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Enantioselective Hydrogenation of Pyruvic Acid Oxime to Alanine on Pd/Alumina

K. Borszeky, T. Mallat, R. Aeschiman, W. B. Schweizer,[1] and A. Baiker[2]

Department of Chemical Engineering and Industrial Chemistry, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092, Zürich, Switzerland

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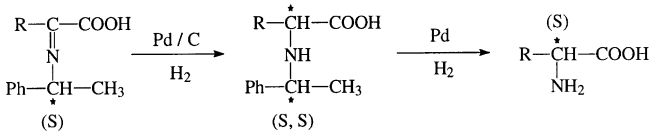
The chemo- and enantioselective hydrogenation of pyruvic acid oxime have been studied on Pd/alumina, the latter in the presence of the 1,2-amino alcohol type alkaloids ephedrine, cinchonidine, and cinchonine. High yields of racemic alanine (90–98%) were obtained in the absence of alkaloids in polar solvents at 0–45°C and 10 bar. Enantioselection increased with higher temperature and alkaloid : oxime molar ratio. A 1 : 1 ephedrine : oxime molar ratio afforded the best enantiomeric excess (26%). The presence of alkaloid resulted in a decrease of reaction rate by a factor of up to 140, compared to the racemic hydrogenation. Based on X-ray crystal structure analysis of the alkaloid–pyruvic acid oxime adduct, a mechanism is proposed for the steric course of the reaction. Extended interactions by multiple H bonds between the adsorbed alkaloid–oxime salt units on the Pd surface is assumed to be at the origin of the moderate enantioselectivity and the very low enantioselective hydrogenation rate.

INTRODUCTION

The heterogeneously catalyzed asymmetric hydrogenation of a C=N functional group has been of interest for a long time, due to the importance of chiral amino acids (for reviews, see 1–4). An important method for the transformation of easily available α-ketoacids to the corresponding α-amino acids is the reductive amination with an amine via the imine (Schiff base) intermediate. Enantiomeric excesses (ee) of 12–81% were reported in the Pd-catalyzed hydrogenation of Schiff bases derived from α-ketoacids and ethylbenzylamine, followed by the hydrogenolytic removal of the benzylic group to produce the amino acid (Scheme 1)



SCHEME 1

[1] Present address: Department of Organic Chemistry, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092, Zürich, Switzerland.

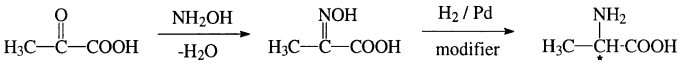
[2] To whom correspondence should be addressed.

(5). Similarly, alanine was obtained with 78% chemical yield and up to 67% enantiomeric excess (6). The source of chiral information can be the optically active amine used for reductive amination (5–9), or the α-ketoacid is transformed to an optically active ester (10, 11) prior to amination.

An alternative to reductive amination is the transformation of α-ketoacids (or their chiral derivatives) to oximes, followed by hydrogenation–hydrogenolysis to primary amines, according to Scheme 2. The formation of oximes is fast and quantitative. The diastereoselective hydrogenation of oximes of chiral α-ketoesters and α-ketoamides provided 12–70% ee, depending on the reaction conditions and the structure of the reactant (10, 12). For example, the Pd-catalyzed reduction of the oxime of pyruvamide containing (*R*)-α-ethylbenzylamine as chiral source yielded alanine after hydrolysis of the amido group with a maximum of 58% yield and 70% ee to the (*S*)-enantiomer (12). The optical purity is considerably lower when the menthyl ester of pyruvic acid is used for the synthesis (10).

The enantioselective hydrogenation of oximes of α-ketoesters to amines over chirally modified metal surface has yet been much less successful than the above mentioned diastereoselective routes (3). The best enantioselection (19% ee) was reported for the electroreduction of benzoylformic acid oxime over a strychnine-modified Hg electrode. The catalytic hydrogenation of pyruvic acid oxime on ephedrine-modified Pd/C yielded 8–56% alanine with a maximum of 10% ee to the (*S*)-enantiomer in 2-propanol or 3% ee to the (*R*)-enantiomer in dioxane (13). The steric course of the reaction has been explained by the formation of a chelated intermediate involving the oxime and a surface Pd atom (1, 2).

The rather low chemical selectivity of the pyruvic acid oxime–alanine transformation in dioxane and simple aliphatic alcohols has not been discussed (13), but it is likely due to secondary or tertiary amine formation. Details of the



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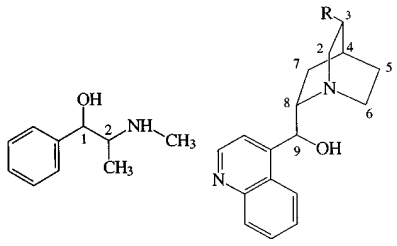
Configuration		R
EP	1*R*, 2*S*	-
CD	8*S*, 9*R*	$-C_2H_3$
HCD	8*S*, 9*R*	$-C_2H_5$
CN	8*R*, 9*S*	$-C_2H_3$



SCHEME 3

chemistry of oxime reduction have been reviewed (14, 15). There are only a few successful examples on the reduction of oximes to primary amines on palladium in neutral solvents.

In this paper we report some interesting and yet uncovered characteristics of the enantioselective hydrogenation of pyruvic acid oxime to alanine. The reaction has been catalyzed by Pd/alumina in the presence of chiral amino alcohols of natural origin (ephedrine, EP; cinchonine, CN; cinchonidine, CD; and dihydrocinchonidine, HCD, Scheme 3). An attempt has been made to propose a model for the mechanism of enantioselection.

EXPERIMENTAL

Materials

Pd/alumina (5 wt%) (Engelhard Escat 14) or Pt/alumina (5 wt%) (Engelhard No. 4759, BET surface area, 185 m^2/g; Pt dispersion as measured by CO chemisorption, 21%) catalysts were used for oxime hydrogenation. Pretreatment of the catalyst in flowing hydrogen was performed at 300°C for 1.5 h.

(1*R*, 2*S*)-(-)-Ephedrine (EP, Janssen Chimica), (8*S*, 9*R*)-Cinchonan-9-ol (Cinchonidine, CD, Fluka), and (8*R*, 9*S*)-Cinchonan-9-ol (Cinchonine, CN, Fluka) were commercial products. 10-11-dihydrocinchonidine (HCD) was prepared from CD by hydrogenation in an aqueous HCl–AcOH mixture using a 5 wt% Pd/C catalyst at room temperature and atmospheric pressure. Neutralization with diluted aqueous KOH resulted in the product as white crystalline solid.

For the preparation of pyruvic acid oxime (designated as oxime), 4.4 g (0.05 mol) of pyruvic acid (Aldrich) in 15 ml EtOH was added to a solution of 10.8 g (0.08 mol) NaOAc and 4.03 g (0.058 mol) hydroxylamine hydrochloride in 10 ml water and was stirred at room temperature for 5 h. Then the pH was decreased to 1 by diluted aqueous HCl and the oxime was extracted with diethyl ether. After removal of solvent the product was obtained as white solid and used without recrystallization. ^{13}C NMR (CD_3OD), δ [ppm]: 167.22 (COOH), 150.16 (C=N), 10.2 (CH_3).

Cinchonidinium pyruvate oxime salt (designated as CD-oxime) was prepared by dissolving 2.944 g (0.01 mol) CD and 1.038 g (0.01 mol) oxime in a warm water : ethanol, 1 : 1 mixture. After evaporation of the solvent a white microcrystalline residue was obtained. Recrystallization from boiling ethanol yielded white needle-like crystals suitable for X-ray diffraction measurements. The ephedrinium pyruvate oxime salt (designated as EP-oxime) was prepared in a similar way, but using only ethanol as solvent (white blocks).

Catalytic Hydrogenation

The reactions were performed in a 100 ml glass autoclave (Büchi) under 10 bar hydrogen pressure. Catalyst (200–500 mg), oxime (0.832 g, (8 mmol), the proper amount of modifier, and solvent (30 ml) were mixed with a magnetic stirrer (1500 rpm). The average reaction rate was derived from gas chromatographic analysis of the reaction mixture at the end of the reaction period. It is defined as the average rate of alanine formation over the reaction period r [mmoles g^{-1} h^{-1}] = moles of alanine formed/(weight of catalyst × reaction time). Due to the low reaction rate, the reaction period was at least 20 h for enantioselective hydrogenations (Tables 2 and 3).

Concerning possible mass transfer effects in the three-phase reactor system, pertinent experimental tests (16) indicated that the reported results of the enantioselective hydrogenation were free of mass transfer effects. In contrast, mass transfer effects influenced the much faster racemic hydrogenation.

After reaction the filtrate was evaporated to dryness *in vacuo*. The remaining water was removed azeotropically using methylene chloride. The residue was used for derivatization without any purification in order to avoid the enrichment of one of the enantiomers.

Before analysis the product alanine was converted to a volatile *N*-trifluoracetyl (TFA)–isopropyl ester derivative (17). The resolution of derivatized enantiomers was performed using a HP 5880A gas chromatograph, equipped with a chiral fused silica capillary column (FS-L-Chirasil-Val-DF-0.10, 25 m × 0.25 mm ID, Chrompack) and FID detector. DL valine was used as the inner standard for the determination of the chemical yield. Enantiomeric excess is defined as the difference between the major and minor enantiomers, in percent.

X-Ray Crystal Structures

Reflection intensities were obtained from an automatic diffractometer (Enraf–Nonius CAD4, graphite-monochromatized Mo$K\alpha$ radiation, $\lambda = 0.71073$ Å). Crystal and data collection parameters are listed in Table 1. The structures were solved by direct methods (SHELXS 86) (18) and refined by least-squares analysis (SHELXL 93) (19). In CD-oxime and in EP-oxime all non-H atoms except the O atom in the ephedrine (Fig. 4) were refined anisotropically. This O atom shows some disorder and was refined isotropically in two different positions.

TABLE 1

Crystal and Data Collection Parameters for Compounds CD-oxime and EP-oxime

Compound	CD-oxime	EP-oxime
Formula	$C_{19}H_{23}N_2O^+ \cdot C_3H_4NO_3^-$	$C_{10}H_{16}NO^+ \cdot C_3H_4NO_3^-$
Molecular weight	397.5	268.31
Cryst. color, habit	white needle	white block
Cryst. size [mm]	$0.6 \times 0.15 \times 0.05$	$0.4 \times 0.3 \times 0.25$
Space group	$C2$, monoclinic	$P2_12_12_1$, orthorhombic
a [Å]	17.693 (6)	8.787 (2)
b [Å]	6.646 (4)	11.399 (3)
c [Å]	19.208 (7)	14.683 (4)
α [°]	90	90
β [°]	109.00 (4)	90
γ [°]	90	90
V [Å^3]	2136	1470.72
D_x [gcm^{-3}]	1.23	1.21
Z	4	4
T[K]	293	293
Reflections indep.	3627	1500
Reflections obs. $[I > 3\sigma(I)]$	1172	1179
R (F)	0.049	0.047
wR (F^2)	0.136	0.145
μ[mm^{-1}]	0.09	0.09
θ_{max}[°]	25	25
Residual electron dens. [eÅ^{-3}]	0.17	0.33
Parameters refined	262	238

Lists of fractional atomic coordinates were deposited with the CSD (Cambridge Structural Database).

Molecular Modeling

Biosym programs Insight II (version 3.0.0, molecular modeling system, Biosym Technologies Inc., 1995) and Discover (version 95.0, molecular simulation program, Biosym Technologies Inc., 1995) were used in the molecular modeling study. Molecular mechanics minimum energy calculations were performed using the ESFF forcefield and the default values as supplied by the software.

RESULTS

Table 2 shows the effect of solvents on the reaction rate and chemical yield. The best solvents for racemic hydrogenation are acetic acid and simple aliphatic alcohols, in which high yields for alanine (90–95% at full conversion) were obtained. No correlation could be found between alanine yield and solvent polarity characterized by the empirical solvent parameter E_T^N (20). Acetic acid and the small chain aliphatic alcohols possess similar polarity ($E_T^N = 0.55$–0.76). In apolar medium such as dioxane or in the most polar solvent water ($E_T^N = 1.0$), the alanine yield was only 20% or less. In the latter case the low yield at full oxime conversion

TABLE 2

Effect of Solvent on the Hydrogenation of Pyruvic Acid Oxime Using a Catalytic Amount of Modifier (200 mg 5 wt% Pd/Alumina, 20 mg Modifier, 30°C, 10 bar)

Solvent	Modifier	Time (h)	Yield (%)	Average rate (mmol/(g cat., h))	ee (%)
MeOH	—	2	95	19.0	—
EtOH	—	5	90	7.2	—
EtOH	CD	20	48	0.96	4.2 (*R*)[a]
EtOH	HCD	20	30	0.6	3.6 (*R*)
EtOH	CN	20	83	1.6	5.1 (*S*)
iPrOH	—	7	90	5.1	—
iPrOH	CN	20	12	0.2	0
AcOH	—	1.5	94	25.0	—
AcOH	HCD	20	75	1.5	1.7 (*S*)

[a] Letter in parenthesis indicates enantiomers in excess.

is attributed to the hydrolysis of the imine intermediate, followed by the reduction of the activated keto group (14, 15).

In the presence of catalytic amounts of cinchona alkaloids (CD, CN) and the simple (prehydrogenated) derivative HCD, the average rate of alanine formation decreased by a factor of 12–26, compared to the rate of racemic hydrogenation. Note that the moderate alanine yields obtained in the presence of modifier are due to the very low reaction rate: the conversion of oxime was incomplete sometimes even after several days of reaction time. The enantiomeric excess was very low in all cases but well reproducible (standard deviation $< \pm 0.5\%$). Substituting CD with the near-enantiomer CN leads to the formation of (*S*)-alanine in excess instead of the (*R*)-enantiomer, expectedly. Using HCD in ethanol, the *R* configuration of alanine was in excess, while in acetic acid a slight excess of *S* configuration was obtained. A similar solvent effect has already been reported for the hydrogenation of pyruvic acid oxime in alcohols and dioxane (13).

Thermal pretreatment of the catalyst in hydrogen, which was found to enhance the ee by 10–40% in the hydrogenation of α-ketoesters (21–23), had no detectable influence on the enantioselection in oxime hydrogenation. Similarly, prehydrogenation of CD to HCD had only a negligible effect on ee. Replacing Pd/alumina by Pt/alumina resulted in a complete loss of ee, independent of the solvent. This is in contrast to the hydrogenation of α-ketoesters on cinchona-modified Pt metals, where Pt provides much higher enantioselectivity than any other metals (23, 24). An important observation is that no enantioselection was obtained when the oxime of pyruvic acid ethyl ester was hydrogenated under identical conditions, irrespective of whether Pd/alumina or Pt/alumina was used as catalyst. The role of the carboxyl group in the reactant–modifier interaction will be discussed later.

The influence of temperature between 0 and 60°C on the reaction rate and ee is shown in Fig. 1. The rate of alanine

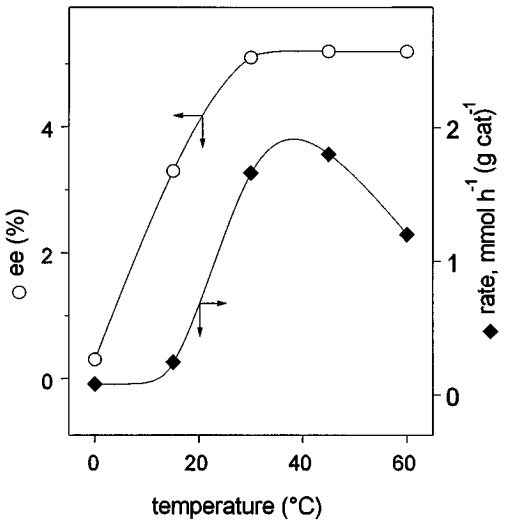


FIG. 1. Effect of temperature on the average rate and enantiomeric excess (ee); (Pd/alumina: 200 mg at 15–60°C and 500 mg at 0°C; time: 20 h at 30–60°C and 70 h at 0–15°C; 20 mg cinchonine, 10 bar, EtOH).

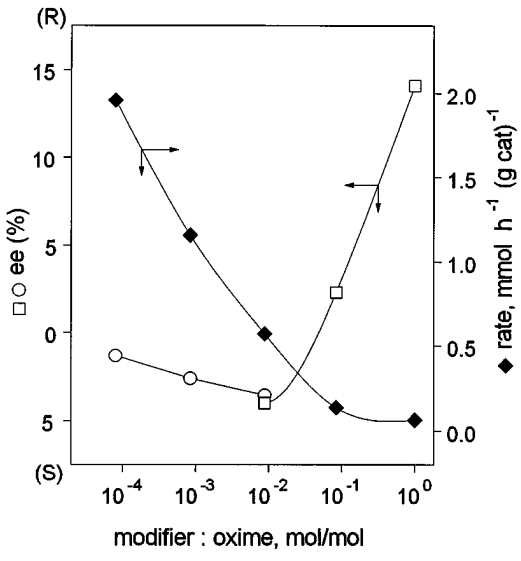


FIG. 2. Effect of modifier : reactant ratio on the average rate of alanine formation and enantioselection (30°C, 10 bar, EtOH; catalyst: 200 mg below and 500 mg above 10^{-1} mol/mol; modifier: HCD at and below 8.4×10^{-3} mol/mol and CD at and above this ratio).

formation increased with ascending temperature and the best yield (90% at almost full conversion) was obtained at 45°C. The decrease of the rate of alanine formation at 60°C is due to side reactions (secondary amine formation) resulting in the suppression of alanine yield to only 60%. Unexpectedly, enantioselection disappeared at low temperature. Usually the enantioselectivity increases at low temperature as the rigid arrangement in the transition state, necessary for asymmetric induction, is favored at low temperature (25). A closely related example on the improved selectivity at low temperature is the asymmetric hydrogenation of imines (2, 13).

Figure 2 shows the influence of modifier : reactant molar ratio on the average reaction rate and ee. The highest yield of alanine (98%) was obtained in the presence of a small amount of HCD (84 μmol/mol oxime). Using CD or HCD, the minor excess of (*R*)-alanine changes to an excess of (*S*)-alanine above 0.03 mol/mol and reaches 14.1% at a 1 : 1 molar ratio. Similarly, the best ee was obtained when EP was used as "modifier" in stoichiometric amount, as shown in Table 3. Above the stoichiometric ratio ee dropped again. Note that mixing the oxime with CD or EP in ethanol before the reaction resulted in partial precipitation of CD- or EP-oxime salts, respectively, as identified by ^{1}H NMR. Another unexpected observation is that both CD and the near-enantiomer CN provide an excess to (*S*)-alanine, when applied in a 1 : 1 molar ratio related to the oxime.

The rapid transformation of oxime to alanine in the absence of alkaloid indicates an unhindered adsorption and reduction of the >C=N–OH moiety on the Pd surface. The presence of chiral 1,2-amino alcohols CD, HCD, CN, or EP decreased the reaction rate by a factor of up to 140, depending on the oxime : alkaloid molar ratio. Likewise, the hydrogenation of α-phenylcinnamic acid with CD-modified Pd/alumina and Pd/titania was reported to be slower by about an order of magnitude, compared to the racemic reaction (26). In contrast, in the enantioselective hydrogenation of α-ketoesters to α-hydroxyesters on Pt/alumina the addition of cinchona alkaloids enhances the reaction rate by about an order of magnitude (21).

In order to study the interactions between the alkaloids (CD, EP) and pyruvic acid oxime, the crystal structures of corresponding 1 : 1 complexes were elucidated. Figures 3 and 4 show ball-and-stick models of parts of the linear chains of CD-oxime and EP-oxime, respectively. Both chain-like structures of the complexes are stabilized by an extensive hydrogen bond network. All possible donor and acceptor atoms are involved in hydrogen bonding. In both cases (Figs. 3 and 4) the oxime molecules are connected to each other by H bonds between the hydroxyl and carboxyl functional groups. In the CD-oxime structure (Fig. 3) the oxime carboxyl group is connected to the

TABLE 3

Hydrogenation of Pyruvic Acid Oxime Using Large Amount of Modifiers (500 mg Pd/Alumina, EtOH, 30°C, 10 bar)

Modifier	Modifier : oxime (mol/mol)	Time (h)	Yield (%)	Average rate (mmol/(g cat., h))	ee (%)
CD	1	70	28	0.064	14.1 (*S*)[a]
CN	1	70	30	0.068	12.0 (*S*)
EP	0.75	20	43	0.34	11.6 (*S*)
EP	1	45	15	0.053	26.0 (*S*)
EP	1.5	100	20	0.029	13.0 (*S*)

[a] Letter in parenthesis indicates enantiomers in excess.

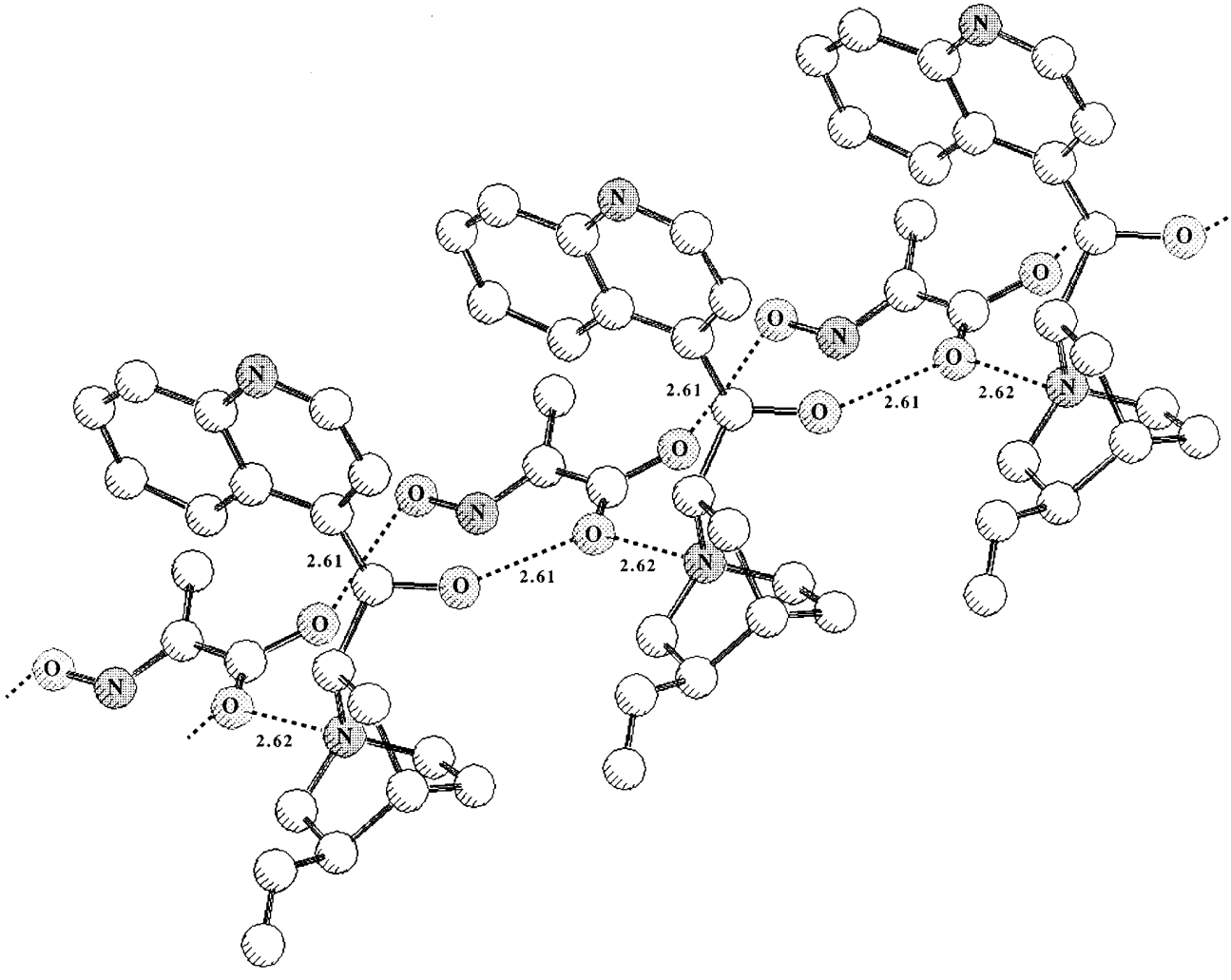


FIG. 3. Part of the chain in the CD-oxime structure with hydrogen bond distances in Å (10^{-1} nm). Molecules (x, y, z), ($-x$, $0.5-y$, $0.5-z$), and (x, $-y$, z) are displayed.

hydroxyl group of CD and the basic nitrogen of the next CD molecule in the chain. In the case of EP-oxime (Fig. 4), the oxime carboxyl group is connected to the basic nitrogen atom and the hydroxyl functional group of the same EP molecule. Besides, the same oxime carboxyl group is bonded to the nitrogen atom of another EP molecule (on the other side of the chain). Another type of H bond connects the oxime nitrogen atom to the nitrogen atom of the second EP molecule. A further characteristic feature of the EP-oxime structure is that both the oxime and the alkaloid possess an alternating position in the chain.

DISCUSSION

The most important question to be discussed is the steric course of the Pd-catalyzed hydrogenation of pyruvic acid oxime. A feasible mechanism should explain the suppressed reaction rate in the presence of alkaloids and the influence of the chiral amino alcohol : oxime molar ratio on enantioselection. In the only paper which to our knowledge has been published on the enantioselective hydrogenation of α-ketoester oximes (13), the authors did not attempt to explain the enantioselection (3–10% ee) obtained. The Pd-catalyzed diastereoselective hydrogenation of optically active oximes of pyruvic acid menthyl ester and pyruvamide derived from α-ethylbenzylamine has been interpreted by the "chelation mechanism" (1, 2, 10, 12, 27, 28). According to this generally accepted model developed by Harada (1), the oxime forms a five-membered ring ("chelate") involving a surface Pd atom, as shown in Scheme 4a for pyruvamide oxime. The plane comprising the C=N bond is assumed to be perpendicular to the Pd surface. Subsequently, this cyclic intermediate is adsorbed on the metal surface from the less bulky side of the molecule and the hydrogenation occurs.

An important point in the mechanism is that only the Z isomer of the oxime is able to form the chelate ring. A

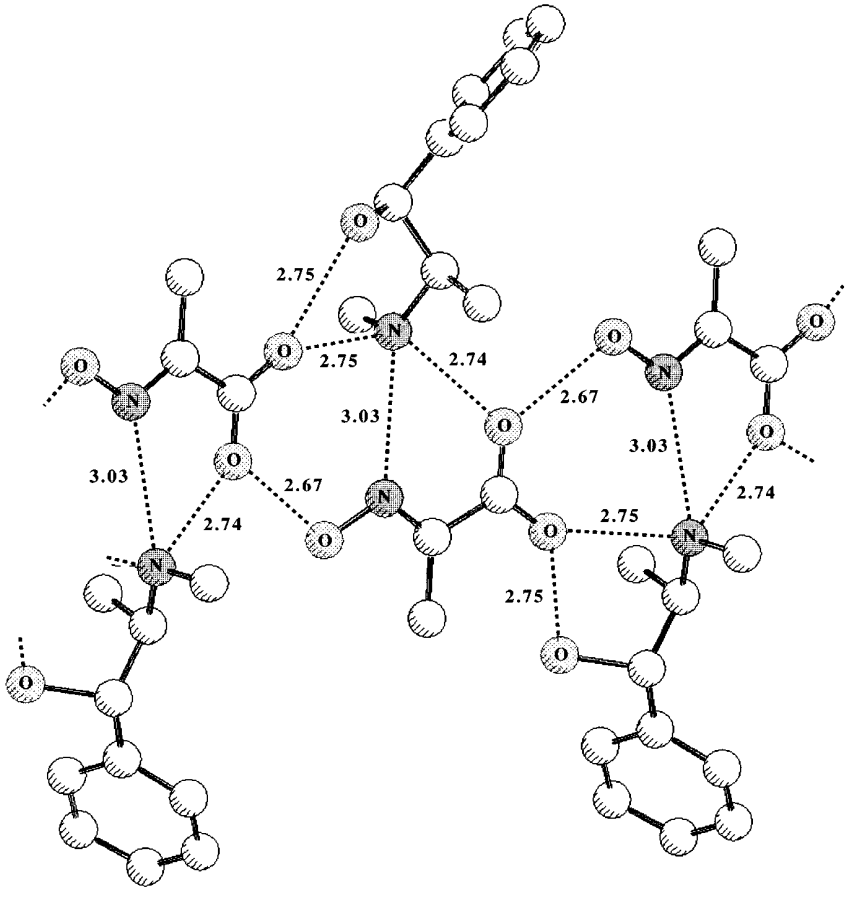
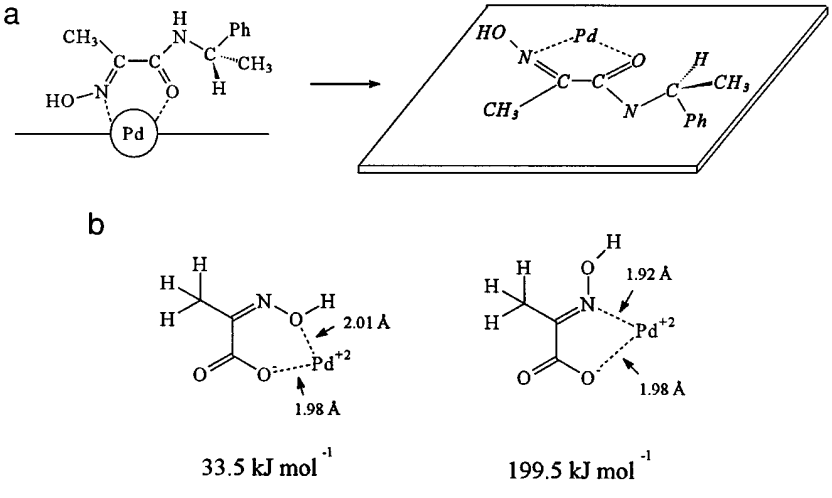


FIG. 4. Part of the chain in the EP-oxime structure with hydrogen bond distances in Å (10^{-1} nm). Molecules (x, y, z), ($x-1$, y, z), and $x-2$, y, z) are displayed.

support for this mechanism is the observation (7) that Z and E oximes isomerize rapidly via the nitroso compound (tautomerism) on Pd/C in ethanol under ambient conditions. However, it is not clear why the N atom in the oxime is assumed to be involved in the chelate ring. The electron density on the hydroxyl O atom of oxime is considerably higher and it should be a better electron donor to Pd than the N atom, resulting in the formation of a six-membered cyclic intermediate. AMPAC (AM1) calculations showed that the electron density of the O atom in the N–O–H structural



SCHEME 4

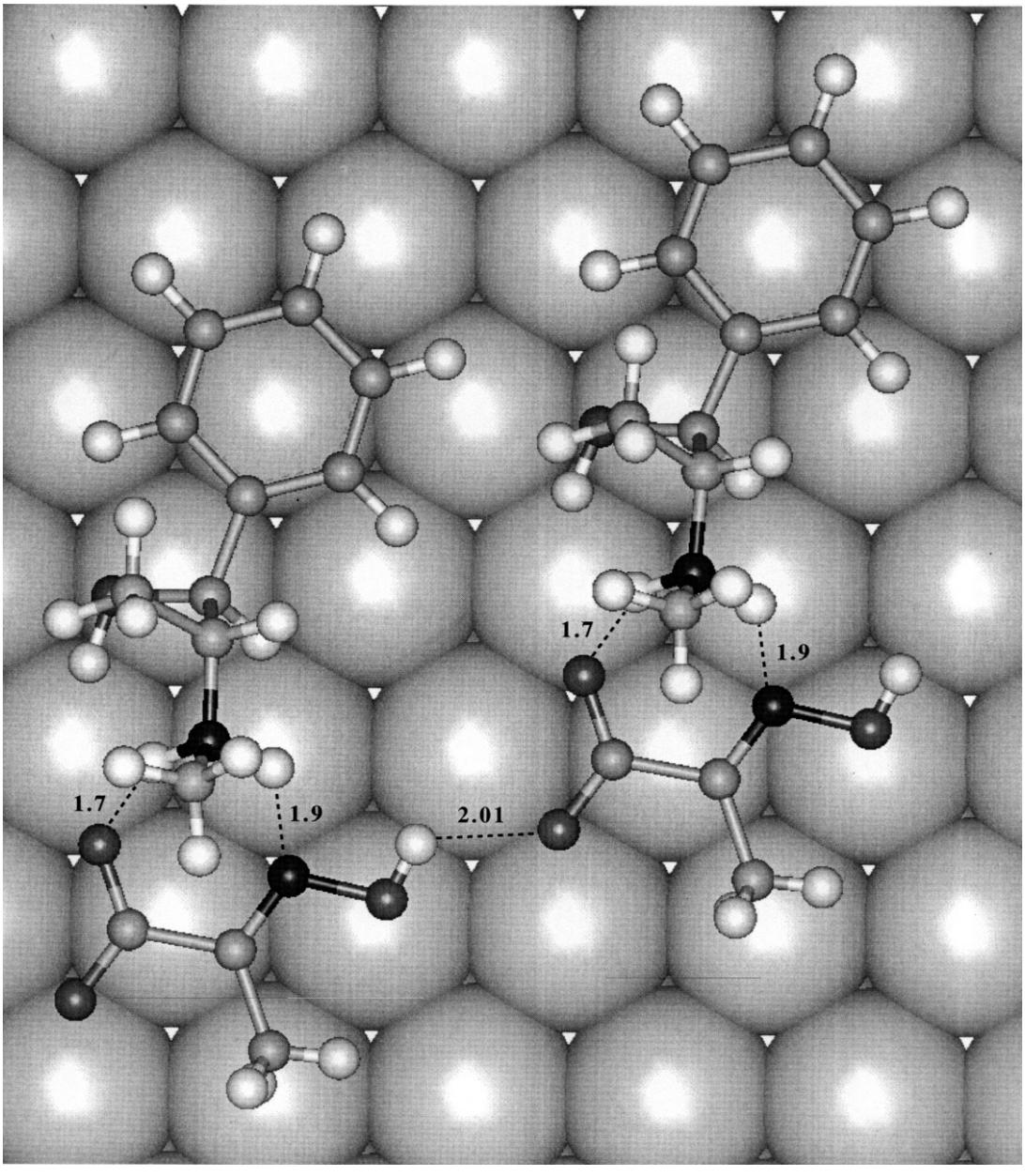


FIG. 5. Proposed adduct formed during enantioselective hydrogenation of pyruvic acid oxime with ephedrine modifier on Pd surface. A Pd (111) surface is used for illustration.

part of pyruvic acid oxime is higher by 0.07–0.25, related to the N atom and depending on whether the acid or its deprotonated form is considered. The six membered ring, formed via electron donation from two O atoms of pyruvic acid oxime, is more stable by 166 kJ mol^{-1} than the five-membered chelate according to Harada's model (Fig. 4b).

A further crucial point concerning the inadequacy of the chelating model in the case of enantioselective hydrogenation of oxime–alkaloid salts is that the expected flexible interaction between the protonated N atom of the alkaloid and the carboxylate group of the oxime cannot give preference (e.g., by steric hindrance) to the adsorption of any "face" of the chelate ring on the Pd surface. In other words, the production of racemic alanine should be expected based on the chelating mechanism.

We propose that the enantio-differentiation observed in the hydrogenation of CD-oxime and EP-oxime salts is due to the extended interaction by H bonding between the adsorbed alkaloid–oxime salt "units" on the Pd surface. The proper position of oxime and alkaloid molecules are stabilized by H bonds between the oxygen and nitrogen atoms of the functional groups. A possible arrangement of two EP-oxime units as a simplified model is shown in Fig. 5 for illustration. In contrast to the alternating structure found

in the solid phase by X-ray analysis, here the pyruvic acid oxime is arranged always in the same position. The modeled complex is located over a Pd(111) surface for illustration. Bond distances and angles are based on the X-ray analysis. Although metal–adsorbate interactions are very important, they cannot yet be calculated for such complex structures. The oxime would result in (*S*)-(+)-alanine upon hydrogenation, assuming H transfer from the Pd surface to the adsorbed face of the C=N bond. It is also assumed that the aromatic ring of the alkaloid and the conjugated π-electrons of pyruvic acid oxime adsorb parallel to the flat Pd surface.

It is clear from the model that even two alkaloid–oxime salt units, connected by H bonding, cannot be easily located on a Pd surface. The most important element of misfitting is that in reality the metal surface of the Pd/alumina catalyst is far from being ideally flat, which likely hinders the flat, parallel adsorption of an extended EP-oxime complex. In the extreme case, when only one alkaloid and one oxime molecule can adsorb together, the enantioselection is expected to be very low due to the missing rigid structure of the complex.

Figure 5 presents a possible model for enantioselection which accounts for the following experimental observations:

(i) the rate of enantioselective hydrogenation is very low compared to that of racemic hydrogenation due to the extended interaction between the adsorbed alkaloid–oxime salt units;

(ii) the enantioselectivity reaches its maximum at an alkaloid : oxime molar ratio of 1 : 1;

(iii) a polar solvent (EtOH) favors the extended H bonding on the Pd surface;

(iv) using the ethyl ester of pyruvic acid oxime results in a complete loss of enantio-differentiation, which is attributed to the absence of some H bonds necessary for the formation of the rather rigid chain shown in Figs. 3–5.

CONCLUSIONS

Relatively little effort has been expended so far in the enantioselective hydrogenation of C=N bonds over chirally modified solid surfaces, compared to the enantioselective reduction of C=O and C=C functional groups, likely due to the difficulties in achieving acceptable enantiodifferentiation. The best ee, obtained in the enantioselective hydrogenation of pyruvic acid oxime in this work, is still rather moderate (26%), but considerably higher than any reported ee for the catalytic (10%) or electrocatalytic (19%) reduction of α-ketoacids to amino acids. The proposed mechanistic model, based on the extended interaction between the adsorbed alkaloid–pyruvic acid oxime salts on the Pd surface, requires further refinement, but even in its present state offers one possible explanation to the moderate enantioselection and the very low reaction rate of enantioselective hydrogenation.

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REFERENCES

1. Harada, K., *ACS Symp. Ser.* **185**, 169 (1982).
2. Harada, K., *in* "Asymmetric Synthesis" (J. D. Morrison, Ed.), Vol. 5, p. 345. Academic Press, Orlando, 1985.
3. Blaser, H. U., *Tetrahedron Asymm.* **2**, 843 (1991).
4. Zhu, Q. C., Hutchins, R. O., and Hutchins, M. G. K., *Org. Prep. Proc. Int.* **26**, 193 (1994).
5. Hiskey, R. G., and Northrop, R. C., *J. Am. Chem. Soc.* **83**, 4798 (1961).
6. Harada, K., *Nature* **212**, 1571 (1966).
7. Harada, K., and Shiono, S., *Bull. Chem. Soc. Jpn.* **57**, 1040 (1984).
8. Sheehan, J. C., and Chandler, R. E., *J. Am. Chem. Soc.* **83**, 4795 (1961).
9. Kanai, A., and Mitsui, S., *J. Chem. Soc. Jpn.* **89**, 183 (1966).
10. Matsumoto, K., and Harada, K., *J. Org. Chem.* **31**, 1956 (1966).
11. Harada, K., and Matsumoto, K., *J. Org. Chem.* **32**, 1794 (1967).
12. Munegumi, T., and Harada, K., *Bull. Chem. Soc. Jpn.* **61**, 1425 (1988).
13. Yoshida, T., and Harada, K., *Bull. Chem. Soc. Jpn.* **44**, 1062 (1971).
14. Rylander, P. N., *in* "Catalytic Hydrogenation in Organic Synthesis," p. 153. Wiley, New York, 1967.
15. Freifelder, M., *in* "Catalytic Hydrogenation in Organic Synthesis," p. 53. Wiley, New York, 1978.
16. Fogler, H. S., "Elements of Chemical Reaction Engineering," p. 665. Prentice Hall, New Jersey, 1992.
17. Zumwalt, R. W., Kuo, K. C. T., Gehrke, C. W., Abeand, B. R., and Kuramoto, S., "Amino Acid Analysis by Gas Chromatography." 1987.
18. Sheldrick, G. M., *Acta Crystallogr. A* **46**, 467 (1990).
19. Sheldrick, G. M., "SHELXL93. Program for the Refinement of Crystal Structures." Univ. of Göttingen, Germany, 1993.
20. Reichardt, C., "Solvents and Solvent Effects in Organic Chemistry," p. 359. VCH, Weinheim, 1988.
21. Orito, Y., Imai, S., and Niwa, S., *J. Chem. Soc. Jpn.* 1118 (1979).
22. Wehrli, J. T., Baiker, A., Monti, D. M., and Blaser, H. U., *J. Mol. Catal.* **49**, 195 (1989).
23. Minder, B., Schürch, M., Mallat, T., and Baiker, A., *Catal. Lett.* **31**, 143 (1995).
24. Blaser, H. U., Jalett, H. P., Monti, D. M., Reber, J. F., and Wehrli, J. T., *Stud. Surf. Sci. Catal.* **41**, 153 (1988).
25. Juaristi, E., "Introduction to Stereochemistry and Conformational Analysis," p. 106. Wiley-Interscience, New York, 1991.
26. Nitta, Y., and Kobiro, K., *Chem. Lett.* 165 (1995).
27. Yoshida, T., and Harada, K., *Bull Chem. Soc. Jpn.* **45**, 3706 (1972).
28. Harada, K., and Matsumoto, K., *J. Org. Chem.* **33**, 4467 (1968).