8. LIST OF PAPERS INCLUDED IN THIS THESIS AND THEIR CITATION ANALYSIS (AUTOCITATIONS EXCLUDED)

1. The influence of both steric and electronic factors on the stereochemistry of products was to a great extent disclosed for both kinetically and thermodynamically controlled alkylation of chiral nickel complexes:

a) Paper I. Jirman, J.; Popkov, A. ^{1}H, ^{13}C, ^{15}N NMR spectra of Ni(II) complexes of Schiff bases of (*S*)-(*N*-benzylprolyl)aminobenzophenone and α-monosubstituted glycine and determination of configuration of the complexes by 2D NOESY spectra *Collect. Czech. Chem. Commun.* **1995**, *60*, 990. IF=0.949 (2006)

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- Higgins, S. J. Nickel 1995 *Coord. Chem. Rev.* **1997**, *164*, 503.
- Pessoa, J. C.; Correia, I.; Galvao, A.; Gameiro, A.; Felix, V; Fiuza, E. Enantioselectivity in Ni(II) Schiff-base complexes derived from amino-acids and (*S*)-*o*-*N*-(*N*-benzylprolyl)aminobenzophenone. Molecular structure of several chiral Ni(II) Schiff-base complexes, circular dichroism and molecular mechanics studies *J. Dalton Trans.* **2005**, 2312.

b) Paper II. Popkov, A.; Langer, V.; Manorik, P. A.; Weidlich, T. Long-range spin-spin interactions in ^{13}C-NMR spectra of the nickel(II) complex of Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and glycine. Quantum-chemical calculations and possible donation of electron density from the π-system of the benzyl group to nickel *Transition Metal Chem.* **2003**, *28*, 475. IF=0.818 (2006)

c) Paper III. Kožíšek, J.; Fronc, M.; Skubák, P.; Popkov, A.; Breza, M.; Fuess, H.; Paulmann, C. Electronic structure of the nickel(II) complex of Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and glycine *Acta Crystallogr. A,* **2004**, *60*, 510. IF=1.791 (2006)

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- Farrugia, L. J.; Frampton, C. S.; Howard, J. A. K.; Mallinson, P. R.; Peacock, R. D.; Smith, G. T.; Stewart, B. Experimental charge-density study on the nickel(II) coordination complex $[Ni(H_3L)][NO_3][PF_6][H_3L]$ = *N*, *N'*, *N''*-tris(2-hydroxy-3-methylbutyl)-1,4,7-triazacyclononane]: a reappraisal *Acta Crystallogr. B* **2006**, *62*, 236.

d) Paper IV. Langer, V.; Popkov, A.; Nádvorník, M.; Lyčka, A. Two new Ni(II) Schiff base complexes: X-ray absolute structure determination, synthesis of a ^{15}N-labelled complex and full assignment of its ^{1}H-NMR and ^{13}C-NMR spectra *Polyhedron* **2007**, *26*, 911. IF=1.957 (2006)

2. Nickel complexes bearing the polymethylsubstituted benzyl group are the most promising amino acids synthons, and are lead structures for further development:

e) Paper V. Popkov, A. N. Synthesis of derivatives of (*S*)-proline with alkylated *N*-benzyl substituents. Benzylation of (*S*)-indoline-2-carboxylic acid *Khim. Geterotsikl. Soedin.* **2000**, 625; Engl. Trans.: *Chem. Heterocycl. Comp.* **2000**, *36*, 544.
IF=0.134 (2006)

f) Paper VI. Popkov, A.; Gee, A.; Nádvorník, M.; Lyčka, A. Chiral nucleophilic glycine and alanine synthons: nickel(II) complexes of Schiff bases of (*S*)-*N*-(2,4,6-trimethylbenzyl)proline (2-benzoylphenyl)amide and glycine or alanine *Transition Metal Chem.* **2002**, *27*, 884. IF=0.818 (2006)

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- Gu, X. Y.; Ndungu, J. A.; Qiu, W.; Ying, J. F.; Carducci, M. D.; Wooden, H.; Hruby, V. J. Large scale enantiomeric synthesis, purification, and characterization of ω-unsaturated amino acids via a Gly-Ni(II)-BPB-complex *Tetrahedron* **2004**, *60*, 8233.
- Saghiyan, A. S.; Dadayan, S. A.; Petrosyan, S. G.; Manasyan, L. L.; Geolchanyan, A. V.; Djamgaryan, S. M.; Andreasyan, S. A.; Maleev, V. I.; Khrustalev, V. N. New chiral Ni(II) complexes of Schiff's bases of glycine and alanine for efficient asymmetric synthesis of alpha-amino acids *Tetrahedron: Asymmetry* **2006**, *17*, 455.
- Saghiyan, A. S.; Manasyan, L. L.; Dadayan, S. A.; Petrosyan, S. G.; Petrosyan, A. A.; Maleev, V. I.; Khrustalev, V. N. Novel modified chiral Ni-II complexes with the Schiff bases of (*E*)- and (*Z*)-2-aminobut-2-enoic acids: synthesis and study *Russ. Chem. Bull.* **2006**, *55*, 442.
- Drabina, P.; Hanusek, J.; Jirásko, R.; Sedlak, M. Iron(II) complexes of 2,6-bis(5-alkyl-1,5-dimethyl-4,5-dihydro-1H-imidazol-4-on-2-yl)pyridine ligands. Synthesis, characterisation and solvolytic stability *Transition Metal Chem.* **2006**, *31*, 1052.

3. NOE interactions in ^{1}H-NMR spectra of the complexes allow correct determination of the stereochemistry of chiral centres of the complexes in the most cases.

Papers I and IV.

g) Paper VII. Popkov, A.; Císařová; Sopková, J; Jirman, J; Lyčka, A.; Kochetkov, K. A. Asymmetric synthesis of (*S*)-2-amino-3-(1-naphthyl)propanoic acid via chiral nickel complex. Crystal structure, circular dichroism, ^{1}H NMR and ^{13}C NMR spectra of the complex *Collect. Czech. Chem. Commun.* **2005**, *70*, 1397. IF=0.949 (2006)

4. Intramolecular interactions were discovered in NMR spectra of the complexes. Continuous efforts are made by theoreticians to explain the nature of the interactions.

h) Paper VIII. Jirman, J.; Nádvorník, M.; Sopková, J.; Popkov, A. Long-range $^{n}J(^{15}N, ^{13}C)$ and $^{n}J(^{13}C, ^{13}C)$ coupling constants *via* metal atom in ^{13}C NMR spectra of square-planar Ni(II) complexes of Schiff base of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and ^{13}C-1, ^{13}C-2 or ^{15}N labelled glycine *Magn. Reson. Chem.* **1998**, *36*, 351.

IF=1.553 (2006)

Cited in

- Prini, G.; Balboni, D.; Camurati, I.; Resconi, L.; Traverso, O. Synthesis and NMR Characterization of Meso-Ethylenebis(4,7-Dimethyl-1-Indenyl) Zirconium Dimethyl *Inorg. Chem. Commun.* **1999**, *2*, 41.
- Contreras, R.H; Peralta, J.E.; Giribet, C.G.; De Azua, M.C.; Facelli, J.C. Advances in theoretical and physical aspects of spin-spin coupling constants *Annu. Rep. NMR Spectrosc.* **2000**, *41*, 55.
- Ueki, H.; Ellis, T. K.;Martin, C. H.; Boettiger, T. U.; Bolene, S. B.; Soloshonok, V. A. Improved synthesis of proline-derived Ni(II) complexes of glycine: Versatile chiral equivalents of nucleophilic glycine for general asymmetric synthesis of alpha-amino acids *J. Org. Chem.* **2003**, *68*, 7104.

i) Paper IX. Popkov, A.; Jirman, J.; Nádvorník, M.; Manorik, P. A. NMR study of the structures of Ni(II) complexes of Schiff bases of 2-bromoglycine with (*S*)-2-(*N*-benzylprolyl)aminobenzophenone or (*S*)-2-(*N*-benzylprolyl)amino-5-chlorobenzo-phenone *Collect. Czech. Chem. Commun.* **1998**, *63*, 990. IF=0.949 (2006)

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- Dialer, H.; Steglich, W.; Beck, W. Metal complexes of biologically important ligands, CXXXIX. A ferrocenylene bridged pseudohexapeptide

$Fe[C_5H_4CH_2OglyBal\text{-}OMe(Val\text{-}Boc)]_2$ *Z. Naturforsch., B: Chem. Sci.* **2001**, *56*, 1084.

- Ueki, H.; Ellis, T. K.; Martin, C. H.; Boettiger, T. U.; Bolene, S. B.; Soloshonok, V. A. Improved synthesis of proline-derived Ni(II) complexes of glycine: Versatile chiral equivalents of nucleophilic glycine for general asymmetric synthesis of alpha-amino acids *J. Org. Chem.* **2003**, *68*, 7104.

5. CD spectra in many cases (*e. g.* complexes derived from α-monosubstituted glycine or protected α-metyrosine) could be useful tool for the determination of the stereochemistry of the alkylated product; in more complicated cases, X-ray structure determination is necessary.

Papers II, IV and VII.

j) Paper X. Mičúch, P.; Fišera, L.; Kožíšek, J.; Popkov, A.; Svoboda, I. The synthesis of chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)-isoxazol-5-carboxylic acid *Arkivoc* **2006**, 92. IF=0.653 (2006)

6. A procedure for the industrial preparation of complexes which output many fewer organic pollutants and nickel cations to waste water was developed and published without holding any patent protection. Chemists from developing countries can now use it:

k) Paper XI. Nádvorník, M.; Popkov, A. Improved synthesis of the Ni(II) complex of the Schiff base of (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone and glycine *Green Chem.* **2002**, *4*, 71. IF=3.255 (2006)

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7. The application of the complexes for syntheses of α-[^{11}C]methyl amino acids was assessed.

l) Paper XII. Popkov, A.; Nádvorník, M.; Jirman, J.; Kružberská, P.; Lyčka, A.; Weidlich, T.; Kožíšek, J.; Breza, M.; Lehel, S.; Gillings N. M. An asymmetric approach to the radiosynthesis of both enantiomers of α-[^{11}C]methylDOPA and α-[^{11}C]methyltyrosine for positron emission tomography *Czech. J. Phys.* **2006**, *56*, D689.

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Belokon, Y. N.; Popkov, A. N.; Chernoglazova, N. I.; Saporovskaya, M. B.; Bakhmutov, V. I.; Belikov, V. M. Synthesis of a chiral nickel(II) complex of an electrophilic glycinate, and its use for asymmetric preparation of α-amino acids *J. Chem. Soc., Chem. Commun.* **1988**, 1336. IF=4.426 (2006)

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- Collet, S.; Bauchat, P.; Danion-Bougot, R.; Danion, D. Stereoselective, nonracemic synthesis of ω-borono-α-amino acids *Tetrahedron: Asymmetry* **1998**, *9*, 2121.

Belokon, Y. N.; Popkov, A. N.; Chernoglazova, N. I.; Bakhmutov, V. I.; Saporovskaya, M. B.; Belikov, V. M. New chiral synthon of an electrophilic glycine, and its reactions with organometallic, C-H, N-H and O-H compounds for asymmetric synthesis of α-substituted α-amino acids *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, Iss.8, 1899; Engl. Trans.: *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1990**, *38*, 1744.

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Popkov, A. N.; Nádvorník, M.; Jirman, J.; Manorik, P. A.; Fedorenko, M. A. Confirmation of the isomeric structure of the Ni(II) complex of Schiff base of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and (*S*)-α-bromoglycine *Zh. Obshch. Khim.* **1999**, *69*, 452; Engl. Trans.: *Russ. J. Gen. Chem.* **1999**, *69*, 435.

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List of plenary and invited lectures

Plenary lectures

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Popkov, A.; Nádvorník, M.; Lyčka, A.; Kružberská, P.; Kožíšek, J.; Breza, M.; Langer, V.; Eisenhut, M.; Gillings, N. M. Stoichiometric asymmetric synthesis of amino acids: from molecular modelling to diagnostic applications. In *XXVIIth Conference of Organic Chemists*, Pardubice, Czech Republic, June 14-17, 2004; Pařík, P., ed. Pardubice University: Pardubice, 2004 (in Czech). PL 08. ISBN 80-7194-671-0.

Invited lectures

Popkov, A. Design of chiral glycine and alanine synthons for the preparation of [^{11}C]amino acids. Presented at DKFZ (German Cancer Research Center) seminar, Heidelberg University, Jan 27, 2000.

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I

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

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^1H, ^{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.

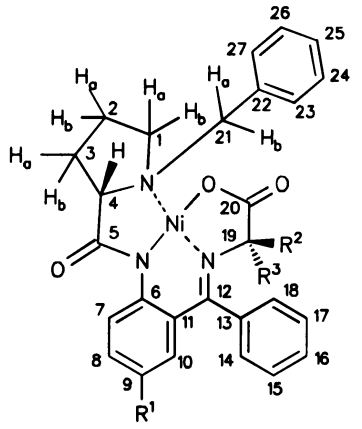
RESULTS AND DISCUSSION

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.

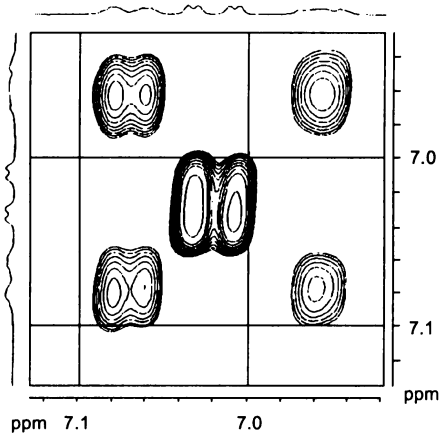


FIG. 1
2D NOESY TPPI NMR spectrum of compound *I* at mixing time value D8 = 2 s, relaxation time D1 = 5 s, spectral width SWH = 75.63 Hz, number of increments TD1 = 16, number of scans NS = 32, number of acquired points of spectrum TD = 32

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.

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

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

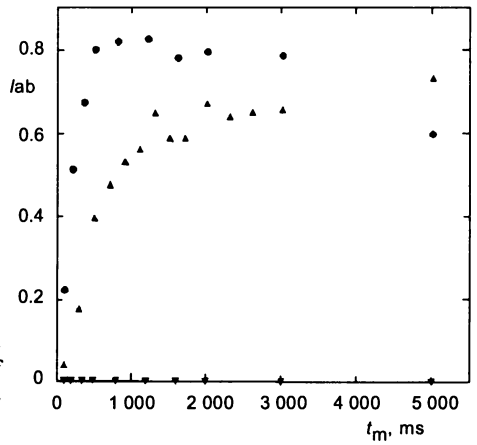


FIG. 2
Dependence of integral intensity of non-diagonal peak *I*ab in 2D NOESY TPPI NMR spectrum of compounds *I* (▲), *II* (●), and *III* (▼) upon mixing time (in ms)

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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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.

II

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Long-range spin–spin interactions in the ^{13}C-n.m.r. spectra of the nickel(II) complex of the Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and glycine. Quantum-chemical calculations and possible donation of electron density from the π-system of the benzyl group to nickel

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Abstract

Long-range [$^nJ(^{13}C, ^{13}C)$, $^nJ(^{15}N, ^{15}N)$ and $^nJ(^{15}N, ^{13}C)$] interactions in the ^{13}C-n.m.r. spectra of $CDCl_3$ solutions of selectively labeled nickel(II) complexes of the Schiff base derived from (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and glycine provide experimental evidence for the necessity of the donation of electron density from the π-system of the benzyl ring to the nickel orbitals. No such interactions were observed in (^{2}H)DMSO solutions, where the complex exists in a different conformation.

Introduction

Extensive studies of the n.m.r. properties of nickel(II) complexes of the Schiff bases of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and α-amino acids (Scheme 1, R = Ph) led to the discovery of three types of long-range interactions: (1) NOE interactions between the α-hydrogen of the proline fragment and substituents at the α-carbon of the amino acid fragment of the complex [1]; (2) Deshielding of H_b2 signals in nickel(II) complexes of the Schiff bases of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide or (*S*)-*N*-benzylproline (2-benzoyl-5-chlorophenyl)amide and α-bromoglycine resulting from long-range H···Br interactions [2]; (3) Long-range [$^nJ(^{13}C, ^{13}C)$, $^nJ(^{15}N, ^{15}N)$ and $^nJ(^{15}N, ^{13}C)$] interactions in $CDCl_3$ solutions of a nickel(II) complex of the Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and glycine (GK) [3] (Scheme 2). Similar long-range spin–spin interactions have been observed in C_6D_6 solutions of *meso*-ethylenebis-(4,7-dimethyl-1-indenyl)-zirconium dimethyl [4]. Our first hypothesis attempted to explain the above mentioned phenomena as a result of spreading the interactions in the plane of the complex by hybrid Ni—N and Ni—O orbitals [3]. This hypothesis can only explain spin–spin interactions but not NOEs and the deshielding, which take place above and below the planes. Further studies of the long-range spin–spin interactions in complexes bearing substituents at the α-carbon of the amino acid fragment (*e.g.* R = Ph, R′ = H, R″ = Br; R = Ph, R′ = R″ = Me, Scheme 1) have shown that the interactions are highly sensitive to conformations and to changes of the distribution of electron density (J. Jirman, A. Lyčka, M. Nádvorník and A. Popkov, unpublished results). This high sensitivity could not be explained by the original hypothesis.

Experimental

The labeled complexes were prepared as previously described [3].

^{13}C-n.m.r. spectra of $CD_3S(O)CD_3$ solutions of the complexes were recorded precisely under the same conditions as were used for recording the spectra in $CDCl_3$ solutions [3].

X-ray data were recorded using a Siemens SMART CCD diffractometer with MoK_α radiation (λ = 0.71073 Å, graphite monochromator) equipped with a LT-2A low-temperature device. A full sphere of reciprocal lattice was scanned by 0.3° steps in ω with a

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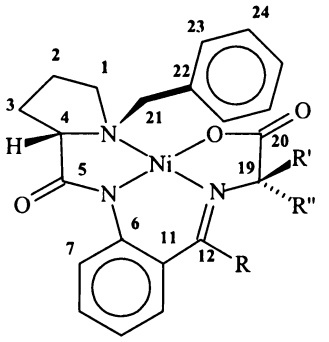


Scheme 1. GK atom numbering.

crystal-to-detector distance of 3.97 cm and exposure time 1 s per frame. The preliminary orientation matrix was obtained from the first frames using SMART [5]. The frames were integrated using the preliminary orientation matrix which was updated every 100 frames. Final cell parameters were obtained by refinement on the positions of reflections 7308 with $I > 10\sigma(I)$ after integration of all of the frames using SAINT [5]. The data were empirically corrected for absorption and other effects using SADABS [6] based on the method of Blessing [7]. The structure was solved by direct methods and refined by full-matrix least squares on all F^2 data using SHELXTL [8]. The non-H atoms were refined anisotropically and hydrogen atoms isotropically. Hydrogen atoms were constrained to the ideal geometry using an appropriate riding model. Crystal data and structure refinement parameters for the title compound are shown in Table 1. Numbering scheme together with thermal ellipsoids at 50% probability level, produced by DIAMOND [9] is presented in Figure 1. Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre, CCDC 183062.

RHF calculations were provided using both GAUSSIAN 98 [10] running on a three-processor NEC SX-4 vector computer and PC GAMESS v 6.0 [11, 12] running on a PC (2xPentium III® 1 GHz, 1 GB RAM, 160 GB hard drives). ROHF, MP2 and MP3 calculations were provided using the PC GAMESS.

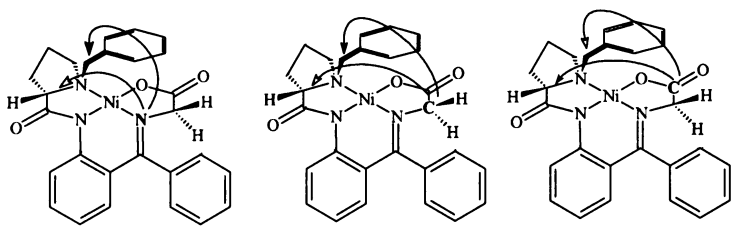
Results and discussion

In order to explain all the observations, a new hypothesis was created: the donation of electron density from the π-system of the benzyl ring to the nickel orbitals forms a diffuse electron cloud between the benzyl group and the nickel atom, which is responsible for the spin–spin interactions. Some part of this cloud may be spread below the plane of the complex, thus accounting for the H···Br interactions in the complex derived from α-bromoglycine. This hypothesis is based on the observed non-equivalence of C22–C23 and C22–C27 bond lengths in the benzyl group found in some similar complexes in the Cambridge Crystallographic Data Centre (Table 2). The difference is not statistically significant, but the hypothesis has been successfully used to design a new stereospecific glycine synthon [13]. Proof of this new hypothesis is the aim of this work. Direct measurement of the electron density distribution in space around the nickel atom by X-ray diffraction is a serious challenge due to supposed diffuseness of electron clouds between the nickel atom and the benzyl group.

Comparison of solid state ^{13}C-n.m.r. spectra of GK and the ^{13}C-n.m.r. spectrum of this complex in $CDCl_3$ solution has shown that conformations of the complex

Table 1. Crystal data and structure refinement of GK

Empirical formula	$C_{27}H_{25}N_3NiO_3$
Formula weight	498.21
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	
a (Å)	8.9416(1) Å
b (Å)	9.6140(1) Å
c (Å)	26.1427 Å
Volume	2247.35(4) Å
Z, Calculated density	4, 1.472 g cm^{-3}
Absorption coefficient	0.899 mm^{-1}
F (0 0 0)	1040
Crystal size	0.80 × 0.70 × 0.60 mm
θ range for data collection	1.56–33.03°
Limiting indices	$-13 \le h \le 13$, $-14 \le k \le 14$, $-39 \le l \le 39$
Reflections collected/unique	41001/8119 [R_{int} = 0.0487]
Completeness to	θ = 33.03 97.1%
Max. and min. transmission	0.6145 and 0.5332
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	8119/0/333
Goodness-of-fit on F^2	1.003
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0320, wR_2 = 0.0684
R indices (all data)	R_1 = 0.0431, wR_2 = 0.0721
Absolute structure parameter	−0.004(7)
Extinction coefficient	0.0014(3)
Largest diff. peak and hole	0.280 and −0.244 e Å^{-3}



Scheme 2. Long-range [$^nJ(^{13}C, ^{13}C)$, $^nJ(^{15}N, ^{15}N)$ and $^nJ(^{15}N, ^{13}C)$] interactions in ^{13}C-n.m.r. spectra of $CDCl_3$ solutions of GK.

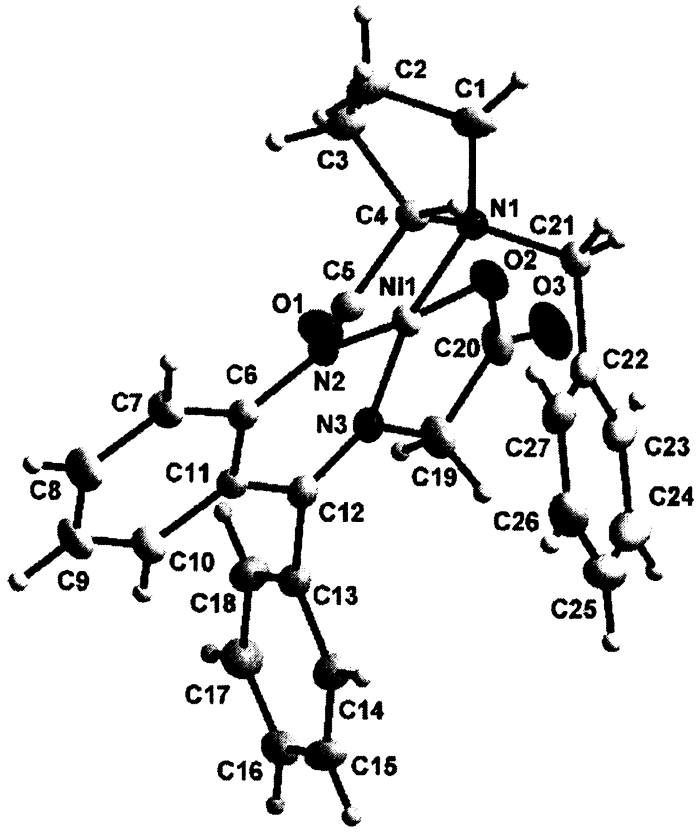


Fig. 1. Molecule structure of GK as determined by X-ray diffraction.

Table 2. Non-equivalence of bond lengths of C22—C23 and C22—C27 bonds of the benzyl group found in some similar complexes (Cambridge Crystallographic Data Centre, CCDC)

Complex, Ref.	R	R′	R″	C22—C23, Å	C22—C27, Å	Ni—C22, Å	T, K	CCDC abbreviation
[14]	H	Me	[a]	1.39	1.41	3.23	295	GIGVEX10
[15]	Me	H	*i*-Pr	1.37	1.41	3.05	295	DAYDOW
[16]	Me	*i*-Pr	H	1.38	1.39	3.17	295	DAZMOG
[17]	Me	H	$CH_2OH \cdot OH_2$	1.40	1.40	3.19	295	DAWGUD10
[18]	Ph		*(Z)*-CH-Me[b]	1.37	1.42	3.22	295	VETPEP
[19]	Ph	H	*(R)*-$CH(CF_3)NH$-$C_6H_4OCH_3$	1.38	1.41	3.15	295	NOKVOY
[20]	Ph	H	*(S)*-$CH(CF_3)CH_2$-COOEt	1.39	1.40	3.15	295	RORHUB
[21][c]	Ph	H	*(R)*-CH(OH)Ph	1.39	1.41	3.07	147	VUJCIM
[22]	Ph	H	$C(OH)Me_2$	1.39	1.39	3.05	188	WEPJAC
[23]	Ph	*(S)*-$CH_2CH(OH)$-$CH_2CH_2P(O)(OEt)_2$	H	1.39	1.39	3.61	295	WEYDUZ
[24]	Ph	H	*(R)*-$CH(OH)CMe_3$	1.39	1.40	2.98	158	ZECLIC

Donation of electron density from the C=C bond to nickel orbitals leads to longer C=C bond.

[a] This binuclear octadentate C_2-symmetric complex was derived from (*2S*, *3S*)-2,3-diamino-2,3-dimethylsuccinic acid. In this complex the short Ni—Ni distance 4.18 Å may indicate Ni—Ni interaction.

[b] α,β-Dehydroamino acid.

[c] This complex was not derived from glycine, but from β-alanine.

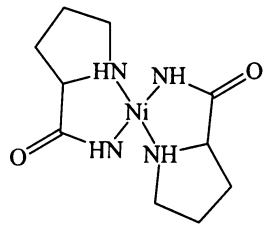
both in the crystalline form and in $CDCl_3$ solution are similar [25]. This allows one to use the crystal state geometry for *ab initio* calculations.

Previously we used B3LYP/6-311G(d) DFT calculations to model the diffuse electron cloud between the benzyl group and the nickel atom. This confirmed

existence of a weak Ni—C22 bond with a calculated bond order of 0.3 [26]. This calculation was done for the singlet state of the complex. Crystallographic data collected at ambient temperature were used [27].

Energy differences between singlet and triplet states of square-planar nickel complexes have been studied by Rulíšek and Havlas [28] at a very accurate CAS SCF/6-311+G(d) level. The authors calculated the energy differences for $[Ni(H_2O)_4]^{2+}$, $[Ni(H_2O)_3HSCH_3]^{2+}$, $[Ni(H_2O)_2(OH)_2]^{2+}$ and $[Ni(H_2O)_3NH_3]^{2+}$ and have found, that 'all four model complexes of Ni^{2+} have high-spin ground states and the lowest singlets by 9500–12,100 cm^{-1} higher in energy.' Based on this result, the authors inferred a triplet state for most square-planar Ni^{2+} coordinated to amino acid side chains and to peptide bond nitrogens (*i.e.* coordinated to peptides). They considered most of peptide ligand sites to be weak 'H_2O-like' ligands.

The Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and glycine is a pseudopeptide. In order to verify the applicability of the above mentioned results, we performed MP2 calculations for both the triplet and singlet states in the same triple zeta valence basis set (Table 3). The energy difference 0.1254 Hartree clearly shows that the complex is more stable in the singlet form. In the ^1H-, ^{13}C- and ^{15}N-n.m.r. spectra of GK in $CDCl_3$ [1–3] we observed narrow signals, which are evidence for the singlet state of the complex. We believe, that Rulíšek and Havlas [28] underestimated the influence of ligands to preferred multiplicity of complexes. In order to test this hypothesis, we calculated the energy difference between triplet and singlet states of a square-planar nickel complex bearing two proline amide ligands (Scheme 3, two water molecules in the outer coordination sphere were omitted) [31]. The geometry from X-ray determination was used. This complex mimics the GK structure; at the same time the ligand strength of the two bidentate proline amide ligands should not be so strong as in case of the tetradentate Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and the glycine ligand. With the TZV basis set, the energy difference at the RHF/ROHF level is 0.0282 Hartree, the triplet state is the lower one. Calculation of Møller–Plesset second order correction shows that the singlet state energy is lower, with the difference of 0.0137 Hartree. One can conclude, that for *ab initio* calculations the multiplicity of the ground states of square-planar nickel complexes of amino acids and/or peptides should not be inferred, but thoroughly calculated in every case.



Scheme 3. Model complex.

Table 4. Calculation of energy for the singlet state of GK in 6-311G basis set

	RHF	RHF MP2	RHF MP3
Singlet energy, Hartree	−2931.3072	−2934.7914	−2934.7851

For nickel McLean/Chandler basis set was used.

The influence of a basis set choice for the complex energy was tested by comparison of RHF MP2 single-point energy calculated in both TZV (Table 3) and less extended 6-311G (Table 4) basis sets. The energy difference 0.1481 Hartree shows that for this structure the energy is very sensitive to the basis set choice. Calculated bond orders in the internal coordinational sphere also strongly depend on the basis set choice. The RHF MP2 TZV calculation gave the following bond orders for bonds which might be involved in the spin–spin interactions (values for RHF MP2 6-311G are given in brackets): Ni—N_{Pro} 0.062 (<0.050), Ni—N_{amid} 0.281 (0.099), Ni—N_{imin} 0.115 (<0.050), Ni—C19 0.060 (<0.050), Ni—O 0.368 (0.306). Application of more extended basis sets is necessary, but limited by the available hardware. Accurate quantum-chemical calculations of spin–spin coupling constants require a non-relativistic [32] or relativistic [33, 34] DFT approach. Such calculations are now in progress for GK.

For the Hartree–Fock calculations, new X-ray data (presented here) were collected at 193 K. Bond lengths and bond angles are given in Table 5. In Table 6, two weak hydrogen bonds are described, responsible for intermolecular interactions in the form of chains: ···O(3)—C(20)—O(2)—Ni(1)—N(1)—C(4)—C(3)—H(3A) ··· and ···O(1)—C(5)—N(2)—Ni(1)—N(3)—C(12)—C(13)—C(18)—C(17)—H(17)···. These weak hydrogen bonds, as the only significant intramolecular interaction, are important.

Table 3. MP2 calculation of energy for both triplet and singlet states of GK in triple zeta valence (TZV) [29, 30] basis set

	RHF	RHF MP2	ROHF	ROHF MP2
Triplet energy, Hartree			−2931.2613	−2934.8141
Singlet energy, Hartree	−2931.3859	−2934.9395		

Table 5. Selected bond lengths (Å) and angles (°) for GK

Bondlength			
Ni(1)—N(3)	1.8357(12)	N(2)—C(6)	1.3799(19)
Ni(1)—N(2)	1.8384(12)	N(3)—C(12)	1.2830(19)
Ni(1)—O(2)	1.8477(12)	N(3)—C(19)	1.4702(19)
Ni(1)—N(1)	1.9229(12)	C(4)—C(5)	1.499(2)
O(2)—C(20)	1.287(2)	C(19)—C(20)	1.501(2)
N(1)—C(4)	1.4858(19)	C(21)—C(22)	1.497(2)
N(1)—C(21)	1.493(2)	C(22)—C(23)	1.387(3)
N(2)—C(5)	1.3687(19)	C(22)—C(27)	1.384(3)
Bond angles			
N(3)—Ni(1)—N(2)	95.33(5)	C(4)—N(1)—Ni(1)	107.70(8)
N(3)—Ni(1)—O(2)	87.50(5)	C(21)—N(1)—Ni(1)	107.53(9)
N(2)—Ni(1)—O(2)	175.88(6)	C(1)—N(1)—Ni(1)	113.21(10)
N(3)—Ni(1)—N(1)	168.84(5)	C(5)—N(2)—Ni(1)	114.17(10)
N(2)—Ni(1)—N(1)	88.72(5)	C(6)—N(2)—Ni(1)	125.43(10)
O(2)—Ni(1)—N(1)	89.04(5)	C(12)—N(3)—Ni(1)	128.93(10)
C(20)—O(2)—Ni(1)	115.30(11)	C(19)—N(3)—Ni(1)	110.18(10)
C(4)—N(1)—C(21)	113.49(12)	N(1)—C(21)—C(22)	114.04(13)
C(4)—N(1)—C(1)	104.80(12)	C(23)—C(22)—C(27)	119.09(17)
C(21)—N(1)—C(1)	110.20(12)		

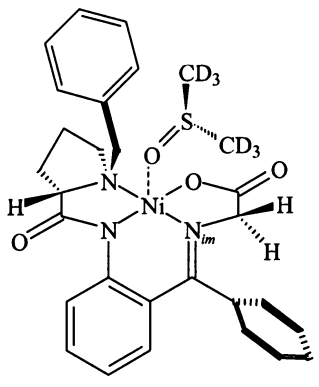
Table 6. Hydrogen bonds for GK (Å and °)

D—H···A	*d*(D—H)	*d*(H···A)	*d*(D···A)	∠(DHA)
C(3)—H(3A)···O(3)[a]	0.99	2.50	3.469(2)	164.5
C(17)—H(17)···O(1)[b]	0.95	2.46	3.402(2)	171.7

Symmetry transformations used to generate equivalent atoms: (a) $x-1$, y, z; (b) $-x+1$, $y+1/2$, $-z+3/2$.

The nickel atom has a square-planar coordination to three nitrogen atoms and to one oxygen atom. The distances to the nitrogen atoms are distinctly different [1.836(1) to N(3), 1.838(1) to N(2) and 1.923(1) Å to N(1)], similar to another compound, compared with [35]. Atoms N(1) and N(3) are bent closer to the phenyl ring C(22)···C(27) by 0.112(1) Å, while atoms N(2) and O(2) bend from this ring by 0.109(1) and 0.115(1) Å, respectively. The nickel atom lies slightly on the opposite side of the mean least-square plane defined by N(1), N(2), N(3) and O(2) atoms, than the above mentioned phenyl ring is by 0.060(1) Å. The distance between the nickel atom and C(22) is 2.928(2) Å, while the perpendicular distance from the mean least-square planes of the phenyl ring C(22)···C(27) is 2.656(1) Å, and the normal to this plane and the vector between the centroid of this ring and Ni(1) atom is 43.8(1)°. Characterization of the ring present in the structure is as follows: ring Ni1—O2—C20—C19—N3 forms an envelope on N3, ring Ni1—N1—C4—C5—N2 is twisted on C4—C5 bond, ring N1—C1—C2—C3—C4 forms an envelope on C1. The six-membered ring C6···C11 is not planar with $\chi^2 = 149.3$ and r.m.s. = 0.009 Å, while the phenyl rings C13···C18 and C22···C27 are close to planar ($\chi^2 = 31.6$ and 10.3, respectively and r.m.s. = 0.003 Å for both of them). Low puckering of the ring C22···C27 does not support the hypothesis about donation of electron density.

Due to hardware limitations associated with the *ab initio* calculations, we used ^{13}C-n.m.r. spectroscopy in a nickel-coordinating solvent to prove the new hypothesis. In a deuteriochloroform solution of GK the benzyl group is situated in an apical position towards the nickel atom [1, 13]. This position enables the donation of electron density from the π-system of the benzyl ring to the nickel orbitals. Suppression of the donation of electron density from the π-system of the benzyl ring to nickel orbitals in GK was achieved by application of a coordinating solvent (^{2}H)DMSO instead of non-coordinating $^2HCCl_3$ (Scheme 4). The resulting ^{13}C-n.m.r. spectra exhibited no long-range spin–spin interactions (Table 7). ^{13}C-n.m.r. spectra of solutions of the complexes in (^{2}H)DMSO provide the only experimental evidence for the donation of electron density for the long-range spin–spin interactions.



Scheme 4. Coordination of $(CD_3)SO(CD_3)$ to GK responsible for no long-range interactions.

Table 7. ^{13}C-n.m.r. spectra and interaction constants measured in $CDCl_3$ solutions [3] (bold font) and in (^{2}H)DMSO solutions (normal font)

Carbon	GK, labelled σ^{13}C (ppm)	^{13}C-19 $^nJ(^{13}$C-19, ^{13}C) (Hz)	GK, labelled σ^{13}C (ppm)	C-20 $^nJ(^{13}$C-20, ^{13}C) (Hz)	GK, labelled σ^{13}C (ppm)	$^{15}N_{im}$ $^nJ(^{15}N_{im}$, ^{13}C) (Hz)
1	**57.4**		**57.4**		**57.4**	
	58.0		57.9		58.0	
2	**23.6**		**23.6**		**23.6**	
	23.4		23.3		23.4	
3	**30.7**		**30.7**		**30.7**	
	30.5		30.4		30.5	
4	**69.8**	**4.4**	**69.8**	**2.8**	**69.8**	**2.9**
	69.3		69.3		69.4	
5	**181.3**		**181.3**		**181.3**	
	181.3		181.2		181.4	
6	**142.5**		**142.5**		**142.5**	**1.1**
	142.6		142.6		142.5	
7	**124.2**		**124.2**		**124.2**	
	123.9		123.8		124.9	
8	**132.2**		**132.2**		**132.2**	
	131.3		131.2		131.8	
9	**120.8**		**120.8**		**120.8**	
	120.3		120.2		120.3	
10	**133.1**		**133.1**		**133.1**	**2.3**
	132.6		132.5		132.6	
11	**125.1**	**3.3**	**125.1**		**125.1**	**2.9**
	124.8	3.1	124.7		124.8	
12	**171.5**	**0.9**	**171.6**	**5.0**	**171.6**	**12.5**
	170.2		170.2	5.0	170.3	12.5
13	**134.6**	**3.7**	**134.6**		**134.6**	**1.2**
	134.6	3.3	134.8		134.9	
14	**126.2**		**126.2**		**126.2**	
	126.7		126.6		126.7	
15	**129.3**		**129.3**		**129.3**	
	129.3		129.2		129.3	
16	**129.7**		**129.7**		**129.7**	
	129.5		129.4		129.5	
17	**129.6**		**129.5**		**129.6**	
	129.4		129.4		126.7	
18	**125.6**		**125.6**		**125.6**	
	126.2		126.2		126.2	
19	**61.2**		**61.2**	**56.8**	**61.2**	**4.8**
	61.1		61.0	55.7	61.1	
20	**177.3**	**56.8**	**177.3**		**177.2**	**3.6**
	175.9	56.7	175.9		176.1	
22	**133.3**		**133.3**		**133.3**	
	134.9		134.9		134.9	
23	**131.7**		**131.7**		**131.7**	
	131.8		131.7		131.7	
24	**128.9**		**128.9**		**128.9**	
	128.7		128.6		128.7	
25	**129.1**		**129.1**		**129.1**	
	129.4		129.4		129.5	
26	**128.9**		**128.9**		**128.9**	
	128.7		128.6		128.7	
27	**131.7**		**131.7**		**131.7**	
	131.8		131.7		131.8	

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III

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Electronic structure of the nickel(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylprolinamide and glycine

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The experimental charge density of the Ni^{II} complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylprolinamide and glycine was derived from high-resolution single-crystal X-ray diffraction data (λ = 0.5604 Å) at low temperature (100 K) with synchrotron radiation at the beamline F1 using a CCD area detector. The central Ni atom is pseudo-square-planar coordinated by three N atoms [1.9414 (3), 1.8559 (3) and 1.8533 (3) Å] and by one O atom [1.8620 (4) Å]. The N(1) atom is 0.359 Å above the plane defined by the atoms Ni(1), N(2) and N(3). The *d*-orbital population analysis reveals an oxidation state for the Ni atom of +2 with the configuration d^8 and a hole mainly in the $d_{x^2-y^2}$ orbital, located in the plane of the four ligating atoms. The prochiral reaction centre was examined by topological analysis.

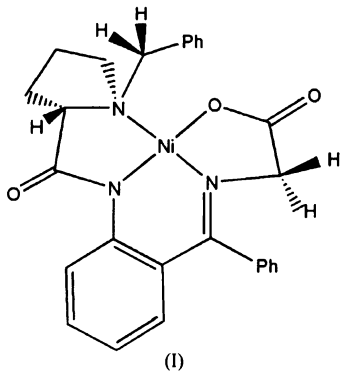
1. Introduction

In the pharmaceutical industry, enantiomerically pure α-methyl amino acids are used as building blocks for peptidomimetic drug design. Owing to environmental constraints, catalytic approaches are favoured as compared to their stoichiometric alternatives. Recent achievements in catalytic asymmetric synthesis of α-methyl amino acids make enantiospecific processes accessible in many cases (Ager, 2002). Less attention is now paid to the development of chiral stoichiometric synthons of α-methyl amino acids for non-industrial purposes. Preparation of ^{11}C-labelled amino acids for positron emission tomography (PET) is an important example (Vaalburg *et al.*, 1976; Plenevaux *et al.*, 1994; Fasth *et al.*, 1995; Långström *et al.*, 1999). Reliable syntheses of compounds labelled with carbon-11 (half-life 20.4 min) are performed on a submicromolar scale in specially designed remote-controlled robotic devices. Limitations brought by very small amounts of a starting compound significantly restrict the applicable procedures. In PET, α-methyl amino acids play a dual role:

(i) as precursors of non-metabolized neurotransmitters (analogues of serotonin, dopamine, tyramine *etc.*) for the study of neurodegenerative diseases;

(ii) as non-metabolized analogues of proteinogenic amino acids for the study of amino acid uptake in normal and cancer cells. Difference in the uptake rates during a PET scan could visualize cancer metastases in a human body.

Clinical applications of such amino acids are very limited due to their poor availability. For the synthesis of the only enantiomerically pure ^{11}C-labelled α-methyl amino acid, α-[^{11}C]methyltryptophan, an industrial procedure was adopted (Crich & Davies, 1989; Bourne *et al.*, 1991; Plenevaux *et al.*, 1994). All attempts to prepare enantiomerically pure α-[^{11}C]methylated tyrosine failed (Gee & Långström, 1991; Rajagopal *et al.*, 1992).



(I)

Our approach to the desired amino acids is based on an improvement of stereodifferentiating the properties of known nickel-based amino acids synthons (Fig. 1) (Belokon, Bakhmutov *et al.*, 1988; Fasth & Långström, 1990; Popkov *et al.*,

2002; Popkov, Nádvorník *et al.*, 2003). Earlier, three ways to meet these goals were suggested.

(i) The first one concerns the conformation of the complexes. As derived from NOE (nuclear Overhauser effect) interactions, the *ortho* protons of the benzyl group are situated closest to the plane of the complex (Jirman & Popkov, 1995). The degree of asymmetric induction of these nickel complexes may be improved by increasing the steric hindrance of the benzyl group by the introduction of methyl substituents in the *ortho* positions.

(ii) The second way concerns the donation of electron density from the π system of the benzyl ring to Ni orbitals. We inferred such a donation of electrons in the complexes. This effect should influence the stereochemical result of alkylation of the complexes under thermodynamically controlled conditions. Two examples supporting our hypothesis were found in the literature: the replacement of the benzyl group in the complex by an electron-rich naphthylmethyl group led to higher asymmetric induction (Belokon, Maleev *et al.*, 1988), whereas the replacement of the benzyl group by various picolyl groups in many cases decreased the induction (De & Thomas, 1997; Blake *et al.*, 2002). We therefore hypothesized that the distance of the benzyl group to the Ni atom will be reduced by the introduction of alkyl substituents in any position on the benzyl group.

(iii) Replacement of the *N*-benzyl group by *N*-(2,4,6-trimethylbenzyl) should disable 'ring-edge' bonding (between the η^2-bonded aromatic ring and the metal atom) due to sterical reasons. Thus only 'ring-centre' bonding where the 2,4,6-trimethylbenzyl group is an 'η^6 ligand' will remain (Popkov *et al.*, 2002).

While the influence of the first factor was proved experimentally and the third one is obvious, existence of the donation of electron density from the π system of the benzyl ring to Ni orbitals is still a hypothesis. This hypothesis was used for explanation of long-range interactions in NMR spectra of ^{13}C- and ^{15}N-labelled complexes (Jirman *et al.*, 1998; Popkov, Langer *et al.*, 2003). In order to estimate this interaction, the electron density from diffraction data has been studied and compared with the theoretical *ab initio* molecular MP2 orbital calculation for an isolated molecule in experimental geometry.

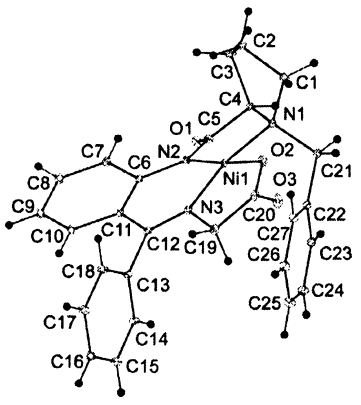


Figure 1
The crystal structure of the title compound with 20% probability thermal displacement ellipsoids (Brandenburg, 1998).

Table 1
Experimental details.

Crystal data	
Empirical formula	$C_{27}H_{25}N_3NiO_3$
Formula weight	498.21
Crystal size (mm)	0.439 × 0.110 × 0.094
Space group	$P2_12_12_1$ (No. 19)
a (Å)	8.9817 (3)
b (Å)	9.6588 (4)
c (Å)	26.2593 (10)
Z	2
Temperature (K)	100.0 (1)
Wavelength (Å)	0.5604
μ (mm^{-1})	0.467
Data collection set	I
Scan type	ω, φ
Max sin θ/λ (Å^{-1})	1.20
Range of indices	
h	−21/21
k	−22/22
l	−59/59
No. of measured diffractions	
after *SAINT*	140195
after *SADABS*	138572
after *XPREP*†	27089
R_{int}	0.0361
$R(\sigma)$	0.0208

† Unique.

2. Experimental

The compound was prepared as described earlier (Nádvorník & Popkov, 2002) and a single crystal was chosen (0.439 × 0.110 × 0.094 mm) and fixed on top of a 0.5 mm glass capillary using UHU-SOFORTFEST glue and a special low-temperature goniometer head. Diffraction data were collected at the synchrotron beamline F1 of the storage ring DORISIII at Hasylab/DESY, Hamburg. Using a wavelength of λ = 0.5604 Å (Si monochromator) with a Bruker Smart1K CCD detector mounted on the detector arm of a κ diffractometer allowed the collection of 140195 Bragg reflections up to sin θ/λ = 1.20 Å^{-1} within 5 d. *SMART*-Kappa 5.A29 software (Bruker, 2001) was used for data collection. During the measurement, the temperature of the crystal was maintained at 100 K. The data reduced to 27089 symmetry-independent reflections. Since a relatively large crystal was used to obtain high-angle data, many low-angle diffractions exceeded the dynamic range of the CCD detector. As a consequence, an Al attenuator was used for a further set of runs for low-angle diffractions in which another 16406 Bragg diffractions were obtained. More details are summarized in Table 1.

3. Data reduction

Orientation matrices for each run were determined by *SMART* software (Bruker, 2001) using about 1000 strongest diffractions equally distributed over the run. Final lattice cell parameters were obtained by weighted least-squares fit of all

Table 2
Summary of least-squares refinements.

Refinement	(I)	(II)	(III)	(IV)
$\sin\theta/\lambda$ (Å^{-1})	0–1.2	0.75–1.2	0–1.2	0–1.2
N_{obs}	26433	18208	26433	26433
N_v	383	382	65	981
$R(F)$	0.0233	0.0226	0.0228	0.0151
$R(F)$†	0.0244	0.0254	0.0239	0.0162
$wR(F)$†	0.0332	0.0238	0.0284	0.0174
$R(F^2)$	0.0399	0.0364	0.0393	0.0217
$R(F^2)$†	0.0399	0.0452	0.0394	0.0218
$wR(F^2)$†	0.0666	0.0469	0.0542	0.0323
S	2.75	1.54	2.67	1.55

† All reflections.

sets of lattice cell parameters for each run. The decrease of the primary-beam intensity was corrected by the local software *SAPRO* (Paulmann, 2001) with simultaneously recorded external monitor data. The intensities were afterwards integrated using the *SAINT* software package (Bruker, 2001). During the integration, each orientation matrix was optimized after every 50 frames. Integrated intensities were further scaled, corrected for the absorption and for some other effects by *SADABS* (Sheldrick, 2002). In the first set, *SADABS* produced 138572 corrected diffractions which were merged by *XPREP* (Bruker, 1997) to 27089 unique diffractions [R_{int} = 0.0361, $R(\sigma)$ = 0.0208]. After truncating at 2.0 Å resolution, the second set (Al attenuator) gave 3955 corrected and finally 297 unique diffractions [R_{int} = 0.0644, $R(\sigma)$ = 0.0334] (see Table 1).[1]

4. Least-squares refinements

Starting parameters were taken from a previous paper (Popkov, Langer *et al.*, 2003) and all refinements were carried out on F^2 using the *XD* (Koritsanszky *et al.*, 1997) suite of programs. The strategy for refinements was as described earlier (Kožíšek *et al.*, 2002). Four different refinements were carried out using statistical weights throughout and the results are summarized in Table 2. Refinement (I) is a traditional independent-atom refinement. Refinement (II) is a high-angle refinement ($0.7 \leq \sin\theta/\lambda \leq 1.20$ Å^{-1}) with the H atoms fixed at the typical distances obtained from neutron diffraction experiments (Allen *et al.*, 1992) and isotropic thermal parameters fixed at the values obtained in refinement (I). Refinement (III) is a κ refinement with the aim of assigning atomic charges (Coppens, 1997). The H-atom positional and thermal parameters were fixed as in refinement (II). A complete atom-centred multipole refinement was carried out in (IV), where the nonspherical atomic electron density (Coppens, 1997) is given by

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference XC5005). Services for accessing these data are described at the back of the journal.

Table 3
Population of the d orbitals.

Orbital	$d_{x^2-y^2}$	d_{z^2}	d_{yz}	d_{xz}	d_{xy}
[e$^-$]	0.36 (2)	1.98 (2)	2.04 (2)	1.82 (2)	1.69 (2)

$$\rho_{at}(r) = P_c\rho_{core}(r) + P_v\kappa^3\rho_{valence}(\kappa r) + \sum_{l=1}^{l_{max}} \kappa'^3 R_l(\kappa' r) \sum_{m=0}^{l} P_{lm\pm} d_{lm\pm}(\theta, \varphi).$$

The H atoms were treated with one bond-directed dipole (l = 1), other atoms were refined up to octupoles, for the Ni atom the hexadecapole level (l_{max} = 4) was used. The local coordinate systems to define multipoles were defined as follows. For non-H atoms: x axis is direction to the closest atom, y axis is perpendicular to the x axis and oriented towards the second closest atom; for H atoms: z axis is direction to the bonding C atom and x axis is perpendicular to the z axis. The same types of H atoms [sp^3 hybridization: H(1), H(2), H(3), H(21); sp^2 hybridization: H(7), H(14) and H(23)] were constrained to have identical multipole expansions.

5. Results and discussion

The central Ni atom is pseudo-square-planar coordinated by three N atoms [N(1), N(2) and N(3), 1.9414 (3), 1.8559 (3) and 1.8533 (3) Å, respectively] and by one O atom [1.8620 (4) Å]. The N(1) atom is 0.359 Å above the plane defined by the atoms Ni(1), N(2) and N(3). As may be seen in Table 2, the multipole refinement achieved a significant improvement of the agreement between the experimental and calculated structure factors. Residual density maps are calculated by a Fourier synthesis where the coefficients are differences between the observed and calculated structure factors corresponding to the converged multipole model. The maximum

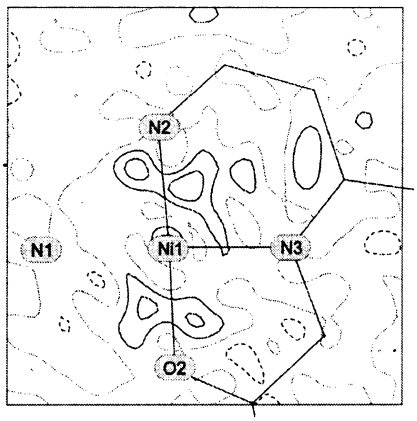


Figure 2
Residual density map in the plane of atoms Ni(1), N(3) and N(2). Positive, negative and zero contours are represented by solid, dashed and dotted curves. Contour spacing 0.05 e Å^{-3}. The maximum positive density in this plane is 0.147 e Å^{-3}, the minimum negative density is −0.074 e Å^{-3}.

Table 4
Electron-density properties at bond critical points.

Bond		Experimental				Theoretical				
Atom *A*	Atom *B*	d_{AB} (Å)	ρ_b (e Å^{-3})	$\nabla^2\rho_b$ (e Å^{-5})	ε	d_A (Å)	d_B (Å)	ρ_b (e Å^{-3})	$\nabla^2\rho_b$ (e Å^{-5})	ε
Ni	O2	1.8620 (4)	0.581 (5)	15.89 (1)	0.03	0.9139	0.9504	0.682	18.700	0.424
Ni	N1	1.9413 (3)	0.522 (5)	11.96 (1)	0.24	0.9344	1.0090	0.668	14.072	0.410
Ni	N2	1.8559 (3)	0.644 (6)	16.60 (1)	0.07	0.8828	0.9736	0.796	17.024	0.222
Ni	N3	1.8533 (3)	0.711 (6)	15.76 (1)	0.07	0.9004	0.9536	0.803	17.284	0.215
O1	C5	1.2288 (5)	2.85 (4)	−38.5 (2)	0.24	0.7771	0.4518	2.605	−13.468	0.032
O2	C20	1.2935 (6)	2.36 (4)	−27.6 (2)	0.16	0.8307	0.4630	2.207	−14.392	0.090
O3	C20	1.2249 (5)	2.76 (4)	−32.5 (2)	0.22	0.7707	0.4543	2.652	−13.728	0.010
N1	C1	1.4925 (5)	1.62 (3)	−7.14 (7)	0.11	0.8380	0.6550	1.552	−9.224	0.049
N1	C4	1.4934 (4)	1.58 (2)	−6.75 (6)	0.08	0.8199	0.6743	1.579	−9.908	0.025
N1	C21	1.5000 (5)	1.56 (2)	−9.32 (7)	0.14	0.8388	0.6613	1.525	−9.148	0.050
N2	C5	1.3750 (4)	2.15 (3)	−21.8 (1)	0.23	0.7856	0.5913	2.031	−17.128	0.032
N2	C6	1.3898 (4)	2.04 (3)	−15.10 (9)	0.13	0.7775	0.6130	1.950	−16.408	0.028
N3	C12	1.2982 (4)	2.56 (3)	−34.6 (2)	0.33	0.7972	0.5016	2.355	−18.180	0.024
N3	C19	1.4689 (4)	1.65 (3)	−9.18 (8)	0.11	0.8360	0.6332	1.579	−9.660	0.048
C1	C2	1.5120 (6)	1.64 (2)	−10.42 (6)	0.12	0.7918	0.7210	1.647	−13.352	0.037
C2	C3	1.5120 (6)	1.61 (2)	−10.22 (5)	0.07	0.7819	0.7509	1.566	−11.732	0.018
C3	C4	1.5553 (5)	1.54 (2)	−8.62 (4)	0.11	0.7651	0.7907	1.518	−10.836	0.032
C4	C5	1.5089 (5)	1.80 (2)	−14.52 (5)	0.22	0.7464	0.7634	1.701	−14.208	0.059
C6	C7	1.4153 (4)	1.99 (2)	−15.18 (6)	0.28	0.7201	0.7030	1.957	−19.048	0.106
C6	C11	1.4212 (4)	2.01 (2)	−17.22 (6)	0.30	0.7183	0.7030	1.930	−18.440	0.155
C7	C8	1.3806 (6)	2.14 (3)	−20.58 (7)	0.30	0.6902	0.6917	2.099	−22.064	0.125
C8	C9	1.3969 (6)	2.13 (3)	−21.22 (7)	0.27	0.7023	0.6950	2.045	−21.148	0.095
C9	C10	1.3817 (5)	2.12 (3)	−20.00 (7)	0.37	0.7025	0.6795	2.112	−22.324	0.134
C10	C11	1.4156 (5)	2.01 (3)	−17.28 (6)	0.29	0.6791	0.7364	1.964	−19.288	0.122
C11	C12	1.4606 (4)	1.85 (2)	−14.26 (5)	0.26	0.7040	0.7567	1.795	−16.116	0.079
C12	C13	1.4964 (4)	1.77 (2)	−12.95 (5)	0.03	0.7584	0.7383	1.694	−14.536	0.013
C13	C14	1.3987 (5)	2.17 (3)	−20.27 (7)	0.26	0.7290	0.6697	1.998	−19.808	0.136
C13	C18	1.3961 (5)	2.17 (2)	−19.54 (7)	0.25	0.6783	0.7179	2.031	−20.560	0.141
C14	C15	1.3949 (6)	2.17 (3)	−21.74 (7)	0.18	0.6779	0.7173	2.031	−20.716	0.113
C15	C16	1.39 44 (7)	2.17 (3)	−21.00 (7)	0.25	0.6725	0.7221	2.045	−21.168	0.106
C16	C17	1.39 39 (7)	2.21 (3)	−19.27 (7)	0.23	0.7130	0.6810	2.058	−21.392	0.109
C17	C18	1.39 54 (5)	2.11 (3)	−18.01 (7)	0.20	0.6828	0.7127	2.018	−20.492	0.112
C19	C20	1.5202 (6)	1.78 (3)	−12.08 (5)	0.15	0.7394	0.7818	1.680	−13.756	0.064
C21	C22	1.5067 (6)	1.75 (2)	−13.24 (5)	0.01	0.7609	0.7358	1.653	−13.756	0.032
C22	C23	1.3973 (7)	2.14 (3)	−20.07 (7)	0.31	0.6788	0.7222	2.018	−20.232	0.128
C22	C27	1.4007 (6)	2.19 (3)	−21.68 (9)	0.19	0.7537	0.6445	2.024	−20.504	0.141
C23	C24	1.3914 (8)	2.19 (3)	−21.5 (1)	0.39	0.7575	0.6357	2.038	−20.908	0.111
C24	C25	1.395 (1)	2.14 (4)	−17.9 (1)	0.38	0.7695	0.6427	2.085	−21.940	0.110
C25	C26	1.404 (2)	2.14 (4)	−19.6 (1)	0.15	0.7595	0.6391	2.072	−21.716	0.108
C26	C27	1.3933 (9)	2.11 (4)	−19.26 (8)	0.17	0.6986	0.6933	2.045	−21.100	0.111

and minimum of the residual density are +0.147 e Å^{-3} at a distance of 1.27 Å from Ni(1) and 0.78 Å from N(2), and −0.074 e Å^{-3} at a distance of 0.58 Å from Ni(1) and 1.33 Å from O(2), respectively; the root-mean-square residual density is 0.032 e Å^{-3} (Fig. 2).

In Figs. 3–7, we present multipole-model static deformation density maps. The equatorial plane (Fig. 3) is defined by the atoms Ni(1), N(3) and N(2). As the atom N(1) is 0.359 Å above this plane, the electron density is not so intensive as for N(2) and N(3). A similar situation is found for O(2) (0.09 Å below). The occupancies of the *d* orbitals calculated from multipole population parameters are given in Table 3. These values are sensitive to a reliable absorption correction. The maximum values should not exceed 2 electrons per orbital; this is a good check of a reliable absorption correction. The *d*-orbital populations in Table 3 are in good agreement with the features observed in Fig. 3 and topological analysis in Table 4: the non-bonding orbitals d_{z^2} and d_{yz} are fully populated. The electron configuration of the Ni atom is nearly d^8; the missing two electrons in the 3*d* shell have been taken to *ca* 80% from the $d_{x^2-y^2}$ orbital. Integration of electron density in the atomic basin by *TOPXD* gives charges for Ni(1) and the following donor atoms: +1.83 for Ni(1), −0.55 for N(1), −0.86 for N(2), −0.88 for N(3) and −0.96 for O(2).

The coordination bond formed by the lone electron pairs of atoms N(1), N(2), N(3) and O(2) point to the space with electron-density depletion (orbital $d_{x^2-y^2}$). Bond strengths correlate with the bonding distances and the values of electron

density ρ_b at bond critical points (BCP) as well. The lowest value of 0.522 (5) e Å^{-3} for N(1) agrees also with the different type of hybridization (sp^3). The ellipticities for all donor atoms indicate mainly σ-bond character, except the Ni(1)—N(1) bond (ε = 0.24). The interatomic distance of 1.9413 (3) Å is significantly longer than Ni(1)—N(2) and Ni(1)—N(3) bonds, so the only explanation is the mechanical strain that deforms the cylindrical symmetry of the σ bond (Bader, 1990). This mechanical strain might be seen also in the adjacent N(1)—C(21) bond with the interatomic distance of 1.5000 (5) Å, which is evidently single (Allen *et al.*, 1992), but its ellipticity is 0.14. The higher value for the N(1)—C(21)—C(22) angle of 113.95 (3)° as compared to the tetrahedral value of 109°28′ and the other angles around the sp^3 C(21) atom (107.7–108.8°) indicates that the benzyl group is pushed away from the Ni^{II} central atom and the ellipticity is a compromise between the sp^3 hybridization of N(1) and this repulsion.

For Ni(1)—O(2), the value of electron density ρ_b (Table 4) is smaller than for the N(2) and N(3) cases (probably due to the higher electronegativity of oxygen). Positive Laplacians $\nabla^2\rho_b$ [11.96 (1)–16.60 (1) e Å^{-5}] indicate strong coordination bonds (Kožíšek *et al.*, 2002; Slouf *et al.*, 2002).

An apparent correlation may be seen when comparing the value of the electron density ρ_b at BCP with the ellipticity. Higher ellipticity values in the case of N(2)—C(5) and C(4)—C(5) bonds are due to the vicinity of the C(5)—O(1) double bond. The highest value for ellipticity at BCP (0.33) was found for the N(3)—C(12) bond, which is evidently double.

In order to examine expected interaction between the benzyl group and the Ni(1) atom [interatomic distances Ni(1)—C(21), Ni(1)—C(22), Ni(1)—C(23) and Ni(1)—C(27) of 2.7836 (4), 2.9397 (4), 3.2817 (5) and 3.6825 (5) Å, respectively], the static deformation density map in the plane of the benzyl group and in the parallel planes (0.3 Å above and below) were calculated (Figs. 4–6). Fig. 4 shows the static electron density in the plane defined by C(22), C(23) and C(27) atoms. The electron density in the plane shifted towards the Ni(1) atom is significantly higher (Fig. 5) than in the

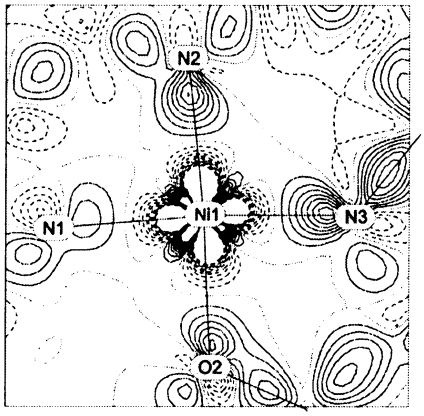


Figure 3
Static electron deformation densities in the plane defined by the atoms Ni(1), N(3) and N(2). Contour spacing 0.1 e Å^{-3}.

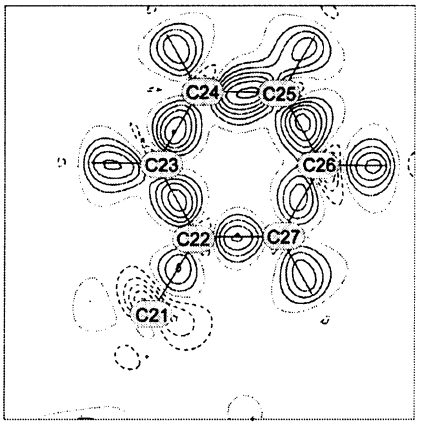


Figure 5
Static electron deformation densities +0.3 Å from the plane defined by the atoms C(22), C(27) and C(23). Contours as in Fig. 3.

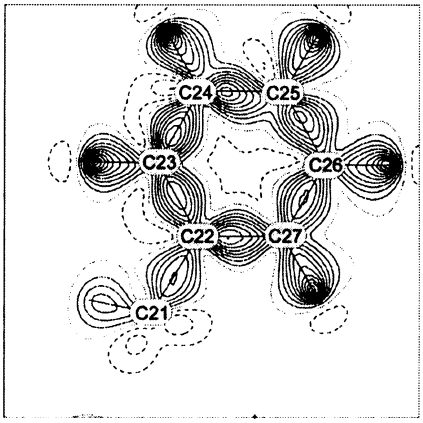


Figure 4
Static electron deformation densities in the plane defined by the atoms C(22), C(27) and C(23). Contours as in Fig. 3.

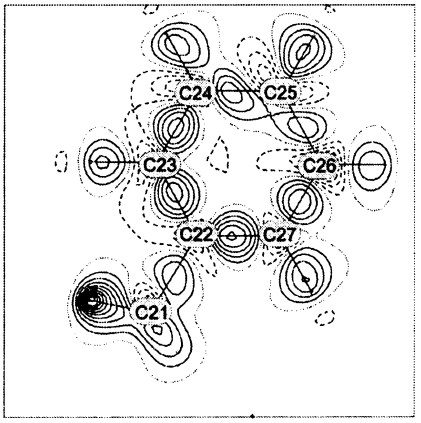


Figure 6
Static electron deformation densities −0.3 Å from the plane defined by the atoms C(22), C(27) and C(23). Contours as in Fig. 3.

opposite direction (Fig. 6) in spite of our expectation (residual Fourier synthesis gave maximum and minimum +0.097 and −0.098 e Å^{-3}, respectively; the root-mean-square residual density is 0.028 e Å^{-3}). To conceive the shape of the area close to the Ni(1) atom in the direction towards the benzyl group, the additional static deformation density map in the plane defined by the atoms Ni(1), C(22) and C(23) was drawn (Fig. 7). The electron density around Ni(1) is mostly in the area of the d_{z^2} orbital (Table 3). The original symmetry of this orbital seems to be lowered by benzyl π-electron repulsion. It might be concluded that no coordination bond between the Ni(1) atom and the benzyl group has been found, but some kind of interaction is evident. Here the question arises whether the electron density pushing into a benzyl group from methyl substituents [similar to the case of the *N*-(2,4,6-trimethylbenzyl) group mentioned above] really supports the desired asymmetric synthesis.

In order to see differences on the prochiral reaction centre, chemical constraints were not applied to atoms H(19*A*) and H(19*B*). Multipole refinement converged with significantly different values for monopoles [for atom H(19*A*) of 1.00 and for H(19*B*) of 0.77]. The residual map in the corresponding plane does not exceed a minimum of −0.11 and a maximum of +0.07 e Å^{-3}, respectively. A shift of the maximum of bonding electron density towards the H atoms (Fig. 8) is in the present study a general feature and might be connected with the systematic error introduced by the scaling and/or weighting procedures of the data with the Al attenuator.

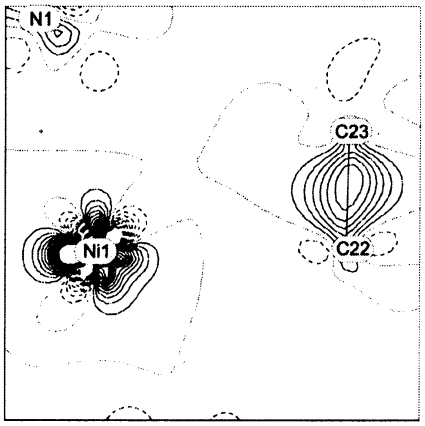


Figure 7
Static electron deformation densities in the plane defined by the atoms Ni(1), C(22) and C(23). Contours as in Fig. 3.

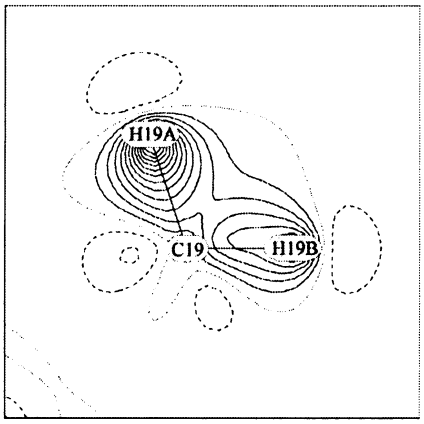


Figure 8
Static electron deformation densities in the plane defined by the atoms C(19), H(19*B*) and H(19*A*). Contours as in Fig. 3.

Ab initio MP2 calculation for the isolated title molecule within experimental geometry has been performed using standard *PC GAMESS* program package (Schmidt *et al.*, 1993; Granovsky, 2003) with TZV basis set for Ni (Rappe *et al.*, 1981) and DZV basis sets for the remaining atoms (Dunning & Hay, 1977). The electronic structure was evaluated in terms of topological analysis of electron density (Bader, 1990) using the *AIM2000* program (Biegler-König *et al.*, 2001; http://www.aim2000.de) such as electron density, Laplacian density and bond ellipticity at the BCP. Comparison of experimental and calculated electron densities (Table 4) exhibits, in general, similar trends. Very good agreement was found for the unsaturated rings as well as for a saturated N(1)−C(1)−C(2)−C(3)−C(4) one. Larger differences may be observed in the Ni(1) coordination polyhedron [especially the Ni(1)−O(2) ellipticity], but the trends in BCP electron density are preserved. Significantly larger differences are in the delocalized subsystems O(2)−C(20)−O(3) and O(1)−C(5)−N(2) as well as in the N(3)−C(12) bond. The greatest portion of these discrepancies might be ascribed to enviromental influences, which are not considered in our quantum-chemical calculations. No bonding paths between the Ni(1) atom and the benzyl group have been found (in agreement with the repulsion interaction indicated by experimental data).

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IV

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Two new Ni(II) Schiff base complexes: X-ray absolute structure determination, synthesis of a ^{15}N-labelled complex and full assignment of its ^{1}H NMR and ^{13}C NMR spectra

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Abstract

The Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-benzylpyrrolidine-2-carboxamide and glycine (**1**) [GKCl] and the hemihydrate of the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and 2-aminoisobutiric acid (**2**) [Me_2GK] were prepared and their absolute structures determined. The conformations of the complexes and their hydrogen bonding are discussed in detail. In complex **2**, the repulsion between the benzyl group and an equatorial methyl group should affect the conformation of the benzyl group, distribution of the π-electron density in this group and distortion of the internal coordination sphere, while for complex **1**, only minor conformational changes were expected. ^{1}H and ^{13}C NMR data for the ^{15}N-labelled complex **2** were acquired and fully assigned in order to study the influence of π-electron density of the benzyl group to the long-range ^{13}C–^{15}N and ^{13}C–^{13}C spin–spin interactions.

Keywords: Complexes; Crystal structure; NMR spectra; Spin–spin interactions

1. Introduction

Ni complexes of Schiff bases of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (BPB) and α-amino acids are stoichiometric synthons of α-amino acids [1]. While efficient catalytic procedures have been suggested for a wide range of α-amino acids [2], development of catalytic syntheses requires time-consuming screening for an optimal catalyst, precursor and reaction conditions. In most cases, chiral stoichiometric α-amino acids synthons are the optimal choice for the preparation of up to kilogram amounts of new α-amino acids [3]. For example, very advanced catalytic approaches were developed for the preparation of β-aryl-substituted alanines by asymmetric hydrogenation of α,β-unsaturated precursors [4]. Alkylation of Ni complexes of Schiff bases of BPB and glycine by arylmethylhalogenides followed by recrystallisation of the alkylated complexes and their hydrolysis also leads to enantiomerically pure β-arylsubstituted alanines. It is usually performed with little optimisation using similar procedures for different target amino acids: 2,2-diphenylalanine [5], 2-naphthylalanine [6], 1-naphthylalanine [7] and 1-pyrenylalanine [8]. An alternative preparation of 2-naphthylalanine via catalytic hydrogenation required the extensive effort of an industrial group of scientists; a special catalyst was developed in order to achieve almost 98% e.e. [9]. Another important application of Ni complexes of Schiff bases of BPB and α-amino acids is preparation of α-[^{11}C]methylDOPA [10] and α-[^{11}C]methyltyrosine

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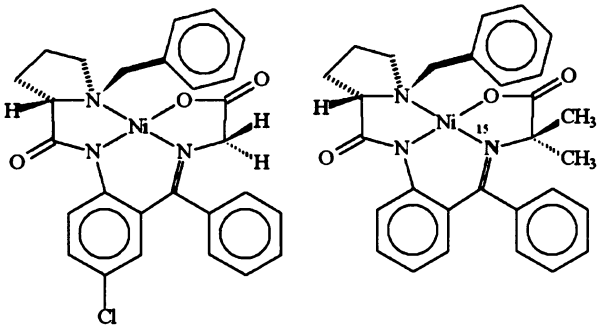
[11] for positron emission tomography (PET) visualization of cancer cells and in vivo metabolism of 3,4-dioxyphenylalanine (DOPA).

Recently, several stereoselective analogous synthons carrying substituents on the benzyl group were developed [12]. Electronic and steric effects influencing the stereochemistry of alkylation of the synthons were thoroughly investigated by a number of physical–chemical approaches. The conformations of the complexes in solutions were disclosed by NMR [7,13].

A number of X-ray structures of related complexes were published, including pairs of diastereomers with opposite configurations of the α-carbon of the amino acid fragments [14] (for overview, see [13c]). The distribution of the electron density in a single crystal of a glycine synthon was studied by X-ray diffraction by Kožíšek et al. [15]. Ab initio quantum-chemical modelling and topological analysis of electron density were also performed for this molecule [13c,15]. A similar but more acidic Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-benzylpyrrolidine-2-carboxamide and glycine was studied by NMR only [13b]. In spite of their synthetic application as intermediates in the synthesis of α-[^{11}C]methyl amino acids, single crystals of complexes with a quaternary α-carbon of the amino acid fragment have never been studied by X-ray diffraction, neither has complete assignment of their ^{1}H and ^{13}C NMR spectra been done. Here we present X-ray structure determinations for both the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-benzylpyrrolidine-2-carboxamide and glycine (**1**) and the hemihydrate of the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and 2-aminoisobutiric acid (**2**), and the full assignment of ^{1}H and ^{13}C NMR spectra of the later structure. These structures are also model compounds for the study of long-range ^{13}C–^{15}N and ^{13}C–^{13}C spin–spin interactions in NMR spectra [13c,16] and circular dichroism [7,17] (see Scheme 1).



1 **2**

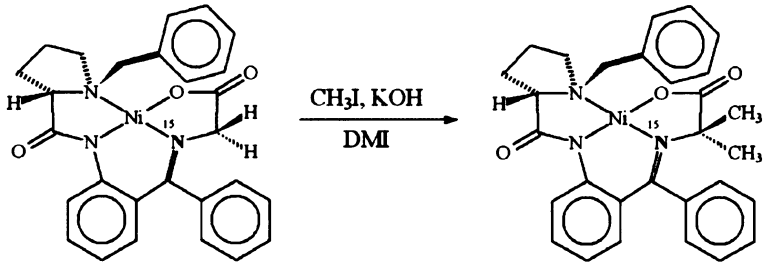
Scheme 1.

2. Experimental

Complex **1** was prepared according to Popkov et al. [13b]. The synthesis of ^{15}N-labelled complex **2**, (^{15}N)Me$_2$GK, was as follows (see also Reaction scheme). To a solution of the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and (^{15}N)glycine ((^{15}N)GK) (20 mg, 0.04 mmol), cf. Jirman et al. [16], in 1,3-dimethylimidazolidin-2-one (DMI, 1 ml) under an atmosphere of Ar at 20 °C, an excess of KOH and CH_3I (12.6 μl, 0.2 mmol) were added and the reaction mixture was stirred for 30 min. The reaction mixture was poured into 10% aqueous citric acid (30 ml), stirred and the resulting red suspension was filtered off and dried in air. The filter was dried and extracted with chloroform. The extract was evaporated in vacuo. (^{15}N)Me$_2$GK was purified by preparative TLC using silica gel (Merck 60H) eluted with CH_2Cl_2. The obtained complex was then purified by chromatography on Sephadex LH-20 with toluene:MeOH = 2:1 as red crystals. Yield: 15 mg (71% related to (^{15}N)GK), m.p. 212–217 °C (from acetone). Calculated mass for $C_{29}H_{29}N_2{}^{15}NO_3Ni$: $[M^+] = 526.1533$. High resolution FAB MS found $[M^+] = 526.1539$.

NMR spectroscopy: Bruker AMX 360, 23 °C, hexamethyldisiloxane ($\delta(^1H) = 0.05$ ppm) was used as an internal standard. Assigned ^{1}H NMR and ^{13}C NMR spectra for (^{15}N)Me$_2$GK are presented in Table 1.

X-ray analysis: Siemens SMART 1K CCD area detector diffractometer equipped with LT-2 low temperature device, using graphite-monochromated Mo Kα characteristic radiation ($\lambda = 0.71073$ Å). Data were collected at 173 K, with a crystal-to-detector distance 3.97 cm, ω-scans covering whole sphere of reciprocal space with



Reaction scheme.

Table 1
^{1}H and ^{13}C NMR chemical shifts (ppm) for (^{15}N)Me_2GK in $CDCl_3$ at 23 °C

Position	$\delta(^{1}H)$	$\delta(^{13}C)$	$J(^{15}N,^{13}C)$
1	2.06, 3.66	57.43	
2	2.13, 3.43	23.86	
3	2.46, 2.66	30.61	
4	3.46	69.99	
5		180.46	
6		141.31	1.1
7	7.92	123.96	
8	7.10	131.49	
9	6.62	120.71	
10	6.71	133.24	2.2
11		128.31	2.9
12		171.61	12.1
13		136.32	1.6
14	7.00	128.01	0.8
15	7.39	128.02	
16	7.43	127.14	
17	7.45	129.25	
18	7.28	130.16	1.0
19		74.55	2.7
20		182.49	4.1
21	3.60, 4.46	63.20	
22		133.41	
23	8.08	131.63	
24	7.39	128.03	
25	7.26	128.98	
26	7.39	128.03	
27	8.08	131.63	
28 (C-CH_3)	1.78	29.92	
29 (C-CH_3)	1.08	28.77	

steps of 0.3° [18a]. Data were corrected for absorption effects [18b]. The structures were solved by direct methods [18c] and refined by least-squares method on F^2 with H-atoms constrained to ideal geometries and riding on their respective pivot atoms [18c]. Graphics were produced by DIAMOND [18d].

Crystal data for complex **1**: $C_{27}H_{24}ClN_3NiO_3$, M_r 532.65, triangular red plate, crystal size (mm) = 0.60 × 0.60 × 0.30, monoclinic, space group $P2_1$, $a = 11.4695(1)$ Å, $b = 7.6323(1)$ Å, $c = 13.7066(2)$ Å, $\beta = 98.077(1)°$, $V = 1187.95(3)$ Å^3, $Z = 2$, $D_{calc} = 1.489$ g cm^{-3}, $\mu_{Mo} = 0.965$ mm^{-1}, $\theta_{max} = 32.78°$, $T_{min} = 0.6143$, $T_{max} = 0.7490$. 20736 measured, 8228 independent ($R_{int} = 0.0206$) and 8026 observed ($I > 2\sigma_I$) reflections, 340 parameters, $R_1 = 0.0265$ for observed and $wR(F^2) = 0.0714$ for all reflections, $S = 1.016$, $\Delta\rho_{max} = 0.483$, $\Delta\rho_{min} = -0.286$ e Å^{-3}.

Crystal data for complex **2**: $C_{29}H_{29}N_3NiO_3 \cdot 0.5H_2O$, M_r 535.27, red block crystal, size (mm) = 1.00 × 0.70 × 0.50, trigonal, space group $P3_121$, $a = 14.2295(1)$ Å, $b = 14.2295(1)$ Å, $c = 21.5928(1)$ Å in hexagonal cell, $V = 3786.33(4)$ Å^3, $Z = 6$, $D_{calc} = 1.408$ g cm^{-3}, $\mu_{Mo} = 0.807$ mm^{-1}, $\theta_{max} = 27.12°$, $T_{min} = 0.3113$, $T_{max} = 0.6683$. 45414 measured, 5579 independent ($R_{int} = 0.0728$) and 4778 observed ($I > 2\sigma_I$) reflections, 365 parameters, $R_1 = 0.0343$ for observed and $wR(F^2) = 0.0840$ for all reflections, $S = 0.978$, $\Delta\rho_{max} = 0.278$, $\Delta\rho_{min} = -0.296$ e Å^{-3}.

3. Results and discussion

Crystals of the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-benzylpyrrolidine-2-carboxamide and glycine (**1**) [GKCl], suitable for X-ray analysis, were obtained by slow evaporation of an acetone solution. Crystals of the Ni(II) complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and 2-aminoisobutiric acid (**2**) [Me_2GK] were grown by the same method. The numbering schemes for complexes **1** and **2** are shown in Figs. 1 and 2, respectively. X-ray structure analysis established unambiguously the absolute structure with Flack parameters [19] being −0.002(5) and −0.031(12), using 3738 and 2452 Friedel pairs for complexes **1** and **2**, respectively. Both complexes show nickel in a square-planar coordination geometry with small pyramidal distortions. In Table 2 we present a selection of bond distances, as well as some stereochemical data. We define the three chelate rings of complexes **1** and **2** as follows: the five-membered ring A is defined by atoms Ni/O2/C20/C19/N3, the six-membered ring B is defined by atoms Ni/N2/C6/C11/C12/N3 and the five-membered ring C is defined by atoms Ni/N1/C4/C5/N2. The conformations of these rings are indicated in Table 2 and they differ substantially between both complexes; while Me_2GK complex **2** adopts an asymmetric λ-envelope/asymmetric δ-boat/asymmetric λ-envelope conformation for rings A/B/C/, respectively,

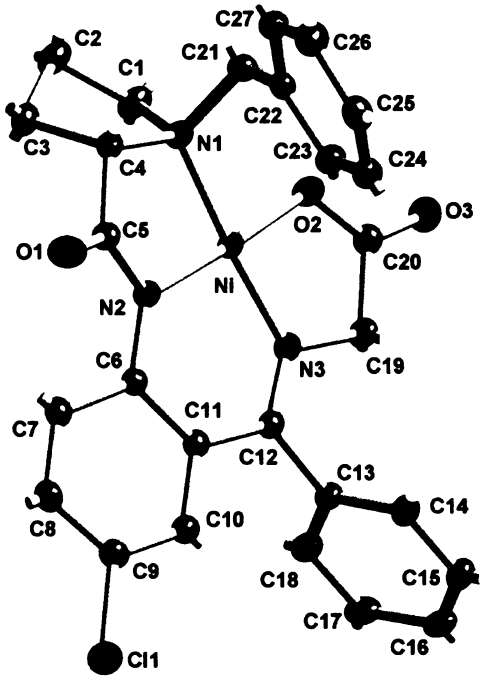


Fig. 1. The numbering scheme of 1 with atomic displacement ellipsoids drawn at the 50% probability level. H atoms are omitted for clarity and indicated by partial bonds only.

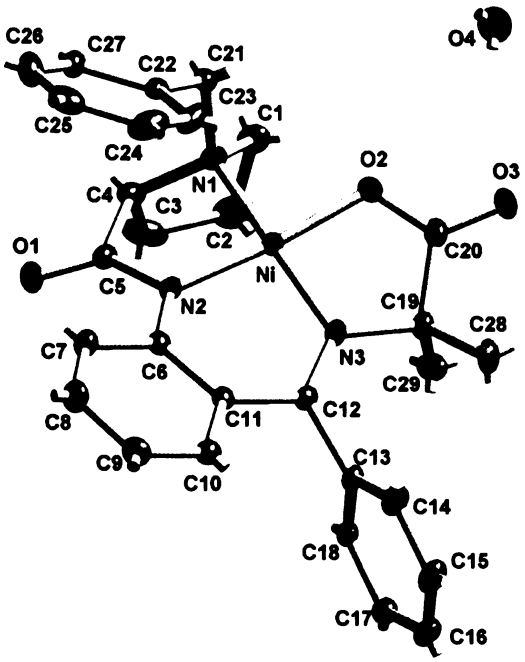


Fig. 2. The numbering scheme of **2** with atomic displacement ellipsoids drawn at the 30% probability level. H atoms are omitted for clarity and indicated by partial bonds only.

Table 2
Selected bond distances (Å) and angles (°) and some structural and stereochemical data

			Complex **1**	Complex **2**
Square-planar centre	Ni–N1		1.941(1)	1.949(2)
	Ni–N2		1.864(1)	1.848(2)
	Ni–N3		1.862(1)	1.880(2)
	Ni–O2		1.869(1)	1.843(2)
	N1–Ni–N2		88.03(4)	86.84(9)
	N2–Ni–N3		95.61(5)	96.69(9)
	N3–Ni–O2		87.52(4)	86.74(9)
	O2–Ni–N1		88.94(4)	90.71(9)
	N1–Ni–N3		175.60(5)	170.24(9)
	N2–Ni–O2		176.12(5)	173.27(9)
RMS deviations from plane			0.036	0.113
Ring A	Ni–O2–C20		116.04(9)	116.1(2)
	O2–C20–C19		114.8(1)	115.8(2)
	C20–C19–N3		109.9(1)	105.4(2)
	C19–N3–Ni		111.50(8)	110.0(2)
Deviation from plane NiN1O2[a]		C19	+0.209(2)	−0.859(4)
		C20	+0.107(2)	−0.358(4)
			asym. δ-env.	asym. λ-env.
Ring B	Ni–N3–C12		129.28(8)	125.4(2)
	N3–C12–C11		122.4(1)	121.3(2)
	C12–C11–C6		123.6(1)	124.0(2)
	C11–C6–N2		122.1(1)	120.4(2)
	C6–N2–Ni		126.09(8)	121.3(2)
Deviation from plane NiN2N3[a]		C12	+0.043(2)	+0.098(4)
		C11	−0.020(2)	+0.607(4)
		C6	−0.125(2)	+0.606(4)
			asym. λ-skew boat	asym. δ-boat
Ring C	Ni–N2–C5		113.73(8)	116.0(2)
	N2–C5–C4		113.1(1)	112.4(2)
	C5–C4–N1		111.08(9)	110.2(2)
	C4–N1–Ni		109.43(8)	106.3(2)
	N2–C5–O1		126.9(1)	127.6(3)
	Ni–N1–C21		113.71(8)	112.9(2)
Deviation from plane NiN1N2[a]		C5	+0.390(2)	−0.250(4)
		C4	+0.167(2)	−0.572(4)
			asym. δ-env.	asym. λ-env.

[a] The deviations are considered positive when the atom is on the same side as the benzyl group atoms (C21 to C27).

the complex GKCl (**1**) adopts an asymmetric δ-envelope/λ-skew boat/asymmetric δ-envelope conformation (for nomenclature see [20]). Thus complex **2** has a similar conformation to the [Ni((*S*)-BBP-L-Ser)] and [Ni((*S*)-BBP-L-aaIm)] complexes reported by Pessoa et al. [17], while complex GKCl (**1**) has a conformation somewhat similar to [Ni((*S*)-BBP-Gly)], reported by the same authors, but published earlier by us [13c,15].

We observed a π-charge delocalization, similar to the recently described structure of the Ni complex of the Schiff base of (*S*)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and (*S*)-2-amino-3-(1-naphthyl)propanoic acid [7], in the proximity of the N2 atom due to the free π-orbital of this nitrogen atom. The bonds {complex **1**: N2–C6 1.3968(16) Å, N2–C5 1.3910(15) Å; complex **2**: N2–C6 1.398(3) Å, N2–C5 1.371(3) Å} are shorter than the published [21] average value for the N–C(sp^2) bond {$d_{C-N} \approx 1.47(1)$ Å}. We also found a small deviation of the C5–O1 bond {complex **1**: 1.2299(15) Å, complex **2**: 1.230(3) Å} from the published [9] value of $d_{C=O} \approx 1.21(1)$ Å for ketones. The situation is less clear at the N3 atom {complex **1**: N3–C12 1.3059(16) Å, N3–C19 1.4838(16) Å; complex **2**: N3–C12 1.300(3) Å, N3–C19 1.509(3) Å}. These values are in good accordance with the average values for 17 similar structures [1f,14, Refs. [17,19,20,22–24] in 13c,22], namely 1.40(3) Å for N2–C6, 1.37(2) Å for N2–C5, 1.231(9) Å for C5–O1, 1.301(13) for N3–C12 and 1.48(2) Å for N3–C19.

The hydrogen bond schemes of the two complexes are different: complex GKCl (**1**) forms a chain along the *c*-axis (Fig. 3) via weak hydrogen bonds of C–H···O type (for details see Table 3), while the Me_2GK complex **2** forms dimers of molecules, mediated by a water molecule located at the crystallographic twofold axis, see Fig. 4.

In order to assign the ^1H NMR and ^{13}C NMR spectra, cross-peaks in 2D NOESY spectra due to a through-space interaction mechanism were obtained for neighbouring protons and, thus, such cross-peaks were found in analogous positions as those observed in the H,H-COSY spectrum based on coupling constants. Conformationally, the most important cross-peaks in the 2D NOESY spectra were found for pairs of resonances at δ 7.00/1.78,

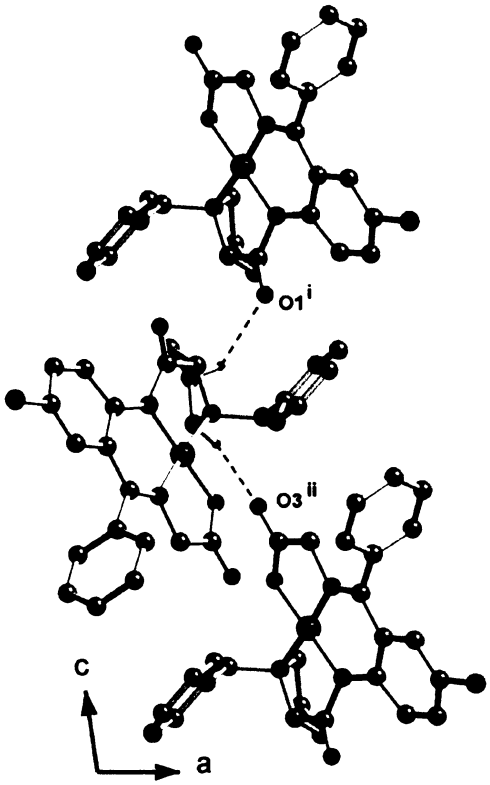


Fig. 3. The hydrogen-bonding pattern in the crystal lattice of **1**. Only H atoms taking part in the presented bonds are shown. For symmetry codes see Table 3. Chains of molecules parallel to c-axis are formed.

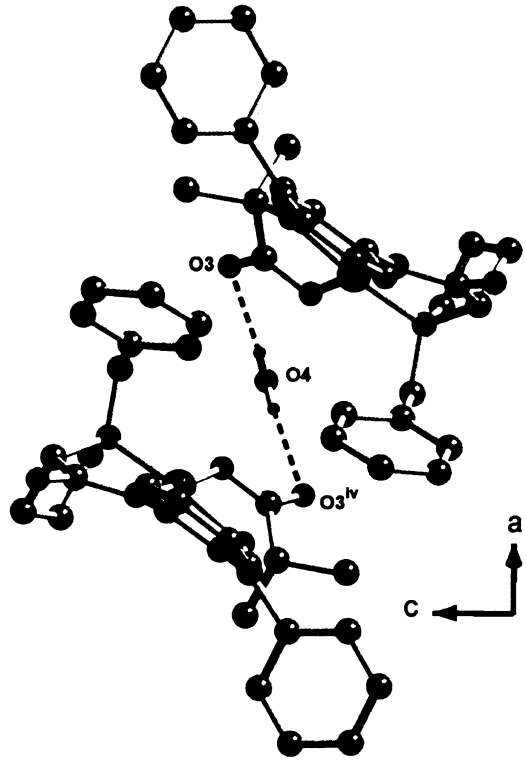


Fig. 4. The hydrogen-bonding pattern in the crystal lattice of **2**. Only H atoms taking part in the presented bonds are shown. Dimers of molecules are formed. Symmetry code: (iv) $-x, -x+y, 1/3-z$.

Table 3
Hydrogen-bonding geometry (Å, °) for GKCl complex (**1**) and Me_2GK complex (**2**)

D–H···A	D–H	H···A	D···A	D–H···A
Complex 1				
C2–H2A···O1^{i}	0.99	2.55	3.2946(17)	131.9
C7–H7···O1	0.95	2.25	2.7089(16)	108.5
C21–H21B···O2	0.99	2.38	2.9247(16)	113.8
C1–H1B···O3^{ii}	0.99	2.51	3.4824(19)	167.8
Complex 2				
O4–H4A···O3	0.79(4)	2.16(4)	2.942(3)	167(4)
C1–H1B···O2	0.99	2.32	2.893(4)	116.2
C7–H7···O1	0.95	2.27	2.807(3)	115.2
C21–H21B···O3^{iii}	0.99	2.58	3.506(4)	155.9
C28–H28B···O3	0.98	2.40	2.819(4)	105.0

Symmetry codes: (i) $2-x, 1/2+y, 2-z$; (ii) $2-x, 1/2+y, 1-z$; (iii) $-1-x+y, 1-x, z-1/3$.

7.28/1.08, 6.71/7.28, 4.46/3.46 and 8.08/3.46 ppm, corresponding to space proximity of protons H14/H28, H18/H29 (the assignment of these two pairs may be mutually interchanged since an absolute assignment is not clear), H10/H18, H4/H21 and H4/H23,27. From these experimental results it follows that the conformation of the Ni complex in solution should be the same as that in the solid state. Similarity of conformations in $CDCl_3$ solution and in the solid state was previously proved for a similar complex derived from glycine [13a,13b], in the case of the complex derived from (*S*)-2-amino-3-(1-naphthyl)propanoic acid, conformations in $CDCl_3$ solution and in the solid state are significantly different [7].

In complex **2**, the repulsion between the benzyl group and an equatorial methyl group affects the conformation of the benzyl group, distribution of π-electron density in this group and distortion of the internal coordination sphere. In strong contrast to the complex (^{15}N)GK [16] derived from non-substituted (^{15}N)glycine, long range through-space spin–spin interactions are not observed in ^{13}C and ^{15}N NMR spectra of complex **2** (Table 1). A longer distance from the benzyl group to the amino acid and the benzophenone fragments of the molecule is probably responsible for this absence of spin–spin interactions. In (^{15}N)GK, a partial positive charge of the nickel atom leads to polarisation of π-electron density of the benzyl group towards the nickel atom [15]. In several similar complexes, MP2 modelling followed by a topological analysis revealed the formation of weak covalent bonds between carbon atoms in the benzyl group and carbons in the benzophenone fragment or oxygen atoms of the carboxy residue [A. Popkov, M. Breza, unpublished results]. Both polarisation and the weak bond formation could be involved in long range through-space spin–spin interactions. In the complex **2**, these two factors do not play their role due to

a more distant position of the benzyl group compared to complex (^{15}N)GK.

Preparation of a labelled analogue of complex **1** from (^{15}N)glycine is underway.

Appendix A. Supplementary material

CCDC 294429 and 294430 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly.2006.09.103.

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V

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SYNTHESIS OF (*S*)-PROLINE DERIVATIVES WITH AN ALKYLATED N-BENZYL SUBSTITUENT. BENZYLATION OF (*S*)-INDOLINE-2-CARBOXYLIC ACID

A. N. Popkov

The synthesis is reported of (S)-proline derivatives which contain a 2,4,6-trimethyl-, 4-tert-butyl-, or pentamethylbenzyl substituent on the nitrogen atom. Under similar conditions the benzylation of indoline-2-carboxylic acid was unsuccessful. Treatment of indoline-2-carboxylic acid with benzyl chloride in the presence of KOH in dimethylacetamide gave the benzyl ester of N-benzylindoline-2-carboxylic acid which is unstable on light.

Keywords: N-benzylproline, proline, chiral synthon, asymmetric synthesis.

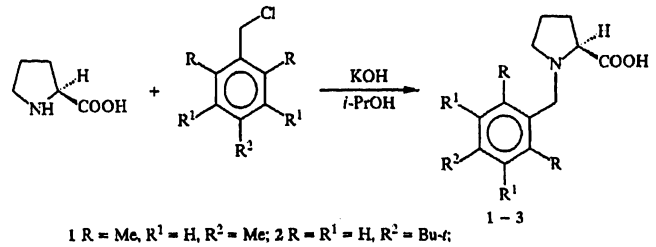
Tightening up of environmental standards has stimulated the development of highly selective catalysts for fine organic synthetic manufacture. In particular, they are of great interest for the synthesis of enantiomerically pure medicines with the aim of eliminating the side effects of the racemic form [1].

N-Benzylproline derivatives are used as chiral catalysts and chiral inductors in various reaction [2-9]. On the basis of a study of the conformation of several chiral synthons which contained an N-benzyl residue, a higher degree of asymmetric induction was anticipated for similar compounds containing substituents in the *ortho* positions of the benzyl group [10]. In this connection it was of interest to study N-benzylprolines substituted in the benzene ring as potential chiral inductors.

N-Benzylprolines, having alkyl substituents in the benzene ring have not been reported before. In this work we describe the synthesis of novel (*S*)-prolines which contain a 2,4,6-trimethyl-, 4-tert-butyl-, or pentamethylbenzyl substituent on the nitrogen atom (**1-3** respectively) and also the methyl esters of the first two amino acids (**4, 5** respectively). For the preparation of compounds **1-3** there was used a method previously reported for the example of the reaction of proline with benzyl chloride [11]. In this way, products **1-3** were synthesized in 32-60% yields (Scheme 1). The reaction conditions were not optimized. Methylation of the acids **1** and **3** with excess of diazomethane solution gave the corresponding esters **4** and **5** in quantitative yield. Compound **1** was used for the preparation of the recoverable chiral reagent (*S*)-2-[N-(2,4,6-trimethylbenzyl)prolyl]-aminobenzophenone, thus permitting the synthesis of (*S*)-[^{11}C]alanine with a 97% enantiomeric excess (e. e.) [12]. From the unsubstituted (*S*)-2-(N-benzylprolyl)aminobenzophenone the (*S*)-[^{11}C]alanine was obtained with 80% e. e.

Laboratory of Biomembranes, University of South Bohemia, Branisovska 31, Ceske Budejovice 37005 Czech Republic; e-mail: sasha@marvin.jcu.cz. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 625-628, May, 2000. Original article submitted January 12, 1998; revision submitted March 5, 1999.

Scheme 1



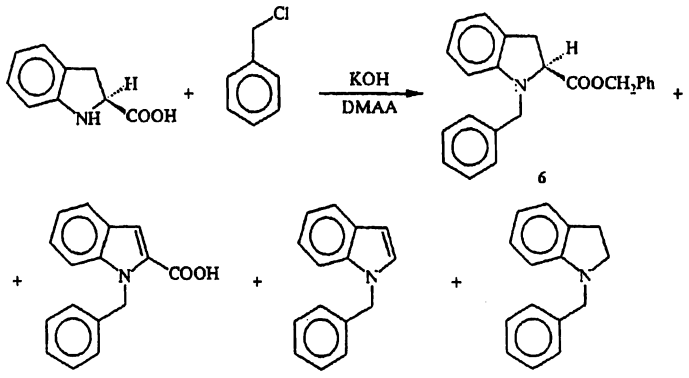
1 – 3

1 R = Me, R^1 = H, R^2 = Me; 2 R = R^1 = H, R^2 = Bu-*t*;
3 R = R^1 = R^2 = Me

We also studied the possible benzylation of a proline analog, indoline-2-carboxylic acid. The racemic ethyl ester of N-benzylindoline-2-carboxylic acid has previously been used for design of the skeleton of α_{12}-adrenoblockers [14]. However, the material obtained by reduction of the corresponding indole-2-carboxylic acid was used without separation in a reaction with the trimethylaluminium ethylenediamine complex. Hence no kinds of parameters were presented for the compound.

The reaction of indoline-2-carboxylic acid with benzyl chloride in the conditions reported in [11] did not lead to N-benzylindoline-2-carboxylic acid. Using a similar reaction in dimethylacetamide (DMAA) we obtained the benzyl ester of N-benzylindoline-2-carboxylic acid (**6**) in 23% yield (according to chromato-mass spectrometry) based on the identified compounds with an indoline / indole skeleton (see Scheme 2). The content of product **6** in neutral chloroform solution in the reaction mixture decreased to 11% over 16 h at + 4°C. The ester is light sensitive and can be used with difficulty on a preparative purposes as an intermediate compound. This is in agreement with published data concerning the light sensitivity of N-benzylindoline [15]. Attempts to lower it by addition of base or acid or removal of solvent proved unsuccessful. A chloroform solution of compound **6** or an amorphous powder prepared by addition of dry ether to this solution became intensely purple or violet in color.

Scheme 2



EXPERIMENTAL

Analytical samples of the synthesized compounds were prepared using preparative TLC on silica gel (methylchloroform–acetone gradient from 10 : 1 to 2 : 1). ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer using $CDCl_3$ solvent and TMS internal standard. Optical rotations were measured on a Schmidt-Haenich Polatronic NH 8 polarimeter using a 5 cm cuvette. Chromato-mass spectra were obtained on a Kratos MS25RFA instrument (70 eV) combined with a Hewlett-Packard 5890 capillary gas chromatograph using an

Ultra-2 column (25 m × 0.22 mm, 5% loading, phenylmethyl silicone, layer thickness 0.11 mm). The sample was introduced into the column. Ionization current 100 μA. Low resolution ($R_{10\%}$) = 600, calibration 28-480 daltons. The temperature of the ion source, the column inlet into the ion source and the injector were 220°C and the temperature program 2 min at 80°C followed by 10°C / min to 280°C.

High resolution mass spectra were obtained on a VG analytical ZAB-SEQ instrument.

(*S*)-Proline derivatives (1-3) were synthesized by a known method [11]. The substituted benzyl chloride (100 mmol) was added to a solution of (*S*)-proline (11.6 g, 100 mmol) and KOH (14 g, 250 mmol) in isopropanol (250 ml) over 30 min with vigorous stirring at 60°C. The reaction mixture was then stirred for 30 min and evaporated in vacuo. Water (50 ml) was added to the residue which was filtered, 10% HCl added with stirring to the filtrate to pH 6-7, and the precipitate formed was washed on the filter with water (200 ml) and dried in vacuo. The dry precipitate was dissolved in a minimum amount of MeOH at 40-50°C, filtered, and added dropwise to diethyl ether (500 ml) with vigorous stirring. The precipitated product **1-3** was then washed on the filter with diethyl ether (200 ml) and dried in vacuo.

(*S*)-N-(2,4,6-Trimethylbenzyl)proline (1). Yield 41%; mp 150-152°C. $[\alpha]_{576}^{25}$ = -44°, $[\alpha]_{546}^{25}$ = -40° (*c*. 0.005, $CHCl_3$). ^1H NMR spectrum: 1.90-3.70 (6H, m, H_{pro}); 2.23 (3H, s, 4-CH_3); 2.41 (6H, s, 2- and 6-CH_3); 4.00-4.20 (1H, m, α -H_{pro}); 4.36 and 4.52 (2H, AB, *J* = 13.6 Hz, $\underline{CH_2}$-Ar); 6.89 ppm (2H, s, H_{Ar}). Found: $[M+H]^+$: 248.1613 (FAB-MS). $C_{15}H_{21}NO_2$. Calculated 248.1651.

(*S*)-N-(4-tert-Butylbenzyl)proline (2). Yield 32%; mp 171-173°C. $[\alpha]_{576}^{25}$ = -24°, $[\alpha]_{546}^{25}$ = -32° (*c*. 0.005, $CHCl_3$). ^1H NMR spectrum: (9H, s, $-C(CH_3)_3$); 1.90-3.70 (6H, m, H_{pro}); 3.95-4.10 (1H, m, α-H_{pro}); 4.33 and 4.45 (2H, AB, J = 12.8 Hz, $\underline{CH_2}$-Ar); 7.41 ppm (4H, s, H_{Ar}). Found $[M+H]^+$: 262.1776 (FAB-MS). $C_{16}H_{23}NO_2$. Calculated 262.1807.

(*S*)-N-(Pentamethylbenzyl)proline (3). Yield 60%; mp 142-146°C. $[\alpha]_{576}^{25}$ = -39°, $[\alpha]_{546}^{25}$ = -47° (*c*. 0.005, $CHCl_3$). ^1H NMR spectrum: 1.95-3.6 (6H, m, H_{pro}); 2.22 (6H, s, 3- and 5-CH_3); 2.24 (3H, s, 4-CH_3); 2.42 (6H, s, 2- and 6-CH_3); 3.40-3.60 (1H, m, α-H_{pro}); 4.30 and 4.35 ppm (2H, AB, *J* = 7.0 Hz, $\underline{CH_2}$-Ar). Found $[M+H]^+$: 276.1888 (FAB-MS). $C_{17}H_{25}NO_2$. Calculated 276.1963.

The methyl ethers of the substituted (*S*)-prolines **4** and **5** were prepared by a known method [16] by treatment of compounds **1** and **2** with an excess of diazomethane solution in diethyl ether.

Methyl Ester of (*S*)-N-(2,4,6-Trimethylbenzyl)proline (4). Yield ~ 100%; oil. ^1H NMR spectrum: 1.70-3.80 (7H, m, H_{pro}); 2.24 (3H, s, 4-CH_3); 2.36 (6H, s, 2- and 6-CH_3); 3.59 (3H, s, OCH_3); 3.63 and 3.82 (2H, AB, *J* = 12.5 Hz, $\underline{CH_2}$–Ar); 6.81 ppm (2H, s, H_{Ar}). Found M^+: 261.1642 (EI-MS). $C_{16}H_{23}NO_2$. Calculated: 261.1729.

Methyl Ester of (*S*)-N-(4-Tert-butylbenzyl)proline (5). Yield ~ 100%. Oil. ^1H NMR spectrum: 1.30 (9H, s, 3-CH_3); 1.70-3.70 (7H, m, H_{pro}); 3.62 (3H, s, OCH_3); 3.62 and 3.88 (2H, AB, *J* = 13.4 Hz, $\underline{CH_2}$–Ar); 7.10-7.50 ppm (4H, m, AA'BB', H_{Ar}). Found M^+: 275.1865 (EI-MS). $C_{17}H_{25}NO_2$. Calculated: 275.1885.

Benzyl Ester of N-Benzylindoline-2-carboxylic Acid (6). Benzyl chloride (2 ml, 17.4 mmol) was added dropwise with vigorous stirring over 30 min at 60°C to a solution of N-benzylindoline-2-carboxylic acid (1 g, 6.13 mmol) and KOH (2 g, 35.7 mmol) in DMAA (15 ml) which had been placed in a flask covered by black paper with the whole under an argon atmosphere. The reaction mixture was stirred for 30 min, an aqueous solution of citric acid (20%, 70 ml) added, and the product extracted with chloroform (3 × 10 ml). The combined extract was immediately analyzed by chromato-mass spectrometry. The mass spectrum identified product **6** (13.3%) in the mixture with *m/z*: 344 (M^+), 10.208 ($M-COOCH_2C_6H_5^+$), 63.91 ($CH_2C_6H_5^+$) 100. The remaining components of the mixture were, %: N-benzylindoline 3.6, N-benzylindole 22.1, N-benzylindole-2-carboxylic acid 1.1, benzyl chloride 19.7, and benzyl alcohol 33.3.

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VI

Transition Metal Chemistry **27**: 884–887, 2002.

Chiral nucleophilic glycine and alanine synthons: nickel(II) complexes of Schiff bases of (*S*)-*N*-(2,4,6-trimethylbenzyl)proline (2-benzoylphenyl)amide and glycine or alanine

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Abstract

A new chiral auxilliary, (*S*)-*N*-(2,4,6-trimethylbenzyl)proline (2-benzoylphenyl)amide, has been synthesised as a potential building block for the preparation of chiral synthons of amino acids. The nickel(II) complex of its Schiff base derivative with glycine has been methylated with 97% d.e. (diastereomeric excess), whilst the nickel(II) complex of its Schiff base derivative with (*RS*)alanine has been ^{13}C-methylated with 66% d.e.

Introduction

In spite of the fact that the development of catalytic asymmetric synthesis of α-amino acids is necessary for multi-ton industrial production [1–6], stoichiometric chiral synthons [7–13] are still in use for special applications such as preparation of labelled amino acids. Our efforts in this area have concentrated on nickel(II) complexes of Schiff bases of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide (**BPB**) and α-amino acids [14–20]. Two groups reported several attempts to increase asymmetric induction by the complexes by introducing various substituents into the benzyl group [21–23], but these experiments met with little success. Previously, we used a combination of solution n.m.r. [24], solid state n.m.r., X-ray crystallography [25] and DFT calculations [26] to disclose the nature of the asymmetric induction achieved with chiral nickel complexes. In this communication a successful design of a stereospecific glycine synthon and a stereoselective alanine synthon is described.

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Experimental

^{1}H- and ^{13}C-n.m.r. spectra were recorded on a Bruker AMX 360 spectrometer using TMS as internal standard. High-resolution EI-mass spectra were recorded on a Finnigan MAT 90 spectrometer.

Preparation of (2)

$SOCl_2$ (0.95 cm^3, 13.2 mmol) was added dropwise to a stirred suspension of (*S*)-*N*-(2,4,6-trimethylbenzyl)proline [27] (2.13 g, 8.62 mmol) in CH_2Cl_2 (20 cm^3) at −78 °C. The reaction mixture was warmed to −5 °C for 10 min, then cooled to −78 °C and a solution of 2-aminobenzophenone (2.24 g, 11.4 mmol) in CH_2Cl_2 (20 cm^3) was added dropwise. The mixture was warmed to +5 °C, stirred for 30 min, quenched with 15% aqueous Na_2CO_3 (15 cm^3) and extracted with CH_2Cl_2 (30 × 30 cm^3). Combined extracts were evaporated *in vacuo* and were used for the next step without purification.

Under an atmosphere of Ar, a suspension of glycine (1.5 g, 20 mmol) in 2 N MeONa/MeOH (50 cm^3) was added dropwise to a stirred solution of the product from the previous step and $Ni(NO_3)_2 \cdot 6H_2O$ (1.16 g, 4 mmol) in MeOH (30 cm^3) at 50 °C. After 30 min the reaction mixture was poured into 5% aqueous citric acid (200 cm^3), stirred and extracted with CH_2Cl_2 (4 × 50 cm^3). Combined extracts were evaporated *in vacuo* and the residue was purified by chromatography

on silica gel with CH_2Cl_2. The first red fraction containing the reaction product was collected. The obtained complex *(2)* was then purified by chromatography on Sephadex LH-20 with toluene: MeOH = 2:1 as a red, non-crystalline solid. Yield: 137 mg (3%). ^{1}H-n.m.r. (360.13 MHz, $CDCl_3$): 8.20 (d, 1H), 7.45 (m, 3H), 7.20 (t, 1H), 7.08 (d, 1H), 6.91 (m, 1H), 6.82 (s, 2H), 6.79 (d, 1H), 6.68 (t, 1H), 4.87 (d, 1H) and 4.21 (d, 1H) (AB system of $-CH_2Ar$, ^2J(H, H) = 14.1 Hz), 3.76 (d, 1H) and 3.63 (d, 1H) (AB system of $-CH_2COO-$, ^2J(H, H) = 20.2 Hz), 3.44 (m, 1H), 3.32 (m, 2H), 3.00–2.20 (very broad signal of two methyl groups, 6H), 2.70 (m, 1H), 2.34 (m, 1H), 2.14 (s, 3H), 2.00 (m, 1H), 1.84 (m, 1H). High-resolution EI-MS (70 eV): for $C_{30}H_{31}N_3O_3Ni$ $[M]^+$ calcd. 539.1711, obs. 539.1710.

Preparation of (3)

Complex *(3)* (10 mg) was prepared in the same way as described for complex *(2)*, starting from racemic alanine instead of glycine. ^{1}H-n.m.r. (360.13 MHz, $CDCl_3$): 8.02 (d, 1H), 7.44 (m, 3H), 7.20 (m, 2H), 6.90 (m, 1H), 6.80 (m, 2H), 6.63 (s, 2H), 4.66 (d, 1H) and 3.99 (d, 1H) (AB system of $-CH_2Ar$, ^2J(H, H) = 14.3 Hz), 3.88 (q, ^3J(H, H) = 8.7 Hz, 1H), 3.68 (m, 1H), 3.32 (m, 2H), 3.06 (broad s, 3H), 2.92 (m, 1H), 2.48 (m, 1H), 2.37 (broad s, 3H), 2.13 (m, 1H), 2.11 (broad s, 3H), 1.88 (m, 1H), 1.53 (d, ^3J(H, H) = 8.7 Hz, 3H). High-resolution EI-MS (70 eV): for $C_{31}H_{33}N_3O_3Ni$ $[M]^+$ calcd. 553.1875, obs. 553.1889.

Methylation of alanine synthons by $^{13}CH_3I$

At 20 °C to a 0.05 M solution of a complex, an excess of KOH and a fivefold excess of $^{13}CH_3I$ were added and the reaction mixture was stirred for 30 min. Yields are quantitative. Diastereomeric excess (d.e.) calculations were based on the ratio of the integral intensities of the $^{13}CH_3$-signals in the ^{13}C-n.m.r. spectra of the mixtures of the diastereomers;

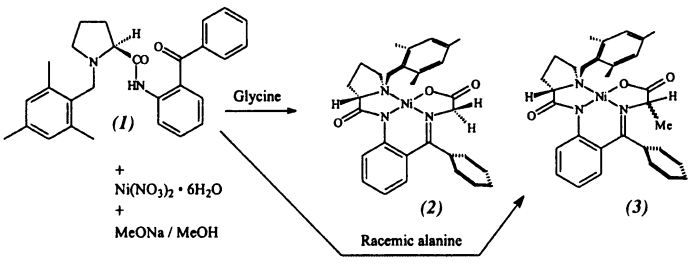
$$\text{D.e.} = 100\text{–}200(a[S,R]/[S,S]^* - b)/(a - b) \times (1 + [S,R]/[S,S]^*)$$

where $[S, R]/[S, S]^*$ is the ratio of the integral intensities of the ^{13}C-signals of the diastereomers: a is the abundance of ^{13}C in starting $^{13}CH_3I$; b is the natural abundance of ^{13}C.

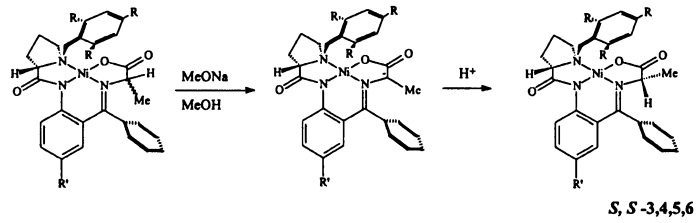
Results and discussion

Two factors were identified which might be used for creating synthons with higher asymmetric induction, as follows. The first concerns the conformations of the complexes. Based on NOE interactions, it was found that the *ortho* protons of the benzyl group are situated closest to the =N—CHR—CO— fragment of the complex [24]. Hence, we hypothesise that the degree of asymmetric induction of these nickel complexes can be improved by increasing the steric hindrance of the benzyl group through the introduction of methyl substituents in the *ortho*-positions. The second factor concerns the donation of electron density from the π-system of the benzyl ring to nickel orbitals. We inferred such a donation of electrons in complex *(4)* (see Scheme 2). Quantum chemical calculations confirmed a weak interaction, which reduces the distance between the plane of the benzyl group and the nickel atom [26]. This effect influences the stereochemical result of alkylation of the complexes under thermodynamically controlled conditions. In addition, two examples supporting our hypothesis can be found in the literature: the replacement of the benzyl group in the complex by an electron-rich naphthylmethyl group led to higher asymmetric induction [21], whereas the replacement of the benzyl group by various picolyl groups in many cases decreased the induction [23]. We therefore hypothesised that the distance of the benzyl group to the nickel atom will be reduced by the introduction of alkyl substituents in any position on the benzyl group. Replacement of the *N*-benzyl group by an *N*-(2,4,6-trimethylbenzyl) group should also result in steric hindrance of 'ring-edge' bonding (between the η^2-bonded aromatic ring and the metal atom), compared to 'ring-centre' bonding where the 2,4,6-trimethylbenzyl group is a η^6-ligand. The polyalkyl-substituted benzyl group may also increase steric hindrance with respect to alkylation of the α-carbon of the glycine or the alanine fragment, thereby enhancing the diastereoselectivity of the reaction.

Based on this reasoning, we prepared auxilliary (*S*)-*N*-(2,4,6-trimethylbenzyl)proline (2-benzoylphenyl)amide



Scheme 1. Template synthesis of *(2)* and *(3)*.



Scheme 2. Retroracemisation of alanine complexes; thermodynamic control.

(1), starting from (*S*)-*N*-(2,4,6-trimethylbenzyl)proline [27], for the synthesis of sterically hindered nickel complexes *(2)* and *(3)* (Scheme 1). In our hands, the only successful method for amide bond formation to give *(1)*, was *via* activation of the carboxylic acid with thionyl chloride.

In order to evaluate these potential chiral auxiliaries, two model sequences were created for both thermodynamic and kinetic control of alkylation diastereoselectivity, as follows. Monoalkylation of glycine synthons led to complexes containing α-alkylglycine residues (for example, α-alanine residue in case of monomethylation) [28]. The diastereomeric purity of the resulting complexes depends on the reaction conditions used. Two hours equilibration of any monomethylated complex in 1 M NaOMe/MeOH at 22 °C led to thermodynamically controlled ratios of the diastereomers regardless of the starting diastereomeric ratio. The same equilibration conditions were applied to the previously described complex *(4)*, new complex *(3)* and two analogs of the complex *(4)* bearing an electron-donating or electron-withdrawing substituent, available to us from previous work *(5)* and *(6)* (Scheme 2) [29]. The observed diastereoselectivities (Table 1) support our hypothesis. Thus, the complex containing two *ortho*-methyl groups and one *para*-methyl group *(3)*, providing both donate electron density to nickel orbitals, and steric hindrance, led to almost exclusive formation of the *S,S*-*(3)* diastereomer.

Alkylation of the alanine complexes led to the corresponding α-methyl-α-amino acid complexes *(7)*–*(9)* (Scheme 3). As these new complexes contain no α-proton, the stereochemistry of the amino acid fragment's α-carbon is controlled kinetically [28]. Methylation with $^{13}CH_3I$ in 1,3-dimethyl-imidazolidin-2-one (DMI) (Scheme 3, Table 2) has been chosen as the most challenging model reaction (the methyl iodide molecule is relatively small, and the observed diastereoselectivity of methylation is lower than in alkylation by bulkier electrophiles). Chromatographic purification of the methylated products on silica gel should not affect the ratio of the diastereomers because $^{12}CH_3$ and $^{13}CH_3$ are chromatographically undistinguishable.

Complex *(2)* has been used for stereospecific preparation of [^{11}C]alanine for positron emission tomography [30].

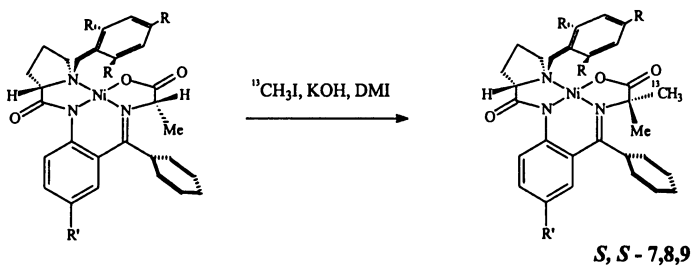
Table 1. Epimerisation of alanine complexes in 1 M MeONa/MeOH; thermodynamic control

Complex	*(3)*	*(4)*	*(5)*	*(6)*
R	Me	H	H	H
R′	H	H	Me	Cl
D.e. of the *S, S* diastereomer (%)[a]	97	83	83	86

[a] D.e.'s were determined by integration of ^{1}H-n.m.r. spectra of the mixtures of the diastereomers.

Table 2. Asymmetric induction of methylation of alanine synthons by $^{13}CH_3I$; kinetic control

Complex	*(3)* → *(7)*	*(4)* → *(8)*	*(5)* → *(9)*
R	Me	H	H
R′	H	H	Me
D.e. of the *S, S* diastereomer (%)	66	43	41



Scheme 3. Methylation of alanine complexes; kinetic control.

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VII

ASYMMETRIC SYNTHESIS OF (*S*)-2-AMINO-3-(1-NAPHTHYL)PROPANOIC ACID VIA CHIRAL NICKEL COMPLEX. CRYSTAL STRUCTURE, CIRCULAR DICHROISM, ^{1}H AND ^{13}C NMR SPECTRA OF THE COMPLEX

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The recently published environmentally friendly preparation of a glycine synthon **2** from regeneratable chiral auxiliary **BPB** ((*S*)-*N*-(2-benzoylphenyl)-*N'*-benzylprolinamide) was used for preparative asymmetric synthesis of the non-coded amino acid 3-(1-naphthyl)alanine (**1**). Full assignment of ^{1}H and ^{13}C NMR of both intermediate complex **3** and **1** and X-ray structure determination of complex **3** were made. Cotton effects observed in circular dichroism spectrum of complex **3** are consistent with published empirical rules.

Keywords: Amino acids; Biomimetic synthesis; BPB; Circular dichroism; Chiral auxiliaries; Crystal structure determination; Naphthylalanine; Nickel; NMR spectroscopy; Schiff bases.

Heavy environmental impact of waste-water and by-products released by chemical and pharmaceutical industry requires development of new "green" synthetic procedures for manufacture of active pharmaceutical intermediates. Efficient catalytic approaches have been suggested for a big number of α-amino acids[1]. Development of such catalytic syntheses often requires time-consuming screening for an optimal catalyst, precursor and reaction conditions. Chiral stoichiometric α-amino acids synthons are often the optimal choice for preparation of small batches of new α-amino acids and for special application like preparation of radiolabeled α-amino ac-

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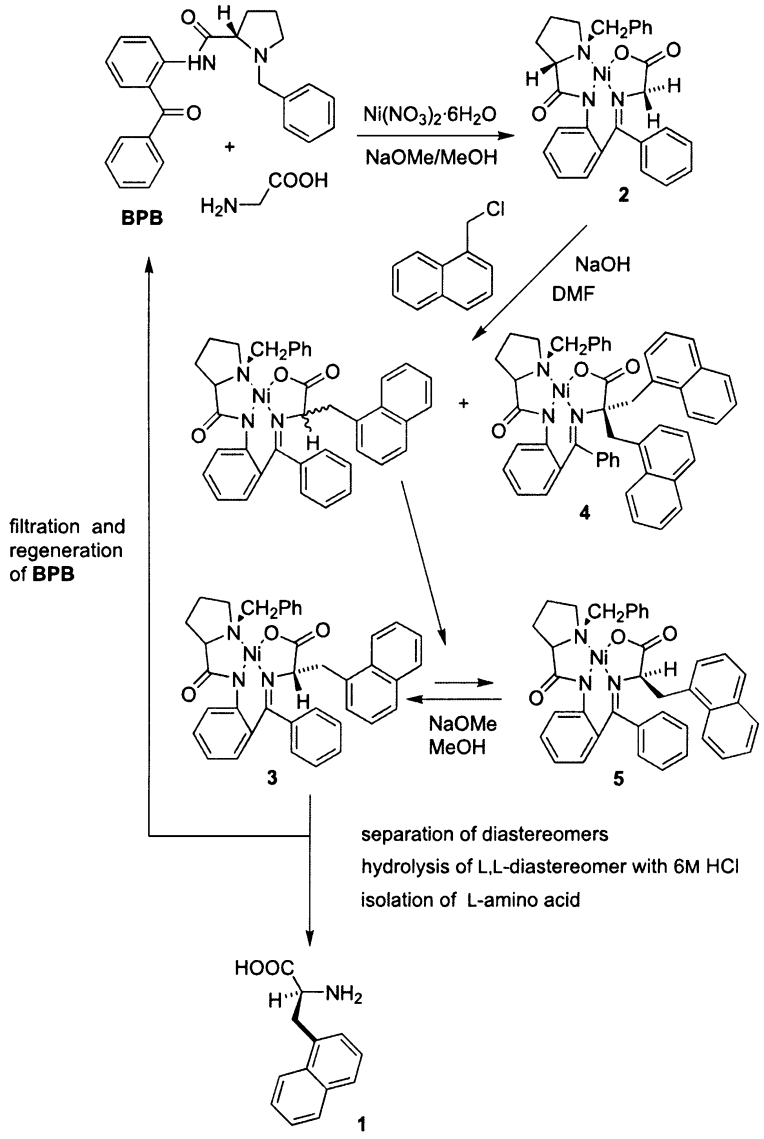
ids[2]. Many stoichiometric approaches lead to destruction of a chiral auxiliary used. A synthetic pathway employing chiral nickel complexes prepared from α-amino acids and chiral auxiliary **BPB** ((*S*)-*N*-(2-benzoylphenyl)-*N'*-benzylprolinamide) is an exception. After preparation of desired α-amino acid, enantiomerically pure **BPB**·HCl is regenerated in high yield (>90%)[3]. The complexes provide easy generation of intermediate carbanion due to high acidity of α-hydrogen of an amino acid fragment ($pK_a \geq 19$)[4]. Unlike many other chiral synthons, they enable asymmetric synthesis of substituted prolines from α,β-unsaturated aldehydes and ketons via 1,4-addition followed by hydrolysis of a complex and reduction of C=N bond[5]. Another unique feature of the complexes is a bis-alkylation of the glycine synthon with CH_2Cl_2 followed by hydrolysis which lead to enantiomerically pure (*S,S*)-2,4-diaminoglutaric acid. This diamino dicarboxylic acid has been prepared by a number of multistep syntheses[6]. Based on known alkylation of the glycine synthon with CH_2Br_2 [7], we developed a very simple approach for bis-alkylation of a glycine synthon where CH_2Cl_2 was used both as an alkylating agent and as a solvent[8]. Recently, a preparative modification of this synthesis was published[9]. Complex of enantiomerically pure (*S,S*)-2,4-diaminoglutaric acid could be also prepared by one-pot reaction of **BPB** with nickel nitrate and *S*-(2-aminoethyl)cysteine in MeONa/MeOH [10]. In this article we describe a preparative asymmetric synthesis of non-coded amino acid 3-(1-naphthyl)alanine ((*S*)-2-amino-3-(1-naphthyl)propanoic acid; **1**) (Scheme 1), full assignment of ^1H and ^{13}C NMR spectra of both the intermediate complex **3** and amino acid **1**, a comparison of X-ray structures of single crystals of glycine synthon **2** and complex **3** and circular dichroism spectra of their methanolic solutions. The synthesis applies a recently published environmentally friendly preparation of the starting metallocomplex glycine synthon **2** (Scheme 2)[11-13].

Preparative applications of the synthon were developed by several groups[14]. Most of the syntheses described in the literature deal with amino acids soluble in water in a wide pH range. This specific property requires sorption–desorption on a cation-exchange resin for separation of amino acid and nickel cations present in aqueous solution after hydrolysis of a single diastereomer of an alkylated complex. Amino acid **1** is not water-soluble at pH 7. The isolation procedure used in this work thus could be considered a model approach for isolation of highly lipophilic amino acids (for another example, see ref.[15]). Earlier we fully assigned NMR spectra of several similar complexes bearing H, NMe_2 or Br substituents on the α-carbon atom on amino acid fragment (C-19)[16]. The spectra of compound **3** (presented here) are more complex due to overlap of a number of aromatic hydrogen

and carbon signals. X-ray structure determination of complex **3** followed by its comparison with the published structure of the starting synthon **2** [17] aimed at deeper understanding of intra- molecular interactions affected

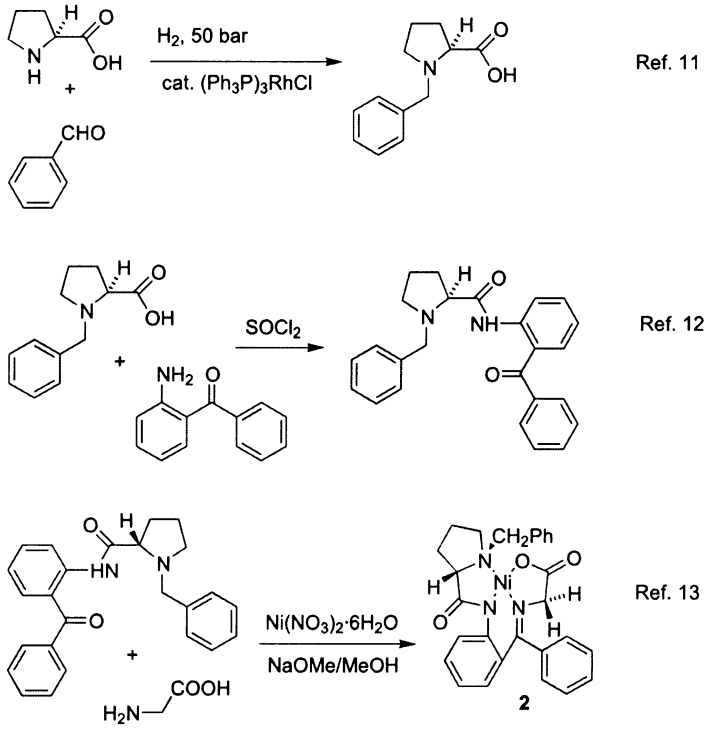


SCHEME 1
Synthesis of **1**

stereochemical outcome of alkylation of complex **2**. Although naphthylalanine **1** is a steric analogue of L-tryptophan, it is a poor substrate for tryptophan decarboxylases, deaminases and hydroxylases. When tryptophan is replaced by naphthylalanine in a peptide, amide bonds formed by naphthylalanine are much more stable to enzymatic transformations. This non-coded amino acid is manufactured by a number of vendors for design of peptidomimetic drug candidates[18].

RESULTS AND DISCUSSION

The most common application of nickel complexes as chiral amino acids synthons consists of several standard steps (Scheme 1): (i) Template preparation of the starting complex **2** from glycine, nickel salt and re-usable chiral auxiliary **BPB**. (ii) Alkylation of complex **2** with an electrophile (1-(chloromethyl)naphthalene in our case) in an aprotic solvent. (iii) Retro-



SCHEME 2
Preparation of complex **2**

racemisation of the reaction mixture in MeONa/MeOH [19]. (iv) Separation of diastereomers of the alkylated complex **3** and **5**, starting complex **2** and a minor amount of a product of bis-alkylation **4**. (v) Optional retroracemisation of the undesired diastereomer **5** in MeONa/MeOH. (vi) Acid hydrolysis of diastereomerically pure complex **3**, isolation of the amino acid and regeneration of **BPB**.

Preparation of the starting complex was optimised in order to reduce the amount of nickel in aqueous-organic waste[13]. The alkylation reaction was performed under heterogeneous conditions employing minimum amount of (toxic) aprotic solvent DMF. High concentrations of reagents increase the speed of the reaction. Stereochemistry of alkylation of such complexes in aprotic solvents is usually kinetically controlled. In order to increase the diastereomeric purity of the alkylated complex, the thermodynamically controlled retroracemisation in MeONa/MeOH should be used for the crude alkylation product[19]. In thermodynamically controlled conditions diastereomeric excess of the desired L,L-diastereomer is favored by repulsion between *ortho*-protons of the benzyl group and equatorial substituents of C-19 [16a]. For separation of predominant diastereomer, flash chromatography of retroracemised crude product was applied. L,L-Configuration of the main product was confirmed by X-ray structure determination taking into account L-configuration of **BPB** [17]. Circular dichroism (CD) spectra were employed for routine determination of configuration at C-19. The difference between CD spectrum of complex **2** and those of alkylated complexes (e.g. complexes **3**–**5**) is due to chromophore distortion introduced by C-19 substituents. In the case of bulky naphthalen-1-ylmethyl substituent the difference is very significant (Fig. 1, solid line corresponds to **3**, dashed line corresponds to **2**). In good agreement with the previously published empirical rules[19,20], methanolic solution of complex **3** demonstrates a positive Cotton effect in the range 610–480 nm and a negative Cotton effect in the range 370–480 nm. Retroracemisation decreased the amount of L,D-diastereomer **5** (nickel complex of a Schiff base of (*R*)-2-amino-3-(1-naphthyl)-propanoic acid and **BPB**) to far less than 1% in crude reaction mixture. Attempts to isolate **5** by preparative TLC on silica gal failed. High-melting complex **4**, the only by-product resulting from bis-alkylation of C-19 (nickel complex of the Schiff base of bis(1-naphthylmethyl)glycine and **BPB**), was isolated in 1% yield only. After hydrolysis of **3**, filtration of **BPB**·HCl, and adjusting pH to 9–10, amino acid **1** was filtered off (Scheme 1). The amino acid could be used for preparation of protected derivatives for peptide synthesis[18] without additional purification. Analytical sample was recrystallised from water–ethanol.

Recrystallised recovered **BPB** was re-used for preparation of **2** thus justifying biomimetic, enzyme-like character of this synthetic approach. We assume that chromatographic purification of **3** is not necessary for high-scale preparation of **1**. After retroracemisation the mixture of complexes (**3** and negligible amounts of **4** and **5**) could be hydrolysed followed by one or two crystallisations of amino acid **1** in order to remove traces of D-enantiomer and bis(1-naphthylmethyl)glycine.

NMR Spectroscopy

The ^{1}H and ^{13}C chemical shifts were assigned using gs (gradient selected)-H,H-COSY, 1D-gs-NOESY, gs-HSQC (optimised for $^{1}J(^{13}C,^{1}H) \approx 160$ Hz) and gs-HMBC (optimised for $^{3}J(^{13}C,^{1}H) = 7$ Hz). H,H-COSY provided us with proton-proton connectivity and 1D-gs-NOESY showed the through-space interaction of amino acid protons H-32 and H-34. The ^{13}C chemical shifts assignment was straightforward using HSQC and HMBC spectra[21,22].

Main arguments for assignment of some crucial signals and space direction of some atoms of complex **3** (for NMR numbering, see Fig. 2) are:

Protons H-4, H-19 and ortho protons of benzyl group (H-23 and H-27) have NOESY cross-peaks. It means they have to be on upper site of the com-

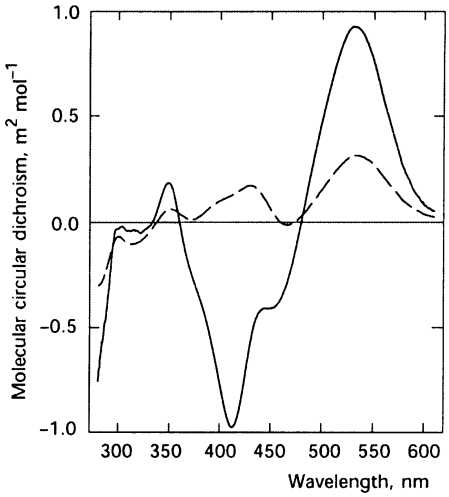


FIG. 1
Circular dichroism spectra of methanolic solutions of complexes **2** (dashed line) and **3** (solid line)

plex plane and benzyl group is rotated towards H-19. Proton H-37 of naphthalene ring has a NOESY cross-peak with H-18 proton. Proton H-37 of naphthalene ring has a NOESY cross-peak with proton H-19 and both methylene protons H-28. Proton H-19 has a NOESY cross-peak with naphthalene ring protons H-36 and H-37. There are positive cross-peaks in NOESY TPPI spectrum between pairs of protons H-14 and H-18 and H-15 and H-17. It means slow rotation of phenyl ring around the bond C-12/C-13. Such rotation has been observed in similar complexes[16a]. H-19 and H-28a should be closer through space then H-19 and H-28b because there exists bigger cross-peak in first pair in NOESY spectrum. It corresponds with its coupling constants that in case of pair H-19/H-28b shows higher dihedral angle of bonds C-19/H-19 and C-28/H-28b.

Previously, ^{13}C and ^{1}H NMR spectra were fully assigned for nickel complex of the Schiff base of L-2-dimethylaminoglycine and **BPB** (L,L-DMGK)[16a]. While having the same stereochemistry of all chiral centres as complex **3**, this complex bears a dimethylamino substituent at C-19. Unlike the dimethylamino group in L,L-DMGK, 1-naphthylmethyl group in complex **3** strongly affects several signals of the nucleus belonging to the core of the complex by its electron-rich aromatic rings, both H_a-3 and H_b-3 signals were shifted 0.99 and 0.73 ppm downfield in ^{1}H NMR spectrum of **3**, respectively. C-12 signal is shifted 3.9 ppm upfield, C-19 signal - 13.81 ppm upfield and C-20 signal - 2.29 ppm downfield. These carbon atoms are proximate to those of 1-naphthylmethyl group; the proximity of H-37 to H-19 was also confirmed by both NOE and X-ray data. *N*-Benzyl group in $CDCl_3$ solution is rotated towards C-19 and the nickel atom. This arrangement is confirmed by NOE cross-peaks between pairs of protons H-4 H-23 (H-27) and H-23 (H-27) H-19. In the single crystal the benzyl group is ro-

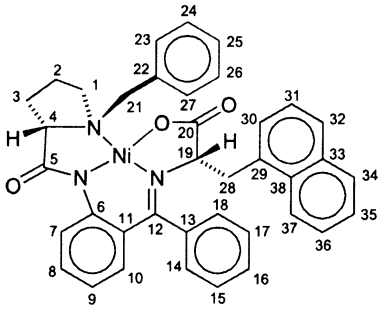


FIG. 2
NMR numbering scheme for **3**

tated outside the nickel atom. Proximity of H-37 to H-18 observed in $CDCl_3$ solution does not occur in the single crystal. Differences between ^{13}C and ^{1}H NMR spectra of 1-naphthylmethyl group in complex **3** and in amino acid **1** are much lower and could be mostly attributed to recording the spectra in different solvents and at different pH.

X-ray Crystallography of Complex 3

Structure description. The molecular structures of the Ni complex of Schiff base of **BPB** and two amino acids (glycine or 3-(1-naphthyl)alanine) were compared (Scheme 1). Molecular structure of **3** with the atom numbering scheme is shown in Fig. 3. The structure of **2** has been published elsewhere[17]. The core of the title compounds, i.e. atoms in the neighbourhood of Ni, has in all structures an approximately planar arrangement. Root-mean-square deviation from the least-square plane fitted through the five central atoms - O2, N1, N2, N3 (atoms that co-ordinate Ni1) and Ni1 ca. 0.065 Å for **3**. The Ni1 atom lies in the centre of a planar core of the two compounds, and is co-ordinated by four atoms, three nitrogens (N1, N2 and N3) and one oxygen (O2). The arrangement of Ni1 co-ordination is

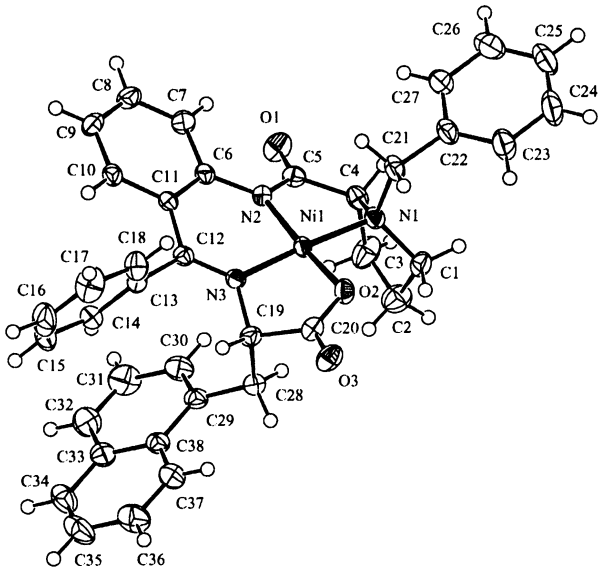


FIG. 3
A perspective view of complex **3** with the atom labelling scheme for non-hydrogen atoms. Displacement ellipsoids are shown at the 50% probability level

square planar. The N–Ni1 and O–Ni1 bond lengths are very close in the two complexes (see Table I), but they are slightly shorter than the published average values – 2.07 Å for the N–Ni1 and 2.06 Å for O–Ni1 [23]. Furthermore, the N1–Ni1 bond lengths are longer by ca. 0.1–0.07 Å than the other three Ni co-ordinated bonds in both structures, whose bond lengths are very close (1.84–1.87 Å).

The phenyl group bonded to the C13 atom is oriented approximately perpendicularly the core plane, taking up a position perpendicular to the phenylene group which is situated with the Ni1 core (C6, C7, C8, C9, C10 and C11). These two aromatic rings form an acute angle of 89.5° in the complex **2**, and an acute angle of 85.57(7)° in the complex **3**. Benzyl group is oriented in both complexes above the Ni(II) plane approximately parallel to this centre plane (see Fig. 3). However, its relative position with respect to the Ni1 atom changes as a function of the complex. In complex **2** it lies towards the Ni1 atom, and in complex **3** it is oriented away from the Ni1 atom (see Fig. 3). The naphthalene ring in this complex lies on the other side of the Ni1 core plane from the N1 benzyl group and away from the Ni1 (see Fig. 3). The benzyl and the naphthalene rings are both positioned parallel to the Ni1 plane. In both **2** and **3** the pyrrolidine ring (C1, C2, C3, C4 and N1) is perpendicular to the Ni1 core plane in the direction below the core plane with respect to the N1 benzyl group. It takes a half-chair conformation.

π-Charge delocalization. We observed a charge delocalization in the proximity of the N2 atom due to the free π-orbital of this nitrogen atom. The bonds between the N2 and C6 and C5 (N2–C6 1.406(2) Å; N2–C5 1.366(3) Å) are shorter than the published average value for N–C(sp^2) bond ($d_{C-N} \approx$ 1.47(1) Å [23], and we find also a small deviation of the bond length of C5–O1

TABLE I
Selected distances (in Å) and angles (in °) of atoms co-ordinating the Ni atom

Distance	2	3	Angle	2	3
Ni1–O2	1.8357(12)	1.868(2)	N1–Ni1–N2	88.72(5)	87.60(7)
Ni1–N1	1.9229(12)	1.936(2)	N1–Ni1–N3	168.84(5)	176.78(8)
Ni1–N2	1.8384(12)	1 857(2)	N1–Ni1–O2	89.04(5)	91.88(7)
Ni1–N3	1.8357(12)	1.845(2)	N2–Ni1–N3	95.33(5)	94.53(7)
			N2–Ni1–O2	175.88(6)	173.69(7)
			N3–Ni1–O2	87.50(5)	86.27(7)

(1.225(3) Å) from the published value $d_{C=O} \approx 1.19(1)$ Å [23]. The situation in the proximity of N3 is more complicated and we observed only small deviations which are not significant, with the exception of the N3=C12 bond (1.296(3) Å) which is shorter than the reference value $d_{N=C} \approx 1.34$ Å.

Crystal packing. In both the complexes the usual hydrogen bond donors N–H, O–H are absent, the hydrogen is involved only in one "hydrogen bond", C(18)–H18···O1 (C···O 3.288(3) Å, H···O 2.51 Å, C–H···O 142°), which is significantly shorter than the sum of van der Walls radii. Neither strong intermolecular interaction of π system of aromatic rings nor any electron donation to Ni1 atom was found in complex **3**, therefore, its crystal packing is probably controlled by weak van der Walls interactions. Detailed description of inter- and intramolecular interactions in crystals of **2** was published elsewhere[17b,17c].

CONCLUSIONS

The described procedure for asymmetric syntheses of α-amino acids is an optimal approach for preparation of small batches of new α-amino acids for research and industrial purposes. Stereochemistry of intermediate chiral complexes could be disclosed by circular dichroism, X-ray crystallography or by NOE interactions in ^{1}H NMR spectra. For extremely demanding applications like preparation of enantiomerically pure [^{11}C]amino acids for positron emission tomography, next generation chiral auxiliaries could be used instead of **BPB** [24].

EXPERIMENTAL

Optical rotation was measured with a Perkin–Elmer M241 polarimeter. Circular dichroism spectra were recorded on Jasco J-715 instrument. The ^{13}C (125.76 MHz) and ^{1}H (500.13 MHz) NMR spectra of compounds **3** and **1** were measured at ambient temperature on a Bruker Avance 500 spectrometer equipped with a 5-mm broadband probe with z-shielding and a SGI O_2 computer. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Amino acid **1** (4 mg) was dissolved in a mixture of D_2O (0.6 ml) and two drops of CF_3COOD. The ^{13}C and ^{1}H NMR chemical shifts were referred to DSS (δ(^{13}C) 0.00, δ(^{1}H) 0.00 in D_2O). Complex **3** (30 mg) was dissolved in $CDCl_3$ (0.5 ml). The ^{13}C and ^{1}H NMR chemical shifts were referred to TMS (δ(^{13}C) 0.00, δ(^{1}H) 0.00 in $CDCl_3$). Two-dimensional gs-H,H-COSY, 1D-gs-NOESY, gs-HSQC, and gs-HMBC spectra were measured using standard microprograms provided by Bruker.

Structure Determination

Crystal data for **3**: $C_{38}H_{33}N_3NiO_3$, M = 638.38, monoclinic, $P2_1$ (No. 4), a = 10.3270(2) Å, b = 8.8190(2) Å, c = 17.4540(3) Å, β = 102.748(1)°, V = 1550.42(3) Å^3, Z = 2, D_x = 1.367 Mg m^{-3}.

A red crystal 0.4 × 0.2 × 0.01 mm was mounted on a glass capillary with epoxy glue and measured on a Nonius KappaCCD diffractometer using monochromatised MoKα radiation (λ = 0.71073 Å) at 150(2) K. Absorption was neglected (μ = 0.669 mm^{-1}). A total of 21 891 measured reflections in the range h = -13 to 13, k = -11 to 11, l = -22 to 2 (θ_{max} = 27.5°), of which 7099 were unique (R_{int} = 0.044), 6553 were observed according to the $I > 2\sigma(I)$ criterion. Cell parameters were obtained from 3745 reflections (θ = 1–27.5°). The structure was solved by direct methods (SIR92)[25] and refined by full-matrix least squares based on F^2 (SHELXL97)[26]. The hydrogen atoms on carbons were fixed in idealised positions (riding model) and assigned temperature factors H_{iso}(H) = 1.2 U_{eq}(pivot atom). The refinement converged (Δ/σ_{max} = 0.002) to R = 0.032 for observed reflections and wR = 0.071, GOF = 1.040 for 406 parameters and all 7099 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.324, $\Delta\rho_{min}$ = -0.324 e $Å^{-3}$). CCDC 261140 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

The mass spectra of compound **4** were measured on a ZAB-SEQ double-focusing mass spectrometer (VG Analytical). The fast atom beam used was generated from xenon ions, which were accelerated to 8 kV. The liquid matrix of bis(2-hydroxyethyl)disulfide (DS) was used for measurement. The samples were dissolved in chloroform and added to the matrix. For high-resolution measurements the instrument was tuned to a resolution of 5000 (10% valley definition).

Note: High-purity argon atmosphere should be used in the alkylation reaction. Argon-vacuum line is strongly recommended. The use of technical nitrogen instead of high-purity argon leads to oxidation of carbanions.

Nickel(II) Complex of the Schiff Base of (*S*)-*N*-(2-Benzoylphenyl)-*N'*-benzylprolinamide and (*S*)-2-Amino-3-(1-naphthyl)propanoic Acid **3**

To a stirred mixture of **2** [11-13] (10 g, 20 mmol) and powdered NaOH (3.6 g, 90 mmol) in DMF (30 ml) was added 1-(chloromethyl)naphthalene (3.9 g, 22 mmol) in two portions under Ar. After 1 h the reaction mixture was poured into a 5% solution of citric acid (400 ml). The red precipitate was filtered, washed with water and air-dried for 15 h. The precipitate was dissolved in MeONa/MeOH (0.5 mol/l, 200 ml) under Ar. After 2 h the reaction mixture was poured into 5% solution of citric acid (400 ml). Methanol and a part of water were evaporated in vacuum. The red precipitate was filtered off, washed with water and air dried for 15 h. The precipitate was purified by column chromatography on silica gel (80 × 5 cm, $CHCl_3$). The first red fraction contains the bis-alkylation product **4**, the second (main) fraction contains complex **3**. Analytical samples were additionally purified by preparative TLC on silica gel followed by gel chromatography on Sephadex LH-20 (toluene/methanol 2:1).

Compound **4**: Red crystals. Yield 0.15 g (1% based on **2**), m.p. 303–305 °C. EI-MS: 777.9 (2.7%), 733.9 (18%), 636.8 (8.2%), 495.6 (10%), 439.5 (10%), 217.3 (13%), 160.3 (100%), 91.17 (73.6%). High resolution FAB-MS: 778.2496; for ($C_{49}H_{41}N_3NiO_3$ + H^+) calculated: 778.2579.

Compound **3**: Red crystals. Yield 11 g (86% based on **2**), m.p. 259–261 °C. ^{1}H NMR (500 MHz, $CDCl_3$): $H1_a$ 1.94 $H1_b$ 3.17, $H2_a$ 1.94 $H2_b$ 3.00, $H3_a$ 2.44 $H3_b$ 2.46, H4 1.94 ^3J_a = 10.1 ^3J_b = 7.1, H7 8.16, H8 7.09, H9 6.60, H10 6.48, H14 7.12, H15 7.30, H16 7.20, H17

6.79, H18 5.91, H19 4.42 ^3J_a = 7.7 ^3J_b = 5.0, H21$_a$ 3.45 H21$_b$ 4.31 ^2J_a = 12.7, H23 8.00, H24 7.28, H25 7.12, H26 7.28, H27 8.00, H28$_a$ 3.82 ^3J_a = 14.1 ^3J_b = 5.0, H28$_b$ 4.05 ^3J_a = 14.1 ^3J_b = 7.7, H30 7.38, H31 7.76, H32 7.35, H34 7.76, H35 7.35, H36 7.19, H37 7.55. ^{13}C NMR (125 MHz, $CDCl_3$): C1 57.02, C2 23.63, C3 30.77, C4 70.44, C5 180.06, C7 123.18, C8 132.24, C9 120.47, C10 133.57, C11 126.11, C12 170.78, C13 134.50, C14 127.25, C15 128.40, C16 129.06[a], C17 128.35, C18 127.49, C19 71.33, C20 178.58, C21 63.01, C22 133.16, C23 131.39, C24 128.76, C25 128.74[a], C26 128.76, C27 131.39, C28 39.87, C29 132.55, C30 126.20, C31 128.26[b], C32 125.45[c], C33 131.85, C34 128.15[b], C35 128.74[c], C36 125.75, C37 123.40, C38 133.11 ([a, b, c] - assignment can be interchanged).

Note: Some assignments of naphthalene ring carbons in ^{13}C NMR spectrum of **3** have a smaller confidence, because experiments were made in inversion mode and resolution in F1 axis was not so good from point of view of very crowded spectrum area belonging to the naphthalene carbons and protons (even in 125 and 500 MHz spectra, respectively). For $C_{38}H_{33}N_3NiO_3$ (637.2) calculated: 71.49% C, 5.21% H, 6.58% N; found: 71.68% C, 5.22% H, 6.52% N.

(*S*)-2-Amino-3-(1-naphthyl)propanoic Acid **1**

A mixture of **3** (9.5 g, 15 mmol), 50 ml MeOH and 6 M HCl was refluxed for 1 h and then evaporated to dryness. Water (50 ml) was added to the residue and the insoluble material (corresponding to **BPB**·HCl) was filtered off, washed with water (4 × 50 ml), dried and stored (similar to ref.[15]). Under stirring, pH of the water solution was adjusted to 9–10 with aqueous NH_3, the precipitate of **1** was filtered off, washed with chloroform (40 ml), water (100 ml), cold MeOH (40 ml), and dried.

Amino acid **1**: Yield (73% based on **3**), m.p. 229–231 °C. $[\alpha]_D^{21}$ -15.0 (*c* 1, 0.3 M HCl), ref.[27] $[\alpha]_D^{20}$ -15.0 (*c* 0.97, 0.3 M HCl). ^{1}H NMR (500 MHz, $CDCl_3$): H19 4.56 ^3J_a = 9.2 ^3J_b = 5.9, H28$_a$ 3.64 ^3J_a = 14.8 ^3J_b = 5.9, H28$_b$ 4.05 ^3J_a = 14.8 ^3J_b = 9.2, H30 7.58, H31 7.63, H32 8.06, H34 8.12, H35 7.73, H36 7.78, H37 8.22. ^{13}C NMR (125 MHz, $CDCl_3$): C19 56.05, C20 174.11, C28 35.89, C29 136.53, C30 131.19, C31 128.52, C32 131.57, C33 132.82, C34 131.87, C35 129.15, C36 129.77, C37 125.63, C38 133.88. For $C_{13}H_{13}NO_2$ (215.3) calculated: 72.54% C, 6.09% H, 6.51% N; found: 72.67% C, 6.15% H, 6.40% N.

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VIII

MAGNETIC RESONANCE IN CHEMISTRY, VOL. 36, 351–355 (1998)

Long-Range $J(^{15}N,^{13}C)$ and $J(^{13}C,^{13}C)$ Coupling Constants via the Metal Atom in ^{13}C NMR Spectra of Square-Planar Ni(II) Complexes of the Schiff Base of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and ^{13}C-1-, ^{13}C-2- or ^{15}N-Labelled Glycine

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ABSTRACT: Chiral synthons containing either ^{13}C- or ^{15}N-labelled glycine were prepared. The ^{13}C and ^{15}N NMR spectra of the Ni(II) complex of the Schiff base of (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and ^{13}C-1-, ^{13}C-2- or ^{15}N-labelled glycine were measured and assigned. The observed splitting of the carbon signals is due to long-range $J(^{13}C,^{13}C)$ and $J(^{15}N,^{13}C)$ couplings. The mutual influence of nuclei is transferred via the central Ni(II) atom in square-planar complexes. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{13}C NMR; ^{15}N NMR; long-range $J(^{13}C,^{13}C)$ and $J(^{15}N,^{13}C)$; ^{13}C- or ^{15}N-labelled glycine; Ni(II) complex; Schiff base

INTRODUCTION

^{13}C- and ^{15}N-labelled amino acids are often used in studies of peptide conformation in solutions or crystals[1] and for several biochemical purposes.[2–4] The Ni(II) complex of the Schiff base of (*S*)-2-(*N*-benzylprolyl) aminobenzophenone and glycine is a very convenient starting synthon for the asymmetric synthesis of commercially unavailable non-coded amino acids. We prepared the chiral synthons from either ^{13}C- or ^{15}N-labelled glycine. The primary aim of the preparation of these synthons was to clarify the structure of a brominated intermediate[5] of the subsequent asymmetric synthesis. During the interpretation of NMR spectra of these labelled complexes we observed an unusual long-range splitting of signals.

EXPERIMENTAL

The ^{13}C- or ^{15}N-labelled glycines (98%) were obtained from Cambridge Isotope Laboratories. Compound **1** (Fig. 1) was prepared according to a literature procedure.[6] Compounds **2**, **3** and **4** were prepared in the same way as described for the Ni(II) complex of the Schiff base from (*S*)-2-(*N*-benzylprolyl)amino-5-methylbenzophenone and glycine.[7]

Ni(II) complex of Schiff base from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and [^{15}N]glycine (**2**): yield 83%; m.p. 215–223 °C [lit.,[6] 208–212 °C (decomp.) for unlabelled compound **1**]. Calculated mass for $C_{27}H_{26}N_2^{15}NO_3Ni$, $[M + H]^+ = 499.1298$; found by high-resolution fast atom bombardment mass spectrometry (FAB-MS), $[M + H]^+ = 499.1349$.

Ni(II) complex of Schiff base from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and [^{13}C-1]glycine (**3**): yield 86%; m.p. 216–227 °C [lit.,[6] 208–212 °C (decomp.) for unlabelled compound **1**]. Calculated mass for $C_{26}{}^{13}CH_{26}N_3O_3Ni$, $[M + H]^+ = 499.1361$; found by high-resolution FAB-MS, $[M + H]^+ = 499.1450$.

Ni(II) complex of Schiff base from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and [^{13}C-2]glycine (**4**): yield 79%; m.p. 225–228 °C [lit.,[6] 208–212 °C (decomp) for unlabelled compound **1**]. Calculated mass for $C^{13}_{26}CH_{26}N_3O_3Ni$, $[M + H]^+ = 499.1361$; found by high-resolution FAB-MS, $[M + H]^+ = 499.1238$.

High resolution FAB-MS

FAB mass spectra were obtained with a ZAB-SEQ double-focusing mass spectrometer (VG Analytical). The fast atom beam used was generated from xenon ions, which were accelerated to 8 kV. The liquid matrix of a mixture of glycerol and thioglycerol was used for measurement. The samples were dissolved in dimethylformamide and added to the matrix. For high-resolution measurements the instrument was tuned to a resolution of 5000 (10% valley definition). The samples give $[M + H]^+$ molecular ions in the spectra.

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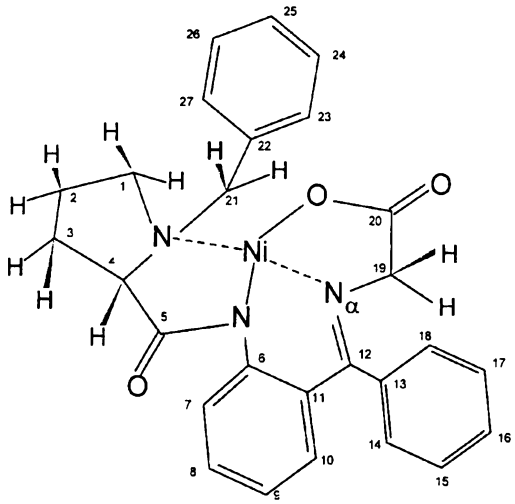

1: natural abundance

2: $N_\alpha = {}^{15}N$ (98%)

3: C19 = ^{13}C (98%)

4: C20 = ^{13}C (98%)

Figure 1. Structures of compounds **1** (^{13}C and ^{15}N in natural abundance) **2**[$N_\alpha = {}^{15}N$ (98%)], **3** [C-19 = ^{13}C (98%)] and **4** [C-20 = ^{13}C (98%)].

NMR measurements

The ^{13}C NMR spectra were obtained in $CDCl_3$ solutions using a Bruker AMX-360 spectrometer equipped with a multinuclear 5 mm tunable probe at 90.56 MHz. ^{13}C chemical shifts are given with respect to the solvent signal ($\delta^{13}C = 77.00$ ppm). The concentration of compounds for measurement of ^{13}C NMR spectra was 20 mg in 0.5 ml of $CDCl_3$. The conditions for ^{13}C NMR measurements were spectral width SW = 15 625 Hz, pulse width $P_1 = 5$ μs (60° flip angle), number of data points after Fourier transformation TD-64K, relaxation delay $D_1 = 2$ s, number of transients NS = 1024 and digital resolution = 0.24 Hz per point.

The ^{15}N NMR spectra were obtained in $CDCl_3$ solutions with the same instrument at 36.49 MHz. ^{15}N chemical shifts are given with respect to external $CH_3{}^{15}NO_2$($\delta^{15}N = 0.00$ ppm). For measurement of ^{15}N NMR spectra, the concentration of **3** and **4** was 130 mg in 0.5 mg of $CDCl_3$ and that of **2** was 50 mg in 0.5 ml of $CDCl_3$. The conditions for ^{15}N NMR measurement of **3** with inverse gated decoupling were as follows: SW = 7814 Hz, $P_1 = 6$ μs (45° flip angle), number of data points after Fourier transformation TD = 32K, acquisition time AQ = 2.1 s, $D_1 = 7$ s, NS = 34 700 digital resolution = 0.24 Hz per point. ^{15}N NMR spectra of **2**, **3** and **4** were measured by refocused INEPT arranged to $J = 3$ Hz,[8] SW = 11 111 Hz, $P_1 = 12$ μs, $P_2 = 24$ μs, AQ = 1.47 s, number of data points after Fourier transformation TD = 32K, $D_1 = 1.5$ s, NS = 17 000 and digital resolution = 0.34 Hz per point.

The $\Delta^{15}N(^{13}C)$ and $^nJ(^{15}N,^{13}C)$ values were obtained from the ^{15}N NMR spectrum of **2** measured by refocused INEPT and optimized to the following parameters: SW = 7353 Hz, $P_1 = 12$ μs, $P_2 = 24$ μs, AQ = 4.45 s, $D_1 = 2$ s, $D_3 = D_4 = 54$ ms and NS = 9432, and processed by Gaussian multiplication with parameters LB = −0.2 Hz and GB = 0.3 to 128K points (digital resolution 0.05 Hz per point.

The ^{15}N NMR spectrum of **2** was also measured with a multinuclear 10 mm probe at a concentration of 500 mg in 2 ml of $CDCl_3$ by inverse gated decoupling with $P_1 = 10$ μs (45°), NS = 9000 and other parameters the same as for **3**.

X-ray analysis

A single red crystal of **2** was grown by crystallization from benzene. The crystal was cut to a size 0.3 × 0.2 × 0.2 mm and used for data collection by a CAD4-MACHIII-PC diffractometer with graphite-monochromated Mo Kα radiation. Lattice characteristics were determined from a least-squares fit of 25 reflections in the range of 13–15°. The crystal is orthorhombic, *P*212121, with the parameters $a = 9.0459$, $b = 9.7219$, $c = 26.455$.

Intensity data were collected using $\theta - 2\theta$ scans in the interval $0 \leqslant 2\theta \leqslant 54°$ (h − 10 to 11, k − 11 to 12, l − 30 to 33). The absorption and extinction correction was applied. Three standard reflections monitored every hour showed some random variation in intensity, maximally about 2.4%. A total of 4182 reflections were collected and were reduced to 3967 unique reflections [$R_{(int)} = 0.022$ and $R_{(\sigma)} = 0.023$]. The structure was solved by direct methods using the program SHELX-86. Refinement was carried out by full-matrix least squares of *F* SHELX-93. Positions of all hydrogen atoms were found from the difference Fourier map. The *B* factors of non-hydrogen atoms were refined anisotropically and those of hydrogen atoms were refined isotropically. The structure was refined to $R = 0.039$ and $wR = 0.087$. A final difference Fourier synthesis showed $\Delta\rho_{(min)} = -0.27$ e Å^{-3} and $\Delta\rho_{(max)} = 0.37$ e Å^{-3}.

RESULTS AND DISCUSSION

The ^{13}C NMR chemical shifts of compounds **1**–**4** (Fig. 1) are given in Table 1. The assignments were made by comparison with recently published NMR spectra of similar complexes.[7,8] There exists a slow (with regard to the NMR time-scale) rotation of a phenyl ring around the C-12—C-13 bond in complexes **1**–**4**. The speed of

Table 1. ^{13}C NMR chemical shifts and coupling $J(^{15}N,^{13}C)$ and $J(^{13}C,^{13}C)$ of compounds 1–4 in $CDCl_3$ at 23 °C

	1	2		3		4	
Carbon	$\delta^{13}C$ (ppm)	$\delta^{13}C$ (ppm)	$^nJ(^{15}N_\alpha, ^{13}C)$ (Hz)	$\delta^{13}C$ (ppm)	$^nJ(^{13}C19, ^{13}C)$ (Hz)	$\delta^{13}C$ (ppm)	$^nJ(^{13}C20, ^{13}C)$ (Hz)
1	57.42	57.43		57.43		57.43	
2	23.63	23.64		23.64		23.64	
3	30.65	30.66		30.66		30.67	
4	69.80	69.81	2.9	69.82	4.4	69.82	2.8
5	181.30	181.31		181.31		181.32	
6	142.46	142.47	1.1	142.49		142.48	
7	124.19	124.20		124.21		124.20	
8	132.15	132.16		132.17		132.16	
9	120.78	120.79		120.79		120.79	
10	133.11	133.13	2.3	133.13		133.12	
11	125.10	125.11	2.9	125.12	3.3	125.11	
12	171.56	171.55	12.5	171.53	0.9	171.56	5.0
13	134.55	134.56	1.2	134.57	3.7	134.56	
14	126.19	126.20		126.21		126.20	
15	129.28	129.29		129.29		129.28	
16	129.67	129.69		129.69		129.68	
17	129.54	129.55		129.55		129.54	
18	125.60	125.62		125.62		125.62	
19	61.20	61.22	4.8	61.24		61.21	56.8
20	177.24	177.24	3.6	177.28	56.8	177.24	
21	63.05	63.06	2.5	63.06	3.5	63.06	2.7
22	133.24	133.25		133.26		133.25	
23	131.66	131.68		131.68		131.67	
24	128.86	128.87		128.87		128.87	
25	129.05	129.07		129.07		129.07	
26	128.86	128.87		128.87		128.87	
27	131.66	131.68		131.68		131.67	

this rotation has been studied previously[8] on similar compounds by the 2D-NOESY technique. Complexes with bulky substituents (dimethylamino) on carbon C-19 do not exhibit such rotation and signals of their C-14 to C-18 carbons could be assigned on the basis of NOESY interactions of H-14 and H-18 protons with other parts of molecule. Carbons C-14 and C-15 are situated above the plane of the complex in the case of frozen rotation. The assignment of C-14 to C-18 in **1–4** has been made by comparison with recently published[8] NMR spectra of both C-19 dimethylamino derivatives of complex **1**.

$J(^{15}N,^{13}C)$

The largest coupling $J(^{15}N,^{13}C)$ was observed on C-12 in **2** (12.5 Hz). This result is not surprising because the interaction is transferred by the shortest sp^2–sp^2 bond. The second one-bond coupling $^1J(^{15}N,^{13}C\text{-}19)$ is more than twice as small (4.8 Hz). The stereospecificity of $^nJ(^{15}N,^{13}C)$ was observed in cases when $n = 2$ and 3 in the neighbourhood of the sp^2-hybridized $^{15}N_\alpha$ nitrogen. The carbons located *trans* from the point of view of the $^{15}N_\alpha$—Ni bond have smaller or no $^nJ(^{15}N,^{13}C)$. Thus $^2J(^{15}N,^{13}C\text{-}11)$ is larger than $^2J(^{15}N,^{13}C\text{-}13)$. The couplings $^3J(^{15}N,^{13}C\text{-}6)$ and $^3J(^{15}N,^{13}C\text{-}10)$ were found to be 1.1 and 2.3 Hz whereas no couplings with ^{15}N were observed on C-14 and C-18. This may be due to either the stereospecificity of $^3J(^{15}N,^{13}C)$ or the presence of the freely rotating phenyl group around the C-12–C-13 bond. This rotation has already been observed in similar complexes.[8] In our case this rotation is not so fast as to cause the coalescence or erasure of the C-14 and C-18 or C-15 and C-17 signals, but the small couplings of *ca.* 1 Hz could be mashed by broadening of these signals. The $^nJ(^{15}N,^{13}C)$ couplings observed in the benzylproline part of **2** cannot be explained by long-range couplings through six or eight C—C and C—N bonds, which should be undetectable. The mechanism of transfer must be different.

Through-space homonuclear long-range couplings have recently been described by Schröder Haslinger[9] and through-space heteronuclear long-range couplings between carbon and fluorine by Lyga *et al.*[10] To our knowledge, there are no reports of heteronuclear through-space long-range interactions between carbon

and nitrogen. Through-space long-range couplings are usually explained by overlapping of atomic orbitals.[9,10] Through-space coupling via lone-pair orbitals of an oxygen[11] or a sulphur[12] atom has also been observed. One of the probable explanations of long-range interactions observed by us is a transfer through the Ni orbitals above the plane of complex. X-ray analysis of **2** has shown that the N—Ni bonds lie in the same plane (see Fig. 2). Full X-ray crystallographic data have been published elsewhere.[13] Carbon C-21 and protons H-21 and H-4 are situated above the plane of the complex. Orbitals of the above-mentioned nuclei can be in contact with or overlap the Ni orbitals. The central Ni^{2+} atom should have the electronic configuration $(e_g)^4(b_{2g})^2(a_{1g})^2(b_{1g})^0$ because the complex shows diamagnetic properties and has a square-like arrangement of a coordination polyhedron as shown on Fig. 2. The doubly degenerate orbital e_g is lower from the energy point of view. The orbital e_g corresponds to the original d_{xz} and d_{yz} orbitals, and the orbital b_{2g} corresponds to the original d_{z^2} orbital. The vacant b_{1g} ($d_{x^2-y^2}$) participates in the hybridization to form d_{sp^2} orbitals. These orbitals are acceptors of electron pairs from ligand donor atoms. These Ni orbitals can transfer the couplings from the glycine to the benzylproline part of molecule. No couplings were observed involving nitrogens with chemical shifts of −270.76 and −349.78 ppm in **3** and **4** and only small couplings of 0.5 and 2.6 Hz were observed with the same nitrogen signals in **2** (see later), which means that couplings are badly transferred in the plane of the complex. No coupling with labelled nuclei was observed on benzylic protons or the H-4 proton in spite of their σ-bonding orbitals being in contact with Ni orbitals above the plane of complex. If the interactions are transferred by orbitals above the plane of the complex they must be transferred only in a single direction through the σ-bonds C-21—H-21 and C-4—H-4 towards the heavier atom (carbon). The other explanation of 'long-range' transfer is that the couplings are transferred in the plane of the complex via N_α—Ni—N bonds. The poor transfer in the plane of the complex noted above can be explained by a usually small value of $^2J(^{15}N,^{15}N)$ in the range 1–8.5 Hz.[14]

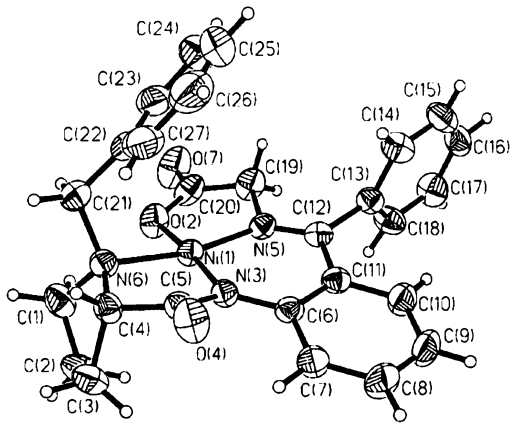

Figure 2. X-ray crystal structure of 2.

$J(^{13}C,^{13}C)$

A similar type of long-range spin–spin interaction observed in ^{15}N-labelled **2** was observed also for ^{13}C-labelled **3** and **4**. The long-range couplings $J(^{13}C,^{13}C)$ were observed in the benzylproline part of the complex on carbons C-4 and C-21 in **3** and **4**. In this case, the transfer of this interaction via Ni orbitals in the plane of complex or above the plane also occurs, since the distance of coupled nuclei is too long through the normal σ-bonds (seven and nine bonds in the **3** and eight and ten bonds in the **4**). Such a type of long-range interactions has not been reported previously.

$\delta^{15}N$

The ^{15}N NMR spectra of **2**, **3** and **4** were measured by refocused INEPT arranged for $J = 3$ Hz. The same value of the coupling constant was successfully used[8] for ^{15}N NMR INEPT measuring some substituted Ni(II) complexes of the Schiff base from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and substituted glycine. None of the three measured compounds gave all three signals of nitrogens with this type of measurement. Only signals with chemical shifts of −195.11 ppm (imine-type nitrogen) and −270.79 ppm (amide-type nitrogen) in **2** were observed. Signals at −195.48 ppm with coupling $^1J(^{15}N,^{13}C) = 4.7$ Hz and a singlet at −270.76 ppm were observed for **3**. Signals at −195.07 ppm with coupling $^2J(^{15}N,^{13}C) = 3.5$ Hz and a singlet at −270.76 ppm were observed for **4**. Compound **3** was also measured by the inverse gated decoupling method and gave three signals. The third signal belongs to a proline-type nitrogen with a chemical shift of −349.78 ppm.

$J(^{15}N,^{15}N)$

X-ray data do not support our theory of C-4 positioned above the plane of the complex. In solution, of course, the conformation of the complex can be different. We tried to confirm if the couplings are also transferred in the plane of complex. We have detected small $J(^{15}N,^{15}N)$ couplings at both unlabelled nitrogens of **2**: 0.5 Hz at ^{15}N with a chemical shift of −270.76 ppm and 2.6 Hz at ^{15}N with a chemical shift of −349.78 ppm. For these measurements it was necessary to use the 10 mm probe with a high concentration of compound. For example, the signal-to-noise ratio was 10710 for the N_α nitrogen, 23 for the amide-type nitrogen ($\delta = -270.76$ ppm) and only 6 for the proline-type nitrogen ($\delta = -349.78$ ppm).

$\Delta^{15}N(^{13}C)$

Isotopic substitution may lead to changes in the nuclear shielding in the ^{15}N NMR spectra of **2**. We observed ^{13}C satellites of the $^{15}N_{\alpha}$ NMR signal of **2** corresponding to the couplings determined in the ^{13}C NMR spectrum. We calculated the intrinsic isotope effect of ^{13}C on the $^{15}N_{\alpha}$ nitrogen in accordance with Gombler's nomenclature[15] as

$$^{n}\Delta^{15}N(^{13}C) = \delta^{15}N(^{12}C) - \delta^{15}N(^{13}C).$$

We calculated four primary intrinsic isotope effects: $^{1}\Delta^{15}N_{\alpha}(^{13}C\text{-}12) = +0.0589$ ppm, $^{1}\Delta^{15}N_{\alpha}(^{13}C\text{-}19) = +0.0258$ ppm, $^{2}\Delta^{15}N_{\alpha}(^{13}C\text{-}20) = +0.0011$ ppm and $^{2}\Delta^{15}N_{\alpha}(^{13}C\text{-}11) = -0.0005$ ppm. The last two values are under the resolution limit of 0.0015 ppm per point and are insignificant. The one-bond intrinsic isotope effect is largest for C-12. This result corresponds to the largest $^{1}J(^{15}N,^{13}C)$ coupling.

CONCLUSION

Stereospecificity of $^{2}J(^{15}N,^{13}C)$ was observed in the neighbourhood of the sp^2-hybridized $^{15}N_{\alpha}$ nitrogen in the Ni(II) complex of the Schiff base from (*S*)-2-(*N*-benzylprolyl)aminobenzophenone and [^{15}N]glycine (**2**). The couplings $^{n}J(^{15}N_{\alpha},^{13}C)$ observed in the benzylproline part of the complex on C-4 and C-21 in **2** and the long-range couplings $^{n}J(^{13}C,^{13}C)$ observed in the benzylproline part of the complex on C-4 and C-21 in **3** and **4** cannot be transferred by C—C or C—N bonds owing to the large distance involved. Transfer of this spin–spin interaction occurs through the Ni atom via orbitals in the plane or above the plane this planar complex. The small splitting of the proline-type nitrogen signal and amide-type nitrogen signal [$J(^{15}N,^{15}N)$] was observed only in the $^{15}N_{\alpha}$-labelled complex **2**.

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IX

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 ^{252}Cf plasma desorption mass spectrometry; a new more hydrolytically stable chloro derivate **4a** was prepared and investigated by 2D NMR.

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

2-Bromoglycine derivatives are an important class of electrophilic glycine synthons[2]. 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 hypothesis[3] 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

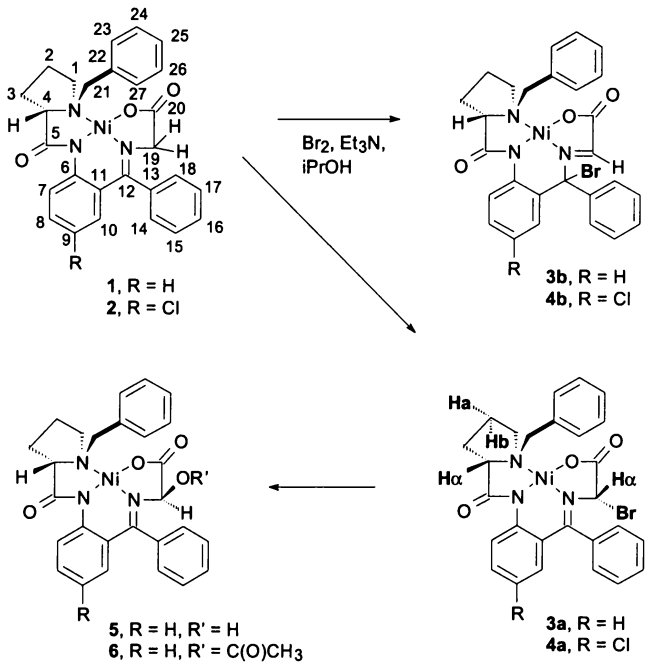
NMR spectra were recorded on a Bruker AMX 360 apparatus[5] at 316.13 MHz for ^1H and at 90.57 MHz for ^{13}C at 23 °C in $CDCl_3$ (concentration of samples 60–70 mg/ml). The following techniques were used for structure elucidation: (i) H,H-homonuclear correlated spectra[6a]; (ii) inverse H,C-heteronuclear 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].

^{252}Cf 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*-benzylprolyl)amino]-5-methylbenzophenone and glycine[7a] starting from (*S*)-2-[(*N*-benzylprolyl)amino]-5-chlorobenzophenone[7b] instead of (*S*)-2-[(*N*-benzylprolyl)amino]-5-methylbenzophenone. Yield 87%, red crystals, m.p. 226–228 °C (benzene). Calculated mass for $C_{27}H_{25}ClN_3NiO_3$ $[M + H]^+$ = 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 ^{13}C NMR spectra see Table I.



SCHEME 1

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

C/H	1		2		3		4		1	2	3	4
No.	$\delta\,^1H_a$	$\delta\,^1H_b$	$\delta\,^1H_a$	$\delta\,^1H_b$	$\delta\,^1H_a$	$\delta\,^1H_b$	$\delta\,^1H_a$	$\delta\,^1H_b$	$\delta\,^{13}C$	$\delta\,^{13}C$	$\delta\,^{13}C$	$\delta\,^{13}C$
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 H_2O (2 ml) and extracted with $CHCl_3$ (3 × 1 ml). The extract was evaporated *in vacuo* and the residue was purified by chromatography on silica gel with $CHCl_3$: Me_2CO = 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 $C_{29}H_{27}N_3NiO_5$ (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 ^{252}Cf 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 ^{13}C NMR gave δ 86.03 for C-19. This is similar to that of the reference (*R*)-2-acetoxyglycine complex **6** ($\delta_{C\text{-}19}$ 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 glycines[5]. 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 found[5] 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 ($\Delta\delta^1H$ 0.72 and $\Delta\delta^1H$ 0.75 ppm relative to δ^1H_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 δ^1H_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 interaction[5] (see above) was discovered as the first type and the long-range $^nJ(^{13}C,^{13}C)$, $^nJ(^{15}N,^{13}C)$ and $^nJ(^{15}N,^{15}N)$ interactions[1] 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 $^{n}J(^{15}N,^{13}C)$ and $^{n}J(^{13}C,^{13}C)$ 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 $^{1}J(^{15}N,^{13}C\text{-}12)$ = 12.5 and $^{1}J(^{15}N,^{13}C\text{-}19)$ = 4.8 Hz. This difference has been attributed to the greater s-character of hybrid orbitals[9] of the double bond N=(C-12) relative to a single bond N–(C-19). In complex **3**, the spin–spin interaction constants $^{1}J(^{15}N,^{13}C\text{-}12)$ = 12.0 and $^{1}J(^{15}N,^{13}C\text{-}19)$ = 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 $^{n}J(^{13}C,^{13}C)$ spin–spin coupling constants in this complex also confirmed the structure **3a** (data for the compound **1** (ref.[1]) are given in brackets): $^{1}J(^{13}C\text{-}19,^{13}C\text{-}20)$ = 62.2 Hz (56.8 Hz), $^{2}J(^{13}C\text{-}19,^{13}C\text{-}12$ = 1.2 Hz (0.9 Hz), $^{3}J(^{13}C\text{-}19,^{13}C\text{-}13)$ = 4.0 Hz (3.70 Hz), $^{3}J(^{13}C\text{-}19,^{13}C\text{-}11)$ = 4.1 Hz (3.34 Hz).

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X

The synthesis of chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid

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Dedicated to Professor Edmunds Lukevics on the occasion of his 70th birthday

Abstract

The chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (**6**) was prepared *via* the cycloaddition of chiral complex of Ni **5** with mesitonitrile oxide **1.** The cycloaddition proceeded with complete regioselectivity to provide 5-substituted isoxazolines **6** and **7**. The approach of the dipole takes place predominantly from the less sterically hindered side of dipolarophile **5**, the diastereoisomers were formed in 96:4 ratio. The detailed structure of **6** was established by X-ray analysis.

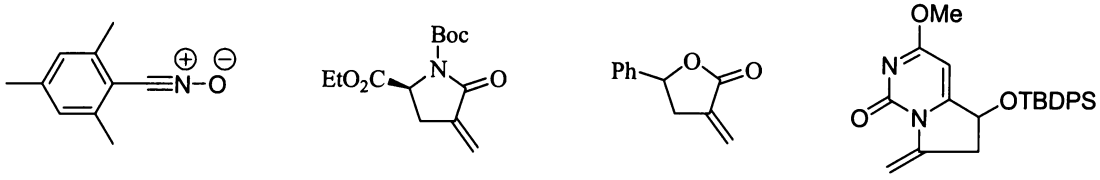
Keywords: Dipolar cycloaddition, diastereoselection, nitrile oxides, chiral complex, spiroisoxazolines, X-ray analysis

Introduction

Spiroisoxazolines are heterocyclic nuclei which have stimulated much interest in medicinal and biological chemistry.[1] Following the first reports of their herbicidal and plant hormonal activity[2-4] some naturally occurring spiroisoxazolines have been found useful in other biomedical areas. Examples include the naturally occurring araplysillins, which have been found to inhibit ATP-ase enzymes,[5] and naturally occurring agelorin, a spiroisoxazoline derived from bromotyrosine which has proved active against pathogens.[6-9] More recently it was found that spiroisoxazoline containing SJ755 shows a remarkable integrin antagonist behavior, showing a new application

for this class of compounds.[10] Some stereoselective synthesis of unnatural spiroisoxazolinoheterocycle-based derivatives in which exomethylene heterocyclic compounds react as a dipolarophile with nitrile oxides is also reported.[11-15]

We have found a strong evidence for a predictive *anti*-diastereoselective 1,3-dipolar cycloadditions of nitrile oxides and nitrones to the substituted heterocyclic compounds possessing an exocyclic double bond. [13-15] The attack of the 1,3-dipole occurred preferentially from the less hindered face of the dipolarophile.[13-15] For example, the reaction of chiral methylene pyrrolidinone **2** and stable mesityl nitrile oxide (**1**) proceeded under the formation of *anti* and *syn* diastereoisomers in the ratio of 67:33, in favor of *anti* diastereomer. The reaction of nitrile oxide **1** with methylenelacton **3** afforded a 90:10 mixture of cycloadducts in favor of *anti* diastereomer (Scheme 1).[13] On the other hand, cycloaddition of the dipolarophile **4** bearing a bulky silyl group proceeded with high stereoselectivity providing 5,7-*trans* isoxazoline exclusively.[14,15]



1 **2** **3** **4**

Scheme 1

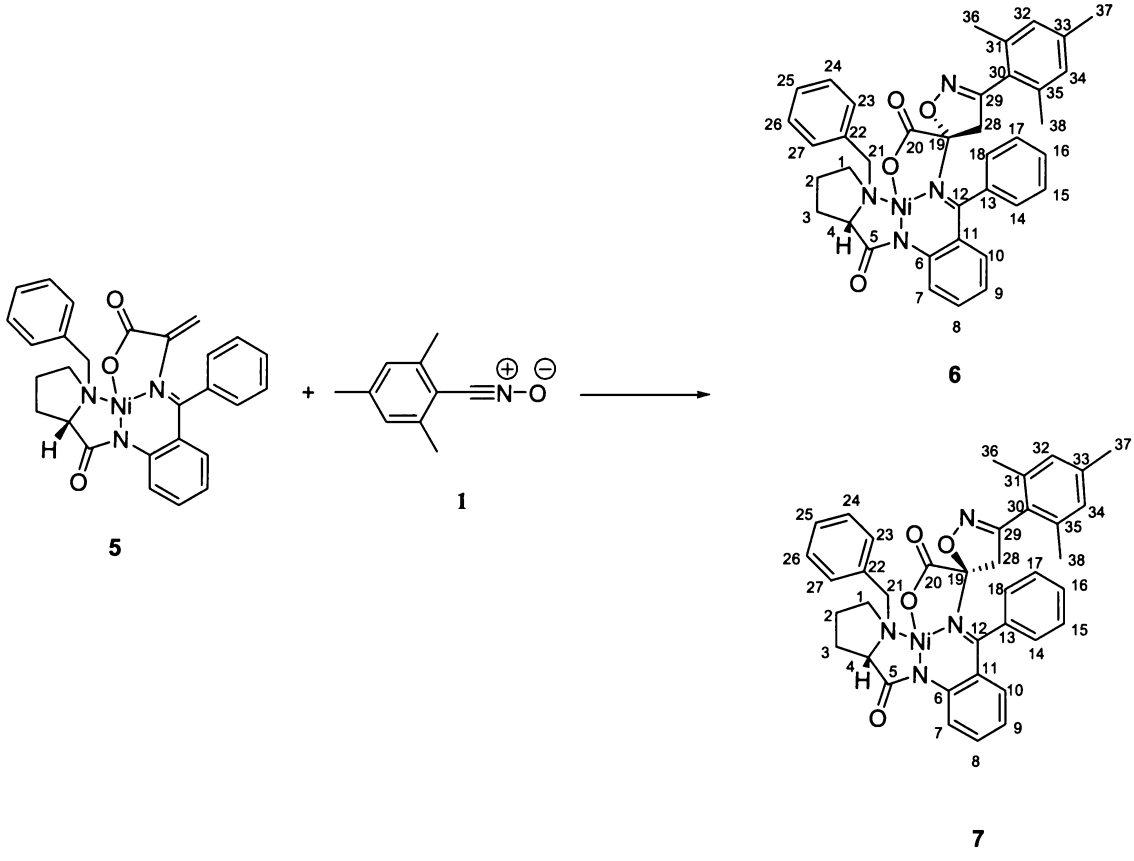
With the goal of developing a simple route to the synthesis of chiral isoxazolinylsubstituted amino acids we focused our attention on the cycloaddition of mesityl nitrile oxide with chiral Ni^{II} complex **5** derived from a Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine. Some years ago Y. N. Belokon *et al.* described asymmetric synthesis of β-substituted α-amino acids via a chiral Ni^{II} complex **5**.[16,17]

Results and Discussion

The chiral Ni^{II} complex **5** of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine was prepared according to ref.[18]. Cycloadditions of chiral Ni^{II} complex **5** with mesitonitrile oxide **1** proceeded with complete regioselectivity to provide 5-substituted isoxazolines **6** and **7** in 72% yield. The structures described were characterized *via* analysis of their respective ^{1}H- and ^{13}C- NMR spectra. The ratio of diastereoisomers was determined from quantitative ^{13}C NMR spectra, by integration of the peaks from spiro-carbon C-19 of the isoxazolines. The cycloaddition proceeded extremely slowly, but the diastereoselectivity was excellent, the diastereoisomers were formed in 96:4 ratio. (Scheme 2).

The major isomer Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (**6**) was purified by column chromatography and was identified as 5-substituted isoxazoline by NMR spectroscopic analysis. The stereochemical arrangement and absolute configuration was subsequently confirmed by X-ray-crystallographic analysis (Figure 1 and experimental section). The analysis of the product configuration in **6** indicates that the major cycloadduct **6** arises from the cycloaddition that has occurred on the more sterically accessible face of the dipolarophile **5**. A chemical shift of spiro-carbon at C-19 of the isoxazoline ring in ^{13}C-NMR of both isolated products (101.9 ppm for **6** and 100.8 ppm for **7**) excludes the possibility that the second isolated product 7 is a regioisomer.

The high diastereoselectivity of the cycloaddition could be due to the fact that the *N*-benzylic group of the chiral Ni^{II} complex **5** is probably attached to the Ni atom and can effectively hinder the approach from *re* face of the alkene. Therefore, the cycloaddition of nitrile oxide **1** arises from the more sterically accessible *si* face of the exocylic double bond of the dipolarophile **5**.



Scheme 2

Conclusions

In conclusion, the chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (**6**) was prepared *via* the cycloaddition of chiral complex of Ni **5** with mesitonitrile oxide **1.** The cycloaddition proceeded with complete regioselectivity to provide 5-substituted isoxazolines **6** and **7** in 72% yield. The analysis of the product configuration in **6** indicates that the major cycloadduct **6** arises from the cycloaddition that has occurred on the more sterically accessible face of the dipolarophile **5**. Thus it is steric factors that are responsible for the observed diastereoselectivity (diastereoisomers were formed in 96:4 ratio).

Experimental Section

General Procedures. All starting materials and reagents are commercially available (Fluka, Merck, Avocado or Aldrich) and were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC glass plates coated with silica 60 F_{254} Merck) was used for monitoring of reaction courses; eluent is given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040-0.063 mm, Merck). Melting points (mp) were determined on a Kofler hot plate apparatus and are uncorrected.

The ^1H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian VXR-300 (300 MHz) instrument, tetramethylsilane (TMS) being the internal reference.

The chiral Ni^{II} complex **5** of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine was prepared from the chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and glycine which, in turn was treated with formaldehyde and acetic anhydride in the presence of Na_2CO_3 according to ref.[18].

Cycloaddition of mesitonitrile oxide (1) with chiral Ni^{II} complex 5 of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine. Mesitonitrile oxide (**1**) (161 mg, 1.000 mmol) and the chiral complex **5** (511 mg, 1.001 mmol) were dissolved under argon in anhydrous CH_2Cl_2 (10 ml) and kept at 0°C 40 d. When no starting material remained (TLC), the solvent was removed *in vacuo* and the mixture of two diastereoisomers (94:6) was purified and separated by flash column chromatography on silica gel, eluting with EtOAc/hexanes 25:75 to give major diastereoisomer **6** (471 mg, 70%) and minor diastereoisomer **7** (12 mg, 2%).

***anti*-Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (6).** Red solid, 70% yield. ^1H NMR δ 6.4-8.3 (m, 9H, H_{Ar}), 6.79 (s, 2H, H-32, H-34), 4.35 (d, J = 6.2 Hz, 1H, H-21a), 4.23 (ddd, J = 4.1, 6.8, 11.4 Hz, 1H, H-1) 3.66 (dd, J = 4.1, 9.7 Hz, 1H, H-4), 3.53 (d, J = 17.7 Hz, 1H, H-28a), 3.40 (d, 1H, H-21b), 3.40 (d, J = 17.7 Hz, 1H, H-28b), 2.74-2.83 (m, 1H, H-2), 2.63 (ddd, J = 6.3, 9.4, 11.4 Hz, 1H, H-1), 2.25-2.40 (m, 2H, H-3), 2.24 (s, 3H, CH_3-37), 2.07 (s, 6H, CH_3-36, CH_3-38), 1.96-2.10 (m, 1H, H-2). ^{13}C-NMR δ 181.9 (C-5), 174.7,

173.5 (C-20, C-12), 156.85 (C-29), 143.1, 139.1, 137.4, 135.8, 134.4, 128.5, 124.5 (C-6, C-11, C-13, C-22, C-30, C-31, C-33, C-35), 134.3, 132.9, 131.0, 130.7, 129.3, 129.1, 128.7, 127.8, 126.8, 123.6, 120.9 (C-7, C-8, C-9, C-10, C-14, C-15, C-16, C-17, C-18, C-23, C-24, C-25, C-26, C-27, C-32, C-34), 101.9 (C-19), 69.9 (C-4), 62.0 (C-21), 59.6 (C-1), 51.4 (C-28), 30.8 (C-3), 23.4 (C-2), 21.1 (C-37), 20.6 (C-36, C-38). Anal. Calcd for $C_{38}H_{36}N_4NiO_4$: C, 67.98; H, 5.40; N, 8.34. Found: C, 67.63; H, 5.61; N, 8.52.

syn-**Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid** (**7**). Red solid, 2% yield. ^{13}C-NMR δ 180.4 (C-5), 174.1, 172.5 (C-20, C-12), 156.3 (C-29), 142.1, 139.3, 137.3, 135.6, 133.5, 129.3, 124.2 (C-6, C-11, C-13, C-22, C-30, C-31, C-33, C-35), 133.5, 132.5, 131.4, 130.9, 129.1, 128.5, 127.6, 127.3, 126.3, 123.8, 121.1 (C-7, C-8, C-9, C-10, C-14, C-15, C-16, C-17, C-18, C-23, C-24, C-25, C-26, C-27, C-32, C-34), 100.8 (C-19), 70.6 (C-4), 63.6 (C-21), 57.6 (C-1), 54.2 (C-28), 30.6 (C-3), 24.2 (C-2), 21.0 (C-37), 20.4 (C-36, C-38).

X-ray Structure Determination of 6.[19-21] The suitable crystals were obtained by slow crystallization from a mixture of ethyl acetate and hexane at room temperature. The crystallographic data were obtained by CAD4 diffractometer. The relevant crystallographic data and structure refinement are given in Table 1. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares technique. Perspective view and the numbering of the atoms are depicted in Figure 1. The hydrogen atoms were refined isotropically in idealized positions riding on the atom to which they are attached. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The corresponding deposition number is CCDC 603354. Copies of the data can be obtained free of charge on request to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408, Fax: +44-1223 336-033).

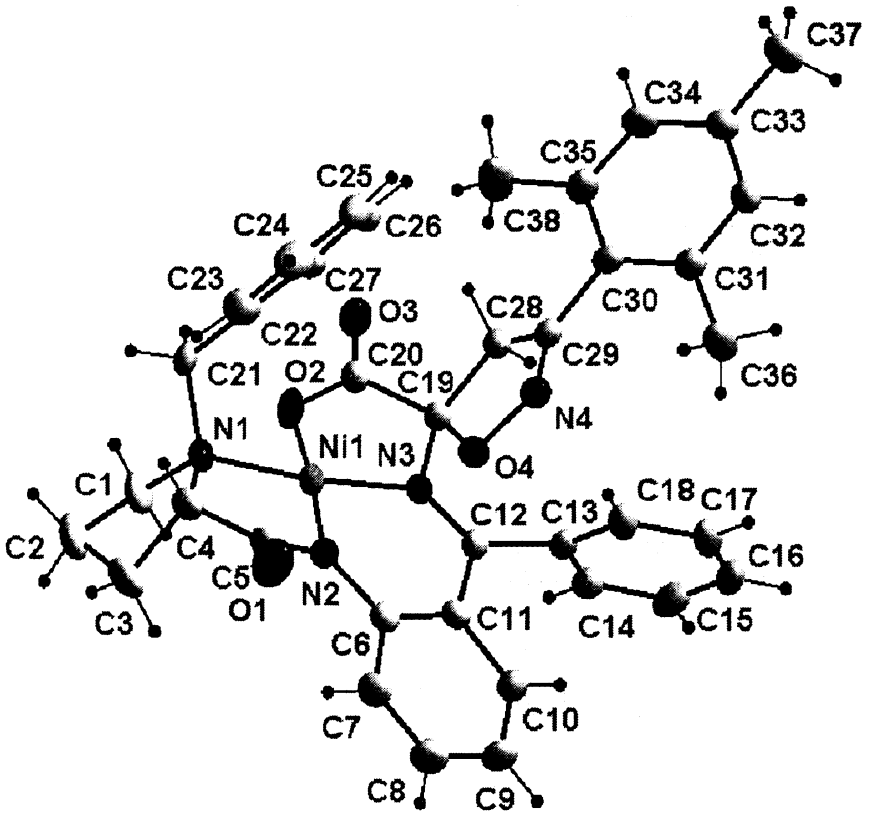


Figure 1. Crystalline structure of compound **6** with crystallographic numbering and 30% ellipsoids.

Table 1. Crystal and experimental data for compound **6**

Empirical formula	$C_{38}H_{36}N_4O_4Ni$
Formula weight	671.41
Temperature, T (K)	299(2) K
Wavelength, λ (Å)	0.71093
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions(Å)	a = 9.843(1) $\alpha = \beta = \gamma = 90^o$
	b = 11.165(2)
	c = 29.173(2
Unit-cell volume, V (Å^3)	3206(1)
Formula units per unit cell, Z	4
Calculated density, D_x (g cm^{-3})	1.391
Absorption coefficient, μ (mm^{-1})	0.080
F(000)	1408
μ (mm^{-1})	0.65
Crystal size (mm)	0.37 x 0.28 x 0.13
Diffractometer	Enraf-Nonius CAD4
Theta range for data collection, (°)	1.99 - 23.98
Index ranges	$-12 \le h \le 3$, $-13 \le k \le 1$, $-35 \le l \le 1$
Reflections collected	5169
Independent reflections [$I>2\sigma(I)$]	4633 (Rint = 0.031)
Absorption correction	Empiric Psi-scan
Max. and min. transmission	0.9151 and 0.8284
Refinement method	Full-matrix least-squares on F^2
Data / parameters	3602 / 209
Goodness-of-fit (all)	0.977
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0295, w$R2$ = 0.0725
R indices (all data)	$R1$ = 0.0632, w$R2$ = 0.0814
Extinction coefficient	0.011(14)
Largest diff. peak and hole	0.283 and -0.416 (e Å^{-3})

Acknowledgements

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XI

Improved synthesis of the Ni(II) complex of the Schiff base of (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone and glycine

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The environmental impact of a known synthesis of the Ni complex of the Schiff base of (*S*)-2-[*N*-(*N'*-benzylprolyl)amino]benzophenone and glycine was decreased by optimisation of the ratio the starting materials; a new starting material, $Ni(NO_3)_2 \cdot 6NH_3$, was evaluated as a nickel source.

For the preparation of non-coded and/or selectively labelled α-amino acids, several chiral glycine and alanine synthons are manufactured and marketed in bulk quantities. The most important are Seebach's[1] and Oppolzer's[2] derivatives and O'Donnell's achiral synthon,[3] for stereospecific alkylation of which an efficient chiral catalyst has been recently developed.[4] Ni(II) complexes of Schiff bases of (*S*)-2-[*N*-(*N'*-benzylprolyl)-amino]benzophenone (BPB) and α-amino acids achieve high asymmetric induction for the synthesis of α-amino acids[5] at ambient temperature. The chiral auxilliary BPB is regenerated but excess nickel in the waste water is a potential environmental problem.

The complexes were developed as artificial analogs of pyridoxal 5'-phosphate (PLP)-dependent enzymes.[6] The central sodium atom of a PLP-dependent enzyme was replaced by nickel in order to form a more stable compound. In spite of the inexpensive and reliable application of these complexes, the fate of the nickel used in their preparation should be carefully controlled. Energy-consuming procedures used for removal of nickel from waste water might significantly increase the cost of α-amino acids production. Nickel from the complexes is easily regenerated when a mixture of an amino acid and nickel chloride (after acidic hydrolysis) is separated on a cation-exchanger. A large amount of metal remains in the methanolic waste solution after preparation of the complexes, due to a two-fold excess of $Ni(NO_3)_2 \cdot 6H_2O$ used in a standard protocol.[7–9] This excess is necessary in order to shift the equilibrium towards complex formation.

Previous attempts to substitute nickel nitrate with nickel acetate, which bears four molecules of water in the internal coordination sphere instead of six in the nitrate, did not shift the equilibrium towards complex formation.[10]

In this work the successful synthetic application of near stoichiometric amounts of $Ni(NO_3)_2 \cdot 6H_2O$ or anhydrous $Ni(NO_3)_2 \cdot 6NH_3$†, minimising amount of Ni^{2+} need to be recovered from waste water, is described (Scheme 1).

Results and discussion

In this work a two-fold excess of glycine instead of five-fold[7–9] was used in order to reduce the amount of nickel chelating amino acid in the waste water.

Experiments did not support the initial hypothesis that anhydrous $Ni(NO_3)_2 \cdot 6NH_3$ would shift the equilibrium towards complex formation. Observed yields of complex formation starting from $Ni(NO_3)_2 \cdot 6H_2O$ were 5–13% higher than the corresponding yields starting from $Ni(NO_3)_2 \cdot 6NH_3$ (Table 1).

When a two-fold excess of any nickel salt was used solid precipitate appeared in the reaction mixture after 90 min. With lower excesses of nickel salts no precipitates were observed. Formation of the precipitate is probably responsible for lower yields of the complexes when using a two-fold excess of a nickel salt compared with 1.2-fold. This may be due to absorbtion of BPB by precipitated nickel oxide/hydroxide. Work-up of the homogeneous reaction mixtures obtained with lower excesses of nickel salts is better suited to scale-up as no separation and processing of solid nickel-containing waste is necessery.

Application of the Ni(II) complex of the Schiff base of BPB and glycine for asymmetric synthesis of α-amino acids often does not require separation of the complex from unreacted BPB (see, for example, ref. 9). In such cases, in spite of lower yields of the complexes, a 1.05-fold excess of nickel salt might be the best ratio. This will decrease the amount of nickel circulating in the process.

Synthesis of more sterically hindered complexes derived from α-monosubstituted glycines (*e.g.* proteinogenic α-amino acids) is in progress in order to test the new ratio of the starting compounds under more challenging conditions.

Green Context

The preparation of speciality α-amino acids requires the large-scale manufacture of various chiral glycine and alanine synthons. Nickel complexes have been shown to be particularly effective in achieving high asymmetric induction for the synthesis of α-amino acids but nickel contaminated waste waters present an environmental problem. Here the synthesis of the nickel complex is optimised including the use of a new nickel source. The net result is a reduction in the environmental impact of the process. ***JHC***

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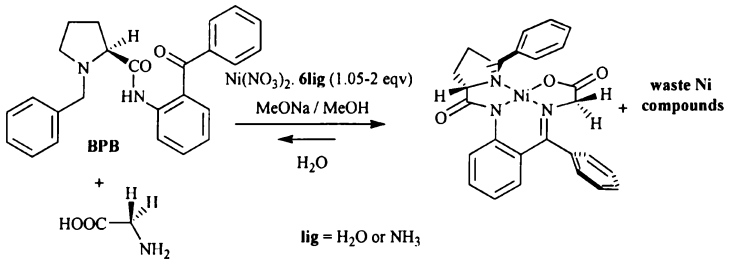

Scheme 1

Table 1 Yields of the Ni(II) complex of Schiff base of BPB and glycine depending on excess of nickel salts

Excess of the nickel salt	2	1.2	1.05
Yield of the complex starting from $Ni(NO_3)_2·6NH_3$ (%)	64	78	67
Yield of the complex starting from $Ni(NO_3)_2·6H_2O$ (%)	77	88	71

Experimental

General procedure for the synthesis of the glycine complex

2.5 M MeONa/MeOH (8 ml, 20 mmol) was added to a stirred suspension of BPB (500 mg, 1.3 mmol), glycine (195 mg, 2.6 mmol) and the corresponding amount of a nickel salt (Table 1) in dry MeOH (4 ml) under argon at 55 °C. The volume of the reaction mixture was then adjusted to 15 ml with dry MeOH. After stirring at 55 °C for 90 min, the mixture was poured into 10% aqueous citric acid (100 ml), stirred and the resulting precipitate was filtered off and dried in air. The dry precipitate was purified by column chromatography using silica gel (Merck 40/63) eluted with chloroform.‡ Yields of complex formation are given in the Table 1. ^1H and ^{13}C NMR data have been reported previously.[11]

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Notes and references

† $Ni(NO_3)_2·6NH_3$ for this work was prepared by bubbling NH_3 gas through a cold methanolic solution of $Ni(NO_3)_2·6H_2O$ and filtering off the resulting precipitate. Aqueous ammonia may be also used instead of NH_3 gas, in this case the content of water in the internal coordinational sphere of $Ni(NO_3)_2·6NH_3$ will be higher.

‡ As chloroform is known to be a human carcinogen, for preparative applications a gradient elution using $CH_2Cl_2 \rightarrow CH_2Cl_2$–$Me_2CO$ = 7:1 or toluene → toluene–Me_2CO = 2:1 is strongly recommended.

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XII

AN ASYMMETRIC APPROACH TO THE RADIOSYNTHESIS OF BOTH ENANTIOMERS OF α-[^{11}C]METHYLDOPA AND α-[^{11}C]METHYLTYROSINE FOR POSITRON EMISSION TOMOGRAPHY

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In PET, α-methyl amino acids can play a dual role: a) precursors of neurotransmitters analogues for the study of neurodegenerative diseases; b) non-metabolised analogues of proteinogenic amino acids for the study of amino acids uptake into normal and cancer cells. The difference in the uptake rates during a PET scan could visualise cancer cells in a human body. Clinical applications of such amino acids are strongly limited due to their poor availability. For the synthesis of α-[^{11}C]methyl-

tryptophan, an industrial procedure was adopted. All attempts to prepare enantiomerically pure α-[^{11}C]methylated tyrosine failed. We carried out [^{11}C]methylation of metalocomplex synthons derived from protected DOPA or tyrosine. Individual diastereomers were successfully separated by preparative HPLC, diluted with excess of water and extracted on C_{18} cartridges. Optimisation of the procedure followed by hydrolysis of the complexes and purification of the enantiomers of α-[^{11}C]methylDOPA and α-[^{11}C]methyltyrosine is underway.

1 Introduction

α-Amino acids bearing α-methyl group instead of α-hydrogen are used for a number of life science applications. For example, in peptides replacement of proteinogenic amino acids with their α-methylated analogues allows to introduce restriction to conformational freedom and increase stability of the peptides towards various enzymes. Thus, asymmetric syntheses of similar α-methyl amino acids isotopically substituted with ^{13}C in the methyl group is an important goal for further NMR investigation of the peptides and their conformations in aqueous solution. In positron emission tomography (PET) α-[^{11}C]methyl amino acids could play a dual role:

- Precursors of neurotransmitters analogues for the study of neurodegenerative diseases.
- Non-metabolised analogues of proteinogenic amino acids for the study of amino acids uptake into normal and cancer cells [1].

Clinical applications of such amino acids are strongly limited due to their poor availability. For the synthesis of the only enantiomerically pure ^{11}C-labelled α-methyl amino acid, α-[^{11}C]methyltryptophan, an industrial procedure was adopted [2-4]. All attempts to prepare enantiomerically pure α-[^{11}C]methylated tyrosine failed [5,6].

Except for ^{11}C-labelled α-methyltryptophan and several ^{14}C-labelled α-methyl amino acids (α-methyltyrosine [7] and α-methylDOPA) no other enantiomerically pure radiolabelled α-methyl amino acid was used for in vivo investigation of human being (α-[^{11}C]methyltryptophan) or laboratory animals. Among published procedures for asymmetric synthesis of non-labelled α-methyl amino acids, none could be used without modification for the preparation of ^{11}C-labelled α-methyl amino acids. [8] Highly stereoselective procedure was published for catalytic alkylation of alanine derivative with large electrophiles [9-13]. Reversed approach, i.e., methylation of tryptophan or tyrosine derivative with easily available $^{11}CH_3I$ or $^{11}CH_3OTf$ or their non-labelled analogues, has never been demonstrated.

Based on previously described application of similar complexes for asymmetric synthesis of [^{11}C]alanine, researchers at Uppsala tested [^{11}C]methylation of metallocomplex synthon of alanine and the Ni(II) complex of the Schiff base of BPB and α-phenylalanine. [14] They found that „... all attempts to alkylate these complexes with ^{11}C-labelled alkyl iodides were unsuccessful. The increased steric hindrance makes the alkylation reaction so slow that very little alkylation was observed even when a large excess of substrate was used." In this communication we present the first successful asymmetric [^{11}C]methylation of chiral metallocomplex amino acids synthons.

2 Experimental

^{11}C-methylation reaction reactions were carried out on state-of-the-art radiochemical robotic line installed in Copenhagen University Hospital.

Circular dichroism spectra were recorded on Jasco J-715 instrument.

The ^{13}C (125.76 MHz) and ^{1}H (500.13 MHz) NMR spectra were measured at ambient temperature on a Bruker Avance 500 spectrometer equipped with 5 mm broadband probe with z-shielding and a SGI O_2 computer.

HPLC-MS spectra were collected with a Waters SymmetryShield C18 150×1 mm column connected to a Finnigan LQ mass spectrometer.

Note: high-quality argon atmosphere should be used for the alkylation reaction. Use of technical nitrogen instead of high-quality argon leads to significant oxidation of carbanions by traces of oxygen.

Synthesis of DOPAK. Ni(II) complex of the Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and (*S*)-3-(3,4-dimethoxyphenyl)alanine ((*S, S*)-DOPAK) was prepared in the same way as described for the similar Ni(II) complex of the Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and *O*-methyl-L-tyrosine ((*S, S*)-TyrK) [15] using (*S*)-3-(3,4-dimethoxyphenyl)alanine instead of *O*-methyl-L-tyrosine. Yield 62% (mixture of diastereomers). An analytical sample was purified by preparative TLC using silica gel (Merck 60H) eluted with CH_2Cl_2. The second red fraction, containing (*S, S*)-DOPAK was collected. The obtained complex was then purified by chromatography on Sephadex LH-20 with toluene: MeOH = 2: 1. (*S, S*)-DOPAK, red solidified oil. ^{1}H NMR (500.13 MHz, $CDCl_3$): 8.20 (d, 1H), 8.00 (d, 2H), 7.49 (m, 2H), 7.37 (t, 1H), 7.27 (m, 3H), 7.12 (m, 2H), 6.85 (d, 1H), 6.70 (t, 2H), 6.63 (m, 3H), 4.26 (d, 1H) and 3.44 (d, 1H) (AB system of -CH_2Ar, ^2J(H, H) = 12.7 Hz), 4.22 (A part of AMX system, dd, 1H), 3.31 (M part of AMX system, dd, 1H), 2.82 (X part of AMX system, dd, 1H), 3.86 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), proline protons: 3.31 (m, 1H), 3.13 (m, 1H) 2.49 (m, 1H), 2.35 (m, 2H), 1.97 (m, 1H), 1.75 (m, 1H). Calculated mass for $C_{36}H_{35}N_3O_5Ni$ $[M]^+$ = 647.1930. High resolution EI-MS found $[M]^+$ = 647.1952.

[^{11}C]Methylation of DOPAK. Under an atmosphere of argon, solution of (*S, S*)-DOPAK (5 mg) and [^{11}C]methyl iodide in 1,3-dimethylimidazolidin-2-one (DMI, 0.3 μL) was added to pulverised NaOH (5-10 mg) at 25 °C. The reaction mixture was shaken and left for 10 min. The diastereomeric excess and the radiochemical yield were determined by reverse phase HPLC analysis of the reaction mixture. Radiochemical yield (decay corrected): (*S, S*)-α-[^{11}C]methylDOPAK 4 %, (*S, R*)-α-[^{11}C]methylDOPAK 5 % (Fig. 1).

Methylation of ((*S, S*)-TyrK(OBu-*t*)) in the same conditions led to 7 % radiochemical yield. Diastereomeric excess of (*S, R*)-α-[^{11}C]methylTyrK(OBu-*t*) was 7-10 %.

3 Results and Discussion

In order to re-investigate published negative results [14], we chose (^{13}C)methylation of sterically hindered complexes (*S, S*)-TyrK and (*S, S*)-DOPAK as model reactions (Schema 1). Similar approach has been previously applied for the assessment of stereodiscriminative power of newly synthesized metalocomplex alanine synthons [16].

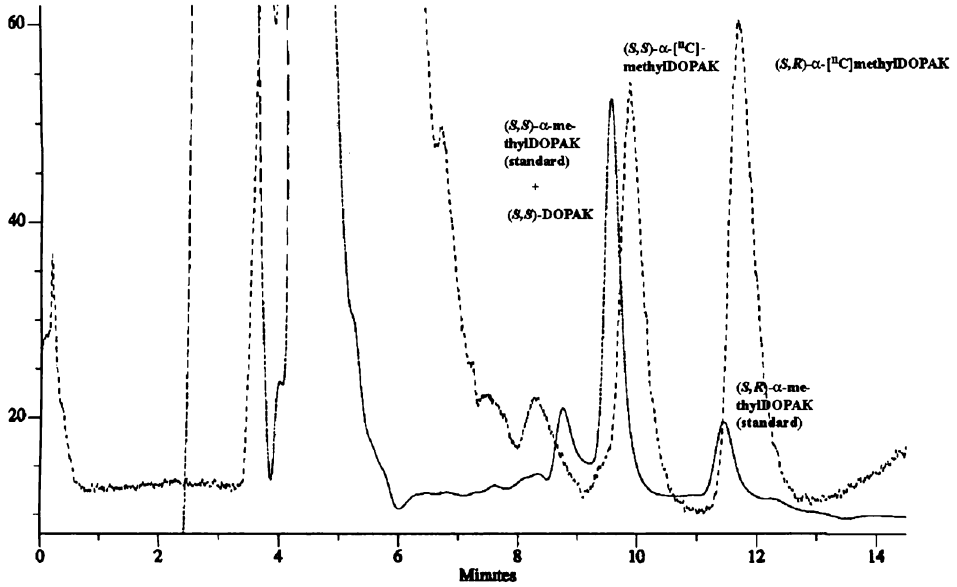
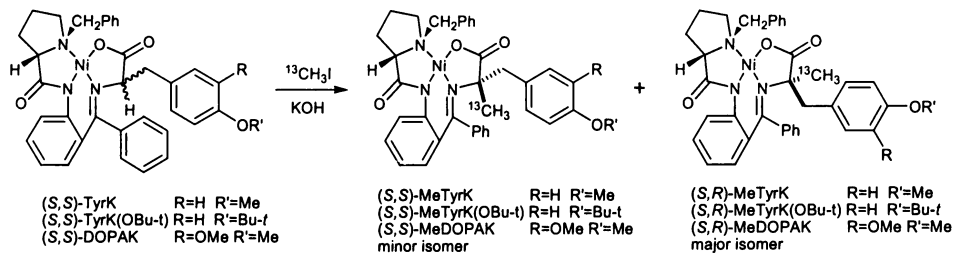


Fig. 1. HPLC separation of diastereomers of α-[^{11}C]methylDOPAK (dotted line, detection by γ-detector); added standards – α-methylDOPAK diastereomers and (*S, S*)-DOPAK were detected by UV-detector (solid line).

Alkylation in the aprotic solvent DMI run as expected for alkylation of sterically hindered tertiary carbon. A 9 % radiochemical yield (decay corrected) of a mixture of the diastereomeric Ni(II) complexes of the Schiff base of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide and 3-(3,4-dimethoxyphenyl)-2-[^{11}C]methylalanine (α-[^{11}C]methylDOPAK, 4 % yield of (*S, S*)-α-[^{11}C]methylDOPAK and 5 % yield of (*S, R*)-α-[^{11}C]methylDOPAK, Fig. 1); or a 7 % radiochemical yield of a mixture of the diastereomeric α-[^{11}C]methyltyrosine complexes[1] was achieved (Scheme 1). Individual diastereomers were successfully separated by preparative HPLC[2], diluted with excess of water and extracted on C18 cartridges. Optimisation of the procedure followed by hydrolysis of the complexes and purification of the enantiomers of α-[^{11}C]methylDOPA and α-[^{11}C]methyltyrosine is underway.



Scheme 1. (^{13}C)Methylation or [^{11}C]methylation of tyrosine or DOPA synthons.

Stereochemistry of the diastereomers of α-(^{13}C)methylTyrK was disclosed by combined application ^{13}C NMR and circular dichroism (CD) spectroscopy. Assignment of predominant signals in ^{13}C NMR spectra of diastereomers of α-(^{13}C)methylDOPAK was done using analogy.

4 Conclusions

A radiomethylation procedure for routine preparation of (*S*)-α-[^{11}C]methylDOPA and (*S*)-α-[^{11}C]methyltyrosine has been developed, final radiochemical synthetic steps are now being optimised in Copenhagen University Hospital.

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[1] Second generation synthon with tert-Bu protective group on the phenolic oxygen was applied due to poor HPLC separation of methylated complexes with OMe protective group. At the same time tert-OBu protective group is much more sensitive to acidic cleavage then OMe protective group. This makes the final deprotection easier and requires application of carbocation scavengers during a deprotection procedure.

[2] The retention times of (S,S)-α-methylDOPAK and starting (S,S)-DOPAK are so close that the mixture of these compounds appears as a single peak on a chromatogram. This fact was discovered by application of the reconstructed ion current technique during HPLC-ESI-MS separation of a mixture of starting (S,S)-DOPAK and both (S,R)-α-(^{13}C)methylDOPAK and (S,S)-α-(^{13}C)methylDOPAK.