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КРАТКИЕ СООБЩЕНИЯ

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A COCRYSTAL OF CAFFEINE AND DIPICOLINIC ACID: SYNTHESIS, CHARACTERIZATION, X-RAY CRYSTALLOGRAPHY, AND SOLUTION STUDIES

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A reaction between caffeine (caff) and dipicolinic acid = 2,6-pyridine dicarboxylic acid (pydc.H_2) in water results in the formation of a cocrystal compound (pydc.H_2.H_2O)(caff) **1**. The characterization of the resulting crystallohydrate is performed using ^1H, ^{13}C NMR and IR spectroscopy and X-ray crystallography. X-ray crystal structure analysis reveals the presence of both starting materials and water in the lattice. It also indicates intensive intermolecular H-bonding interactions between carboxylic acid, caffeine, and water as well as π—π stacking between the pydc.H_2 and caff rings as constituents of the cocrystal. The hydrogen bonding and non-covalent interactions play roles in the formation of the cocrystal. The crystal system is triclinic with the space group *P*-1 and two formula units per unit cell. The unit cell parameters are $a = 6.906(2)$ Å, $b = 8.451(3)$ Å, $c = 14.68$ (4) Å with $\alpha = 81.51(3°)$, $\beta = 78.47(3°)$, and $\gamma = 78.14(3°)$. The final *R* value is 0.0660 for 7943 measured reflections.

Keywords: crystal chemistry, single crystal X-ray diffraction, proton transfer, hydrogen bonding, caffeine, dipicolinic acid.

Cocrystallization is a deliberate attempt at bringing together different molecular species within one periodic crystal lattice without making or breaking covalent bonds [1]. Cocrystalization provides a helpful mean for probing the importance and balance between different intermolecular interactions and thus offers practical guidelines for developing new methodologies in supramolecular synthesis. The role of hydrogen bonding and π—π stacking for these purposes is well established [2]. Smith and co-workers have prepared a series of cocrystal compounds from the reaction of 2-aminopyrimidine, 3-amino-1,2,4-triazole, and 5-nitroquinoline with heterocyclic carboxylic acids, such as 2,6-dihydroxybenzoic acid, 4-aminobenzoic acid, phenoxyacetic acid, salicylic acid [3], indole-3-acetic acid, thiophen-2-carboxylic acid [4], and indole-2-acetic acid [5]. The design of cocrystal compounds from pharmaceutical agents has already been of interest in the field of solid-state science [6]. The role of cocrystals in pharmaceutical science has been reviewed by Zaworotko *et al*. [7]. In this contribution, the series of cocrystals of caffeine with adipic acid and hydroxyl naphthoic acids have been reported [8—10]. In connection with such compounds, we became interested in making a cocrystal compound containing caffeine and dipicolinic acid. Our goal was to investigate the influence of caffeine on the structural properties of the resulting cocrystal compound.

1,3,7-Trimethylxanthine (caffeine, caff) and its derivatives are the most widely and regularly consumed biologically active substances. The main actions of caff are mood altering and cardiovascular. Some aspects of the biological activity of caff result from its interaction with biopolymers, such as

enzymes and nucleic acids. There are some evidences of the inhibition of DNA repair by caff. It has been shown that caff is capable of reducing the toxicity of the typical DNA intercalator such as ethidium bromide and the efficacy of a number of aromatic anti-cancer drugs [11]. Caff also has shown beneficial *in vitro* and *in vivo* protective effects, some of which include radioprotection properties, inhibition of tumor genesis of certain chemicals, modulation of antitumor activity of antitumor agents and enhancement of p-450 and phase II detoxification enzymes. Caff has been found to be a suitable ingredient in skin cream to produce a wrinkle reducing, skin protecting, and moisturizing compound [12]. Ingestion of a modest amount of caff enhances the intensity of hypoglycemic warning symptoms in patients with type 1 diabetes without altering their standard of glycemic control [13]. In addition to its importance in biological system, the reactivity of its basic sites with the proton and other electrophiles such as metal ions also presents an interesting challenge [14]. The protonation equilibrium of caff has been studied by ^{1}H, ^{13}C NMR and UV spectroscopy in aqueous sulfuric and perchloride acids [15].

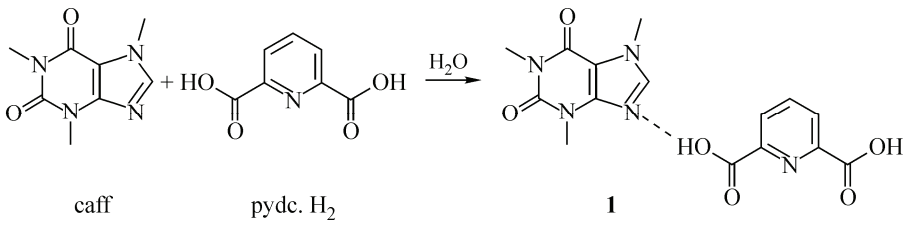
The anionic form of dipicolinic acid = 2,6-pyridine dicarboxylic acid (pydc.H_2) is an effective tridentate chelating ligand forming stable complexes [16]. It also participates in the construction of extinctive H-bonding networks within the lattice [17]. In our previous works, we have introduced a number of proton transfer compounds synthesized from pydc.H_2 [18]. Here we report the synthesis, characterization, X-ray crystal structure and solution studies of a cocrystal compound obtained from caff and pydc.H_2.

Experimental. General procedure. Caffeine and dipicolinic acid were purchased from Merck. The IR spectrum was measured with a Perkin-Elmer 343 spectrometer, using KBr discs. Melting points were determined with an Electrothermal IA-900. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-300 Avance spectrometer (250 MHz and 62.5 MHz respectively). Chemical shifts were reported on the δ scale relative to TMS. The absorption spectra were recorded using a UV-VIS 2100 Shimadzu spectrophotometer (controlled to ±0.1 °C).

Preparation of cocrystal (caff) (pydc.H_2.H_2O), 1. A solution of caff (0.50 g, 1 mmol) in water was added to a vigorously stirred suspension of pydc.H_2 (0.42 g, 1 mmol) in water. The mixture was cooled down to room temperature. After 24 h, the resulting white crystal was filtered and dried to obtain 0.83 g of **1** in 91 % yield; mp. 195°C. IR υ_{max} (KBr)/cm^{-1} 3551(m), 3415(s), 1739(m), 1708(m), 1669(s), 1618(m), 1550(w), 1506, 1432, 1384, 1340, 1302, 1267, 1233 (w), 1175 (m), 1082, 1038, 999, 887, 760, 746, 612, 484, 427, 376 (w). δ_H 8.20(3H, pydc.H_2), 8.00(s, 1H, caff), 3.88(s, 3H, CH_3 caff), 3.45(s, 3H, CH_3 caff), 3.21(s, 3H, CH_3 caff) ppm. δ_C 165.4(C pydc.H_2), 154.5(C pydc.H_2), 150.9(C caff), 148.0($C_{2,6}$ pydc.H_2), 142.7(C caff), 139.1(C_4 pydc.H_2), 127.4($C_{3,5}$ pydc.H_2), 33.00(CH_3 caff), 29.30(CH_3 caff), 27.40(CH_3 caff) ppm.

X-ray crystallography. X-ray structural analysis of a single crystal of **1** was carried out on a STOE IPDS-II diffractometer with graphite monochromated MoK_α radiation. The data were collected at a temperature of 120(2) K to a maximum θ value of 29.16° and in a series of ω scans in 1° oscillations with 420-second exposures. The crystal-to-detector distance was 110 mm. The data were corrected for Lorentz and polarizing effects. A numerical absorption correction was applied [19, 20]. The structure was solved by a direct method using the ShelxS program, and was refined by the SHELXL program [21]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located in the difference Fourier map and refined isotropically. The final cycle of the full-matrix least-squares refinement [22] on F^2 was based on 4049 unique reflections.

Results and discussion. Preparation and spectroscopic characterization. The reaction between pydc.H_2 and caff in water in the 1:1 molar ratio leads to the formation of white crystalline **1** (Scheme 1) in 91 % yield. The melting point of **1** was quite sharp and different from that of the starting materials. The characterization of **1** was performed using NMR (^{1}H,^{13}C NMR), IR spectroscopy, and X-ray crystallography. The ^{1}H NMR spectrum shows five resonances from which the one at 8.20 ppm is assigned to pydc.H_2 and the remaining four resonances correspond to caff. In the ^{13}C NMR spectrum, four signals at 127.4 ppm, 139.1 ppm, 148.0 ppm, and 165.4 ppm out of eleven total signals could definitely be assigned to pydc.H_2 and other peaks can be assigned to carbon atoms of



Scheme 1. Preparation route for **1**

caff. From the number of resonances in both spectra and the integration of ^{1}H resonances, it can be concluded that **1** consists of both caff and pydc.H_2 fragments in the 1:1 molar ratio. The most definitive feature in the IR spectrum of **1** is the characteristic loss of the broad carboxyl O—H stretching frequency (2500—3300 cm^{-1}). And also, the carbonyl stretching frequencies at 1669 cm^{-1} and 1708 cm^{-1} corresponding to the C=O group of pydc.H_2 and caff indicate the presence of both caff and pydc.H_2 species in **1**. From the IR and NMR data presented, it is logical to accept that **1** consists of one pydc.H_2 and one caff fragments. The structure of **1** has been confirmed by the X-ray crystal structure.

Solution studies. It has been reported that pydc.H_2 and 2,6-pyridinediamine (pyda) show maximum absorbance at 271.5 nm and 304.8 nm respectively, while the resulting proton transfer compound (pydaH$_2$)(pydc) possesses two absorption maxima at 269.1 nm and 328.2 nm [17a]. The observed large red shift toward larger wavelengths and the formation of a new peak have been correlated to proton transfer from the diacid to the amine and the consequent interaction of the resulting oppositely charged species. As is seen from Fig. 1, electronic spectra of pydc.H_2 with increasing concentration of caff in acetonitrile (AN) show a small red shift. Such behavior could be due to the lack of proton transfer and therefore was distinguished as a result of a probable cocrystal formation and hydrogen bonding interactions. The small red shift as well as the existence of new bands in the IR spectrum of **1** promoted us to obtain the X-ray crystallographic structure to verify the cocrystal formation.

Crystallographic investigations. The numbering scheme and ORTEP diagram of (caff)(pydcH$_2$.H$_2$O) **1** are presented in Fig. 2. X-ray crystallographic data for **1** is given in Table 1 while some selected bond lengths, bond angles and torsion angles are given in Table 2. Table 3 lists H-bonding data for the compound **1**. As seen in Fig. 3, the crystal structure of compound **1** shows that H-bonding is the basic phenomenon leading to the formation of a cocrystal compound. The structural analysis revealed extensive H-bonding interactions, including moderate H-bonding between the carboxylic acid functional group and caff nitrogen as well as H-bonding between carboxylic acid functional

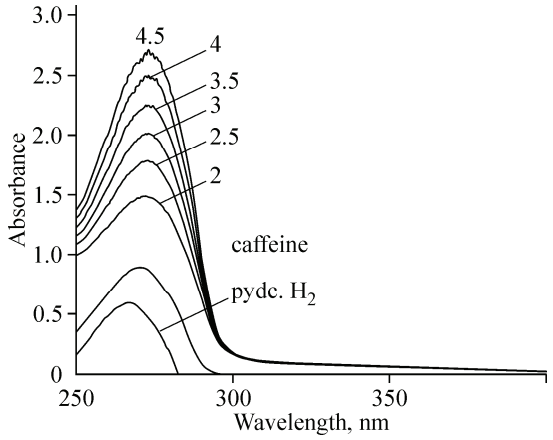


Fig. 1. Electronic absorption spectra of starting materials (pydc.H_2 (5.0×10^{-5} M), caff (1.0×10^{-4} M) and pydc.H_2) with increasing concentration of caff at various molar ratios

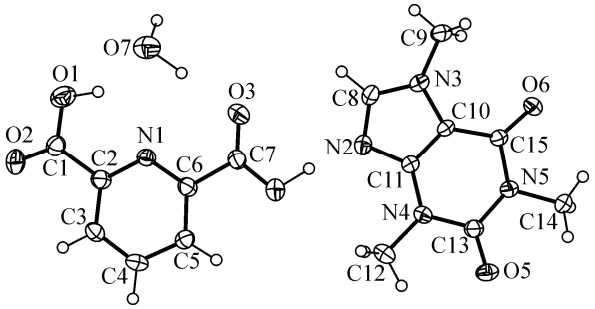


Fig. 2. ORTEP diagram for **1**

Table 1

Crystallographic data of compound **1**

CCDC deposit #	724063
Empirical formula	$C_7H_5NO_4 \cdot C_8H_{10}N_4 \cdot H_2O$, $C_{15}H_{17}N_5O_7$
Formula weight	379.34
Temperature, K	120(2)
Wavelength, Å	0.71073
Crystal system; Space group	Triclinic; *P*-1
Unit cell dimensions *a*, *b*, *c*, Å;	6.906(2), 8.451(3), 14.683(4);
α, β, γ, deg.	81.51(3), 78.47(3), 78.14(3)
Unit cell volume, Å^3	816.6(5)
Z; Calculated density, g/cm^3	2; 1.543
Absorption coefficient, mm^{-1}	0.125
F(000)	396
Crystal size, mm	0.55×0.05×0.04
θ range for data collection, deg.	2.48 to 29.16
Limiting indices	$-9 \le h \le 9$, $-11 \le k \le 11$, $-17 \le l \le 19$
Reflections collected / unique	7943 / [*R*(int) = 0.0381]
Completeness to θ = 29.16 %	91.6
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4049 / 0 /312
Goodness-of-fit on F^2	1.113
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0563$, $wR_2 = 0.1377$
R indices (all data)	$R_1 = 0.0704$, $wR_2 = 0.1458$
Largest diff. peak and hole, e/Å^{-3}	0.326 and –0.345

Table 2

Selected bond lengths (Å), *bond angles* (deg.) *and torsion angles* (deg.) *of compound* **1**

C(1)—O(2)	1.206(2)	C(7)—O(4)	1.309(2)
C(1)—O(1)	1.323(2)	C(7)—O(3)	1.228(2)
C(1)—C(2)	1.510(3)	C(6)—C(7)	1.505(3)
C(2)—N(1)	1.342(16)	C(6)—N(1)	1.347(16)
C(8)—N(2)	1.341(2)	C(11)—N(2)	1.364(2)
O(1)—H(1)	0.94(3)	O(4)—H(4B)	1.04(4)
O(7)—H(7A)	1.06(5)	O(7)—H(7B)	1.22(5)
O(2)—C(1)—O(1)	121.1(2)	O(3)—C(7)—O(4)	124.9(2)
O(2)—C(1)—C(2)	121.17(18)	O(4)—C(7)—C(6)	113.03(16)
O(1)—C(1)—C(2)	117.78(17)	O(3)—C(7)—C(6)	122.06(17)
N(1)—C(2)—C(1)	116.74(16)	N(1)—C(6)—C(7)	114.54(16)
C(3)—C(2)—C(1)	119.97(17)	C(5)—C(6)—C(7)	122.00(16)
N(3)—C(8)—N(2)	112.98(16)	N(2)—C(11)—N(4)	127.05(16)
C(8)—N(3)—C(9)	127.90(15)	C(11)—N(4)—C(12)	120.99(16)
O(5)—C(13)—N(4)	121.87(17)	O(6)—C(15)—C(10)	127.20(16)
C(13)—N(5)—C(14)	116.36(15)	C(15)—N(5)—C(14)	116.00(15)

Continued Table 2

O(2)—C(1)—C(2)—N(1)	173.1(2)	C(5)—C(6)—C(7)—O(3)	–179.42(19)
O(1)—C(1)—C(2)—N(1)	–6.7(3)	N(1)—C(6)—C(7)—O(4)	–178.78(17)
O(2)—C(1)—C(2)—C(3)	–6.4(3)	N(1)—C(6)—C(7)—O(3)	1.3(3)
O(1)—C(1)—C(2)—C(3)	173.9(2)	C(5)—C(6)—C(7)—O(4)	0.5(3)
N(1)—C(2)—C(3)—C(4)	0.5(3)	C(4)—C(5)—C(6)—N(1)	0.6(3)
C(1)—C(2)—C(3)—C(4)	179.87(18)	C(4)—C(5)—C(6)—C(7)	–178.55(18)
N(3)—C(10)—C(11)—N(2)	–0.8(2)	N(3)—C(8)—N(2)—C(11)	–0.3(2)
C(15)—C(10)—C(11)—N(2)	178.45(17)	N(2)—C(11)—N(4)—C(13)	179.63(18)
O(5)—C(13)—N(5)—C(14)	–1.2(3)	O(6)—C(15)—N(5)—C(14)	–1.7(3)

Table 3

Selected hydrogen bonds data of compound **1**

D—H···A	*d*(D—H)	*d*(H···A)	*d*(D···A)	∠(D—H···A)	Symmetry code
O1—H1…O7	0.93(3)	1.78(3)	2.610(3)	147(3)	—
O4—H4B…N2	1.04(4)	1.58(4)	2.614(2)	171(4)	—
O7—H7A…O3	1.09(5)	1.80(5)	2.862(3)	166(4)	–1–*x*, 2–*y*, 2–*z*
O7—H7B…O3	1.04(3)	1.95(3)	2.986(2)	177(2)	—

groups and the H_2O molecule. Hydrogen O—H…O and O—H…N bonds form closed associates from two caff molecules, two dipicolinic acid molecules, and two water molecules. The two O—H bonds of two —COOH functional groups in each pydc.H_2 molecule are oriented differently; one toward pydc.H_2 nitrogen and another far from it. So, two —COOH functional groups connected to the H_2O molecule by OH and C=O through H-bonding form an 8-member ring (Fig. 3). Fig. 4 presents parallel layers of two components of the cocrystal compound indicating the presence of π—π interaction between caff and dipicolinic acid rings.

As shown in Fig. 4, adjacent molecules are further linked by $\pi_{py}\ldots\pi_{imid}$ interactions. For the $\pi_{py}\ldots\pi_{imid}$ interactions, the centroid-centroid distance is about 3.473 Å. These intermolecular interac-

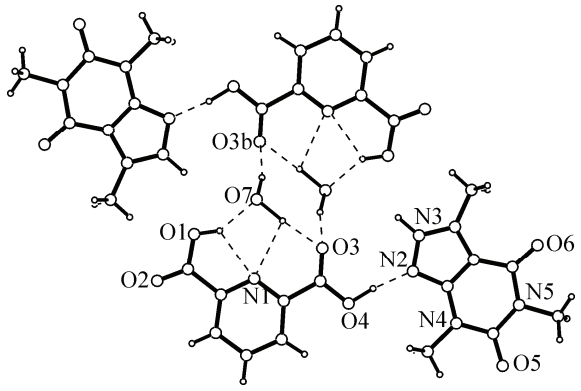


Fig. 3. Hydrogen bonding in the crystal of **1**. Hydrogen bonds are shown by dashed lines

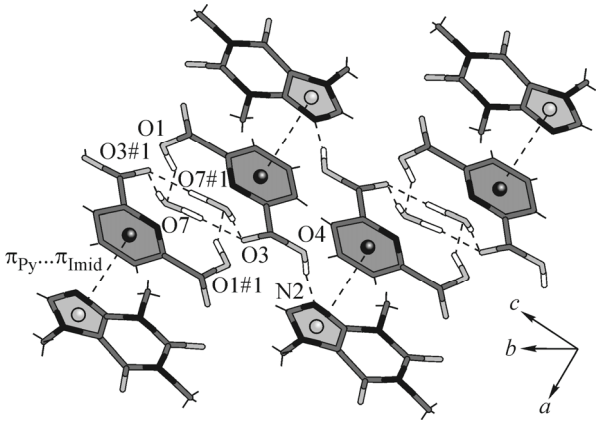


Fig. 4. Representation of the part of the unit cell content of **1**, showing classical O—H…O and O—H…N hydrogen bonds, and $\pi_{Py}\ldots\pi_{Imid}$ interactions. Some of hydrogen bonds are shown in the wireframe style for clarity. Symmetry code #1 –1–*x*, 2–*y*, 2–*z*

tions act as cooperative factors with several classical hydrogen bonds to generate a three-dimensional packing.

Conclusions. A novel crystallohydrate of caff and pydc.H_2 showed an intense intramolecular H-bonding and π—π stacking between two fragments in the lattice. Upon the role of cocrystals in pharmaceutical science, the design of a cocrystal of caff with a good ionic agent (pydc.H_2) might be a good synergy. Furthermore, the biological activities of caff, pydc.H_2 and some transition metals such as palladium, vanadium or cobalt, constituting metal complexes with cocrystals, will be an interesting approach to the future.

Acknowledgements. We gratefully acknowledge the support of this work by the Imam Hossein University.

Supplementary material. Crystallographic data for the structure of **1** has been deposited with the Cambridge Crystallographic Data Center, CCDC 724063. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-(1223-336033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk; e-mail for deposition: deposit@ccdc.cam.ac.uk).

REFERENCES

1. *Aakeröy C.B., Salmon D.J.* // J. Cryst. Eng. Comm. – 2005. – **7**. – P. 439 – 448.
2. *Ranjbar R.Z., Morsali A., Zhu L.G.* // J. Mol. Struct. – 2007. – **826**, N 1. – P. 29 – 35.
3. *Lynch D.E., Smith G., Frency D., Byriel K.A., Kennard C.H.L.* // Aust. J. Chem. – 1994. – **47**, N 6. – P. 1097 – 1115.
4. *Lynch D.E., Latif T., Smith G., Byriel K.A., Kennard C.H.L., Parson S.* // Aust. J. Chem. – 1998. – **51**, N 5. – P. 403 – 408.
5. *Lynch D.E., Latif T., Mistry N., Smith G., Byriel K.A., Kennard C.H.L.* // Aust. J. Chem. – 1998. – **51**, N 9. – P. 813 – 818.
6. *Schultheiss N., Newman A.* // Crystal Growth & Design. – 2009. – **9**, N 6. – P. 2950 – 2967.
7. *Vishweshwar P., McMahon J.A., Bis J.A., Zaworotko M.J.* // J. Pharm. Sci. – 2006. – **95**, N 3. – P. 499 – 516.
8. *Bučar D.K., Henry R.F., Lou X., Borchardt T.B., Zhang G.G.Z.* // Chem. Commun. – 2007. – N 5. – P. 525 – 527.
9. *Bučar D.K., Henry R.F., Lou X., Duerst R.W., Borchardt T.B., MacGillivray L.R., Zhang G.G.Z.* // Mol. Pharmaceutics. – 2007. – **4**, N 3. – P. 339 – 346.
10. *Bučar D.K., Henry R.F., Duerst R.W., Lou X., MacGillivray L.R., Zhang G.G.Z.* // J. Chem Crystallogr. – 2010. – **40**, N 11. – P. 933 – 939.
11. *Poltev V.I., Grokhlina T.I., González E., Deriabina A., Cruz A., Grob L., Eszczynski J., Djimant L.N., Veselkov A.N.* // J. Mol. Struct. (Theochem). – 2004. – **709**, N 1-3. – P. 123 – 128.
12. *Stadler R.H., Fay L.B.* // J. Agric. Food Chem. – 1995. – **43**, N 3. – P. 1332 – 1338.
13. *Silva V., Szczesiul A., Rudroff G.* U.S. Patent 0150597A1, 2002.
14. *Watson J.M., Jenkins E.J.E., Hamilton P.* // J. Diabetes Care. – 2000. – **23**, N 4. – P. 455 – 459.
15. *Benoit R.L., Fréchette M.* // Can. J. Chem. – 1985. – **63**, N 11. – P. 2821 – 2823.
16. *Moghimi A., Sheshmani Sh., Shokrollahi A., Shamsipur M., Kickelbick G., Aghabozorg H.* // Z. Anorg Allg. Chem. – 2005. – **631**. – P. 160 – 169.
17. *Moghimi A., Ranjbar M., Aghabozorg H., Falali J., Shamsipur M., Chadha K.K.* // Can. J. Chem. – 2002. – **80**, N 12. – P. 1635 – 1642.
18. (a) *Moghimi A., Ranjbar M., Aghabozorg H., Falali J., Shamsipur M., Yap G.P.A., Rahbarnoohi H.* // J. Mol. Struct. – 2002. – **605**, N 2-3. – P. 133 – 149. (b) *Moghimi A., Sharif M.A., Shokrollahi A., Shamsipur M., Aghabozorg H.* // Z. Anorg. Allg. Chem. – 2005. – **631**, N 5. – P. 902 – 908. (c) *Moghimi A., Sheshmani Sh., Shokrollahi A., Aghabozorg H., Shamsipur M., Kickelbick G., Aragoni M.C., Lippolis V.* // Z. Anorg. Allg. Chem. – 2004. – **630**. – P. 617 – 624. (d) *Moghimi A., Khavassi H.R., Dashtestani F., Kordestani D., Ekram Jafari A., Maddah B., Moosavi S.M.* // J. Mol. Struct. – 2011. – **996**, N 1-3. – P. 38 – 41.
19. Stoe & Cie, X-RED 1.28b (2005), Program for data reduction and absorption correction. – Stoe & Cie GmbH: Darmatadt, Germany.
20. Stoe & Cie, X-SHAPE 2.05 (2004), Program for crystal optimization for numerical absorption correction. – Stoe & Cie GmbH: Darmatadt, Germany.
21. *Sheldrick G.M.* SHELX-97, Program for Crystal Structure Refinement. – University of Göttingen, Germany, 1997.
22. Least squares function minimized; $\sum[w(F_0^2 - F_0^2)^2/\sum(N_0 - N_\upsilon)]^{1/2}$.