

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/261674988>

Probing Weak Intermolecular Interactions by Using the Invariom Approach: A Comparative Study of s-Tetrazine

ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · JUNE 2014

Impact Factor: 5.73 · DOI: 10.1002/chem.201304551

CITATIONS

4

READS

24

3 AUTHORS, INCLUDING:



[Konstantin A Lyssenko](#)

Russian Academy of Sciences

761 PUBLICATIONS 6,110 CITATIONS

SEE PROFILE

■ Electron Density Modeling

Probing Weak Intermolecular Interactions by Using the Invariom Approach: A Comparative Study of *s*-TetrazineYulia V. Nelyubina,^{*,[a]} Alexander A. Korlyukov,^[a, b] and Konstantin A. Lyssenko^[a]*In memory of Mikhail Yu. Antipin*

Abstract: A comparative study of chemical bonding peculiarities in 1,2,4,5-tetrazine was carried out to test the performance of a recently developed invariom approach against a conventional charge density analysis of high-resolution X-ray diffraction data and quantum chemical calculations

within the plane-wave functional theory. The amazing similarity between the intermolecular features thus obtained for this van der Waals crystal showed the invariom approximation to now emerge as a fast and convenient way towards reliable description of weak intermolecular interactions.

Introduction

Although electron density studies by X-ray diffraction have officially “come of age”^[1] following the progress in X-ray techniques, equipment, and theoretical background, many efforts are still made to go beyond small ordered molecules with excellent reflective power. Among other options, transferred multipolar models were developed, one of them being based on a recently introduced concept of invarioms.^[2] They were devised to replace an independent atom model (IAM)^[3,4] by using database entries of multipolar parameters obtained within the Hansen–Coppens aspherical-atom formalism^[5] from X-ray measurements of high quality^[6] or from quantum chemical calculations.^[2,7] As well as taking as less time than IAM to employ,^[8,9] their use allows reaching the accuracy of conventional multipole refinement against high-resolution data.^[8] If the latter is somehow not an option, transferred multipolar modeling is a good alternative towards electron density distribution and does not require time- and recourse-consuming experimental techniques and computations, because it is based on a database approach.

Among available aspherical atom libraries^[10] giving consistent results, the invariom database^[11] seems superior.^[12] It uses calculated multipole populations (free from the experimental “noise”) assigned to an atom in a particular bonding situation that can be obtained for any model compound at a given level

of theory and thus provides the largest variety of chemical environments.^[9]

Having gained the popularity in the last decade, the invariom approach has already been successfully applied for describing different organic systems and helping with different chemical problems inaccessible by full experimental multipole refinement. Those include a more reliable absolute structure determination for light-atom compounds,^[13] charge density studies from low (normal) resolution datasets,^[9,14,15] only collectible with copper radiation,^[4] and of larger molecules with poor reflective power,^[16] identification and treatment of a disorder,^[17] and so on. Thus, being an extremely promising approach, it can even use other starting geometries than from X-ray diffraction, for example, those obtained from quantum chemistry or NMR spectroscopy.^[8]

Numerous studies to date performed with the invariom formalism showed it to successfully reproduce features of covalent bonds^[18,19] with the same accuracy as that of full multipole refinement (sometimes higher^[8]). Although by the definition of invarioms,^[2] the resulting electron density does not contain the information on crystal packing effects, attempts have been made to use them for examining intermolecular interactions in organic crystals, but in all cases H-bonds were mostly commented on.^[4,12,15,19,20] Their influence on molecular and crystal properties was quantified by the analysis of Hirshfeld surfaces,^[15,19,21] mapping of electrostatic potential (thus revealing important implications for drug research),^[4,8,9,12,15,20,21] or by topological features within Bader’s “Atoms in Molecules” theory (AIM).^[4,19] The results were encouraging, but still conventional multipole refinement against high-resolution X-ray diffraction data is recommended for studying crystal packing effects that are a priori not included in the invariom density.^[9,21,22]

Weak intermolecular interactions, on the other hand, have been rarely probed by the transferred multipolar models, and even then by using database with experimental multipole pop-

[a] Dr. Y. V. Nelyubina, Prof. A. A. Korlyukov, Prof. K. A. Lyssenko
A.N. Nesmeyanov Institute of Organoelement Compounds
119991, Vavilova Str., 28, Moscow (Russia)
Fax: (+7) 4991355085
E-mail: unelya@xrlab.ineos.ac.ru

[b] Prof. A. A. Korlyukov
Pirogov Russian National Research Medical University
117997, Ostrovitianova Str., 1, Moscow (Russia)

Supporting information for this article is available on the WWW under
<http://dx.doi.org/10.1002/chem.201304551>.

ulations,^[3] not the invariom approach. We, therefore, decided to check how it would perform in the case of weak interactions with no interference from H-bonds, as in a van der Waals crystal (like benzene), for which less perturbation of molecular density by crystal environment is expected.^[23]

For this purpose, we have chosen 1,2,4,5-tetrazine or *s*-tetrazine (Figure 1), a compound long-known^[24] for its optical prop-

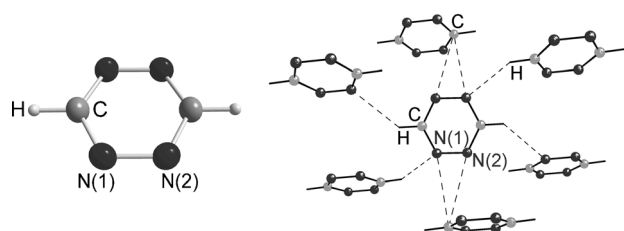


Figure 1. General view of *s*-tetrazine in representation of atoms through thermal ellipsoids ($p = 80\%$; left) and intermolecular contacts it forms in a crystal (right).

erties,^[25] then recognized as an efficient anion receptor^[26] and its derivatives as energetic materials, pharmaceuticals, solar cells, nonlinear optics (NLO) materials, and so on.^[27] It matches perfectly the requirement, as it forms only weak van der Waals interactions in a crystal.

Among the most powerful tools to identify and describe weak interactions is the topological analysis of an electron density distribution $\rho(r)$ within the AIM theory.^[28] Revealed by a presence of bond critical points (bcps),^[28] intermolecular interactions may be easily quantified, for example, based on a value of local potential energy $v(r)$ in a bcp by using its correlation^[29,30] with interaction energy (E_{int}). Although the latter was initially proposed by Espinosa, Molins, and Lecomte (EML) for H-bonds,^[29,30] it was then successfully applied for estimating the energy of other types of interactions.^[31] In particular, the sum of E_{int} values in a crystal has been shown to reproduce with high accuracy a sublimation enthalpy, being the case of, among others, bis(η^6 -benzene)chromium,^[32] [2.2]-paracyclophane,^[33] *o*-carborane derivatives,^[34] and polymorphs of paracetamol.^[35] Its failure in some other instances has been discussed in Ref. [36].

As for *s*-tetrazine, the experimental sublimation enthalpy is not available; its estimates may instead be obtained from periodic quantum chemical calculations within the plane-wave density functional theory (PW-DFT).^[37,38] In this case, calculations performed for a crystal and a pseudo-isolated molecule created by deleting all but one molecule from the crystal lattice lead to the energy of intermolecular interactions (the average energy per molecule in a crystal), which should be close to the sublimation enthalpy. The results from quantum chemistry for *s*-tetrazine will be compared to the conventional multipole refinement and the invariom refinement performed against X-ray diffraction data sets both collected up to high resolution ($d = 0.433 \text{ \AA}$) and truncated down to normal resolution ($d = 0.71 \text{ \AA}$).

Results and Discussion

In a crystal, the molecule of *s*-tetrazine occupies a special position, an inversion center, with almost equal N–C bond lengths (1.3355(6) and 1.3347(6) Å). Atoms N(1) and N(2) formally identical in the gas phase (D_{2h} symmetry) are crystallographically non-equivalent (Figure 1). However, the symmetry of the molecule closely resembles D_{2h} , agreeing with the weakness of intermolecular interactions in the crystalline *s*-tetrazine. Therefore, use of invarioms with one set of multipole and kappa parameters for two nitrogen atoms having the same covalent environment is a good approximation for the experimental electron density of *s*-tetrazine, and as such it should provide similar results as full multipole refinement.

It seems so at the level of deformation electron density (DED) distribution. In all cases, DED mapping within the *s*-tetrazine molecule displays the expected features (Figure 2), such

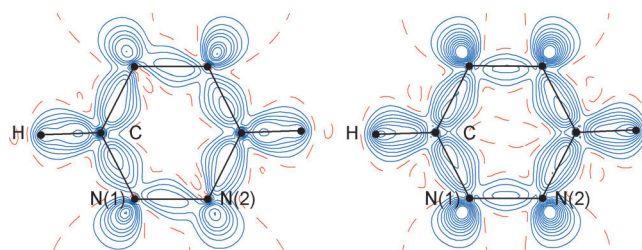


Figure 2. DED distributions in the molecular plane of *s*-tetrazine obtained by multipole (left) and invariom (right) refinement against high-resolution X-ray diffraction data. The contours are drawn through 0.1 e \AA^{-3} , the negative contours are dashed. For experimental $-\nabla^2\rho(r)$ distributions in *s*-tetrazine, see Figure S1 in the Supporting Information.

as its accumulation along covalent bonds and in the lone pair (lp) region of the nitrogen atoms. Note that the use of a truncated data set for the invariom refinement gave exactly the same picture of electron density distribution as that of the high-resolution data.

There are, however, some minor differences between the multipole and invariom models. The most pronounced among them concern the regions around the two nitrogen atoms, which are expectedly identical in the invariom density but different in the multipole density. This may be easily explained by the different involvement of these nitrogen atoms in intermolecular contacts (Figure 1), as judged by the shortest distances $\text{N}(1)\cdots\text{C}/\text{N}(2)\cdots\text{C}$ and $\text{N}(1)\cdots\text{H}$ being 3.155(1)/3.229(1), and 2.57(1) Å, respectively. The latter assemble *s*-tetrazine molecules into three-dimensional framework in which the nearest neighbors form a “T-shaped” associate. As these interactions influence negligibly the molecular geometry of *s*-tetrazine, they are supposed to be very weak, as expected for a van der Waals crystal. In particular, they do not affect the positions of lone pairs of the two nitrogen atoms (as mirrored through the maxima in the minus Laplacian) that are governed by the molecular geometry: their distances from the nuclei of the nitrogen atoms (as mirrored through the maxima in the multipole electron density) are 0.396(1) and 0.394(1) Å.

It also seems that in the invariom density, maxima along the covalent bonds within the heterocyclic core are shifted inwards to a greater extent than in the multipole density. This shift somewhat agrees with the same “banana-type” of N–N bonds observed previously in experimental DED analysis for 3,6-dimethoxy-1,2,4,5-tetrazine and 3-phenyl-1,2,4,5-tetrazine^[39] and attributed to the repulsion between lps of nitrogen atoms and accumulation of $\rho(r)$ in their interatomic areas. Also found in ammonia crystal,^[37,38] this trend in the case of the invariom modeling may result from approximating of chemical environments of constituting atoms upon the “invariom transfer”. However, the inspection of bond paths both in the multipole and invariom densities shows that their deviation from a straight line is equally infinitesimal.

To quantify the observed discrepancies/similarities in the molecular densities obtained from multipole and invariom refinements, we performed a topological analysis of the resulting $\rho(r)$ functions within the AIM formalism.^[28] Accordingly, all chemical bonds in *s*-tetrazine correspond to the shared type of interatomic interactions, having negative values of both $\nabla^2\rho(r)$ and electron energy density ($h_e(r)$) at their bcps (Table S1, the Supporting Information). When going from the multipole to the invariom model, the $\rho(r)$ and $\nabla^2\rho(r)$ values for the bonds N–C and N–N changes by $0.08 \text{ e}\text{\AA}^{-3}$ and $0.89 \text{ e}\text{\AA}^{-5}$, which can be accounted for their “natural spread”^[40] ($0.1 \text{ e}\text{\AA}^{-3}$ and $3\text{--}4 \text{ e}\text{\AA}^{-5}$). For the bonds involving hydrogen atoms, the discrepancy is slightly above these “transferability indices” ($0.09 \text{ e}\text{\AA}^{-3}$ and $5.84 \text{ e}\text{\AA}^{-5}$), being an indirect sign of the fact that the invariom model does not take explicitly into account the C–H...N interactions. Note that the invariom refinement against the truncated data set causes these parameters to vary within $0.01 \text{ e}\text{\AA}^{-3}$ and $0.05 \text{ e}\text{\AA}^{-5}$ only.

Despite the very similar topological features of experimental electron density for covalent bonds in *s*-tetrazine, the fact that the invariom approximation does not take into account crystal packing effects and the multipole refinement does, should cause the expected differences in atomic parameters, such as volume, charge, and energy (Table 1). In particular, one may assume these three parameters to be distinct for the two nitrogen atoms, which are involved in different intermolecular interactions, in the case of the multipole density. Nevertheless, both the multipole and invariom models provided quantitatively similar results, with a difference in atomic charges, volumes, and energies being at most 0.21 e , 0.64 \AA^3 , and

0.324 a.u. observed for carbon, hydrogen, and nitrogen atoms, respectively. The use of the truncated data set for the invariom refinement resulted only in very small changes in these values by no more than 0.001 e , 0.001 \AA^3 , and 0.0026 a.u. , respectively. Even so, the charges obtained by integrating the multipole and invariom densities over atomic basins (Ω)^[28] for N(1) and N(2) appeared to be the same within 0.01 e , and their volumes varied by 0.60 \AA^3 only.

Being more sensitive to fine details in electron density distribution, atomic energies,^[41,42] estimated by integrating $h_e(r)$ over Ω ,^[28] shows that the difference between the two crystallographically non-equivalent nitrogen atoms is again rather small (less than 0.0066 a.u.), but significant between the two experimental models (as high as 0.3240 a.u.). In total, the obtained values of atomic energies lead to an “experimental energy of a molecule” from the multipole refinement higher by 1.7432 a.u. than the invariom one; this difference is, however, meaningless, as the absolute value of atomic energy derived in two ways clearly depends on a model (multipole or invariom) used.

On the other hand, the difference in the atomic energies of N(1) and N(2), estimated from the multipole and invariom models to be qualitatively equal (1.0 and $4.1 \text{ kcal mol}^{-1}$), is rather reliable for formally identical atoms with slightly distinct supramolecular environments in a crystal. It is to be mentioned that the formation of interatomic interactions may be accompanied by an increase as well as a decrease in atomic energy.^[43–45] Moreover, its change is usually observed not only for atoms involved in the interaction, but is also the case of their surroundings,^[44,45] and is impossible to estimate for the rest of the C and H atoms in the absence of a relevant benchmark.

The amazing similarity in molecular parameters of *s*-tetrazine (except for atomic energies, which is rather expected) obtained by the full multipole refinement and the invariom modeling of both high- and normal resolution data sets is clearly the result of very weak intermolecular interactions perturbing its molecular density only to a slight extent.

To unambiguously identify and quantify all these interactions in the crystal of *s*-tetrazine, we performed a topological analysis of the corresponding experimental (multipole and invariom) electron densities. The search for bcps unexpectedly showed that in all cases the characteristic set of critical points was identical, with the intermolecular bond paths linking the

same atoms and with very similar topological features (Figure 3, Table 2). Surprisingly, it also did not matter whether high or normal resolution data set was used for the invariom refinement.

Accordingly, four symmetry-independent interactions were found to hold the *s*-tetrazine molecules together. Among them, only one involved the atom N(2) but with the neigh-

Table 1. Selected atomic characteristics for *s*-tetrazine.^[a]

	N(1)	N(2)	C(1)	H(1)
q_{at} [e]	−0.31//−0.38	−0.30//−0.38	+0.45//+0.66	+0.16//+0.11
V_{at} [\AA^3]	13.54//13.63	14.11//14.24	9.83//8.97	5.46//6.10
E_{at} [a.u.]	−54.5912//−54.8951	−54.5929//−54.9017	−38.1478//−37.9352	−0.5368//−0.5720

[a] The first//second entries denote the values from multipole//invariom refinements of high-resolution experimental data. In both cases, the charge leakage was practically zero. The sum of atomic volumes (42.94 and 42.93 \AA^3) perfectly reproduced the volume of an independent part of the unit cell (42.96 \AA^3) with a relative error not more than 0.07% . Although integrated Langrangian ($L(r) = -1/4\nabla^2\rho(r)$) for every atomic basin has to be exactly zero, a reasonably small value averaging to $0.1 \times 10^{-3} \text{ a.u.}$ was obtained.

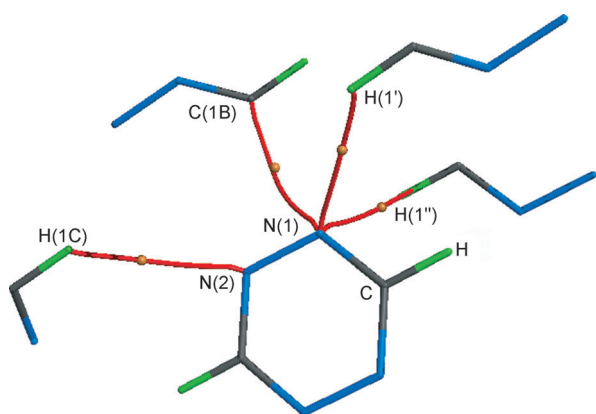


Figure 3. Intermolecular interactions in a crystal of *s*-tetrazine identified by bcps (orange spheres) and bond paths (red lines) in the electron density obtained by both the multipole and invariom refinements, including one performed against normal-resolution X-ray diffraction data within the invariom approach.

Table 2. Topological parameters of $\rho(r)$ in bcps for the intermolecular interactions in a crystal of *s*-tetrazine from the multipole and invariom refinements.^[a]

Interaction ^[b]	N(1)···H(1')	N(1)···H(1'')	N(1)···C(1B)	N(2)···H(1C)
$\rho(r)$ [$\text{e}\text{\AA}^{-3}$]	0.06//0.06	0.03//0.03	0.05//0.05	0.03//0.03
$\nabla^2\rho(r)$ [$\text{e}\text{\AA}^{-5}$]	0.87//0.82	0.45//0.43	0.61//0.59	0.50//0.49
$h_e(r)$ [a.u.]	0.0021//0.0018	0.0013//0.0012	0.0014//0.0013	0.0013//0.0013
$-v(r)$ [a.u.]	0.0049//0.0049	0.0024//0.0021	0.0035//0.0035	0.0026//0.0025
E_{int} [kcal mol ⁻¹]	1.5//1.5	0.8//0.7	1.1//1.1	0.8//0.8

[a] The first//second entry denotes the values from multipole//invariom refinement of high-resolution experimental data; the use of normal-resolution dataset for invariom refinement gave exactly the same values as obtained from high-resolution data. [b] Atoms H(1'), H(1''), C(1B), and H(1C) are obtained from the basic ones by symmetry operations $-x+0.5, y-0.5, -z+0.5$; $-x+1, -y+1, -z+1$; $x+0.5, -y+0.5, z+0.5$ and $x-0.5, -y+0.5, z+0.5$, respectively.

boring hydrogen instead of the carbon atom, as it was depicted on Figure 1, and three others were formed by the nitrogen atom N(1); those were N(1)···H(1'), N(1)···H(1''), and N(1)···C(1B). Topological parameters in the bcps classify all these intermolecular interactions as of a closed-shell type with low $\rho(r)$, positive $\nabla^2\rho(r)$ and $h_e(r)$ values, which varied in a narrow ranges of 0.03–0.06 $\text{e}\text{\AA}^{-3}$, 0.43–0.87 $\text{e}\text{\AA}^{-5}$, and 0.0021–0.0049 a.u., respectively. Note that the use of a truncated data set in the invariom refinement gave exactly the same values as that of the high resolution. Thus, the difference between these parameters obtained from the multipole and two invariom models is less than 0.01 $\text{e}\text{\AA}^{-3}$, 0.05 $\text{e}\text{\AA}^{-5}$, and 0.0003 a.u. The first two values are very within the above “transferability indices” (0.1 $\text{e}\text{\AA}^{-3}$ and 3–4 $\text{e}\text{\AA}^{-5}$).^[40]

If considering the interaction energies (E_{int}) derived from the different experimental electron densities for *s*-tetrazine, one could see that they are in an extremely good agreement. Estimated on the basis of $v(r)$ values^[29,30] through the EML correlation^[29,30] applicable for various types of weak interactions,^[31] the energy of 0.7–1.5 kcal mol⁻¹ only was assigned to the interactions N···H and N···C, as consistent with a van der Waals nature of the crystalline *s*-tetrazine. Regardless of the model

chosen for the refinement against experimental data, these values vary only slightly (within 0.1 kcal mol⁻¹). Thus, the difference in the total energy of the interactions formed by the atoms N(1) and N(2) taken separately gave 2.6 or 2.5 kcal mol⁻¹, whether multipole or invariom density is chosen; this is in a semi-quantitative agreement with a low difference in their atomic energies (1.0 and 4.1 kcal mol⁻¹).

Note that whether simple 0.5- $v(r)$ correlation proposed by Espinosa et al.^[29,30] is used to approximate an interaction energy or its more complex analogues based on $v(r)$ ^[36] or $g(v)$ ^[46] values, the similarity of these estimates by invariom and multipole modeling would still hold.

The fact that the invariom approximation reproduces amazingly well the features of intermolecular interactions obtained by the conventional multipole refinement is in tune with the conclusion on the “importance of promolecule”.^[47] However, in the model electron density for *s*-tetrazine composed only from non-interacting overlapping spherical atoms (a pro-crystal),^[48]

the number and type of intermolecular interactions coincided, but their properties did not (Table S3, the Supporting Information). Given that $\rho(r)$ in intermolecular regions should be close to that produced by superposition of the pro-molecule electron densities, the values of $v(r)$ in bcps and hence E_{int} for the pro-crystal electron distribution are slightly shifted from those obtained for the experimental $\rho(r)$ ^[47] through the multipole refinement, especially for weak intermolecular interactions. In the case of *s*-tetrazine, their energy was higher by about 25%. Respectively, the agreement between these values becomes much better, if aspherical pseudo-atoms within the invariom approach are used to model the electron density distribution.

Although intermolecular contacts that are so weak as in *s*-tetrazine are considered poorly accessible by experimental electron densities, the AIM approach was very successfully used to find even the weakest and weirdest interactions^[49,50] and the EML correlation to accurately quantify them,^[29,30] as it follows from total interaction energies coincided with sublimation enthalpies.^[32–35] To further compare the results from the multipole and invariom refinements in terms of intermolecular interactions and their energy in a crystal, we also estimated the sublimation enthalpy of *s*-tetrazine based on the X-ray diffraction data and PW-DFT calculations by using PBE, PBE0, optPBE, and rPW86 functionals with different dispersion corrections schemes. The corresponding experimental ΔH_{subl}^0 value for *s*-tetrazine is absent in literature; however, there are some old theoretical estimates from atom-atom potential methods ranging from 8.7 to 11.7 kcal mol⁻¹,^[51] and our use of intermolecular Gavezzotti potentials^[52,53] gives 16.6 kcal mol⁻¹.

From the electron density analysis, the sublimation enthalpy was calculated as a total energy of all the intermolecular interactions formed by one molecule of *s*-tetrazine in a crystal, of which only one forth is symmetry-independent (Table 2), similar to bis(η^6 -benzene)chromium.^[32] The respective value was found to be 16.8 and 16.3 kcal mol⁻¹ according to the multi-

Table 3. The values of ΔH_{subl}^0 [kcal mol⁻¹] for *s*-tetrazine according to multipole (XRD) and invariom modeling of experimental data and PW-DFT calculations.

ΔH_{subl}^0	XRD	Invariom ^[a]	PBE ^[b]	PBE0	PBE-D2	optPBE-vDW	rPW86-vDW2
Crystal minus isolated molecule	–	–	7.7	9.0	22.7	25.7	22.4
EML	16.8	16.3	16.1	14.3	16.4	13.5	15.0
		16.3	10.5	10.0	10.4	10.9	11.3

[a] The first and second entries denote the values from the invariom refinement against high-resolution and normal-resolution datasets, respectively. [b] The first and second entries give the values for the optimized and fixed unit cell, respectively.

pole refinement and the invariom modeling of both the high- and normal resolution data sets (Table 3). For comparison, the sublimation enthalpy of benzene,^[54] pyrazine^[55] and 1,3,5-triazine^[56] is 10.8, 13.5, and 13.9 kcal mol⁻¹, respectively.

The PW-DFT calculations of *s*-tetrazine using the functionals PBE (offering the best performance in estimating the binding energy for weak interactions),^[57] PBE0 and optPBE and a refitted PW86^[58] functional (used for comparison) gave the values of calculated sublimation enthalpies varying from 5 to 25 kcal mol⁻¹ (Table 3) depending on the dispersion correction or optimization/no optimization used. Note that in all cases, the optimization of a unit cell led to geometrical parameters for the intermolecular contacts quite different from the experimental ones as a result of a significant contraction of the unit cell (up to 13% in the case of optPBE) and an accompanying shortening of all intermolecular N...H and N...C distances (Table S2, the Supporting Information).

The use of PBE-D2 with no optimization of a unit cell gives the best agreement with the electron density analysis (16.2 vs. 16.8 and 16.3 kcal mol⁻¹); for comparison, the same theoretical background for pyrazine^[55] resulted in the value of 15.0 kcal mol⁻¹, which is the closest to its measured sublimation enthalpy (13.5 kcal mol⁻¹) among others (3.7–20.6 kcal mol⁻¹). Although there is a huge discrepancy in the sublimation enthalpy for *s*-tetrazine calculated as a difference between its crystal and an isolated molecule, the values estimated through the EML correlation and AIM theory applied to the calculated electron densities suffer less from the dependence on the dispersion correction used (Table 3). In particular, they vary within a much narrower range from 10.0 to 16.4 kcal mol⁻¹.

The similarity of sublimation enthalpy for *s*-tetrazine estimated on the basis of Gavezzotti potentials, PW-PBE calculations, and X-ray diffraction data indicates the reliability of the bonding situation in a crystal as revealed by both the multipole and invariom refinements, with the latter also performed for a normal resolution data set.

Conclusion

Although still considered with great caution as needing further critical scrutiny, the invariom approach offers huge opportunities for charge density analysis. Devised to approximate atoms

in a covalent environment, the invariom formalism was nevertheless used to probe H-bonds for which it gave rather promising results, but clearly its strength is a priori in weak intermolecular interactions. Because they perturb molecular density to a minor extent, all the features of covalent bonds should be reproduced very well, as was found in the case of *s*-tetrazine.

Our comparative study, however, showed that the invariom approximation provided an accurate description far beyond intramolecular bonding: it performed amazingly well in revealing and describing weak intermolecular interactions in a van der Waals crystal. Sometimes thought to be inaccessible even by a multipole refinement of a high-resolution data set, they may be, however, identified and quantified within the invariom approach based on conventional X-ray diffraction data. This provides a versatile short-cut towards exploring weak intermolecular interactions, which govern many properties of crystalline materials,^[35] that are hard to discover and describe otherwise.

Computational Methods

Crystals of *s*-tetrazine (C₂H₂N₄, *M_w* = 82.08) are monoclinic, space group *P*2₁/*n*, at 120 K: *a* = 5.1100(10), *b* = 5.6520(10), *c* = 6.4170(10) Å, β = 111.99(2)°, *V* = 171.85(6) Å³, *Z* = 2 (*Z'* = 0.5), *d*_{calcd} = 1.586 g cm⁻³, $\mu(\text{MoK}\alpha)$ = 1.19, *F*(000) = 84. Intensities of 6869 reflections were measured with a Rebuild Syntex P2–1/Siemens P3 four-circle diffractometer [$\lambda(\text{MoK}\alpha)$ = 0.71072 Å, $\theta/2\theta$ -scans, $2\theta < 110^\circ$], and 2159 independent reflections [*R*_{int} = 0.0352] were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against *F*² in the anisotropic-isotropic approximation. Hydrogen atoms were located from the difference Fourier synthesis of the electron density and refined in the isotropic approximation. The refinement converged to *wR*2 = 0.1221 and GOF = 1.000 for all the independent reflections (*R*1 = 0.0445) was calculated against *F* for 1365 observed reflections with *I* > 2σ(*I*). All calculations were performed using SHELXTL PLUS 5.0.^[59] CCDC-658496 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Experimental data set was modeled using the Hansen–Coppens formalism^[5] as implemented in the program package XD;^[60] input files were generated with the program MoleCoolQt.^[61] The C–H bond distances were fixed at the value of 1.08225 Å from the invariom database.^[11] For the invariom refinement, multipolar populations (up to hexadecapolar level) and kappa parameters from the invariom library^[11] were assigned to all atoms, and then positional and displacement atomic parameters together with a scale factor were refined against full ($2\theta = 110^\circ$ or *d* = 0.433 Å) and limited ($2\theta = 60^\circ$ or *d* = 0.71 Å) data sets. The refinements were carried out against *F* and converged to *R* = 0.0337 and 0.0199, *Rw* = 0.0213 and 0.0185, GOF = 1.4753 and 2.1484 for 1348 and 398 merged reflections with *I* > 3σ(*I*), respectively.

For the conventional multipole refinements, the order of multipole expansion included octupoles for all non-hydrogen atoms and dipoles for hydrogens; those were adjusted against measured high-resolution data. The refinement was carried out against *F* and converged to *R* = 0.0325, *Rw* = 0.0250 and GOF = 1.4954 for 1397 merged reflections with *I* > 3σ(*I*).

In all cases, the residual electron density maps were featureless, and the largest and the lowest values were as high as 0.12 e Å⁻³

and as low as $-0.13 \text{ e}\text{\AA}^{-3}$. The Hirshfeld test^[62] yielded a highest difference in mean square displacement amplitudes along the bonds of $3 \times 10^{-4} \text{ \AA}^2$ after the invariom refinement (even at normal resolution) and of $8 \times 10^{-4} \text{ \AA}^2$ after the full multipole refinement, indicating a rather good deconvolution of thermal motion and electron density.

Topological analysis of the resulting functions $\rho(r)$ was carried out using the WINXPRO program package.^[63] Potential energy density $v(r)$ was evaluated through the Kirzhnits's approximation^[64] for kinetic energy density function $g(r)$. Accordingly, the $g(r)$ function is described as $(3/10)(3\pi^2)^{2/3}[\rho(r)]^{5/3} + (1/72)|\nabla\rho(r)|^2/\rho(r) + 1/6\nabla^2\rho(r)$, giving in conjunction with the virial theorem ($2g(r) + v(r) = 1/4\nabla^2\rho(r)$)^[28] the expression for $v(r)$. The interaction energies were estimated by means of the EML correlation Scheme: A semi-quantitative relation between the energy of an interaction and the value of the potential energy density function $v(r)$ in its bcp.^[29,30] Having a very simple form as $0.5v(r)$, it was repeatedly shown to give accurate estimates in many cases (those are succinctly summarized in ref. [31]). The discrepancy between the crystal lattice energies estimated in such a manner from X-ray diffraction data and those measured experimentally can be as small as $0.2 \text{ kcal mol}^{-1}$. The latter value, divided by a number of interactions used to obtain the sublimation enthalpy by this approach, may be thought of as uncertainty in the interaction energies estimated by EML correlation thus being of $\approx 0.02 \text{ kcal mol}^{-1}$.

Note that both using H-ADPs estimated with the SHADE server^[65] and including higher multipoles from the invariom database for H atoms^[14,18] gave virtually identical results; the energy of intermolecular interactions varied within $0.01 \text{ kcal mol}^{-1}$ only.

PW-DFT calculations were carried out using VASP 5.3.3 program.^[66–69] Exchange and correlation parts of total energy were described by means of PBE,^[70] PBE0,^[70] optPBE,^[71] and rPW86^[58] functionals with different dispersion correction schemes (none, DFT-D2, vdW-DF Scheme by Dion et al.^[72] and vdW-DF2 Scheme of Langreth and Lundqvist groups^[73]). The optPBE and rPW86 exchange-correlation functionals used with vdW-DF and vdW-DF2 dispersion correction schemes were additionally optimized in the correlation part.^[71] Optimization of atomic positions has been started from experimental data using a plane wave basis set. Residual forces on atoms were less than $10^{-2} \text{ m dyn \AA}^{-2}$ as well as energy variations near the end of geometry optimization were less than 10^{-3} eV . To test the accuracies of different exchange-correlation functionals and estimate the effects of unit cell optimization, we performed quantum chemical calculations with cell parameters fixed to experimental values and with fully optimized cell vectors. To account for core electrons, projected augmented wave (PAW) potentials were used.^[74] The part of the wave function corresponding to valence electrons was decomposed in a plane-wave expansion with 700 eV kinetic energy cut-off. The electron density functions were obtained in separate single point calculations using high kinetic energy cut-off (1000 eV) and dense fast Fourier transformation grid ($280 \times 320 \times 360$ points). The topological analysis of calculated electron density functions was carried out using AIM program^[75] implemented in ABINIT program package.

Isolated molecules were optimized by the same theoretical background, basis sets, and convergence criteria by using quantum chemistry calculations of a single molecule in a cubic box with a side of 15 \AA . The structures of isolated molecules were tested on stability by calculating vibrational frequencies; no negative ones were obtained. Unfortunately, the exact calculation of vibrational frequencies in the case of periodic boundary conditions was difficult due to large requirements of computer time. As a result, no zero point correction was applied to sublimation energy. On the

other hand, the plane wave basis set has no superposition error in contrast to ordinary Gaussian basis sets.

Acknowledgements

This study was financially supported by the Russian Foundation for Basic Research (Projects 13–03–00772 and 13–03–12197) and the Russian Science Support Foundation.

Keywords: chemical bonding • density functional calculations • topological analysis • weak interactions • X-ray diffraction

- [1] P. Coppens, *Angew. Chem.* **2005**, *117*, 6970–6972; *Angew. Chem. Int. Ed.* **2005**, *44*, 6810–6811.
- [2] B. Dittrich, T. S. Koritsansky, P. Luger, *Angew. Chem.* **2004**, *116*, 2773–2776; *Angew. Chem. Int. Ed.* **2004**, *43*, 2718–2721.
- [3] S. Domagala, P. Munshi, M. Ahmed, B. Guillot, C. Jelsch, *Acta Crystallogr. B* **2011**, *67*, 63–78.
- [4] B. Dittrich, M. Weber, R. Kalinowski, S. Grabowski, C. B. Hubschle, P. Luger, *Acta Crystallogr. B* **2009**, *65*, 749–756.
- [5] N. K. Hansen, P. Coppens, *Acta Crystallogr. Sect. A* **1978**, *34*, 909–921.
- [6] V. Pichon-Pesme, C. Lecomte, H. Lachezar, *J. Phys. Chem.* **1995**, *99*, 6242–6250.
- [7] A. Volkov, T. Koritsansky, P. Coppens, *Chem. Phys. Lett.* **2004**, *391*, 170–175.
- [8] J. J. Holstein, C. B. Hubschle, B. Dittrich, *CrystEngComm* **2012**, *14*, 2520–2531.
- [9] C. J. Schürmann, K. Propper, T. Wagner, B. Dittrich, *Acta Crystallogr. B* **2012**, *68*, 313–317.
- [10] J. M. Bak, S. Domagala, C. Hubschle, C. Jelsch, B. Dittrich, P. M. Dominiak, *Acta Crystallogr. Sect. A* **2011**, *67*, 141–153.
- [11] B. Dittrich, C. B. Hubschle, K. Propper, F. Dietrich, T. Stolper, J. J. Holstein, *Acta Crystallogr. B* **2013**, *69*, 91–104.
- [12] M. Weber, S. Grabowski, A. Hazra, S. Naskar, S. Banerjee, N. B. Mondal, P. Luger, *Chem. Asian J.* **2011**, *6*, 1390–1397.
- [13] B. Dittrich, M. Strumpel, M. Schafer, M. A. Spackman, T. S. Koritsansky, *Acta Crystallogr. Sect. A* **2006**, *62*, 217–223.
- [14] B. Dittrich, C. B. Hubschle, J. J. Holstein, F. P. A. Fabbiani, *J. Appl. Crystallogr.* **2009**, *42*, 1110–1121.
- [15] P. Luger, M. Weber, C. Hubschle, R. Tacke, *Org. Biomol. Chem.* **2013**, *11*, 2348–2354.
- [16] B. Dittrich, T. Koritsansky, A. Volkov, S. Mebs, P. Luger, *Angew. Chem.* **2007**, *119*, 2993–2996; *Angew. Chem. Int. Ed.* **2007**, *46*, 2935–2938.
- [17] J. J. Holstein, P. Luger, R. Kalinowski, S. Mebs, C. Paulmann, B. Dittrich, *Acta Crystallogr. B* **2010**, *66*, 568–577.
- [18] B. Dittrich, M. A. Spackman, *Acta Crystallogr. Sect. A* **2007**, *63*, 426–436.
- [19] R. Kalinowski, B. Dittrich, C. B. Hubschle, C. Paulmann, P. Luger, *Acta Crystallogr. B* **2007**, *63*, 753–767.
- [20] J. Bacsa, M. Okello, P. Singh, V. Nair, *Acta Crystallogr. C* **2013**, *69*, 285–288.
- [21] N. Dadda, A. Nassour, B. Guillot, N. Benali-Cherif, C. Jelsch, *Acta Crystallogr. Sect. A* **2012**, *68*, 452–463.
- [22] B. Dittrich, C. B. Hubschle, M. Messerschmidt, R. Kalinowski, D. Girnt, P. Luger, *Acta Crystallogr. Sect. A* **2005**, *61*, 314–320.
- [23] B. Dittrich, E. Sze, J. J. Holstein, C. B. Hubschle, D. Jayatilaka, *Acta Crystallogr. Sect. A* **2012**, *68*, 435–442.
- [24] A. Pinner, *Chemische Berichte* **1897**, *30*, 1871.
- [25] J. M. J. Kennedy, *Spectroscopic Studies on s-Terazine*, Naval Postgraduate School, Monterey, California, **1968**.
- [26] C. Garau, D. Quinonero, A. Frontera, A. Costa, P. Ballester, P. M. Deya, *Chem. Phys. Lett.* **2003**, *370*, 7–13.
- [27] Q. Zhou, *Synthesis of new tetrazines functionalized with photoactive and electroactive groups*, These de doctorat de l'école normale supérieure de Cachan, **2012**.
- [28] R. F. W. Bader, *Atoms in Molecules. A Quantum Theory*, Clarendon Press, Oxford, **1990**.

- [29] E. Espinosa, E. Molins, C. Lecomte, *Chem. Phys. Lett.* **1998**, *285*, 170–173.
- [30] E. Espinosa, I. Alkorta, I. Rozas, J. Elguero, E. Molins, *Chem. Phys. Lett.* **2001**, *336*, 457–461.
- [31] K. A. Lyssenko, *Mendeleev Commun.* **2012**, *22*, 1–7.
- [32] K. A. Lyssenko, A. A. Korlyukov, D. G. Golovanov, S. Y. Ketkov, M. Y. Antipin, *J. Phys. Chem. A* **2006**, *110*, 6545–6551.
- [33] K. A. Lyssenko, A. A. Korlyukov, M. Y. Antipin, *Mendeleev Commun.* **2005**, *15*, 90–92.
- [34] I. V. Glukhov, K. A. Lyssenko, A. A. Korlyukov, M. Y. Antipin, *Faraday Discuss.* **2007**, *135*, 203–215.
- [35] Y. V. Nelyubina, I. V. Glukhov, M. Y. Antipin, K. A. Lyssenko, *Chem. Commun.* **2010**, *46*, 3469–3471.
- [36] C. Gatti, E. May, R. Destro, F. Cargnoni, *J. Phys. Chem. A* **2002**, *106*, 2707–2720.
- [37] C. A. Morrison, M. M. Siddick, *Chem. Eur. J.* **2003**, *9*, 628–634.
- [38] C. A. Morrison, M. M. Siddick, *Angew. Chem.* **2004**, *116*, 4884–4886; *Angew. Chem. Int. Ed.* **2004**, *43*, 4780–4782.
- [39] M. Y. Antipin, T. V. Timofeeva, D. S. Yufit, J. Sauer, *Russ. Chem. Bull.* **1995**, *44*, 2337–2345.
- [40] L. Chęcinska, S. Mebs, C. B. Hübschle, D. Forster, W. Morgenroth, P. Luger, *Org. Biomol. Chem.* **2006**, *4*, 3242–3251.
- [41] I. S. Bushmarinov, K. A. Lyssenko, M. Y. Antipin, *Russ. Chem. Rev.* **2009**, *78*, 283–302.
- [42] Y. V. Nelyubina, K. A. Lyssenko, *J. Phys. Chem. A* **2013**, *117*, 3084–3092.
- [43] R. F. W. Bader, D. C. Fang, *J. Chem. Theory Comput.* **2005**, *1*, 403–414.
- [44] U. Koch, P. L. A. Popelier, *J. Phys. Chem.* **1995**, *99*, 9747–9754.
- [45] A. Vila, E. Vila, R. A. Mosquera, *Chem. Phys.* **2006**, *326*, 401–408.
- [46] I. Mata, I. Alkorta, E. Espinosa, E. Molins, *Chem. Phys. Lett.* **2011**, *507*, 185–189.
- [47] M. A. Spackman, *Chem. Phys. Lett.* **1999**, *301*, 425–429.
- [48] V. Tsirelson, Y. Abramov, V. Zavodnik, A. Stash, E. Belokoneva, J. Stahn, U. Pietsch, D. Feil, *Struct. Chem.* **1998**, *9*, 249–254.
- [49] J. Hernández-Trujillo, C. Matta, *Struct. Chem.* **2007**, *18*, 849–857.
- [50] Y. V. Nelyubina, K. A. Lyssenko, *Chem. Eur. J.* **2012**, *18*, 12633–12636.
- [51] H. A. Govers, *Acta Crystallogr. Sect. A* **1975**, *31*, 380–385.
- [52] A. Gavezzotti, *Acc. Chem. Res.* **1994**, *27*, 309–314.
- [53] A. Gavezzotti, G. Filippini, *J. Phys. Chem.* **1994**, *98*, 4831–4837.
- [54] R. M. Stephenson, S. Malanowski, *Handbook of the Thermodynamics of Organic Compounds*, Elsevier, New York, **1987**.
- [55] J. Tjebbes, *Acta Chem. Scand.* **1962**, *16*, 916–921.
- [56] H. G. M. DeWit, J. C. Van Miltenburg, C. G. DeKruif, *J. Chem. Thermodyn.* **1983**, *15*, 561.
- [57] Y. Zhao, D. G. Truhlar, *J. Chem. Theory Comput.* **2005**, *1*, 415–432.
- [58] E. D. Murray, K. Lee, D. C. Langreth, *J. Chem. Theory Comput.* **2009**, *5*, 2754–2762.
- [59] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122.
- [60] A. Volkov, P. Macchi, L. J. Farrugia, C. Gatti, P. Mallinson, T. Richter, T. Koritsanszky, in *XD2006—A computer program for multipole refinement, topological analysis of charge densities and evaluation of intermolecular energies from experimental or theoretical structure factors* **2006**.
- [61] C. B. Hübschle, B. Dittrich, *J. Appl. Crystallogr. J.* **2011**, *44*, 238–240.
- [62] F. L. Hirshfeld, *Acta Crystallogr. Sect. A* **1976**, *32*, 239–244.
- [63] A. Stash, V. Tsirelson, *J. Appl. Crystallogr.* **2002**, *35*, 371–373.
- [64] D. A. Kirzhnits, *Sov. Phys. JETP* **1957**, *5*, 64–72.
- [65] A. O. Madsen, *J. Appl. Crystallogr.* **2006**, *39*, 757–758.
- [66] G. Kresse, J. Hafner, *Phys. Rev. B* **1993**, *47*, 558.
- [67] G. Kresse, J. Hafner, *Phys. Rev. B* **1994**, *49*, 14251.
- [68] G. Kresse, J. Furthmüller, *Comput. Mater. Sci.* **1996**, *6*, 15.
- [69] G. Kresse, J. Furthmüller, *Phys. Rev. B* **1996**, *54*, 11169.
- [70] J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865–3868.
- [71] J. Klimeš, D. R. Bowler, A. Michaelides, *J. Phys. Condens. Matter* **2010**, *22*, 022201.
- [72] M. Dion, H. Rydberg, E. Schröder, D. C. Langreth, B. I. Lundqvist, *Phys. Rev. Lett.* **2004**, *92*.
- [73] K. Lee, É. D. Murray, L. Kong, B. I. Lundqvist, D. C. Langreth, *Phys. Rev. B* **2010**, *82*.
- [74] G. Kresse, D. Joubert, *Phys. Rev. B* **1999**, *59*, 1758.
- [75] X. Gonze, J.-M. Beuken, R. Caracas, F. Detraux, M. Fuchs, G.-M. Rignane, L. Sindic, M. Verstraete, G. Zerah, F. Jollet, M. Torrent, A. Roy, M. Mikami, P. Ghosez, J.-Y. Raty, D. C. Allan, *Comput. Mater. Sci.* **2002**, *25*, 478–492.

Received: November 20, 2013

Revised: March 12, 2014

Published online on April 15, 2014