1,2,4,5-Tetrazines *vs.* Carboxylic Acid Dimers: Molecular Chemistry *vs.* Supramolecular Chemistry

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Dedicated to Professor *Jack D. Dunitz* on the occasion of his 80th birthday

The structures of six new tetrazines have been determined and their molecular packing has been compared to the supermolecular architecture observed in related carboxylic acid dimers. In the tetrazines, covalent N–N bonds are considered to replace the intermolecular O–H···O hydrogen bonds of the carboxylic acids. In the systems investigated, it is apparent that, in the majority of cases, the covalent six-membered ring of the tetrazine is an appropriate replacement for the carboxylic acid synthon. This apparent interplay between molecular and supramolecular units may have applications in the crystal engineering of new materials.

1. Introduction. – Supramolecular chemistry is chemistry beyond the single molecule. Supramolecular chemistry is based on the intermolecular noncovalent bond, just as molecular chemistry is based on the covalent bond [1][2]. Molecular chemistry has created a wide range of ever more-sophisticated molecules and materials, and has developed a very powerful arsenal of procedures for constructing them from atoms linked by covalent bonds. The aim of supramolecular chemistry is to develop complex chemical systems from components that interact through noncovalent intermolecular forces.

When comparing supramolecular chemistry to molecular chemistry, different terms are used to describe the building blocks and bonding interactions. In supramolecular chemistry, intermolecular interactions are used instead of covalent bonds, molecules instead of atoms, supramolecular entities instead of molecules, cells instead of supramolecular entities, tissues instead of cells, organisms instead of tissues, and so on. Supramolecular chemistry has developed as the chemistry of the entities generated by intermolecular noncovalent interactions. *Schmidt*, in 1971, introduced the term crystal engineering [3], which has been defined by *Desiraju* as the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties [4]. Years later, *Dunitz* described an organic crystal as a '*supramolecule par excellence*' [5].

In this context, a question emerges: is it possible to replace a covalent bond with a noncovalent bond without changing the empirical rules that govern the packing? How

narrow is the gap between the intermolecular bond and covalent bond? It is known that some of the strongest intermolecular interactions are stronger than the weakest covalent bond [6]. The *Cambridge Structural Database* (*CSD*) contains over a quarter of a million compounds [7], which should be a large enough sample to provide examples where H-bonds replace covalent bonds without great distortion of the crystal packing.

2. Methodology. – The main objective of this work was to find crystal isostructures from entities that differ in the substitution of H-bonds by covalent bonds. The OH···O interaction was chosen because it is one of the strongest H-bonds observed in organic molecular crystals, and a dimeric association is very commonly observed. Two molecules held together through an intermolecular contact could possibly be replaced by one single molecule with a covalent bond replacing the intermolecular H-bond. Since the covalent single bond has multiple conformational possibilities, it is easier to study a planar synthon with less conformational freedom. The first that came to mind was the well-known carboxylic acid dimer (in *Etter/Bernstein* graph set descriptors [8], R_2^2 (8)) (*Fig. 1,a*), which is also the most common mode of association of carboxy groups *via* a centre of symmetry, namely *ca.* 96% when the carboxy group is the only strong H-bond donor/acceptor group present [9]. Thus, the challenge is to find a covalent six-membered planar ring with similar space-filling properties.

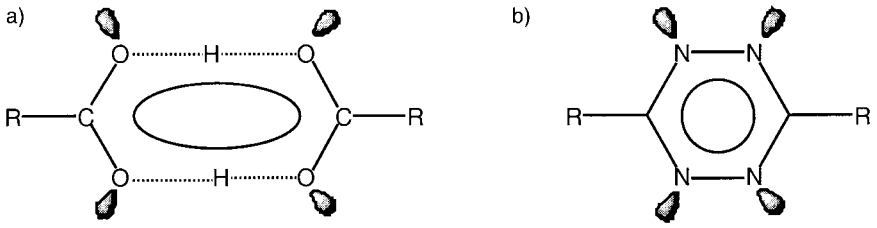

Fig. 1. a) *Carboxylic acid dimer*, b) *six-membered 1,2,4,5-tetrazine ring*

We used the CSD search program ConQuest to retrieve possible six-membered rings with any non-H-atom (Z) in positions 1, 2, 4, or 5, and C(sp^2)in positions 3 or 6, from CSD release 5.24, November 2002. *Pedireddi et al.* suggested the carboxylic acid dimer synthon as an appropriate analogue to the Ph rings [10], but we have restricted our search to those rings without H bonds to the Z-atoms to give similar electrostatic environment around these atoms. We obtained 28 hits and three different ring systems. We kept just the 1,2,4,5-tetrazine rings (*Fig. 1,b*) as possible substitutes for the carboxylic acid dimer synthon because of the lack of planarity of the other two rings, (1,4 = N, 2,5 = S or O). We found 13 centrosymmetric 1,2,4,5-tetrazines comparable with the equivalent carboxylic acid dimers, of which there are only four examples exactly comparable with the carboxylic acid available in the CSD (CSD refcode: ACETAC, PICOLA02, CINMAC03, and BENZAC02). The first two form a H-bond motif that is incompatible with tetrazine rings. The third one, CINMAC03 [11], and its analogue tetrazine, XAYVOI [12], show similar substructures, with tapes that run through the crystal as shown in *Fig. 2*, but these tapes pack differently in the full crystal structure. The last pair, BENZAC02 [13] *vs.* PTETAZ [14], gives the first observed

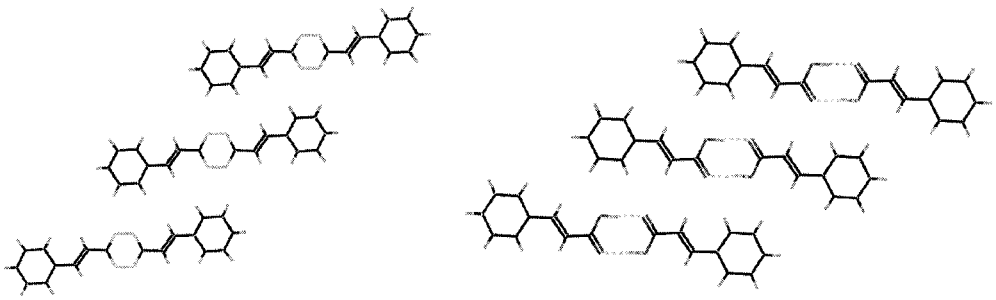

Fig. 2. *Tape arrangements for XAYVOI* (left) *and CINMAC03* (right)

carboxylic acid/tetrazine isostructural pair that gives impetus to this work. We undertook a study of derivatives of PTETAZ (**1**, *Fig. 3*), that do not contain strong H-bond-donor groups that could distort in the intermolecular contact arrangement, and for which analogue carboxylic acids were reported in the CSD. Crystalline samples of six derivatives [15] were obtained, and the crystal and molecular structures of the tetrazine derivatives **2**–**7** were determined by X-ray single-crystal analysis so that the structural information could be compared with that of the related carboxylic acid dimers.

3. Results and Discussion. – 3.1. *Molecular Structures of 1,2,4,5-Tetrazine Derivatives.* The tetrazine compounds **1**–**7** crystallize in centrosymmetric space groups, ($P\bar{1}$ and $P2_1/c$). Except for **5**, all the molecules are located on a centre of symmetry, and a half molecule constitutes the asymmetric unit. Compound **5** presents one and a half independent molecules in the asymmetric unit, and both conformations, *cis* and *trans* for the NO_2 group with respect to the tetrazine ring, are observed. The complete independent molecule shows a *cis* conformation, while the other half independent molecule generates through a symmetry centre a molecule that displays a *trans* conformation. The molecular structure and the atom-labelling scheme of compounds **2**–**7** are depicted in *Fig. 4*.

The distortion observed in the internal angles of the phenyl ring for the compounds **2**–**7**, when compared with the parent compound **1** (PTETAZ), can be attributed to the electronic properties of substituents at C(6) or C(7) (*Table 1*). This effect reveals the electron-withdrawing nature of the Cl, NO_2, and MeO substituents *vs.* the donating nature of the Me substituents. The electron-withdrawing groups expand the *ipso* angle and contract the contiguous ones, whereas the Me group closes the *ipso* angle and opens the adjacent angles. This premise does not fit very well for the internal angle at the C(8) atom in any of the compounds, indicating that the value of this angle in compound **1** is overestimated. The magnitudes of these deformations does not match those reported by *Domenicano* and *Murray-Rust* [16] probably because of the lack of precision in the parent compound **1** (PTETAZ), *R* factor = 0.13. The phenyl rings are twisted with respect to the tetrazine ring up to a maximum of 16° in the centrosymmetric molecule of compound **5**. The NO_2 group for the compounds **4** and **5** are slightly twisted by up to 11°, while, for compound **7**, the MeO group is in the phenyl plane.

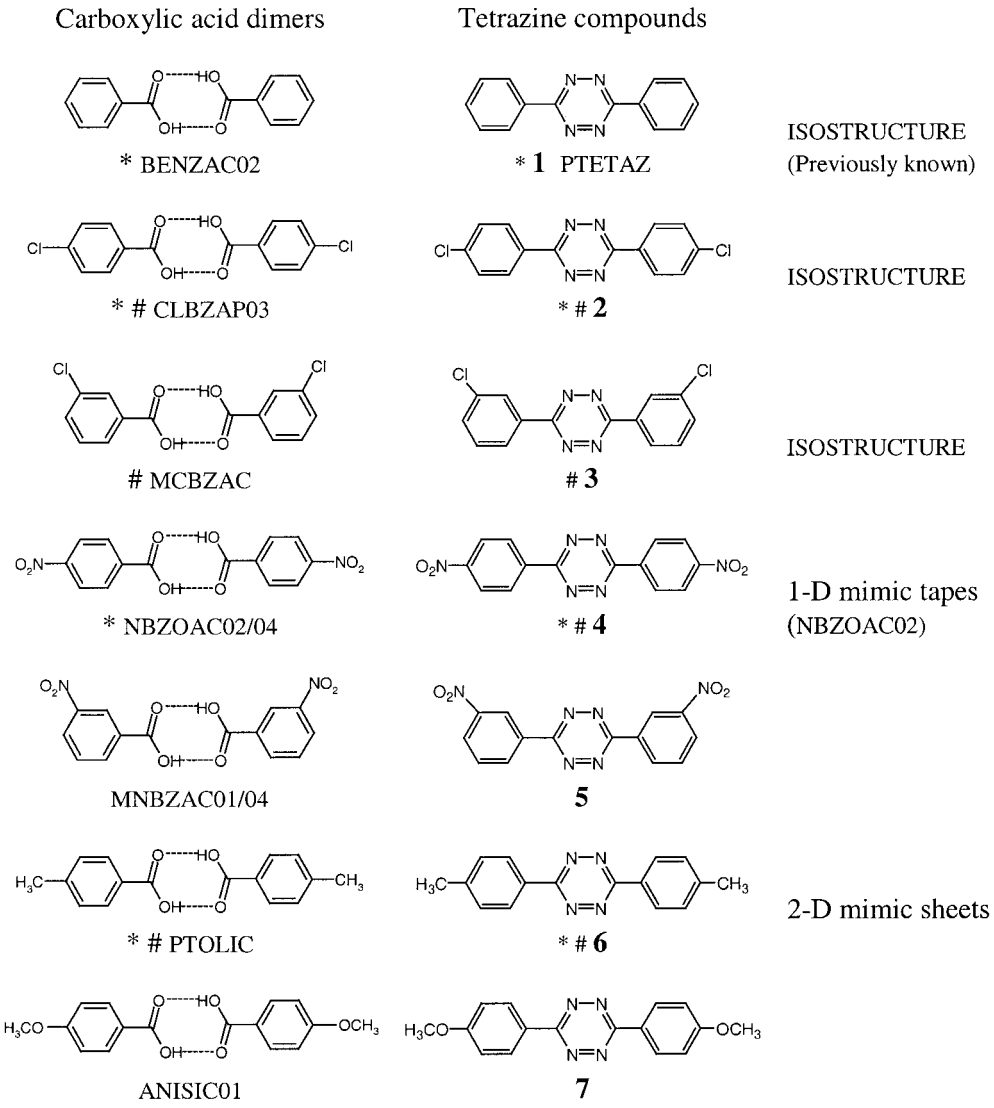

Fig. 3. *Pairs of comparable compounds.* *: Compounds that form a tape arrangement as shown in *Fig. 5*. #: Compounds that display planar sheets in their crystal structure.

3.2. *Comparison of Molecular Geometry of 1,2,4,5-Tetrazines with the Corresponding Carboxylic Acid Dimers.* The main differences between the tetrazine compounds and the carboxylic acid dimers are in those geometric parameters involving the substitution of H-bonds by the covalent bonds (*Tables 1* and *2*). While the distances N–N in the tetrazine compounds are in the range (1.314–1.326 Å), the distances O···O for the carboxylic acid dimers are almost twice as long, (2.559–2.663 Å). The covalent bonds joining the C- and the N-atoms for **1**–**7** are longer than the covalent

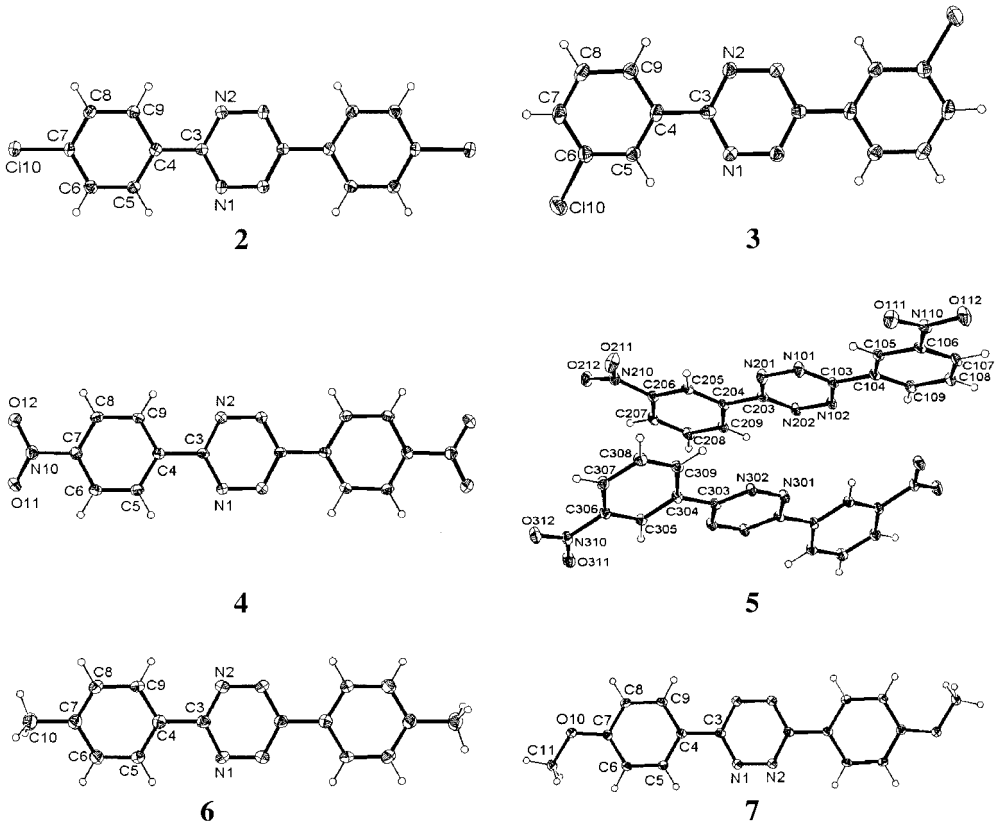

Fig. 4. *Molecular structures showing the atomic numbering for the compounds* **2**–**7**. Displacement ellipsoids are scaled to enclose 30% probability.

bonds that join the C- and O-atoms in the carboxylic acid derivatives. The overall effect is that the central ring is *ca.* 1.24 Å longer in the C⋯C direction for the carboxylic acid dimers *vs.* the tetrazine compounds.

3.3. *Crystal Structure of 1,2,4,5-Tetrazine Derivatives.* Tetrazine derivatives **1**–**7** have H-bond acceptor groups and no strong donor groups, but alternative weak CH⋯N H-bonds are observed (*Table 3*). For the compounds **1**, **2**, **4**, and **6**, these interactions guide the assembly of the discrete molecules into infinite 1-D tapes (*Fig. 5*).

The tapes in compound **1** form layers parallel to (001) by stacking of the phenyl rings with the 'heterorings'. The 3-D structure is formed through contact CH⋯π between phenyl rings in contiguous layers (*Fig. 6* and *Table 3*).

Packing of compounds **2** and **6** can be comparable from the point of view that both form similar planar sheets from the tapes. While in compound **2** the tapes are joined through Cl⋯Cl contacts (*Fig. 7* and *Table 3*), in compound **6** only *Van der Waals* interactions are observed (Me⋯Me and Me⋯Ph; *Fig.* 8 and *Table 3*). The stacking of the sheets permits contacts between the rings.

Table 1. *Selected Geometric Parameters* [Å, °] *from the 1,2,4,5-Tetrazine Structures.* X(10) = C(10) for the compounds **2** and **3**, N(10) for the compounds **4** and **5**, C(10) for **6**, and O(10) for **7**. The complete atom labelling for the compound **5** can be obtained by adding the value of *n* to the label of the atom, *i.e.*, N(1), *n* = 100 means N(101), *etc.* See *Fig. 4* for the atom labelling scheme.

Compound	**1**	**2**	**3**	**4**	**5**			**6**	**7**
	PTETAZ				*n* = 100	*n* = 200	*n* = 300		
N–N	1.314	1.322(4)	1.325(4)	1.326(4)	1.325(2)	1.323(2)	1.320(2)	1.314(5)	1.325(2)
N(1)–C(3)	1.338	1.347(5)	1.346(5)	1.345(4)	1.338(3)	1.336(2)	1.349(2)	1.344(5)	1.349(2)
N(2)–C(3)	1.352	1.347(5)	1.344(5)	1.333(5)	1.347(2)	1.346(2)	1.344(2)	1.340(5)	1.347(2)
C(3)–C(4)	1.454	1.473(6)	1.462(6)	1.482(5)	1.481(2)	1.481(2)	1.472(3)	1.475(5)	1.473(3)
C(6/7)–X(10)	–	1.745(5)	1.737(4)	1.468(4)	1.470(2)	1.469(2)	1.475(3)	1.514(6)	1.364(3)
X(10)–O/C(11)	–	–	–	1.226(4)	1.222(2)	1.220(2)	1.225(2)	–	1.439(3)
N(10)–O(12)	–	–	–	1.228(4)	1.229(2)	1.225(2)	1.227(2)	–	–
C(3)–N(1)–N	118.9	117.8(3)	118.4(3)	117.2(3)	117.9(2)	117.6(2)	117.6(2)	117.8(3)	118.0(1)
C(3)–N(2)–N	119.3	118.4(3)	117.5(3)	118.1(3)	117.4(2)	117.8(2)	118.5(2)	118.2(3)	117.9(1)
N(1)–C(3)–N(2)	121.8	123.8(3)	124.1(4)	124.6(3)	124.6(2)	124.7(2)	123.9(2)	123.9(4)	124.1(1)
N(1)–C(3)–C(4)	118.8	117.9(3)	118.0(4)	116.8(3)	117.5(2)	117.8(2)	118.3(2)	118.1(4)	118.0(2)
N(2)–C(3)–C(4)	119.4	118.3(3)	118.0(3)	118.6(3)	117.9(2)	117.5(2)	117.8(2)	118.0(3)	117.9(2)
C(3)–C(4)–C(5)	121.0	121.1(3)	120.4(4)	120.2(3)	119.3(2)	120.2(2)	120.4(2)	121.0(4)	120.5(2)
C(3)–C(4)–C(9)	119.5	120.0(4)	120.7(4)	120.4(3)	120.8(2)	120.1(2)	119.6(2)	120.9(4)	121.1(2)
C(9)–C(4)–C(5)	119.5	118.9(3)	118.9(4)	119.4(3)	119.9(2)	119.8(2)	120.0(2)	118.2(4)	118.4(2)
C(4)–C(5)–C(6)	120.6	120.7(3)	120.3(4)	121.1(3)	118.1(2)	118.1(2)	117.8(2)	120.9(4)	121.2(2)
C(5)–C(6)–C(7)	119.8	119.1(4)	121.2(4)	118.4(3)	123.2(2)	123.1(2)	122.9(2)	121.1(4)	119.6(2)
C(6)–C(7)–C(8)	118.8	121.7(4)	119.2(4)	122.4(3)	118.3(2)	118.0(2)	118.8(2)	117.8(4)	119.5(2)
C(7)–C(8)–C(9)	121.9	119.0(3)	121.1(4)	118.1(3)	120.5(2)	120.4(2)	120.0(2)	121.7(4)	120.7(2)
C(8)–C(9)–C(4)	119.3	120.6(4)	119.3(4)	120.6(3)	120.1(2)	120.5(2)	120.6(2)	120.3(4)	120.6(2)
C(6/5)–C(7/6)–X(10)	–	119.6(3)	118.9(3)	118.6(3)	118.1(2)	118.4(2)	118.5(2)	121.2(4)	124.6(2)
C(8/7)–C(7/6)–X(10)	–	118.7(3)	120.0(3)	119.0(3)	118.7(2)	118.5(2)	118.6(2)	120.9(4)	115.9(2)
C(7/6)–X(10)–O/C(11)	–	–	–	118.2(3)	118.6(2)	117.9(2)	118.2(2)	–	117.4(1)
C(7/6)–N(10)–O(12)	–	–	–	117.8(3)	118.1(2)	118.6(2)	118.0(2)	–	–
O(11)–N(10)–O(12)	–	–	–	124.0(3)	123.3(2)	123.5(2)	123.9(2)	–	–
N–N(1)–C(3)–C(4)	178.5	180.0(3)	179.1(3)	179.5(3)	−179.5(2)	179.4(2)	−179.5(2)	179.7(3)	−179.2(1)
N(1)–C(3)–C(4)–C(5)	2.2	9.3(5)	−11.0(5)	7.1(5)	2.8(3)	6.0(3)	16.0(2)	−6.0(5)	−4.7(2)
C(5)–C(6)–C(7)–X(10)	–	180.0(3)	–	178.1(3)	–	–	–	178.1(4)	−178.6(2)
C(4)–C(5)–C(6)–Y(10)	–	–	179.5(3)	–	−178.1(2)	−177.4(2)	−177.8(2)	–	–
C(6/5)–C(7/6)–X(10)–O/C(11)	–	–	–	−9.8(4)	6.3(3)	−11.4(3)	−7.6(2)	–	−0.8(2)

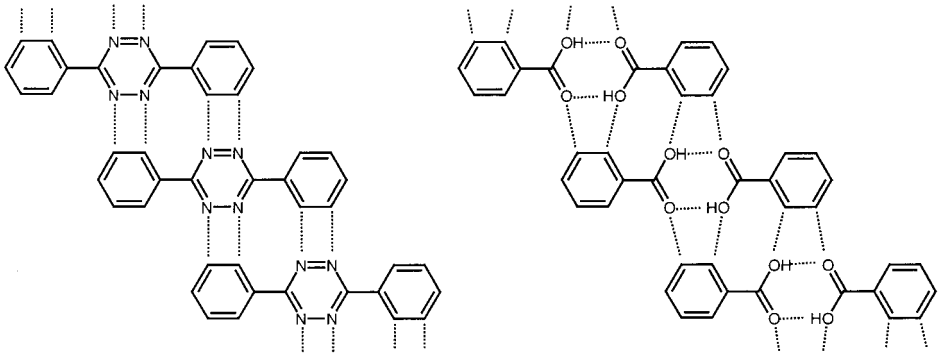

Fig. 5. *Diagram of a tape arrangement for 1,2,4,5-tetrazine and carboxylic acid compounds*

Table 2. *Selected Geometric Parameters* [Å, °] *from the Carboxylic Acid Structures.* X(10) = C(10) for the compounds CLBZAP03 and MCBZAC, N(10) for the compounds NBZOAC02/04 and MNBZAC01/04, C(10) for PTOLIC, and O(10) for ANISIC01. The atom labelling has been chosen to be able to compare with the 1,2,4,5-tetrazine compounds (see *Fig. 4*).

CSD Refcode	BENZAC02	CLBZAP03	MCBZAC	NBZOAC02	NBZOAC04	MNBZAC01		MNBZAC04		PTOLIC	ANISIC01
						mol. 1	mol. 2	mol. 1	mol. 2		
O···O	2.627	2.612(1)	2.663	2.623	2.648(1)	2.559	2.642	2.663(2)	2.614(3)	2.630	2.632
O(1)–C(3)	1.258	1.239(1)	1.303	1.317	1.316(1)	1.257	1.261	1.249(2)	1.244(3)	1.272	1.288
O(2)–C(3)	1.268	1.306(1)	1.222	1.248	1.231(1)	1.256	1.274	1.285(3)	1.288(3)	1.274	1.254
C(3)–C(4)	1.484	1.479(1)	1.483	1.482	1.487(1)	1.488	1.476	1.321(3)	1.482(3)	1.476	1.469
C(7/6)–X(10)	–	1.735(1)	1.744	1.473	1.470(1)	1.470	1.464	1.470(3)	1.473(3)	1.499	1.356
X(10)–O/C(11)	–	–	–	1.225	1.230(1)	1.197	1.227	1.224(2)	1.217(3)	–	1.435
N(10)–O(12)	–	–	–	1.220	1.227(1)	1.215	1.206	1.229(2)	1.223(3)	–	–
C(3)–O(1)···O	118.7	122.9(1)	111.0	114.6	111.1(1)	118.8	120.6	121.1(1)	122.9(1)	119.9	116.2
C(3)–O(2)···O	117.7	114.1(1)	126.3	123.0	125.2(1)	117.7	117.0	114.7(1)	113.7(1)	117.2	121.3
O(1)–C(3)–O(2)	123.5	123.0(1)	122.7	122.3	123.5(1)	123.5	122.2	123.4(2)	123.4(2)	122.9	122.4
O(1)–C(3)–C(4)	118.7	121.6(1)	114.8	116.6	114.6(1)	117.4	117.9	123.9(2)	119.3(2)	118.4	117.3
O(2)–C(3)–C(4)	117.8	115.5(1)	122.5	121.1	121.9(1)	119.1	119.9	112.4(2)	117.3(2)	118.8	120.3
C(3)–C(4)–C(5)	120.5	119.5(1)	121.7	121.3	120.9(1)	118.8	118.8	118.9(2)	118.3(2)	120.8	121.0
C(3)–C(4)–C(9)	119.9	120.3(1)	118.5	118.7	118.3(1)	120.4	120.6	130.4(2)	121.3(2)	120.6	120.1
C(9)–C(4)–C(5)	119.7	120.2(1)	119.7	120.0	120.8(1)	120.8	120.6	107.5(2)	120.4(2)	118.6	118.9
C(4)–C(5)–C(6)	119.5	120.1(1)	119.0	120.9	119.7(1)	118.1	118.9	122.3(2)	118.2(2)	120.2	121.1
C(5)–C(6)–C(7)	120.7	118.9(1)	121.8	117.4	118.3(1)	123.0	122.2	122.8(2)	122.5(2)	121.5	119.1
C(6)–C(7)–C(8)	119.8	122.0(1)	118.9	123.2	123.3(1)	118.1	118.9	118.4(2)	118.4(2)	118.4	120.2
C(7)–C(8)–C(9)	120.2	118.7(1)	121.4	118.2	117.9(1)	121.2	120.3	120.2(2)	120.9(2)	121.4	120.2
C(8)–C(9)–C(4)	120.0	120.2(1)	119.2	120.3	120.0(1)	118.8	119.2	127.9(2)	119.5(2)	119.9	120.5
C(6/5)–C(7/6)–X(10)	–	119.2(5)	119.4	119.5	118.4(1)	118.1	119.6	118.1(2)	118.0(2)	120.2	124.3
C(8/7)–C(7/6)–X(10)	–	118.8(1)	118.8	117.2	118.4(1)	118.9	118.3	119.1(2)	119.5(2)	121.4	115.5
C(7/6)–X(10)–O/C(11)	–	–	–	117.9	118.0(1)	119.2	117.5	118.1(2)	118.3(2)	–	118.1
C(7/6)–N(10)–O(12)	–	–	–	118.3	117.6(1)	118.8	118.7	118.1(2)	117.8(2)	–	–
O(11)–N(10)–O(12)	–	–	–	123.8	124.5(1)	122.0	123.8	123.8(2)	123.9(2)	–	–
O···O(1)–C(3)–C(4)	176.8	–178.9	–178.7	175.5	–175.1	176.6	–178.8	–176.0	–177.6	178.4	–176.2
O(1)–C(3)–C(4)–C(5)	1.0	–6.4(1)	2.1	0.4	–1.7(1)	–6.4	–3.0	9.0(3)	–0.8(3)	2.8	2.9
C(5)–C(6)–C(7)–X(10)	–	–179.6(1)	–	–179.2	–179.6(1)	–	–	–	–	–178.6	180.0
C(4)–C(5)–C(6)–Y(10)	–	–	–178.0	–	–	179.5	178.8	172.6(2)	178.9(2)	–	–
C(6/5)–C(7/6)–X(10)–O/C(11)	–	–	–	11.8	–14.5(1)	2.2	–1.1	–21.7(3)	–4.8(3)	–	3.5

Table 3. *Geometry of H-Bonds for the Compounds* **1**–**7** (distances in Å and angles in °). Cph represents the centroid of the phenyl rings and Ci represents the centroid of the 1,2,4,5-tetrazine rings.

	D–H	H···A	D···A	D–H···A
Compound **1**				
C(5)–H(5)···N(1) (1 – *x*, – 1 – *y*, – *z*)	1.08(–)	2.80(–)	3.584(–)	129(–)
C(6)–H(6)···N(2) (1 + *x*,1 + *y*,*z*)	1.08(–)	2.65(–)	3.578(–)	143(–)
Cph···Ci (x,1 + y,z)			3.691(–)	
C(7)–H(7)···Cph (1 – *x*,1/2 + *y*,1/2 – *z*)	1.08(–)	3.20(–)	4.136(–)	145(–)
Compound **2**				
C(8)–H(8)···N(1) (1 + *x*, – 1 + *y*,*z*)	0.95(–)	2.69(–)	3.458(6)	139(–)
C(9)–H(9)···N(2) (1 – *x*, – 1 – *y*, – *z*)	0.95(–)	2.73(–)	3.473(6)	136(–)
Cl···Cl (1 – *x*, – 2 – *y*, – 1 – *z*)			3.362(5)	
Ci···Ci (1 + *x*,*y*,*z*)			3.853(5)	
Compound **3**				
C(7)–H(7)···N(2) (1 – *x*, – 1/2 + *y*,3/2 – *z*)	0.95(–)	2.56(–)	3.497(5)	168(–)
C(7)–H(7)···N(1) (1 – *x*, – 1/2 + *y*,3/2 – *z*)	0.95(–)	2.67(–)	3.499(5)	146(–)
Cl···Cl (2 – *x*, – *y*,1 – *z*)			3.563(2)	
Ci···Ci (1 + *x*,*y*,*z*)			3.901(1)	
Cph···Cph (1 + *x*,*y*,*z*)			3.901(1)	
Compound **4**				
C(5)–H(5)···N(1) (– *x*,1 – *y*, – *z*)	0.95(–)	2.78(–)	3.417(4)	125(–)
C(6)–H(6)···N(2) (*x*,1 + *y*,*z*)	0.95(–)	2.52(–)	3.369(5)	149(–)
C(9)–H(9)···O(11) (*x*,*y* – 1,*z*)	0.95(–)	2.56(–)	3.437(5)	153(–)
C(8)–H(8)···O(12) (2 – *x*, – 1/2 + *y*,1/2 – *z*)	0.95(–)	2.59(–)	3.505(4)	162(–)
Cph···Cph (1 – *x*,1 – *y*, – *z*)			3.910(1)	
Compound **5**				
Cph(1)···Cph(2) (*x* – 1,*y*,*z*)			3.736(1)	
C(108)–H(108)···O(211) (*x* – 1,*y* + 1,*z*)	0.95(–)	2.43(–)	3.122(3)	129(–)
C(105) – H(105)···O(211) (1 – *x*,1/2 + *y*,1/2 – *z*)	0.95(–)	2.89(–)	3.030(2)	89(–)
Cph(3)···Cph(3) (1 – *x*, – *y*,1 – *z*)			3.696(1)	
N(310)···O(311) (2 – *x*, – *y*,1 – *z*)			2.982(2)	
Ci(3)···Cph(2) (*x*,*y*,*z*)			3.973(1)	
C(207)–H(207)···N(302) (1 + *x*,*y*,*z*)	0.95(–)	2.42(–)	3.284(2)	151(–)
Compound **6**				
C(5)–H(5)···N(1) (3 – *x*, – *y*,1 – *z*)	0.95(–)	2.74(–)	3.525(5)	141(–)
C(6)–H(6)···N(2) (*x*,*y* – 1,*z*)	0.95(–)	2.80(–)	3.530(5)	134(–)
Ci···Cph (1 + *x*,*y*,*z*)			3.675(1)	
Compound **7**				
Ci···Cph (*x* – 1,*y*,*z*)			3.869(1)	
C(11)–H(11a)···O(10) (1 – *x*,1/2 + *y*,3/2 – *z*)	0.98(–)	2.61(–)	3.333(4)	131(–)
C(11)–H(11b)···N(2) (– *x*,1 – *y*,2 – *z*)	0.98(–)	2.75(–)	3.468(4)	131(–)

In compound **3**, the molecules are held together to form sheets through a CH···(N–N) bifurcated H-bond and Cl···Cl contacts (*Fig. 9* and *Table 3*). Overlapping of the rings with $\pi\cdots\pi$ stacking is observed between consecutive sheets (*Fig. 10*).

In compound **4**, C–H···O interactions assemble tapes in planar sheets parallel to the (104) plane allowing overlapping with $\pi\cdots\pi$ stacking of the phenyl rings (*Fig. 11* and *Table 3*).

The packing of compound **5** does not show the tape substructure, and can be described as stacking of alternative layers parallel to (001) of *cis* and *trans* molecules

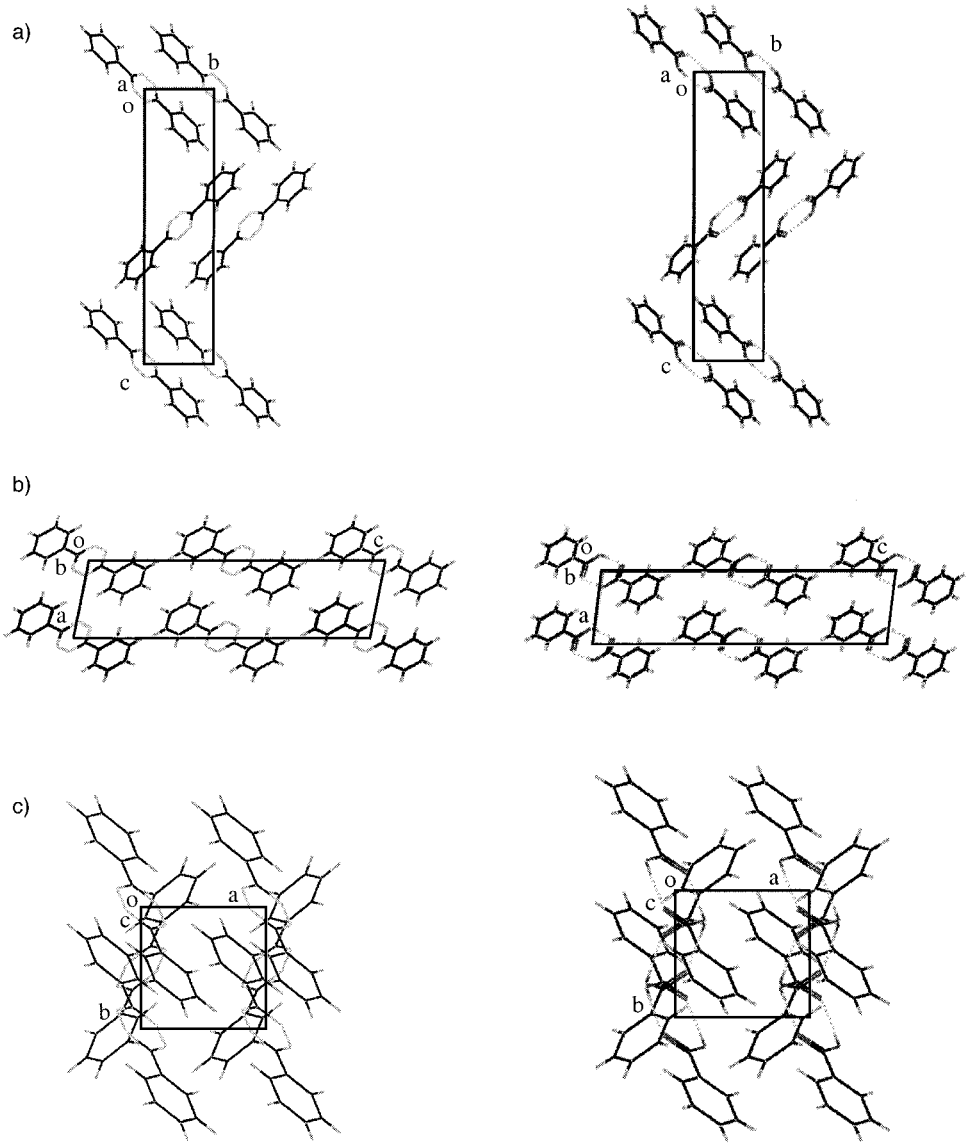

Fig. 6. *Packing for PTETAZ* (**1**) *and BENZAC02 along the axes* a) a, b) b, *and* c) c

(*Fig. 12* and *Table 3*). The *cis* molecules are held together through CH···O H-bonds and $\pi\cdots\pi$ contacts. In the *trans* layer, the molecules are joined by contacts between the NO_2 groups and $\pi\cdots\pi$ interactions between the phenyl substituents. Weaker interlayer CH···N interactions and $\pi\cdots\pi$ contacts assemble the layers into the crystal.

In compound **7**, nonplanar sheets are observed through CH···O interactions between MeO groups (*Fig. 13* and *Table 3*). The crystal is constructed through CH···N

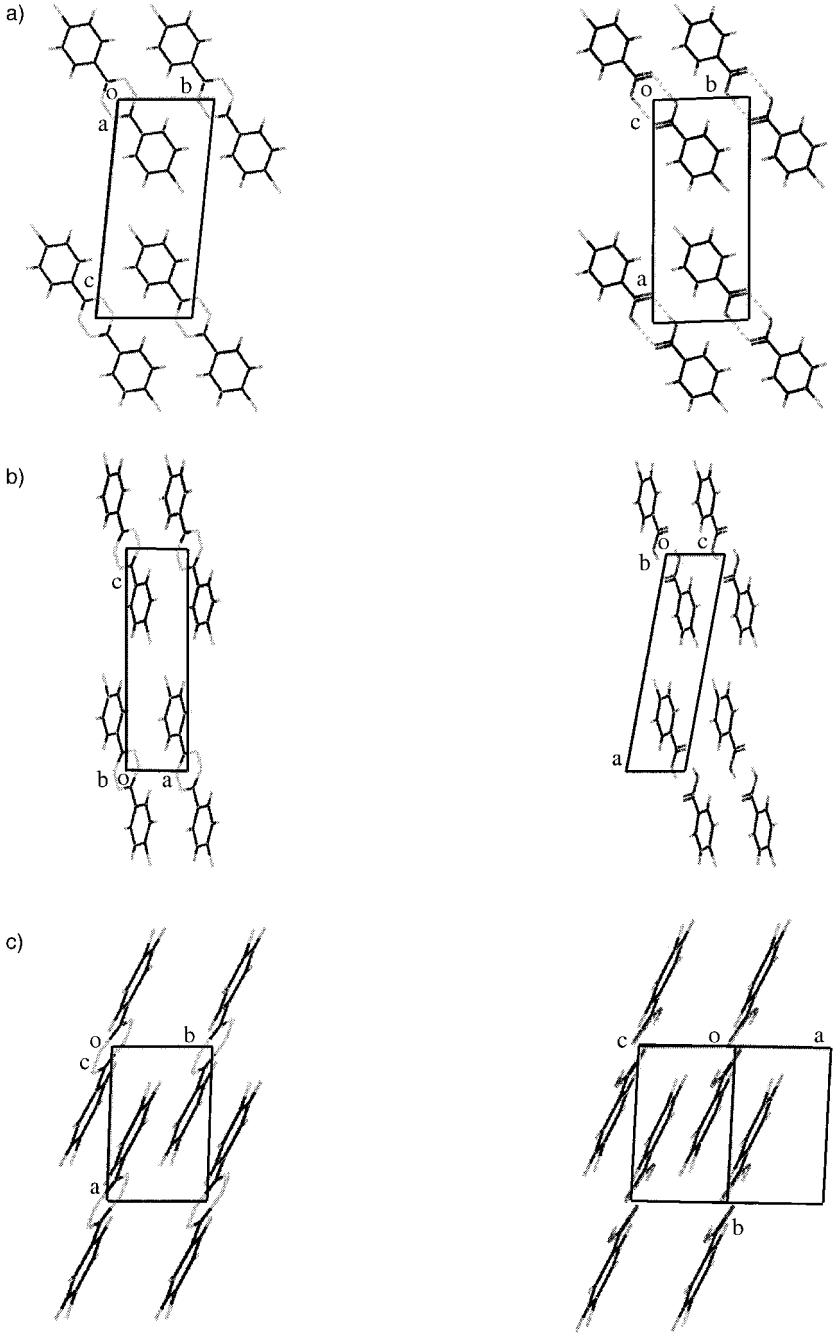

Fig. 7. *Packing for* **2** *and CLBZAP03 along the axes* a) a, b) b, *and* c) c for **2** *and along the equivalent one in CLBZAP03*

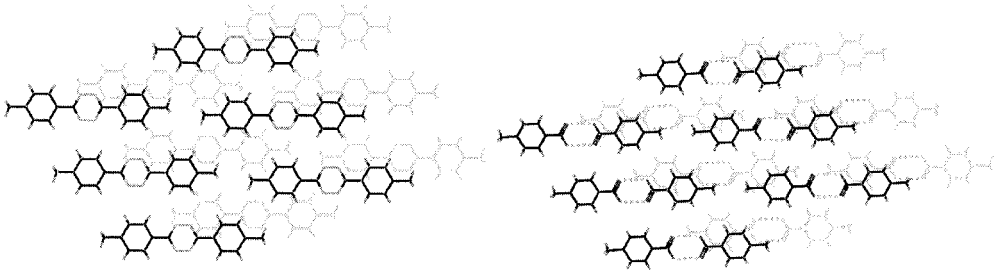

Fig. 8. *Perpendicular view of a sheet for* **6** *and PTOLIC*. In light grey is shown the contiguous sheet.

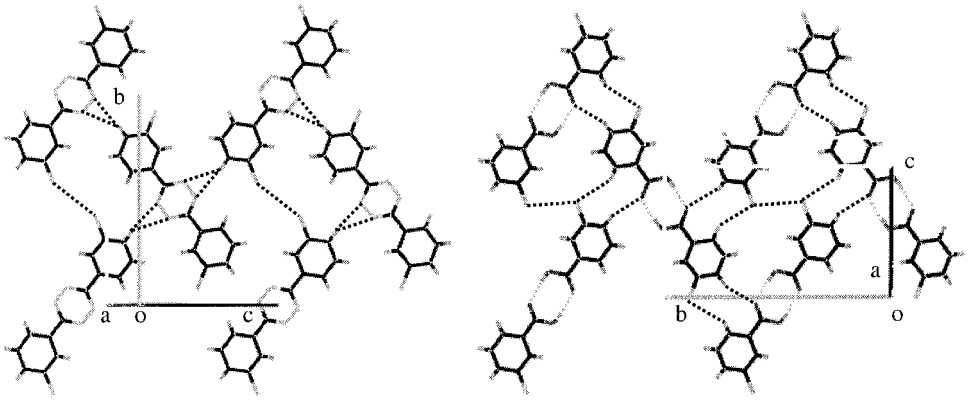

Fig. 9. *View of one sheet for* **3** *and MCBZAC*

interactions and $\pi\cdots\pi$ contacts that hold together the sheets. The tape substructure can be seen in this compound but in different packing through CH$\cdots$N interactions with the MeO groups.

3.4. *Comparison of the 1,2,4,5-Tetrazine Structures with the Corresponding Carboxylic Acid Dimers. Table 4* shows a brief summary of the space groups and the cell parameters for the seven pairs of compounds. From this table, we observe that these

Table 4. *Space Group, Unit-Cell Dimensions, and Volume for the Seven Pairs of Compounds for Comparison*

Carboxylic acid	Space group	Cell parameters [Å, °]	V_{cell} [Å^3]	Tetrazine	Space group	Cell parameters [Å, °]	V_{cell} [Å^3]
BENZAC02	$P2_1/c$	5.5, 5.1, 22.0, 90, 97, 90	614.0	PTETAZ	$P2_1/c$	5.4, 5.2, 20.6, 90, 102, 90	566.6
CLBZAP03	$P\bar{1}$	14.4, 6.1, 3.8, 87, 101, 93	326.7	**2**	$P\bar{1}$	3.9, 6.0, 13.6, 96, 91, 92	313.8
MCBZAC	$P2_1/c$	3.8, 16.0, 11.2, 90, 95, 90	688.3	**3**	$P2_1/c$	3.9, 14.4, 11.5, 90, 92, 90	643.2
NBZOAC02	$P2_1/c$	5.4, 5.2, 24.7, 90, 97, 90	682.5	**4**	$P2_1/c$	6.8, 7.4, 13.2, 90, 100, 90	654.3
NBZOAC04	$A2/a$	12.9, 5.0, 21.0, 90, 97, 90	1346.8	–	–	–	–
MNBZAC01	$P2_1/n$	7.8, 11.2, 17.2, 90, 93, 90	1485.1	**5**	$P2_1/c$	7.8, 9.9, 26.1, 90, 94, 90	2008.6
MNBZAC04	$P2_1/c$	13.2, 10.7, 10.3, 90, 91, 90	1461.3	–	–	–	–
PTOLIC	$P\bar{1}$	8.9, 7.9, 7.6, 121, 119, 94	359.5	**6**	$P\bar{1}$	5.0, 7.3, 9.3, 77, 86, 81	328.3
ANISIC01	$P2_1/a$	17.0, 11.0, 4.0, 90, 98, 90	730.6	**7**	$P2_1/c$	6.8, 6.1, 16.2, 90, 98, 90	675.7

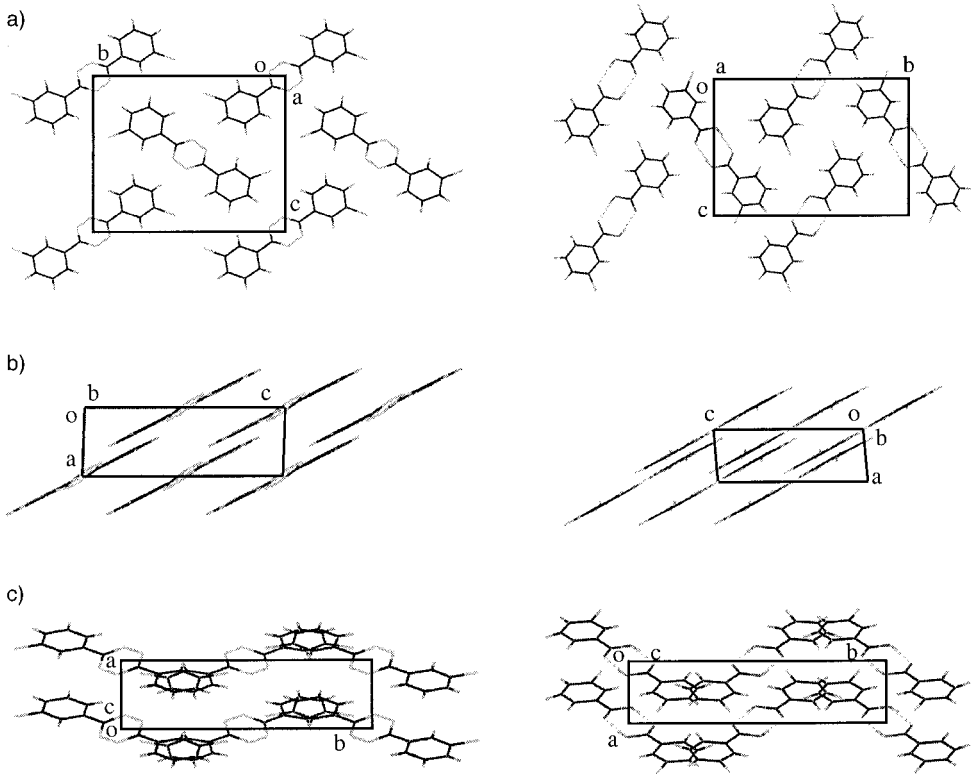

Fig. 10. *Packing for* **3** *and MCBZAC along the axis* a) a, b) b, *and* c) c

compounds have a preference for the space groups, $P\bar{1}$ (No. 2) and $P2_1/c$ (No. 14), which are the space groups most frequently found in organic crystal structures. Molecular volumes for the carboxylic acid dimers (calculated as $V_{cell}/2Z$) show an increase of 3–11% compared with those in their equivalent tetrazine compounds.

As noted above, the assembly of dimers into the 1-D tapes (*Fig. 5*) is to be expected, and it is observed in BENZAC02, CLBZAP03, NBZOAC02, and PTOLIC with similar tape architecture to the tetrazines.

We have found two new isostructures (*Tables 3* and *5*): **2**/CLBZAP03 (*Fig. 7*) and **3**/MCBZAC (*Figs. 9* and *10*). The former is a full isostructure with a unit-cell transformation $(-c,b,a+c)$ in CLBZAP03 (3.778, 6.132, 14.175 Å, 92.30, 94.69, 92.54°). The other example, MCBZAC, is not a full isostructure. The packing is topologically identical, but the molecules are rotated 180° about the long molecular axis (the line joining the C(7) atoms) (*Fig. 10*). When we fit the relative orientation of the molecules in the sheets by interchanging the axes *b* and *c*, we have almost the same molecular arrangement with glide planes replacing two-fold axes (*Fig. 9*).

The compound 4-nitrobenzoic acid, NBZOAC02/04, crystallizes in two different polymorphic forms. NBZOAC02 shows a tape arrangement, which mimics its partner tetrazine **4**, but with different packing of the tapes (*Fig. 11*). In structure **4**, all the tapes

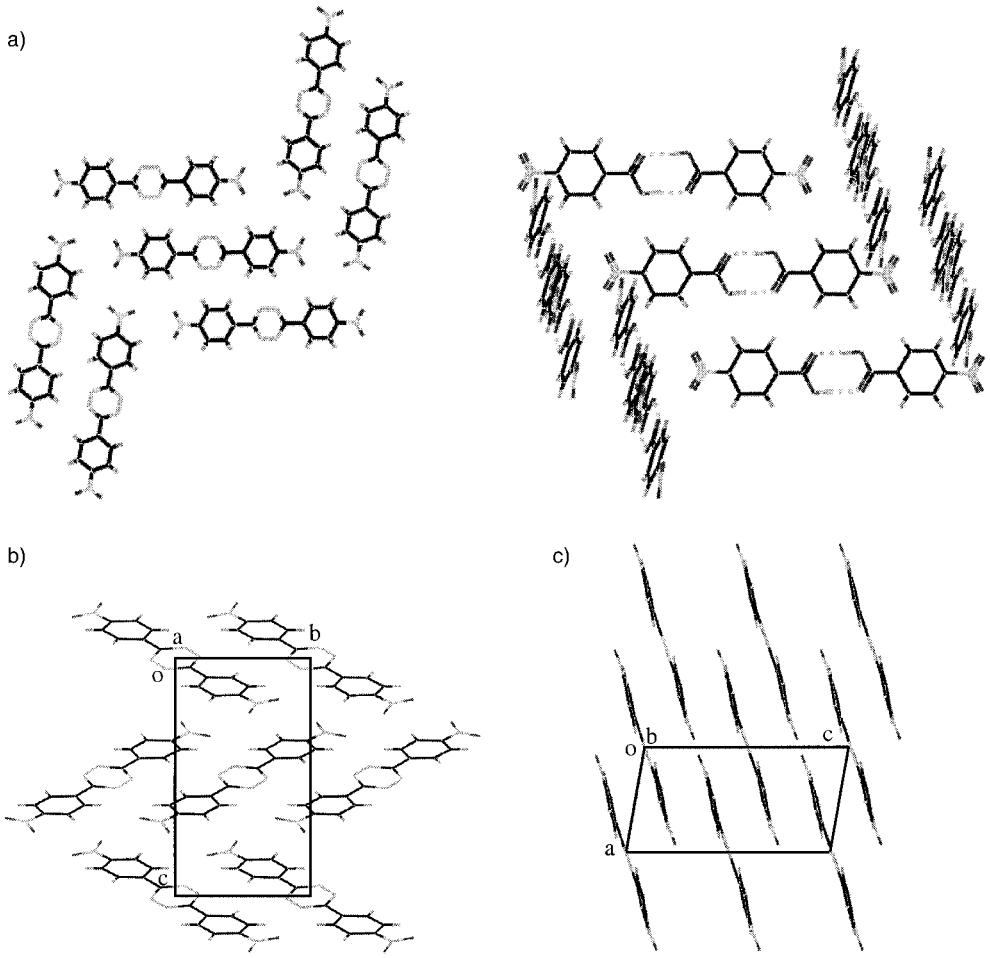

Fig. 11. a) *View of one tape and the neighboring molecules for* **4**, *and NBZOAC02*. Packing of **4** along the axes *b*) *a* and *c*) *c*.

are parallel, forming planar sheets, while, in the NBZOAC02 polymorph, the neighboring tapes are twisted. The other polymorph, NBZOAC04, forms a different tape arrangement as shown in *Fig. 14*.

The pair **6**/PTOLIC show similar 2-D planar sheet patterns (*Fig. 8*), but the sheets are packed giving different relative positions of the molecules as seen in the perpendicular projection in *Fig. 8*.

The remaining compounds **5** and **7** have structures different from the equivalent carboxylic acid derivatives. In compound **5**, both conformations of the NO_2 group with respect to the tetrazine ring are found for the molecules in the crystal, while the molecules for the comparable carboxylic acid crystallize with the different conformations of the dimers in different polymorphs, *cis* (MNBZAC01) and *trans* (MNBZAC04) (*Fig. 15*).

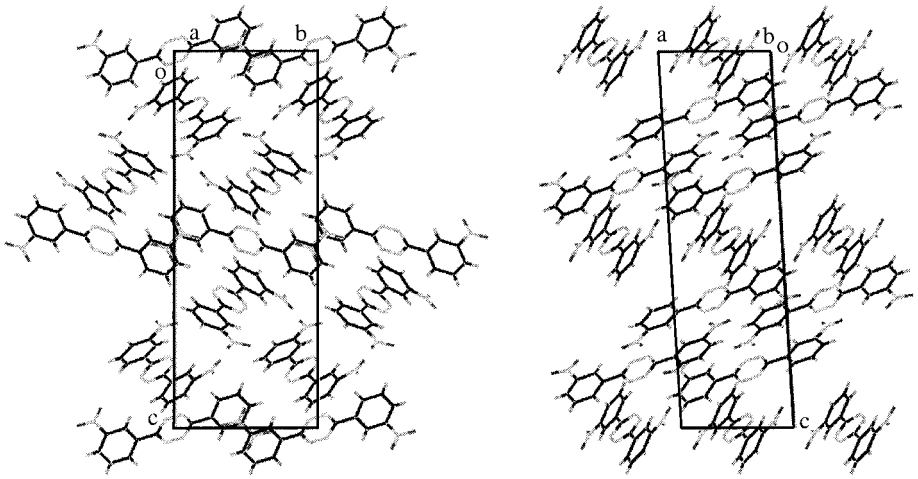

Fig. 12. *Packing for compound* **5** *along the axes* a *and* b

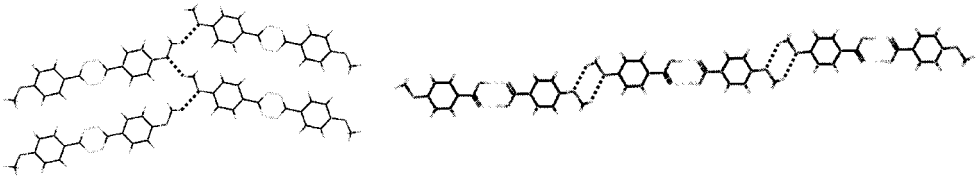

Fig. 13. *View of one chain for* **7** *and one tape for ANISIC02*

Table 5. *Geometry of H-Bonds for the Compounds BENZAC02, CLBZAP03 and MCBZAC* (distances in Å and angles in °). Cph represents the centroid of the phenyl rings and Ci represents the centroid of the H-bond synthon rings.

	D–H	H···A	D···A	D–H···A
BENZAC02				
C(5)–H(5)···O(1) $(1-x,-1-y,-z)$	0.96(–)	2.65(–)	3.528(–)	152(–)
C(6)–H(6)···O(2) $(1+x,1+y,z)$	0.91(–)	2.74(–)	3.575(–)	152(–)
Cph···Ci $(x,1+y,z)$			4.095(–)	
C(7)–H(7)···Cph $(1-x,1/2+y,1/2-z)$	0.97(–)	3.43(–)	4.292(–)	150(–)
CLBZAP03				
C(8)–H(8)···O(1) $(x,1+y,1+z)$	0.99(1)	2.57(1)	3.430(1)	146(1)
C(9)–H(9)···O(2) $(-x,1-y,1-z)$	0.98(1)	2.50(1)	3.396(1)	152(1)
Cl···Cl $(1-x,-2-y,2-z)$			3.396(1)	
Ci···Ci $(x,y,1+z)$			3.778(1)	
MCBZAC				
C(7)–H(7)···O(2) $(1+x,1/2-y,1/2+z)$	0.95(–)	2.57(–)	3.432(–)	151(–)
C(9)–H(9)···Cl $(-1+x,1/2-y,-1/2+z)$	1.01(–)	2.92(–)	3.778(–)	143(–)
Cl···Cl $(-x,1-y,-1-z)$			3.878(–)	
Cl···Cl $(1+x,y,z)$			3.845(–)	
Ci···Ci $(1+x,y,z)$			3.845(–)	
Cph···Cph $(1+x,y,z)$			3.845(–)	

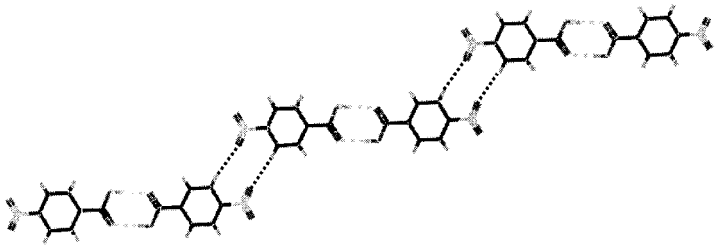

Fig. 14. *View of one tape for NBZOAC04*

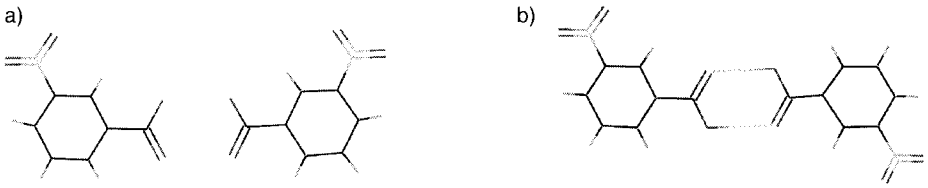

Fig. 15. *View of the independent molecules for* a) *MNBZAC01 and* b) *MNBZAC04*

The dimers for the compound ANISIC01 are held together through CH···O(MeO group) contacts to form tapes that are different from the layer arrangement observed in the equivalent tetrazine system **7** (*Fig. 13*).

4. Conclusions. – Starting from the only isostructure, **1**, retrieved from the CSD, we have selected six new tetrazine derivatives by the most-fundamental rules of crystal engineering. We have found two tetrazine compounds, **2** and **3**, that probably construct the crystal by the same steps as for the known carboxylic acid derivative, and another two compounds, **4** and **6**, that present similarities in the 1-D tapes or 2-D sheets. The remaining two compounds, **5** and **7**, have very few points of similarity with their carboxylic acid equivalents. Note that we have not studied the possibility of obtaining different polymorphs from different solvents. These results show that six-membered 1,2,4,5-tetrazine rings can be an adequate replacement for the carboxylic acid dimer synthon $R_2^2(8)$.

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Experimental Part

The synthesis of the 1,2,4,5-tetrazines studied in this work has been previously described by *Sauer* [15]. Crystallization details and relevant crystallographic data for compounds **2**–**7** are given in *Table 6*.

For compounds **2**, **3**, **4**, and **7**, X-ray crystallographic data collection was carried out, at $T = 150$ K, on a *Nonius Kappa CCD* diffractometer equipped with MoK_a radiation and a graphite monochromator, and an *Oxford Cryostream* crystal-cooling device. Intensity measurements were obtained using ω- and ϕ-scans. Data collection was run using the *Nonius Collect* software [17], and cell refinement and data reduction were performed in the *Nonius HKL Denzo* and *Scalepack* software [18]. Multi-scan absorption correction was performed on data from compounds **2**, **4**, and **7** using the *Sortav* software [19].

Data collection for the compounds **5** and **6**, at $T = 150$ K, was carried out on Station 9.8 at the *Daresbury SRS* facility with a *Bruker AXS SMART 1K CCD* diffractometer equipped with a silicon 111 monochromator

Table 6. *Crystal Analysis Parameters for the Compounds* **2**–**7** (*T* 150 K)

	2	**3**	**4**	**5**	**6**	**7**
Recrystallization						
Method	Layered solvents	Vapor diffusion	Layered solvents	Vapor diffusion	Vapor diffusion	Vapor diffusion
Solvent	$CHCl_2$	CCl_4	CH_2Cl_2	$CHCl_3$	AcOEt	CCl_4 with AcOEt
Precipitant	EtOH	EtOH	EtOH	EtOH	EtOH	EtOH
Crystal Data						
Empirical formula	$C_{14}H_8Cl_2N_4$	$C_{14}H_8Cl_2N_4$	$C_{14}H_8N_6O_4$	$C_{14}H_8N_6O_4$	$C_{16}H_{14}N_4$	$C_{16}H_{14}N_4O_2$
Crystal habit	Plate	Needle	Block	Needle	Block	Block
Crystal size [mm]	$0.03 \times 0.15 \times 0.22$	$0.03 \times 0.03 \times 0.30$	$0.13 \times 0.13 \times 0.15$	$0.03 \times 0.06 \times 0.25$	$0.10 \times 0.10 \times 0.40$	$0.15 \times 0.20 \times 0.30$
Symmetry	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$
a [Å]	3.853(5)	3.9013(4)	6.8256(4)	7.7749(5)	5.0462(16)	6.836(5)
b [Å]	6.002(5)	14.3882(14)	7.3933(4)	9.9265(7)	7.260(2)	6.137(5)
c [Å]	13.648(5)	11.4658(14)	13.1744(9)	26.0786(15)	9.316(3)	16.249(5)
α [°]	95.834(5)	90	90	90	76.870(13)	90
β [°]	90.952(5)	91.953(3)	100.214(2)	93.635(4)	85.693(14)	97.594(5)
γ [°]	91.512(5)	90	90	90	81.297(13)	90
V [Å^3], Z	313.8(5), 1	643.23(12), 2	654.29(7), 2	2008.6(2), 6	328.28(17), 1	675.7(8), 2
D_c [g/cm^3], M, $F(000)$	1.604, 303.1, 154	1.565, 303.1, 308	1.646, 324.3, 332	1.608, 324.3, 996	1.327, 262.3, 138	1.447, 294.3, 308
Data Collection						
Radiation type	MoK_α	MoK_α	MoK_α	Synchrotron	Synchrotron	MoK_α
Wavelength [Å]	0.7107	0.7107	0.7107	0.69340	0.69340	0.7107
θ Range [°]	3.9–22.7	3.6–26.4	3.0–23.2	3.6–25.4	4.0–21.4	3.6–26.4
Data set	−4:4; −6:6; −14:14	−4:4; −17:17; −14:14	−7:7; −8:8; −14:14	−9:8; −11:11; −31:29	−4:5; −7:7; −9:9	−8:8; −7:7; −20:20
Tot., Uniq. Data, R(int)	3264, 838, 0.075	9122, 1307, 0.163	5943, 934, 0.090	12940, 3479, 0.051	2174, 742, 0.032	4675, 1390, 0.056
Obs. data [$I > 2.0\ \sigma(I)$]	642	593	631	2924	496	974
Absorption Correction						
μ [mm^{-1}]	0.510	0.498	0.126	0.124	0.083	0.099
Type	Multi-scan [19]	None	Multi-scan [19]	Multi-scan [21]	Multi-scan [21]	Multi-scan [19]
Transmission factors; Max., Min.	0.988, 0.832	–	1.010, 0.919	0.9963, 0.9698	0.9918, 0.9677	0.986, 0.835
Structure Solution						
Software	SIR97 [22]	SIR92 [23]	SHELXS-86 [24]	SHELXS-97 [25]	SIR97 [22]	SIR97 [22]
Refinement						
N_{ref}, N_{par}	838, 91	1307, 91	934, 109	3479, 326	742, 92	1390, 101
R, wR, S	0.048, 0.105, 1.15	0.057, 0.130, 0.97	0.053, 0.172, 1.11	0.050, 0.146, 1.14	0.074, 0.251, 1.20	0.044, 0.115, 1.05
Weights[a]): k_1, k_2	0.0357, 0.0818	0.0490, 0.000	0.1003, 0.0690	0.0726, 0.3990	0.1565, 0.0109	0.0430, 0.1954
Max/Av. final Shift/Error	0.00/0.00	0.00/0.00	0.01/0.00	0.00/0.00	0.00/0.00	0.00/0.00
$\Delta\rho$ (min,max) [eÅ^{-3}]	−0.30, 0.23	−0.26, 0.28	−0.36, 0.32	−0.33, 0.45	−0.28, 0.28	−0.19, 0.19

[a]) $w = 1/[\sigma^2(F_o^2) + (k_1P)^2 + k_2P]$ where $P = (F_o^2 + 2F_c^2)/3$

and an *Oxford Cryostream* crystal-cooling device. Intensity measurements were obtained with ω-scans. Data collection was run with the *Bruker* SMART software, version 5.054 [20], and cell refinement, data reduction and multi-scan absorption correction were performed in the *Bruker* SAINT software version 6.28a [21].

Structure solution was carried out using direct methods [22–25] (see *Table 6*). Least-squares refinement was performed in SHELXL97 [25] with F^2 magnitudes. Aromatic and Me H-atom types were constrained as riding atoms fixed to the parent atoms with distances of 0.95 and 0.98 Å resp. The isotropic displacement parameters were fixed to 120% of that of the parent atom for aromatic and 150% for Me H-atoms.

Molecular graphics were produced with the programmes Ortep-3 for Windows [26] and MERCURY [27]. WinGX publication routines [28] were used to prepare crystallographic data for publication.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-202200, 202201, 202202, 202203, 202204 and 202205 for **2**, **3**, **4**, **5**, **6**, and **7** respectively. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

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