **2**, requires catalysts with a high degree of chemoselectivity (selective hydrogenation of the carbonyl versus the internal olefinic double bond), regioselectivity (hydrogenation of the exocyclic C_{21} carbonyl group), and stereoselectivity (selective obtention of the 21(*S*)-OH alcohol).

The order of activity for the monometallic catalysts was Pd > Rh > Pt > Ir > Os; the order of chemoselectivity was almost the opposite: Os > Ir > Pt = Pd > Rh. No metal gave any required diastereoselectivity. However, silica-supported Rh, Pd, and Pt exhibited 100% d.e. for the hydrogenation of the C_3 carbonyl group.

Pt/SiO_2 exhibited a low chemoselectivity (24%), but its TON was relatively high ($42 \times 10^3\ s^{-1}$). $Pt_s\{Sn\}_n/SiO_2$ catalysts, prepared by the interaction of $Sn(CH_3)_4$ with reduced Pt/SiO_2 under H_2 at room temperature, exhibited a significant increase of chemoselectivity compared to Pt/SiO_2, but still a low diastereoselectivity to the desired 21(*S*)-OH unsaturated ketoalcohol, **2**. In parallel, the diastereoselectivity at the C_3 carbonyl group decreased from 100% to 34%. The addition of (−)cinchonidine and hydrocinchonidine on the platinum–tin catalysts sharply increased the diastereoselectivity at C_{21} in favor of the 21(*S*)-OH unsaturated ketoalcohol from 14% to 70% without changing the chemoselectivity.

The experimental conditions to achieve the best chemo-, regio-, and diastereoselectivities were found to be the following: H_2 pressure of 80 atm, temperature of 0°C, ratio Sn/surface platinum of 0.5, and ratio cinchonidine/surface platinum of 4.6. In these conditions, oxopromegestone was hydrogenated into Trimegestone with 91% chemoselectivity, 64% regioselectivity, and 72% diastereoselectivity at C_{21}.

In the case of Trimegestone, these very promising results are still below those of the enzymatic catalysis. But it has been demonstrated that the limiting step which is the overreduction in hydrogenation of polyfunctional substrates by a heterogeneous catalyst could be partially suppressed by the use of a chemoselective catalyst such as $Pt_s\{Sn\}_{0.5}/SiO_2$. The significant influence on the stereodifferentiation of several modifiers is still not well understood. Nevertheless, we have shown that a double asymmetric induction with a chiral ligand can be obtained in heterogeneous catalysis and that the quinuclidine structure has a peculiar effect in the stereoselectivity. These two fields are currently under development.

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