The effect of anions in the coordination sphere of Mg complexes of *N*-acetyldehydrophenylalanyl-(*S*)-valine on the diastereoselectivity of hydrogenation

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Diastereoselective hydrogenation in ethanol over Pd/C of *N*-acetyldehydrophenylalanyl-(*S*)-valine (**1**) as complexes with Mg salts of strong acids gives predominantly *N*-acetyl-(*S*)-phenylalanyl-(*S*)-valine (*de* up to 60%). In the case of complexes of **1** with Mg salts of weak acids, the sign of asymmetric induction changes. Data of ^{19}F NMR spectroscopy of *N*-acetyldehydro(*p*-fluorophenylalanyl)-(*S*)-valine indicate that in the former case, the anion of a strong acid does not enter the coordination sphere of the complex, whereas in the latter case, the anion of the weak acid does. The nature of the solvent also influences the reaction stereoselectivity.

Key words: *N*-acetyldehydrophenylalanyl-(*S*)-valine, *N*-acetyldehydro(*p*-fluorophenylalanyl)-(*S*)-valine, hydrogenation, magnesium salts, anions, complexes.

Complexation with transition and nontransition metals plays a crucial role in many reactions of asymmetric synthesis, which actually occur in the coordination sphere of metal complexes. Alkaline earth metals are no exception. It was shown in several studies that divalent metal ions (Ca, Mg, Zn, *etc.*) influence substantially the spatial organization of molecules of organic compounds in synthetic processes and in natural biochemical processes.[1–3]

Previously we showed[4] that the diastereoselectivity of hydrogenation of *N*-acetyl-α,β-dehydrodipeptides (DHDP) over a Pd/C catalyst in ethanol changes markedly upon the formation of complexes of DHDP with CaX_2 and MgX_2 salts. In this case, the reaction involves coordinated ligands and the rigidity of chelate rings results in a higher asymmetric induction. These complexes in an ethanolic solution can incorporate several (up to five) ligand molecules, depending on the metal/DHDP ratio.[5]

However, the effect of the anion X in alkaline earth metal salts on the value and the sign of asymmetric induction has not been specially considered. This study was undertaken in order to elucidate the influence of the nature of the anions in the MgX_2 salts on the state of complexes formed in solution and diastereoselectivity of their hydrogenation.

We chose *N*-acetyldehydrophenylalanyl-(*S*)-valine (**1**) PhCH=C(NHAc)CONHCH(Pr^i)COOH as the investigation object. The double bond in this compound is markedly shielded due to the branched structure of valine, which is favorable for asymmetric induction. In addition, good resolution in the ^1H NMR spectra of the signals of the methyl group protons in the diastereomeric *N*-acetyl-(*S*)- and -(*R*)-phenylalanyl-(*S*)-valines (**2**) formed allows one to determine their ratio reliably. The multiplet at 1.13 ppm corresponds to (*SS*)-**2** and the multiplet at 0.93 ppm is due to (*RS*)-**2**.

In our opinion, the influence of the anions on the course of the reaction is mainly determined by their basicity, which is correlated in the first approximation with nucleophilicity, reflecting the ability of an anion to be coordinated by a metal ion. Low-basicity anions X do not enter the coordination sphere of the Mg^{2+} ion in the complex with **1**; this increases the probability of the formation of rigid chelate structures, which are favorable for diastereoselective hydrogenation. If X is a highly basic anion, it is tightly bound to the Mg^{2+} ion. This situation is sketched in Scheme 1, according to which the use of a Mg salt with an anion derived from a weak acid HX makes the formation of chelated structures impossible (or less probable); conversely, these structures are apparently formed if HX is a strong acid.

As promoters of asymmetric induction, we studied salts formed by strong acids, $MgCl_2$, $Mg(NO_3)_2$, $MgSO_4$, and $Mg(BF_4)_2$, and by weak acids, $Mg(OAc)_2$ and $Mg(OMe)_2$. Table 1 contains the values for diastereomeric excess (*de*) of (*SS*)-**2** and (*RS*)-**2**, formed upon hydrogenation of the complexes of **1** with these salts.

It follows from Table 1 that hydrogenation of compound **1** as a complex with a magnesium salt with anions derived from strong acids results in the predominant

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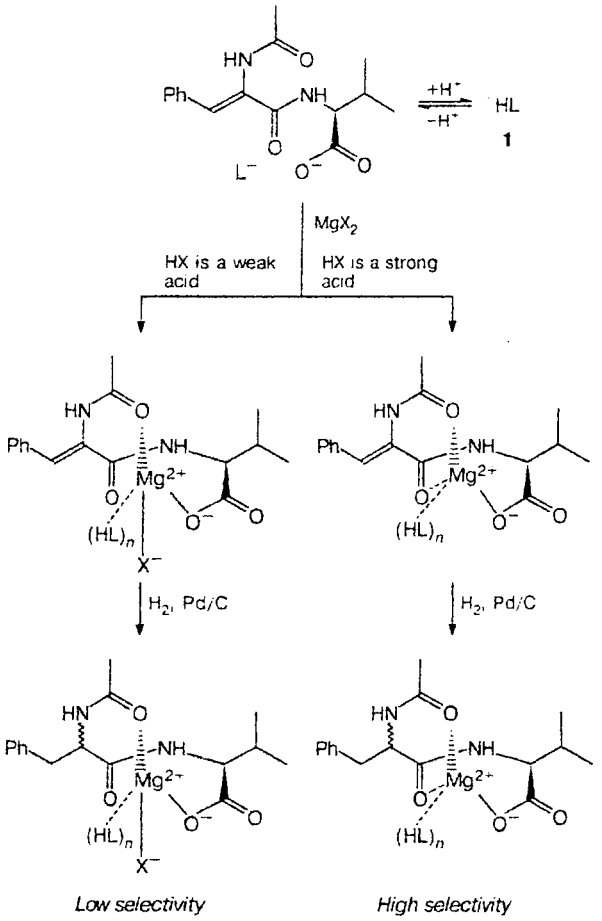
Scheme 1



formation of (*SS*)-**2** (entries *3*—*6*); *de* can be as high as 60%. Complexes of **1** with magnesium salts formed by weak acids ($Mg(OAc)_2$, $Mg(OMe)_2$) invert the stereoselectivity toward isomer (*RS*)-**2** (see Table 1, entries *7* and *8*) and the values of *de* are much smaller than those in the case of strong acids.

Table 1. Effect of the anions in the reagents NaX and MgX_2 on the diastereoselectivity of hydrogenation of complexes of **1** in 96% EtOH over Pd/C

Entry	Reactants (in the order of addition)	*de* (%) (configuration)
1	—	10 (*SS*)
2	NaOH	22 (*SS*)
3	NaOH, $MgCl_2$	22 (*SS*)
4	NaOH, $Mg(NO_3)_2$	36 (*SS*)
5	NaOH, $MgSO_4$	60 (*SS*)
6	NaOH, $Mg(BF_4)_2$	50 (*SS*)
7	NaOH, $Mg(OAc)_2$	17 (*RS*)
8	$Mg(OMe)_2$	4 (*RS*)
9	$Mg(OMe)_2$, Na_2SO_4	8 (*RS*)
10	$Mg(OMe)_2$, $NaBF_4$	10 (*RS*)

It was also found that the change in the order of addition of salts containing, on the whole, the same anions and cations to a solution of compound **1** in EtOH (see Table 1, entries *5*, *9* and *6*, *10*) has a crucial effect on the sign and the value of asymmetric induction. This interesting finding indicates that the order of assemblage of the complexes determines their structure in solution and, hence, the diastereoselectivity of their hydrogenation.

The anions occurring in the coordination sphere of the Mg^{2+} ion should affect the electronic structure of ligands **1**. In a previous communication,[5] we showed that the character of distribution of the electron density on the atoms of ligands **1** in the complex can be judged adequately from the ^{19}F NMR spectra of derivatives having an indicator fluorine atom in the *para*-position of the phenyl group. We used this technique to study the electronic properties of the complexes of *p*-$FC_6H_4CH{=}C(NHMe)CONHCH(Pr^i)COOH$ (*p*-F-**1**) with Mg salts. Table 2 presents the ^{19}F chemical shifts observed for the species in question.

Analysis of the results obtained indicates that the signal for the fluorine atom in the carboxylate anion formed from *p*-F-**1** occurs at a relatively high field (see Table 2, entry *2*). Neutralization of the negative charge upon protonation (see Table 2, entry *1*) or upon complexation of *p*-F-**1** with Mg salts formed by weak acids (see Table 2, entries *3* and *8*—*11*) normally results in a downfield shift of this signal to δ −1.95 to −2.05; the subsequent addition of magnesium salts with anions of strong acids does not change this value. In the case of Mg salts with anions of strong acids (except for $MgSO_4$), an even greater downfield shift is observed, indicating that the Mg cation is involved in the binding of ligands **1** to even a greater extent. These observations are consistent with the hypothesis outlined above concerning the influence of the nature of the anions in MgX_2 on the stereoselective effects observed during hydrogenation of compound **1**.

Table 2. Effect of the conditions of the synthesis of complexes *p*-F-**1** on the chemical shift of the indicator *p*-FC_6H_4 group in the ^{19}F NMR spectra

Entry	Reactants (in the order of addition)	δ ^{19}F
1	—	−1.97
2	NaOH	−1.63
3	$Mg(OMe)_2$	−2.02
4	NaOH, $MgSO_4$	−2.06*
5	$MgSO_4$, NaOH	−1.95
6	NaOH, $MgCl_2$	−2.22
7	NaOH, $Mg(NO_3)_2$	−2.21
8	NaOH, $Mg(OAc)_2$	−1.99
9	$Mg(OMe)_2$, NaCl	−2.05
10	$Mg(OMe)_2$, $NaNO_3$	−2.04
11	$Mg(OMe)_2$, $NaBF_4$	−2.03

* $MgSO_4$ is incompletely soluble under the experimental conditions.

Table 3. Effect of the solvent on the stereoselectivity of hydrogenation of complexes of **1** prepared under various conditions

Entry	Reactants (in the order of addition)	*de* (%) (configuration)	
		in EtOH	in Bu^{t}OH
1	—	10 (*SS*)	18 (*RS*)
2	NaOH	22 (*SS*)	26 (*RS*)
3	NaOH, $MgCl_2$	22 (*SS*)	32 (*SS*)
4	NaOH, $Mg(NO_3)_2$	36 (*SS*)	32 (*SS*)
5	NaOH, $MgSO_4$	60 (*SS*)	28 (*SS*)

The results presented in Table 3 demonstrate that the solvent also influences the asymmetric induction. When ethanol is replaced by *tert*-butyl alcohol, even the sign of the induction changes in some cases. Apparently, the nature of the solvent also influences the type of the complex formed in the solution. In the majority of cases, the best results are attained in 96% ethanol.

The results outlined above lead to the conclusion that diastereoselectivity of hydrogenation of the complexes of *N*-acetyldehydrophenylalanyl-(*S*)-valine with MgX_2 depends on the basicity of the anion in these salts and is ultimately determined by whether or not the anion X is incorporated in the coordination sphere of the complex.

Experimental

^{1}H NMR spectra were recorded on a Bruker WP-200SY spectrometer in CD_3OD. Complexes *p*-F-**1** with metal salts were prepared and their ^{19}F NMR spectra (in MeOH) were recorded as described in our previous communication.[5]

***N*-Acetyldehydrophenylalanyl-(*S*)-valine (1)** was prepared by a previously described procedure.[5]

***N*-Acetyldehydro(*p*-fluorophenylalanyl)-(*S*)-valine (*p*-F-1).** 1. 2-Methyl-4-(*p*-fluorobenzylidene)oxazol-5-one (azlactone) was prepared by a previously described procedure.[6] Yield 57%, m.p. 154 °C. Ref. 6: m.p. 153—154.5 °C.

2. An equivalent amount of an alkali (4.9 mL of 1 *M* NaOH) was added to a suspension of L-valine (0.57 g, 4.9 mmol) in 5 mL of acetone. After complete dissolution of the amino acid, azlactone (1 g, 4.9 mmol) was added in portions, and the mixture was stirred for 1 h; during this period, the azlactone completely dissolved. The solution was acidified by hydrochloric acid (4.5 mL of 2 *M* HCl). The precipitate was dissolved in 3 *M* aqueous ammonia and precipitated by 2 *M* HCl. The white precipitate was filtered off and dried *in vacuo* to give 1.39 g of *p*-F-**1** (88.5%), m.p. 219 °C. Found (%): C, 58.68; H, 6.04; N, 8.37. $C_{16}H_{19}FN_2O_4 \cdot 0.5H_2O$. Calculated (%): C, 58.01; H, 6.04; N, 8.46. ^{1}H NMR, δ: 1.07 (m, 6 H, CH(C$\underline{H}_3$)$_2$); 2.14 (s, 3 H, $COCH_3$); 2.29 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$); 4.45—4.50 (m, 1 H, C$\underline{H}$COOH); 7.18—7.64 (m, 5 H, Ph, H—C=C).

Hydrogenation (general procedure). A solution of NaOH (0.1 mmol) in EtOH and a metal salt (0.1 mmol) or a solution of $Mg(OMe)_2$ (0.1 mmol) and Na_2SO_4 (0.1 mmol) (or $NaBF_4$ (0.2 mmol)) were added to a solution of compound **1** (0.1 mmol) in 5 mL of EtOH. The mixture was stirred for 1—3 h and hydrogenated under atmospheric pressure at –20 °C over 10% Pd/C (the substrate : catalyst ratio was 10 : 1, w/w). The course of the reaction was monitored by UV spectroscopy. The end of the hydrogenation was detected as the disappearance of the absorption at λ = 280 nm, corresponding to the system of conjugated double bonds. According to ^{1}H NMR and UV spectroscopy, the yield of the hydrogenation product was nearly quantitative. The catalyst was filtered off and washed with EtOH, the filtrate was concentrated, and the residue was dried *in vacuo* and analyzed by ^{1}H NMR spectroscopy.

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