Complexation and hydrogenation of methionine-containing *N*-acetyle-dehydrodipeptides

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The hydrogenation of the Fe^{II} complex of *N*-Ac—ΔPhe-(*S*)- or -(*R*)-Met over a Pd/C catalyst affords mainly *N*-Ac-(*R*)-Phe-(*S*)-Met or *N*-Ac-(*S*)-Phe-(*R*)-Met, correspondingly. In the reaction of mixed dipeptide complexes with Ca^{II} and Fe^{II} the predominance of one of the diastereomers increases from 26 % (for complexes with Fe ions) to 38 %.

Key words: *N*-acetyl-dehydrodipeptides; complexation with metals; diastereoselective hydrogenation.

As we have previously demonstrated,[1] methionine-containing dehydrodipeptides form stable complexes with the Pd^{II} ion which coordinates with the S atom of the methionine molecule and plays the role of an internal catalyst, *i.e.*, a hydrogen carrier. Therefore, these complexes undergo hydrogenation in the absence of an external catalyst to afford one of the diastereomers with a predominance of about 40 %. In this case, though, $PdCl_2$ is not only the catalyst but also the reagent, since it is spent in the process in equimolar quantities. And so, strictly speaking, this process can not be considered a catalytic one. In this connection, it seemed interesting to obtain dehydrophenylalanyl methionine complexes with other metals and to investigate their behavior in the hydrogenation reaction. The *N*-Ac—ΔPhe—Met dipeptide in an aqueous-ethanol solution in the presence of $FeSO_4$ forms a labile complex which is easily hydrogenated over a chiral Pd/C catalyst to afford one of the diastereomers with 26 % predominance. This figure is lower than the one obtained by the application of $PdCl_2$ (40 %), but it is achieved using a common industrial catalyst.

According to the potentiometric titration data, the Fe^{II} ion in 95 % methanol does not coordinate at the carboxyl group of the dehydrodipeptide, since in its presence no rise in the acidity of the COOH group is observed. The UV spectra of the complex and the starting substrate are actually identical. However, the fact that the *N*-Ac—ΔPhe—Met complex with Fe^{II} does undergo hydrogenation over the palladium catalyst, whereas the initial dehydrodipeptide does not,[1] is indicative that the S atom in the complex is inaccessible to palladium and the catalyst in these circumstances can act. This allows one to make the assumption that the Fe^{II} ion in the complex is coordinated with the S atom.

To generate even more rigid structures, mixed complexes of the dehydrodipeptide with the two metals, *i.e.*, Fe^{II} and Ca^{II}, were obtained.

As is known,[2] the nearest analog of our substrate, *N*-Ac—Met, forms stable complexes with $CaCl_2$ in which, according to X-ray analysis, the Ca atom coordinates with the O atoms of the carboxyl and carbonyl groups not interacting with the S atom. The *N*-Ac—ΔPhe—Met dipeptide also gives a complex with $CaCl_2$: according to the potentiometric titration, in a 95 % methanolic solution the complexation of the calcium ion occurs at the caboxyl group of the peptide, since the acidity of the latter increases by 0.46 p*K* units.

We assumed that every metal, according to its own nature, coordinates with the different functional groups of the dehydrodipeptide, *i.e.*, Fe^{II} coordinates with S, whereas Ca^{II} coordinates with the O atoms of the carboxyl and carbonyl groups. This should result in a further increase in the conformational rigidity of the complex formed.

The mixed complexes of *N*-Ac—ΔPhe—Met with Fe^{II} and Ca^{II} ions obtained were hydrogenated over a Pd/C catalyst. The results of the hydrogenation are presented in the Table 1.

Table 1. The hydrogenation of the complexes of *N*-Ac—ΔPhe-(*S*)-Met with Fe^{II} and Ca^{II} ions

Metal ion	—	Fe	Ca	Fe + Ca
Predominance of the *R,S*-diastereomer (%)	—*	26	—*	38

* No hydrogenation occurs.

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The hydrogenation of the mixed complex of *N*-Ac—ΔPhe-(*S*)-Met with Ca^{II} and Fe^{II} ions affords mainly *N*-Ac-(*R*)-Phe-(*S*)-Met similar to the hydrogenation of the $PdCl_2$-dipeptide complex, whereas the (*R*)-methionine-containing complex forms primarily *N*-Ac-(*S*)-Phe-(*R*)-Met with the same predominance.

Experimental

Standard hydrogenation method. A solution of 0.5 mmol of *N*-Ac—ΔPhe—Met obtained by the known method[1] and 0.5 mmol of $CaCl_2$ in 10 mL of EtOH was stirred till the complete dissolution of the salt (about 10 min). Then an equimolar amount of $FeSO_4 \cdot 7H_2O$ was added and stirred for 2 h more. The complex obtained was hydrogenated at atmospheric pressure over 10 % Pd/C (substrate : catalyst ratio 10 : 1). The reaction was monitored by the following disappearance of the absorption band of the conjugated double bond at 280 nm. The hydrogenation was complete in 48 h. The diastereomeric composition of the resulting product was deduced from the ratio of the intensities of the MeS protons signals in the ^1H NMR spectra. The assignement of the signals of the diastereomers was carried out as described earlier.[3]

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