annealing protocol that cements a target structure in place. It can be expected that these wirelike assemblies, insulated similarly to shrink-wrapped electrical cord, can be extended to a variety of redox-active endgroups with various coordination geometries. This novel family of building blocks is certain to have applications in nanotechnology.

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[26] CH_2Cl_2, 100 mV s^{-1}, E° vs SCE (ferrocene = 0.46 V), **10**/**9**: $E_{p,a}$ 1.259/1.261 V; $E_{p,c}$ 1.168/1.143 V; E° 1.214/1.202 V; ΔE 91/118 mV.

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cis–*trans* Selectivity of Enzyme-Catalyzed Additions to 4-Substituted Cyclohexanones—Correlation with the Prelog/Ringold Model of Enzymatic Hydrogenation**

Franz Effenberger,* Jürgen Roos, and Christoph Kobler

Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

V. Prelog and co-workers were the first to use the conformational stability of cyclic ketones and alcohols to make a statement about the topography of the active site of an enzyme.[1] The enzymatic hydrogenation of 4-substituted cyclohexanones using NADH-dependent horse-liver alcohol dehydrogenase (LADH; NADH = nicotinamide adenine dinucleotide, reduced form) was particularly suitable for this

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purpose. Assuming a defined spatial arrangement of the amino acid residues and the NADH for the "hydride ion" transfer in the enzyme–substrate complex, then the different binding modes of the cyclohexanones in the active site must be responsible for the formation of *cis* and *trans* isomers.

Based on this idea, H. J. Ringold and co-workers investigated the influence of substituents in the 3- and 4-positions of cyclohexanone on the stereochemical outcome of the LADH-catalyzed hydrogenation to cyclohexanols.[2] Comprehensive correlations of hydrogenation rates and the stereochemistry of product formation resulted in models for two types of enzyme–substrate complexes, capable of plausibly explaining the stereoselectivity of hydrogenation.[2] "Horizontal" orientation of the cyclohexanone in the active site should give the *cis* isomer, and a "vertical" orientation should give the corresponding *trans* isomer (Figure 1).[2b]

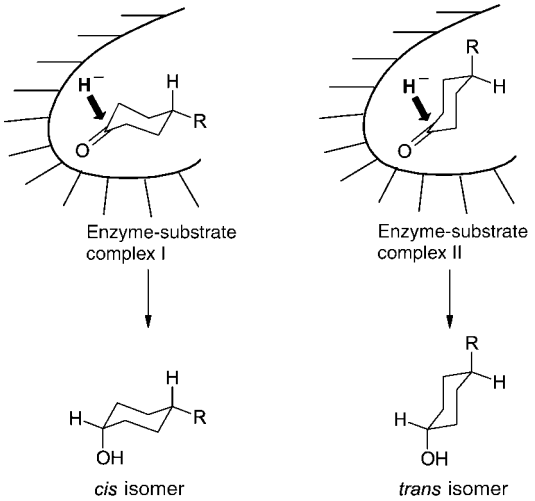


Figure 1. Formation of the *cis* and *trans* alcohol by the LADH-catalyzed hydrogenation of 4-substituted cyclohexanones.[2b]

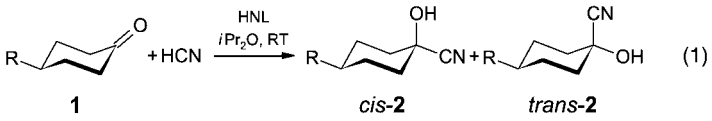
Although X-ray crystal structures of LADH have been published[3a, b] and the structure of ketone–enzyme adducts for drosophila ADH was also solved,[3c] the Prelog/Ringold model based on the stereoselectivity of cyclohexanone hydrogenation has not been confirmed.

The NADH-dependent enzymatic hydrogenation of carbonyl compounds mechanistically resembles the hydroxynitrile-lyase (HNL) catalyzed addition of HCN to carbonyl compounds, which yields cyanohydrins.[4] In both cases, the primary addition of the nucleophile, either hydride or cyanide, determines the stereochemistry of the product formation.

In the past few years, the HNL-catalyzed addition of HCN to prochiral aldehydes and alicyclic ketones, to give optically active cyanohydrins, has been intensively investigated.[5, 6] Herein, we report the corresponding reaction with 4-substituted cyclohexanones. This reaction is of interest in two respects: first, how well the results fit to the Prelog/Ringold model, and second, the stereoselective preparation of 4-substituted cyclohexanone cyanohydrins as starting compounds for, for example, substituted tetronic acids, known to be potent herbicides and insecticides.[7]

The synthesis of very few 4-substituted cyclohexanone cyanohydrins has been described to date.[8–10] In all cases, mixtures of *cis*–*trans* isomers were obtained. For the 4-methyl compound, the *cis*:*trans* ratio is 1:2 and in the case of the 4-*tert*-butyl derivative, the *cis*:*trans* ratio is 1:3. These ratios are the same under base catalysis,[10a] and are therefore assumed to correspond to the thermodynamic equilibria.

In the HNL-catalyzed preparation of the 4-substituted cyclohexanone cyanohydrins **2**, the hydroxynitrile lyases from almonds ((*R*)-PaHNL) and cassava ((*S*)-MeHNL) have been applied. The cyclohexanones **1** are good substrates for both enzymes [Eq. (1)], which exhibit high *cis* and *trans* selectivity,



(1)

respectively (Table 1). The structures of the stereoisomers were assigned by NMR spectroscopy, by comparison with literature data.[11] The (*R*)-PaHNL-catalyzed reaction afforded almost exclusively *trans* isomers with all ketones **1a–g** (Table 1), but (*S*)-MeHNL catalyzes the HCN addition to **1** in favor of the *cis* isomers. Only 4-methylcyclohexanone (**1a**) shows a low stereoselectivity. The reaction rate with (*S*)-MeHNL is considerably faster than that with (*R*)-PaHNL,

Table 1. Preparation of cyclohexanone cyanohydrins **2** by (*S*)-MeHNL- and (*R*)-PaHNL-catalyzed addition of HCN to the 4-substituted cyclohexanones **1** [Eq. (1)] and comparison to the addition without enzyme catalysis.[a]

		(*S*)-MeHNL[b]			(*R*)-PaHNL[b]			Without enzyme[c]	
	R	*t* [h]	conversion [%]	*cis*:*trans* [%]	*t* [h]	conversion [%]	*cis*:*trans* [%]	conversion [%]	*cis*:*trans* [%]
a	Me	2	80	35:65	1.5	99	3:97	4	17:83
b	Et	5	quant	74:26	22	99	2:98	0.5	16:84
c	Pr	5	93	96:4	31	83	2:98	< 1	15:85
d	*i*Pr	5	quant	97:3	22	94	1:99	< 1	13:87
e	*t*Bu	3	82	99:1	216	50	10:90	2	13:87
f	H_2C=CMe	9	99	98:2	24	99	1:99	2.5	11:89
g	Ph	3	95	99:1	264	71	4:96	28	9:91

[a] The support was treated as described previously.[5] [b] Substrates **1** (1 mmol) and HCN (150 μL, 3.9 mmol) were treated in diisopropyl ether (5 mL) with (*S*)-MeHNL (180 U) or (*R*)-PaHNL (200 U), as catalyst. Conversion and isomeric ratios were determined by GC after acetylation. [c] The enzyme solution was replaced by the same volume of sodium citrate buffer (0.02 M, pH 5.4). The reaction times were the same as those of the (*R*)-PaHNL-catalyzed conversions.

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even in case of the sterically demanding substrates **1e** and **1f** (Table 1).

The X-ray crystal structure of MeHNL[4] reveals that the active site is accessible by a narrow channel and consists of a smaller (S_1) and a larger binding pocket (S_2). In the acetone–MeHNL complex, the carbonyl group of the substrate is bound by hydrogen bonds from Thr11 and Ser80.[4] Whereas in the LADH hydrogenation, the hydride ion attacks the carbonyl group of cyclohexanone from "above" (Figure 1), the addition of cyanide in the MeHNL-catalyzed reaction occurs from "below",[4] so that, according to the Prelog/Ringold model, the *cis* isomer should be generated from the vertically positioned cyclohexanone ring. Superposition of the catalytically inactive mutant MeHNL–Ser80Ala complexed with acetone cyanohydrin, onto the MeHNL–acetone complex structure, reveals that the cyanohydrin is bound in an analogous manner to the ketone.[12]

Assuming the binding by hydrogen bonding in the active site, and the chair conformation of the cyclohexane ring with a preferentially equatorial *tert*-butyl group,[13] the *cis* selectivity of MeHNL can easily be explained by use of molecular-modeling calculations, as shown for **2e**. The *cis* isomer **2e** in its "vertical" position, bound by hydrogen bonds to Thr11 and Ser80, fits perfectly into the channel and the active site (Figure 2a). The corresponding "horizontally" positioned

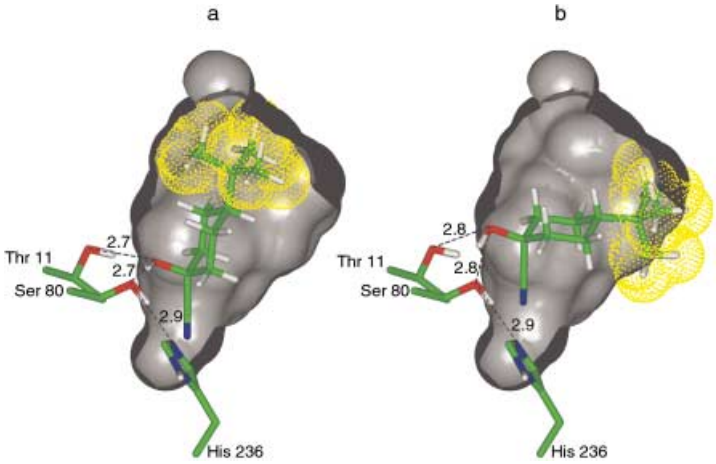

Figure 2. Molecular-modeling representation of the *cis* (a) and *trans* conformation (b) of 4-*tert*-butylcyclohexanone cyanohydrin **2e**, in the active site of (*S*)-MeHNL.

trans isomer **2e**, however, clearly clashes with the channel wall (Figure 2b). This model also explains the low stereoselectivity of the 4-methyl derivative **2a**, in which both the "vertical" and "horizontal" binding modes are sterically possible. Hence, it is not surprising that the *cis*:*trans* ratios for the HCN addition to **1a** vary, and depend, for example, on enzyme activity and reaction conditions.

The major isomer of cyanohydrin **2f**, obtained by MeHNL-catalyzed HCN addition to **1f**, was crystallized as the *p*-nitrobenzoyl derivative. Its X-ray crystal structure[14] (Figure 3) provides clear experimental evidence for the formation of the *cis* isomer (Table 1) and thus supports the modeling calculations for the *tert*-butyl derivative **2e**. The *trans* selectivity of PaHNL cannot yet be explained by structural arguments, because too little is known about the enzyme structure.[15]

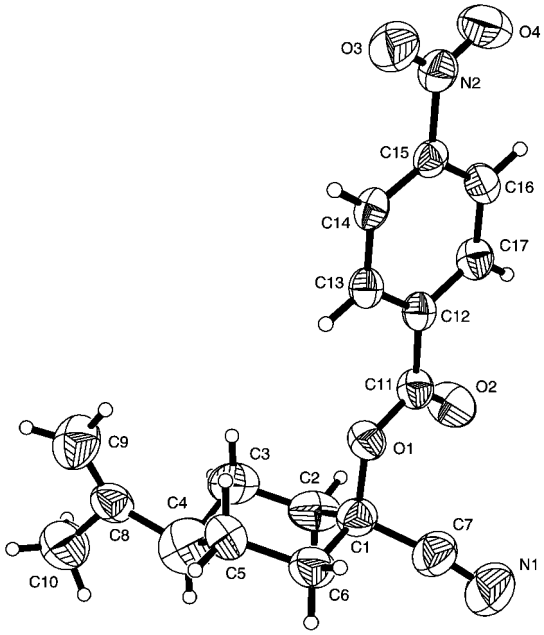

Figure 3. X-ray crystal structure of the *p*-nitrobenzoyl derivative of **2f**.

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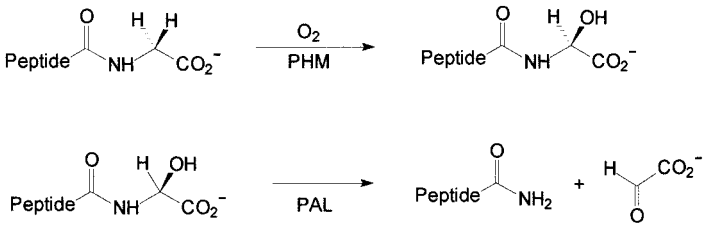
Selective α-Carbon Hydroxylation of Glycine in Nickel(II)–Cyclotetrapeptide Complexes by Oxygen**

Katharina Haas, Harald Dialer, Holger Piotrowski, Jan Schapp, and Wolfgang Beck*

Dedicated to Professor Ernst-Ludwig Winnacker on the occasion of his 60th birthday

The copper-containing bifunctional enzyme peptidylglycine α-amidating monooxygenase (PAM) catalyzes the bioactivation of peptide hormones by amidation.[1] In the first step the copper-containing peptidylglycine α-hydroxylating monooxygenase (PHM) catalyzes the stereospecific hydroxylation of the C-terminal glycine to give an α-hydroxyglycine peptide (Scheme 1). A second enzyme, the peptidyl-α-hydroxyglycine

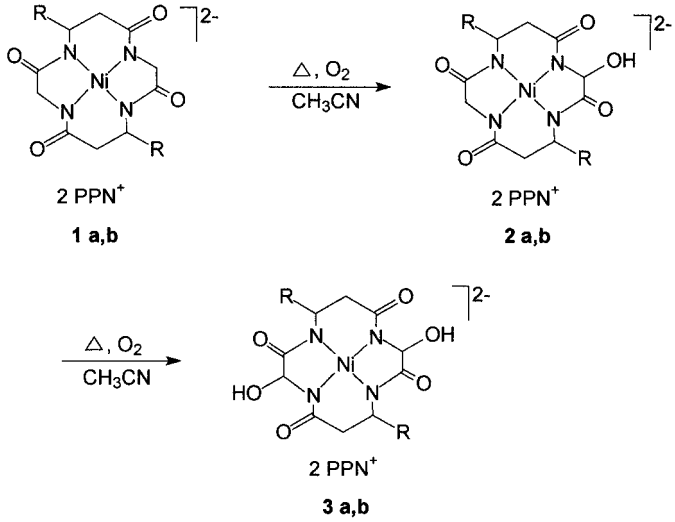


Scheme 1. Steps in the bioactivation of peptide hormones.

α-amidating lyase (PAL) generates the bioactive peptide amide and glyoxylate under α-C–N cleavage. Some reactions which are related to these transformations have been reported:

- The reactions of nickel(II) complexes of open-chain peptides with oxygen occur via nickel(III) intermediates to give oxidative cleavage of the terminal glycine α-C–N bond.[2]
- The nickel(II) complex [Ni^{II}(Gly-Gly-His)] is decarboxylated and α-C hydroxylated by oxygen via a nickel(III) intermediate.[3] This reaction can lead to the formation of DNA adducts.[4]
- α-C hydroxylation of the amino acid component in Ni^{II} Schiff base complexes from salicylaldehyde and α-amino acid esters which is followed by C–N cleavage was observed by Paul Pfeiffer,[5] one of the fathers of coordination chemistry.
- The copper(II)-mediated α-hydroxylation of an *N*-acylglycine,[6] the glycine-specific α-C–N cleavage of a dipeptide by nickel and copper peroxide,[7] and especially the α-hydroxylation of glycine-containing dipeptide ligands in a Co^{III} terpyridine complex by oxygen[8] are models for PAM.

The cyclocondensation of non-activated dipeptide esters at Cu^{II}, Ni^{II}, and Pd^{II} templates is a simple and attractive synthesis of cyclotetrapeptides.[9, 10] Cyclotetrapeptides are of interest for, among others, the formation of optically active, C-substituted cyclams. Following the method which was introduced by Neumann et al.[11] for the reduction of cyclopentapeptides, the carbonyl functions of cyclotetrapeptides can be reduced with $LiAlH_4$.[12] We have now found that α-hydroxylation of the glycine components of the cyclopeptide ligands in the nickel(II) complexes **1a**, **b** occurs stepwise on heating the complexes in acetonitrile in air to give the compounds **2** and **3** (Scheme 2). The monohydroxylated



Scheme 2. α-C hydroxylation of the cyclotetrapeptide complex **1** by atmospheric oxygen. **1a**–**3a**: R = H; **1b**–**3b**: R = CO_2Me.

species **2a**-$(PPN)_2$ (PPN = triphenyl[triphenylphosphoranylidene)amino]phosphonium) precipitates from the solution as orange crystals, which on heating in a saturated acetonitrile solution react with the oxygen in the air to afford the dihydroxylated complex **3a**-$(PPN)_2$. Because of the strong bonding of the cyclotetrapeptide to the Ni^{II} center an α-C–N cleavage does not take place and the rare α-hydroxyglycine unit remains intact.

In the mass spectra (FAB or ESI) of **2** and **3** the ions [M^{2-}] (171, **3a**) and [$M^{2-}+H^+-H_2O$] (M = **2a**, **b**, **3b**) were detected. The transformation of the C_2-symmetric complex **1a** to the

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