Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 16 (2005) 3188–3197
Tetrahedron: *Asymmetry*

Configurational assignment of *vic*-amino alcohols from their circular dichroism spectra with dirhodium tetracetate as an auxiliary chromophore

Jadwiga Frelek,* Marcin Górecki, Jarosław Jaźwiński, Marek Masnyk, Patrycja Ruśkowska and Rafał Szmigielski

Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw, Poland

Received 19 July 2005; accepted 23 August 2005
Available online 28 September 2005

Abstract—The circular dichroism spectra of a variety of *vic*-amino alcohols in the presence of dirhodium tetraacetate as an auxiliary chromophore were measured in ethanol as the solvent. The method was tested with several model compounds, representing both acyclic and cyclic amino alcohols, including biologically important adrenergic drugs as well as amino sugars. The study demonstrated that the sign of the Cotton effects is determined by the preferred helicity of the O–C–C–N unit in the chiral complex formed in situ. The combined analysis of the CD, UV–vis, ^{1}H and ^{13}C NMR indicated predisposition to form chiral complexes by initial coordination of the amino alcohol at the axial coordination site followed by migration to the equatorial position. Finally, after migration of the ligand to an equatorial position(s) a bridging or a chelating complex is formed. Hence, *vic*-amino alcohols in ethanol act as bidentate ligands in the end.

1. Introduction

In the course of our studies on the application of transition metal complexes as auxiliary chromophores for the absolute configuration determination of *vic*-amino alcohols by means of circular dichroism (CD) spectroscopy, we demonstrated that dirhodium tetraacetate [$Rh_2(OAc)_4$] is a valuable reagent for this purpose.[1] In the previous part of our work on the stereochemical assignment of *vic*-amino alcohols,[2] we demonstrated that [$Rh_2(OAc)_4$] in ethanol forms in situ complexes with optically active *vic*-amino alcohols, CD spectra of which allowed us to determine the absolute configuration of the ligand on the basis of the proposed helicity rule. Surprisingly, if acetonitrile or chloroform are used as solvents, the shapes of the CD curves and the signs of the particular Cotton effects differ considerably in respect to those recorded in ethanol for the same compounds, as can be seen in Figure 1 for D- and L-phenylalaninol.

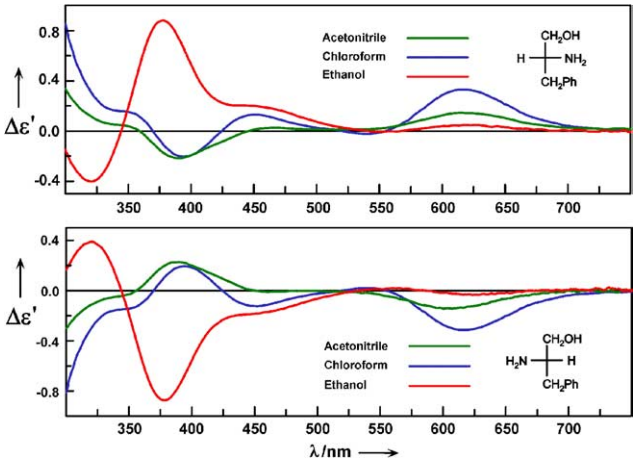


Figure 1. CD spectra of D-phenylalaninol (top) and L-phenylalaninol (bottom) in the presence of [$Rh_2(OAc)_4$] in acetonitrile, chloroform and ethanol.

The different shapes of the CD curves in ethanol versus acetonitrile and/or chloroform may originate from differences of the type of chiral complex formed in various solvents. Very recently, on the basis of the combined analysis of the NMR, UV–vis, CD and ESI MS

* Corresponding author. Tel.: +48 22 3432013; fax: +48 22 6326681; e-mail: frelek@icho.edu.pl

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.08.028

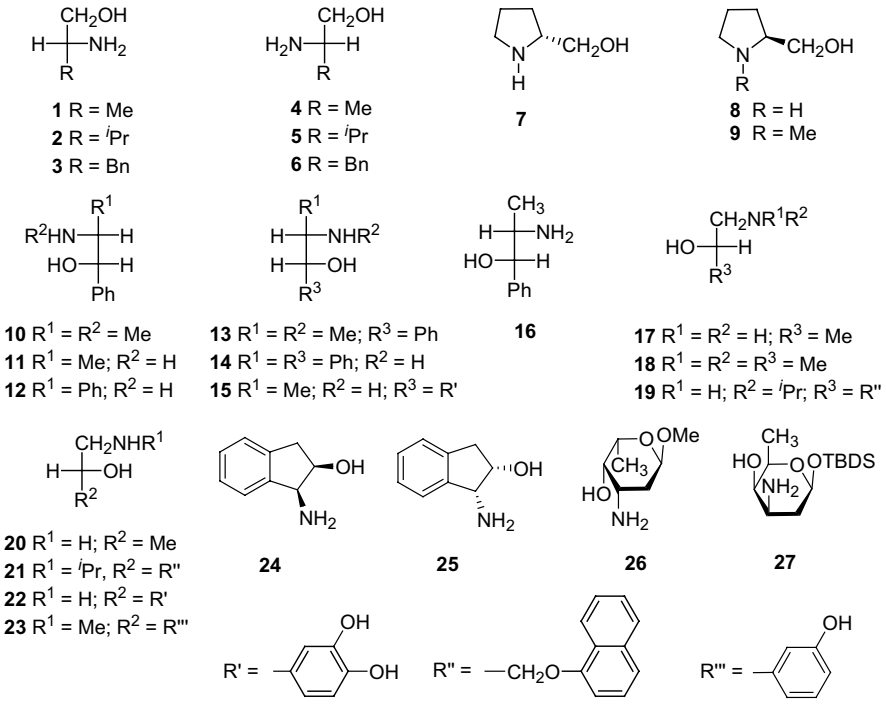


Figure 2. Investigated *vic*-amino alcohols **1**–**27**.

experiments, we concluded that in acetonitrile and chloroform solutions *vic*-amino alcohols act as unidentate ligands and coordinate to the Rh_2-core axially through the amino group to form 1:1 or/and 2:1 chiral complexes predominately.[3] In contrast, a bidentate mode of binding of an amino alcohol to the Rh_2-core leading to bridging or chelating complexes was assumed to be the most probable in ethanol solution.[2]

Herein, we report our efforts to determine the structure of the complexes formed in ethanol in order to explain the observable differences in the CD spectra depending on the solvent used. For this purpose, we decided to apply the spectroscopic methods used previously for acetonitrile and chloroform solutions, that is NMR, UV–vis, as well as ESI MS spectrometry.[3]

Our studies focused also on the proof of the validity of the helicity rule over a broad variety of adducts including the biologically important adrenergic drugs as well as amino sugars. To achieve such a goal, we have undertaken chiroptical studies on a variety of amino alcohols of both ephedrine and adrenaline types **1**–**27** presented in Figure 2.

2. Results and discussion

We started our extended studies with experiments designed to establish the best experimental conditions for the formation of the chiral complex in ethanol. For this purpose, the dependence of the CD spectra on the ligand-to-metal molar ratio and on time was investigated. D-Phenylalaninol **3** as the representative amino alcohol subject was chosen.

2.1. The CD spectra dependency on ligand-to-metal molar ratio

Measurements were performed in 0.5:1, 1:1, 1.5:1, 3:1, 5:1 and 10:1 ligand-to-metal ratios 24 h after mixing of the constituents. As can be seen in Figure 3, for different molar ratios no differences in the shape of the CD curves were observed. The increase of the ligand concentration caused an increase of the band intensities only. So, the conclusion is that the shape of CD curves does not depend on the ligand-to-metal molar ratio. However, to obtain well-developed Cotton effects, it is recommended to work with at least 1:1 ligand-to-metal molar ratio.

2.2. The UV–vis and CD spectra dependency on time

To test the stability of the chiral complex in ethanol, the electronic absorption spectra in the visible region and CD measurements over an extended period of time were

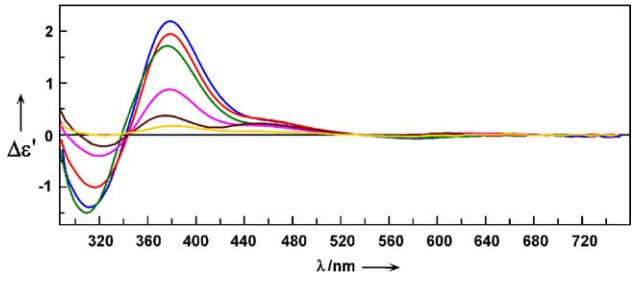


Figure 3. CD spectra dependency on the ligand-to-metal molar ratio in ethanol: 0.5:1 (——), 1:1 (——), 1.5:1 (——), 3:1 (——), 5:1 (——), 10:1 (——). For the 0.5:1 and 1:1 molar ratios the CD curves are three- and twofold enhanced, respectively.

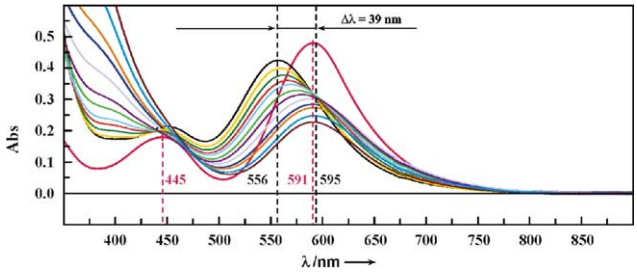


Figure 4. Time-dependency of the long-wavelength absorption bands I and II of D-phenylalaninol **3** with $[Rh_2(OAc)_4]$ in ethanol after: dissolving (—), 0.5 h (—), 1 h (—), 1.5 h (—), 2 h (—), 3 h (—), 4 h (—), 6 h (—), 9 h (—), 12 h (—), 24 h (—), 48 h (—) and of the stock complex (—).

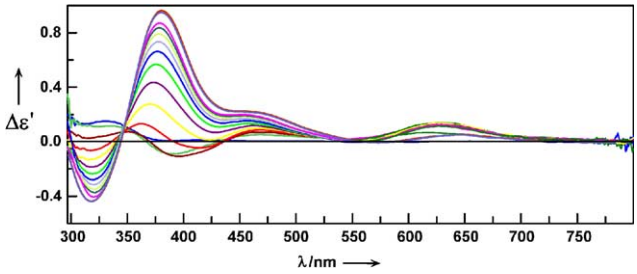


Figure 5. CD spectra of in situ formed Rh-complexes of D-phenylalaninol **3** recorded in ethanol in the 1.5:1 metal-to-ligand ratio after: 0.25 h (—), 1 h (—), 2 h (—), 3 h (—), 4 h (—), 5 h (—), 6 h (—), 7 h (—), 8 h (—), 9 h (—), 10 h (—), 12 h (—), 24 h (—) and 6 days (—).

carried out (>96 h). The electronic absorption spectrum of $[Rh_2(OAc)_4]$ in ethanol consists of two weak bands in the visible region, namely band I at 591 nm and band II at 445 nm (Fig. 4). These bands, attributed to the $\pi^*(Rh–Rh) \rightarrow \sigma^*(Rh–Rh)$ and $\pi(Rh–O) \rightarrow \sigma^*(Rh–O)$ transitions, respectively,[4] are very diagnostic for the purpose of differentiating between the type of complexes formed. This is due to the fact that they are strongly influenced by the changes in the axial and equatorial substitution. In general, band I is shifted to the lower wavelength depending on the nature of axially coordinating ligands whilst band II is more sensitive to the change of the identity of the equatorial binding ligands.[4]

The absorption measurements of $[Rh_2(OAc)_4]$ with D-phenylalaninol **3** as a ligand were performed in the visible region every 10 min over the period of 48 h. As can be seen in Figure 4 showing the most representative curves, the position of bands I and II revealed a quite significant time dependency. The long wavelength band I was found at 556 nm immediately after dissolution and became red-shifted by about 39 nm within ca. 12 h. After that, its position remained unchanged at least over the next 36 h.

In contrast, the initial position of band II remained unchanged for the first 1.5 h. During the next 6 h, the maximum of this band was blue shifted to ≈400 nm. Over the next period of time, the band underwent an additional shift to lower wavelength becoming visible only as a shoulder of band III occurring at 250 nm. The shift of bands I and II positions was accompanying by colour changes of the solution from violet to navy blue. The changes in energy of both these bands strongly indicated changes in the coordination mode.[4b] Those observations suggested that the formation of chiral complexes occurred by the initial coordination of amino alcohol at the axial coordination site ($\lambda_{max} = 556$ nm), followed by the migration from axial to the equatorial position ($\lambda_{max} = 595$ nm). Similar migration of ligands from the axial to an equatorial coordination side has been observed in analogous dirhodium compounds.[5] According to the literature data,[4b] the axial coordination through the amino group should shift the long wavelength band from ca. 600 to ≈550 nm. On the other hand, dirhodium tetraacetate (soft acid) represents an alcohol acceptor which is not strong enough to form chiral complexes by axial ligation of, for example, alcohols and diols (hard bases).[6] In this context, it can be proposed that the initial axial coordination occurred via amino group.

The time-dependency was also observed in the CD curves, which were measured at room temperature every 30 min continuously over 12 h. After 12 h, the subsequent measurements were repeated at 12 h intervals. As is evident from Figure 5, an increase of band intensities with accompanying small changes in band positions could only be observed during the first 3.5 h. After that, the shape of CD curves began to change. These shape changes stopped after ≈9 h and subsequently only the intensity of CD bands increased to reach the maximum approximately after 24 h after preparing of the chiral complex. Such a behaviour was observed independently of the ligand to the stock complex molar ratios. It is worth to note that solutions of chiral complexes are stable over a very long period of time (>96 h).

If the time-dependent CD measurements were recorded at 50 °C, the equilibrium in solution was reached after 2.5 h (spectra recorded every 10 min for 6 h). Afterwards, the magnitude of particular CD bands was comparable with that observed after 24 h standing at room temperature. Thus, the intensity end-value could be obtained much quicker by warming up the solution to 50 °C.

The significant time-dependency of the shapes of CD spectra additionally confirmed the assumption that a succession of different adducts was present, depending on time.

2.3. ^1H, ^{13}C and low-temperature NMR studies

Despite many attempts, we were not able to obtain single crystals suitable for an X-ray analysis. Therefore, to resolve the problem of identification of the coordination mode, we decided to apply the NMR spectroscopy. A sample of the chiral complex prepared from the stock complex and D-phenylalaninol **3** (see Section 4) was measured in CD_3OD. The ^1H and ^{13}C NMR spectra recorded in CD_3OD at room temperature indicate that one molecule of **3** coordinates to one molecule of the dirhodium core. Moreover, the clearly visible (in both

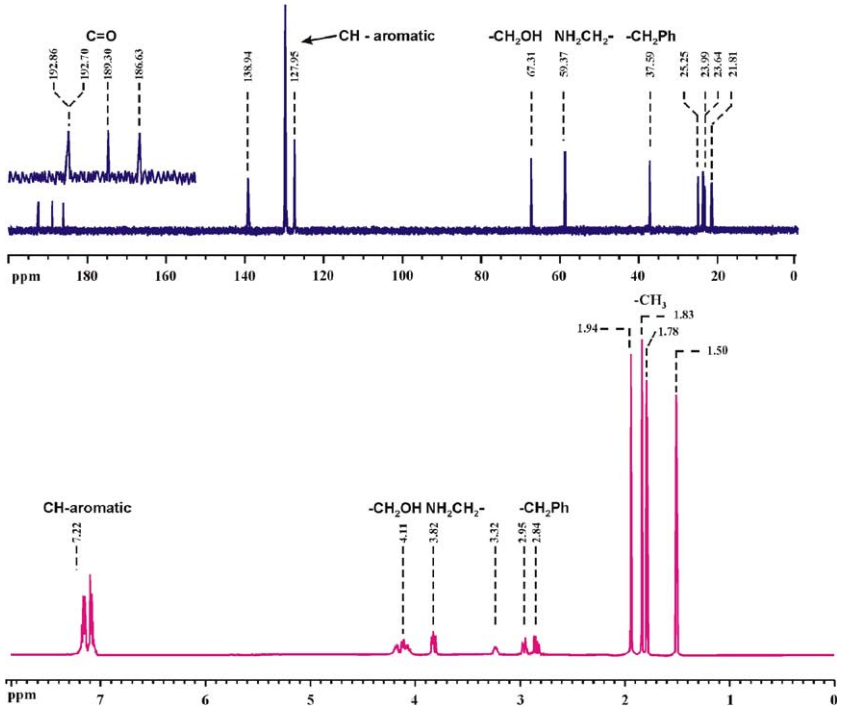


Figure 6. ^{1}H (bottom) and ^{13}C (top) NMR spectra of the chiral complex of the D-phenylalaninol **3** coordinated to the dirhodium tetraacetate in CD_3OD.

^{1}H and ^{13}C NMR spectra) differentiation of four methyl and carbonyl groups strongly suggests their nonequivalence (Fig. 6). Thus, the formation of a bridged or a chelating cyclic unit with two or one of the rhodium atoms, respectively, can be assumed.[7]

To gain more insight into the coordination mode in alcohol solution, we decided to measure low-temperature NMR spectra. Although the complexation of the stock dirhodium acetate by ligand is a driving force transporting $[Rh_2(OAc)_4]$ into solution, the solubility of components in CD_3OD was not sufficient to reach minimum concentration needed for recording of well-resolved NMR spectra. Therefore, for sample preparation an ultrasonic bath was used and the sample was measured immediately after decantation of insoluble material. Such a procedure, however, leads to a difference between a real composition of mixture in solution than the one estimated on the basis of quantity of reagents. The real composition, however, can be approximated by the signal integration. For example, a mixture of 5 mmol of D-phenylalaninol **3** and 10 mmol of $[Rh_2(OAc)_4]$ gives the solution containing 1.4:1 ligand-to-metal ratio instead of the expected 0.5:1 ratio, due to incomplete solubility of dirhodium tetraacetate.

The results of NMR titration experiment in CD_3OD solution at 233 K are shown in Figure 7. As can be seen, the spectra do not contain NH_2 and OH signals, due to exchange with solvent deuterium atoms. The shape of multiplets at ca. 3.75 ppm in all spectra suggests that at the beginning of titration (1.4:1 mixture) at least two species are present in the solution, probably 1:1 and 2:1 adducts. The spectra taken by higher concentration of the ligand, for examples, 2.2:1 and 2.8:1 mixtures, contain signals of adduct(s) and also of the free ligand. The most diagnostic signal in all spectra recorded appears to be the singlet at 1.9 ppm, attributed to the four methyl groups of the dirhodium core. This singlet unequivocally indicates an equivalency of all four methyl groups.

The NMR experiment performed at low-temperature leads to the following conclusions:

(1) adduct formation induces low-field shifts of all ligand signals,
(2) there is only one signal (singlet) of $[Rh_2(OAc)_4]$ methyl groups on the spectrum, thus, all methyl groups in $[Rh_2(OAc)_4]$ unit are equivalent. Hence, only 1:1, 2:1, or both axial adducts (Fig. 7), being in equilibrium, exist in the solution,
(3) the signals of adducts and signals of free ligand can be observed separately at low-temperature spectra.

In the spectra recorded at room temperature, typically, only one set of signals of all species being in equilibrium is observed.[3] The signals of free ligand are present in the spectrum of 2.2:1 ligand-to-metal mixture, whereas such signals are absent in the spectrum of 1.4:1 mixture. Lack of free ligand signals in the later spectrum suggest that D-phenylalaninol **3** forms at least two kinds of adducts, namely 1:1 and 1:2. The different shape of multiplet at ca. 3.75 ppm in both spectra is an additional proof of the presence of more than one adduct in the solution.

The mixture of ligand and dirhodium stock complex in CD_3OD is unstable at room temperature and changes

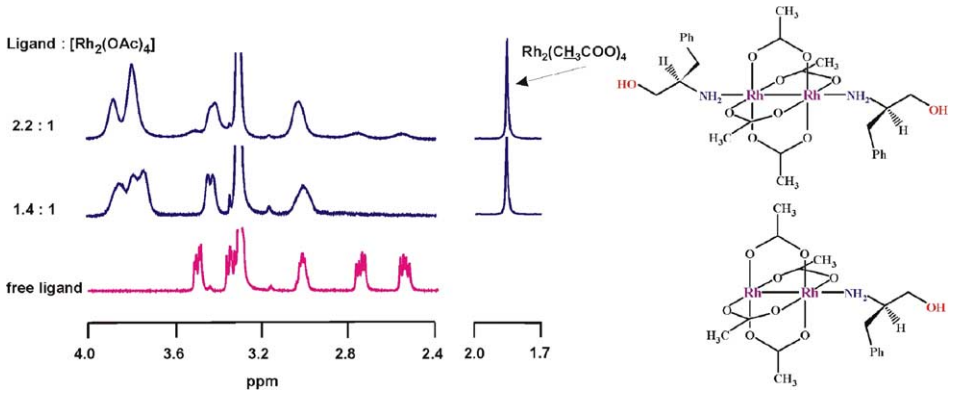


Figure 7. ^{1}H NMR titration of in situ formed complex of $[Rh_2(OAc)_4]$ with D-phenylalaninol in CD_3OD solution at 233 K (left) and postulated structures of the axial complexes formed under these conditions (right).

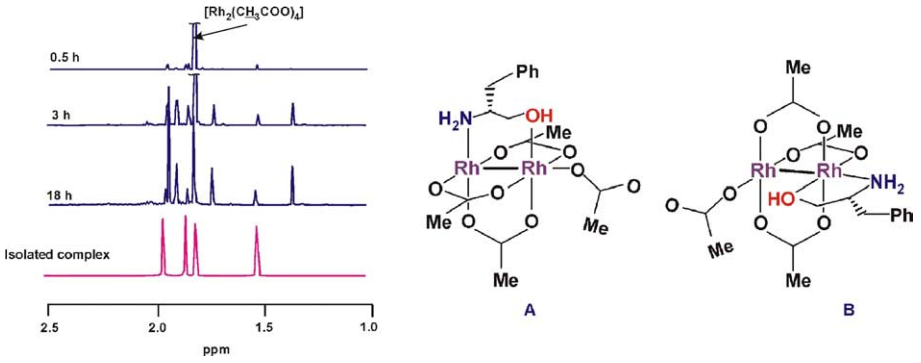


Figure 8. Time-dependency of the ^{1}H NMR spectra of the complex formed in situ from dirhodium tetraacetate and D-phenylalaninol **3** at room temperature (blue lines) and of the complex isolated by column chromatography (red line) {left} and postulated structure of the complexes formed in ethanol solution: A—bridging and B—chelating complexes {right}.

within few hours. An axial adduct rearranges slowly to give bridging or chelating complexes (Fig. 8). The numerous signals of nonequivalent methyl groups of $[Rh_2(OAc)_4]$ unit appear at the range from 2.5 to 1 ppm. The signals are visible separately even at room temperature (Fig. 8). In the spectrum taken after 18 h from the complex formation there are seen at least two sets of four singlets present, corresponding to the two chiral complexes with four nonequivalent methyl groups of the acetate units. This nonequivalence indicates that the amino alcohol is equatorially bounded to the stock complex. In addition, there is also present a singlet, which can be attributed to the equivalent methyl groups of the dirhodium core. It means, that a small amount of complexes with axially bonded amino alcohol ligand(s) are also present in the solution.

The NMR data presented above correlate to the CD and UV–vis results, demonstrating that the initial ligation occurs at the axial side(s) of the stock complex. The observed close similarity of the CD spectra recorded in ethanol within approximately 2 h after mixing of constituents and those recorded in acetonitrile and chloroform gives a proper basis for the above assumption (Fig. 9). In the latter solvents, an axial ligation of the *vic*-amino alcohol ligand to form 1:1 or 2:1 complexes has been proven by us very recently.[3] Next, the axial complexes undergo ligand migration to form complexes

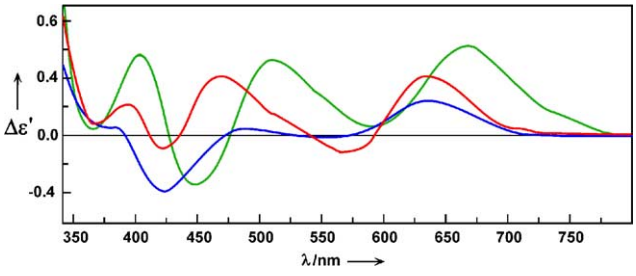


Figure 9. CD spectra of in situ formed Rh-complexes of D-phenylalaninol **3** recorded in acetonitrile (——), chloroform (——) and ethanol (——). The green curve measured after 2 h after mixing of constituents is fourfold enlarged.

with a bridging or chelating arrangement of the amino alcohol unit(s) to the stock complex, as demonstrated in Figure 8. This means that in ethanol solution the amino alcohol molecules act finally as bidentate ligands to form equatorial complexes of a bridging (β-type) or a chelating (α-type) mode of binding with the dirhodium dimmer.

However, the bridged type of bidentate ligation seems to be more probable because such a ligation mode is favoured for Rh-complexes with various bidentate ligands, such as acetamidates or phosphino-phenoxides.[8] Nevertheless, regardless of whether the α- or β-type of

complexes is formed subsequent to the ligation of an amino alcohol, the achiral rhodium chromophore is incorporated into a chiral ring ('chiral second sphere')[9] and the resulting CD should be governed mainly by a 'helicity rule'. It means that the sign of the torsional angle of the amino alcohol unit determines the signs of the Cotton effects and also, to a great extent, their magnitude.

2.4. Electrospray ionization mass spectrometry

Electrospray ionization mass spectrometry (ESI MS) has become an important tool for probing the noncovalently bounded species (complexes) that are formed in the polar solutions between the small organic molecules as well as biopolymers.[10] This unique feature of ESI arises from its analytical simplicity and, on the other hand, from the softness of ionization mode among all other mass spectrometry techniques available. The latter allows transferring ions from liquid to the gaseous phase at a very low energy level, making possible that even a very weakly bonded ion–molecule aggregate will be transferred without decomposition.

ESI mass spectrum acquired on Mariner ESI time of flight (TOF) mass instrument (Perseptive Biosystem) with a sample flow-rate of 8 μL/min for the solution prepared by dissolving dirhodium tetraacetate and D-phenylalaninol in 1.5:1 ligand-to-metal molar ratio in ethanol reveals the presence of two characteristic peaks at 745 and 594 Th (Fig. 10). High-resolution mass measurements indicated that the former corresponds to the ion of the composition $C_{26}H_{39}N_2O_{10}Rh_2$, whereas the latter to the ion of the composition $C_{17}H_{26}NO_9Rh_2$. These data suggest that, in both cases, a formation of protonated dirhodium-type complex ions (differing in number of coordinated D-phenylalaninol **3** ligands) occurred. In particular, the ion at 745 Th corresponds to the complex between dirhodium tetraacetate and D-phenylalaninol in 1:2 ratio, whereas the one at 594 Th corresponds to the complex with 1:1 stoichiometry. The mass spectra presented in Figure 10 showed two common peaks at 685 and 534 Th, as well. The fragmentation analysis confirms that both signals arise from the dissociation processes of ions at 745 and 594 Th, respectively, in the course of acetate radical loss. Moreover, the data obtained from the cone voltage experiments revealed that ion at 594 Th does not form from the ion at 745 Th. The main fragmentation pathway of the ion at 745 Th is the elimination of the acetate radical. The MSI data confirms the presence of two kinds of chiral complexes of 1:1 or 1:2 metal-to-ligand ratio in the solution. The ions 594 and 745 may correspond to the axial as well as to the equatorial complexes both observed in the NMR spectra and discussed in Section 2.3.

2.5. The circular dichroism study

The results presented above have demonstrated that CD bands in the chiral complexes achieved the maximum of their intensity after approximately 24 h storage in room temperature. Moreover, these results have shown that the shapes of CD curves remained unchanged within the studied range of ligand-to-metal molar ratios, achieving encouraging intensities of CD bands for 1.5:1 concentration ratio. On this basis, we regarded the 1.5:1 molar ratio of the constituents as the best for our chiroptical study. Moreover, we decided to measure the CD spectra of amino alcohols **1**–**27** with the Rh_2-core in ethanol solutions after 24 h from the moment of chiral complex formation. The CD data of the in situ formed Rh-complexes recorded under the above mentioned conditions are summarized in Table 1.

Although, we previously published the CD data of Rh-complexes of compounds **1**–**6**, **8** and **10**,[2] the results are repeated here for comparison purposes. The differences in the magnitude of particular Cotton effects between current results and previously reported data are related to the differences in ligand-to-metal molar ratios used in both cases. Currently, this molar ratio amounts 1.5:1.

Similarly to dimolybdenum tetraacetate,[11] the dirhodium tetraacetate forms optically active complexes with the salts of *vic*-amino alcohols very slowly and with poor efficiency. Therefore, in the case of compounds **10**, **13**, **19**, **21**, **23** and **26**, which were investigated as respective hydrochlorides, no Cotton effects could be observed prior to release of a free amine from its salt. However, an addition of a drop of aqueous NaOH to the complex solution resulted in most cases in rapid development of several intense Cotton effects.

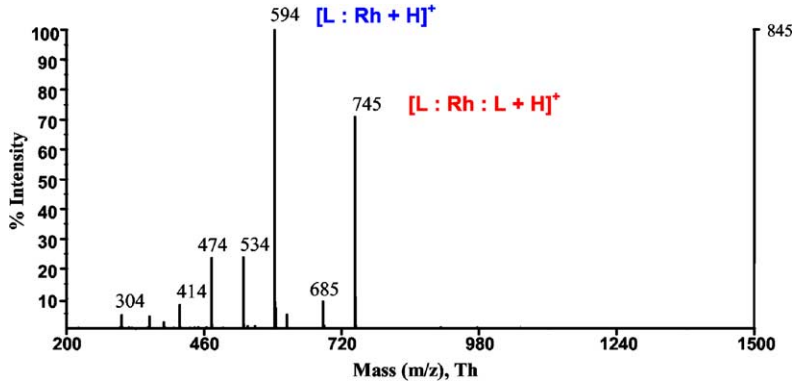


Figure 10. Electrospray mass spectrum of the solution containing dirhodium acetate and D-phenylalaninol **3** in 1.5:1 ligand-to-metal molar ratio recorded in EtOH. L = D-phenylalaninol **3**; Rh = $[Rh_2(OOCCH_3)_4]$.

Table 1. CD data of in situ formed Rh-complexes of compounds **1**–**27** recorded in ethanol after 24 h after dissolving (ligand-to-metal molar ratio 1.5:1)[a]

Compound	Band A	Band B	Band C	Band D	Band E
1	−0.05 (587.0)	+0.11 (461.0)	a (444.0)	+1.07 (379.0)	−0.38 (312.5)
2	−0.05 (582.5)	+0.14 (467.0)	a (432.0)	+0.82 (381.0)	−0.36 (321.0)
3	+0.01 (627.0)	+0.16 (462.5)	a (438.0)	+0.88 (377.5)	−0.40 (320.5)
4	+0.05 (588.5)	−0.11 (472.0)	b (445.0)	−(378.0) 1.25	+0.45 (312.0)
5	+0.06 (569.5)	−0.15 (466.5)	b (435.0)	−(378.5) 1.00	+0.40 (318.5)
6	−0.03 (623.5)	−0.17 (460.0)	b (440.0)	−0.87 (378.0)	+0.39 (320.0)
7	+0.04 (613.0)		a (552.0)	+0.26 (440.5)	−0.18 (331.0)
8	−0.03 (618.0)		b (551.0)	−0.27 (440.5)	+0.21 (330.0)
9			+0.01 (579.0)	−0.05 (449.5)	+0.12 (340.5)
10			+0.48 (438.5)	−0.30 (373.0)	+0.43 (305.0)
11			+0.37 (437.0)	−1.60 (371.5)	b (301.0)
12	−0.01 (574.5)		+0.10 (456.5)	−0.13 (384.0)	b (360.0)
13			−0.40 (441.0)	+0.37 (377.0)	−0.42 (310.5)
14	+0.01 (573.0)		−0.12 (458.5)	+0.17 (381.0)	a (362.5)
15			−0.24 (433.5)	b (382.5)	−0.66 (331.5)
16			+0.13 (448.0)	−0.56 (375.5)	+0.22 (306.0)
17	+0.05 (589.0)	−0.04 (473.0)	b (440.0)	−1.20 (370.5)	+0.28 (312.5)
18		−0.03 (485.5)	+0.05 (434.5)	−0.26 (382.5)	+0.29 (330.5)
19		−0.01 (509.0)	+0.04 (442.5)	−0.14 (378.0)	
20	−0.04 (592.5)	+0.02 (476.5)	a (443.0)	+1.09 (372.0)	−0.26 (311.5)
21		+0.02 (506.0)	−0.05 (440.0)	+0.16 (379.0)	
22	−0.08 (593.0)	+0.12 (475.0)	a (439.0)	+0.59 (378.0)	−0.48 (318.0)
23	+0.07 (612.0)	+0.08 (500.5)	−0.30 (437.0)	+1.21 (375.0)	
24				−0.56 (404.0)	+0.20 (333.5)
25				+0.58 (406.0)	−0.25 (332.0)
26	−0.06 (591.0)		−0.33 (443.0)	+1.01 (375.5)	−1.00 (316.5)
27	+0.13 (603.0)		+0.02 (453.5)	−1.25 (380.0)	+0.31 (308.5)

Values are given as $\Delta\varepsilon'$ (nm).

[a] For explanation of term $\Delta\varepsilon'$ see text; a—positive minimum (curve minimum which lies above the baseline); b—negative minimum (curve maximum which lies below the baseline; according to Ref. 16).

As expected, the CD curves obtained for both enantiomers of a particular amino alcohol are mirror images (Table 1, Fig. 11). The small differences observed in the magnitude of particular Cotton effects can be attributed to the fact that the precise concentration of the chiral complex in each of the studied solutions is not known. Therefore, the CD data are presented as $\Delta\varepsilon'$ values. These $\Delta\varepsilon'$ values are calculated in the usual way as $\Delta\varepsilon' = \Delta A/c \times d$, where c is the molar concentration of the amino alcohol, assuming 100% complexation.

As can be seen from Table 1, the rhodium complexes formed in situ with *vic*-amino alcohols exhibit three prominent bands in the 650–300 nm range. Two bands with the same sign appear near 310 nm (E) and 440 nm (C) and a third one (D), of opposite sign to the first two, occurs at 380 nm. The 440 nm band is, in many cases, detectable only as a distinct minimum or maximum (Table 1). Most probably, this Cotton effect is too weak to completely override the contribution of the very strong neighbouring D band. The C, D and E bands are most intense and therefore most suitable for the absolute configuration determination.

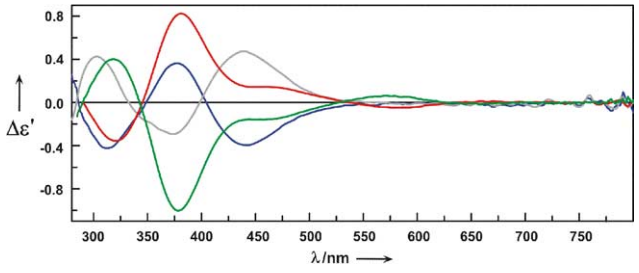


Figure 11. CD spectra of in situ formed Rh-complexes of amino alcohols **2** (——), **5** (——), **10** (——) and **13** (——) recorded in ethanol after 24 h storage in room temperature with ligand-to-metal ratio 1.5:1.

A correlation between the signs of these three Cotton effects and the sign of the N–C–C–O torsional angle, allowing fast and easy configurational assignment within an amino alcohol subunit, has been previously proposed by us.[2] The helicity rule correlates a positive (negative) sign of the N–C–C–O torsional angle with a positive (negative) sign of Cotton effect around 310 and 440 nm or with a negative (positive) sign of the Cotton effect around 380 nm.

It has to be added that in the chiral complex, the antiperiplanar orientation of both O–C–C–R and N–C–C–R units should be energetically preferred. This is due to the fact that only in such a conformation does the sterically demanding R-groups point away from the rest of the complex and thus avoids the close interaction with the remaining acetate ligands in the stock complex.[1,12] Thus, the conformation of the flexible amino alcohol becomes fixed to some extent after ligation to the Rh_2-core and thereby the relative configuration of the O–C–C–N

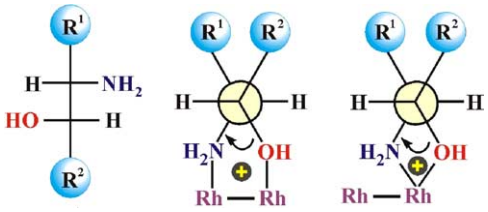


Figure 12. Preferred antiperiplanar conformation of an aliphatic 1,2-amino alcohol from ephedrine type when complexed to Rh-dimer: bridged (middle) and chelating (right) type of complexes.

unit can be established. In the next step, the sign of the O–C–C–N torsional angle obtained from the CD spectrum allows to determine unequivocally the absolute configuration. Therefore, the absolute configuration can be determined on the basis of the chiroptical data alone. The preferred conformation of the Rh-complex with 1,2-amino alcohol **16** with a positive torsional angle of the O–C–C–N unit in both bridged and chelating complexation modes is shown in Figure 12.

The aforementioned discussion leads to the conclusion that the diagnostic Cotton effects can be correlated with the torsional angle of an amino alcohol unit. In this regard, the amino alcohols showing a positive sign of the C and E bands and a negative sign of the D band follow the P-helicity, whilst the amino alcohols displaying an opposite sign sequence, that is, negative–positive–negative for the C, D and E bands, respectively, adopt the M-helicity.

The amino alcohols **1**–**27** independently of their cyclic or acyclic form and of their ephedrine or adrenaline type follow the helicity rule without exception. Thus, the applicability of helicity rule is now extended to a large variety of *vic*-amino alcohols. However, certain CD results presented here are more complex and require thorough analysis. Such a complex situation is observed, for example, in the case of *erythro*-aminoethanols **12** and **14,** where the two O–C–C–Ph and N–C–C–Ph units are not able to adopt in the complex an antiperiplanar conformation at the same time (Fig. 13). Thus, the configuration at one of secondary carbon atoms will solely determine the preference for the torsional angle and, consequently, also its sign. A negative sign of Cotton effects at 329 and 406 nm for **12** and a positive one for Cotton effects in the same spectral region for **14** indicates a negative/positive O–C–C–N torsional angle in the complexed form, respectively. Therefore, in the cases of compounds **12** and **14**, the sign-determining factor allowing configurational assignment is the configuration at the carbon atom bearing hydroxy group.

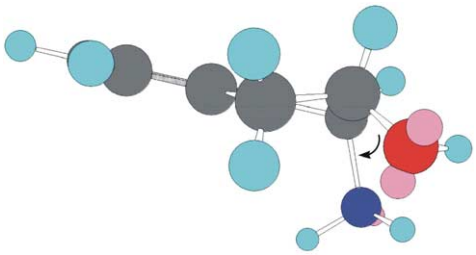


Figure 14. The calculated ground state structure of amino alcohol **24** by the PM3 method.

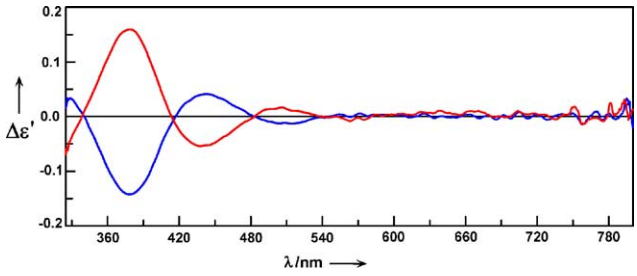


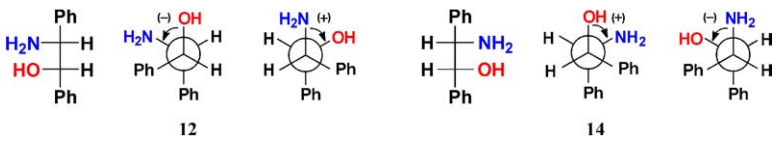
Figure 15. CD spectra of in situ formed Rh-complexes with (*R*)- and (*S*)-propanolols **19** (——) and **21** (——), respectively, recorded in ethanol.

To obtain the necessary information about the sign of the torsional angle O–C–C–N in bicyclic compounds **24** and **25**, we decided to apply molecular modelling calculations. A search by PM3 calculations[13] revealed that in the case of amino alcohol **24**, the O–C–C–N torsional angle sign is positive whereas in the case of **25** it is negative (Fig. 14). A positive Cotton effect around 330 nm for **24** as well as a negative one at 332 nm for **25** corroborate the applicability of the helicity rule for these bicyclic compounds.

The absolute configuration of *vic*-amino alcohols possessing an additional chromophoric system in the molecule can also be determined by this method. Propranolols **19** and **21**, representing adrenergic drugs, present such an example. Although their naphthalene chromophore absorbs very close to the CD band E, the assignment can be nevertheless successfully done on the basis of the sign of bands C and D (Fig. 15, Table 1).

3. Conclusions

It has been shown that the dirhodium tetraacetate in ethanol can successfully be used as an auxiliary chromo-



12 **14**

Figure 13. Possible preferred conformations of (1*S*,2*R*)-2-amino-1,2-diphenylethanol **12** and (1*R*,2*S*)-2-amino-1,2-diphenylethanol **14** in the Rh-complex.

phore in the stereochemical studies of several types of *vic*-amino alcohols. For the stereochemical assignment, the helicity rule correlating a positive/negative sign of the N–C–C–O torsional angle with a positive/negative sign of CD bands occurring at around 330 and 440 nm can be applied.

The observed dependency of relevant absorption maxima on time in both the CD and visible absorption spectra strongly indicates the changes in coordination mode of ligand to the metal core. It means, that dissociative ring opening of the leaving acetate group follows an initial coordination of the amino alcohol molecule(s) in the axial position(s). In this way, an equatorial site becomes free for the coordination by the incoming amino alcohols. Thus, a migration to an equatorial position(s) with formation of a bridging or a chelating complex can take place. The nonequivalence of four acetate methyl and carbonyl groups in both ^{1}H and ^{13}C NMR spectra fully support this supposition. On the basis of these results, it can be stated that in ethanol solution formation of a chiral complex proceeds as a dynamic process. Finally, after bidentate coordination of the ligand to the dirhodium dimmer, the equatorial complexes of a bridging or chelating mode of binding are formed.

The results allow a further conclusion to be drawn, namely, that due to the different structure of chiral complexes formed in ethanol versus acetonitrile or chloroform, the helicity rule developed for ethanol solution is not applicable in the case of the two latter solvents. Very recently, we have demonstrated that in acetonitrile and chloroform chiral complexes are formed exclusively by axial ligation of the ligand to the metal atom(s) of the dirhodium core.[3]

Since acetonitrile, like ethanol, belongs to the coordinating solvents, the question arises why different complexes are formed in both coordinating solvents. One of the possible explanations may be the one given by Cotton et al.[14] that in contrast to the ethanol, the acetonitrile molecules are small and linear. Therefore, most likely, the axial positions of the Rh_2-cluster are not entirely blocked by these molecules, thus allowing a closer approach by the incoming amino alcohol.

From practical point of view, ethanol and chloroform or acetonitrile can be used as a solvent for determination of the absolute configuration of *vic*-amino alcohols by the dirhodium complexation method. The choice mainly depends on solubility of components (*vic*-amino alcohols and chiral Rh-complex formed) in particular solvents. In many cases, amino alcohols which are not soluble in chloroform are good soluble in ethanol or acetonitrile. Therefore, the solvents are complementary. However, one must keep in mind that the origin of diagnostic CD bands occurred in different solvents is different, that is, complexes formed in ethanol solutions are govern by the helicity rule whilst the ones formed in chloroform or acetonitrile solutions by the sector rule.

The in situ dirhodium complexation method can be regarded as a straightforward and versatile method for the determination of absolute configuration of *vic*-amino alcohols, complementary to other methods, for example, exciton chirality method.[15] In comparison to the ECCD the fact that no quantitative values are obtained could be regarded as a disadvantage of the proposed method. However, for the purpose of determination of the absolute configuration only the signs and the relative magnitudes of the Cotton effects are important, not their absolute values. On the other hand, this disadvantage is compensated for by the fact that there is no need to synthesize, isolate and purify any derivatives before obtaining the CD spectrum. It is additionally worth to consider that, in general, less than 1 mg of the potential ligand is sufficient to obtain a very good and reproducible CD spectrum.

4. Experimental

UV–vis spectra were measured on a Cary 100 spectrophotometer in ethanol. CD spectra were recorded in the 250–800 nm range, at room temperature, with a Jasco 715 spectropolarimeter using ethanol solutions in cells of 2, 10, or 20 mm path length. Depending on the S/N ratio the λ-scan speed was 0.2 or 0.5 nm/s. For CD measurements at 50 °C an Julabo F33 thermostat connected to the CD instruments was used.

For CD standard measurements, the solid chiral amino alcohol (1–5 mg, ca. 0.003 M/L) was dissolved in a stock solution of the dirhodium tetraacetate (6–7 mg, ca. 0.002 M/L) in ethanol so that the molar ratio of the stock complex to ligand was about 1:1.5, in general. In special cases, for example, concentration-dependent CD measurements, other metal-to-ligand ratios were used (see text). Some of the $\Delta\varepsilon'$-values were very small, but nevertheless the signal-to-noise ratio in all cases was better than at least 10:1.

Due to insolubility of Rh-complexes of compounds **15** and **22** in ethanol, their spectra were measured in a 1:1 mixture of ethanol and water.

All NMR measurements were conducted on a Bruker DRX-500 spectrometer equipped with 5 mm triple broadband inverse probe with *z*-gradient coil.

4.1. Preparation of the chiral Rh_2-complex for NMR measurements

A mixture of D-phenylalaninol (100 mg, 0.68 mmol), dirhodium tetraacetate (200 mg, 0.45 mmol) and ethanol (40 mL) was stirred at room temperature for 3 h. Then, the solvent was removed in vacuo and the residue was chromatographed on silica gel (230–400 mesh, methylene chloride–isopropanol 97:3). Green coloured fractions were collected. The oiled product (56 mg, 21%) was obtained after solvent removal.

Source of compounds: compounds **1**–**27** were purchased from Fluka and/or Sigma–Aldrich and were used without further purification. Dirhodium tetraacetate as well as ethanol (Uvasol purity), were purchased from Aldrich

and Merck, respectively, and were used without further purification.

Acknowledgements

The authors are thankful to the Polish State Committee for Scientific Research (KBN) for Grants No. 7T0 9A 00421 and 7T0 9A 06025. The authors thank Aldrich/Sigma Poland, for kindly providing the samples **15** and **23**.

References

1. (a) Frelek, J.; Perkowska, A.; Snatzke, G.; Tima, M.; Wagner, U.; Wolff, H. P. *Spectrosc. Int. J.* **1983**, *2*, 274–295; (b) Frelek, J.; Majer, Z.; Perkowska, A.; Snatzke, G.; Vlahov, I.; Wagner, U. *Pure Appl. Chem.* **1985**, *57*, 441–451; (c) Frelek, J.; Konował, A.; Piotrowski, G.; Snatzke, G.; Wagner, U. *Stud. Org. Chem.* **1986**, *26*, 509–519; (d) Frelek, J.; Klimek, A.; Ruśkowska, P. *Curr. Org. Chem.* **2003**, *7*, 1081–1104.
2. Frelek, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2809–2816.
3. Frelek, J.; Jaźwiński, J.; Masnyk, M.; Ruśkowska, P.; Szmigielski, R. *Tetrahedron: Asymmetry* **2005**, *16*, 2437–2448.
4. (a) Cotton, F. A.; Walton, R. A. *Multiple bonds between metal atoms*; Clarendon Press: Oxford, 1993; (b) Boyar, E. B.; Robinson, S. D. *Coord. Chem. Rev.* **1983**, *50*, 109–208.
5. (a) Pruchnik, F. P. *Pure Appl. Chem.* **1989**, *61*, 795–804; (b) Pruchnik, F. P.; Starosta, R.; Ciunik, Z.; Opolski, A.; Wietrzyk, J.; Wojdat, E.; Duś, D. *Can. J. Chem.* **2001**, *79*, 868–877.
6. (a) Gerards, M.; Snatzke, G. *Tetrahedron: Asymmetry* **1990**, *1*, 221–236; (b) Moeller, S.; Albert, D.; Duddeck, H.; Simon, A.; Toth, G.; Demchuk, O.; Pietrusiewicz, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3609–3616.
7. (a) Lahuerta, P.; Moreno, E.; Monge, A.; Muller, G.; Perez-Prito, J.; Sanau, M.; Stiriba, S.-E. *Eur. J. Inorg. Chem.* **2000**, 2481–2485; (b) Lahuerta, P.; Perez-Prito, J.; Sanau, M.; Stiriba, S.-E. *Inorg. Chim. Acta* **2001**, *323*, 152–156.
8. (a) Dennis, A. M.; Korp, J. D.; Bernal, I.; Howard, R. A.; Bear, J. L. *Inorg. Chem.* **1983**, *22*, 1522–1529; (b) Dunbar, K. R.; Matonic, J. H.; Saharan, V. P. *Inorg. Chem.* **1994**, *33*, 25–31.
9. Snatzke, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *81*, 380–393.
10. (a) *Electrospray Ionization Mass Spectrometry. Fundamentals, Instrumentation and Application*; John Willey and Sons: New York, 1997; (b) Pramenik, B. N.; Ganguly, A. K.; Gross, M. L. *Applied Electrospray Mass Spectrometry*; Marcel Dekker: New York, 2002; (c) Hop, C.; Bakhtiar, R. *Biospectroscopy* **1997**, *3*, 259–280; (d) Naylor, S.; Kumar, R. *Adv. Protein Chem.* **2003**, *65*, 217–248.
11. Frelek, J.; Klimek, A.; Ruśkowska, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2461–2469.
12. (a) Frelek, J.; Snatzke, G. *Fresenius' Z. Anal. Chem.* **1983**, *316*, 261–264; (b) Frelek, J.; Majer, Zs; Perkowska, A.; Snatzke, G.; Vlahov, I.; Wagner, U. *Pure Appl. Chem.* **1985**, *57*, 441–451; (c) Liptak, A.; Frelek, J.; Snatzke, G.; Vlahov, I. *Carbohydr. Res.* **1987**, *164*, 149–159.
13. CS ChemOffice Ultra suite of applications by CambridgeSoft Corp., 2001.
14. Cotton, F. A.; Hillard, E. A.; Liu, Ch. Y.; Murillo, C. A.; Wang, W.; Wang, X. *Inorg. Chim. Acta* **2002**, 233–246.
15. (a) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 6345–6359; (b) Huang, X. F.; Rickman, B. H.; Boran, B.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 6185–6186; (c) Zan, S.; Canary, J. W. *Org. Lett.* **1999**, *1*, 861–864; (d) Gawronski, J.; Skowronek, P. *Curr. Org. Chem.* **2004**, *8*, 65–82.
16. Salvadori, P.; Ciardelli, F. *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism*; Heyden and Son: London, New York, Rheine, 1973; p 12.