DOI: 10.6060/mhc140485v

On a Way to New Types of the Hybrid Polyazomethine–Pyrazolate Metal Pseudomacrobicyclic Complexes: the Synthesis and Structure of their Ligand Synthones

Svitlana V. Kats,[a] Oleg A. Varzatskii,[b] Larysa V. Penkova,[a] Anna V. Vologzhanina,[c] Valentin V. Novikov,[c] Ekaterina G. Lebed,[c] and Yan Z. Voloshin[c@]

Dedicated to Academician of Russian Academy of Sciences Oleg N. Chupakhin on the occasion of his 80th birthday

[a]*Taras Shevchenko National University of Kyiv, 01601 Kyiv, Ukraine*
[b]*Vernadskii Institute of General and Inorganic Chemistry of the National Academy of Sciences of Ukraine, 03680 Kyiv, Ukraine*
[c]*Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, 119991 Moscow, Russia*
[@]*Corresponding author E-mail: voloshin@ineos.ac.ru*

3-Acetylpyrazole hydrazone, its formyl- and carboxymethyl-containing analogs and the bis-pyrazolyl azine derivative were obtained in moderate yields by condensation under vigorous reaction conditions and characterized using elemental analysis, LC-mass spectrometry, IR, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopies, and X-ray diffraction crystallography (for a bis-pyrazolyl azine compound). The X-rayed molecule occupies a special position with an inversion centre; beside planarity of its C=N–N=C moiety, the corresponding C–N and N–N bond lengths suggest the absence of a conjugation in this diazomethine fragment, whereas those in the pyrazolyl cycles clearly suggest a delocalization of the electron density. The azine molecules form hydrogen-bonded layers that are parallel to the crystallographic plane (100). Although these molecules are almost planar, π-stacking interactions between them are absent, and 2D layers are connected via van-der-Waals C–H…π interactions at the distances of 2.695 Å. The compounds obtained were described to be suitable organic synthones for the synthesis of mono- and binuclear hybrid polyazomethine-pyrazolate metal pseudomacrobicyclic complexes.

Keywords: Macrocycles, clathrochelates, pyrazole derivatives, azines, hydrazones, X-ray crystallography.

К новым типам гибридных полиазометин–пиразолатных псевдомакробициклических комплексов: синтез и структура синтонов их лигандных синтонов

С. В. Кац,[a] О. А. Варзацкий,[b] Л. В. Пенкова,[a] А. В. Вологжанина,[c] В. В. Новиков,[c] Е. Г. Лебедь,[c] Я. З. Волошин[c@]

Посвящается Академику РАН Олегу Николаевичу Чупахину по случаю его 80-летнего юбилея

[a]*Киевский национальный университет им. Тараса Шевченко, 01601 Киев, Украина*
[b]*Институт общей и неорганической химии им. В.И. Вернадского НАН Украины, 03680 Киев, Украина*
[c]*Институт элементоорганических соединений РАН им. А.Н. Несмеянова, 119991 Москва, Россия*
[@]*E-mail: voloshin@ineos.ac.ru*

Были получены 3-ацетилпиразол гидразон, его формил- и карбоксиметилсодержащие аналоги и производное бис-пиразолилазина. Эти соединения предложены в качестве синтонов для синтеза моно- и биядерных гибридных полиазометин-пиразолатных комплексов металлов.

Ключевые слова: Макроциклы, клатрохелаты, производные пиразола, азины, гидразоны, рентгеноструктурный анализ.

Introduction

Organic pyrazole derivatives and their metal complexes (*i.e.* scorpionates and tris-pyrazoloximates[1-3]) are described in [4-12] to be efficient and prospective antimalarial, antibacterial, antitumor and antiviral drug candidates. The cage metal complexes (clathrochelates,[13] Scheme 1, **1** and **2**) are also proposed as so-called "topological drugs" for therapy of viral and tumor deceases[14,15] and, very recently, as potent antifibrillogenic agents.[16] The azomethine derivatives of pyrazolyl ketones seem to be suitable organic synthones for the design of various types of metallochelate building blocks, polynuclear and multicentered macrocyclic and pseudoclathrochelate metal complexes (Scheme 2) owing to their structural (*i.e.* possible tautomerizm) and conformational lability; these reactive ligand synthones can also undergo well-known organic functionalization reactions. Only one paper[17] describing the synthesis and properties of 3-acetylpyrazole hydrazone was, however, found in literature. At the same time, we earlier reported the synthesis, structure and properties of the two new types of cage metal complexes, which are the hybrid macrocyclic and macrobicyclic dioximatopyrazoloximates (Scheme 1, **3** and **4**[18]) and tris-pyrazoloximate metal pseudoclathrochelates (Scheme 1, **5**[19]); those are the derivatives of 3-acetylpyrazole oxime. In the latter case, the template condensation of this organic synthone with phenylboronic acid on a corresponding *3d*-metal ion as a matrix gave an unusual pseudomacrobicyclic encapsulating ligand with one of the capping fragments formed by a chloride anion forming three strong intramolecular hydrogen bonds with HN-groups of its ribbed pyrazoloximate chelate moieties. The high-spin paramagnetic *3d*-metal complexes of this type possess unexpectedly high oxidation potentials[19] and unusual EPR characteristics.[20] However, our atemps to perform covalent macrobicyclization of these pseudoclathrochelate complexes using the different types of capping (cross-linking) agents were unsuccessful. Here, we aim on obtaining polydentate and multinucleating hydrazonate and azine ligand synthones with reactive terminal hydrazonate groups as the first and key stage for the design and synthesis of new types of cage metal complexes (in particular, those shown in Scheme 2). We report synthetic procedures, X-ray structure and spectral characteristics of 3-acetylpyrazole hydrazone **2** and its azine derivative **3** as well as those for the corresponding formyl- and carboxymethylhydrazones **5** and **6**, Scheme 3.

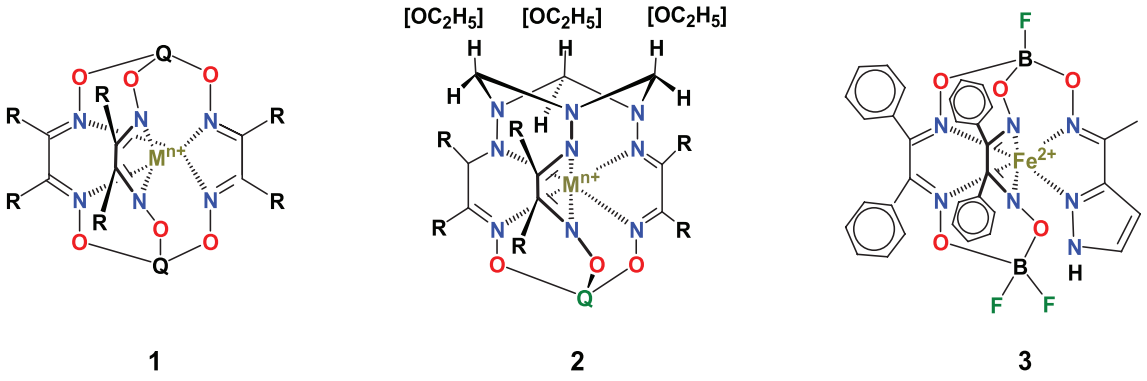
Experimental

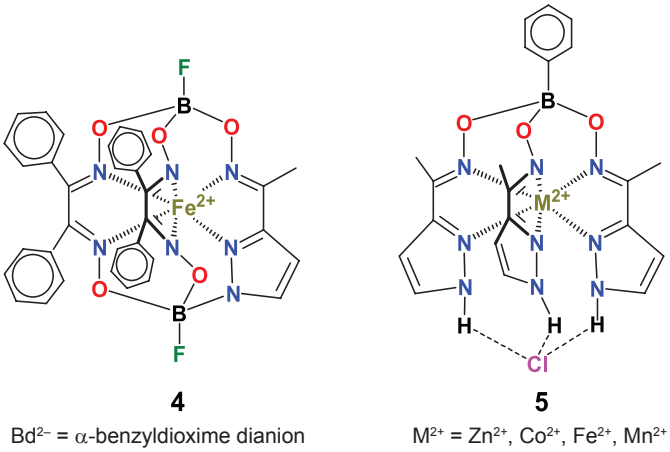
The reagents used, 3-acetylpyrazole, hydrazine monohydrate (64-65 % hydrazine) reagent grade, sorbents, organic bases, and solvents, were obtained commercially (SAF and Enamine).

Analytical data (C, H, N contents) were obtained with a Carlo Erba model 1106 microanalyzer.

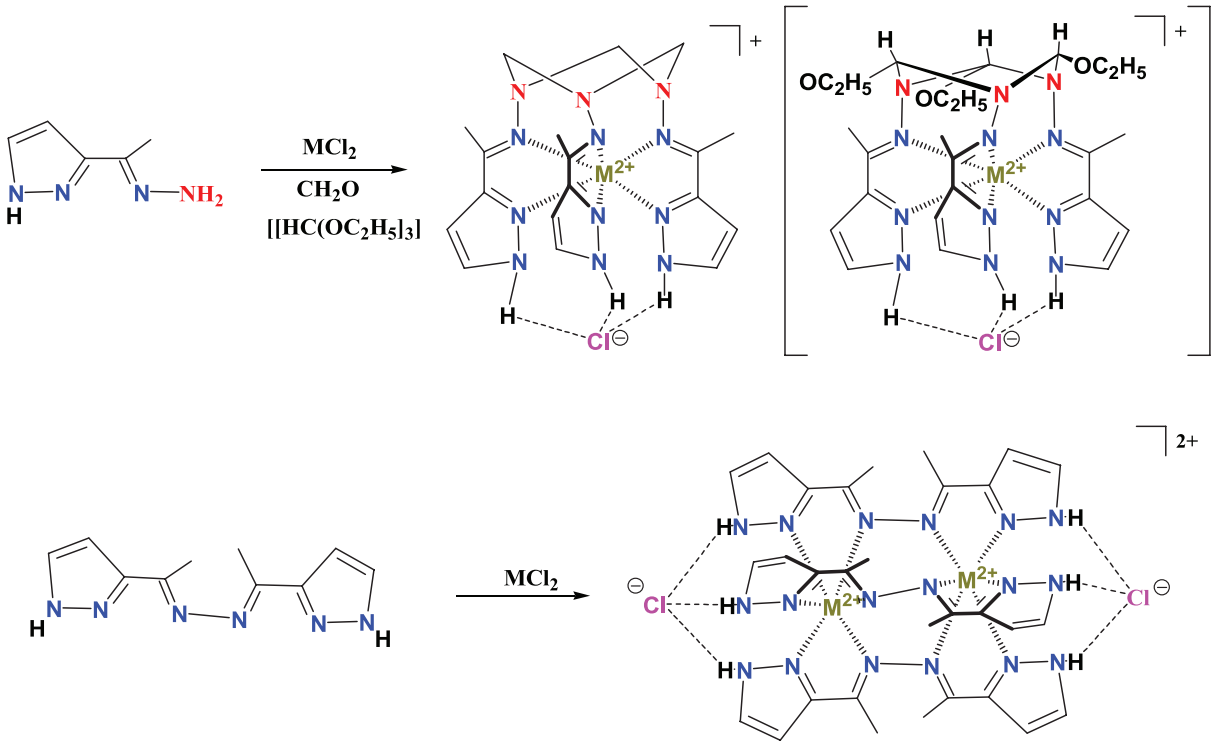
Chemical ionization mass spectra (CI–MS) were recorded with an Agilent 1100 LCMSD SL spectrometer.

Infrared (IR) spectra of the solid samples (KBr tablets) in the range of 400-4000 cm^{-1} were recorded with a Perkin-Elmer FT-IR Spectrum BX II spectrometer.

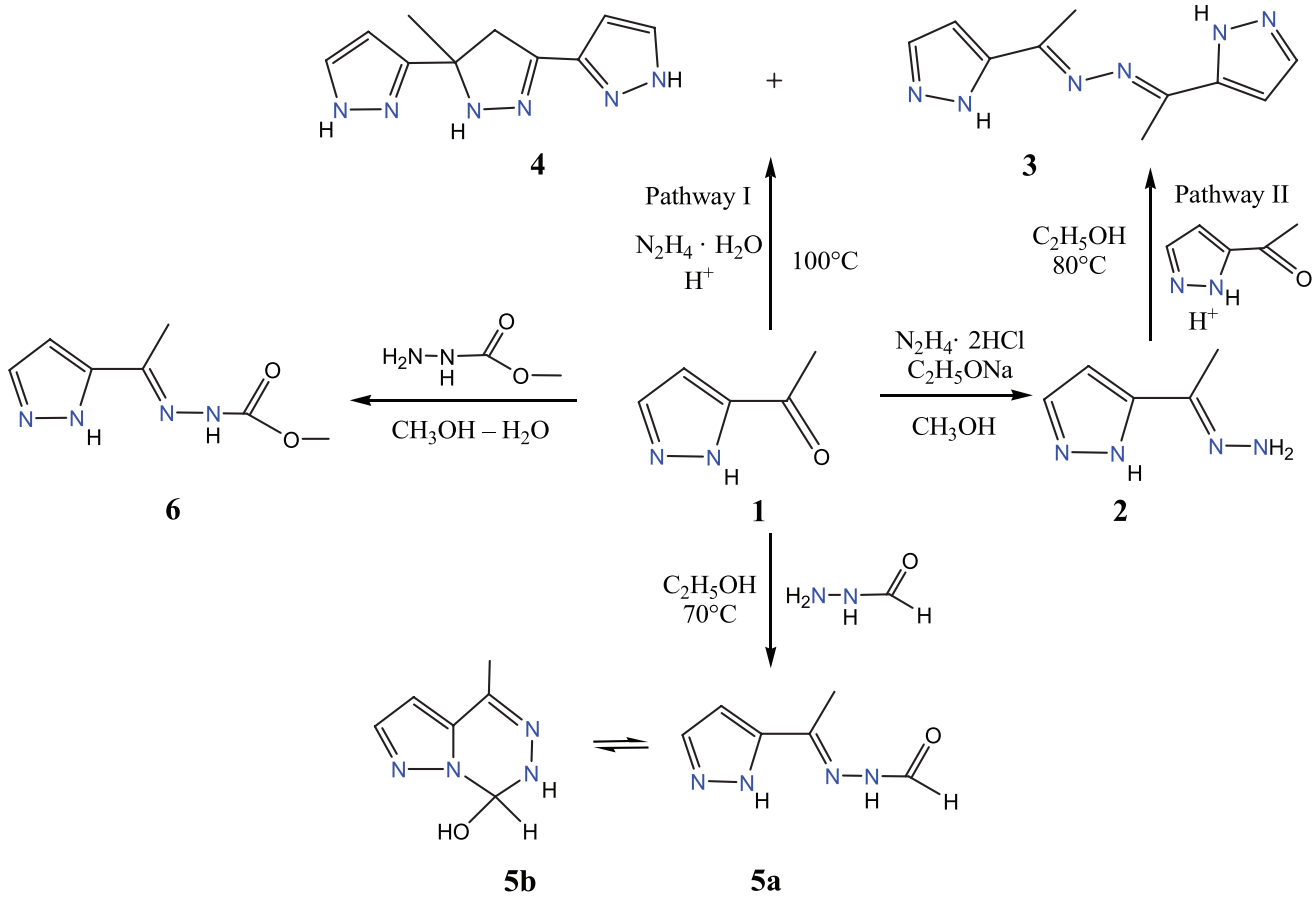




Scheme 1.



Scheme 2.



Scheme 3.

^{1}H and ^{13}C NMR spectra were recorded from DMSO solutions with a Bruker AC 200 spectrometer. The measurements were done using the residual signals of deuterated solvent (δ^{1}_{H} = 1.95 ppm, δ^{13}_{C} = 39.5 ppm).

X-Ray crystallography. Single crystals of the bis-pyrazolyl azine **3** were grown at room temperature from methyl *tert*-butyl ether-methanol mixture. Yellow prismatic crystals of $C_{10}H_{12}N_6$ (M = 212.26) are monoclinic; at 100 K: a = 5.4490(7), b = 5.0987(7), c = 19.958(3) Å, β = 108.741(3)°, V = 525.10(12) Å^3, space group $P\,2_1/c$, Z = 2, $D_{calcd.}$ = 1.368 g cm^{-3}, μ = 0.091 mm^{-1}. The intensities of 4998 reflections were measured with a Bruker APEX II diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å, $2\theta_{max}$ = 60°) from a single crystal with 0.42×0.21×0.19 mm dimensions. The absorption correction was applied using SADABS program.[21] The structure was solved by direct method and refined by full-matrix least squares against F^2_{hkl}. The positions of hydrogen atoms were calculated and included in the refunement in isotropic approximation by the riding model with $U_{iso}(H) = 1.5U_{eq}(C_i)$ for the methyl group and $U_{iso}(H) = 1.2U_{eq}(X_i)$ for the other atoms, where $U_{eq}(X)$ are the equivalent thermal parameters of the parent atoms. The final convergence factors were: R_f = 0.040 for 1321 reflections with I > σ2(I) and wR2 = 0.095 for all 1522 the independent reflections, GOF = 1.006, 74 refined parameters. All calculations were performed by using the SHELXTL ver. 5.10 package.[22] Crystallographic information file is available from the Cambridge Crystallographic Data Center (CCDC) upon request (*http://www.ccdc.cam.ac.uk*, deposition number 997207).

Synthesis

*3-Acetylpyrazole hydrazone (**2**). Procedure I.* Hydrazine hydrate (0.68 g, 13.6 mmol) and sodium ethylate (0.486 g, 7.15 mmol) were dissolved in methanol (25 ml) and 3-acetylpyrazole hydrochloride **1** (1 g, 6.8 mmol), and sodium ethylate (1.864 g, 27.4 mmol) were added under stirring. The reaction mixture was stirred for 8 h at 45 °C, left overnight and then filtered off. The yellow-brown filtrate was evaporated to dryness, and the fine-crystalline residue was washed with a cold methanol (10 ml), methyl *tert*-butyl ether and then recrystallized from hot methanol. The yield of a pale-yellow product was 0.226 g (26.8 %). *Procedure II.* 3-Acetylpyrazole hydrochloride **1** (1 g, 6.8 mmol) was dissolved in hydrazine hydrate (4 ml). The reaction mixture was refluxed for 4 h at 130 °C, then cooled to 40 °C, and the solvent was decantated from a yellow oily product. This product was left at 4 °C overnight and then filtered off the precipitate was, washed with a small amount of water, methyl *tert*-butyl ether and dried *in vacuo*. Yield: 0.63 g (75 %). The melting point: 162-163 °C. ^{1}H NMR (DMSO-d_6) δ ppm: 2.03 (s, 3H, Me), 5.95 (br. s, 2H, NH_2), 6.33 (d, 1H, Pz-H4), 7.46 (d, 1H, Pz-H5), 12.51-12.63 (br. s, 1H, NH). CI-MS: *m/z:* 125.1 $[M + H^+]^+$. IR (KBr) ν cm^{-1}: 1098 ν(N–N) (Hz), 1052 ν(N–N) (Pz), 1531, 1643 {ν(C=N) + ν (C=C)}, 3137 ν(N–H) (Pz), 3352 ν (N–H) (Hz).

*Bis-pyrazolyl azine (**3**).* 3-Acetylpyrazole (0.5 g, 3,4 mmol) and 3-acetylpyrazole hydrazone **2** were dissolved in ethanol (4 ml), and acetic acid (50 μl) was added. The reaction mixture was refluxed for 4 h, then evaporated to a small volume (approximately 2 ml) and left overnight. The product was washed with methyl *tert*-butyl ether, filtered and dried *in vacuo*. Yield: 0.661 g (90 %). ^{1}H NMR (DMSO-d_6) δ ppm: 2.20 (s, 6H, Me), 6.72 (d, 2H, Pz-H4), 7.76 (d, 2H, Pz-H5), 13.05 (br. s, 2H, NH). ^{13}C{^{1}H} NMR (100.61 MHz, DMSO-d_6) δ ppm: 14.36 (s, Me), 102.31, 129.66 (two s, CH (Pz)), 150.10 (s, C=N (Pz)), 146.30 (s, C=N–NH_2). LC-MS *m/z*: 217.2 $[M + H^+]^+$. IR (KBr) ν cm^{-1}: 1051 ν(N–N) (Pz), 1085 ν(N–N) (azine), 1536, 1688 {ν(C=N) + ν(C=C)}, 3131 ν(N–H) (Pz).

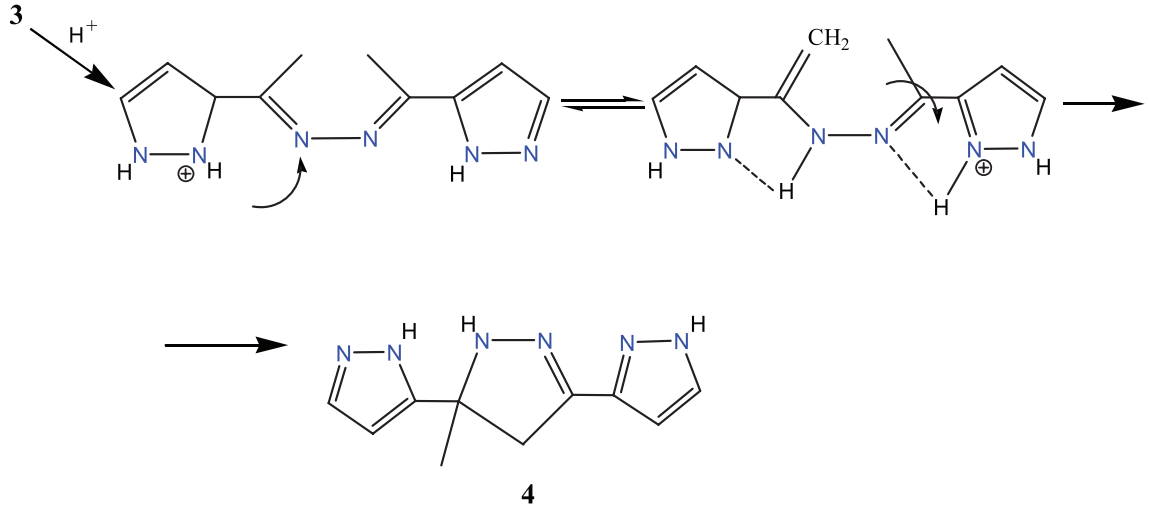
*3-Acetylpyrazole formylhydrazone (**5**).* 3-Acetylpyrazole hydrochloride (0.733 g, 5 mmol), formyl hydrazine (0.33 g, 5.5 mmol) and $NaHCO_3$ (1.26 g, 15 mmol) were dissolved in 15 % aqueous methanol (20 ml), and this solution was acified to p*H* 7 by formic acid. The reaction mixture was stirred and boiled for 30 min. Then the dark-brown precipitate obtained was filtered and recrystallized from ethanol. The yield of pale-yellow crystalline product was 0.57 g (75 %).

5a. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.27 (s, 3H, Me), 6.56 (br s, H, Pz-H4), 7.74 (br s, H, Pz-H5), 8.69 (d, J = 9.5 Hz, 1H, HC=O), 12.93 (br s, H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 13.85 (s, Me), 102.20 (s, Pz-C4), 130.34 (s, Pz-C5), 146.85 (s, MeC), 150.60 (s, Pz-C3), 166.11 (s, HC=O).

5b. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.25 (s, 3H, Me), 6.58 (br s, 1H, Pz-H4), 7.75 (br s, 1H, Pz-H5), 8.11 (br s, 1H, HC–O), 10.67 (br s, 1H, NH). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 13.77 (s, Me), 102.65 (s, Pz-C4), 130.33 (s, Pz-C5), 157.56 (s, HC–O), 150.60 (s, Pz-C3); other ^{13}C NMR signals are overlapped with those of **5a**.

CI-MS *m/z*: 153.1 $[M + H^+]^+$. IR (KBr) ν cm^{-1}: 1039 ν(N–N) (Pz), 1077 ν(N–N) (Hz), 1230, 1309 ν(C–N), 1553, 1688 {ν(C=N) + ν(C=C) + ν(C=O)}, 3200 ν(N-H) (Pz).

*3-Acetylpyrazole carboxymethylhydrazone (**6**).* 3-Acetyl-pyrazole hydrochloride (0.5 g, 3.4 mmol) and metyl hydrazino-carboxylate (0.612 g, 6.8 mmol) were dissolved in methanol-water 1:1 mixture (6 ml) under stirring. The reaction mixture was stirred for 2 h at 70 °C, and then the yellow-brownish precipitate formed was filtered and recrystallized from ethanol. Yield: 0.334 g (54 %). ^{1}H NMR (DMSO-d_6) δ ppm: 2.27 (s, 3H, Me), 3.71 (s, 3H, OMe),



Scheme 4.

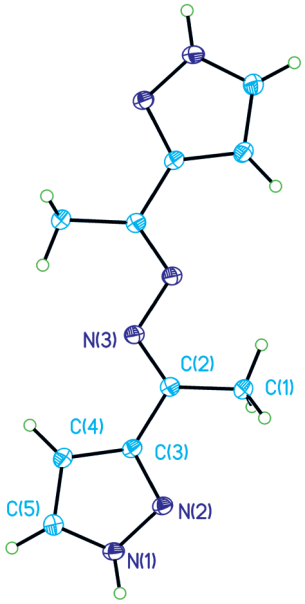


Figure 1. General view of **3** in representation of atoms with thermal ellipsoids drawn at p = 50 %; only its crystallographically independent atoms are labeled.

6.51 (d, 1H, Pz-H4), 7.80 (d, 1H, Pz-H5), 12.20 (br s, 1H, HNCOO), 13.49 (br s, 1H, HN(Pz)). CI-MS *m/z*: 183.1 $[M + H^+]^+$. IR (KBr) ν cm^{-1}: 1045 ν(N-N) (Pz), 1099 ν (N-N) (Hz), 1057, 1289 ν(C-OMe), 1536, 1681 {ν(C=C) + ν(C=N)(Pz)}, 1615 ν(C=N) (Hz), 1722 ν(C=O), 3130 ν(N-H) (Pz).

Results and Discussion

The preparation of 3-acetylpyrazole hydrazone **2** is described in literature,[17] but we failed to obtain a pure product using these reported procedures. This hydrazone was obtained by Scheme 2 and has a melting point and NMR spectra that are different from those reported in [17]. It should be noted that the carbonyl group of its precursor **1** has a lower reactivity (probably due to the presence of an intramolecular hydrogen bond), and this effect is seen in its reactions with hydrazine derivatives; so we used the synthetic procedures in vigorous reaction conditions (a reflux for a long time in an excess of the corresponding hydrazine). The carboxymethyl-containing hydrazone **6** was isolated only in a *syn*-form; the hydrogen bonding between its hydrazine group and pyrazolyl nitrogen atom caused a broadening of the ^{1}H NMR signal of terminal NH_2-protons at δ^1_H = 12.2 ppm. 3-Acetylpyrazole formylhydrazone **5** was found to be in two (open **5a** and cyclic **5b**) forms in DMSO solution. Besides NMR signals of its open form, the additional signals assigned to the cyclic form **5b** were detected with their ratio of 3:1; spectral assignment was assisted by 2D COSY, HSQC and HMBC NMR spectra.

The direct 2:1 condensation of 3-acetylpyrazole **1** with hydrazine hydrate by Pathway I (gave a poorly separable mixture of the target azine **3** and the product **4** of its intramolecular cyclocondensation this product was characterized only in solution by NMR spectroscopy). This azine was obtained in a high yield by H^+-catalyzed condensation of 3-acetylpyrazole hydrazide **2** as an intermediate product of this reaction with the parent ketone **1** in ethanol (Pathway II).

As follows from the NMR and CI-MS solution spectra, the azine **3** easily undergoes its hydrolytic cleavage giving the initial ketone **1** as well as intramolecular azine-pyrazolyl condensation (*vide supra*): the reflux of **3** in 20 % aqueous acetic acid gave a mixture of 3-acetylpyrazole **1** (50 %) and a cyclic product **4** (20 %) with the starting compound (30 %). A possibility of the azine moiety to exist in a protonated methylene-pyrazolyne tautomeric form facilitates such rearengement easily proceeding in aqueous solutions at H^+-catalysis by acetic acid (Scheme 4).

The compounds obtained were characterized using elemental analysis, CI-mass spectrometry, IR, ^{1}H and ^{13}C{^{1}H} NMR spectroscopies, and X-ray diffraction crystallography (for **3**).

X-Rayed molecular structure of the bis-pyrazolyl azine **3** is shown in Figure 1; the molecule occupies a special position with an inversion centre. Although the C=N–N=C moiety is planar (the average deviation of these four atoms from its meanplane is equal to 0.00(1) Å), the C(2)-N(3) and N(3)-N(3A) bond lengths (1.293(1) and 1.402(2) Å, respectively), we suggest the absence of a conjugation in this diazomethine fragment. In contrast, the N(1)-N(2), N(2)=C(3), C(3)-C(4), C(4)=C(5) and C(5)-N(1) bond lengths (1.355(1), 1.344(1), 1.412(2), 1.373(2) and 1.352(1) Å, respectively) clearly suggest a delocalization of the electron density in its pyrazolyl cycles. The hydrogen-donor HN-group forms a strong hydrogen bond N(1)-H···N(2) with r_i(N···N) = 2.887(1) Å and the angle N-H-N equal to 154°. As a result, the azine molecules form hydrogen-bonded layers that are parallel to the crystallographic plane (*100*). Although these molecules are almost planar (the average deviation of atoms from their mean planes is approximately 0.013(1) Å), π-stacking interactions between them are absent; so these 2D layers are connected *via* van-der-Waals C-H···π interactions between a hydrogen atom of the methyl substituent and the π-donor pyrazolyl cycle of the molecule **3** from the neighboring layer at the distances of 2.695 Å.

Conclusions

Thus, we obtained in moderate yields and characterized 3-acetylpyrazole hydrazone, its formyl- and carboxymethyl-containing analogs and the bis-pyrazolyl azine derivative, which are suitable organic synthones for the synthesis of mono- and binuclear hybrid polyazomethine-pyrazolate metal pseudomacrobicyclic complexes.

Acknowledgements. Financial support from the RFBR (grants 12-03-00955 and 13-03-90452), RAS (program 6) and the Marie Curie International Research Staff Exchange Scheme (IRSES) of the 7th EU Framework Program (grant 295160) is greatly appreciated.

References

1. Trofimenko S. *Scorpionates: The Coordination Chemistry of Polypyrazolylborate Ligands*. Imperial College Press: London, **1999**.

2. Pettinari C. *Scorpionates II: Chelating Borate Ligands*. Imperial College Press: London, **2008**.
3. Santini C., Pellei M., Gioia Lobbia G., Papini G., *Mini-Rev. Org. Chem.* **2010**, *7*, 84-124.
4. Voloshin Y.Z., Kostromina N.A., Kramer R. *Clathrochelates: Synthesis, Structure and Properties*. Elsevier: Amsterdam, The Netherlands, **2002**.
5. Novikov V.V., Varzatskii O.A., Negrutska V.V., Bubnov Y.N., Palchykovska L.G., Dubey I.Y., Voloshin Y.Z. *J. Inorg. Biochem.* **2013**, *124*, 42-45.
6. Varzatskii O.A., Novikov V.V., Shulga S.V., Belov A.S., Vologzhanina A.V., Negrutska V.V., Dubey I.Y., Bubnov Y.N., Voloshin Y.Z. *Chem. Commun.* **2014**, *50*, 3166-3168.
7. Losytskyy M.Y., Kovalska V.B., Varzatskii O.A., Sergeev A.M., Yarmoluk S.M., Voloshin Y.Z. *J. Fluoresc.* **2013**, *23*, 889-895.
8. Kovalska V.B., Losytskyy M.Yu., Varzatskii O.A., Cherepanov V.V., Voloshin Y.Z., Mokhir A.A., Yarmoluk S.M., Volkov S.V. *Bioorg. Med. Chem.* **2014**, *22*, 1883-1888.
9. Sakai K., Tomita Y., Ue T., Goshima K., Ohminato M., Tsubomura T., Matsumoto K., Ohmura K., Kawakami K. *Inorg. Chim. Acta* **2000**, *297*, 64-71.
10. Broomhead J.A., Rendina L.M., Webster L.K. *J. Inorg. Biochem.* **1993**, *49*, 221-234.
11. Broomhead J.A., Lynch M. *Inorg. Chim. Acta* **1995**, *240*, 13-17.
12. Onoa G.B., Moreno V., Font-Bardia M., Solans X., Pérez J.M., Alonso C. *J. Inorg. Biochem.* **1999**, *75*, 205-212.
13. Pons J., Ros J., Llagostera M., Pérez J.A., Ferrer M., Spanish Patent No. 01494, **2003**.
14. Baraldi P.G., Beria I., Cozzi P., Geroni C., Espinosa A., Gallo M.A., Entrena A., Bingham J.P., Hartley J.A., Romagnoli R. *Bioorg. Med. Chem.* **2004**, *12*, 3911-3921.
15. Xia Y., Dong Z.W., Zhao B.X., Ge X., Meng N., Shin D.S., Miao J.Y. *Bioorg. Med.Chem.* **2007**, *15*, 6893-6899.
16. Bandgar B.P., Gawande S.S., Bodade R.G., Gawande N.M., Khobragade C.N. *Bioorg. Med. Chem.* **2009**, *17*, 8168-8173.
17. Smolyar N.N. *Russ. J. Org. Chem.* **2010**, *46*, 122-125.
18. Varzatskii O.A., Kats S.V., Penkova L.V., Volkov S.V., Dolganov A.V., Vologzhanina A.V., Bubnov Y.N., Voloshin Y.Z. *Eur. J. Inorg. Chem.* **2013**, 1987-1992.
19. Varzatskii O.A., Penkova L.V., Kats S.V., Dolganov A.V., Vologzhanina A.V., Pavlov A.A., Novikov V.V., Bogomyakov A.S., Nemykin V.N., Voloshin Y.Z. *Inorg. Chem.* **2014**, *53*, 3062-3071.
20. Azarkh M., Penkova L., Kats S., Varzatskii O., Voloshin Y., Groenen E. *J. Phys. Chem. Lett*. **2014**, *5*, 886-889.
21. Sheldrick G.M. SADABS v.2.01, Bruker/Siemens Area Detector Absorption Correction Program, Bruker AXS, Madison, Wisconsin, USA, **1998**.
22. Sheldrick G.M. *Acta Cryst.* **2008**, *A64*, 112.

Received 04.04.2014
Accepted 25.04.2014