Complexation equilibrium in a substrate—$MgCl_2(CaCl_2)$—Pd/C catalytic system and the influence of its position on asymmetric induction in hydrogenation of *N*-acetyl-dehydrophenylalanyl-*S*-proline

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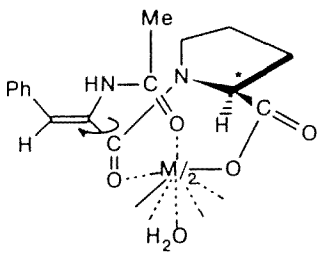
The role of Ca and Mg salts as promoters of asymmetric induction in hydrogenation of *N*-acetyl-dehydrophenylalanyl-*S*-proline in a substrate—MX_2—Pd/C catalytic system was studied. The data of potentiometric titration, ^1H NMR spectroscopy, and the value of diastereomeric excess (*de*) of the resulting *N*-acetyl-*R*-phenylalanyl-*S*-proline indicate the complexation of the substrate with calcium and magnesium chlorides in an alcoholic solution. Ionization and equilibrium constants of the complex were determined. Excess salt shifts the equilibrium toward the complex formation, which increases *de* up to 70 %.

Key words: diastereoselective hydrogenation, magnesium chloride, calcium chloride, complexation, promoters, catalysis, *N*-acyldehydrodipeptides, *N*-acyldipeptides.

Compounds of transition metals, boron, and some other elements are used in asymmetric catalysis[1,2]; however, the participation of II Group metals almost has not been studied, except for Zn complexes with ethyl ester of *N*-acetyl-L-tryptophan and other aromatic amino acids, which catalyze enantioselective condensation of *p*-nitrobenzaldehyde with acetone.[3] Meanwhile, it is known that Ca and Mg ions play an important role in biological processes forming mobile complexes with biomolecules.[4]

We have shown[5] that these ions are the constituents of a catalytic system for diastereoselective hydrogenation of *N*-acyldehydrodipeptides (DHDP) in the presence of an achiral catalyst, and in many cases they substantially affect the asymmetric induction. However, the structure and reactivity of intermediate complexes are poorly studied.[6]

We supposed[7] that this effect is caused by the formation of complexes in which a metal ion is bound to O atoms of carboxyl and carbonyl groups.



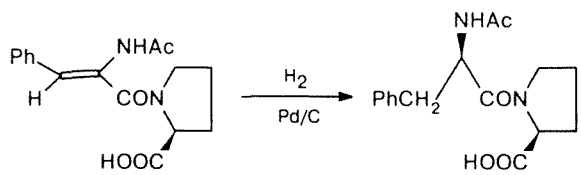
The resulting intermediate chiral cyclic structures decrease the conformational mobility of a substrate molecule. A similar phenomenon has also been studied[8]: the transfer of the chiral induction through the cycles closed at the intermediate stage of asymmetric synthesis.

The formation of cyclic structures of this kind in crystals of Ca and Mg complexes with amino acids and their derivatives was established by X-ray diffraction analysis.[9]

The stereoselectivity can be enhanced if the concentration of such complexes in solution is maximum, *i.e.*, the equilibrium of complexation (1) should be maximally shifted to the right:

$$DHDP + MX_2 \rightleftharpoons DHDP \cdot MX_2. \qquad (1)$$

This work is devoted to the study of equilibrium (1) and of its effect on the diastereoselectivity of hydrogenation of DHDP in the presence of the achiral catalyst Pd/C. *N*-Acetyl-dehydrophenylalanyl-*S*-proline (**1**), for which the most definite results are obtained in diastereoselective hydrogenation,[7] was used as a substrate.



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Experimental

***N*-Acetyl-dehydrophenylalanyl-*S*-proline** was synthesized by a known procedure.[10]

Potentiometric titration was carried out in 95 % (v/v) MeOH with a 0.0135 *M* solution of MeONa in MeOH on a VirTis pH-meter with digital reading. A glass Russell electrode with a connecting bridge filled with 0.1 *M* KCl in 95 % MeOH was calibrated using benzoic acid (pK_a = 7.47 in 95 % MeOH [11]). After addition of each portion of the titrant, the mixture was kept for several min to achieve the equilibrium pH value. No correction to the salt effect was made. $CaCl_2$ and $MgCl_2$ are not titrated under the experimental conditions.

^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker WM-250 instrument (Me_4Si as the internal standard).

Complexes of *N*-Ac-ΔPhe-Pro with metal salts. A 0.27 *M* solution of MeONa in MeOH (1 equiv.) was added to a solution of compound **1** (30 mg, 0.01 mmol) in 5 mL of EtOH followed by addition of the calculated amount of $CaCl_2$ or $MgCl_2$. The solution was kept for 30 min and used for hydrogenation.

Hydrogenation of complexes. 10 % Pd/C (Merck—Schuchardt, 10 mg) was added to a solution of complexes obtained as described above. Hydrogenation, isolation of the product, and determination of its diastereomeric composition were performed as described previously.[5,12] Hydrogenation was monitored by following a decrease in absorption at 280 nm on a Specord UV-VIS UV-spectrometer. Chemical yields are close to quantitative ones.

Results and Discussion

Potentiometric titration. Complexation is accompanied by a decrease in pH; therefore, potentiometric titration was used for the study. The carboxyl group of compound **1** is titrated with a solution of MeONa in 95 % MeOH in a pH range from 5 to 10. In the presence of $CaCl_2$ or $MgCl_2$, waves are observed, which correspond to titration of one proton, but at lower pH values. Effective dissociation constants for compound **1** and its complexes were calculated for several points of the titration curve by the equation $K_{eff} = HT/(1 - T)$, where T is the relative amount of equivalents of the titrant and H is the concentration of H_3O^+ ions in the T range from 0.05 to 0.95 registered at a given point. The dependences of the obtained effective pK values on T for different ratios $CaCl_2$: **1** and $MgCl_2$: **1** are shown in Fig. 1 *a*, *b*. It can be seen that at the ratio MX_2 : **1** = 1 the curve corresponds to titration of several acids with different pK (the total consumption of the titrant was 1 equiv./equiv.). An increase in the amount of the salt to 4 and 8 equiv./equiv. results again in the appearance of the dependences typical of one monobasic acid, from which (in the buffering zone at T = 0.2—0.8) pK of the formed complexes can be obtained. The following values were obtained: for **1**, pK_1 = 8.7 (σ = 0.06); for **1** · $n$$CaCl_2$, $pK_{1'}$ = 6.9 (σ = 0.1); and for **1** · $n$$MgCl_2$, $pK_{1'}$ = 7.0 (σ = 0.07).

To estimate the position of equilibrium by Eq. (1), the simplest model (2) was considered, in which the anion $\mathbf{1}^-$ is bound in a complex with the salt

$$\mathbf{1} \overset{K_1}{\rightleftharpoons} \mathbf{1}^- + H^+,$$

$$\mathbf{1}^- \cdot n MX_2 \overset{K_c}{\rightleftharpoons} \mathbf{1}^- + n MX_2. \qquad (2)$$

The K_c values calculated according to this model from the experimental curves for different T are negative, which is meaningless.

For a more complicated model, according to which the complex of nondissociated compound **1** with the salt, **1** · $n$$MX_2$(**1'**), is formed at first, compounds **1** and **1'** are the titratable acids, and the system has the form:

$$\mathbf{1} \overset{K_1}{\rightleftharpoons} \mathbf{1}^- + H^+,$$

$$\mathbf{1}' \overset{K_c}{\rightleftharpoons} \mathbf{1} + n MX_2, \qquad (3)$$

$$\mathbf{1}' \overset{K_{1'}}{\rightleftharpoons} [\mathbf{1} \cdot n MX_2]^- + H^+.$$

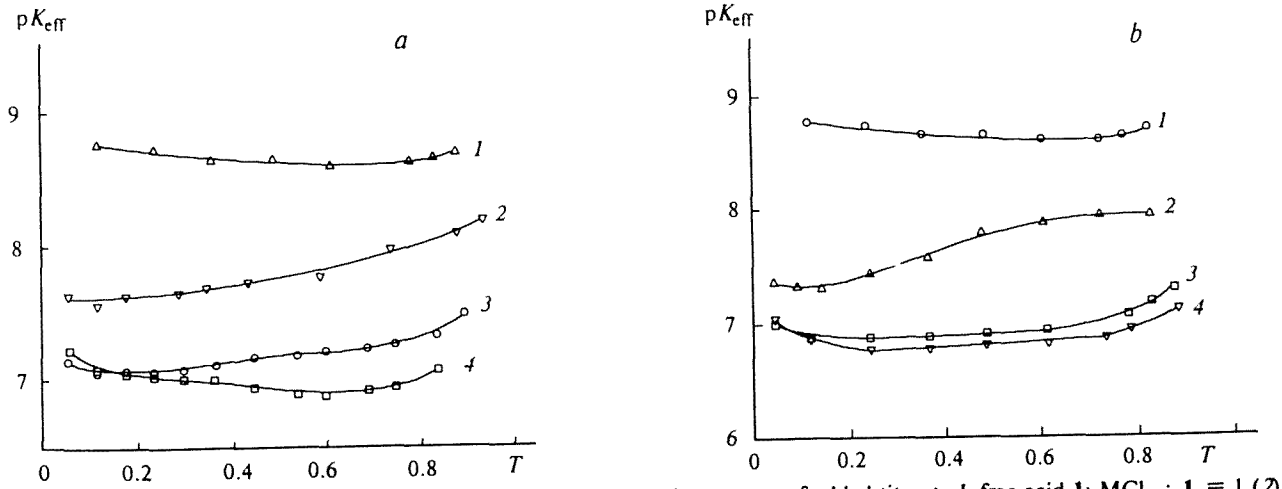

Fig. 1. Dependences of pK_{eff} of compound **1** and its complexes on the amount of added titrant: *1*, free acid **1**; MCl_2 : **1** = 1 (*2*), 5 (*3*), and 8 (*4*). M = Mg^{2+} (*a*); Ca^{2+}(*b*).

Table 1. ^{1}H NMR spectral data for complexes of compound **1** with $MgCl_2$

Amount of the added reagent (equiv./equiv. **1**)		Chemical shift, ppm (ratio of conformers*)			
MeONa	$MgCl_2$	C(O)Me	C*H	=CH—	NH
—	—	1.97	4.25; 4.71 (4 : 1)	6.03; 6.24 (1 : 4)	9.76; 9.79 (4 : 1)
—	0.5	1.98	4.26; 4.71 (3 : 1)	6.04; 6.26 (1 : 3)	9.81
—	2.0	1.99	4.27; 4.71 (3 : 1)	6.07; 6.28 (1 : 3)	9.88
1	0.5	1.93; 1.97 (1 : 1.4)	4.27; 4.50 (1.4 : 1)	6.25; 6.39 (1 : 1.4)	9.66; 9.77
1	8.0	1.98; 2.02 (1 : 1.5)	4.27; 4.55 (1.5 : 1)	6.37; 6.43 (1 : 1.5)	9.71; 9.97

* Signals of two conformers appear in the spectra due to hindered rotation around the =C—C bond[7]; coalescence of signals occurs at 60 °C.

In this case, the reasonable positive value $K_c \approx 0.5$ mol L^{-1} is obtained at $n \approx 0.5$. This value is approximately retained in the buffer zone of titration curves at different salt concentrations. The value $K_c \approx 0.9$ mol L^{-1} can be obtained in a simpler way from the consideration of Fig. 1 *a*, *b*, if it is accepted that equilibrium (1) shifts to the right by more than 95 % in the presence of 8 equiv. salt.

Of course, a combination of many equilibria including (2) and (3) exists in solution, and all the stability constants for complexes in aqueous solutions can be computed. We could not use this in our case (for 95 % MeOH), because the initial data were insufficient.

It is likely that the complex of **1** with $CaCl_2$ is not formed in an aqueous solution, unlike the alcoholic solution, because the addition of equimolar amounts of $CaCl_2$ and alkali to dehydropeptide exerts no effect on either the pK value[7] or the stereoselectivity of hydrogenation.

It follows from the presented data on potentiometric titration that the equilibrium between the dehydropeptide and its complexes exists in an alcoholic solution. An increase in the concentration of metal ions shifts the equilibrium to the complex formation and, hence, it should result in an increase in diastereoselectivity of hydrogenation, which is observed in fact.

^{1}H NMR spectra. Certain information on complexation can be obtained from ^{1}H NMR spectra. As can be seen from Table 1, the addition of $MgCl_2$ and an increase in its concentration in the absence of MeONa exert almost no effect on the chemical shifts of protons and the ratio of intensities of signals for the conformers. A small downfield shift of the signal for the N—H proton is observed. However, the stereoselectivity of hydrogenation (Table 2) and the acidity increase noticeably. This is evidence of an insignificant change in the spatial and electronic state of the dehydrodipeptide molecule as a whole, except for a strong change in the state of the O—H bond in the carboxyl group. It is likely that the —C(=O)—O(H)···M^{2+} structure is realized.

Table 2. Results of hydrogenation of complexes of compound **1** with $MgCl_2$

Amount of the added reagent (equiv./equiv. **1**)		Reaction time /h	*de* (%)
MeONa	$MgCl_2$		
—	—	3	17
—	0.5—1	6	34
—	2	6	38
1	1	36	56
1	2	24	62
1	4	24	70
1	8	24	70

Table 3. Results of hydrogenation of complexes of compound **1** with $CaCl_2$

Amount of the added reagent (equiv./equiv. **1**)		Reaction time /h	*de* (%)
MeONa	$CaCl_2$		
—	—	3	17
1	2	36	27
1	8	36	38

In the presence of MeONa, the addition of $MgCl_2$ noticeably affects the chemical shifts of the vinyl proton and the proton of the N—H bond. The ratio of intensities of dehydrodipeptide conformers changes substantially. This indicates a considerable rearrangement of its spatial structure and electronic state. The diastereoselectivity increases substantially. It is likely that in this case chelate cycles are formed, as in the aforementioned model of the complex optimized by the Desktop Molecular Modeller program of molecular mechanics.

Hydrogenation was carried out in an alcohol solution under conditions described previously.[5] The ratio of diastereomers obtained by hydrogenation was determined by enantiomeric analysis from the ratio of *R*- and *S*-Phe isolated after acid hydrolysis of the reaction product using the known GLC procedure.[12] It follows from the data presented in Tables 2 and 3 that the diastereoselectivity of hydrogenation of complexes of compound **1** with metal salts depends to a great extent on the metal salt : peptide ratio, *i.e.*, on the concentration of the complex in the reaction medium. These results agree well with the potentiometric titration data. A further increase in the concentration of metal salt (higher than 4 equiv./equiv. **1**) exerts no noticeable effect on the position of equilibrium and, hence, on the result of hydrogenation.

The maximum chiral induction in hydrogenation likely takes place in the case of the $[1 \cdot nMCl_2]^-$ anion. A metal salt and a base for ionization of the acidic proton of peptide are necessary for the formation of this anion. An equimolar amount of MeONa is optimum.

A considerable increase in the time of hydrogenation of the complex compared to that of the initial dehydropeptide testifies to the formation of sterically hindered species with the shielded C=C bond, which agrees with the ^1H NMR data and previously obtained results.[6]

Thus, the mechanism of the action of calcium and magnesium salts as promoters of asymmetric induction in the substrate—MX_2—Pd/C catalytic system is the formation of mobile complexes, in which the hydrogenated double bond is strongly shielded.

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References

1. *Catalytic Asymmetric Synthesis*, Ed. I. Ojima, VCH Publishers, New York, 1993; R. Noyory, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, 1994; V. V. Dunina and I. P. Beletskaya, *Zh. Org. Khim.*, 1992, **28**, 1929; 1992, **28**, 2368; 1993, **29**, 806 [*Russ. J. Org. Chem.*, 1992, **28**; 1993, **29** (Engl. Transl.)].
2. H. Waldmann, *SYNLETT*, 1995, 133; E. J. Corey and J. O. Link, *J. Am. Chem. Soc.*, 1992, **114**, 1906.
3. M. Nakagawa, H. Nakao, and K. Watanabe, *Chem. Lett.*, 1985, 391.
4. B. E. Ehrlich, E. Kaftan, S. Bezprozvannaya, and I. Bezprozvanny, *Trends Pharmacol. Sci.*, 1994, **15**, 145.
5. I. N. Lisichkina, A. I. Vinogradova, B. O. Tserevitinov, M. B. Saporovskaya, V. K. Latov, and V. M. Belikov, *Tetrahedron: Asymmetry*, 1990, **1**, 567; I. N. Lisichkina, A. I. Vinogradova, N. B. Sukhorukova, E. V. Tselyapina, M. B. Saporovskaya, and V. M. Belikov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 601 [*Russ. Chem. Bull*, 1993, **42**, 569 (Engl. Transl.)].
6. V. M. Belikov, I. N. Lisichkina, and A. I. Vinogradova, *Zh. Org. Khim.*, 1995, **31**, 220 [*Russ. J. Org. Chem.*, 1995, **31** (Engl. Transl.)].
7. I. N. Lisichkina, A. I. Vinogradova, N. B. Sukhorukova, M. B. Saporovskaya, and V. M. Belikov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1667 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1293 (Engl. Transl.)].
8. S. Blank and D. Seebach, *Liebigs Ann. Chem*,. 1993, 889; D. Seebach, T. Gees, and F. Schuler, *Liebigs Ann. Chem.*, 1993, 785.
9. H. Schmidbaur, J. Back, D. L. Wilkinson, and G. Muller, *Chem. Ber.*, 1989, **122**, 1433; H. Schmidbaur, P. Kiprof, O. Kumberger, and J. Riede, *Chem. Ber.*, 1991, **124**, 1083.
10. J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, John Wiley and Sons, New York—London, 1961.
11. F. L. Bacarolla, E. Grunwald, H. P. Marshall, and E. Lee Purlee, *J. Org. Chem.*, 1955, **20**, 747.
12. M. B. Saporovskaya, L. M. Volkova, and V. A. Pavlov, *Zh. Anal. Khim.*, 1989, **44**, 525 [*J. Anal. Chem. USSR*, 1989, **44** (Engl. Transl.)].

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