Inorg. Chem. **2004**, *43*, 3433–3440

Synthesis, Characterization, and Solution Behavior of Optically Active *cis* β Organocobalt Salen Complexes with L-Amino Acids

Renata Dreos,*,† Giorgio Nardin,† Lucio Randaccio,*,‡ Patrizia Siega,† and Giovanni Tauzher†

Dipartimento di Scienze Chimiche, Università di Trieste, via Licio Giorgieri 1, 34127 Trieste, Italy, and Centro di Eccellenza di Biocristallografia, Dipartimento di Scienze Chimiche, Università di Trieste, via Licio Giorgieri 1, 34127 Trieste, Italy

Received September 8, 2003

The reaction of a *cis* β folded organocobalt derivative with a salen-type ligand, **1**, isolated as racemic compound of Δ and Λ enantiomers, with enantiomerically pure α-L amino acids is reported. The reaction between racemic **1** and L-tyrosine afforded a mixture of the two diastereoisomers Δ-**2** and Λ-**2**, which could be separated by fractional crystallization owing to the lower solubility of Δ-**2**. The absolute configuration of the two diastereomers was unequivocally assigned from the X-ray structure, using the known absolute configuration of the asymmetric carbon of the amino acid as internal reference. The reaction of racemic **1** with *trans*-4-hydroxy-L-proline afforded only the diastereoisomer with a Δ configuration of the tetradentate ligand, as proved by X-ray diffractometric analysis. For both L-tyrosine and *trans*-4-hydroxy-L-proline, the amino acid initially coordinates both to the Δ and to the Λ enantiomers of **1**, leading to an about equimolar mixture of diastereoisomers. In the case of L-tyrosine the diastereoisomers have about the same energy, so that the successive isomerization is negligible. In the case of *trans*-4-hydroxy-L-proline, Δ-**3** is much more stable than Λ-**3**, and the isomerization reaction Λ-**3** → Δ-**3** goes practically to completion.

Introduction

Metal complexes with tetradentate Schiff base ligands derived from salicylaldehyde and diamines (salen-type ligands) generally adopt a *trans* planar geometry, but in some instances, the quadridentate ligand may assume a *cis* β configuration.[1] Generally, this folded configuration is induced by steric constraints, as a lengthening of the polymethylenic chain between the imine nitrogens[2] or the presence of bulky substituents on the imine nitrogens and the phenyl rings.[3] A bidentate ligand, as an α-amino acid, which occupies two *cis* sites in the coordination sphere, may also induce the formation of metal complexes having the quadridentate ligand in the strained *cis* β configuration.[4] In the last years, the interest in the *cis* β metal Schiff base complexes has been renewed, as they are well suited, in principle, for enantioselective catalysis, being chiral and having two labile mutually *cis* coordination sites. Quite recently, some *cis* β cobalt (III) salen-type derivatives proved to be efficient catalysts for the enantioselective Baeyer−Villiger oxidation[5] and in the asymmetric sulfoxidation.[6]

We have recently reported the synthesis and the characterization of a *cis* β folded organometallic cobalt derivative with a salen-type ligand, **1** (Chart 1).[7] Complex **1** does not show particular steric requirements and contains two unidentate ligands in *cis* position. The folding occurs by intramolecular reaction of the axial chloromethyl group of the *trans* planar CH_2ClCo(tmsalen) with the equatorial

* Corresponding authors. E-mail: dreos@univ.trieste.it (R.D.); randaccio@univ.trieste.it (L.R.).

† Dipartimento di Scienze Chimiche, Università di Trieste.

‡ Centro di Eccellenza di Biocristallografia, Dipartimento di Scienze Chimiche, Università di Trieste.

(1) (a) Calligaris, M.; Nardin, G.; Randaccio, L. *Coord. Chem Rev.* **1972**, *7*, 385. Yamada, S. *Coord. Chem. Rev.* **1999**, *190*, 537.

(2) (a) Tisato, F.; Refosco, F.; Mazzi, U.; Bandoli, G.; Dolmella, A. *Inorg. Chim. Acta* **1991**, *189*, 97. (b) Gatehouse, B. M.; Reichert, B. E.; West, B. *Acta Crystallogr., Sect. B* **1976**, *32*, 30.

(3) (a) Choudhary, N. F.; Connelly, N. G.; Hitchcock, P. B.; Leigh, G. J. *J. Chem. Soc., Dalton Trans.* **1999**, 4437. (b) McInnes, J. M.; Swallow, D.; Blake, A. J.; Mountford, P. *Inorg. Chem.* **1998**, *37*, 5970.

(4) (a) Carroll, K. M.; Schwartz, J.; Ho, D. M. *Inorg. Chem.* **1994**, *33*, 2707. (b) Calligaris, M.; Manzini, G.; Nardin, G.; Randaccio, L. *J. Chem. Soc., Dalton Trans.* **1979**, *729*. (c) Kushi, Y.; Tada, T.; Fujii, Y.; Yoneda, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1834 and references therein.

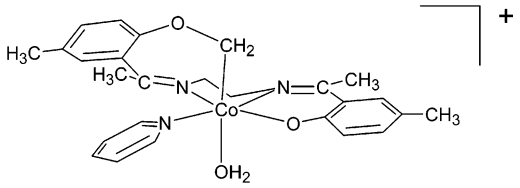
(5) Uchida, T.; Katsuki, T.; Ito, K.; Akashi, S.; Ishii, A.; Kuroda, T. *Helv. Chim. Acta* **2002**, *85*, 3078.

(6) Saito, B.; Katsuki, T *Tetrahedron Lett.* **2001**, *42*, 3873.

(7) Dreos, R.; Nardin, G.; Randaccio, L.; Siega, P.; Tauzher, G.; Vrdoljak, V. *Inorg. Chem.* **2003**, *42*, 6805.

10.1021/ic035059w CCC: $27.50
Published on Web 04/24/2004

Chart 1. Λ Enantiomer of **1**



chelate in coordinating solvents. In this case, the driving force of the reaction is the high reactivity of the axial chloromethyl group together with the relative flexibility of the tetradentate ligand.

Complex **1** is chiral, due to the helical arrangement of the quadridentate ligand, even if the reaction product is a racemic compound. It has been previously outlined that the unidentate ligands of **1** can be easily replaced by other ligands.[7] Therefore, we thought that the reaction of racemic **1** with enantiomerically pure ligands could lead to the preferential formation of one of the possible diastereoisomers. In the present paper, we describe the synthesis and the characterization of the complexes obtained by substitution of the unidentate ligands of **1** by L-tyrosine (Λ-**2** and Δ-**2**) and *trans*-4-hydroxy-L-proline (Δ-**3**), both the amino acids acting as bidentate ligands (Chart 2).

Experimental Section

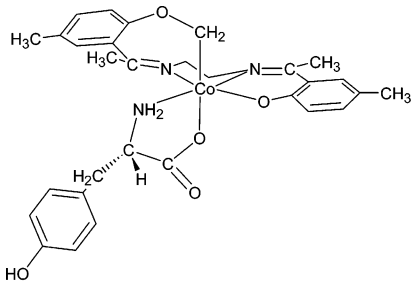
General Details. Complex **1** was synthesized as previously described.[7] All other reagents were analytical grade and used without further purification. NMR spectra were recorded on a JEOL EX-400 (^{1}H at 400 MHz and ^{13}C at 100.4 MHz). CD spectra were obtained with a Jasco J-170 spectropolarimeter and UV−vis spectra by an UVIKON 941 PLUS spectrophotometer. Electrospray mass spectra were recorded in positive mode by using an API 1 mass spectrometer (Perkin-Elmer).

Caution: Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great care.

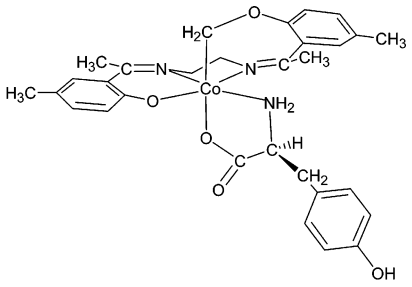
Synthesis of Δ-2 and Λ-2. A suspension of L-tyrosine (0.032 g, 0.18 mmol) in water (10 mL) was added to **1** (0.10 g, 0.17 mmol,) dissolved in methanol (30 mL), and NaOH was added until the complete dissolution of L-tyrosine (pH = 11). The color of the solution changed rapidly from dark red to dark orange. The solution was filtered and set aside for evaporation at room temperature. When dark orange crystals began to precipitate, the solution was placed at −18 °C overnight. Then, a first crop of dark red crystals was collected by filtration (100% Δ-**2**). The filtered solution was concentrated by evaporation under vacuum and, after 1 h, a second crop of red crystals was collected by filtration. The product consisted of at least 90% Λ-**2**, but in some instances, pure Λ-**2** was obtained. In both fractions, the precipitates contained some crystals of X-ray quality, which were withdrawn from the solution before the filtration and immediately covered with Paratone to prevent the loss of solvent.

Δ-2. Yield: 30.1 mg (29%). Anal. Calcd for $C_{30}H_{34}CoN_3O_5 \cdot 1H_2O$: C, 60.70; H, 6.11; N, 7.08. Found: C, 60.0; H, 6.10; N, 7.06. ESI-MS (90 V, CH_2Cl_2) *m*/*z*+ Calcd for Δ-**2**: 575.5. Found: 576.2 (37.6%). Further peaks: 395.2 (Δ-**2** − L-tyrosinate, 100%). ^{1}H NMR (400 MHz, DMSO-d_6, TMS): δ (ppm) = 0.44 (m, 1H, NH_2), 1.51 (1H, m, NH_2) 2.14 (s, 3H, H−C41), 2.15 (s, 3H, H−C131), 2.35 (s, 3H, H−C101), 2.38 (m, 1H, H−C3a), 2.49 (s, 3H, H−C71), 2.62 (m, 1H, H−C2a), 2.94 (m, 1H, H−C3a), 3.33 (m, 1H, H−C8), 3.80 (m, 1H, H−C9), 4.04 (m, 1H, H−C8), 4.39 (m, 1H, H−C9), 5.89 (d, 1H, H−C17), 6.37 (d, 1H, H−C2), 6.59 (m, 3H, H−C17, H−C6a, H−C8a), 6.77 (m, 3H, H−C3, H−C5a, H−C9a), 7.09 (m, 2H, H−C14, H−C15), 7.21 (bs, 1H, H−C12), 7.30 (bs, 1H, H−C5), 9.17 (s, 1H, H−O3a). ^{13}C{^{1}H} NMR (100.4 MHz, DMSO-d_6, TMS): 18.69 (C71), 20.69 (C41), 21.14 (C131), 23.81 (C101), 39.57 (C3a), 55.25 (C9), 56.70 (C8), 58.66 (C2a), 85.75 (C17), 115.67 (C8a, C6a), 121.30, 121.72, 122.94 (C15), 123.05 (C2), 123.63, 129.69 (C12), 129.89 (C5), 130.16 (C9a, C5a), 131.92, 133.21 (C3), 133.36 (C14), 134.69, 154.12, 156.20, 162.31, 169.57, 176.69, 177.26. UV−vis (CH_2Cl_2): 340 nm (log ϵ = 3.74), 426 nm (log ϵ = 3.53). CD (CH_2Cl_2): 327.4 nm ($\Delta\epsilon$ = −1.92 M^{-1} cm^{-1}), 383.2 nm ($\Delta\epsilon$ = 5.08 M^{-1} cm^{-1}), 429.6 nm ($\Delta\epsilon$ = −14.76 M^{-1} cm^{-1}), 481.6 nm ($\Delta\epsilon$ = 4.84 M^{-1} cm^{-1}).

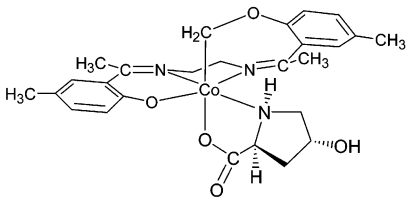
Chart 2



Λ–2



Δ–2



Δ–3

Δ-2. Yield: 32.8 mg (32%). Anal. Calcd for $C_{30}H_{34}CoN_3O_5 \cdot 2H_2O$: C, 58.92; H, 6.26; N, 6.87. Found: C, 58.3; H, 6.00; N, 6.91. ESI-MS (90 V, CH_2Cl_2) *m*/*z*+ Calcd for **Λ-2**: 575.5. Found: 576.2 (52%). Further peaks: 395.2 (**Λ-2** − L-tyrosinate, 100%). ^{1}H NMR (400 MHz, DMSO-d_6, TMS): 0.85 (m, 1H, NH_2), 1.84 (m, 1H, NH_2), 2.13 (s, 3H, H−C41), 2.26 (s, 3H, H−C101), 2.29 (s, 3H, H−C131), 2.45 (s, 3H, H−C71), 2.56 (m, 1H, H−C3a) 2.85 (m, 1H, H−C3a), 3.02 (m, 1H, H−C2a), 3.33 (m, 1H, H−C8), 3.79 (m, 1H, H−C9), 4.01 (m, 1H, H−C8), 4.62 (m, 1H, H−C9), 6.16 (d, 1H, H−C17), 6.31 (d, 1H, H−C2), 6.63 (d, 1H, H−C17), 6.70 (bs, 5H, H−C12, H−C5a, H−C6a, H−C8a, H−C9a), 7.08 (d, 1H, H−C15), 7.24 (dd, 1H, H−C14), 7.27 (bs, 1H, C5−H), 9.31 (s, 1H, H−O3a). ^{13}C{^{1}H} NMR (100.4 MHz, DMSO-d_6, TMS): 18.55 (C71), 20.68 (C41), 21.02 (C131), 23.69 (C101), 37.62 (C3a), 55.21 (C9), 56.94 (C8), 57.93 (C2a), 86.42 (C17), 115.76 (C6a,C8a), 121.18, 121.27, 122.98 (C2), 123.60 (C15), 128.34, 129.34 (C5), 130.38 (C12, C5a, C9a), 131.31, 133.03 (C3), 133.55 (C14), 154.52, 156.38, 162.93, 168.98, 175.27, 178.93. UV−vis (CH_2Cl_2): 340 nm (log ϵ = 3.72), 427 nm (log ϵ = 3.50). CD (CH_2Cl_2): 332.4 nm ($\Delta\epsilon$ = −0.31 M^{-1} cm^{-1}), 382.2 nm ($\Delta\epsilon$ = −4.30 M^{-1} cm^{-1}), 434.0 nm ($\Delta\epsilon$ = 8.22 M^{-1} cm^{-1}), 485.4 nm ($\Delta\epsilon$ = −3.74 M^{-1} cm^{-1}).

Synthesis of Δ-3. *trans*-4-Hydroxy-L-proline (0.020 g, 0.15 mmol) was added to **1** (0.084 g, 0.14 mmol) dissolved in methanol (40 mL). NaOH dissolved in the minimum amount of water was added to the solution until the complete dissolution of the *trans*-4-hydroxy-L-proline (pH = 10−11). The color of the solution changed rapidly from dark red to dark orange. After the addition of 2 mL of H_2O, the solution was filtered and set aside for a slow evaporation of the solvent. After 8 days dark red crystals were collected by filtration. Some crystals of X-ray quality were withdrawn from the solution before the filtration and immediately covered with Paratone to prevent the loss of solvent.

Yield: 46.2 mg (62%). Anal. Calcd for $C_{26}H_{32}CoN_3O_5 \cdot H_2O$: C, 57.46; H, 6.30; N, 7.73. Found: C, 57.1; H, 6.25; N, 7.40. ESI-MS (60 V, MeOH) *m*/*z*+ Calcd for **Δ-3**: 525.5. Found: 526.0 (100%). Further peaks: 395.2 (**Δ-3** − *trans*-4-hydroxy-L-prolinate, 40%). ^{1}H NMR (400 MHz, DMSO-d_6, TMS): 1.30 (m, 1H, H−C5a), 1.66 (m, 2H, H−C3a), 2.10 (m, 1H, H−N1a), 2.13 (s, 3H, H−C41), 2.28 (m, 1H, H−C5a), 2.29 (s, 3H, H−C131), 2.41 (s, 3H, H−C101), 2.46 (s, 3H, H−C71), 3.26 (m, 1H, H−C8), 3.40 (m, 1H, H−C2a), 3.84 (m, 1H, H−C9), 3.90 (bs, 1H, H−C4a), 3.99 (m, 1H, H−C8), 4.29 (bs, 1H, OH−C4a), 4.57 (m, 1H, H−C9), 6.03 (d, 1H, H−C17), 6.32 (d, 1H, C2−H), 6.58 (d, 1H, H−C17), 6.74 (dd, 1H, C3−H), 7.23 (d, 1H, H−C15), 7.28 (bs, 1H, H−C5), 7.32 (dd, 1H, H−C14), 7.43 (bs, 1H, H−C12). ^{13}C-{^{1}H} NMR (100.4 MHz, DMSO-d_6, TMS): 18.55 (C71), 20.70 (C41), 21.06 (C131), 24.23 (C101), 38.84 (C3a), 52.31 (C5a), 55.28 (C9), 56.85 (C8), 63.16 (C2a), 69.18 (C4a), 85.39 (C17), 121.43, 123.04 (C2), 123.64 (C15), 129.78 (C5),130.02 (C12), 131.44, 133.12 (C3), 133.99 (C14), 135.16, 154.27, 162.75, 169.04, 176.57, 179.50. UV−vis (CH_2Cl_2): 341 nm (log ϵ = 3.71), 430 nm (log ϵ = 3.50). CD (CH_2Cl_2): 329.4 nm ($\Delta\epsilon$ = −2.58 M^{-1} cm^{-1}), 387.2 nm ($\Delta\epsilon$ = 7.36 M^{-1} cm^{-1}), 435.2 nm ($\Delta\epsilon$ = −22.23 M^{-1} cm^{-1}), 485.0 nm ($\Delta\epsilon$ = 5.25 M^{-1} cm^{-1})

Kinetic and Equilibrium Studies. The isomerization kinetics for **Δ-2** ⇄ **Λ-2** were followed by monitoring the CD spectra of a 5.0×10^{-5} M solution of the **Δ-2** complex in methanol at 25 °C in the wavelength range 375−500 nm. The k_{obs} values, calculated at 424 nm, were obtained from the linear plot of $\log|\theta_t - \theta_\infty|$ versus time, where θ_t is the ellipticity at time t and θ_∞ is the final ellipticity.

The equilibrium constant for the reaction **Δ-2** ⇄ **Λ-2** was measured in methanol at 25 °C by recording the CD spectra of 5.0×10^{-5} M solutions of 100% **Δ-2** and 100% **Λ-2** immediately after the dissolution and when the equilibrium was reached, after several days. The K value, calculated at 425 nm, was obtained by the equation

$$K = \frac{\theta_\infty - \theta_{\Delta-2}}{\theta_{\Lambda-2} - \theta_\infty}$$

where $\theta_{\Delta-2}$ and $\theta_{\Lambda-2}$ are the values of the ellipticity of pure **Δ-2** and **Λ-2**, respectively, and θ_∞ is the ellipticity of the solution at the equilibrium.

The isomerization kinetics for **Δ-3** ⇄ **Λ-3** were followed by monitoring the CD spectra of a 5.0×10^{-5} M solution of a mixture of **Δ-3** and **Λ-3** (∼70% **Δ-3**) in methanol at 25 °C in the wavelength range 375−500 nm. The k_{obs} values, calculated at the wavelength of the maximum (430 nm), were obtained from the linear plot of $\log|\theta_t - \theta_\infty|$ versus time, where θ_t is the ellipticity at time t and θ_∞ is the final ellipticity.

Structure Determinations. Single crystals of **Δ-2**, and **Λ-2**, and **Δ-3**, suitable for X-ray data collection, were obtained as reported in the Syntheses section. X-ray diffraction data were collected at room temperature, with a Nonius DIP 1030 H System, using graphite monochromated MoKα radiation (λ = 0.71069 Å). For all compounds a total of 30 frames were collected, using the Xpress program,[8] over a half of reciprocal space with rotation of 6° about the φ axis. A Mac Science Image Plate (diameter = 300 mm) was used, and the crystal-to-plate distance was fixed at 90 mm. The determination of unit-cell parameters, integration of reflection intensities, and data scaling were performed using MOSFLM and SCALA from the CCP4 program suite.[9] Reflections, which were measured on previous and following frames, were used to scale the frames on each other, a procedure that partially eliminated absorption effects, taking into account also any crystal decay. The structures were solved with direct methods,[10] followed by Fourier syntheses, and refined by full-matrix least-squares (on F^2) cycles.[11] Compounds **Δ-2** and **Λ-2** crystallized with two independent solvent molecules (water and methanol), while **Δ-3** cocrystallized with three water molecules. The solvent molecule was fully ordered and refined anisotropically without restraint. The H atoms were included at calculated positions, in the final refinements. A suite of programs[12] was also used in the geometrical and final calculation. Crystal and refinement data of interest are given in Table 1.

Computational Details. All the calculations were carried out with the Gaussian-98 program, using the 6-31g* (for H, C, N, and O) and Ahlrichs' VTZ (for Co) basis sets.[13]

Results and Discussion

Synthesis of Δ-2, Λ-2 and Δ-3. The reaction between racemic **1** and L-tyrosine afforded a mixture of the two diastereoisomers **Λ-2** and **Δ-2** (Chart 2). If the product was recovered by evaporation of the solvent almost to dryness, an about equimolar mixture of the diastereoisomers was obtained. However, a separation of **Δ-2** and **Λ-2** by fractional

(8) Schierbeek, B. *Nonius*; Delft: The Netherlands, 1998.
(9) Collaborative Computational Project, Number 4. *Acta Crystallogr.* **1990**, *46A*, 467.
(10) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. SIR92—A program for crystal structure solution. *J. Appl. Crystallogr.* **1993**, *26*, 343.
(11) Sheldrick, G. M. SHELXL97—*Programs for Structure Refinement*; Universität Göttingen: Göttingen, Germany, 1998.
(12) Farrugia, L. J. *Appl. Crystallogr.* **1999**, *32*, 837.
(13) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571.

Table 1. Crystallographic Data for Δ-**2**, Λ-**2**, and Δ-**3**

compd	Δ-**2**	Λ-**2**	Δ-**3**
formula	$C_{31}H_{40}CoN_3O_7$	$C_{31}H_{40}CoN_3O_7$	$C_{26}H_{35}CoN_3O_{6.5}$
fw	625.59	625.59	552.50
T, K	293(2)	293(2)	293(2)
cryst syst, space group	orthorhombic, $P2_12_12_1$	orthorhombic, $P2_12_12_1$	monoclinic, $P2_1$
a, Å	8.177(4)	8.17(3)	10.285(2)
b, Å	18.907(7)	18.996(36)	18.702(7)
c, Å	19.642(8)	19.862(38)	14.868(5)
α, deg	90	90	90
β, deg	90	90	97.39(2)
γ, deg	90	90	90
V, Å^3	3037(2)	3082(14)	2836(2)
Z, ρ_{calcd} Mg/m^3	4, 1.368	4, 1.368	4, 1.294
μ, mm^{-1}	0.616	0.607	0.649
F(000)	1320	1320	1164
cryst size, mm^3	0.30 × 0.30 × 0.15	0.15 × 0.10 × 0.85	0.45 × 0.40 × 0.25
refinement method	*a*	*a*	*a*
data/restraints/params	5909/0/387	5006/0/177	8888/1/660
reflns number [$I > 2\sigma(I)$]	4489	1383	5274
GOF on F^2	1.020	0.913	0.957
final *R* indices [$I > 2\sigma(I)$]	R1[b] = 0.055, wR2[c] = 0.135	R1 = 0.124, wR2 = 0.284	R1 = 0.086, wR2 = 0.225
R indices (all data)	R1 = 0.080, wR2 = 0.156	R1 = 0.326, wR2 = 0.413	R1 = 0.134, wR2 = 0.273

[a] Full-matrix least-squares on F^2. [b] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR2 = [\sum w(|F_o|^2 - |F_c|^2)^2/\sum w|F_o^2|^2]^{1/2}$.

crystallization could be achieved by exploiting the lower solubility of Δ-**2**. Indeed, dark red crystals of Δ-**2** precipitated initially from the reaction mixture, by slow evaporation of the solvent, whereas the successive fractions contained increasing amounts of Λ-**2**. In order to obtain a better separation, the reaction mixture was placed overnight at −18 °C, after the formation of the first crystals of pure Δ-**2** at room temperature. In this manner, the precipitation of Δ-**2** was favored, and the isomerization reaction slowed. After the recovery of Δ-**2** by filtration, the solvent was evaporated rapidly under vacuum, and a second fraction was isolated. The diastereomeric composition of this fraction was at least 90% in Λ-**2**, but in some instances, pure Λ-**2** was obtained.

The absolute configuration of the two diastereomers was unequivocally assigned from the X-ray structure, using the known absolute configuration of the asymmetric carbon of the amino acid as internal reference (see below).

The reaction of racemic **1** with *trans*-4-hydroxy-L-proline afforded a single solid product, which X-ray crystallography has shown to have the Δ configuration of the tetradentate ligand (Chart 2). A mixture of Δ-**3** and Λ-**3** could be obtained by rapid evaporation of the solvent under vacuum at 0 °C, immediately after the mixing of **1** and *trans*-4-hydroxy-L-proline. The mixtures so obtained showed a variable diastereoisomeric composition, but Λ-**3** was always present in lower percentage (no more than 30%).

X-ray Structures. The complexes Δ-**2** and Λ-**2** are isomorphous and crystallize with two (water and methanol) solvent molecules, located in very similar positions in the two structures. In Δ-**2**, O1w forms an H-bond with methanol (O1w···O1Me = 2.826 Å) and with O1A (O1w···O1A [$-x + 2$, $y + {}^1/_2$, $-z + {}^3/_2$] = 2.719 Å). Moreover, O3A is H-bonded with the translated water O1w (O3A····O1w [$x - 1$, $y - 1$, z] = 2.636 Å). A similar H-bonds scheme is present in Λ-**2**, while an additional H-bond connects the methanol oxygen with the carboxylic oxygen of the amino acid residue (O1Me···O2A = 2.712 Å).

Compound Δ-**3** crystallizes with three water molecules: one, O2w, connects the two crystallographically independent molecules in the unit cell (O3A···O2w = 2.670 Å, O2w···O2A′ [$x + 1$, y, $z + 1$] = 2.890 Å) whereas O1w and O3w are H-bonded to the oxygen atoms of *trans*-4-hydroxy-L-prolinate (O1w···O1A′ [$x + 1$, y, z] = 2.897 Å and O3A′···O3w [x, y, $z - 1$] = 2.966 Å).

The ORTEP drawings of the complexes Δ-**2**, Λ-**2**, and Δ-**3** are depicted in Figure 1. In all structures the tetradentate ligand coordinates to Co in a *cis* fashion, the other two positions being occupied by the L-tyrosinate (Δ-**2**, Λ-**2**) and the *trans*-4-hydroxy-L-prolinate (Δ-**3**) species. The amino acids coordinate to the Co atom through the amine N and the carboxylate O, acting as bidentate ligands. The overall geometry around the cobalt is pseudo-octahedral.

The L-tyrosinate complexes are diastereoisomers with $\Delta_{Co}S_C$ and $\Lambda_{Co}S_C$ configurations in Δ-**2** and Λ-**2**, respectively. The *trans*-4-hydroxy-L-prolinate derivative crystallizes with two independent molecules in the cell, both showing the $\Delta_{Co}S_{C2}R_{C4}S_N$ configuration. The coordination of the amine nitrogen to the metal creates a new chirality center on the nitrogen donor of *trans*-4-hydroxy-L-proline. The *S* absolute configuration of this center is forced by the *S* configuration of the α carbon of the L-proline.[14]

The boatlike conformation of the seven-membered metallocycle is very similar in the three complexes (see the interplanar angles in Table 2), while the atoms of the salicylaldiminate residue are almost coplanar (±0.11 Å). Comparison of the geometry of the salicylaldiminate (sal) moiety with that of methoxy-iminate (imi) one in the most accurate structure of Δ-**2** clearly supports the previous observation that the delocalization is significantly lost in the seven-membered ring.[7]

It should be noticed that the Co−N1a distance in Δ-**3** is significantly longer than in the corresponding Δ-**2** L-

(14) Siemion, I. Z.; Kubik, A.; Jezowska-Bojczuk, M.; Kozłowski, H. *J. Inorg. Biochem.* **1984**, *22*, 137.

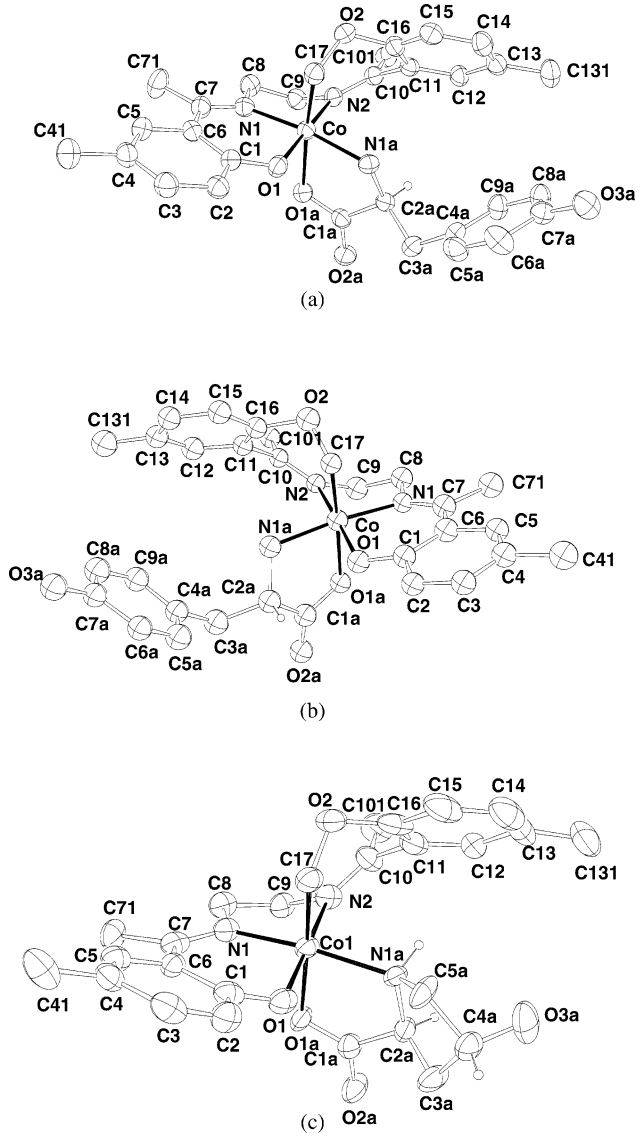


Figure 1. ORTEP drawing with the numbering scheme for the non-hydrogen atoms of Δ-**2** (a), Λ-**2** (b), and Δ-**3** (c).

tyrosinate analogue. Furthermore, the consequent opening of the N2−Co−N1a angle by about 6° and the narrowing of the O1−Co−N1a angle by about 7° in Δ-**2** with respect to Δ-**3** are observed. This may reflect the larger bulk of the *trans*-4-hydroxy-L-prolinate ligand. Significantly longer Co−O_{axial} values are found in Δ-**2**, compared with the same distances in other Co(III) tyrosinate derivatives (1.903[15] and 1.882 Å,[16] respectively). The difference of about 0.2 Å can be attributed to the strong *trans* influence of the OCH_2 group in our derivatives.

Theoretical calculation by the HF ab initio method, carried out on the isolated molecules of the Δ-**2** and Λ-**2** diastereoisomers, indicated that they have very close energies, Λ-**2** being more stable than Δ-**2** only by 0.32 kcal mol^{-1}. Accordingly, the product of the synthesis is an about equimolar mixture of the two diastereoisomers. Similar calculations carried out on the Δ-**3** and Λ-**3** diastereoisomers indicated that the energy of the latter is 2.47 kcal mol^{-1} higher than that of the former, according to the experimental finding that Δ-**3** is the thermodynamic product of the reaction. However, comparison of the calculated distances for Λ-**3** with the experimental ones of Δ-**3** did not reveal any particular crowding in the former diastereoisomer.

Table 2. Selected Bond Distances (Å) and Angles (deg) for Δ-**2**, Λ-**2**, and the Two Structurally Independent Molecules of Δ-**3**

	Δ-**2**	Λ-**2**	Δ-**3**	
Co−O1	1.855(5)	1.90(1)	1.854(9)	1.870(8)
Co−N1	1.902(5)	1.91(2)	1.866(9)	1.869(9)
Co−N2	1.932(5)	1.97(1)	1.916(10)	1.920(10)
Co−N1a	1.977(5)	1.97(2)	2.020(8)	2.011(9)
Co−O1a	2.079(4)	2.11(1)	2.050(8)	2.105(8)
Co−C17	1.931(6)	1.96(2)	1.94(1)	1.944(11)
		(sal)		
C1−O1	1.315(6)	1.34(2)	1.33(1)	1.30(1)
C7−N1	1.308(6)	1.37(2)	1.29(2)	1.28(1)
C6−C7	1.464(9)	1.35(3)	1.50(2)	1.44(1)
		(imi)		
O2−C16	1.385(6)	1.41(2)	1.37(2)	1.36(1)
N2−C10	1.300(6)	1.30(2)	1.30(1)	1.31(2)
C10−C11(C15)	1.484(8)	1.50(2)	1.48(2)	1.50(1)
O1−Co−N1	93.6(2)	94.7(6)	93.2(4)	91.3(4)
N1−Co−N2	85.9(2)	86.3(6)	85.9(4)	85.8(4)
N1A−Co−N2	97.6(2)	93.5(7)	91.3(4)	92.5(4)
N1A−Co−O1	82.6(2)	85.2(7)	89.5(4)	89.2(4)
N1A−Co−N1	172.4(2)	172.5(7)	170.5(4)	172.2(3)
N1A−Co−O2a	80.4(2)	81.7(6)	83.8(3)	82.7(3)
O1−Co−C17	87.3(2)	88.0(7)	86.4(4)	86.8(4)
N1−Co−C17	92.7(2)	93.1(7)	92.2(4)	92.2(4)
N2−Co−C17	95.0(2)	94.6(7)	94.8(4)	94.9(3)
O1−Co−N2	177.7(2)	177.1(7)	178.5(3)	176.7(3)
O2A−Co−C17	173.6(2)	174.7(7)	174.6(5)	175.6(4)
1−2[a]	77.66	84.92	70.29	74.66
2−3	89.38	86.10	84.92	84.54
1−3	87.36	77.77	89.10	88.74
4−5	61.61	63.31	66.27	64.75
6−7	22.26	19.45	18.22	20.39
7−8	55.72	58.14	59.07	55.92

[a] Planes: (1) Co O1a N1a C1a C2a; (2) Co O1 N1 C1 C2 C3 C4 C5 C6 C7; (3) Co C17 O2 N2; (4) Co C17 O2 N2 C10; (5) O2 C10 C11 C12 C13 C14 C15 C16; (6) Co N2 C17; (7) C17 O2 N2 C10; (8) O2 C10 C11 C16.

Characterization in Solution. The behavior of the isolated diastereomers Δ-**2** and Λ-**2** in solution depends strongly on the nature of the solvent. Time-dependent ^{1}H NMR spectra show that they are stable in aprotic solvents ($CDCl_3$, DMSO-d_6, acetone-d_6), while they undergo epimerization in protic solvents (see below). The ^{1}H NMR spectra in DMSO-d_6 of the isolated Δ-**2** and Λ-**2** show similar features (Figures S-1 and S-2), and the assignment of the signals was carried out through 2-dimensional NMR experiments (HETCOR, COSY, ROESY) as previously described for **1**.[7]

Besides the signals of the coordinated L-tyrosine, the spectra exhibit two sets of signals due to the planar and the cyclized half of the tetradentate ligand.

The CD spectra of 5.0×10^{-5} M solutions in CH_2Cl_2 of the two isolated diastereoisomers are quasi-mirror-images in the range 300−600 nm, showing the presence of a negative maximum for Δ-**2** and a positive maximum for Λ-**2** at almost the same frequency (429.6 and 434.0 nm, respectively) (Figure 2).

(15) Harrowfield, J. M.; Sargeson, A. M.; Springberg, J.; Snow, M. R.; Taylor, D. *Inorg. Chem.* **1983**, *22*, 186.
(16) Kobayashi, K.; Takahashi, H.; Nishio, M.; Umezawa, Y.; Tsuboyama, K.; Tsuboyama, S. *Anal. Sci.* **2000**, *16*, 1103.

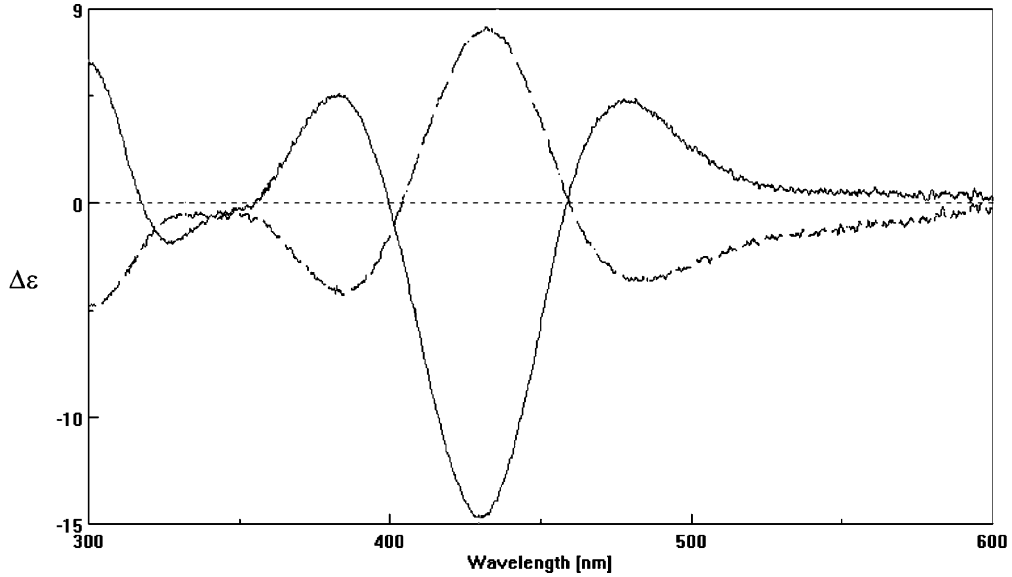


Figure 2. Circular dichroism spectra of 5.0×10^{-5} M solutions of Δ-**2** (—) and Λ-**2** (- - -) in CH_2Cl_2 at room temperature.

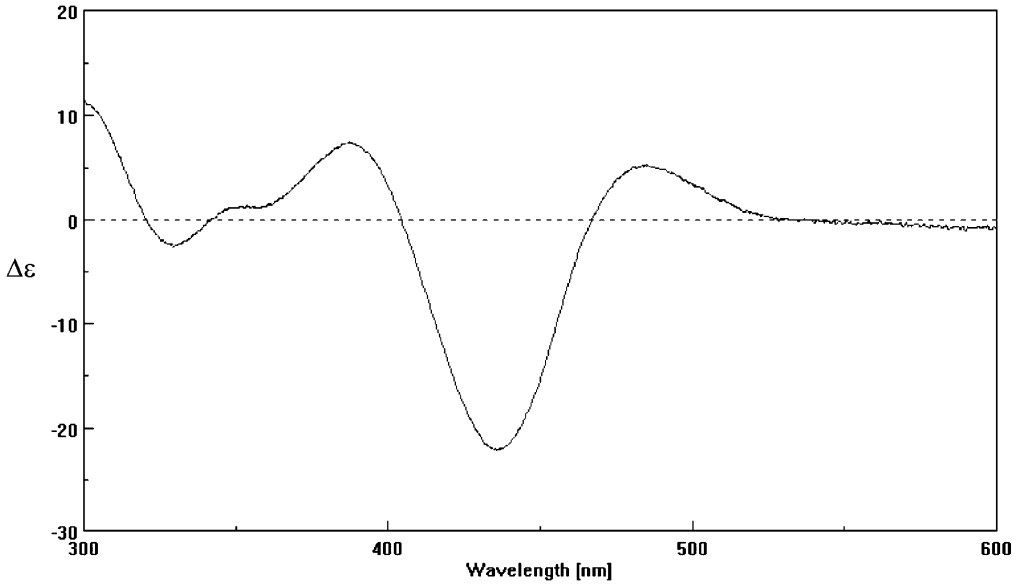


Figure 3. Circular dichroism spectra of a 5.0×10^{-5} M solution of Δ-**3** in CH_2Cl_2 at room temperature.

The ^{1}H NMR spectrum of Δ-**3** in DMSO-d_6 confirms the presence of only one diastereoisomer (Figure S-3), and the CD spectrum in CH_2Cl_2 exhibits a negative maximum at 435.2 nm, very close to that of Δ-**2** (Figure 3).

Reaction of 1 with L-Tyrosine and *trans*-4-Hydroxy-L-proline in Methanol. When an equimolar amount of L-tyrosine was added to a methanolic solution of **1** at basic pH (pH >10), a very fast change of absorbance took place in the UV−vis spectrum. Further spectra did not show any variation. A parallel experiment, carried out under the same experimental conditions, but monitored by CD spectroscopy, showed an initial ellipticity close to zero. Successive variations were in the limits of the experimental error. Furthermore, the ^{1}H NMR spectra monitored immediately after the addition of L-tyrosine to a solution of **1** in CD_3OD showed the presence of two species, whose concentration did not vary with time.

When the same experiments were carried out by addition of *trans*-4-hydroxy-L-proline to **1**, the UV−vis spectra showed the behavior reported above, but a large negative maximum developed with time in the CD spectra, starting from an initial ellipticity very close to zero. The process was almost complete in 1 day. Furthermore, the ^{1}H NMR spectra in CD_3OD evidenced the presence of two main species, together with a small amount (10%) of side products, which were not further characterized. Only one species was still present after 1 day.

The fast process, evidenced by UV−vis spectroscopy, has been attributed to the substitution of the unidentate ligands by the amino acid, acting as a bidentate ligand. Indeed, at these pH values both the donating groups of the amino acids are in basic form and can coordinate to the metal center giving a neutral species. The chelate effect favors the substitution of both the unidentate ligands, even in the

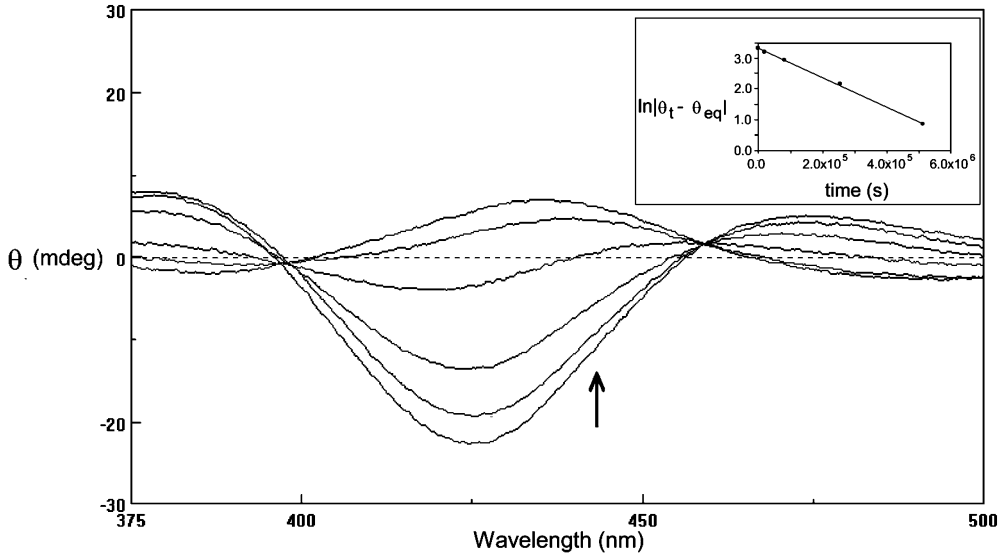


Figure 4. Circular dichroism monitoring of the isomerization reaction Δ-**2** ⇄ Λ-**2** in methanol at 25 °C. The inset shows the best fit to the data measured at 425 nm according to a first-order rate law.

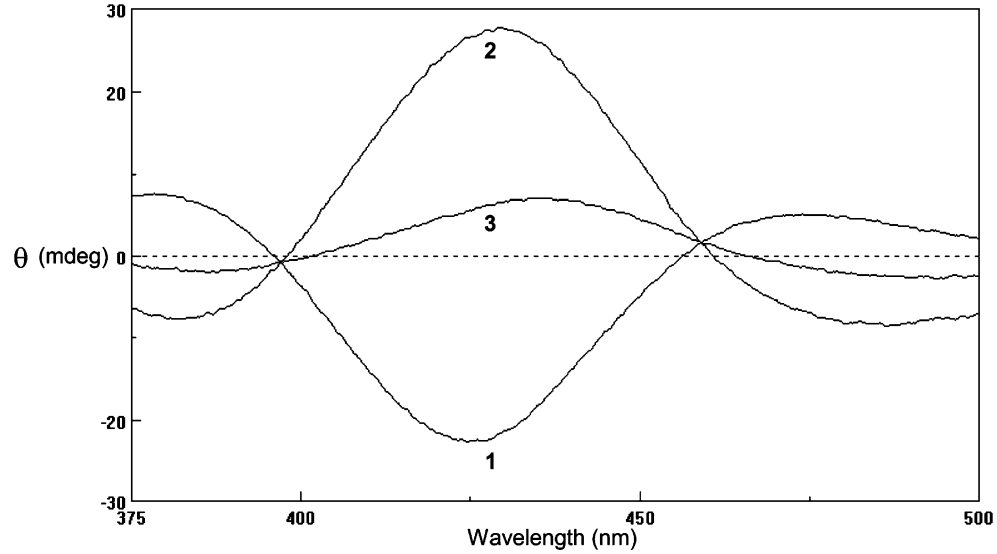


Figure 5. Circular dichroism spectrum of (1) a 5.0 × 10^{-5} M solution of Δ-**2** in methanol at 25 °C, immediately after the dissolution; (2) a 5.0 × 10^{-5} M solution of Λ-**2** in methanol at 25 °C immediately after the dissolution; (3) the equilibrated solution.

presence of an equimolar amount of amino acid. The slow process, evidenced by the CD and the ^{1}H NMR spectra, is attributed to the isomerization reaction between diastereoisomers having different (Δ or Λ) configuration with respect to the tetradentate ligand.

The Isomerization Reaction in Methanol. The isomerization reaction between the L-tyrosinate derivatives

$$\Delta\text{-}\mathbf{2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \Lambda\text{-}\mathbf{2} \qquad (1)$$

has been studied at 25 °C by monitoring the decrease of the ellipticity in the CD spectra of a solution of 100% Δ-**2** in methanol. Good isodichroic points were observed in the wavelength range 375−500 nm, confirming the absence of further optically active species in solution, beside Δ-**2** and Λ-**2** (Figure 4).

As the reaction is reversible, the observed rate constant, k_{obs} = (4.8 ± 0.1) × 10^{-6} s^{-1}, is related to the forward and reverse first-order rate constants, k_1 and k_{-1}, respectively, by the equation

$$k_{obs} = k_1 + k_{-1}$$

The k_1 and k_{-1} values were obtained from this equation and the equilibrium constant at the same temperature

$$K = \frac{k_1}{k_{-1}}$$

The K value was calculated from the CD spectra of 5.0 × 10^{-5} M solutions of 100% pure Δ-**2** and Λ-**2** in methanol, monitored immediately after the dissolution of the complexes and when the equilibrium was reached (Figure 5).

At 25 °C for reaction 1, K = 1.33 ± 0.05, k_1 = (2.7 ± 0.1) ×10^{-6} s^{-1}, and k_{-1} = (2.1 ± 0.1) ×10^{-6} s^{-1}. The epimerization reactions of the *trans* −4-hydroxy-L-prolinate

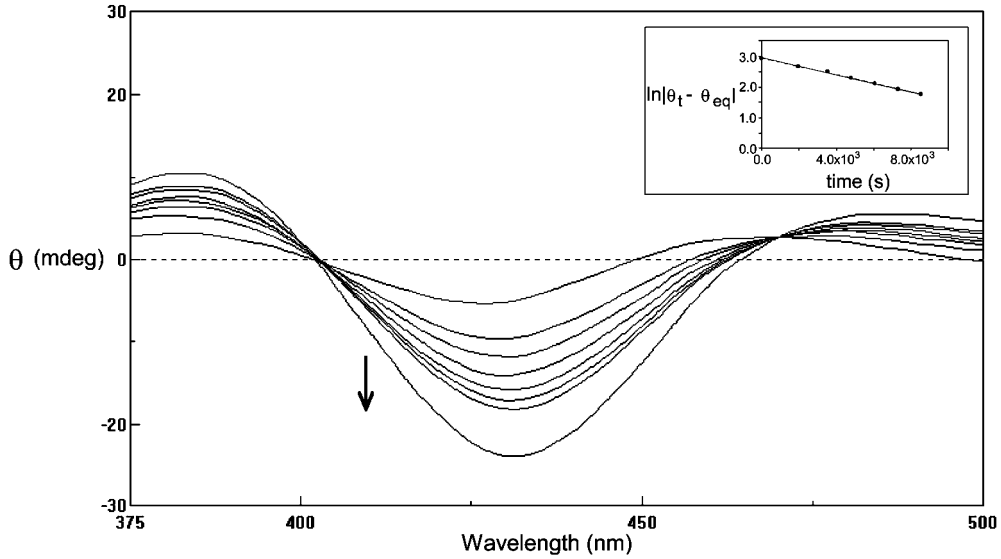


Figure 6. Circular dichroism monitoring of the isomerization reaction Δ-**3** ⇄ Λ-**3** in methanol at 25 °C. The inset shows the best fit to the data measured at 430 nm according to a first-order rate law.

derivative

$$\Delta\text{-}\mathbf{3} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \Lambda\text{-}\mathbf{3} \qquad (2)$$

have been followed at 25 °C by monitoring the increase of the ellipticity with time in the CD spectra of a solution containing a mixture of Δ-**3** and Λ-**3** (∼70% Δ-**3**) in methanol (Figure 6). In this case the equilibrium is completely shifted to the left, so that

$$k_{obs} = k_1 + k_{-1} \approx k_{-1}$$

The k_{-1} value so obtained, $(1.39 \pm 0.03) \times 10^{-4}$ s^{-1}, is about 2 orders of magnitude greater than the corresponding rate constant for the isomerization of the L-tyrosinate derivatives.

Conclusions

The above results show that, for both L-tyrosine and *trans*-4-hydroxy-L-proline, the amino acid initially coordinates both to the Δ and to the Λ enantiomers of **1**, leading to an about equimolar mixture of diastereoisomers. In the case of L-tyrosine, both the diastereoisomers have similar energy, so that the successive isomerization is negligible, but in the case of *trans*-4-hydroxy-L-proline Δ-**3** is much more stable than Λ-**3** and the isomerization reaction Λ-**3** → Δ-**3** goes practically to completion.

The reactions of planar Co(II) *N,N*′-ethylenebis(α-methylsaliylideneamine) complexes with α-L amino acids under aerial oxidation conditions, leading to Co(III) complexes with a *cis* β configuration of the tetradentate ligand, have been previously studied.[4c] In that case, the folding of the tetradentate ligand was induced by the α-L amino acid itself. In most cases the reaction led to the formation of the Λ diastereoisomers. The reaction with L-proline involved the initial formation of the thermodynamically unstable Λ diastereoisomer, the kinetic product of the folding reaction, followed by the epimerization Λ→ Δ, which led to Δ diastereoisomer with almost 100% stereoselectivity.[4c] In the present case, the rate of substitution of the monodentate ligands by *trans*-4-hydroxy-L-proline in the Δ and Λ enantiomers of **1** is very similar, although the thermodynamically preferred product is again the Δ diastereoisomer.

Acknowledgment. This work was supported by MIUR (PRIN 2003 No. 2003037580). P.S. thanks CIRCMSB (Consorzio Interuniversitario per la Ricerca sui Metalli nei Sistemi Biologici) for a grant. We thank Prof. Vinicio Galasso for performing calculations and Dr. Fabio Hollan for recording mass spectra.

Supporting Information Available: X-ray crystallografic files in CIF format, the ^{1}H NMR spectra in DMSO-d_6, and the UV−vis spectra in CH_2Cl_2 of Δ-**2**, Λ-**2**, and Δ-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC035059W