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New data on the effect of steric constraints on the chiral induction in the Orito reaction: Hydrogenation of activated steroid ketones

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ABSTRACT

Hydrogenation of α-ketoesters containing steroid groups at the ester side and at the keto carbonyl function of substrates was investigated the first time on Pt–alumina–cinchona alkaloids chiral catalysts using mild experimental conditions (room temperature, 1 bar hydrogen pressure, modifier concentration 1 mM) in the presence of acetic acid. Catalysts modified by cinchona alkaloids ensured enantioselective hydrogenation with 10–70% ee, depending on the steric structure of the substrate. In the absence of cinchonas racemic hydrogenation takes place, i.e. the chiral centers of the substrates do not participate in chiral induction. Experimental data so far obtained support the assumption that under stereochemical conditions not inhibiting adsorption of the substrate and after optimization of the experimental conditions, the Orito reaction may be rendered suitable for the asymmetric hydrogenation of bulky activated ketones. These results also supply additional evidence for the determinant role of the H-bonded adsorbed intermediate, the 1:1 complex of cinchona alkaloid and substrate in chiral induction under protic conditions.

1. Introduction

It is an important research area to increase the selectivities (regio-, stereo-, enantioselectivities) of the organic catalytic transformations [1]. Among these it is no more necessary to underline nowadays the significance of asymmetric syntheses for a readership of professionals well versed in chemistry and biology. Due to its well-known advantages, the preparation of chiral compounds using heterogeneous catalytic hydrogenation is a synthetic method of outstanding significance. Two methods have been applied in heterogeneous catalytic hydrogenations (which have been reviewed regularly): (i) enantioselective hydrogenation [2], (ii) diasteroselective hydrogenation [3]. Industrial application of the enantioselective hydrogenation of activated ketones (Orito reaction [4] (Fig. 1) in which enantioselectivities exceed 90% [5]) has already been realized [6].

Since the present manuscript describes the results of the diastereoselective hydrogenation of α-ketoesters with steroid skeletons not studied before, Section 1 only summarizes the preliminaries of the hydrogenation of steroid ketones. Hydrogenation of the keto-groups of steroids can be achieved both by chemical reductants (e.g.) [7] and catalytic hydrogenation [8]. The data in the special literature on the metal-catalyzed hydrogenation of steroid ketones suggest that the determinant factor in the stereochemistry of the hydrogenation is the mode of adsorption of the steroid molecule on the surface.

In this respect a characteristic example is shown in Fig. 2, demonstrating the determinant role of the adsorption of molecule. In the case illustrated in Fig. 2 the C_{12} alcohol of equatorial orientation is formed in 100% regio- and diastereoselectivity, because, in the starting diketone the C_{12} ketone is on the α-face and the C_{11} ketone is on the β-face. Since the adsorption of C_{11} ketone is prevented and only the C_{12} ketone could be in contact with the metal surface, this oxo group is hydrogenated [9].

As regards the stereochemistry of the hydrogenation of compounds with the oxo group positioned outside the steroid skeleton under the conditions of the Orito reaction, to our best knowledge only two papers have been published in this field. According to one of these [10a] trigemestone was synthesized in 72% diastereoselectivity (de) after optimizing the experimental conditions of the hydrogenation of oxoprogemestone and varying the chiral modifier (Fig. 3). It has to be specially emphasized that the molecule to be hydrogenated contains five hydrogenable bonds. It was estab-

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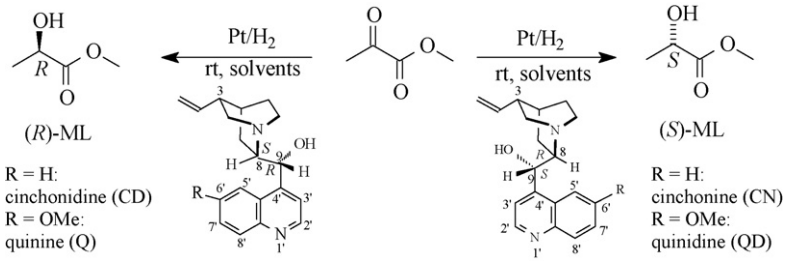

Fig. 1. The Orito-reaction [4].

lished on the stereochemistry of the hydrogenation that "... the chirality of the modifier plays a secondary role in diastereoselectivity; the main factor is the chirality of the substrate itself" [10a]. The other paper [10b] describes preliminary studies on a derivative of lithocholic acid.

Knowing the above, and based on the results of varying the bulkiness of the substituents of the substrates (i.e. the substituent next to the oxo group to be hydrogenated and the one in the ester function) [11] the following objectives were set: (i) generalization of the above described conclusion [10a] regarding the de of the hydrogenation; (ii) studies of the effect of bulky groups on the diastereoselectivity of the Orito reaction and (iii) application of the Orito reaction for the hydrogenation of steroid ketones. From the results, novel information was expected to be obtained about the stereochemistry of the Orito reaction. The asymmetric hydrogenation of the steroid compounds **1**–**4** (see Section 2) was studied.

2. Experimental

2.1. General remarks

The cinchona alkaloids (CD, CN, Q, QD), solvents and compounds used in synthesis of **1**–**4** were Fluka or Aldrich products. All solvents were dried, purified and distilled according to conventional methods. The lithocholic acid methyl ester was synthesized according to a literature procedure [12]. β-ICN preparation has been described elsewhere [13]. Melting point was measured on Boëtius micromelting point apparatus (uncorrected value). Column chromatography was performed using hexane/acetone (5:2) solvent system on Fluka silica gel 60 (70–230 mesh ASTM), analytical TLC on Fluka Silica gel/TLC cards.

2.2. Syntheses

The steroid esters of pyruvic and phenylglyoxylic acids (**1**, **2**) were prepared by the reaction of the crude acid chloride and steroid alcohol in the presence of Et_3N (or pyridine) and DMAP in CH_2Cl_2 at room temperature. Literature procedures were followed in the preparation of pyruvic chloride [14] and phenylglyoxylic chloride [15].

5α-Cholestan-3β-yl pyruvate (**1**): white solid (65% yield), melting point: 388–389 K, TLC R_f: 0.67 (hexane/acetone 5:2).

5α-Cholestan-3β-yl phenylglyoxylate (**2**): 64% yield, melting point 376.5–377.5 K (lit. [16]: 376–378 K), TLC R_f: 0.86 (hexane/diethyl ether 8:2).

3-Phenylglyoxyloxy-lithocholic acid methyl ester (**3**): white solid (52% yield), melting point 339–341 K, TLC R_f: 0.52 (hexane/acetone 5:2).

Methyl 3α-acetoxy-23-oxo-5β-cholan-24-oate (**4**): white solid (67% yield), melting point: 389-391 K, TLC R_f: 0.55 (hexane/diisopropyl ether 7:3). The preparation was followed according to [10b].

2.3. Spectroscopic measurements

The NMR spectra were obtained by the use of (^{1}H at 500 MHz, ^{13}C at 125 MHz) in $CDCl_3$ solution, using Me_4Si as the internal standard. The ESI-MSD and ESI-MSD-ion-trap (AGILENT 1100 LC-MSD TRAP SL ion-trap MS) was operated under positive ion and auto MS-MS mode as described earlier [17].

VCD spectra at a resolution of 4 cm^{-1} were recorded in chloroform-*d* solution with a Bruker PMA 37 VCD/PM-IRRAS module connected to an Equinox 55 FTIR spectrometer. The instrument was optimized for the fingerprint spectral region and calibrated for VCD intensity with a CdS multiple-wave plate. A BaF_2 cell with a pathlength of 50 μm and sample concentrations of 120 mg/mL were used. In order to improve the signal/noise ratio interferograms were accumulated for 7 h, corresponding to ~24,500 scans. Baseline correction was achieved by subtracting the spectrum of the solvent obtained under the same conditions.

2.4. Molecular modeling and computation of VCD spectra

Geometry optimizations and the computation of vibrational frequencies and VCD rotatory strengths were performed at the B3LYP/6-31G(d) DFT levels with the Gaussian 03 quantum chemical software package [18] the vibrational frequencies being scaled by a factor of 0.97. VCD curves were simulated from the calculated wavenumber and rotatory strength data by using Lorentzian band shape and a half-width at half-height value of 3 cm^{-1}.

2.5. Hydrogenation

From the pretreatment methods (high temperature reductive, ultrasound [17c,19]) used for activation of the catalyst we have used

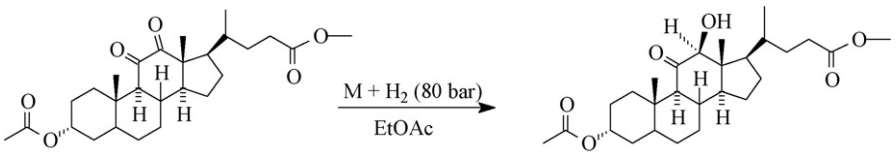

Fig. 2. Hydrogenation of a steroid-diketone catalyzed by supported catalysts (M = Pd-, Pt-, Rh-, Ru-SiO_2) [9].

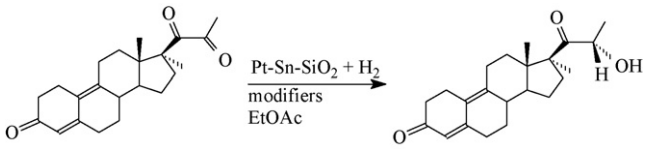

Fig. 3. Diastereoselective hydrogenation of oxopromegestone to trimegestone [10a].

the former method. According to Ref. [17c] 5% Pt–alumina catalyst from Engelhard (E 4759) was pretreated before use in a fixed bed reactor (or a quartz vessel) by flushing with 30 mL min^{-1} helium at 298–673 K for 30 min and 30 mL min^{-1} hydrogen and at 673 K for 100 min. After cooling to room temperature in hydrogen, the catalyst was flushed with helium for 30 min.

The hydrogenation was performed in a conventional atmospheric glass batch reactor or in a hydrogenation autoclave. The catalytic system including the catalyst and the solvent was flushed with hydrogen several times and filled to the desired pressure and stirred (~800–1000 rpm). After the prehydrogenation (30 min) first the modifier and then the reactant were introduced and stirred in the presence of hydrogen for the required reaction time. Standard conditions were: 12.5 mg of E4759, 297–301 K, 1 bar of hydrogen pressure, 1 mmol L^{-1} modifier concentration, solvent: 2 mL AcOH + 0.5 mL of toluene, hydrogenation time: 3 h, substrate: 0.125 mmol.

After the hydrogenation the catalyst was filtered off, the filtrate was evaporated at reduced pressure (30 Torr). With the aim on determining of de 2 mL of 10% NaOH solution was added to 10 mg of residue and the mixture was stirred for 24 h. The solution was extracted with 2× 10 mL of $CHCl_3$, the water layer was acidified with 10% HCl solution then evaporated at reduced pressure. Ethereal diazomethane was added to the solid residue then the ethereal solution was analysed.

In the case of **1**–**3** ees were measured by GC as methyl lactate (ML) or methyl mandelate (MM). The conversion and enantiomeric excess [ee % = ([*R* − *S*] × 100/[*R* + *S*])] were monitored by GC (30-m-long cyclodex-B (Agilent 6890 N + FID capillary column, 383 K, 25 psi of He uncertainty ±2%). Retention times (min): MP 4.8, (*R*)-ML 6.3, (*S*)-ML 6.8; MBF 18.0, (*R*)-MM 29.7, (*S*)-MM 30.7. The configuration of C23 atom of **4** was determined by VCD spectra.

Table 1
Experimental data of enantioselective hydrogenation of **1**–**4** steroid ketones on Pt–cinchona alkaloids chiral catalyst (standard conditions: see Section 2)

Entry	Substrate	Modifier	Conversion (%)	De (%)
1	**1**	–	5	0
2	**1**	CD	60	47 *R*
3	**1**[a]	CD	96	38 *R*
4	**1**	CN	60	50 *S*
5	**1**	Q	66	53 *R*
6	**1**	QD	75	45 *S*
7	**1**	β-ICN	60	40 *S*
8	**2**	–	38	0
9	**2**	CD	74	34 *R*
10	**2**[a]	CD	100	42 *R*
11	**2**	CN	35	20 *S*
12	**3**	–	13	0
13	**3**	CD	15	14
14	**3**	CN	5	2
15	**4**	–	22	0
16	**4**	CD	100	62 *R*

[a] 40 bar, 1 h.

3. Results and discussion

3.1. Results of hydrogenation (Table 1, Fig. 4)

Experimental conditions for hydrogenation were chosen on the basis of preliminary experiments. Of the two solvents that had proven to be the best in the Orito reaction (AcOH, toluene (T)), a 4:1 mixture of AcOH/T was selected. Although increasing hydrogen pressure accelerated the reaction, hydrogenation was nevertheless conducted at a hydrogen pressure of 1 bar, because increasing hydrogen pressure had practically no effect on de. The favorable effect of reducing reaction temperature on ee is well-known (e.g. [2f,h]); owing to the slow reaction rate, however, it did not seem expedient to carry out the measurement series below room temperature. Considering the extended reaction time (3 h) and in spite of the fact that a cinchona concentration of 0.01 mmol L^{-1} had proven to be sufficient on Pt–alumina catalyst in AcOH [2f], the concentration of the chiral modifier was chosen as 1 mmol L^{-1} because the quinoline skeleton of cinchona alkaloids is also hydrogenated in the course of the hydrogenation reaction [20]. In addition to parent

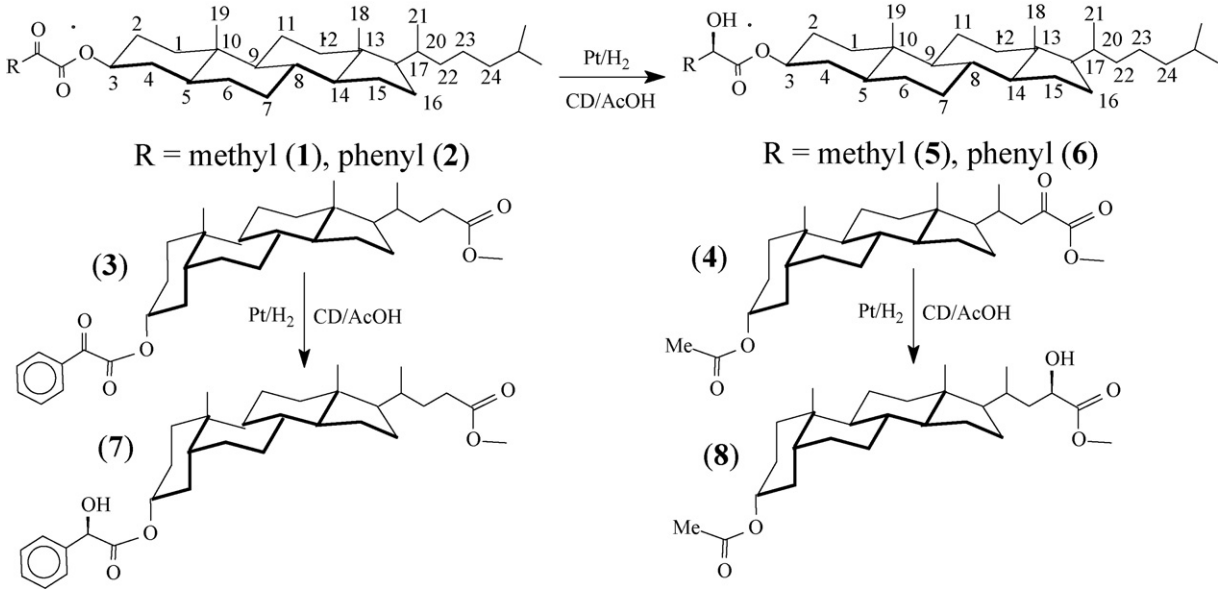

Fig. 4. Hydrogenation of **1**–**4** steroids on Pt–alumina catalyst modified by CD.

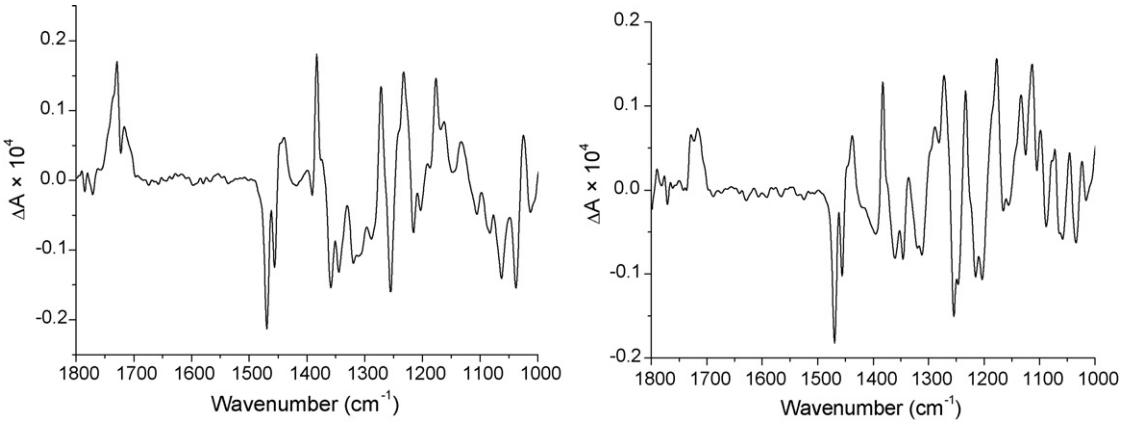

Fig. 5. VCD spectra of compounds **4** (left) and **8** (right) recorded in chloroform-*d* solution.

cinchona alkaloids (CD, CN, Q, QD) β-isocinchonin (β-ICN) was also used as chiral modifier. The results of the study of cyclic ethers [21] have led to the application of β-ICN as chiral modifier in the Orito reaction, to the discovery of the unexpected inversion of enantioselection, and to a proposed interpretation of this phenomenon [22].

Results of hydrogenations performed under the standard conditions described in Section 2 are shown in Table 1 and Fig. 4. According to experimental results it can be established.

(i) The most apparent difference as compared to what is known at present is that the steroid ketones studied are hydrogenated significantly slower than α-ketoesters containing bulky substituents [11]; (ii) hydrogenation without chiral modifier (racemic hydrogenation) yields a racemate; the order of reaction rates is **2** > **3** > **1**; (iii) hydrogenation in the presence of chiral modifier (diastereoselective hydrogenation) is somewhat faster than racemic hydrogenation; the order of reaction rates is **4** > **1** ∼ **2** > **3**; (iv) the de of the hydrogenation of **1** and **2** varies between 40 and 60% and that of **3**, between 2 and 14% depending on the chiral modifier used; (v) after preparative hydrogenation followed by recrystallization of the raw product, in the case of, e.g. **2** ee values of 55–70% were attained; (vi) the presence of CD or Q led to the formation of the alcohol with *R*-configuration, whereas in the presence of CN, QD or β-ICN the alcohol with *S*-configuration was formed.

3.2. VCD spectroscopic measurement (Figs. 5 and 6)

We recorded the VCD spectra of **8** and of its carbonyl precursor **4** having an achiral carbon atom at position 23. From the high similarity of their VCD spectra (Fig. 5) it is evident that vibrations of the groups attached to the chiral center 23 of compound **8** (particularly C–H and OH bending vibrations) have only small contributions to the VCD spectrum. In order to identify these critical VCD bands and to minimize the contribution of the steroid moiety, we subtracted the VCD spectrum of **4** from the VCD spectrum of **8** and the resulting difference spectrum was compared with the calculated spectrum of (*R*)-ML (Fig. 6).

The difference VCD spectrum contains much more bands than the calculated spectrum of (*R*)-ML since the original structures are larger (and thus have much more vibrational modes), however, there are evident similarities. The bands at 1398, 1288 and 1245 cm^{-1} in the difference VCD spectrum are assigned to the $\beta_{OH} + \delta_{C-H}$ coupled vibration at 1417 cm^{-1}, the $\beta_{OH} + \delta_{C-H} + \nu_{as\ C-CO-O}$ coupled vibration at 1272 cm^{-1}, and the $\delta_{C-H} + \nu_{as\ CO-O-C} + \beta_{OH}$ coupled vibration at 1228 cm^{-1}, respectively, in the calculated spectrum of (*R*)-ML (the participating groups are listed in the order of their contribution to the coupled vibration). These critical bands are in good agreement both in terms of frequency and sign, thus one can conclude that the absolute configuration of the asymmetric carbon 23 of **8** is also *R*.

3.3. Discussion

General empirical observations regarding the rate of the hydrogenation of ketones [8,23] hold for steroid ketones too. These new experimental results are also in agreement with the results obtained in studies on the Orito reaction of other α-ketoesters with bulky substituents [11]. It is commonly observed in the Orito

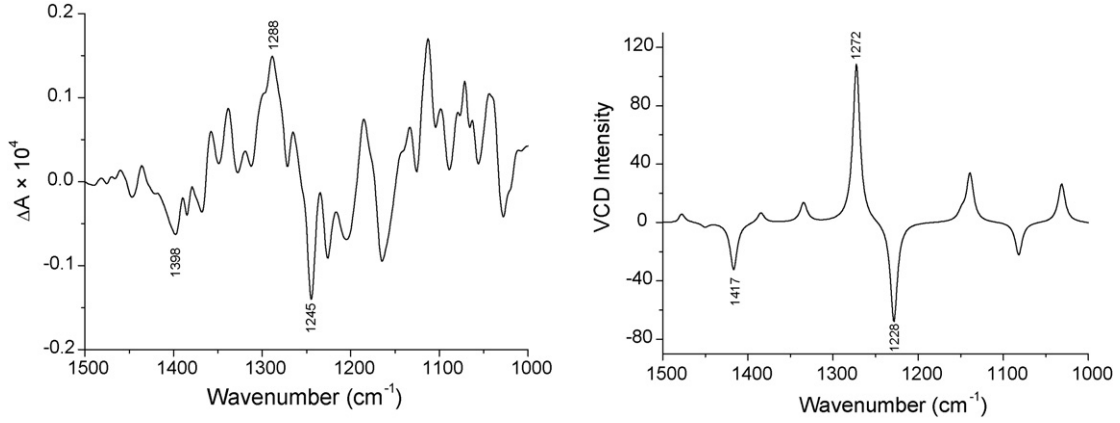

Fig. 6. Difference of the VCD spectra of compounds **8** and **4** (left) and the calculated VCD spectrum of the lowest-energy conformer of (*R*)-ML (right) (see Fig. 1).

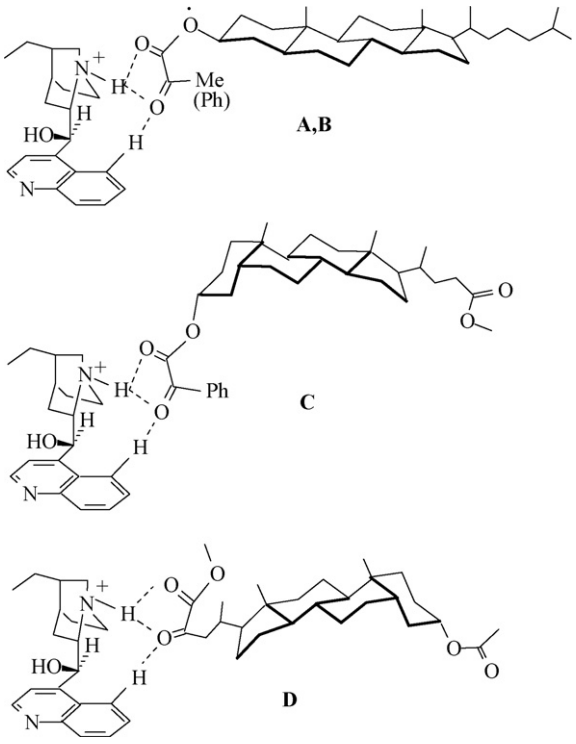

Fig. 7. The proposed structures of adduct complexes of CD with **2**, **3** and **4** steroid ketones.

reaction that in most cases a high ee is accompanied by a high hydrogenation rate [24]. Indeed in the present case the rate of enantioselective hydrogenation is somewhat higher than that of racemic hydrogenation. As to the adsorption of the C=O group to be hydrogenated, regrettable that the effect of bulky groups on adsorption, is not touched upon by the papers cited [25].

From values of ee attained in the case of activated ketones carrying the bulkiest substituents so far studied it appears that in the case of the steroid ketones studied, steric factors play a more important role in determining both rate and diastereoselectivity than do electronic factors. Namely, according to Ref. [11] although an de as high as 80–90% could be attained in the hydrogenation of α-ketoesters less bulky than the steroid substituent, hydrogenation of **1** and **2** produces an de hardly exceeding 60% (Table 1, Fig. 4). On the other hand, the role of steric factors is suggestively demonstrated by the results obtained using **3**, namely by the fact that adsorption of **3** is so excessively inhibited by *cis* anellation of rings A and B that de barely exceeds 10%. An interesting new observation is that the steroid group at the keto carbonyl function (**4**) decreased neither the rate nor de as compared to **1**–**3**, in which the steroid group is in the ester function.

Neither did comparative experiments on the parent cinchonas (CD, CN, Q, QD) reveal any characteristic differences in hydrogenation rate or de like the ones observed in the case of α-ketoesters containing less bulky substituents [11,26]. These results also indicate that the formation of the surface intermediate responsible for chiral induction is more inhibited by bulky substituents of the substrate than by the ethyl group of the alkaloids CN and QD close to the surface [26b].

It can be established regarding the stereochemistry of the hydrogenation of steroid ketones that a strong interaction of the steroid α-face with the catalyst can take place, since the adsorption on the β-face is prevented by the two C_{18} and C_{19} Me groups (Fig. 7). In the former case a sterically less inhibited side of the steroid molecule may be adsorbed (Fig. 7A and B). In the case of the inhibited adsorption, the bulky steroid groups presumably are situated not on the surface, but in the liquid phase and are solvated by the solvent (e.g. Fig. 7C and D).

According to our results the chiral atoms of the steroid molecules does not affect the stereochemistry of hydrogenation. The probable reason is that the C=O group to be hydrogenated is far way from the stereogenic centers. In Ref. [10a], however, the C=O to be hydrogenated was much closer to the chiral carbon atoms (Fig. 3). The timeliness of research on this phenomenon is confirmed by the recently published review entitled "Asymmetric catalysis induced by the substrate itself" [27]. This review emphasizes – in addition to the importance of "double stereodifferentiation" – the role of "the relative proximity of the stereogenic centers" in case of various reactions.

4. Conclusion

In the present manuscript the application of Orito reaction [4] for the diastereoselective hydrogenation of steroid ketones is described over Pt–alumina catalyst modified by cinchona alkaloids (CD, CN, Q, QD, β-ICN) in AcOH (Fig. 1 and Ref. [22]). The steroid group was incorporated at both locations: a steroid group at the keto carbonyl function and a steroid substituent in the ester group. The steric structure of the substrate is a determinant factor in the process of hydrogenation regarding both the rate and de. De varies in the range of 10–60% depending on the three-dimensional structure of the steroid molecule. The hydrogenation rate of ketones is subject to a generally accepted empirical rule, namely that the reaction rate is negatively influenced by the steric effects of the substituent.

The sense of enantioselection on hydrogenated carbonyl group is not influenced by stereogenic centers present in the steroid molecule. Experiments so far performed suggest that, after optimization of the experimental conditions, the Orito reaction can be rendered suitable for the diastereoselective hydrogenation of activated ketones containing steroid skeleton under conditions not inhibiting substrate adsorption. Based on our experimental data and on the verified open-3 conformation of cinchona alkaloids [28] as well as on the suggested and the widely accepted model [24,29] in protic solvents the proposed structure of intermediates responsible for the diastereoselection is outlined in Fig. 7. The one-point [24,29] or two-point [30] H-bonding models involving protonated quinuclidine or nucleophilic quinuclidine nitrogen have been proposed based on experimental evidences.

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