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Piperazine–Based N_4–Type 16–Membered Macroheterocycles and Their Nickel(II) Complexes

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*Square-planar diamagnetic nickel(II) complexes **5a** and **5b** containing 16-membered diamino-diimino ligands were prepared from the corresponding open-chain complexes **2a** and **2b** via condensation with o-phthalic dialdehyde in methanol. The solid-state structure of the starting complex **2b** revealed the cisoid conformation of aryl groups compared to the transoid one found in the case of **2a**. At the same time, the cisoid conformation is not retained in acetone solution: rather, the tert-Bu-substituted complex **2b** was fully transformed into the trans form whereas its analogue **2a**exhibits both cis and transforms in acetone solution. The cisoid conformation was also observed for the cyclic structures **5a** and **5b** by X-ray analysis and VT NMR experiments. The borohydride reduction of **5a** with subsequent cyanide-assisted removal of nickel led to a new 16-membered tetraazamacrocycle **6**. Its X-ray structure showed a cisoid conformation supported by two intramolecular hydrogen bonds that was also sustained in solution. VT NMR experiments revealed the degenerative interconvertion of a macrocycle with activation energy ca. 41.9±0.8 kJ/mol.*

Keywords*:* 16-Membered macroheterocycles, diamagnetic nickel(II) complexes, positron emission tomography, X-ray diffraction, NMR spectroscopy, conformational analysis.

Новые 16–членные тетраазамакроциклы на основе пиперазина и их никелевые комплексы

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*Конденсацией открыто-цепных диамагнитных комплексов никеля(II) **2a** и **2b** с фталевым альдегидом получены плоско-квадратные комплексы **5a** и **5b**, содержащие 16-членные диамино-диимино-макроциклические лиганды. В кристалле для **2b** найдена цисоидная конформация арильных групп, в то время как для аналога **2a** присутствует трансоидная. Найденные в кристалле конформации не сохраняются в растворе: трет-бутилсодержащий комплекс **2b** полностью превращается в транс-форму, для комплекса **2a** установлено сосуществование обоих конформеров. Цисоидная конформация макроциклических лигандов как в твердом виде, так и в растворе установлена методами РСА и динамического ЯМР для продуктов циклизации **5a** и **5b**. Восстановление иминных связей в **5a** борогидридом натрия с последующим удалением никеля с помощью цианида калия приводит к новому 16-членному тетрааминомакроциклу **6**. Исследование методом РСА показало для **6** в кристалле наличие цисоиодной конформации, поддержанной двумя внутримолекулярными водородными связями. Методами динамического ЯМР установлено, что найденная для твердого состояния*

конформация сохраняется и в растворе, однако макроцикл оказался конформационно гибким – он подвергается вырожденной интерконверсии с активационным барьером 41.9±0.8 кДж/моль.

Ключевые слова: 16-Членные макрогетероциклы, диамагнитные комплексы никеля(II), позитронно-эмиссионная томография, рентгеновская дифракция, ЯМР спектроскопия, конформационный анализ.

Introduction

The diagnostics and treatment of neurodegenerative diseases constitute one of the main problems of current neuroscience.[1] The early detection of the symptoms of cognitive deficiency is one of the main challenges in health sciences. Therefore, the creation of new and modification of known neuroimaging approaches becomes necessary for the solving of this key problem. The development of molecular-biological bases of novel diagnostical radiopharmaceuticals (RP) forms a comprehensive complex interdisciplinary problem in current biology, chemistry, physics and medicine.[2]

One of the main questions of the current radiopharmacology is the low efficiency of the diagnostical and therapeutic resources used in practice. The key problem of using of RP for positron-emission tomography (PET) is either the short radionuclide decay time or the complexity of its incorporation into the working molecule. The problem of short decay time can be solved by use of new RP-containing long-lived isotopes, particularly ^{64}Cu. To do this, we propose the elaboration of easily modified ligand systems with high affinity for the metal cation as well as wide possibilities of chemical modifications including conjugation to the biological vectors. One very promising approach is to explore chelate (Figure 1, top) and macrocyclic (Figure 1, bottom) effects at the ligand design stage, which includes the choice of the central diazacore, the nature (Q's) and length (k's) of the pendant arms and/or of the cyclizing units (n's).

With this paper we start to explore the series of diazamono- and bicycles as the central parts in the potentially useful ligand families. Some of our previous work on diazamono- and bicycles (piperazines;[3,4] homopiperazines;[5] bispidines[6,7]) is already published. In the context of this challenge, we noted with interest the complexes of tetradentate piperazine-based ligands recently studied by Wieghardt and co-workers,[8] and further developed by us.[9]

An interesting feature of the piperazine-based ligands in refs.[8,9] was the non-planar, pseudo-C_2 symmetric conformation that they adopt (with one phenyl ring tilted up and one down), even for the four-coordinate complexes with no additional axial donor ligand(s). We envisaged that such a conformation might, in the long term, allow for asymmetric synthetic applications for metal-ligand multiply-bonded complexes containing such ligands. Finally, we noted that the coordination chemistry of piperazines[10,11] and their open-chain[8,12–16] and macrocyclic[17–23] derivatives has only been developed for late transition metals.

The coordination and supramolecular, as well as synthetic, chemistry of piperazine-based molecules is a currently emerging area. This activity is defined, first of all, by the conformational features of the piperazine ring. For example, in a recent paper Stucchi *et al*. reported the application of piperazine-based peptidomimetics.[24]Although Thirunarayanan *et al*. reported the complexation properties of piperazinophanes,[25] they did not adequately address the conformational behavior of the ring. The other direction of the application of piperazine-based ligands is the use of titanium complexes designed for the ring-opening polymerization of *rac*-lactide.[26] Piperazine-based macrocycles are known to form supramolecular tubular structures[27] and promising receptor-mimic phanes.[28]

In the present work we have synthesized and studied the crystal and solution structures of two Cu(II) and four Ni(II) complexes with N_4-type ligands (Figure 2).

For **1a** and **1b** it has been shown that anilinic protons could be easily changed for $SiMe_3$ groups by the action of TMSCl/DABCO (trimethylsilyl chloride/1,4-diazabicyclo-[2.2.2]octane).[9] The already-mentioned interesting feature of the ligands **1a** and **1b** in their Ni, Cu, Pd and Ti complexes studied so far,[8,9] is the non-planar, *pseudo*-C_2 symmetric (*transoid*) conformation that they adopt.

Complexes **5a** and **5b** were included in this study because they contain the imine nitrogen that favors strong Ni-N bonding due to back-donation from Ni to the $\pi^*_{N=C}$ orbital. Another feature of cyclic diimine ligands **4a** and **4b** is the rigid xylylidene bridge between imine nitrogens, which creates an additional reason for the *cisoid* conformation. This conformation is of particular interest for catalysis due to one

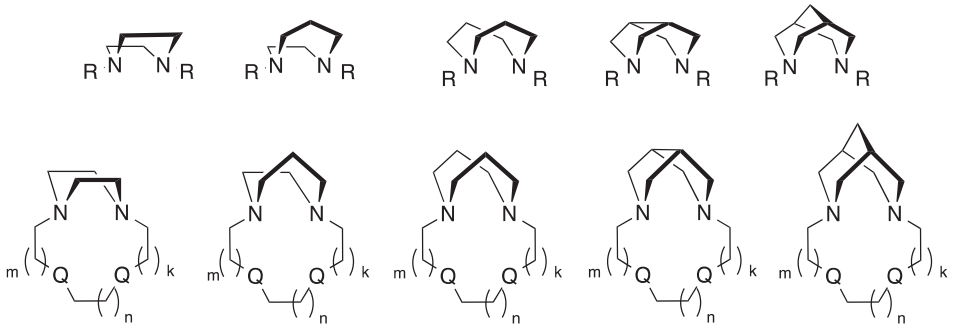
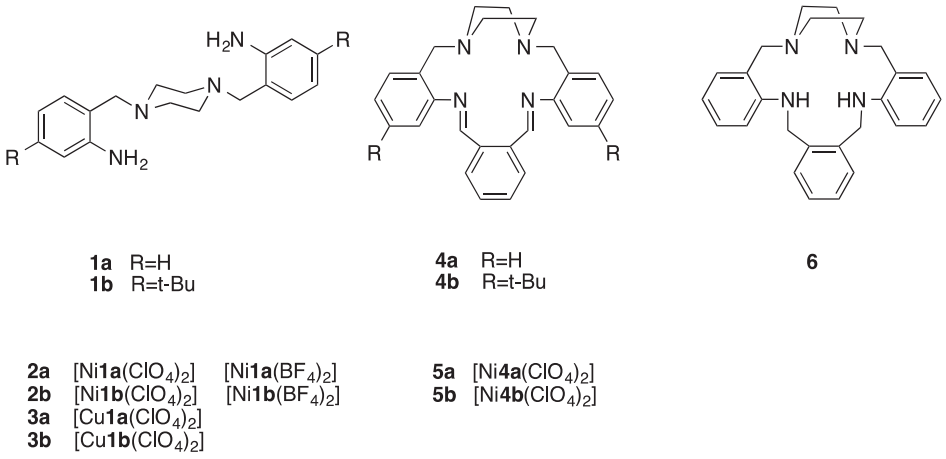


Figure 1. Structural design principles for the construction of potent ligands for ^{64}Cu PET.



1a R=H
1b R=t-Bu

4a R=H
4b R=t-Bu

6

2a [Ni**1a**$(ClO_4)_2$] [Ni**1a**$(BF_4)_2$]
2b [Ni**1b**$(ClO_4)_2$] [Ni**1b**$(BF_4)_2$]
3a [Cu**1a**$(ClO_4)_2$]
3b [Cu**1b**$(ClO_4)_2$]

5a [Ni**4a**$(ClO_4)_2$]
5b [Ni**4b**$(ClO_4)_2$]

Figure 2. Compounds studied in this work with their numbering.

of the sides of NiN_4 plane being available for the coordination of reagents. The *cisoid* conformation reinforced by their intrinsic cyclic nature was found in structure of ligand **4a** (within complex **5a**) and its reduced nickel-free form **6**.

Experimental

Methods and Instrumentation

All air-sensitive manipulations were carried out under an atmosphere of N_2 or Ar using standard Schlenk-like or dry-box techniques. Solvents were pre-dried over activated 4 Å molecular sieves and refluxed over K (hexane, THF), Na (toluene), Na/K (diethyl ether, pentane), or CaH_2 (dichloromethane) under an atmosphere of N_2 and collected by distillation. C_6D_6 was dried over K, and $CDCl_3$ dried over CaH_2. All deuterated solvents were distilled under reduced pressure and stored under N_2 in Young's ampoules in a dry box.

NMR samples were prepared in a dry box in Young's Teflon valve 5 mm tubes. ^1H and ^{13}C NMR spectra were recorded at 27 °C on a Bruker DPX 300 spectrometer. Chemical shifts were referred to the signals of the deuterosolvents (7.26 ppm and 77.0 ppm for $CDCl_3$, 5.32 ppm and 53.8 ppm for CD_2Cl_2, 2.05 ppm and 29.8 ppm for $(CD_3)_2CO$, respectively). IR samples were prepared in a dry box as Nujol mulls between KBr plates. Spectra were recorded on a Perkin Elmer 1600 Series FTIR spectrometer.

Syntheses

*1,4-Bis(o-aminobenzyl)-1,4-diazacyclohexane (**1a**).* 1,4-Bis-(*o*-nitrobenzyl)-1,4-diazacyclohexane (15.62 g, 0.044 mol) was dissolved in ethanol (250 ml) with stirring to give a yellow suspension and graphite (3 g) was added as a catalyst. The mixture was degassed, oxygen-free hydrazine monohydrate (46.08 g, 0.92 mol) was added and the reactants heated to reflux under a nitrogen blanketing atmosphere for 68 hours. After this time, the hot mixture was filtered and the residue extracted with chloroform (350 ml). Upon cooling to room temperature, colorless crystals grew from the ethanol filtrate and were isolated. The ethanol and chloroform solutions were combined and the solvents removed by rotary evaporation to yield a white solid with yellow traces which was recrystallized from a large volume of hot ethanol. The product in each case was dried *in vacuo*, yielding near-colorless crystals (10.25 g, 79 %). Found: C72.76, H 8.41, N 18.60 %. $C_{18}H_{24}N_4$ requires: C 72.94, H 8.16, N 18.90 %. *m/z* (IE) (%) 296 (M^+). IR (KBr) ν_{max} cm^{-1}: 3440vs [ν_{asym}(N-H)], 3264vs [ν_{sym}(N-H)]. ^1H NMR ($CDCl_3$, 300 K) δ_H ppm: 2.42 (8H, br.s, piperazine); 3.50 (4H, s, NCH_2Ar); 4.75 (4H, br.s, ArNH_2); 6.65 (4H, overlapping m, ArH); 6.97 (2H, dd $^3J_{HH}$=7.4, $^4J_{HH}$=1.2 Hz, ArH); 7.09 (2H, td, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.5 Hz, ArH).

*1,4-Bis(p-tert-butyl-o-aminobenzyl)-1,4-diazacyclohexane (**1b**).* 1,4-Bis(*p-tert*-butyl-*o*-nitrobenzyl)-1,4-diazacyclohexane (9.85 g, 0.021 mol) was dissolved in ethanol (200 ml) with stirring and graphite (3 g) was added as a catalyst. The flask was purged with argon, oxygen-free hydrazine monohydrate (22.53 g, 0.45 mol) was added and the mixture heated to reflux under an argon blanketing atmosphere for 68 hours. After this time, the hot mixture was filtered and the black residue extracted with chloroform (150 ml). Upon cooling to room temperature, colorless crystals grew from the ethanol filtrate and were isolated. The ethanol and chloroform solutions were combined and the solvents removed by rotary evaporation to yield a semisolid which was subsequently recrystallized from ethanol (150 ml) to yield a second batch of colorless crystals. The product in each case was dried *in vacuo* (5.91 g, 69 %). Found: C 76.27, H 10.02, N 13.51 %. $C_{26}H_{40}N_4$ requires: C 76.42, H 9.87, N 13.71. *m/z* (IE) 468 (M^+). IR (KBr) ν_{max} cm^{-1}: 3443vs , 3325vs [ν(N-H)]. ^1H NMR ($CDCl_3$, 300 K) δ_H ppm: 1.28 (18H, s, C$(CH_3)_3$); 2.41 (8H, br.s, piperazine); 3.46 (4H, s, NCH_2Ar); 4.71 (4H, br, ArNH_2); 6.68 (4H, overlapping m, ArH); 6.98 (2H, d $^3J_{HH}$=7.5, ArH). ^1H NMR ($(CD_3)_2CO$, 298 K) δ_H ppm: 1.23 (18H, s, C$(CH_3)_3$); 2.39 (8H, br s, piperazine); 3.40 (4H, s, NCH_2Ar); 4.97 (4H, br.s, ArNH_2); 6.58 (2H, dd $^3J_{HH}$=7.8, $^4J_{HH}$=1.9, ArH); 6.71 (2H, d $^4J_{HH}$=1.9, ArH); 6.84 (2H, d $^3J_{HH}$=7.8, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 300 K) δ ppm: 31.4 (C(CH_3)$_3$); 34.4 ($C(CH_3)_3$); 53.0 (piperazine); 61.6 (NCH_2Ar); 112.8, 114.7, 119.5, 130.1, 146.5, 151.6 (Ar).

*[Ni(**1a**)$(ClO_4)_2$] (**2a**).* The synthesis is in accordance with the procedures in ref. [8], using **1a** (2.0 g, 6.7 mmol) and $Ni(ClO_4)_2 \cdot 6H_2O$ (2.5 g, 6.8mmol) of to yield 3.67 g (98 %) of complex. *m/z* (FAB): 353 (Ni**1a**+H). IR (KBr) ν_{max} cm^{-1}: 3257; 3217; 3123 (ν_{N-H}). ^1H NMR ($(CD_3)_2CO$, 298 K) δ_H ppm: (**2a**-*cis*): 2.65, 2.99 (2H, each m, piperazine axial); 3.24, 3.65 (2H, each d, $^2J_{HH}$=12.9, NCH_2Ar); 3.83, 4.48 (2H, each m, piperazine equatorial); 7.33–7.66 (8H, set of m, aryl). (**2a**-*trans*): 2.67, 2.86 (2H, each m, piperazine axial); 3.27, 3.66 (2H, each d $^2J_{HH}$=12.8, NCH_2Ar); 4.20 (4H, m, piperazine equatorial); 7.30-7.73 (8H, set of m, aryl).

*[Ni(**1b**)$(ClO_4)_2$] (**2b**).* A solution of **1b** (1.2 g, 2.9 mmol) in chloroform (30 ml) and $Ni(ClO_4)_2 \cdot 6H_2O$ (1.07 g, 2.9 mmol) was refluxed for 30 minutes. After cooling, the reaction mixture was cooled in a freezer (–18 °C) for 7 hours. An orange-red solid was filtered off, washed with chloroform (3 times) and diethyl ether

(3 times) to yield the product (1.74 g), an additional amount of which (0.33 g) could be obtained in the same manner from the mother liquor after one day in freezer. The product was air-dried and the total yield was 2.61 g (89 %). Found: C 41.66, H 5.30, N 7.12 %; requires: C 41.28, H 5.26, N 7.13 %. IR (KBr) ν_{max} cm^{-1}: 3276; 3200; 3126; 3077. ^{1}H NMR ($(CD_3)_2CO$, 298 K) δ_H ppm: 1.39 (18H, s, *t*-Bu); 2.70, 2.83 (2H, each m piperazine axial); 3.22, 3.54 (2H, each d, $^2J_{HH}$=13.0, NCH_2Ar); 4.21 (4H, m, piperazine equatorial); 7.45-7.55 (6H, m, aryl). $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$, 298 K) δ ppm: 31.4 (C(CH_3)$_3$); 35.8 ($C(CH_3)_3$); 54.7, 55.3, 55.9 (CH_2N); 123.3, 125.5, 131.6 (CH aryl); 126.8, 143.6, 155.1 (C aryl).

*[Ni(**1a**)(BF$_4$)$_2$].* The synthesis was similar to that of **2a**. From 0.5 g (1.7 mmol) of **1a** and 0.574 g (1.7 mmol) of $Ni(BF_4)_2{\cdot}6H_2O$ were obtained 0.81 g (87 %) of an orange-red complex in the form of a monohydrate. Found: C 39.77, H 4.38, N 10.03 %. $C_{18}H_{26}B_2F_8N_4NiO$ requires: C 39.54, H 4.79, N 10.25 %. IR (KBr) ν_{max} cm^{-1}: 3288; 3225; 3148 ($\nu_{N\text{-}H}$). *m/z* (FAB): 441 (Ni(**1a**)(BF_4)); 353 (Ni(**1a**)+H). NMR is similar to **2a**.

*[Ni(**1b**)(BF$_4$)$_2$].* A green solution of $Ni(BF_4)_2{\cdot}6H_2O$ (0.83 g, 2.45 mmol) in ethanol (15 ml) was added to a stirred solution of **1b** (1 g, 2.45 mmol) in chloroform (15 ml). Upon mixing, an immediate color change was observed and the resulting red solution was refluxed for 3 hours before being allowed to cool to room temperature. The solvents were subsequently removed by rotary evaporation to yield an orange-red solid, which was scraped down and washed with diethyl ether (20 ml), before being dried *in vacuo* to give the desired product as an orange powder in the form of a monohydrate (1.47 g, 91 %). Found: C 47.89, H 6.52, N 8.50 %. $C_{26}H_{42}N_4B_2F_8NiO$ requires: C 47.39, H 6.42, N 8.50. *m/z* (FAB) 553 ([Ni**1b**(BF_4)])$^+$. IR (KBr) ν_{max} cm^{-1}: 3301, 3232, 3162 [$\nu_{N\text{-}H}$]. ^{1}H NMR ($(CD_3)_2CO$, 298 K) δ_H ppm: 1.39 (18H, s, C(CH_3)$_3$); 2.83 (2H, br.s, piperazine); 3.02 (2H, br.s, piperazine); 3.32 (2H, br.d, NCH_2Ar); 3.55 (2H, d, $^2J_{HH}$=13.2, NCH_2Ar); 4.20 (4H, br.m, piperazine); 7.74 (2H, br.s, ArH); 7.52 (4H, br.s, ArH). $^{13}C\{^1H\}$($(CD_3)_2CO$, 298 K) δ ppm: 31.3 C(CH_3)$_3$); 35.8 ($C(CH_3)_3$); 54.5, 55.1, 55.6 (CH_2); 123.3, 125.6, 127.0, 131.6, 143.6, 155.1 (Ar).

*[Cu(**1a**)(ClO$_4$)$_2$] (**3a**).* The synthesis is in accordance with the procedures in ref. [8]

*[Cu(**1b**)(ClO$_4$)$_2$] (**3b**).* Synthesis is similar to **3a**. Yield 76 % (in the form of dihydrate). Found: C 44.71, H 6.05, N 7.39 %. $C_{26}H_{44}Cl_2CuN_4O_{10}$ requires: C 44.16; H 6.27; N 7.92 %.

*[Co(**1a**)(ClO$_4$)$_2$].* Synthesis is similar to that of **3a**. 0.6 g (2 mmol) of **1a** and 0.5 g (2 mmol) of $Co(OAc)_2{\cdot}4H_2O$ in $CHCl_3$/EtOH with subsequent changing of the anion by use of aqueous $HClO_4$. Yield 66 %. Found: C 39.27, H 4.31, N 10.15 %. $C_{18}H_{24}Cl_2CoN_4O_8$ requires: C 39.01, H 4.36, N 10.11.

*[Ni(**4a**)(ClO$_4$)$_2$]* (***5a***). Solution of 0.419 g (3.1 mmol) of phthalic dialdehyde in MeOH was added to solution of 0.836 g (1.5 mmol) of **2a** in MeOH (total 50 ml). After 3 hours of stirring the yellow precipitate started to form. The reaction mixture was left overnight with stirring at room temperature. After 17 hours the reaction was quenched by filtering off the yellow product. Air-drying gave yield 75 % (0.706 mg). Recrystallization of the product from acetone gave analytically pure compound as the acetone trisolvate. Found: C 51.39, H 5.44, N 6.98 %. $C_{35}H_{44}Cl_2N_4NiO_{11}$ requires: C 50.87; H 5.37; N 6.78 %.^{1}H NMR ($(CD_3)_2CO$, 298 K) (atoms notations see Figure 6) δ_H ppm: 2.67, 2.98 (2H, each m, $H^{a,c}$); 3.47, 3.92 (2H, each d $^2J_{HH}$=13.1, $H^{e,f}$); 3.99, 4.34 (2H, each m, $H^{b,d}$); 7.44–7.64 (8H, set of m, *Ar*CH_2); 8.09, 8.19 (2H, each m, *Ar*(CH=N-)$_2$); 8.78 (2H, s, CH=N). $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$, 298 K) δ ppm: 53.6, 55.9, 56.4 (NCH_2); 124.4 (CH^5); 129.7 (C^1); 130.5 (CH^3, C^6); 131.3 (CH^2); 132.3 (CH^4); 134.6 (CH^9); 137.9 (CH^8); 146.4 (C^7); 177.4 (CH=N).

*[Ni(**4b**)(ClO$_4$)$_2$] (**5b**).* Synthesis is similar to **5a**. Yield 57 %, yellow powder in the form of a dihydrate. Found: C 51.58, H 5.63, N 7.02 %. $C_{34}H_{46}Cl_2N_4NiO_{10}$ required: C 51.02, H 5.79, N 7.00 %. ^{1}H NMR ($(CD_3)_2CO$, 298 K) (for atom notations see Figure 6) δ_H ppm: 1.34 (18H, s, C(CH_3)$_3$); 2.63, 2.95 (2H, each m, $H^{a,c}$); 3.43, 3.84 (2H, each d, $^2J_{HH}$=12.9, $H^{e,f}$); 3.87, 4.33 (2H, each m, $H^{b,d}$); 7.42 (2H, d, $^3J_{HH}$=7.9, H^2); 7.57 (2H, dd, $^3J_{HH}$=7.9, $^4J_{HH}$=1.8, H^3); 7.60 (2H, d, $^4J_{HH}$=1.8, H^5); 8.05 (2H, m, H^9); 8.17 (2H, m, H^8); 8.77 (2H, s, CH=N). $^{13}C\{^1H\}$ NMR ($(CD_3)_2CO$, 298 K) δ ppm: 31.4 (C(CH_3)$_3$); 35.9 ($C(CH_3)_3$); 53.6, 56.7 (NCH_2 piperazine); 55.9 (NCH_2Ar); 121.3 (CH^5); 126.8 (C^1); 127.3 (CH^3); 130.4 (C^6); 131.1 (CH^2); 134.4 (CH^9); 137.7 (CH^8); 146.5 (C^7); 156.3 (C^4); 177.5 (CH=N).

*$C_{13}H_{15}N_2$ (**6**).* A mixture of **5a** (0.63 g, 0.8 mmol) and $NaBH_4$ (0.15 g, 3.9 mmol) of was refluxed in H_2O (50 ml) for 15.5 hours. Then to the cooled reaction mixture NaCN (0.2 g, 4.1 mmol) was added. The reaction mixture was heated for 5.5 hours. After work up 0.17 g of product **6** was obtained (53 %) in the form of semihydrate. Found: C 76.64, H 7.49, N 13.62 %. $C_{26}H_{32}N_4O$ requires: C 76.62, H 7.67, N 13.75. ^{1}H NMR (CD_2Cl_2, 300 K) (atoms notations see Figure 6) δ_H ppm: 2.08 (4H, m, $H^{a,c}$); 2.65 (4H, m, $H^{b,d}$); 3.40 (4H, s, $H^{e,f}$); 4.27 (4H, d, $^3J_{HCNH}$=4.4, $H^{g,h}$); 6.53 (2H, br.s, NH); 6.58 (2H, t, $^3J_{HH}$=7.3, H^3); 6.75 (2H, d, $^3J_{HH}$=7.9, H^5); 6.93 (2H, d, $^3J_{HH}$=7.2, H^2); 7.18 (2H, t, $^3J_{HH}$=7.7, H^4); 7.34, 7.50 (2H, each m, $H^{8,9}$). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 300 K) δ ppm: 44.8 (CH_2NH); 48.9 ($N(CH_2CH_2)_2N$); 60.9 ($N(CH_2CH_2)_2NCH_2$); 109.8, 116.3, 128.0, 128.8, 130.0, 132.1 (CH aryl); 122.8, 138.2, 149.1 (C aryl). ^{1}H NMR (CD_2Cl_2, 177 K) δ_H ppm: 1.75, 2.16 (2H, each br s, $H^{a,c}$); 2.33, 2.72 (2H, each br.s, $H^{b,d}$); 2.92, 3.70 (2H, each d, $^2J_{HH}$=12.0, $H^{e,f}$); 4.07 (2H, t, $^2J_{HH}$=10.0, $^3J_{HCNH}$=10.0, $H^{g\text{ or }h}$); 4.25 (2H, d, $^2J_{HH}$=10.0, $H^{h\text{ or }g}$); 6.55 (2H, t $^3J_{HH}$=7.0, H^3); 6.68 (4H, m, NH, H^5); 6.91 (2H, d, $^3J_{HH}$=6.8, H^2); 7.14 (2H, t, $^3J_{HH}$=7.2, H^4); 7.31, 7.39 (2H, each m, $H^{8,9}$). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 177 K) δ ppm: 43.2 (CH_2NH); 46.1, 49.0 ($N(CH_2CH_2)_2N$); 59.6 ($N(CH_2CH_2)_2NCH_2$); 108.6, 115.2, 127.1, 127.8, 129.0, 131.4 (CH aryl); 121.8, 136.9, 147.7 (C aryl).

Crystallographic Studies

Crystal data collection and processing parameters are given in Table 1. Data were collected using a Stoë Stadi-4 four-circle diffractometer equipped with an Oxford Cryosystems low-temperature device. Data were collected at 150 K using ω or ω–2θ scans with Mo-*K*α radiation (λ=0.71073 Å) and absorption corrections were applied as necessary to the data. Equivalent reflections were merged and the structures were solved by direct methods. Subsequent Fourier-difference syntheses revealed the positions of all other non-hydrogen atoms. All non-H atoms were refined anisotropically and hydrogen atoms were placed geometrically: these were refined in a riding model with fixed isotropic displacement parameters, and suitable weighting schemes were applied. Crystallographic calculations were performed using SHELXS-97,[29] SHELXL-2014/7,[30] SIR92,[31] and CRYSTALS.[32] CCDC numbers: CCDC 1503842-1503844.

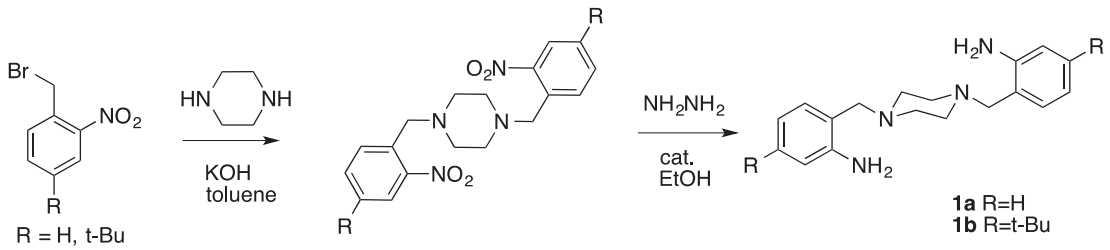
Results and Discussion

Preparation of Starting Materials

4-*tert*-Butyl-1-methyl-2-nitrobenzene was synthesized from 4-*tert*-butyltoluene according to the published method.[33] This compound was subsequently converted to 1-bromomethyl-4-*tert*-butyl-2-nitrobenzene as described in[34].

Syntheses of starting piperazine-based ligands **1a** and **1b** were performed according to the published procedures[8,9] (Scheme 1).

2-Nitrobenzylbromide or its *tert*-Bu congener and powdered potassium hydroxide were added as solids to a stirred suspension of piperazine in toluene and the



Scheme 1. Syntheses of ligands **1a** and **1b**.

mixture heated to 60 °C for 20 hours. After this time, a red-orange solution containing precipitate had formed, which was cooled and filtered before solvent removal was carried out to give an oily orange-yellow solid. Washing the solid with diethyl ether and drying the product *in vacuo* yielded 1,4-bis(2-nitrobenzyl)-1,4-diazacyclohexane or 1,4-bis(4-*tert*-butyl-2-nitrobenzyl)-1,4-diazacyclohexane, respectively, as pale yellow powders. Of concern, however, is the low yield (19 %) obtained for this coupling reaction in the case of *tert*-Bu substituted compound when compared with high yields (76 %) achieved for nonsubstituted species. Attempts to improve the yield by increasing the reaction temperature and/or using longer reaction times were unsuccessful and resulted in even lower yields (with apparently increased generation of polymeric side product).

Nitro-containing compounds were subsequently reduced to give **1a** and **1b** according to a modified version of the Wieghardt's procedure. Thus, a solution of the starting compound in ethanol in the presence of graphite catalyst was purged with argon and oxygen-free hydrazine monohydrate was added with stirring. The mixture was subsequently heated to reflux for 68 hours under an argon blanketing atmosphere. After this time, the mixture was filtered whilst still hot and the product **1a** or **1b** was isolated as colorless crystals upon cooling the filtrate to room temperature. Further product **1b** was obtained by extraction of the filtration residue with chloroform, combing the extracts with the ethanol filtrate and removing the solvents by rotary evaporation. Purification was subsequently achieved by recrystallization from ethanol.

The ligand **1a** was fully characterized in[8], its X-ray structure in[3], and the X-ray structure of its *tert*-Bu analogue **1b** in[9]. The main structural features of **1b** resemble those of **1a**. The piperazine ring adopts a thermodynamically favorable chair conformation with the benzyl substituents occupying equatorial positions. There are, in addition, weak intramolecular hydrogen bonds [NH···N = 2.4(1) Å] between the piperazine nitrogen atoms and one of the 2-amino group hydrogen atoms. The conformational preferences for central piperazine moiety with NH_2-substituents lying at the opposite sides of the ring obviously preclude successive intramolecular [1+1]-type macrocyclizations.

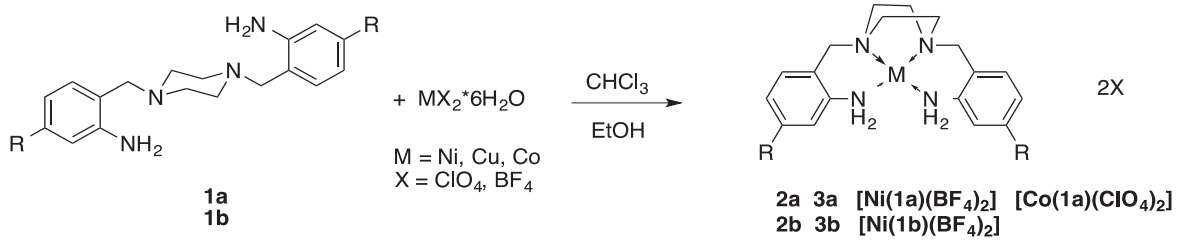
Cyclization Attempts

The above mentioned conformational features of piperazine-based ligands could be used to account for the impossibility of free ligands to form the desired cyclic products in the reactions with C_2, C_3 and C_4 di-electrophiles, such as glyoxal, 1,2-dibromoethane, 1,1,2,2-tetramethoxypropane, acetylacetone and *o*-phthalic dialdehyde. Only polymeric products were formed.

Thus, we decided to use the template effect of metal coordination, because it was found that in the solid state Ni, Cu and Pd complexes of **1a** had piperazine backbone in a boat conformation and both NH_2-fragments in close proximity.[8] We applied the synthesis to both copper and nickel complexes, but nickel derivatives were found to be diamagnetic, allowing more detailed NMR analysis of product mixtures.

Complexes **2a**, **2b, 3a** and **3b** were prepared in high yields using the published procedure for **1a**[8] by refluxing of mixtures of equimolar solutions of ligands in $CHCl_3$ and metal salts in EtOH for 30 min (Scheme 2). The structure of **2b** in the solid state was determined by single-crystal X-ray diffraction studies (see below).

In order to check the effect of the counterion on the cyclization, the complexes [Ni(**1a**)$(BF_4)_2$] and [Ni(**1b**)$(BF_4)_2$] were also prepared in a similar manner. A solution of $Ni(BF_4)_2 \cdot 6H_2O$ in ethanol was added to a stirred solution of the ligand in chloroform. The resulting red solution was refluxed for 3 hours, allowed to cool and the solvent was removed by rotary evaporation. The solid obtained was



Scheme 2. Synthesis of complexes **2a, 2b**.

thoroughly washed with diethyl ether before drying *in vacuo* to yield the desired product as an orange powder.

Initial work on cyclization using [Ni(**1a**/**b**)$(BF_4)_2$] focused on a number of non-Schiff base reactions. A variety of bases (K_2CO_3, NaOMe) and electrophiles (α,α'-dibromo-*o*-xylene, $TsO(CH_2)_2OTs$) was employed with little success. Indeed, a common feature of these reactions was removal of the nickel template from the complex following reaction with base, this presumably arising due to the water-sensitive nature of the neutral complex formed following deprotonation.

The cyclizations of perchlorate complexes with C_2-dielectrophiles were also attempted under different conditions. Reactions of **2a** with aqueous glyoxal or 2,3-butanedione in MeOH or acetone resulted in formation of unidentified dark products. Reactions of **2a** or **2b** with 1,2-dibromoethane in the presence of DABCO resulted within one minute in a change of color from orange to deep purple with subsequent fast decolourization of solution. However, only starting ligands were isolated. These observations could be explained by the primary formation of deprotonated complexes [Ni(**1**-H)ClO_4] or even [Ni(**1**-2H)] with their consequent decomposition by the action of moisture. For this reason all further reactions (unless stated) were carried out in Schlenk-type vessels with solvents free of water and oxygen. Even under these conditions no products of C_2-dielectrophile reactions were isolated. Another explanation for the color change is that the amine is acting not as a base, but as an additional ligand with formation of less stable five- or six-coordinate complexes: with the NCS ligand the color of the latter was found to be deep blue.[8]

Also no products could be isolated from the reaction of **2a** with Li hexamethyldisilylazide with subsequent addition of 1,2-dibromoethane in THF, or from the reaction of **2a**/**2b** with $(PhCO)_2$.

In the case of two C_3-dielectrophiles two different types of products were found. Reaction of **2a** with 1,1,2,2-tetramethoxypropane in MeOH resulted in a yellow powder, barely soluble in common organic solvents, thus preventing proper characterization. When acetylacetone was used in MeOH, the formation of blue powder was observed. Its NMR and IR spectra were consistent with open-chain products with 1:2 composition.

In the case of C_4-dielectrophiles, reactions of **2a** and 1,2-dibromoxylene either with DABCO in acetone or with K_2CO_3 in methanol did not result in any products.

Reactions of orange methanolic solutions of **2a** and **2b** with two equivalents of *o*-phthalic dialdehyde at room temperature in a degassed Schlenk-type flask resulted in the formation of fine yellow powders, **5a** and **5b**, respectively (Scheme 3). The yields of products were 74 % and 57 %, respectively, after recrystallization from acetone. The structures of **5a** and **5b** were confirmed by IR and NMR spectroscopy, FAB mass-spectrometry, elemental composition and X-ray analysis for **5a**.

While the reactions of **2a** and **2b** with phthalic dialdehyde in methanol yielded the expected Schiff-base macrocyclic complexes **5a** and **5b** as clean yellow precipitates in good yields, [Ni(**1a**)$(BF_4)_2$] reacted under the same conditions to form a yellow product (yield 32 %) together with a light brown solid which gave broad, ill-defined NMR features, characteristic of the presence of paramagnetic species. Therefore, it would appear that the presence of perchlorate as the anion is necessary to facilitate template-based synthesis of this class of macrocycles. Indeed, the importance of the anion in the template process is widely recognized, since the balance between the size of the cation and anion will determine the degree of dissociation of the metal salt in the reaction medium.[35] A number of studies have also indicated that the perchlorate anion is one of the best anions to use in template-based syntheses.[36]

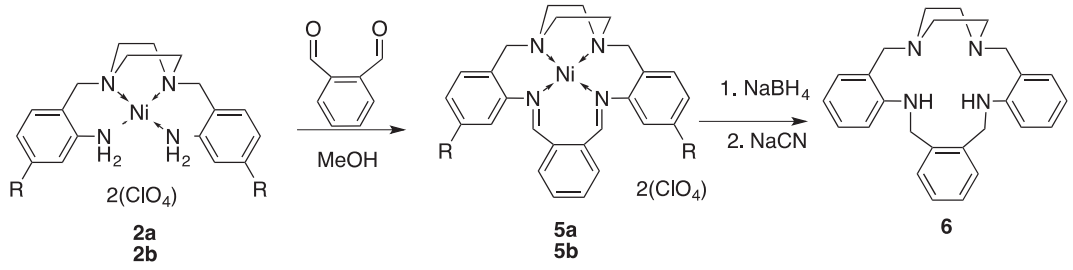
Attempts to remove nickel metal from the complexes **5a** and **5b** to obtain the free macrocycles **4a** and **4b** or to reduce the imine bond while preserving of the metal inside the cavity proved unsuccessful. The only promising result was obtained in the sequence "reducing of imine – removing the nickel" (Scheme 3). In this case the new 16-membered tetraazamacrocycle (**6**) was isolated from the reaction mixture with moderate yield. The structure of **6** in the solid state and solution was proved by single-crystal X-ray diffraction study and by different NMR techniques (see below).

It should be mentioned here that the synthesis of 16-membered tetraazamacrocycles is a separate task. While the composition [3.3.3.3] (the figure means a number of carbon atoms in between N's) is widespread in chemistry due to thousands of cyclic tetra(methynopyrroles) belonging to porphyrin family and some other structures like products of template condensation of beta-dicarbonyls with 1,3-diamines, the corresponding [2.3.4.3] system was virtually unknown before this work: data were taken from the Cambridge Structural Database [37] and SciFinder.

X-Ray Studies

In this paper we report on the crystal structure of nickel complexes **2b**, **5a**, and tetraazamacrocycle **6** (Figure 3, Table 2).

Complexes **2b** and **5a** contain a square-planar nickel(II) ion (the sum of the *cis* valence angles around each metal is



Scheme 3. Synthesis of 16-membered cyclic complexes and macrocycle **6**.

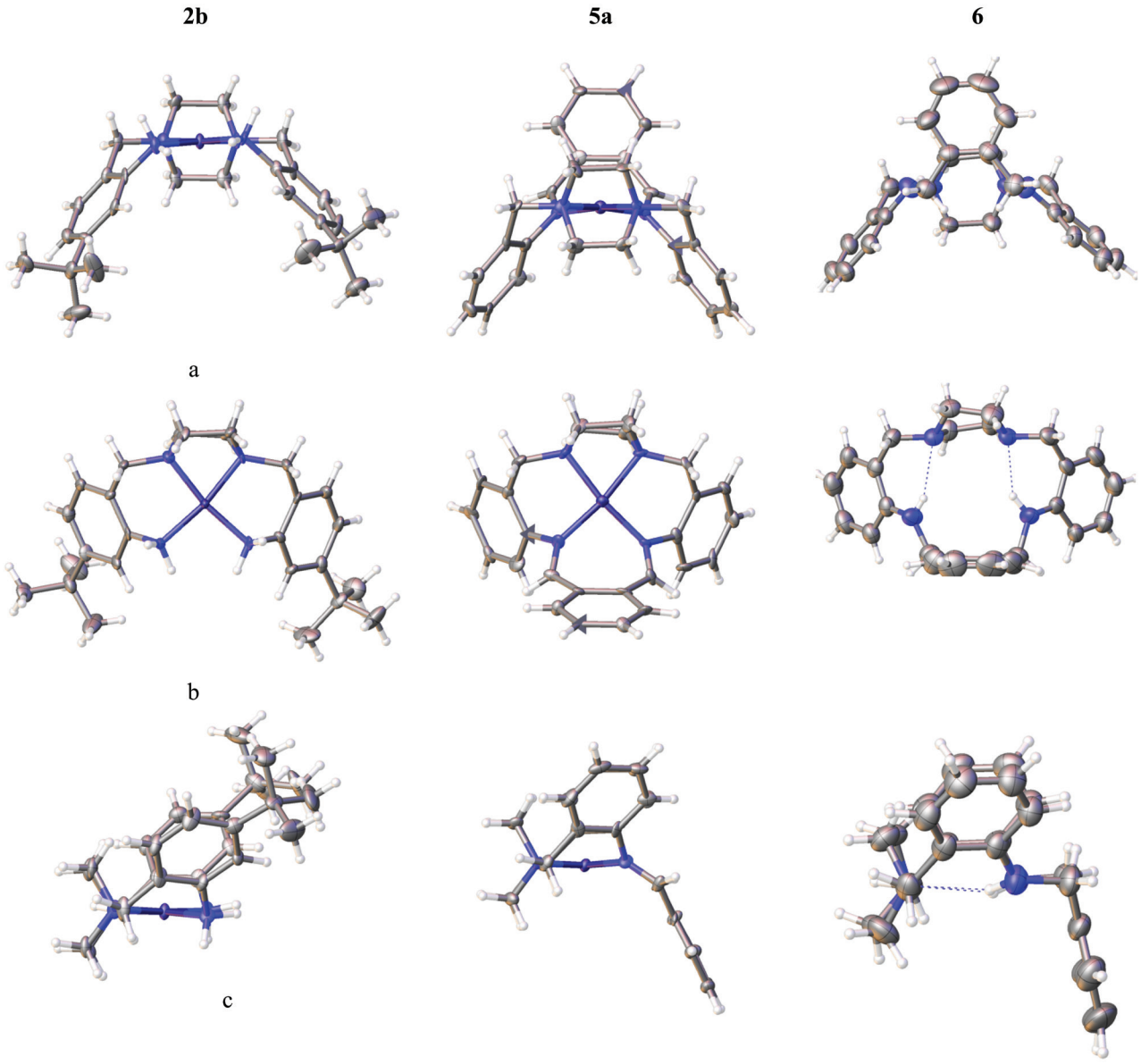


Figure 3. Three projections of molecular structures of **2b**, **5a** and **6**. Projections to mean planes of methylene carbon atoms of piperazine moiety (a); projections to mean planes of four nitrogen atoms (b); side projections (c). All solvent molecules are omitted for clarity. For complexes **2b** and **5a** the couteranions are not shown. In case of **6** (views b,c), the intramolecular hydrogen bonds are shown as dotted lines. For **5a** and **6** only one of two independent molecules is shown. Figures were generated using OLEX2.[40]

close to 360°, and the deviations of the Ni atoms from the N_4 least-squares mean planes are no more than 0.003Å for **2b** and 0.083 Å for **5a**), coordinated to a tetradentate ligand **1b** and **4a**, respectively, and uncoordinated perchlorate ions. The shortest distance between a nickel center and a perchlorate oxygen atom is 2.826(5) Å for **5a**; this weak interaction might explain the bigger nickel deviation from the N_4 mean plane in the case on cyclic diimine ligand **4a** compared to that of **2b**. However, in the crystal structure of **2b** a weak bifurcated intermolecular hydrogen bond between oxygen atom of perchlorate anion and two NH's (NH···O 2.15 and 2.14 Å) is observed.

The structure of **2b** is highly interesting as it contrasts with that of **2a**, obtained by Wieghardt, for which the benzene rings are found to be *trans* to each other.[8] Indeed, the presence of the bulky ^{t}Bu-groups in ligand **1b** might be expected to favor the *transoid* geometry even more strongly but this is not the case. This situation might be explained by the presence of above mentioned hydrogen bond keeping two N-H fragments in close proximity (NH···HN 2.23 Å).

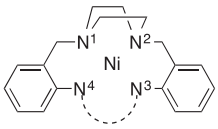
The same *cisoid* configuration of the organic ligand **4a** is found within the structure of **5a**. The conformation of the macrocycle **4a** in **5a** resembles, to some extent, the one published for Ni(II) complexes with 15-membered tetraazaannulenes[38] – both benzylic fragments are oriented up and the residue of phthalic aldehyde is pointed down (see Figure 3c, middle).

The conformation of **6** in the solid state is somewhat similar to that of **4a** within the structure of **5a** – both benzylic fragments are oriented up and the residue of phthalic aldehyde

Table 1. Crystallographic data for structures **2b**, **5a**·**0.5(C$_3$H$_6$O)** and **6**.

	2b	**5a**·**0.5(C$_3$H$_6$O)**	**6**
Empirical formula	$C_{26}H_{40}Cl_2N_4NiO_8$	$C_{29}H_{32}Cl_2N_4NiO_9$	$C_{13}H_{15}N_2$
Formula weight	666.24	710.19	199.28
Crystal system	monoclinic	orthorhombic	triclinic
Space group	$P2_1/n$	$P2_12_12_1$	P-1
a (Å)	12.624(5)	8.431(4)	12.2353(15)
b (Å)	11.300(3)	20.148(6)	12.2229(9)
c (Å)	21.279(7)	35.329(11)	16.3753(13)
α (°)	90	90	81.265(6)
β (°)	90.40(4)	90	69.877(7)
γ (°)	90	90	84.484(10)
V (Å^3)	3035.4(18)	6001(4)	2270.2(4)
Z	4	8	4
Dc	1.458	1.572	1.166
μ (mm^{-1})	0.868	0.887	0.07
F(000)	1400	2944	856
Radiation type	Mo-Kα	Mo-Kα	Mo-Kα
θmax (°)	25.08	25.01	25.01
Reflections collected	6051	6278	10334
Reflections with I>2σ(I)	3432	4301	5178
Parameters refined	370	880	541
Flack parameter	–	0.15(3)	–
Goodness-of-fit	1.13	1.22	1.13
Refinement on:	F	F^2	F
R and wR (F^2 refinement, I>2σ(I))	–	0.0803, 0.135	–
R and R_w (F refinement, I>2σ(I))	0.085, 0.047	–	0.0685, 0.0476

Table 2. Selected geometric parameters (Å) of molecular structures of **2b**, **5a** and **6**.



	N^1-N^2	N^3-N^4	Ni-N^1 Ni-N^2	Ni-N^4 Ni-N^3	N^1-N^4 N^2-N^3
2a[8]	2.402	2.831	1.925(5) 1.920(6)	1.928(5) 1.916(6)	2.800 2.827
2b	2.379(7)	2.871(6)	1.914(5) 1.937(4)	1.936(5) 1.919(5)	2.816(7) 2.810(7)
5a	2.373(9)	2.743(9)	1.929(6) 1.936(6)	1.881(6) 1.886(6)	2.806(9) 2.830(8)
	2.392(9)	2.749(9)	1.928(6) 1.919(6)	1.898(6) 1.886(6)	2.806(9) 2.804(8)
6	2.587(3)	4.093(3)	n.a.*	n.a.*	2.885(3) 2.862(3)
	2.598(3)	4.118(4)			2.850(3) 2.847(3)

n.a. – not applicable

is pointed down (see Figure 3c, right), but the difference in the nature of nitrogen functions (amine *vs*. imine) and the absence of a nickel ion makes the structure of the macrocycle more relaxed compared to **4a** – all distances between nitrogen atoms are significantly longer (see Table 2). In contrast to the nickel complexes **2b** and **5a**, molecules of **6** possess intramolecular hydrogen bonds (2.14/2.15 Å and 2.16/2.21 Å for two independent molecules) between piperazine nitrogens and secondary amines arose upon the reduction of imine double bond.

It is important to notice that the distance between anilinic/imine/amine nitrogen pairs (N^3-N^4, Table 2) differs for all compound types, being the biggest for the free ligand **6**. At first glance, this distance in the starting compounds **2b** could be responsible for the unsuccessful results for the cyclizations with C_2 and C_3 dinucleophiles, depending on whether it matched the distance between the reacting sides of the reagent. Of course, this will depend on the reaction type and mechanism (see, for example, Alabugin's discussion of the Baldwin rules[39]). Since there are no crystal structures of [2.3.4.3] tetraazamacrocycles or of their nickel complexes, we compared the crystal data for nickel complexes with [3.2.3.2] type ligands, where the imine nitrogens are separated by two-carbon atoms bridges, and [2.2.2.3] systems, where the imine nitrogens are separated by three-carbon atoms bridge. The N…N distances in the former case lie in the range 2.552-2.729 Å, whilst for the latter the values 2.765 Å and 2.776 Å are found. Our data for the complex **5a** possessing four-carbon atom bridges between two imine nitrogens are 2.743(9)/2.749(9) Å, the acyclic complexes **2a** and **2b** possess the values 2.831 Å and 2.871(6) Å, respectively.

While analyzing the crystal data in order to estimate the geometric "fitness" for the cyclization reaction to occur, one should keep in mind that the solid-state conformation is not necessary sustained in solution. The examples are given in the next section.

NMR Studies

The noticeable feature of ^{1}H NMR spectra of complexes with perchlorate and tetrafluoroborate counteranions is that the spectra of the perchlorate compounds are much sharper than those of the tetrafluoroborate salts, the latter possessing broad signals with poorly resolved couplings. This feature is presumably due to differences in the degree of anion coordination in solution.

When analyzing the conformation (*transoid vs. cisoid*) of the ligands within acyclic complexes **2a,b**, the main question is how to define the solution conformation of molecules that could be intrinsically flexible. For example, the aliphatic part of the ^{1}H NMR spectrum of **2b** contains three multiplets centred at 2.70, 2.83 and 4.21 ppm. In the ^{13}C NMR spectrum of **2b** three signals at 54.7, 55.3 and 55.9 ppm – one being due to the benzylic carbons, the others arising from the two unequivalent sets of piperazine carbons – are clearly seen, but these data do not convey any informationabout the conformation of the complexes.

The unequivocal proof of the conformation in the complex is based on the establishment of the spin system of the piperazine protons. For the *transoid* conformation (C_2 symmetry, Figure 4, top), the signals of piperazine protons should give an ABCD spin system, which can give rise to up to six pairwise spin-spin interactions. This means that in the COSY spectrum one could envisage up to six cross-peaks. In contrast, in the *cisoid* conformation (C_s symmetry, Figure 4, bottom), the piperazine protons give rise to two unbound spin systems *AA'BB'* and *CC'DD'*, for which in COSY spectrum only two cross-peaks corresponding to geminal coupling interactions might be seen.

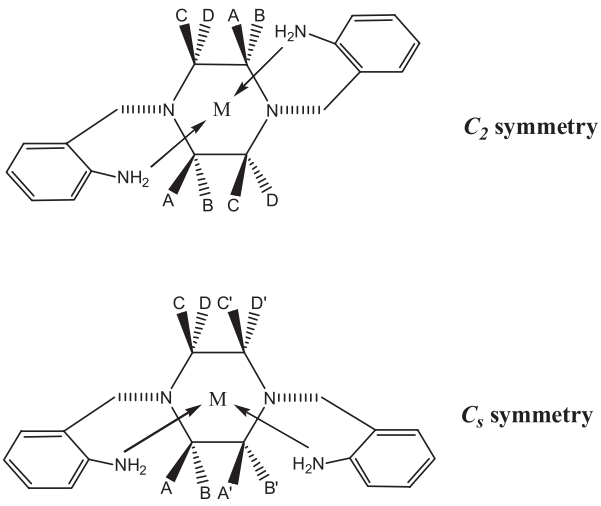


Figure 4. Schematic representation of ligand conformations with the local symmetry showing the proton systems discussed in text: top – *transoid*, bottom – *cisoid*.

In the *COSY45* spectrum of **2b**, besides two cross-peaks belonging to benzylic protons, three cross-peaks corresponding to interactions A-C, A-B and C-D are clearly seen (Figure 5a, see also Figure 4 for references). These data unequivocally confirm the *transoid* conformation for **2b** in acetone solution. Now we can suggest the following assignments of aliphatic signals: 2.70 and 2.83 ppm (A and C axial protons), and 4.21 ppm (B and D equatorial protons).

In contrast, in the *COSY45* spectrum of **2a** two sets of cross-peaks are seen for piperazine protons. This allows us to propose for **2a** the existence of a mixture of *transoid* and *cisoid* conformations in solution.

Two sets of signals of piperazine and benzylic protons, corresponding to *cisoid* and *transoid* conformations, are observed in the ^{1}H spectrum of complex **2a**. It is confirmed by the *COSY45* spectrum, in which there are three cross-peaks of piperazine protons of *transoid* form and two cross-peaks of those of *cisoid* form. The ratio of the two conformations is not constant. Heating a sample of **2a** in $(CD_3)_2CO$ to 333 K followed by cooling to 215 K leads to isomerization of the initially predominant *cisoid* configuration to the *transoid* one. In this case the aliphatic moiety of the proton spectrum is similar to that in the spectrum **2b**. The *transoid* conformation is probably the more stable in solution.

Complexes **5a** and **5b** with cyclic diaminodiimine ligands **4a** and **4b** in both solid state and in solution might exist only in the *cisoid* conformation due to ligand rigidity. This is confirmed by *COSY45* spectrum of **5b**, in which

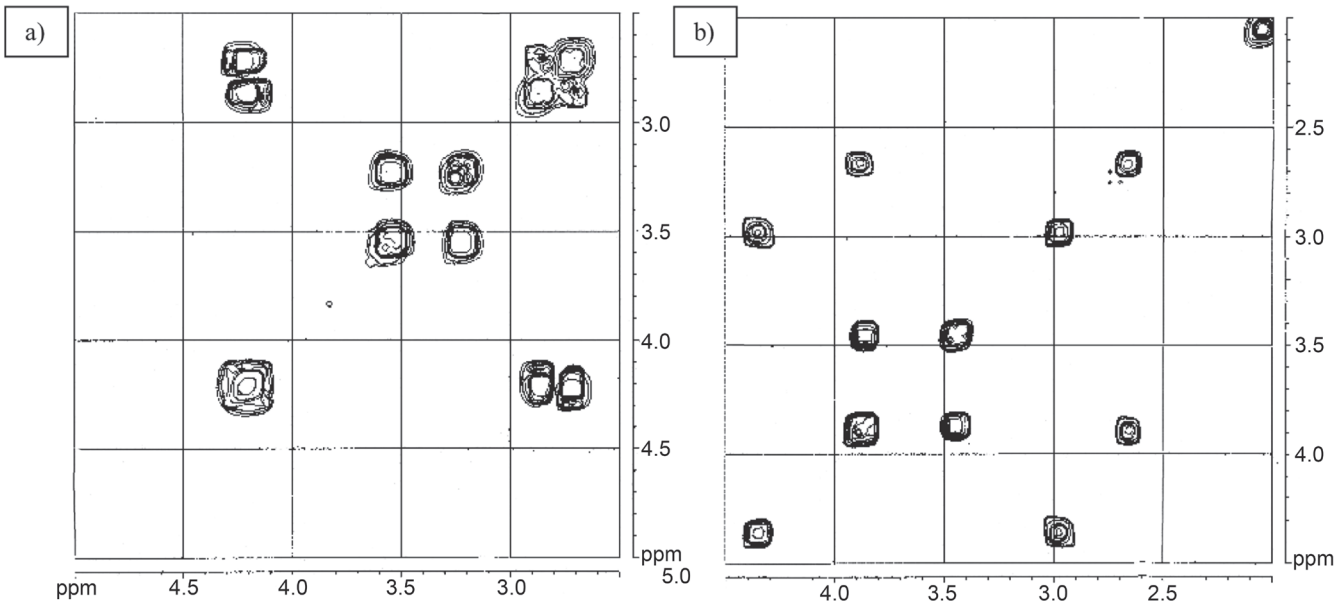


Figure 5. *COSY45* spectra for (a) **2b** and (b) **5b**.

only two cross-peaks between piperazine proton multiplets at 3.87 and 2.63 ppm (*AA'* and *XX'* protons), and at 4.33 and 2.95 ppm (*BB'* and *YY'* protons) are seen (Figures 5,b and 6). The same is true for complex **5a**. The assignment of signals in pairs **a**,**b** and **c**,**d** is made based on the assumption that axial protons (**a**, **c**) generally are more shielded than equatorial ones (**b**, **d**).

More detailed signal assignment in the proton spectrum of **5a** was made on the basis of NOE difference spectra (see notations in Figure 6). Saturation of CH=N protons leads to emergence of NOE at neighboring protons H^8 and H^5, irradiation of *t*-Bu protons gives NOE at H^3 and H^5. Irradiation of equatorial protons at 4.33 ppm (H^b or H^d) gives a response on neighboring axial protons H^a or H^c (2.95 ppm) and also at one of benzylic protons H^f or H^e (3.84 ppm). Irradiation of one of the axial protons at 2.95 ppm (H^a or H^c) gives a response only on neighboring equatorial one at 4.33 ppm (H^b or H^d), at the same time saturation of another axial proton at 2.63 ppm (H^c or H^a) gives NOE at one of benzylic protons H^e or H^f (3.84 ppm) and on opposed to it axial proton (H^a or H^c) at 2.95 ppm beside neighbor geminal (H^d or H^b) at 3.87 ppm (although the first two effects are much less pronounced).

A *2D XHCORR* spectrum allowed the full assignment of CH_n signals, with the exception of the carbons of piperazine because of ambiguity of pairwise assignment of axial and equatorial protons. The pair cross-peaks 53.5 ppm – 2.63, 3.87 ppm and 56.7 ppm – 2.95, 4.33 ppm, related to CH^aH^b and CH^cH^d or *vice versa*, are observed in the spectrum.

Taking into account the effect of *t*-Bu substituent, ^1H and ^{13}C NMR spectra of **5a** are almost identical with those of **5b**, showing their equivalent stereoconfiguration in solution. Using of increments of *t*-Bu group allowed for a full assignment of ^{13}C signals in aromatic range of spectra for both complexes **5a** and **5b**.

NMR studies of tetraazamacrocycle **6** revealed that in CD_2Cl_2 solution the molecule exhibits dynamic behavior due to degenerated macrocycle ring inversion called by us "flying pterodactyl" because of resemblances of the benzylic rings to wings and the phenylene ring to the tail, and the piperazine moiety to the head with teeth (Scheme 4).

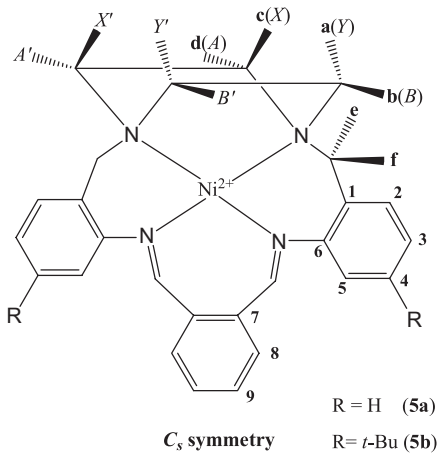
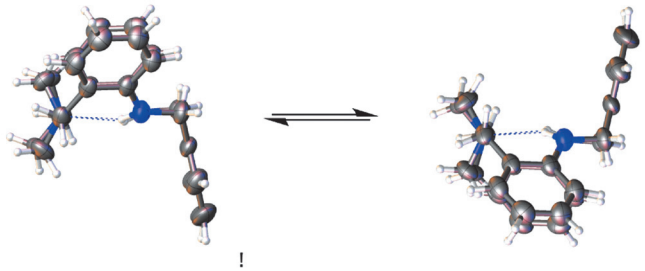


Figure 6. The proton notations in the molecules of **5**.



Scheme 4. The "flying pterodactyl" ring inversion for 16-membered tetraazamacrocycle **6**.

Table 3. The results of conformation study.

Compound	Solid state data	Solid state form	Solution form	Solution data
2a[8]	X-ray	*Transoid*	*Transoid* +*Cisoid*	VT NMR
2b	X-ray	*Cisoid*	*Transoid*	NMR
[Ni(**1a**)$(BF_4)_2$]	–	–	*Transoid* +*Cisoid*	NMR
[Ni(**1b**)$(BF_4)_2$]	–	–	*Transoid*	NMR
3a[8]	X-ray	*Transoid*	–	–
5a	X-ray	*Cisoid*	*Cisoid*	NMR
5b	–	–	*Cisoid*	NMR
6	X-ray	*Cisoid*	*Cisoid*	VT NMR

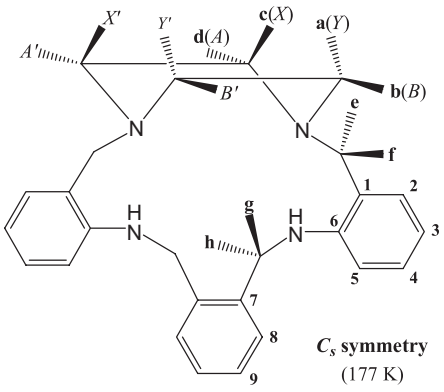


Figure 7. The proton notations in the molecules of **6**.

The ring inversion was confirmed by a VT NMR study, which shows the slowing of the macrocycle ring inversion in the range from 300 K to 177 K. This process lowers the symmetry of the molecule from C_{2v} to C_s (the pseudo-mirror going through four nitrogen atoms disappears) which leads to the doubling of signals of protons and carbons of piperazine core and both pairs of benzylic protons (see *Experimental* and Figure 7).

At 300 K the piperazine protons are observed as an *AA'XX'* spin system. Upon lowering the temperature, two independent *AA'XX'* and *BB'YY'* spin systems arise. In the *COSY45* spectrum at 177 K, two cross-peaks for piperazine protons are seen at 2.33 and 1.75 ppm (*AA*' and *XX*' protons) and at 2.72 and 2.16 ppm *(BB*' and *YY*' protons). As mentioned above, the same situation exists for complexes **5a** and **5b** having the *cisoid* conformation in solution.

In addition, for **6** new crosspeaks are observed between NH and one of the benzylic protons $H^{g,h}$. The assignment of signals in pairs **a**,**c** and **b**,**d** is made on the assumption that axial protons (**a**,**c**) generally are more shielded than equatorial ones (**b**,**d**).

The ring inversion barrier estimated by us on the basis of four coalescence temperatures of piperazine and benzylic protons is equal to $\Delta G^{\ddagger}$=41.9±0.8 kJ/mol (10.0±0.2 kcal/mol).

The results of structural studies are summarized in Table 3. The Ni complexes with open-chain ligands **1a** and **1b** show opposite conformations in the solid state to complexes **2a** and **2b**, presumably due to the H-bonding support of counteranion for the latter. In contrast, in solution **2b** exists exclusively in the *transoid* conformation whereas **2a** exists as a mixture of conformations. The reason for the latter observation is not clear at the moment. All 16-membered macrocycles studied (**4a** and **4b** within complexes **5a** and **5b** and free ligand **6**) show *cisoid* conformations in the solid state and in solution. We attribute this result to the conformational rigidity of the tetraazamacrocycles.

Conclusions

The above-mentioned interesting feature of the ligands **1a** and **1b** in their Ni, Cu, Pd and Ti complexes studied so far[8,9] is a non-planar, *pseudo*-C_2 symmetric (*transoid*) conformation that they adopt. However, in this study we have found that ligand **1b** in Ni complex **2b** has a *pseudo*-C_s (*cisoid*) conformation in solid state, but transforms into the *transoid* form upon dissolution. In contrast, both the Ni complexes with BF_4^- counteranions and complex **2a** show mixtures of both conformations in solution. The diaminodiimino macrocyclic ligands **4a** and **4b** adopt the *cisoid* conformation in the corresponding complexes **5a** and **5b**. Retention of this conformation in solution is confirmed by various NMR spectroscopic techniques. The new 16-membred tetraazamacrocycle **6** undergoes a degenerated ring inversion with the inversion barrier estimated at $\Delta G^{\ddagger}$=41.9±0.8 kJ/mol (10.0±0.2 kcal/mol). The data obtained are important for the study of new metal complexes including those that are used for PET.

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