^{1}H, ^{13}C, AND ^{15}N NMR SPECTRA OF Ni(II) COMPLEXES OF SCHIFF BASES OF (*S*)-2-(*N*-BENZYLPROLYL)AMINOBENZOPHENONE AND α-MONO-SUBSTITUTED GLYCINE AND DETERMINATION OF CONFIGURATION OF THE COMPLEXES BY 2D NOESY SPECTRA

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^{1}H, ^{13}C, and ^{15}N NMR spectra have been measured of substituted Ni(II) complexes of Schiff bases of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and glycine. The absolute configuration at C19 of the substituted glycine can be determined from 2D NOESY spectra using the NOESY interactions with the proton of the second chiral centre of the complex. It is possible to determine the rate of rotation of phenyl group of benzophenone unless its rotation is prevented by "equatorial" orientation of dimethylamino group as it is the case with the Ni(II) complex of Schiff base of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and (*S*)-α-dimethylaminoglycine.

Preparative methods of asymmetric synthesis of α-amino acids are widely used in pharmaceutical chemistry. Recently, new procedures have been developed in asymmetric synthesis[1], inter alia, the reactions at α-carbon atom of Ni(II) complexes of amino acids and Schiff bases of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone which were prepared earlier[2–4] and were intensively investigated[1,5] by Belokon et al. In the present contribution we have continued our NMR studies[6] of Ni(II) complex of Schiff base of (*S*)-2-(*N*-benzylprolylamino)-5-methylbenzophenone and glycine. We were particularly interested in the study of differences between the nonsubstituted complex and those carrying one substituent at the α carbon atom of glycine. So far the configuration at α carbon atom of glycine fragment in similar complexes has been determined on the basis of Cotton effect in CD or ORD spectra. The empirical relationships were formulated on the basis of comparison of the spectra with those of the complexes whose configuration at chiral centres had been determined by X-ray analysis[3,7–9] of the corresponding crystals. The aim of the present work is to decide whether the arrangement of substituents above and below the plane of the complex is suitable for determination of absolute configuration at α carbon atom of glycine with the help of the NOE interactions.

EXPERIMENTAL

Preparation of Ni(II) Complexes

The Ni(II) complex of Schiff base of (*S*)-2-(*N*-benzylprolylamino)-5-methylbenzophenone and glycine *I* was prepared according to ref.[6]. The Ni(II) complex of Schiff base of (*S*)-2-(*N*-benzylprolyl)-aminobenzophenone and (*R*)-α-dimethylaminoglycine *II* and Ni(II) complex of Schiff base of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and (*S*)-α-dimethylaminoglycine *III* were prepared according to refs[10,11].

Measurements of NMR Spectra

The ^{1}H and ^{13}C NMR spectra were measured with a Bruker AMX 360 apparatus at 360.13 and 90.57 MHz, respectively, using an inverse tunable 5 mm probe in deuteriochloroform solution at 23 °C with the concentrations of the substances 42–52 mg/0.75 ml. The following measurement techniques were used: H,H-homonuclear correlated spectrum[12]; inverse H,C-heteronuclear correlated spectrum via heteronuclear zero and double quantum coherence using BIRD sequence, phase sensitive using TPPI with decoupling during acquisition[13]; inverse H,C-heterocorrelated spectrum 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[14]; H,H-homonuclear correlated spectrum via dipolar coupling, phase sensitive using TPPI, dipolar coupling may be due to NOE or chemical exchange[15]. The ^{15}N NMR spectra were measured at 36.50 MHz using a tunable 5 mm probe in deuteriochloroform solution at 23 °C with the same sample as that used in the measurements of ^{1}H and ^{13}C NMR spectra. The measurement adopted the INEPT technique for non-selective polarization transfer without decoupling during acquisition[16] with optimization on the coupling constant $^{n}J(^{15}N,^{1}H) = 3$ Hz. The ^{15}N chemical shifts are referenced to external $CH_3{}^{15}NO_2$ in a sealed coaxial capillary.

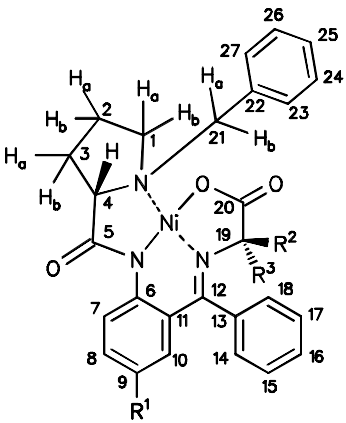
RESULTS AND DISCUSSION

Three model complexes were synthesized: the glycine complex *I* (containing a methyl group in the benzophenone cycle to facilitate the interpretation of the aromatic part of spectrum) and two diastereoisomers *II* and *III* containing a sterical equivalent of valine, (*R*)- or (*S*)-α-dimethylaminoglycine[10,11].

The ^{1}H and ^{13}C NMR chemical shifts of compounds *II* and *III* are given in Table I, and the ^{1}H and ^{13}C signals were assigned with the help of the H,H-homocorrelated and H,C-heterocorrelated spectra optimized on $^{1}J(^{13}C,^{1}H)$ which were measured with the samples of about 50 mg/0.75 ml concentration in $CDCl_3$ in the inverse arrangement and with the help of the chemical shifts of compound *I* published earlier[6]. When comparing the chemical shifts of protons in various complexes our attention was attracted by the fact that the differences in chemical shifts of the proline part in (*S*,*R*) and (*S*,*S*) complexes in chloroform solution are often greater than the differences in chemical shifts of H19 protons of the diastereoisomers *II* (*S*,*R*) and *III* (*S*,*S*), which obviously indicates different conformations of proline ring in compounds *II* and *III* (ref.[7]). No detailed analysis of the spin system in the benzylproline part of molecule of compounds *II* and *III* has been carried out. Information about mutual arrangement of pairs of geminal

protons H_a and H_b at the C1–C3 carbon atoms can be derived from the perceptible ^3J(H,H) interactions in H,H-COSY spectrum, starting from a firm point – the H4 proton directed above the plane of complex because the ligand for preparation of the complex had been synthesized from L-proline. With compound *II* the H,H-COSY spectrum shows the following ^3J(H,H) interactions: H4-$H3_a$, $H3_b$-$H2_b$, $H2_b$-$H1_b$, and with compound *III* the following three interactions: H4-$H3_a$, $H3_a$-$H2_a$, $H2_b$-$H1_a$.

The NOE studies showed that the NOESY spectra of the complexes exhibit both direct interactions of H4 proton of proline part of complex with the protons or substituents at C19 carbon atom of the amino acid part of complex and the interactions of the two above-mentioned groups with *ortho* protons of benzyl group H23 and/or H27. This fact allows a direct determination of configuration of the amino acid part of complex with respect to the known configuration of L-proline. The interaction of substituents of both chiral centres with the *ortho* protons of benzyl group was observed in the 2D NOESY spectra of all three complexes studied (*I*, *II*, *III*). A direct NOE interaction of H4 proton of the proline part of complex with H19 proton or with dimethylamino group of substituted glycine was only observed with the complexes *II* and *III*. This means that the bulky group at C19 carbon with its steric influence decreases the distance between the H4 and H19 protons in the complex *III*.



	R^1	R^2	R^3
I	CH_3	H	H
II	H	$N(CH_3)_2$	H
III	H	H	$N(CH_3)_2$

TABLE I
^{1}H and ^{13}C NMR chemical shifts of compounds *II* and *III*

Atom	*II*		*III*		*II*	*III*
	H_a	H_b	H_a	H_b	^{13}C	
1	2.34	3.91	3.52	2.02	57.50	56.30
2	1.92	2.90	2.06	3.32	23.45	23.24
3	2.26	2.38	2.47	2.73	30.54	30.70
4	3.51	–	3.44	–	69.44	69.93
5	–	–	–	–	181.99	180.53
6	–	–	–	–	142.78	142.69
7	8.35	–	8.23	–	124.40	123.76
8	7.24	–	7.16	–	132.35	132.38
9	6.71	–	6.65	–	120.85	120.66
10	6.88	–	6.74	–	133.87	133.35
11	–	–	–	–	126.34	126.12
12	–	–	–	–	176.08	174.68
13	–	–	–	–	135.35	134.59
14	7.03 or 7.23		7.11	–	124.88 or 130.29	125.60
15	7.40	–	7.41	–	127.08 or 127.98	127.87
16	7.40	–	7.42	–	128.68	127.80
17	7.40	–	7.40	–	127.98 or 127.08	128.88
18	7.23 or 7.03		7.02	–	130.29 or 124.88	129.00
19	4.02	–	4.10	–	84.57	85.14
20	–	–	–	–	176.23	176.29
21	3.79	4.53	3.64	4.44	62.35	62.89
22	–	–	–	–	133.18	132.98
23	7.92	–	7.98	–	131.70	131.60
24	7.42	–	7.35	–	128.94	128.77
25	7.37	–	7.20	–	129.08	129.00
26	7.42	–	7.35	–	128.94	128.77
27	7.92	–	7.98	–	131.70	131.60
28	2.21	–	2.46	–	39.73	40.12

Other noteworthy NOE interactions (*A*–*C*) should also be mentioned:

A. The interaction of *ortho* protons of benzyl ring with the proline part in (*S*,*R*) complex *II* which can be explained by the benzyl group being more often located above the proline part of molecule in one of the three possible arrangements[17]. This arrangement is energetically less favourable for complexes having no steric demands above the complex plane in the region of C19 carbon atom. This statement is supported by the fact that the (*S*,*S*) complex *III* has less interactions of this type and the glycine complex *I* has none.

B. The interaction of H4 proton of proline with H7 proton. This interaction is manifested in the spectrum of complex *II* (*S*,*R*) only, which can indicate different extent of distortion of ring plane of benzophenone in different complexes. For this interaction to be interpreted, it must be presumed that in the *II* complex (*S*,*R*) a part of the ligand is slightly deviated above the plane of complex and, hence, the H7 proton can exhibit the interaction with the H4 proton of *N*-benzylproline.

C. The interaction of protons of phenyl ring in benzophenone part of complex *I* with the substituents (or protons in *I*) at C19 carbon atom and with protons of the neighbouring phenyl ring which is fixed by *ortho* substitution and cannot rotate. All the cross peaks of this 2D NOESY TPPI spectrum have negative amplitudes and the diagonal peaks have positive amplitudes. The diagonal peak with the chemical shift of ca 7 ppm showed an unusually large peak area. Neither the expanded spectrum offered any explanation, but after a measurement of analogous experiment with very small spectral width Fig. 1 clearly shows cross peaks with positive amplitudes, which proves the existence of a slow (with regard to NMR time scale) exchange between the H14 and H18 protons, and this indicates rotation of phenyl group around the C12–C13 bond.

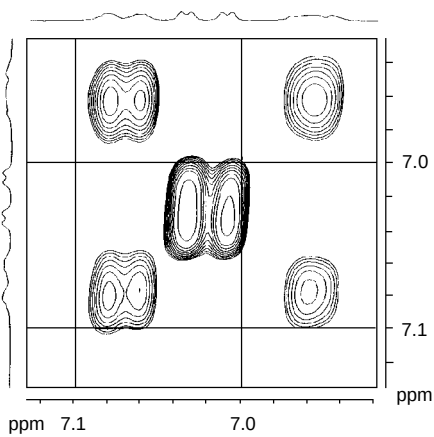


FIG. 1
2D NOESY TPPI NMR spectrum of compound *I* at mixing time value D8 = 2 s, relaxation time D1 = 5 s, spectral width SWH = 75.63 Hz, number of increments TD1 = 16, number of scans NS = 32, number of acquired points of spectrum TD = 32

From comparison of the spectra it is evident that there occurs rotation of phenyl group around the C12–C13 bond, such rotation being absent from the *III* complex. The reason lies in the fact that in the 2D NMR spectrum no NOESY TPPI cross peaks of *ortho* protons with positive amplitudes are observed, while these cross peaks are very intensive with the *I* and *II* complexes measured at the same experimental conditions. In order to find the rate of rotation around C12–C13 bond in the complexes *I*, *II*, and *III*, we carried out series of measurements monitoring the integral intensity of the non-diagonal peak due to the exchange of H14 and H18 protons as a function of the mixing time in 2D NOESY TPPI experiment. The results are presented in Fig. 2.

It can be seen that in the complex *III* (*S*,*S*) no rotation of phenyl group takes place because the bulky dimethylamino group has "equatorial" orientation here, i.e. it is placed in the plane of complex and prevents motions of the phenyl ring. The rate constants of rotation of phenyl group around the C12–C13 bond determined by optimizing Eq. (*1*) (refs[18,19]) for compounds *I* and *II* are $k = 0.353 \pm 0.053$ and 2.05 ± 0.87 s^{-1}, respectively.

$$I\mathrm{aa}/I\mathrm{ab} = [(1 + \exp(-2kt_m)) \exp(-t_m/T_{1a})]/[(1 - \exp(-2kt_m)) \exp(-t_m/T_{1b})] \quad , \quad (1)$$

where *I*aa is the integral intensity of diagonal peak (determined as unity), *I*ab is integral intensity of non-diagonal peak, t_m stands for mixing time in 2D NOESY TPPI experiment, T_{1a} is spin-lattice relaxation time of proton whose integral intensity was taken as unity in the row of 2D spectrum (the diagonal peak with higher chemical shift out of the pair of exchanging *ortho* protons), and T_{1b} is spin-lattice relaxation time of the

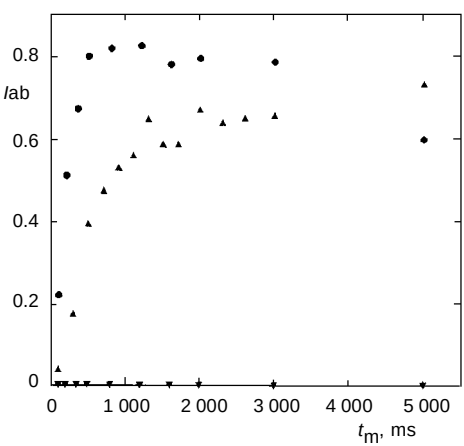


FIG. 2
Dependence of integral intensity of non-diagonal peak *I*ab in 2D NOESY TPPI NMR spectrum of compounds *I* (▲), *II* (●), and *III* (▼) upon mixing time (in ms)

proton with lower chemical shift in the pair of exchanging *ortho* protons. Using real nondegasified samples of complex *I* and *II* in the method of inversion recovery we found the T_{1a} values of 1.408 and 1.273 s, respectively, and the T_{1b} values of 1.496 and 1.374 s, respectively. The optimization of above-given equation without the exponential terms involving the relaxation times led to a worse correlation result. The closest correlation was obtained by optimizing the modified equation (*2*),

$$Iab/Iaa = [(1 - \exp(-2kt_m)) \exp(-t_m(1/T_{1b} - 1/T_{1a}))]/(1 + \exp(-2kt_m)) \quad , \qquad (2)$$

where the expression $(1/T_{1b} - 1/T_{1a})$ is substituted by the parameter *P* which is calculated by optimizing this two-parameter equation. The calculated parameters of optimization have the following values: For complex *I* $k = 0.656 \pm 0.05$ s^{-1} and $P = 0.106 \pm 0.017$ s^{-1}; for complex *II* $k = 2.50 \pm 0.17$ s^{-1} and $P = 0.109 \pm 0.011$ s^{-1}.

The cross peaks with negative amplitudes in the 2D NOESY TPPI spectra between the H19 proton of glycine and *ortho* protons H14 and H18 in both the complexes *II* and *III* indicate the fact that one of the H14 and H18 protons exhibits a much stronger NOESY interaction, hence the proton with higher chemical shift ($\delta = 7.11$) giving the more intensive cross peak is above the plane of complex in compound *III*, and the *ortho* proton with lower chemical shift in compound *II* ($\delta = 7.03$) is below the plane of complex. Therefore, dimethylamino groups (due to their bulkiness) have NOESY interactions of comparable intensity with both the protons H14 and H18. The difference NOE spectrum measured by the method of steady-state saturation with complex *I* gave no response of protons H14 and H18 upon irradiation of proton H10 and both H19. This means that the complexes of this type measured at 360 MHz fulfil the condition of $\tau_c >> 1/\omega_0$, and their dipole–dipole interactions can be studied by the transient NOE measurement or 2D NOESY methods[18] better than by the steady-state saturation methods.

In contrast to compound *I* (which gave unsatisfactory results[6]), the ^{15}N NMR spectra of complexes *II* and *III* were measured successfully by the technique of nonrefocused INEPT. The difference between experiments is in the sample concentrations in this case. At a concentration of ca 50 mg substance per 0.5 ml $CDCl_3$, the relaxation times *T*1 of the protons of compounds *I*, *II*, *III* measured by the inversion recovery technique vary in the limits of 340–713 ms for aliphatic protons and 1.1–1.65 s for aromatic protons. When optimizing the INEPT for $^nJ(^{15}N,^1H)$ ca 3 Hz, it is possible to get a spectrum with the ratio of *S/N* = 17 to 18 after 25 000 scans, the intensity of imine nitrogen atom of the Schiff base is roughly half that of signals of proline and amidic nitrogen atoms. The ^{15}N chemical shifts were assigned by analogy with the data published[6] for compound *I* as follows: Complex *II*: –177.7 ppm (imine nitrogen atom of glycine), –267.1 ppm (amide nitrogen atom of benzophenone), and –342.4 ppm (amine

nitrogen atom of benzylproline). Complex *III*: –181.6 ppm (imine nitrogen atom of glycine), –271.4 ppm (amide nitrogen atom of benzophenone), and –349.6 ppm (amine nitrogen atom of benzylproline). The ^{15}N signals of dimethylamino group were detected neither in compound *II* nor in *III*, which can be due to long relaxation times of these nitrogen atoms since the experiment for measuring ^{15}N was adjusted for the pulse repetition of ca 3 s (inclusive of the acquisition time).

In conclusion it can be stated that the absolute configuration of C19 chiral centre in Ni(II) complexes of Schiff bases of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and glycine with substituents at α carbon atom of glycine (C19) can be determined with the help of interactions in 2D NOESY NMR spectra. Spatial interactions of substituents and/or protons in glycine with *ortho* protons of benzyl group in *N*-benzylproline indicate that the benzyl group *ortho* positions are the most useful positions to introduce a bulky substituent with the aim of increasing the asymmetric induction of this complex.

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REFERENCES

1. Duthaler R. O.: Tetrahedron *50*, 1539 (1994).
2. Belokon Yu. N., Zeltzer I. E., Ryzhov M. G., Saporovskaya M. B., Bakhmutov V. I., Belikov V. M.: J. Chem. Soc., Chem. Commun. *1982*, 180.
3. Belokon Yu. N., Bulychev A. G., Vitt S. V., Struchkov Yu. T., Batsanov A. S., Timofeeva T. V., Tsyrapkin V. A., Ryzhov M. G., Lysova L. A., Bakhmutov V. I., Belikov V. M.: J. Am. Chem. Soc. *107*, 4252 (1985).
4. Fishwick C. W. G., Sanderson J. M., Findlay J. B. C.: Tetrahedron Lett. *35*, 4611 (1994).
5. Belokon Yu. N.: Pure Appl. Chem. *64*, 1917 (1992).
6. Jirman J., Popkov A.: Collect. Czech. Chem. Commun. *59*, 2103 (1994).
7. Belokon Yu. N., Maleev V. I., Vitt S. V., Ryzhov M. G., Kondrashov Yu. D., Golubev S. N., Vauchskii Y. P., Kazika A. I., Novikova M. I., Krasutskii P. A., Yurchenko A. G., Dubchak L., Shklover V. E., Struchkov Yu. T., Bakhmutov V. I., Belikov V. M.: J. Chem. Soc., Dalton Trans. *1985*, 17.
8. Belokon Yu. N., Bulychev A. G., Vitt S. V., Batsanov A. S., Struchkov Yu. T., Bakhmutov V. I., Belikov V. M.: J. Chem. Soc., Perkin Trans. I *1986*, 1865.
9. Belokon Yu. N., Chernoglazova N. I., Bacanov A. S., Garbalinskaya N. S., Bakhmutov V. I., Struchkov Yu. T., Belikov V. M.: Izv. Akad. Nauk SSSR, Ser. Khim. *1987*, 852.
10. Belokon Yu. N., Popkov A. N., Chernoglazova N. I., Saporovskaya M. B., Bakhmutov V. I., Belikov V. M.: J. Chem. Soc., Chem. Commun. *1988*, 1336.
11. Belokon Yu. N., Popkov A. N., Chernoglazova N. I., Bakhmutov V. I., Saporovskaya M. B., Belikov V. M.: Bull. Acad. Sci. U.S.S.R., Div. Chim. Sci. (Engl. Trans.) *38*, 1744 (1989).
12. Nakayama K., Kumar A., Ernst R. R., Wuthrich K.: J. Magn. Reson. *40*, 321 (1980).
13. Bax A., Subramain S.: J. Magn. Reson. *67*, 565 (1986).
14. Bax A., Summers M. F.: J. Am. Chem. Soc. *108*, 2093 (1986).
15. Bodenhausen G., Kogler H., Ernst R. R.: J. Magn. Reson. *58*, 370 (1983).

16. Morris G. A., Freeman R.: J. Am. Chem. Soc. *101*, 760 (1979).
17. Lindeman S., Timofeeva T. V., Maleev V. I., Belokon Yu. N., Ryzhov M. G., Belikov V. M., Struchkov Yu. T.: Acta Crystallogr., C *41*, 1290 (1985).
18. Ernst R. R., Bodenhausen G., Wokaun A.: *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Chap. 9. Clarendon Press, Oxford 1987.
19. Hull W. E. in: *Two-Dimensional NMR Spectroscopy – Applications for Chemists and Biochemists* (W. R. Croasmun and R. M. K. Carlson, Eds), 2nd ed., Chap. 2. VCH Publishers, New York 1994.

Note Added in Proof

The assignment of ^{1}H and ^{13}C chemical shifts in complex *I* is given in our previous work[6]. We have found that the assignment of pairs No. 5/20 and 19/21 was interchanged in ref.[6]. The correct assignment is as follows: δ ^{13}C (C-5) = 181.07, δ ^{13}C (C-20) = 177.18, δ ^{13}C (C-19) = 61.09, δ ^{1}H (H-19) = 3.60 and 3.75, δ ^{13}C (C-21) = 62.99, δ ^{1}H (H-21) = 3.50 and 4.39.