

NMR STUDY OF THE STRUCTURES OF Ni(II) COMPLEXES OF SCHIFF BASES OF 2-BROMOGLYCINE WITH (S)-2-[(N-BENZYLPROLYL)AMINO]-BENZOPHENONE OR (S)-2-[(N-BENZYLPROLYL)AMINO]-5-CHLOROBENZOPHENONE*

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Dedicated to Professor Yuri Belokon on the occasion of his 60th birthday.

The structure of a hydrolytically unstable Ni(II) complex of Schiff base of **3a** with 2-bromoglycine was confirmed by NMR and ²⁵²Cf plasma desorption mass spectrometry; a new more hydrolytically stable chloro derivate **4a** was prepared and investigated by 2D NMR.

Key words: Amino acids; ²⁵²Cf Plasma desorption mass spectrometry; Nickel; NMR spectroscopy; Schiff bases.

2-Bromoglycine derivatives are an important class of electrophilic glycine synthons². Due to the low stability of such derivatives they are generally used without NMR or X-ray structure characterization.

This work was initiated by Vitt's hypothesis³ of the existence of two possible isomers of the Ni(II) complex of the Schiff base of (S)-2-[(N-benzylprolyl)amino]benzophenone and 2-bromoglycine (**3a** and **3b**), which differ by the position of the C=N bond (Scheme 1). The hypothesis attempted to explain the reactivity of **3** (**3a** or **3b**) with dimethylamine^{4a}.

* Part IV in the series; Part III see ref.¹.

EXPERIMENTAL

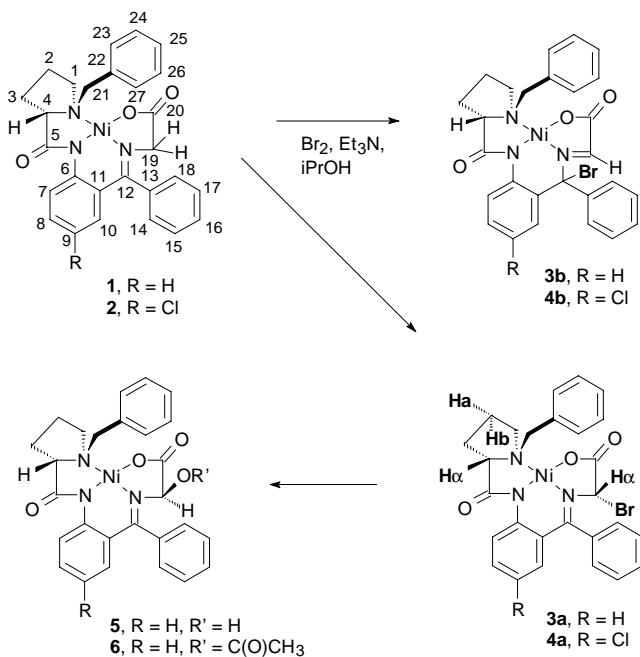
NMR spectra were recorded on a Bruker AMX 360 apparatus⁵ at 316.13 MHz for ¹H and at 90.57 MHz for ¹³C at 23 °C in CDCl₃ (concentration of samples 60–70 mg/ml). The following techniques were used for structure elucidation: (i) H,H-homonuclear correlated spectra^{6a}; (ii) inverse H,C-heteronuclear correlated spectra *via* heteronuclear zero and double quantum coherence optimized on long-range couplings with low-pass *J*-filter to suppress one-bond correlations, quantum coherence using BIRD sequence, phase sensitive using TPPI with decoupling during acquisition^{6b}; (iii) inverse H,C-heterocorrelated spectra *via* heteronuclear zero and double quantum coherence optimized on long-range couplings with low-pass *J*-filter to suppress one-bond correlations without decoupling during acquisition^{6c}.

²⁵²Cf PD mass spectra and FAB (matrix thioglycerol + glycerol) mass spectra were obtained with MSBX (Selmi) and ZAB-SEQ (VG Analytical) spectrometers, respectively.

Synthesis of 4

Complex **2** was prepared in the same way as described for a Ni complex of a Schiff base of (*S*)-2-[(*N*-benzylpropyl)amino]-5-methylbenzophenone and glycine^{7a} starting from (*S*)-2-[(*N*-benzylpropyl)amino]-5-chlorobenzophenone^{7b} instead of (*S*)-2-[(*N*-benzylpropyl)amino]-5-methylbenzophenone. Yield 87%, red crystals, m.p. 226–228 °C (benzene). Calculated mass for C₂₇H₂₅ClN₃NiO₃ [M + H]⁺ = 532.0938. By high-resolution FAB MS found [M + H]⁺ = 532.0908.

Bromination of **2** was provided following the described procedure for the complex **1** (ref.⁴). Yield 67%, red non-cystalline solid, for ¹H NMR and ¹³C NMR spectra see Table I.



SCHEME 1

TABLE I
 ^1H NMR and ^{13}C NMR chemical shifts of the compounds 1–4

C/H	1		2		3		4		1	2	3	4
	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ $^1\text{H}_a$	δ $^1\text{H}_b$				
No.	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ $^1\text{H}_a$	δ $^1\text{H}_b$	δ ^{13}C	δ ^{13}C	δ ^{13}C	δ ^{13}C
1	2.13	3.66	2.12	3.65	2.09	3.56	2.10	3.60	57.43	57.66	57.84	58.34
2	2.05	3.32	2.07	3.30	2.22	4.04	2.64	4.05	23.64	23.37	23.92	24.04
3	2.40	2.55	2.36	2.44	2.54	2.74	2.56	2.69	30.66	30.44	30.80	30.91
4	3.66	–	3.41	–	3.45	–	3.44	–	69.82	69.71	70.44	70.64
5	–	–	–	–	–	–	–	–	181.31	181.20	181.81	181.06
6	–	–	–	–	–	–	–	–	142.49	140.95	143.66	142.36
7	8.26	–	8.20	–	8.00	–	7.94	–	124.21	125.28	124.45	125.36
8	7.18	–	7.06	–	7.14	–	7.09	–	132.17	131.36	133.52	133.26
9	6.68	–	–	–	6.59	–	–	–	120.79	125.99	121.07	127.23
10	6.78	–	6.68	–	6.65	–	6.61	–	133.13	131.53	133.89	132.32
11	–	–	–	–	–	–	–	–	125.12	125.04	126.06	127.23
12	–	–	–	–	–	–	–	–	171.58	170.47	173.85	173.12
13	–	–	–	–	–	–	–	–	134.57	133.55	132.18	131.52
14	6.96	–	6.91	–	7.10	–	7.10	–	126.21	125.80	127.26	126.57
	or		or		or		or			or	or	or
	7.07		7.06		7.15		7.15			125.28	126.63	127.16
15	7.48	–	7.48	–	7.50	–	7.53	–	129.29	129.27	128.67	129.27
											or	or
											129.21	129.43
16	7.48	–	7.48	–	7.50	–	7.53	–	129.69	129.64	130.19	130.68
17	7.48	–	7.48	–	7.50	–	7.53	–	129.55	129.64	128.67	129.27
											or	or
											129.21	129.43
18	6.96	–	6.91	–	7.10	–	7.10	–	125.62	125.80	127.26	126.57
	or		or		or		or			or	or	or
	7.07		7.06		7.15		7.15			125.28	126.63	127.16
19	3.66	3.76	3.63	3.74	5.31	–	5.20	–	61.24	61.10	62.36	62.07
20	–	–	–	–	–	–	–	–	177.28	176.58	174.11	173.96
21	3.65	4.46	3.49	4.39	3.47	4.35	3.38	4.34	63.06	63.11	63.16	63.52
22	–	–	–	–	–	–	–	–	133.26	133.38	133.43	133.75
23	8.05	–	8.09	–	8.10	–	8.14	–	131.68	131.32	131.41	131.40
24	7.41	–	7.38	–	7.37	–	7.39	–	128.87	128.63	128.95	129.13
25	7.29	–	7.25	–	7.20	–	7.22	–	129.07	128.85	129.04	129.03
26	7.41	–	7.38	–	7.37	–	7.39	–	128.87	128.63	128.95	129.13
27	8.05	–	8.09	–	8.10	–	8.14	–	131.68	131.32	131.41	131.40

Synthesis of **6**

To a stirred solution of **3** (57 mg, 0.1 mmol) in DMF (2 ml) at 20 °C NaOAc (100 mg, 1 mmol) was added. After 4 h the mixture was evaporated *in vacuo*, the residue was mixed with H₂O (2 ml) and extracted with CHCl₃ (3 × 1 ml). The extract was evaporated *in vacuo* and the residue was purified by chromatography on silica gel with CHCl₃ : Me₂CO = 7 : 1. The second red fraction, containing the reaction product was collected. Recrystallization from benzene gave 35 mg of **6** (63 %), red crystals, m.p. 210–211 °C (benzene); $[\alpha]_{589}^{25} = 765$ (MeOH, $c = 0.0654$). For C₂₉H₂₇N₃NiO₅ (556.24) calculated: 62.62% C, 4.89% H, 7.55% N; found: 62.60% C, 4.67% H, 7.55% N.

RESULTS AND DISCUSSION

The low stability of compound **3** results in thermal decomposition above 40 °C and partial decomposition during chromatographic purification on silica gel. Neither positive- nor negative-ion FAB MS showed a peak of the molecular ion. It was, therefore, necessary to use negative ²⁵²Cf plasma desorption mass-spectrometry to see this peak. The first question to be answered was what is the nature its instability. The main by-product of the bromination reaction (Scheme 1) was found to be 2-hydroxyglycine complex **5**. This compound gave a peak of the molecular ion in the positive ion FAB MS. The ¹³C NMR gave δ 86.03 for C-19. This is similar to that of the reference (*R*)-2-acetoxylglycine complex **6** (δ_{C-19} 82.87) prepared by S_N2 reaction of **3** with sodium acetate in DMF. A small amount of **5** was found in fresh samples of **3** immediately after chromatographic purification on silica gel. The amount of **5** increased rapidly if the sample was not protected from air moisture.

To increase the stability of **3** towards hydrolysis, its chlorinated analogue **4** was prepared by bromination of the Ni(II) complex of the Schiff base of (*S*)-2-[(*N*-benzylprolyl)amino]-5-chlorobenzophenone and glycine **2**. This compound was found to be more stable than **3** and allowed NMR spectra to be recorded without experimental difficulties.

The structure of complex **4** was found to be similar to the structures of the complexes of 2-monosubstituted glycines⁵. On the basis of the NOE interaction^{5,6d} of the proline α -proton with the α -proton of the bromoglycine fragment in compound **4**, the configuration of the bromoglycine asymmetric centre was found⁵ to be (*S*). In both **3a** and **4a**, the interactions of H_b-2 with the bromine atom below the plane of the complex shifts the signal downfield ($\Delta\delta^1\text{H}$ 0.72 and $\Delta\delta^1\text{H}$ 0.75 ppm relative to $\delta^1\text{H}_b$ -2 in complexes **1** and **2** (Table I)). Based on this similarity, the (*S*) configuration was inferred for the bromoglycine asymmetric centre of compound **3a**. The downfield shift cannot be explained by the diamagnetic ring current of the phenyl ring (C-13–C-18) in structures **3b** and **4b** since in an analogous complex, such a current led to an upfield shift of 0.50 ppm (ref.⁸). This $\delta^1\text{H}_b$ -2 shift is an example of a third type of long-range interactions in Ni complexes of Schiff bases of (*S*)-2-[(*N*-benzylprolyl)amino]benzophenone and α -amino acids. The long-range NOE interaction⁵ (see above) was discovered as the first type and the long-range $^nJ(^{13}\text{C}, ^{13}\text{C})$, $^nJ(^{15}\text{N}, ^{13}\text{C})$ and $^nJ(^{15}\text{N}, ^{15}\text{N})$ interactions¹ as the second type.

The nature of these interactions and possible role of Ni orbitals are the subject of our investigation.

In order to verify the position of the C=N bond in compound **3** the values of $^nJ(^{15}\text{N}, ^{13}\text{C})$ and $^nJ(^{13}\text{C}, ^{13}\text{C})$ spin-spin coupling constants were compared with the corresponding values for the unsubstituted Ni(II) complex **1** (ref.¹). In the unsubstituted complex prepared from ^{15}N -labelled glycine the coupling constants were $^1J(^{15}\text{N}, ^{13}\text{C}-12) = 12.5$ and $^1J(^{15}\text{N}, ^{13}\text{C}-19) = 4.8$ Hz. This difference has been attributed to the greater s-character of hybrid orbitals⁹ of the double bond N=(C-12) relative to a single bond N-(C-19). In complex **3**, the spin-spin interaction constants $^1J(^{15}\text{N}, ^{13}\text{C}-12) = 12.0$ and $^1J(^{15}\text{N}, ^{13}\text{C}-19) = 4.8$ Hz confirm the structure **3a** and not **3b**. It should be noted that chemical shifts of C-12 and C-19 are not very sensitive to α -substitution by bromine (Table I). The C-19 chemical shift, δ 62.36, was verified by the measurement of ^{13}C NMR spectrum of **3a** labelled with ^{13}C at position C-19. If the structure **3b** existed, it would exceed δ 100. Distribution of the values of $^nJ(^{13}\text{C}, ^{13}\text{C})$ spin-spin coupling constants in this complex also confirmed the structure **3a** (data for the compound **1** (ref.¹) are given in brackets): $^1J(^{13}\text{C}-19, ^{13}\text{C}-20) = 62.2$ Hz (56.8 Hz), $^2J(^{13}\text{C}-19, ^{13}\text{C}-12) = 1.2$ Hz (0.9 Hz), $^3J(^{13}\text{C}-19, ^{13}\text{C}-13) = 4.0$ Hz (3.70 Hz), $^3J(^{13}\text{C}-19, ^{13}\text{C}-11) = 4.1$ Hz (3.34 Hz).

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