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Diastereoselective Hydrogenation of Indenols: Evidence for Sterically and Electronically Unfavorable Adsorption on Palladium

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The stereochemistry of hydrogen addition to C=C bonds was studied in the diastereoselective hydrogenation of selected indene derivatives over an alumina-supported Pd catalyst. In all cases hydrogenation occurred via bottom-side *syn* addition of two hydrogen atoms to the chemisorbed substrate. Hydrogenation of indenol derivatives demonstrated that methyl or ethyl groups are not sufficiently bulky to hinder the adsorption and hydrogenation of the substrate in a sterically and electronically unfavorable ("upside down") position, in which the alkyl group points toward and the OH group points away from the metal surface. The implications of this observation for understanding the mechanism of asymmetric hydrogenation over metal catalysts are discussed. © 1999 Academic Press

Key Words: **asymmetric hydrogenation; adsorption; indenol; stereochemistry of hydrogen addition; Pd/alumina, bottom-side *syn* addition.**

INTRODUCTION

Hydrogenation with metal catalysts is a widely used method in laboratory and industrial synthesis. Considerable effort has been expended in the past decades to understand the steric course of the elementary reaction steps over the metal surface (1–3). The mostly applied models assume that the electron-rich part of the reactant (e.g., C=C double bond, OH group, and aromatic ring) anchors to the platinum metal and the molecule adsorbs on the sterically less hindered side (4–6). It has also been proposed that allylic alcohols adsorb on palladium preferentially with the hydroxyl group directed away from the catalyst surface (7, 8). This suggestion was made based on hydrogenation of cyclic allylic alcohols, where the hydrogen atoms added to the opposite side with respect to the OH group. However, these results can reflect the isomerizing ability of palladium rather than the weak adsorption of the OH group (9). Palladium is an excellent catalyst for double bond migration, and this side reaction can frequently be the origin of the unexpected stereochemistry of hydrogen addition (4, 10).

The mode of hydrogen addition to the chemisorbed reactant is crucial for understanding the mechanism of asymmetric hydrogenation. According to the most accepted model, hydrogenation occurs by stepwise addition of two H-atoms from the metal surface to the adsorbed molecule via "bottom-side" *syn* addition (11, 12). A critical discussion of this concept can be found in a recent book (13). The mechanistic models developed for interpreting of the sense of stereodifferentiation over chirally modified metal surfaces assume, with one exception (14), bottom-side *syn* addition of hydrogen (15–21).

Here we report a systematic study on the stereochemistry of hydrogen addition in the Pd-catalyzed diastereoselective hydrogenation of some indene derivatives in which the bulkiness of the group responsible for steric hindrance was varied.

EXPERIMENTAL

Hydrogenations of 1-alkyl-2,3-dimethyl indenol derivatives (**1a**–**1c**, Scheme 1) and a bulky phenyl indene derivative were studied. The indenol derivatives were prepared in a four-step synthesis starting with Horner–Emmons reaction between acetophenone and triethyl propiophosphonate (22). The conventional method for converting *E* and *Z* dimethyl cinnamic acids to their acid chloride afforded 2,3-dimethyl indenone practically in quantitative yield, regardless of the configuration of the reactant acid (*E* or *Z*). Grignard reaction between dimethyl indenone and the corresponding alkyl halide provided the racemic target compounds. 1-*Tert*-butyl-2,3-diphenyl indene (**2**) was synthesized in two steps, starting with Grignard reaction between 2,3-diphenyl-1-indenone (Aldrich) and *tert*-butyl chloride, followed by dehydroxylation in AcOH/HI (23). The racemic mixtures of compounds **1a**–**1c** and **2** were applied in hydrogenation. Compounds **1a**–**1c** and **2** were identified by NMR and elemental analysis. Details of the synthesis are available from the authors on request.

Pd/Al_2O_3 (5 wt% Engelhard 40692, Pd dispersion = 0.21 as determined by TEM) was used for hydrogenations in a 100-ml glass autoclave equipped with a magnetic stirrer.

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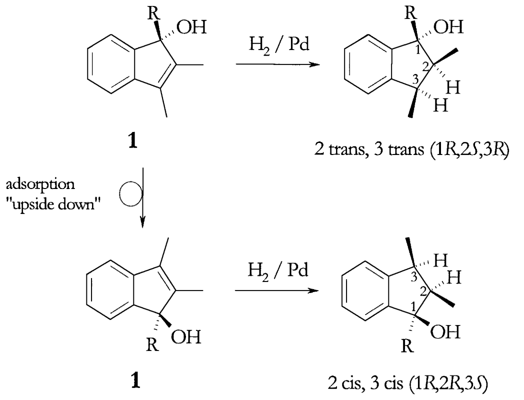


1	R	(2t, 3t) / (2c, 3c)
a	i-C_4H_9	100 / –
b	C_2H_5	97 / 3
c	CH_3	88 / 12

SCHEME 1. Product distribution in the hydrogenation of alkyl indenols as a function of bulkiness of the *R* alkyl substituent (in table, 100% conversion, $2t,3t = 1R,2S,3R$ and $1S,2R,3S$, $2c,3c = 1R,2R,3S$ and $1S,2S,3R$).

The following conditions were applied: 100 mg reactant, 10 mg catalyst, 20 ml toluene, room temperature, and 1 bar. The products were analyzed by gas chromatography using a chiral CP-cyclodextrin-2,3,6-*M*-19 (Chrompack) capillary column and identified by NMR analysis.

Theoretical calculations for the conformational optimization of **4** were performed at the Hartree Fock level of theory using a 3-21G standard basis set, implemented in the Gaussian program package. Geometry optimization was performed using the Berny-algorithm.

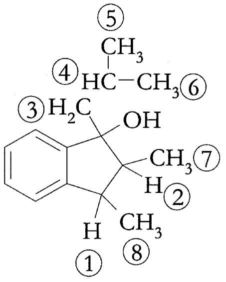
RESULTS

The 2,3-disubstituted indenol derivatives are suitable for studying the stereochemistry of hydrogen addition, since free rotation about the C–C bond is eliminated in the product (Scheme 1). Configuration of the stereogenic C-atoms in the hydrogenation product provides information on the adsorption mode. The alkyl groups at C1 (R) in **1a**–**1c** decrease in size (^{i}Bu > Et > Me). Hydrogenation of the C=C bond over Pd/Al_2O_3 occurred rapidly under the reaction conditions applied, affording 100% chemoselectivity to the saturated product when hydrogenating **1a**, while hydrogenolysis of the C–O bond was observed only to a small extent (<3%) when hydrogenating **1b** and **1c**. Two enantiomers formed from **1a**, whereas the hydrogenation of **1b** and **1c** afforded four stereoisomers.

As an example, we describe the identification of the hydrogenation product of **1a** (Scheme 2), which was performed by ^{1}H NMR where signal assignment was assisted through nuclear Overhauser enhancement spectroscopy (NOESY). The aromatic protons appeared between δ7.19 and 7.34. H1 and H2 were observed as a multiplet at δ3.40 and 2.46, respectively, having the same coupling constant ($J = 7.3$ Hz). H4 and H3 appeared as multiplets at δ2.02 and 1.65, respectively. NOESY identified H8 at δ1.18 and H7 at δ0.88 through coupling with H1 and H2, respectively. The two doublets at δ1.08 and 0.94 were assigned to H5 and H6. For H3 NOESY showed cross-peaks with H7 and H8 indicating a close proximity, while no cross-peaks with H1 and H2 were found. Clearly, both hydrogen atoms added to the same side of **1a** (*syn* addition) and were situated in *cis* position with respect to the OH group (1*R*-isobutyl-2*S*,3*R*-dimethyl-1-indanol and its enantiomer). Hence *anti* addition of hydrogen can be ruled out by the NOESY analysis.

In the hydrogenation of **1b** and **1c** one additional enantiomer pair was formed. Both enantiomer pairs were identified by the same molecular weight (GC-MS), revealing that they were in diastereomer relationship. The adsorption geometry in the hydrogenation of **1a**–**1c** is determined by electronic (aromatic ring, OH group) and steric (*R*) effects. In the dominant adsorption mode the aromatic ring, the C=C bond, and the OH group are involved in the reactant–Pd interaction affording parallel adsorption to an ideal, flat surface with the *R* group pointing away from the metal (Scheme 1). *Syn* addition of two hydrogen atoms from the Pd surface results in high diastereomeric excess to the 2*t*,3*t* isomers (1*R*,2*S*,3*R* and 1*S*,2*R*,3*S*, Scheme 1). The bulky isobutyl group prevented the adsorption (and hydrogenation) of **1a** in a position with the OH group pointing away from the catalyst and afforded the exclusive formation of the 2*t*,3*t* isomers. As the bulkiness of the *R* group decreased, the contribution of the sterically and electronically unfavorable adsorption mode of **1b** and **1c** increased. Bottom-side *syn* addition of hydrogen in this position results in isomers in which the methyl groups at C2 and C3 are in *cis* position with respect to the OH group (2*c*,3*c* isomers (1*R*,2*R*,3*S* and 1*S*,2*S*,3*R*)).

In another experiment **2** was hydrogenated over Pd/Al_2O_3 according to Scheme 3. Note that here only one adsorption mode is shown with the catalyst surface lying



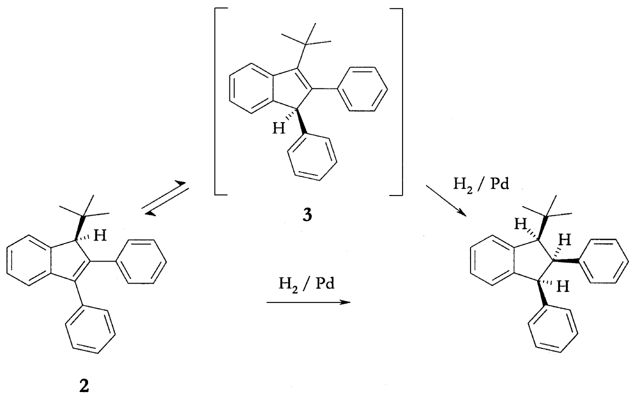
SCHEME 2. Assignment used in NMR analysis of 1-isobutyl-2,3-dimethyl-1-indanol.

parallel to the drawing plane (top view). Compound **2** possesses no OH (or other electron-rich) functional group which can direct the adsorption; thus only the *tert*-butyl group in allylic position determines which face anchors to the metal surface. Hydrogenation provided only that isomer in which the phenyl groups are *cis* with respect to the *tert*-butyl group. Similar to that seen with **1a**, hydrogenation of **2** can occur exclusively via adsorption on the sterically less hindered side, opposite to the alkyl group, and the hydrogen atoms add from the metal (bottom-side *syn* addition). A possible C=C double bond migration in **2** would lead to **3**. Desorption and readsorption of **3** on the opposite side would furnish *trans* isomers. However, **3** can adsorb only on the same side as **2** due to remaining steric hindrance by the phenyl group. Therefore, **3** would provide the same isomer which is formed directly from **2**.

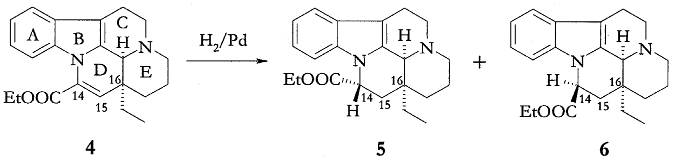
DISCUSSION

Hydrogenation of **1a**–**1c** and **2** demonstrates (i) *syn* addition of two hydrogen atoms which is likely a bottom-side *syn* addition and (ii) that bulky groups, such as isobutyl or *tert*-butyl can completely eliminate the adsorption and hydrogenation in the sterically and electronically unfavorable position. Steric hindrance imposed by a methyl or ethyl group does not rule out the less favored adsorption mode and formation of two stereoisomers.

Interestingly, sterically hindered adsorption is rejected by several authors. They assume top-side addition of two hydrogen atoms, rather than bottom-side *syn* addition in a sterically unfavorable position. A recent example is the diastereoselective hydrogenation of apovincaminic acid ethyl ester (**4**) (vinpocetine) shown in Scheme 4 (14). The alkaloid possesses a C=C bond at C14 which undergoes facile hydrogenation over Pd, resulting in two epimers (**5** and **6**). The authors proposed that the formation of the major isomer **5** (71–85%), where the H atom at C14 is in *trans* position with respect to the ethyl group at C16, could only be attributed to "top-side" addition of hydrogen. Their conclusion was based on the assumption that **4** has a special "boat" form, and its adsorption on the Pd surface could occur exclusively on the sterically less hindered side of the molecule.



SCHEME 3. Asymmetric hydrogenation of 1-*tert*-butyl-2,3-diphenylindene directly and via a possible isomerized intermediate affording the same hydrogenation product.



SCHEME 4. Hydrogenation of apovincaminic acid ethyl ester (**4**) resulting in two epimers.

However, there is an alternative explanation for the observed product distribution. Besides the suggested more stable closed conformation of **4**, theoretical calculations indicated the possibility of an open conformation which was also identified in the solid state by X-ray crystallography (24). The open conformer can adsorb on both faces of the molecule on Pd without significant steric hindrance; thus the formation of **5** and **6** may be attributed to bottom-side addition of two hydrogen atoms to **4** adsorbed on the two different faces of the molecule.

CONCLUSIONS

In liquid phase hydrogenations over metal catalysts, direct information on the adsorption mode of substrate is rarely available. Instead, some assumptions are usually made concerning the adsorption geometry. The assumptions are based on the general knowledge of adsorption of organic compounds on metals, though most of this information has been derived from gas/solid interfaces of the adsorption of simple molecules on single crystal surfaces at very low pressures. We propose that in many cases a sterically less favorable adsorption mode, rather than direct top-side addition of hydrogen, can account for the unexpected isomer distribution in the (asymmetric) hydrogenation of unsaturated compounds over metal surfaces. Investigation of the diastereoselective hydrogenation of several indene derivatives revealed that an adsorption mode, which is usually rejected as sterically hindered and electronically unfavorable, can rationalize the formation of a puzzling minor isomer as hydrogenation product. It seems that *syn* addition of two hydrogen atoms from the metal surface is a reasonable assumption for describing the stereochemistry of (asymmetric) hydrogenation of unsaturated compounds over Pd and likely over other metal catalysts active in hydrogenation reactions.

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