NMR and CD Studies of Sulfur Chirality Center in Pd(II) Complexes with S-benzyl-cysteine and Glycyl-S-benzyl-L-cysteine

HENRYK KOZŁOWSKI

Institute of Chemistry, University of Wroclaw, Joliot-Curie St. 14, 50383 Wroclaw, Poland

BRIGITTE DECOCK-LE-REVEREND, JEAN-LUC DELARUELLE, CLAUDE LOUCHEUX

Laboratoire de chimie macromoléculaire ERA 827 du CNRS, Université de Lille I, 59655 Villeneuve d'Ascq, Cedex, France

and BERNARD ANCIAN

Institut de Topologie et de Dynamique des Systèmes LA No 34 du CNRS, Université de Paris VII, 1, rue Guy de la Brosse, 75221 Paris Cedex 05, France

Received June 12, 1982

^1H NMR and CD spectra have shown the creation of chirality centers on thioether sulfur atoms when bound to metal ions in Pd(II) complexes with S-benzyl-L-cysteine and glycyl-S-benzyl-L-cysteine. Two diastereomers are formed with R or S configuration on the sulfur. The ^1H NMR and CD spectra as well as the molecular model considerations were used to suggest the absolution configuration of the respective diastereomers in the series of Pd(II) complexes with S-methyl, S-ethyl and S-benzyl-L-cysteine derivatives. The S-substituent was also found to have a critical influence on the absolute configuration of sulfur atom in the studied complexes.

Introduction

The creation of a chirality center on thioether sulfur when bound to a metal ion results in several characteristic spectroscopic and structural features [1–6].

The studies on the S-alkyl cysteine complexes of Pd(II) and Pt(II) revealed among others that two diastereomers are usually formed and their relative concentrations may depend on the ligand used in the study.

The S-aralkyl cysteine derivatives are less common among the studied systems though some of them are known to possess antitumor activity [7, 8].

TABLE 1. ^1H NMR Parameters for SBC, Gly-SBC and their Pd(II) Complexes. Chemical Shifts are related to TSP Standard.

Compound	pH	ν_A[b]	ν_B[b]	ν_C	ν_{CH_2}	J_{ABCH_2}	ν_{CH_2Gly}	J_{ABCH_2Gly}
SBC	0.93	3.006	3.107	4.156	3.860			
	6.2	2.972	3.032	3.852	3.857			
	10.9	2.745	2.806	3.424	3.815			
Pd SBC	0.3(1)[a]	3.199	3.039	3.506	4.504, 4.242(AB)	13.43		
	(2)	2.907	3.106	3.980	4.310			
Gly-SBC	0.66	2.932	3.054	4.623	3.850		3.850	
	3.24	2.858	2.983	4.394	3.805		3.793	
	4.9	2.859	2.985	4.391	3.815		3.809	
	8.4	2.884	2.981	4.393	3.821		3.592	
	11.3	2.89	2.970	4.385	3.812		3.296	
Pd Gly-SBC	4.3(1)	3.032	3.097	4.055	4.295, 4.137(AB)	14.7	3.707, 3.627(AB)	17.1
	(2)	3.027	3.170	4.237	4.274 (A_2)		3.843, 3.718(AB)	17.1

[a](1) major species, (2) minor species. [b]Two side lines are not seen and ν_A and ν_B cannot be calculated explicitly.

0020-1693/83/0000-0000/$03.00

TABLE II. Rotamer Populations and Coupling Constants for SBC Residue in SBC and Gly-SBC and their Pd(II) Complexes.

Compound	pH	J_{AB}	J_{AC}	J_{BC}	P_I	P_{II}	P_{III}
SBC	0.93	15.1	8.5	3.6	0.12	0.55	0.33
	6.2	14.9	9.5	2.5	0.02	0.64	0.34
	10.9	13.7	8.5	3.5	0.10	0.55	0.35
Pd SBC	0.3(1)[a]	14.1	10.3	5.3	0.26	0.71	0.03
	(2)	12.7	11.6	4.6	0.17	0.83	0
Gly-SBC	0.66	14.1	8.5	4.5	0.19	0.55	0.26
	3.24	13.7	8.6	3.9	0.14	0.56	0.30
	4.9	13.9	8.5	3.9	0.14	0.55	0.31
	8.4	13.1	8.5	3.9	0.14	0.55	0.31
	11.3	13.0	7.9	3.9	0.14	0.50	0.36
Pd Gly-SBC	4.3(1)	11.8	7.0	2.6	0.03	0.42	0.55
	(2)	14.5	7.6	1.4	0	0.49	0.61

[a](1) major species, (2) minor species.

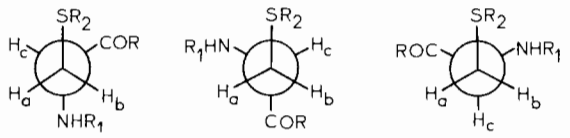
TABLE III. CD Spectra of SBC and Gly-SBC and their Pd(II) Complexes.

Compound	pH	λ (mn)	Δe
SBC	4.2	217	+3.7
		213	+3.5
PdSBC	0.8	400	−0.8
		354	+0.57
		297	−0.26
		265(sh,b)	+0.9
		238	+4.7
		210	−10.7
	2.2	400	−0.66
		354	+0.56
		274(sh,b)	+0.8
		238	+3.7
		212	−10.3
Gly-SBC	5.8	221	+13.3
Pd Gly-SBC	5.9	338	−2.1
		277	−0.99
		248	+1.88
		220	+0.1 (?)

The bulky aromatic ring of S-substituted cysteine may play a critical role in the distribution of diastereomer population by introducing considerable steric effects in the coordinated ligand molecule. As a continuation of our studies on the interaction of metal ions with thioether amino acid residue, we present in this work the NMR and CD results on Pd(II) complexes with S-benzyl-L-cysteine and glycyl-S-benzyl-L-cysteine.

Experimental

Glycyl-S-benzyl-L-cysteine was synthesized by coupling of both aminoacids via N-hydroxy-succinimide [9]. S-benzyl-L-cysteine was obtained from Fluka.



I II III

Fig. 1. Rotamer notation for thioether aminoacid residue.

^{1}H NMR spectra were recorded on 80 (WP 80) and 200 MHz (WP 200) Bruker spectrometers with a peptide concentration of 10^{-2} *M* at 300 ± 2 K.

Analysis and simulation of the proton ABC spectra were carried out on an Apple II computer. CD spectra were measured on a Mark III Jobin-Yvon dichrograph in the 800–200 nm range with metal ion concentration 5 × 10^{-3} *M*. Absorption spectra were recorded on a Cary 219 spectrometer with metal ion concentration 10^{-3} or 5 × 10^{-4} *M*.

Results and Discussion

^{1}H NMR parameters for S-benzyl-L-cysteine (SBC) and glycyl-S-benzyl-L-cysteine (Gly-SBC) are presented in Table I. The comparison of these results with those of S-methyl-L-cysteine (SMC) and glycyl-S-methyl-L-cysteine (Gly-SMC) [1, 2] shows only a minor effect of aromatic ring on the rotamer distribution in the SBC residue (Table II, Fig. 1).

Also CD spectra of the studied metal-free ligands resemble those of SMC with possible involvement of the intrasulfur transitions observed in the 190–250 nm region [2, 10] (Table III).

TABLE IV. U.V. Spectra of SBC and Gly-SBC and their Pd(II) Complexes.

Compound	pH	λ (nm)	ε
SBC	1.7	266	580
		260	880
		253	1100
		211	6400
Pd SBC	1.7	385	770
		280	4800
		255	8300
Gly-SBC	4.1	267	950
		261	900
Pd Gly-SBC	4.4	330	1944

TABLE V. Diastereomer Assignment.

Complex	I_1/I_2 [a]	Dominant Diastereomer
Pd SMC	2.0	C_2(R)S(S)
Pd SEC [b]	2.0	C_2(R)S(S)
Pd Gly-SMC	1.2	C_2(R)S(S)
Pd SBC	0.5	C_2(R)S(R)
Pd Gly-SBC	0.3	C_2(R)S(R)

[a] I_1 and I_2 correspond to relative signal intensity of diastereomers with $C_\alpha H$ (or S-CH_3) resonance at lower and higher magnetic field, respectively. [b] S-ethyl-L-cysteine complex, I_1/I_2 is taken from ref. 6.

In the absorption spectra, the main bands at around 250–260 nm derive from intra-aromatic ring transitions (Table IV) overlapping most likely with the intrasulfur transition observed in SMC derivatives at about 250 nm [2, 10].

^{1}H NMR spectra of Pd SBC solutions consist of two sets of the resonances derived from two diastereomers formed during the complexation of SBC by metal ion [1, 2]. The chemical shift variations upon the Pd(II) ion coordination are close to those found in the Pd SMC system (Table I). The latter result strongly suggests {NS} coordination mode in the S-benzyl-L-cysteine complex, as in Pd SMC. It also allows us to assume that two respective diastereomers of both complexes have similar chemical shift pattern *e.g.* the lowfield $C_\alpha H$ resonances correspond to the same diastereomer in both complexes.

The presence of the S-benzyl substituent in the Pd SBC complex leads, however, to considerable variation in the relative diastereomer population when compared to Pd SMC. The diastereomer in Pd SMC with $C_\alpha H$ and S-CH_3 protons shifted downfield is a major species in solution (2:1 molar ratio). In Pd SBC this absolute configuration becomes less favored and the relative molar ratio changes to 1:2. The benzyl group destabilizes also the rotamer III population in the complex molecule (Table II) due to stronger steric effects of this group as compared to S-CH_3 in Pd SMC.

The methylene protons of S benzyl group (which exhibit a singlet resonance in metal free SBC) give two AB quartets in the Pd SBC complex. The unequivalence of these protons derives most likely from the formation of a chirality center on the sulfur atom and the presence of aromatic ring in a S aralkyl group.

Proton NMR spectra of Pd Gly-SBC show also the formation of two diastereomers in the studied solutions. The chemical shift variation indicates the same

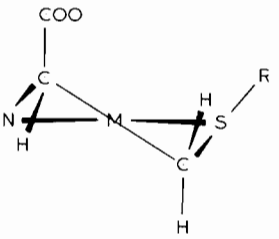


Fig. 2. S absolute configuration on sulfur atom in δ conformation of chelate ring.

binding mode as in Pd Gly-SMC, *i.e.* {N N S} (Table I, ref. 2).

The methylene protons of glycine residue exhibit two sets of AB quartets. The origin of the Gly-CH_2 unequivalence seems to be attributed to the formation of the two diastereomers. The different conformations of chelate rings of Gly or SBC residue may also contribute to the methylene proton unequivalence, as suggested earlier for the Pd Gly-SMC complex [2].

The glycine residue in Pd Gly-SBC system seems to be an important factor when deciding on the chelate ring conformation of SBC residue. The rotamer III in Pd Gly-SBC becomes the dominant conformer (Table II) while in Pd SBC its population was close to zero. Even if one takes into account the possible deviation of χ angle around the C_α–C_β bond when SBC residue is involved in chelate ring formation (see *e.g.*, Table II, the unusually small J_{BC} values in the minor diastereomer of Pd Gly-SBC complex), the large P_{III} value suggests the increase of δ conformer population of SBC chelate ring in Pd Gly-SBC complex. The same influence of glycine residue was observed in Pd Gly-SMC complex and more detailed discussion of this problem is given in ref. 2. The increase of δ conformer of SBC chelate ring in Pd Gly-SBC causes further decrease of the

population of the diastereomer characterized by lowfield resonances. The relative intensity decreases from 1:2 in Pd SBC to 1:3 in Pd Gly-SBC (Table V).

The variation of the diastereomer populations when a more bulky group is used as a substituent on sulfur on the chelate ring conformation change from λ(Pd SMC, Pd SEC, Pd SBC) to δ(Pd Gly-SMC, Pd Gly-SBC) allows us to propose the assignment of absolute configuration on sulfur atom in particular diastereomers. It seems to be clear that the increase of δ conformer population in Pd(II) dipeptide complexes in comparison to Pd(II) aminoacid complexes would destabilize considerably S configuration on the sulfur center, as a result of the steric effects between an axial (in δ conformer) carboxyl group and a respective substituent on sulfur (Fig. 2). Thus, the comparison of population changes in Pd SMC, Pd Gly-SMC and Pd SBC, Pd Gly-SBC pairs of complexes (Table V) may suggest that the diastereomer with lowfield $C_\alpha H$ resonance has an absolute configuration S and the other one absolute configuration R. This assignment seems to be ascertained also by the consideration of the steric effects in Pd SMC and Pd SBC or Pd Gly-SMC and Pd Gly-SBC pair of complexes. The chelate ring conformation of thioether residue in Pd Gly-SMC and Pd Gly-SBC seems to be similar in both complexes (see p_i values in Table II and ref. 2). Thus the more bulky benzyl group should destabilize the S configuration on sulfur much more considerably than would the methyl group of SMC residue. This result can be easily seen in Table V. Similar arguments can derive from the comparison of Pd SMC and Pd SBC complexes, in which the steric effects of benzyl group are also of critical importance for the diastereomer population distribution (Table V).

CD spectra of Pd SBC solution exhibit two extrema in the d–d region at 400 (A) and 345 (E) nm (Table III) which seem to be characteristic bands for {NS} coordination mode [2, 11].

The formation of Pd SBC complex results in three new CD bands in the UV region, at 297, 265 and 238 nm (Table III). The 297 and 238 nm bands may be assigned as $\pi S \rightarrow$ Pd(II) and $\sigma S \rightarrow$ Pd(II) charge transfer transitions [2, 11–14] respectively. The 265 nm band observed as a broad shoulder may consist of more than one transition. The intrasulfur transition observed in this region of the CD spectra may be accompanied by intra-aromatic ring transition. The latter transitions (seen in absorption spectra around 260 nm, Table IV), may be activated by the chirality center on sulfur in Pd-SBC complex. At higher pH than 2 the CD bands at ≅270 nm become very broad and the extraction of all CD transitions from this spectrum was not possible. CD spectra of Pd Gly-SBC exhibit only one d–d transition band at 338 nm (A + E) close in energy to that of Pd Gly-SMC. Two other bands at 248 and 277 nm are $\sigma S \rightarrow$ Pd and $\pi S \rightarrow$ Pd charge transfer bands. It is likely, however, that both of these bands contain also other transitions *i.e.* intrasulfur and intra-aromatic ring transitions. The absorption spectra of Pd SBC and Pd Gly-SBC complexes are less clear than CD spectra. Their similarities to those of Pd SMC and Pd Gly-SMC (Table IV, ref. 2), (excluding intra-aromatic ring transitions), support, however, conclusions about the same coordination mode and similar structures in both pairs of complexes.

The main differences in CD spectra between SMC and SBC complexes (Table III, ref. 2) are seen in $\Delta\epsilon$ values and the signs of Cotton effects, *i.e.* the $\Delta\epsilon$ values of the transitions for Pd Gly-SBC are one order of magnitude higher than those of Pd Gly-SMC. The main reason for this particular difference may arise from the fact that in Pd Gly-SMC, the diastereomer ratio was close to 1 while in Pd Gly-SBC the S(R) diastereomer (Table V) is about three times more populated than the S(S) one.

The strong increase of $\Delta\epsilon$ values clearly indicates the predominance of the vicinal effect of sulfur chiral center on the transitions of the complex while the contribution derived from carbon C_2 center plays only a minor role in inducing of the CD bands. The $\Delta\epsilon$ values found in the Pd SMC and Pd SBC complexes are close to each other, due to similar though reversed molar ratios of two diastereomers. The signs of Cotton effects of some of CD transition in both complexes are, however, opposite, *e.g.* for the complexes studied at pH > 2, the A(d–d) transition has positive Cotton effect in Pd SMC while in Pd SBC it is negative (ref. 2, Table III). In the same conditions the $\sigma S \rightarrow$ Pd transitions have also opposite Cotton effects though their $|\Delta\epsilon|$ values are close to each other.

Thus the CD spectra seem to support our previous conclusion derived from NMR spectra (see above) about the possible variation of the favored absolute configuration on sulfur atom (Table V) in Pd(II) complexes with thioether aminoacids.

Acknowledgements

The authors thank Dr. P. Decock for the help in computer analysis of NMR spectra and Dr. M. H. Loucheux-Lefebvre and C. Denis for the CD spectra measurements.

References

1 H. Kozłowski, Z. Siatecki, B. Jeżowska-Trzebiatowska and A. Allain, *Inorg. Chim. Acta, 46*, L25 (1980).
2 B. Decock-Le-Révérend, C. Loucheux, T. Kowalik and H. Kozłowski, *Inorg. Chim. Acta, 66*, 205 (1982).
3 M. Kubiak, A. Allain, B. Jeżowska-Trzebiatowska, T.

Glowiak and H. Kozłowski, *Acta Cryst., B36,* 2246 (1980).
4 T. Isago, K. Igi and J. Hidaka, *Bull. Chem. Soc. Japan, 52,* 407 (1979).
5 K. Yamanaki, J. Hidaka and Y. Shimura, *Bull. Chem. Soc. Japan, 50,* 2299 (1977).
6 N. Hadjiliadis, V. Theodorou, I. Photaki, R. W. Gellert and R. Bau, *Inorg. Chim. Acta., 60,* 1 (1982).
7 L. Cheng, Y. Kwang and C. C. Cheng, *J. Med. Chem., 15,* 13 (1972).
8 B. Shohat, H. Shlesinger, N. Grossowicz and N. Lichtenstein, *Ist. J. Med. Sci., 8,* 29 (1972).
9 G. W. Anderson, J. E. Zimmerman and F. M. Callaham *J. Am. Chem. Soc., 85,* 8039 (1963); R. G. Hiskey, L. M. Beacham, V. G. Math, J. N. Smith, E. B. Williams, Jr., A. M. Thomas and E. T. Walters, *J. Org. Chem., 36,* 488 (1971).
10 C. Toniolo and G. M. Bonora, *Can. J. Chem., 54,* 70 (1976) and references therein.
11 T. Kowalik, H. Kozłowski and B. Decock-Le-Révérend, *Inorg. Chim. Acta, 67,* L39 (1982).
12 V. M. Miskowski, J. A. Thich, R. Solomon and H. J. Schugar, *J. Am. Chem. Soc., 98,* 8344 (1976).
13 H. Lam-Thanh, K. Lintner, M. Mannot, F. Piriour and S. Fermandjian, *J. Chim. Phys., 75,* 755 (1978).
14 H. Lam-Thanh and S. Fermandjian, *J. Chim. Phys., 74,* 361 (1977).