REACTION OF N-ACETYLDEHYDROPHENYLALANYL-S-PROLINE WITH Ca(II) AND Ni(II) IONS AND ITS ROLE IN ASYMMETRIC HYDROGENATION

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N-Ac-ΔPhe-S-Pro forms strong coordination complexes with the CO_2H group of the proline residue and weak coordination complexes through the —C(=O)—N groups with Ca(II) and Ni(II) ions in 95% aqueous methanol as indicated by the pK_a values, PMR spectroscopy, and paramagnetic broadening of the ^{13}C NMR signals in the nickel complex. Complex formation enhances the rigidity of the dehydrodipeptide conformation, leading to a strong increase in the optical yield upon hydrogenation over achiral catalysts.

Keywords: *asymmetric hydrogenation, dipeptides, dehydrodipeptides, complexes.*

We have shown that the results of the asymmetric hydrogenation of N-acetyldehydrodipeptides depend significantly on the presence of metal salts in the reaction medium [1]. This effect is attributed to the rigid structure of the substrate as a result of complexation in solution. We also studied the structure of several of the complexes formed. Thus, N-acetyl-ΔPhe-Met forms a 1:1 complex with $PdCl_2$, which exists both in solution and as a solid. The bond of palladium to the dehydropeptide is accomplished through the sulfur atom of the methionine part of the peptide, while both the carboxyl and amide groups do not participate in complexation [2].

In the present work, we studied the structure of complexes of N-acetyldehydrophenylalanyl-S-proline (N-Ac-ΔPhe-(S)-Pro) (**1**) with $CaCl_2$ and $Ni(NO_3)_2$ in solution since high optical yields (up to 88%) have been found in the hydrogenation of these compounds [1].

The formation of complexes **1** with salts in dilute solution should be accompanied by an increase in the acidity of the hydrogen atoms in the groups participating in the complexation due to the effect of the positively charged metal ion as found in saturated dipeptides [3]. Indeed, potentiometric titration in a solution of sodium methylate in 95% aqueous methanol indicated that the pK_a of the carboxyl group in **1** in the presence of Ca(II) and Ni(II) ions is decreased by 1.1 and 2 units, respectively (see below). The amide proton is not titrated under these conditions.

In aqueous solution, the carboxyl group in **1** does not coordinate with calcium ions, and the pK_a of the carboxyl group is not altered by the presence of Ca(II) or Ni(II) ions.

The PMR spectra* of complex **1** with $CaCl_2$ in comparison with free **1** show slight changes in the chemical shifts of the protons of the acetyl group ($\Delta \sim 0.07$ ppm), vinyl group ($\Delta \sim 0.06$ ppm), and proton at the asymmetrical carbon atom ($\Delta \sim 0.06$ ppm), which indicates the lack of dissociation of the AcNH group and weak coordination of the Ca(II) ion with the other groups in **1**. The effect of Ca(II) and Ni(II) ions on the pK_a of carboxyl group in **1**:

Solvent	**1**	**1** + $CaCl_2$	**1** + $Ni(NO_3)_2$
95% aq. CH_3OH	8.2	7.1	6.2
H_2O	3.5	3.5	3.5

A more definite picture is observed in the NMR spectra of complex **1** with $Ni(NO_3)_2$. Unfortunately, direct information cannot be obtained from the NMR spectra of this complex due to its paramagnetism. However, the addition of 5% $Ni(NO_3)_2$

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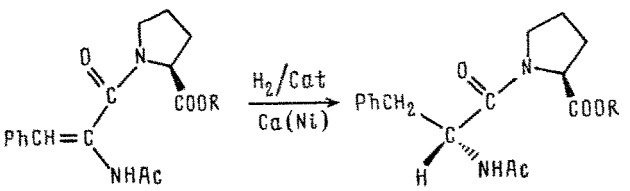
to a solution of **1** in CD_3OD leads to paramagnetic broadening in the ^{13}C NMR spectra without change in the shifts of the signals of the carbon atoms close to the nickel ions: strong broadening of the signal of the carboxyl group (175.9 ppm) and signals of the proline ring adjacent to this group (63.8 and 60.6 ppm) and slight broadening of the signals of the carbonyl carbon of the peptide (169.7 ppm) and acetyl groups (17.30 ppm). This indicates strong coordination of the Ni(II) ion with the carboxyl group and weak coordination with the oxygen atoms of the carbonyl groups. Apparently, it is specifically this coordination of the Ca(II) and Ni(II) ions, which produces the rigid structures of the complexes, whose hydrogenation proceeds with high optical yield.

The x—ray diffraction structural analysis data for the calcium adduct of N-Ac-*D*,*L*-methionine [4] has shown that the oxygen atoms of the carboxyl and acetyl groups and water molecule participate in the complexation with the calcium ion with coordination number 6 and 7.

In order to confirm the predominant effect of coordination of the metal ion with the carboxyl group on the result of the asymmetric hydrogenation, we obtained the methyl ester of **1**, namely, N-Ac-ΔPhe-Pro-OMe (**2**) and carried out the hydrogenation of this derivative in the presence of an equivalent of $CaCl_2$ and in the absence of this salt.



R=H(**1**), CH_3(**2**).

We observed a sharp decrease in the optical yield of the product and lack of effect of the metal ion on the diastereomer excess (DE). Thus, weak coordination of the dehydrodipeptide with the metal ion is insufficient for creating a rigid structure. Strong coordination of the metal ion with at least one of the groups of the substrate is required.

The calcium complex of **1** was obtained as a solid upon the reaction of **1** with a suspension of $Ca(OH)_2$ in absolute ethanol. The analysis data indicate that this complex has the formula [N-Ac-ΔPhe-(S)-Pro]$_2$Ca·$2H_2O$.

The results of the hydrogenation of **1** and its methyl ester **2** are as follows:

Substrate	1	1+$CaCl_2$	1+$Ni(NO_3)_2$	2	2+$CaCl_2$
ED of reaction product with RS configuration, %	40	88	78	24	26

We note another interesting feature of **1**. The PMR spectrum of this compound shows splitting of the signal of the proton at the vinyl carbon atom (δ = 6.49 and 6.25 ppm in 2.63:1 ratio), which indicates the existence of two isomers on the NMR time scale due, in our opinion, to hindered rotation about the amide C—N bond of the rigid proline ring. This isomerism is clearly seen in the ^{13}C NMR spectrum, which shows splitting of virtually all the carbon signals. *Z*—*E* isomerism is much less likely since the signal of the vinyl proton of the *E* isomer is usually shifted downfield by 0.5 ppm in comparison with the *Z* isomer. This is not observed in the case of **1**.

The PMR spectrum of the peptide in DMSO-d_6 at 20 and 64°C permitted us to calculate the direct and reverse isomerization rate constants: $k_{-1} = 4.18 \cdot 10^1$ sec^{-1} and $k_1 = 1.1 \cdot 10^2$ sec^{-1}. Coalescence of the signals of the vinyl proton occurs at 64°C, which indicates interconversion of the isomers.

EXPERIMENTAL

The potentiometric measurements were carried out on a Vir Tronics 43-DPH-CR titrator with combined glass—calomel electrode of the same firm in a solution of sodium methylate in 95% aq. methanol. The bridge salt used was a solution of KCl in 95% aq. methanol. The time for establishing a constant reading was about 15 min. The potentiometric cell was calibrated using benzoic and picric acids according to our previous procedure [5]. The concentration of the substrate in the cell was $2 \cdot 10^{-2}$ *M* and the effect of ionic strength was not taken into account.

Hydrogenation. A sample of 0.1 mmole $CaCl_2$ or $Ni(NO_3)_2$ was added to a solution of 0.1 mmole **1** in 5 ml abs. ethanol and maintained with stirring for 2 h until the salt was dissolved (10 min in the case of $Ni(NO_3)_2$). Then, 0.2 mmole MeONa was added and the solution was hydrogenated after 1 h according to our previous procedure [2].

The diastereoselective composition of the hydrogenation product was determined according to our procedure [2].

The NMR measurements were carried out on a Bruker WP-200 spectrometer relative to CD_3OD if not specifically indicated otherwise.

N-Ac-ΔPhe-Pro (1) was obtained by the azlactone method according to Greenstein and Vinits [6].

N-Ac-ΔPhe-Pro-OMe (2) was obtained as an oil from **1** and thionyl chloride in absolute methanol at 0°C. The yield of **2** was 75%. The product partially crystallizes upon standing. PMR spectrum (δ, ppm): 2.05 s (3H, $COCH_3$), 3.68 s (3H, OCH_3), 4.47 m (1H, CH), 6.38 and 6.02 (1H, =CH), 7.38 m (5H, Ph). Found, %: N 8.36. $C_{17}H_{20}O_4N_2$. Calculated, %: N 8.86.

(N-Ac-ΔPhe-Pro)$_2$Ca·2H$_2$O was obtained from **1** and excess anhydrous $Ca(OH)_2$ in absolute ethanol. The mixture was stirred for 3 h, centrifuged, and evaporated in vacuum to give white crystals with mp 115°C. Found, %: C 56.05; H 5.50; Ca 6.04; N, 8.36. $C_{32}H_{34}CaN_4O_8·2H_2O$. Calculated, %: C 56.60; H 5.60; Ca 5.90; N 8.26.

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