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 interconversion 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 $N_4$–тип 16–членные тетраазамакроциклы на основе пиперазина и их никелевые комплексы

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Конденсацией открытой-цепных диамагнитных комплексов никеля(II) 2a и 2b с фталевым альдегидом получены плоско-квадратные комплексы 5a и 5b, содержащие 16-членные диаминодииминомакроциклические лиганды. В кристалле для 2b найдена цисоидная конформация арильных групп, в то время как для аналога 2a присутствует трансопозиция. Найденные в кристалле конформации не сохраняются в растворе: третбутилсодержащий комплекс 2b полностью превращается в транс-форму, для комплекса 2a установлена 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 тетраазамакроциклу 6. Исследование методом РСА показало для 6 в кристалле наличие цисоидной конформации, поддерживаемой двумя внутримолекулярными водородными связями. Методами динамического ЯМР установлено, что найденная для твердого состояния...
Introduction

The diagnostics and treatment of neurodegenerative diseases constitute one of the main problems of current neuroscience.[11] 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 64Cu. 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 bicyclic 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 chelate (Figure 1, top) and macrocyclic (Figure 1, bottom) logical vectors. One very promising approach is to explore chemical modifications including conjugation to the bio affinity for the metal cation as well as wide possibilities of the elaboration of easily modified ligand systems with high long-lived isotopes, particularly 64Cu. 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).

An interesting feature of the piperazine-based ligands in refs.[8,9] was the non-planar, pseudo-C₃, 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[12-16] and macrocyclic[17-20] 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 complexion 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 N₄-type ligands (Figure 2).

For 1a and 1b it has been shown that anilinic protons could be easily changed for SiMe₃ groups by the action of TMSCl/DABCO (trimethylsilyl chloride/1,4-diazabicyclo-[2.2.2]octane).[19] 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-C₃, 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 π⁺*-C=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 ⁶⁴Cu PET.

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

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of the sides of Ni₃ 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 N₂ 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 CaH₂ (dichloromethane) under an atmosphere of N₂ in vacuo.

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[Ni(1a)ClO₄] (2a). The synthesis is in accordance with the procedures in ref. [9], using 1a (2.0 g, 6.7 mmol) and Ni(II)ClO₄ (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 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 and 0.57 g (1.7 mmol) of Ni(BF₄)₂ were used. Next, 0.5 g (2 mmol) of Co(OAc)₂ was added to an ethanol (15 ml) solution containing 0.6 g (1.74 g), an additional amount of 0.81 g (87 %) of an orange-red complex in the form of a dihydrate. Found: C 44.71, H 6.05, N 7.39 %.

NMR ((CD₂)₂SO): 3.54 (2H, each d, 2JHH = 7.9, H4); 7.57 (2H, dd, 2JHH = 7.9, 2JHN = 1.8, H6); 7.60 (2H, H, 2JHH = 1.8, H); 8.05 (2H, m, H7); 8.17 (2H, m, H8); 8.77 (2H, sy, CH=N); 13C(N) H NMR (CDCl₃, CO, 298 K) δ ppm: 31.4 (C(CH₃)); 109.8, 110.6, 124.4, 134.6 (CH); 137.9 (CH²); 146.4 (C); 177.4 (CH=N).

NMR ((CD₂)₂SO) δ ppm: 3.38 (2H, each d, 2JHH = 12.8, H²); 3.86, 4.33 (2H, each m, H²); 7.42 (2H, 2JHH = 7.9, H²); 7.57 (2H, dd, 2JHH = 7.9, 2JHN = 1.8, H6); 7.60 (2H, 2JHH = 1.8, H); 8.05 (2H, m, H7); 8.17 (2H, m, H8); 8.77 (2H, sy, CH=N). 13C(N) H NMR (CDCl₃, CO, 298 K) δ ppm: 31.4 (C(CH₃)); 109.8, 110.6, 124.4, 134.6 (CH); 137.9 (CH²); 146.4 (C); 177.4 (CH=N).

Results and Discussion

Crystallographic Studies

Crystal data collection and processing parameters are given in Table 1. Data were collected using a Stoe Stadi-4 four-circle diffractometer equipped with an Oxford Cryosystems low-temperature device. Data were collected at 150 K using o or o–20 scans with Mo-Kα 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 riding model with fixed isotropic displacement parameters, and suitable weighting schemes were applied. Crystallographic calculations were performed using SHELXS-97,[30] SHELXL-2014[31] SIR92,[32] 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-bromo-4-methyl-4-tert-butyl-2-nitrobenzene as described in[10].

Syntheses of starting piperazine-based ligands 1a and 1b were performed according to the published procedures[9,10] (Scheme 1).

2-Nitrobenzylboride or its tert-Bu congener and powdered potassium hydroxide were added as solids to a stirred suspension of piperazine in toluene and the...
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 NH₂-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 C₂, C₃ and C₄ di-electrophiles, such as glyoxal, 1,2-dibromoethylene, 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 NH₂-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 CHCl₃ 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)(BF₄)₂] and [Ni(1b)(BF₄)₂] were also prepared in a similar manner. A solution of Ni(BF₄)₂·6H₂O 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
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)(BF₄)₂] focused on a number of non-Schiff base reactions. A variety of bases (K₂CO₃, NaOMe) and electrophiles (a,a’-dibromo-o-xylene, TsO(CH₃)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 C₅-dielectrophiles were also attempted under different conditions. Reactions of 2a with aqueous glyoxal or 2,3-butandione 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 decolorization of solution. However, only starting ligands were isolated. These observations could be explained by the primary formation of deprotonated complexes [Ni(I-H)ClO₄] or even [Ni(I-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 C₅-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.[38]

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)₆.

In the case of two C₅-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 C₅-dielectrophiles, reactions of 2a and 1,2-dibromomethane either with DABCO in acetone or with K₂CO₃ 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)(BF₄)] 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.[39] A number of studies have also indicated that the perchlorate anion is one of the best anions to use in template-based syntheses.[38]

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 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

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

[Diagram of Scheme 3]
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(C₃H₆O) and 6.

<table>
<thead>
<tr>
<th></th>
<th>2b</th>
<th>5a 0.5(C₃H₆O)</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td>Empirical formula</td>
<td>C₂₆H₄₀Cl₂N₄NiO₈</td>
<td>C₂₉H₄₂Cl₂N₄NiO₈</td>
<td>C₁₃H₁₅N₂</td>
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<tr>
<td>Formula weight</td>
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<td>710.19</td>
<td>199.28</td>
</tr>
<tr>
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<td>orthorhombic</td>
<td>triclinic</td>
</tr>
<tr>
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<td>P₂₁/n</td>
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<td>P-1</td>
</tr>
<tr>
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<td>11.300(3)</td>
<td>20.148(6)</td>
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<td>c (Å)</td>
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<td>35.329(11)</td>
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<td>β (°)</td>
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<td>γ (°)</td>
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<td>90</td>
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<td>V (Å³)</td>
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<td>6001(4)</td>
<td>2270.2(4)</td>
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<tr>
<td>Z</td>
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<td>Mo-Kα</td>
<td>Mo-Kα</td>
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<td>Reflections with I&gt;2σ(I)</td>
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<td>1.13</td>
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<td>F²</td>
<td>F</td>
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<td>R and wR (F² refinement, I&gt;2σ(I))</td>
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<td>0.0803, 0.135</td>
<td>–</td>
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<td>0.0685, 0.0476</td>
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</table>

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

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<tr>
<th></th>
<th>N¹-N²</th>
<th>N³-N⁴</th>
<th>Ni-N¹</th>
<th>Ni-N³</th>
<th>N¹-N⁴</th>
<th>N²-N³</th>
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<td>2a[8]</td>
<td>2.402</td>
<td>2.831</td>
<td>1.925(5)</td>
<td>1.928(5)</td>
<td>2.800</td>
<td>2.827</td>
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<tr>
<td>2b</td>
<td>2.379(7)</td>
<td>2.871(6)</td>
<td>1.914(5)</td>
<td>1.916(6)</td>
<td>2.816(7)</td>
<td>2.810(7)</td>
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<tr>
<td>5a</td>
<td>2.373(9)</td>
<td>2.743(9)</td>
<td>1.929(6)</td>
<td>1.886(6)</td>
<td>2.806(9)</td>
<td>2.830(8)</td>
</tr>
<tr>
<td>6</td>
<td>2.587(3)</td>
<td>4.093(3)</td>
<td>1.919(6)</td>
<td>1.886(6)</td>
<td>2.804(8)</td>
<td>2.885(3)</td>
</tr>
</tbody>
</table>

n.a. – not applicable
Piperazine-Based N<sub>2</sub>-Type 16-Membered Macr<h3>heterocycles and Their Nickel(II) Complexes</h3>

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/ammine nitrogen pairs (N<sup>1</sup>-N<sup>1</sup>′, 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<sub>2</sub> and C<sub>1</sub> 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<sup>[39]</sup>). 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 1H 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 than those of the tetrafluoroborate salts, the latter possessing broad signals with poorly resolved couplings. This feature than those of the tetrafluoroborate salts, the latter possessing broad signals with poorly resolved couplings. This feature 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.

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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.

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 1H NMR spectrum of 2b contains three multiplets centred at 2.70, 2.83 and 4.21 ppm. In the 13C NMR spectrum of 2b three signals at 54.7, 55.3 and 55.9 ppm – one being due to the benzyllic carbons, the others arising from the two unequivocal aliphatic sets of piperazine carbons – are clearly seen, but these data do not convey any information about 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<sub>2</sub> 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<sub>2</sub> 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.](image-url)

In the COSY45 spectrum of 2b, besides two cross-peaks belonging to benzyllic 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 benzyllic protons, corresponding to cisoid and transoid conformations, are observed in the 1H 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<sub>3</sub>)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 diaminodimine 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...
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 5b 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 5). Saturation of CH=N protons leads to emergence of NOE at neighboring protons H8 and H5; irradiation of t-Bu protons gives NOE at H5 and H8. Irradiation of equatorial protons at 4.33 ppm (H’ or H”) gives a response on neighboring axial protons H’ or H” (3.84 ppm) and also at one of benzylic protons Hf or He (3.87 ppm). Irradiation of one of the axial protons at 2.95 ppm (H’ or H”) gives a response only on neighboring equatorial one at 4.33 ppm (H’ or H”), at the same time saturation of another axial proton at 2.63 ppm (H’ or H”) gives NOE at one of benzylic protons H’ or H” (3.84 ppm) and on opposed to it axial proton (H’ or H”) at 2.95 ppm beside neighbor geminal (H’ or H”) at 3.87 ppm (although the first two effects are much less pronounced).

A 2D XHCCORR spectrum allowed the full assignment of CH 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 CHaHb and CHcHd or vice versa, are observed in the spectrum.

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

NMR studies of tetraazamacrocyle 6 revealed that in CD2Cl2 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).
exists exclusively in the solid state and in solution. We attribute this result to the conformational rigidity of the tetraaza macrocycles.

Conclusions

The above-mentioned interesting feature of the ligands 1a and 1b in their Ni, Cu, Pd and Ti complexes studied so far is a non-planar, pseudo-$C_4$ symmetric (transoid) conformation that they adopt. However, in this study we have found that ligand 1b in Ni complex 2b has a pseudo-$C_4$ (cisoid) conformation in solid state, but transforms into the transoid form upon dissolution. In contrast, both the Ni complexes with BF$_2$ counteranions and complex 2a show mixtures of both conformations in solution. The diaminodimino macroyclic 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-membered tetraaza macrocycle 6 undergoes a degenerated ring inversion with the inversion barrier estimated at $\Delta G^\circ=41.9\pm0.8$ kJ/mol (10.0$\pm$0.2 kcal/mol). The data obtained are important for the study of new metal complexes including those that are used for PET.

Acknowledgements. This work was supported by Russian Science Foundation (grant №16-13-00114).

References

5. Vatsadze S.Z., Krainova Y.V., Kovalkina M.A., Zyk N.V.

Table 3. The results of conformation study.

<table>
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<tr>
<th>Compound</th>
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<th>Solid state form</th>
<th>Solution form</th>
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<td>Transoid</td>
<td>Transoid +Cisoid</td>
<td>VT NMR</td>
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<td>NMR</td>
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<td><a href="BF$_2$">Ni(1a)</a>$_2$</td>
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</table>

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 $C_{4v}$ to $C_4$ (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 $^{13}$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$^3$. 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 $\Delta G^\circ=41.9\pm0.8$ kJ/mol (10.0$\pm$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.