^{1}H, ^{13}C AND ^{15}N NMR SPECTRA OF Ni(II) COMPLEX OF SCHIFF BASE FROM (*S*)-2-(*N*-BENZYLPROLYL)AMINO-5-METHYLBENZOPHENONE AND GLYCINE

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Received February 17, 1994
Accepted April 16, 1994

Nickel(II) complex of Schiff base derived from (*S*)-2-(*N*-benzylprolyl)amino-5-methylbenzophenone and glycine (*I*) was prepared. It was characterized by mass, ^{1}H, ^{13}C and ^{15}N NMR spectra. The NMR signals were assigned and the data thus obtained can serve for study of products in the asymmetric synthesis of amino acids, starting from this complex.

Metal complexes of Schiff bases of amino acids can be utilized in asymmetric amino acid syntheses. Ni(II) complexes of Schiff bases formed from (*S*)-2-(*N*-benzylprolyl)-aminobenzophenone with amino acids belong to complexes with the highest asymmetric induction[1–3]. The structure of such complexes is studied mainly by X-ray analysis[4–6] for solid compounds and by NMR spectra for their solutions. In many cases, the structural determination by NMR spectroscopy is difficult because of incomplete interpretation of the spectrum.

A partial interpretation has been published of the aliphatic part of the spectrum of (*S*,*S*) and (*S*,*R*) complexes of Ni(II) with Schiff bases derived from 2-(*N*-benzylprolyl)-aminoacetophenone and valine[7]. Also the signals in ^{13}C NMR spectra of Ni(II) complexes of Schiff bases from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and glycine, (*S*)- and (*R*)-alanine, (*S*)-phenylalanine[8], and β-amino acids[4] have been partially assigned.

The aim of the present study is to interpret the NMR spectra and to assign the chemical shifts of Ni(II) complex of Schiff base from (*S*)-2-(*N*-benzylprolyl)amino-5-methylbenzophenone and glycine (*I*). The methyl group on the benzophenone ring serves only for better interpretation of the spectrum and cannot principally affect the asymmetric induction of the complex. Using this model, the assignment can be utilized for confirmation or rejection of structure of Schiff base from (*S*)-2-(*N*-benzylprolyl)amino-benzophenone and α-bromoglycine[9,10] which is an intermediate for the preparation of optically pure amino acids.

EXPERIMENTAL

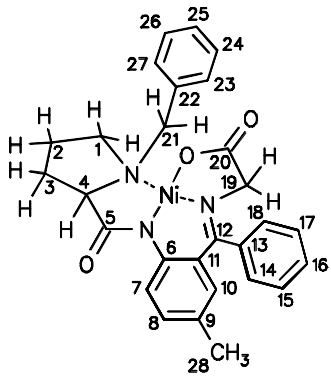
Preparation of Ni(II) Complex of Schiff Base from (*S*)-2-(*N*-Benzylprolyl)amino-5-methylbenzophenone and Glycine (*I*)

A suspension of glycine (6 g, 80 mmol) in 3 M methanolic sodium methoxide (60 ml) was added at 50 °C under argon to a stirred suspension of (*S*)-2-(*N*-benzylprolyl)amino-5-methylbenzophenone[11] (4 g, 10 mmol) and nickel(II) acetate tetrahydrate (5 g, 20.1 mmol) in methanol (50 ml). After 1 h, the reaction mixture was poured into water (400 ml), stirred and filtered. The solid material on filter was dissolved in chloroform and the solution was again filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel in toluene–acetone (2 : 1). The obtained red complex *I* was then purified on Sephadex LH-20 in toluene–methanol (2 : 1) and crystallized from benzene. Yield 4.3 g (84% related to (*S*)-2-(*N*-benzylprolyl)amino-5-methyl- benzophenone), m.p. 140 – 145 °C. For $C_{28}H_{27}N_3NiO_3$ (512.3) calculated: 65.66% C, 5.31% H, 8.20% N; found: 64.59% C, 5.00% H, 8.15% N. Mass spectrum (EI), *m*/*z*: 511 (M^+).

NMR Spectral Measurements

^1H and ^{13}C NMR spectra were measured in deuteriochloroform at 23 °C on an AMX 360 (Bruker) instrument at 360.13 and 90.57 MHz, respectively, using a tunable 5 mm probe. For the ^1H measurements, hexamethyldisiloxane ($\delta(^1H) = 0.05$) was used as internal standard, the ^{13}C chemical shifts were referenced to the solvent signal ($\delta(^{13}C) = 77.00$). The following measurement techniques were employed: H,H-homonuclear correlated spectrum[12], H,C-heteronuclear correlated spectrum with composite 180° transmitter pulse[13], H,C-heterocorrelated spectrum via long-range couplings with H-H decoupling in F1 (ref.[14]) and selective INEPT via long-range couplings[15].

^{15}N NMR spectra were measured at 36.50 MHz in deuteriochloroform at 23 °C, using a tunable 10 mm probe; concentration 800 mg of *I* in 2.5 ml of solvent. The 30° pulse and repetition time 20 s were used in both the gated decoupling (proton coupled spectra with NOE) and the inverse gated decoupling experiment (proton decoupled spectra without NOE). The ^{15}N chemical shifts are referenced to external standard $CH_3{}^{15}NO_2$ in a sealed coaxial capillary.



I

RESULTS AND DISCUSSION

Alhough repeatedly performed, the elemental analyses of complex *I* deviated from the calculated values, particularly for the carbon content. A similar deviation was observed[16] for an analog of this complex. The authors assumed the presence of crystal water which, however, has not been proven by X-ray analysis. For the time being, we have no explanation for this deviation.

The ^{1}H and ^{13}C NMR signals have been assigned and are given in Table I. For reading accurate values of ^{1}H chemical shifts we made use of a projection into the F2 axis in two-dimensional homonuclear *J*-resolved spectrum. The proton signals were assigned using homocorrelated and H,C-heterocorrelated spectrum. Although the conformation of the proline part of the molecule was not determined, the 2D H,H-COSY spectrum shows that, in addition to interactions of the geminal protons which in the spectrum afford cross-peaks, also interactions with greater ^3J(H,H), i.e. *trans* related protons, are operative. These interactions exist between the following pairs of protons: H-4 (δ = 3.49)–H-3 (δ = 2.50), H-3 (δ = 2.37)–H-2 (δ = 2.00), H-2 (δ = 2.00)–H-1 (δ = 3.70). The assignment of protons on the phenyl group, which contains magnetically nonequivalent nuclei C-14 to C-18, is not completely solved. This phenyl group either does not rotate fast enough or, more probably, its rotation is entirely sterically hindered by the protons H-19 and H-10. The ring cannot be coplanar with the neighbouring phenyl ring because in the NOE difference spectrum neither H-14 nor H-18 afford a

TABLE I
^{1}H and ^{13}C NMR chemical shifts for compound *I* in deuteriochloroform at 23 °C

Position	δ(^{1}H)	δ(^{13}C)	Position	δ(^{1}H)	δ(^{13}C)
1	2.10 3.70	57.43	15	7.48[a]	129.14[b]
2	2.00 3.26	23.52	16	7.45	129.53
3	2.50 2.37	30.52	17	7.40[a]	129.37[b]
4	3.49	69.81	18	6.95[c]	125.47[d]
5	–	177.18	19	3.50 4.39	62.99
6	–	140.02	20	–	181.07
7	8.19	123.96	21	3.60 3.75	61.09
8	6.99	133.18	22	–	133.40
9	–	134.49	23	8.08	131.53
10	6.53	132.53	24	7.40	128.70
11	–	124.89	25	7.25	128.88
12	–	171.37	26	7.40	128.70
13	–	129.90	27	8.08	131.53
14	7.08[c]	126.07[d]	28	1.99	20.29

[a – d] Signals with the same label can be interchanged.

signal on irradiation of proton H-10. The same negative result was obtained in the NOE difference spectrum on irradiation of both protons H-19.

The assignment of quaternary carbon atoms was based on 2D-COLOC spectra measured separately for the aromatic and aliphatic parts of the proton spectrum to get better digital resolution in the F1 domain. In this experiment, there was folding of undesired signals from the other part of the proton spectrum in the axis F1, resulting in artifacts in the 2D spectra. Therefore, the assignment of quaternary carbon atoms was supported by selective INEPT technique via ^3J(C,H) from the following protons: H-7, H-8, H-10 and protons of the benzyl CH_2 group. These experiments also supported the assignment of protons H-7, H-8 and H-10 because in the ^{1}H spectrum the constant ^4J(H-8,H-10) was unmeasurable even after substantial mathematical line narrowing prior to the Fourier transformation. Further, the selective INEPT also confirmed the fact that the "rotating" phenyl is actually the benzyl ring because the polarization transfer from protons H-21 afforded the signal of carbons C-23 and C-27 which is of double intensity in normal ^{13}C NMR spectrum. This experiment also confirmed the assignment of ^{1}H chemical shifts of the benzyl CH_2 AB system. In the already cited paper[16], proton signals of only two AB systems of benzyl and glycine were assigned in an analogous Ni(II) complex derived from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and glycine. From the analysis of heterocorrelated spectra of compound *I* it is evident that the above-cited assignment[16] is incorrect and that the benzyl and glycine chemical shifts were interchanged. As already mentioned, the unsubstituted phenyl ring of benzophenone in complex *I* is not coplanar with its substituted neighbour and on the NMR time scale it does not rotate fast enough; therefore the assignment of signals C-14, C-15, C-17 and C-18 in Table I is not specified. For a similar complex of Schiff base from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and (*E*)-2-amino-2-butenoic acid, X-ray analysis[6] shows that the angle between the plane of the phenyl group and that of the complex is 66°.

The ^{15}N NMR spectrum of compound *I* exhibits three signals of δ −194.9, −271.7 and −349.6. As follows from the literature data, it is practically clear that the highest-field signal is due to the benzylproline nitrogen atom because ^{15}N chemical shifts of amino acids range from −330 to −355 ppm (ref.[17]). Proline in its cationic form resonates at −323 ppm (ref.[17]), its chemical shift being not markedly affected by metal complexation of the amino acid. Thus, e.g. glycine in its protonated form has δ(^{14}N) −331 and in a Co(III) complex δ(^{14}N) −340 (*cis*) and δ(^{14}N) −399 (*trans*) (ref.[18]). For amides, ^{15}N chemical shifts range from −245 to −280 ppm (ref.[17]) and therefore the signal of δ −271.7 ppm can be assigned to the amide nitrogen of the 2-amino-5-methylbenzophenone moiety. For the imine nitrogen of the Schiff base remains the shift of −194.85 ppm. The inverse gated decoupling experiment (for conditions see Experimental) showed after 4 000 scans the same signal to noise ratio S/N = 14 for all the three nitrogen atoms. In normal gated decoupled experiment (proton coupled spectra with

NOE) we have found after 6 000 scans a positive signal with *S*/*N* ratio amounting to 11 for the benzylproline nitrogen atom, and negative signals with *S*/*N* of about 5.6 for both the remaining nitrogen atoms. This result supports the above assignment because ^{15}N has a negative gyromagnetic ratio and therefore signals of nitrogen atoms with no or only weak NOE should have a negative, or in some cases even zero, amplitude.

All the nitrogen signals obtained without decoupling during the acquisition afford multiplets from which we can assess the coupling constants across more than two bonds to be about 2 – 2.5 Hz. The INEPT experiment[19], optimized for coupling constant 2.5 Hz, requires the polarization transfer time of 100 ms. In so adjusted experiment no signals were observed even after 3 000 scans, whereas with other compounds the signals are discernible already after tens or hundreds scans. This failure of INEPT in the measurement of ^{15}N NMR spectra of compound *I* probably consists in that the protons, from which the polarization should be transferred, relax faster than is the set interval of 100 ms; this can be expected, considering the magnitude of the molecule and the presence of metal.

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Translated by M. Tichy.