J Chem Crystallogr (2012) 42:600–605
DOI 10.1007/s10870-012-0287-8

ORIGINAL PAPER

Syntheses and Crystal Structures of Two Unsymmetrical 1,2,4,5-tetrazine Derivatives

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Received: 23 December 2011 / Accepted: 7 February 2012 / Published online: 25 February 2012

Abstract Two unsymmetrical 1,2,4,5-tetrazine derivatives, (6-(3,5-dimethyl-*1H*-pyrazol-1-yl)-1,2,4,5-tetrazin-3-ylamino)methanol ($C_9H_{13}N_7O$, **3**) and 4-(6-(3,5-dimethyl-*1H*-pyrazol-1-yl)-1,2,4,5-tetrazin-3-yl) morpholine ($C_{11}H_{15}N_7O$, **4**), were synthesized from 3,6-bis(3,5-dimethyl-*1H*-pyrazol-1-yl)-1,2,4,5-tetrazine and the corresponding aliphatic amine (2-aminoethanol and morpholine, respectively), there structures were confirmed by single-crystal X-ray diffraction methods. Both molecules have very similar bond length and angle patterns, The crystal structures show that compound **3** is stabilized by intermolecular O–H–N, N–H–O hydrogen bonds and π–π interactions, while compound **4** is stabilized by π–π interactions. The structure analyses establish that compound **3** belongs to the monoclinic system, space group $P2(1)/c$, with crystal data $a = 6.979(2)$ Å, $b = 9.563(3)$ Å, $c = 16.542(5)$ Å, $V = 1084.4(5)$ Å^3, $Z = 4$, $F(000) = 496$, $R_1 = 0.0488$, $wR_2 = 0.1063$. Compound **4** belongs to the orthorhombic system, space group $P2(1)2(1)2(1)$, with crystal data $a = 6.544(14)$ Å, $b = 12.085(3)$ Å, $c = 15.753(4)$ Å, $V = 1245.7(5)$ Å^3, $Z = 4$, $F(000) = 552$, $R_1 = 0.0403$, $wR_2 = 0.0913$.

Keywords 1,2,4,5-tetrazine · Syntheses · Crystal structure · Unsymmetrical · X-ray diffraction

Introduction

The 1,2,4,5-tetrazine ring is an important structural motif found in many biologically and pharmaceutically active compounds. Over the past few years, both 1,2,4,5-tetrazines and their derivatives have attracted much attention because they possess a wide spectrum of biological activities, such as anticancer [1], anti-inflammatory [2], antiviral [3] and insecticidal [4]. Some 1,2,4,5-tetrazines are being tested and clinically evaluated as potential new drugs. For example N,N′-bis(2-methylphenyl)-3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboamide (ZJGDHu-1), was reported to have a strong effect against several tumor cell lines [5]. Motivated by the afore-mentioned findings, and as a continuation of our program in the field of unsymmetrical 1,2,4,5-tetrazines [6, 7], two 3,6-unsymmetrical substituent-1,2,4,5-tetrazines (**3** and **4**) are synthesized by the substitution reaction of 3,6-bis(3,5-dimethyl-*1H*-pyrazol-1-yl)-1,2,4,5-tetrazine (**2**) and corresponding aliphatic amine in acetonitrile (Scheme 1), and their crystal structures were determined by X-ray diffraction methods.

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Experimental

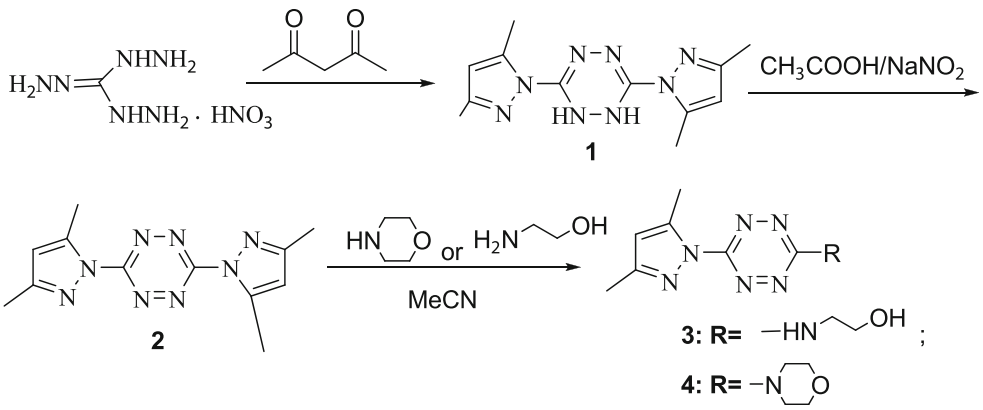
3,6-bis(3,5-dimethyl-1H-pyrazol-1-yl)-1,4-dihydro-1,2,4,5-tetrazine (BDT) (**1**) [8]

To a well stirred solution of triaminoguanidine nitrate (33.4 g, 0.2 mol) in water (200 ml) was added dropwise acetylacetone at 60 °C within about 30 min, then the reaction mixture was warmed to 70 °C for 4 h. After cooling, the product was filtered, washed by water (50 ml) and dried to get the pale yellow powder (22.3 g, 83.0%).

3,6-bis(3,5-dimethyl-1H-pyrazol-1-yl)-1,2,4,5-tetrazine (BT) (**2**) [8]

To a stirred solution of BDT (23 g, 0.08 mol) in N-methyl pyrrolidone (120 ml) and acetic acid solution (160 ml,

Scheme 1 Preparation of the two target 3,6-unsymmetrical 1,2,4,5-tetrazines



$w = 10\%$) was slowly added dropwise aqueous solution of sodium nitrite (100 ml, $w = 10\%$) at 20–30 °C. The reaction mixture was kept at room temperature with continuous stirring for 3 h, then filtered, washed by water (50 ml) and dried to get the red powder (20.5 g, 94.9%).

3-(*3,5-dimethyl-1H-pyrazol-1-yl)-6-alkylamino-1,2,4, 5-tetrazine* (**3** and **4**)

To a solution of BT (2.7 g, 0.01 mol) in acetonitrile (40 ml) was added dropwise corresponding alkylamine (0.012 mol). The reaction mixture was heated to 40–50 °C for 2–3 h with TLC monitoring (ethyl acetate:hexane = 7:3), which was then cooled on ice, the red solid was filtered and recrystallized from methanol.

Compound **3**: m.p. 153–155 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 2.56 (s, 3H), 3.84 (t, $J = 5.0$ Hz, 2H), 3.90 (t, $J = 5.0$ Hz, 2H), 6.12 (s, 1H). IR(KBr) ν cm^{-1}, 3340, 3141, 1567, 2875, 1480, 1419, 1080, 1049, 962,789; Anal. Calcd for $C_{11}H_{15}N_7O$: C, 45.95; H, 5.57; N, 41.68; O, 6.80; Found: C, 46.01; H, 5.60; N, 41.57; O, 6.72. m/z = 236.1[M + H]$^+$.

Compound **4**: m.p. 114–115 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 2.56 (s, 3H), 3.85 (t, $J = 4.9$ Hz, 4H), 4.01 (t, $J = 4.9$ Hz, 4H), 6.09 (s, 1H); IR(KBr) ν cm^{-1}, 2990, 2918, 2858, 1572, 1484, 1450, 1396, 1305, 1262, 1083, 946; Anal. Calcd for $C_{11}H_{15}N_7O$: C, 50.56; H, 5.79; N,37.53; O, 6.12; Found: C, 50.75; H, 5.92; N, 37.59; O, 6.20. m/z = 262.1[M + H]$^+$.

X-ray Crystallography

X-ray quality crystals were obtained by slow evaporation of ethyl acetate solution for compound **3** and **4**. Diffraction data were collected at 103 K by the ψ–ω scans technique, on a Rigaku AFC10 diffractometer with a Saturn724+ CCD detector using graphite-monochromated MoK α radiation from rotating anode graphite source ($\lambda = 0.71073$ Å).The structures were solved with SHELXS97 and refined with the full-matrix least-squares procedure on F^2 by SHELXL97 [9]. Scattering factors incorporated in SHELXL97 were used. The function $\sum w(|F_o|^2-|F_c|^2)^2$ was minimized, with $w^{-1} = [\sigma^2(F_o)^2+(AP)^2+BP]$, where $P = [\mathrm{Max}(F_o^2,0)+2F_c^2/3]$.The final values of A and B are listed in Table 1 together with relevant crystal data and refinement details. All non-hydrogen atoms were located in a difference Fourier map and refined anisotropically. All hydrogen atoms located at geometrically calculated positions and treated by a mixture of independent and constrained refinement.

Results and Discussion

The results of the ^{1}HNMR, IR, MS and elemental analysis are in agreement with the structures of the compounds **3** and **4**. Figures 1, 2 show the perspective views of the molecules **3** and **4**, respectively, which were drawn with the program ORTEP-3 [10]. Table 2 compares the geometric parameters of both molecules. The bond lengths and angles in both compounds are very similar, and even the results of the normal probability plot set [11] confirm that the differences between the molecules are mainly of statistical nature. Within the pyrazole ring of compound **3**, the bond lengths of N(1)–C(2) [1.328(19) Å] and C(3)–C(4) [1.370(2) Å] are both longer than their typical values [1.29 and 1.34 Å, respectively [12]; the bonds C(2)–C(3) [1.403(2) Å], N(2)–C(4) [1.378(19) Å] and N(1)–N(2) [1.381(16) Å] are shorter than their typical values [1.47, 1.43 and 1.45 Å], respectively [12]. The bond lengths of the tetrazine ring C(6)–N(6) [1.324(19) Å], N(5)–C(7) [1.345(19) Å], N(4)–C(7) [1.367(19) Å] are shorter than C–N single bonds [1.43 Å], but longer than C=N double bonds [1.29 Å]; similarly, N(5)–N(6) [1.334(18) Å], N(3)–N(4) [1.312(17) Å] and N(3)–C(6) [1.343(19) Å] are shorter than N–N single bonds [1.45 Å], but longer than

Table 1 Crystal data and experimental crystallographic details

Compound	**3**	**4**
Empirical formula	$C_9H_{13}N_7O$	$C_{11}H_{15}N_7O$
Formula weight	235.26	261.30
Temperature (K)	163 (2)	163 (2)
Wavelength (Å)	$\lambda = 0.71073$	$\lambda = 0.71073$
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_12_12_1$
Cell dimensions		
a (Å)	6.979 (2)	6.5437 (14)
b (Å)	9.563 (3)	12.085 (3)
c (Å)	16.542 (5)	15.753 (4)
β (°)	100.777 (4)	90.00 (2)
Volume (Å^3)	1084.4 (5)	1245.7 (5)
Z	4	4
Density(calculated) (Mg/m^3)	1.441	1.393
Absorption coefficient (mm^{-1})	0.104	0.098
F000	496	552
Crystal size (mm)	0.36 × 0.24 × 0.19	0.32 × 0.28 × 0.24
θ range for data collection (°)	3.29–29.10	2.12–29.13
hkl range	$-9\leq h\leq 9$, $-12\leq k\leq 13$, $-20\leq l\leq 22$	$-8\leq h\leq 8$, $-16\leq k\leq 14$, $-20\leq l\leq 21$
Reflections collected	9262	10902
Unique (R_{int})	2893 (0.0349)	3304 (0.0344)
Weighting scheme		
A	0.0359	0.0435
B	0.5680	0.1600
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2893/0/164	3304/0/175
Goodness-of-fit on F^2	0.999	0.999
Final R indices [I>2σ(I)]	$R_1 = 0.0488$, $wR_2 = 0.0966$	$R_1 = 0.0403$, $wR_2 = 0.0872$
R indices (all data)	$R_1 = 0.0726$, $wR_2 = 0.1063$	$R_1 = 0.0499$, $wR_2 = 0.0913$
Largest diff. peak and hole (e Å^{-3})	0.263/−0.248	0.236/−0.191
CCDC deposit no.	819022	819023

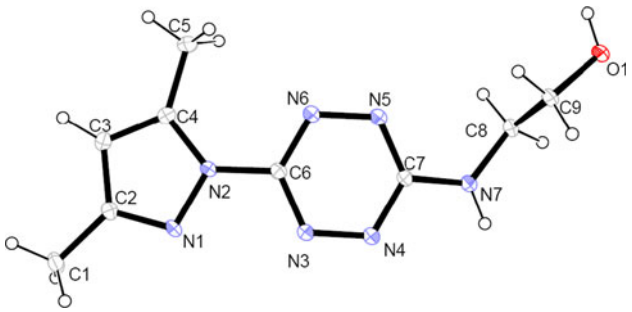


Fig. 1 Molecular structure of the compound **3**. Displacement *ellipsoids* shown at 30% probability

N=N double bonds [1.25 Å]. Furthermore, the bond lengths N(2)–C(6) [1.406(19) Å] and N(7)–C(7) [1.340(2) Å] in Fig. 1 are both shorter than their typical values [1.43 Å]. The above results shows that the pyrazole ring, tetrazine ring and atoms N(7) are conjugated system. A similar situation also occurs in compound **4**.

As can be seen in Table 2, the internal and external angles of the pyrazole ring in both of the two title compounds follow the set of empirical rules given by Bonati and Bovio [13], taking compound **3** for example, such that (a) C(2)–N(1)–N(2) [104.52(12)°] is smaller than N(1)–N(2)–C(4) [111.96(12)°]; (b) C(3)–C(2)–N(1) [111.28(13)°] is larger than C(2)–N(1)–N(2) [104.52(12)°], C(2)–C(3)–C(4) [106.97(13)°] and C(3)–C(4)–N(2) [105.27(13)°]; (c) C(2)–C(3)–C(4) is not the largest internal angle; (d) N(1)–N(2)–C(6) [118.23(12)°] is smaller than C(4)–N(2)–C(6) [129.78(13)°]; (e) N(1)–C(2)–C(1) [120.47(14)°] is smaller than C(3)–C(2)–C(1) [128.24(14)°].

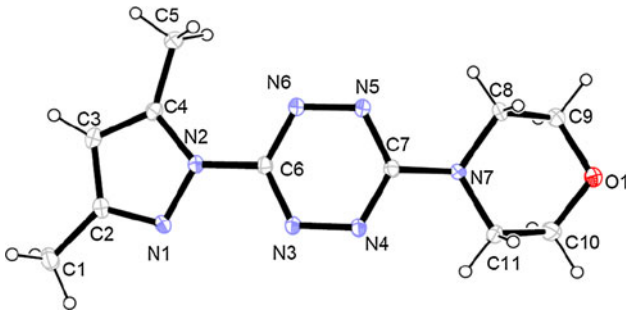


Fig. 2 Molecular structure of the compound **4**. Displacement *ellipsoids* shown at 30% probability

Table 2 Selected bond distances (Å) and angles (°) of the compound **3** and **4**

	3	**4**
N1–C2	1.328(19)	1.321(18)
C3–C4	1.370(2)	1.366(19)
C2–C3	1.403(2)	1.414(2)
N2–C4	1.378(19)	1.384(17)
N1–N2	1.381(16)	1.383(16)
N1–C2	1.328(19)	1.321(18)
N2–C6	1.406(19)	1.407(16)
C6–N6	1.324(19)	1.336(18)
N5–N6	1.334(18)	1.322(16)
N5–C7	1.345(19)	1.356(17)
N4–C7	1.367(19)	1.361(18)
N3–N4	1.312(17)	1.320(16)
N3–C6	1.343(19)	1.334(17)
C7–N7	1.340(2)	1.347(17)
N7–C8	1.458(2)	1.470(17)
C8–C9	1.517(2)	1.512(2)
O1–C9	1.423(18)	1.424(19)
N1–C2–C3	111.28(13)	111.48(12)
C2–C3–C4	106.97(13)	106.77(12)
C3–C2–C1	128.24(14)	128.09(14)
N1–C2–C1	120.47(14)	120.43(13)
C2–N1–N2	104.52(12)	104.55(11)
C3–C4–N2	105.27(13)	105.28(12)
C3–C2–N1	111.28(13)	111.48(12)
C4–N2–C6	129.78(13)	129.94(12)
N1–N2–C6	118.23(12)	118.12(11)
N1–N2–C4	111.96(12)	111.92(11)
C6–N6–N5	117.30(12)	117.47(12)
N6–N5–C7	116.79(12)	117.15(12)
N5–C7–N4	124.08(13)	123.87(12)
C7–N4–N3	117.25(12)	117.41(12)
N4–N3–C6	117.02(12)	117.28(12)
N5–C7–N7	119.65(14)	118.46(12)
N4–C7–N7	116.21(13)	117.67(12)

In compound **3,** the pyrazole ring are almost coplanar within 0.001 Å. The atoms N(3), N(4), N(5) and N(6) are almost coplanar within 0.002 Å, while C(6),C(7) and N(7) deviate from the plane by 0.085, 0.117 and 0.306 Å, respectively. The plane N(3)/N(4)/N(5)/N(6) make a dihedral angles of 6.92 (2) and 86.82 (2)° with the pyrazole ring and C(8)/C(9)/O(1) chain, respectively. In compound **4**, the pyrazole ring, N(3)/N(4)/N(5)/N(6) and the C(8)/C(9)/C(10)/C(11) planes are almost coplanar within 0.001, 0.002 and 0.005 Å, respectively. C(6) and C(7) deviate from the N(3)/N(4)/N(5)/N(6) plane by 0.074 and 0.094 Å, respectively. N(7) and O(1) deviate from the plane C(8)/C(9)/C(10)/C(11) by 0.673 and 0.588 in the opposite direction, which causes the morpholine ring to exhibit a chair conformation. The plane N(3)/N(4)/N(5)/N(6) makes dihedral

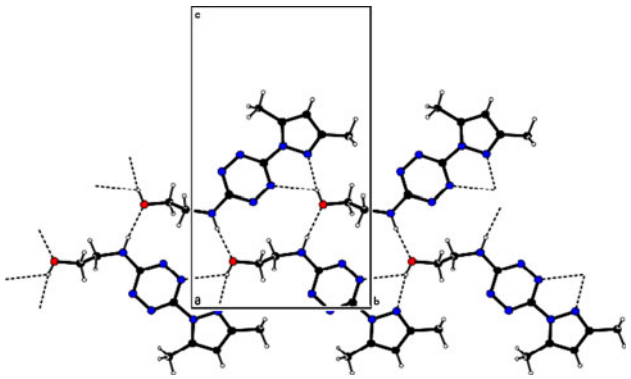


Fig. 3 The hydrogen bonded chains of molecules **3** as seen along a direction. Hydrogen bonds are shown as *dashed lines*

Table 3 Hydrogen-bonding geometry (Å, °)

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
O1–H10···N1^{i}	0.85	2.14	2.984(2)	170
O1–H10···N3^{i}	0.85	2.47	2.990(2)	120
N7–H7N···O1^{ii}	0.88	1.99	2.861(4)	172

Symmetry codes: (i) x, −1 + y, z; 1 − z; (ii) 1 − x, 1/2 + y, 1/2 − z

Table 4 Intermolecular π–π interaction (Å)

Cg–Cg	Cg–Cg (Å)
3	
Cg1–Cg2^{i}	3.574(12)
Cg1–Cg2^{ii}	3.629(12)
4	
Cg1–Cg2^{iii}	3.517(12)
Cg1–Cg2^{iv}	3.494(12)

Symmetry codes: (i) −x, 2−y, −z; (ii) 1−x, 2−y, −z; (iii) −1/2+x, 1/2−y, 1−z; (iv) 1/2+x, 1/2−y, 1−z. Cg1 is the centroid of the pyrazole ring; Cg2 is centroid of the tetrazine ring

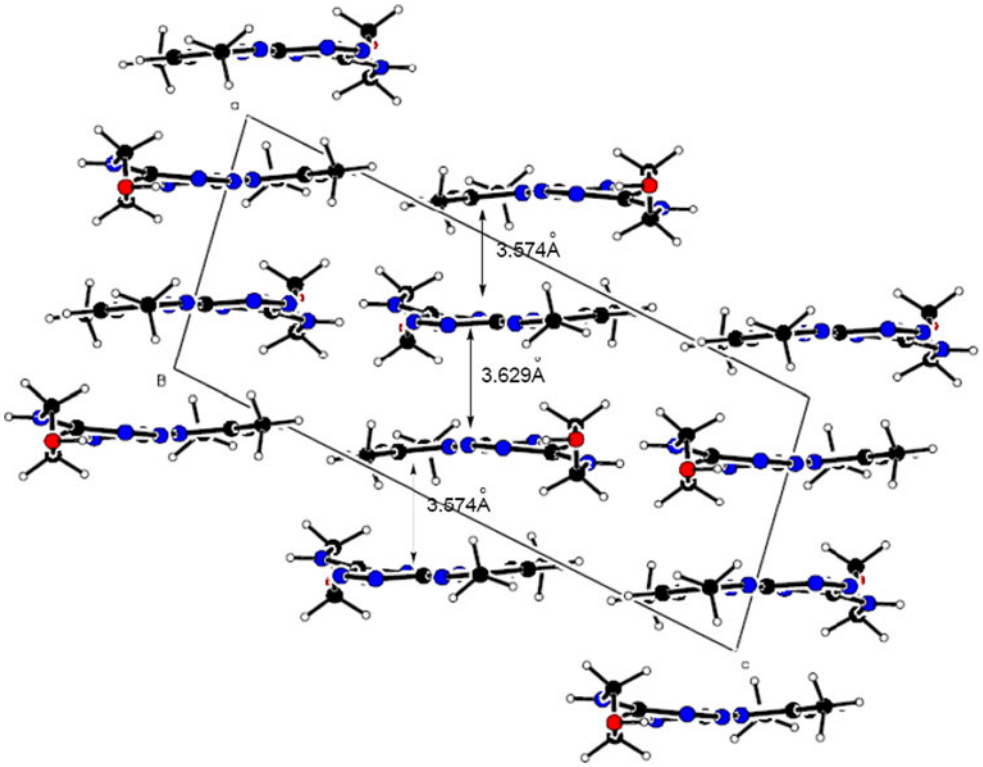


Fig. 4 The crystal packing of **3** viewed down the b axis. A portion of the intermolecular π–π interactions are shown as *double headed arrows*

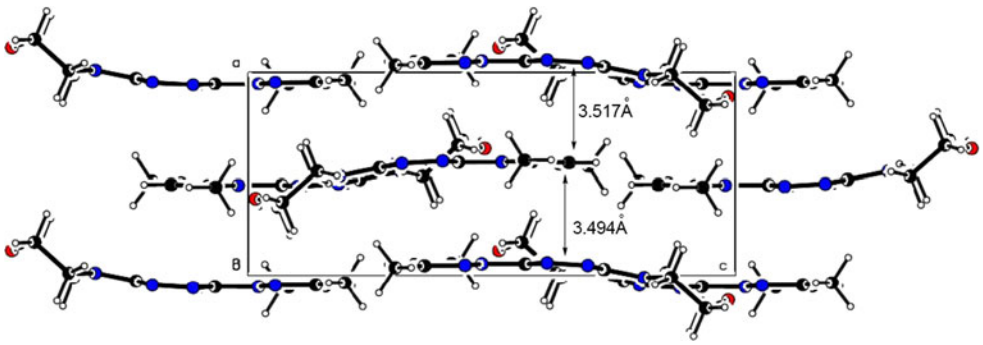


Fig. 5 The crystal packing of **4** viewed down the *b* axis. A portion of the intermolecular π–π interactions are shown as *double headed arrows*

angle with the pyrazole ring, 4.72(2)°, while the twist with respect to the plane C(8)/C(9)/C(10)/C(11) is 38.29(2)°.

In compound **3**, intermolecular interactions involving two directionally specific O–H–N and one N–H–O interactions stabilize the packing along the ***b*** direction (Fig. 3; Table 3), which forms twelve membered rings involving three molecules and five membered rings involving two molecules. In **4**, no interesting intra- and inter-molecular hydrogen bonding is seen within the molecule.

Intermolecular π–π interactions in **3** and **4** between pyrazole rings and tetrazine rings are shown in Table 4. As can be seen from Fig. 4, the crystal packing shows that the molecular layers of **3** arranged along [10–1] direction. The centroid–centroid distances among adjacent three layers are different; the similar situation also occurred in compound **4**. In Fig. 5, the molecular layers are extended along [001] direction, the adjacent three layers also show different centroid–centroid distances (Table 4).

Acknowledgments We are very grateful to the Foundation of Taizhou Vocational and Technical College for support (grant No. 2012ZD05).

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