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Out of cross-conjugation: The unexpected structure of tetrazinones

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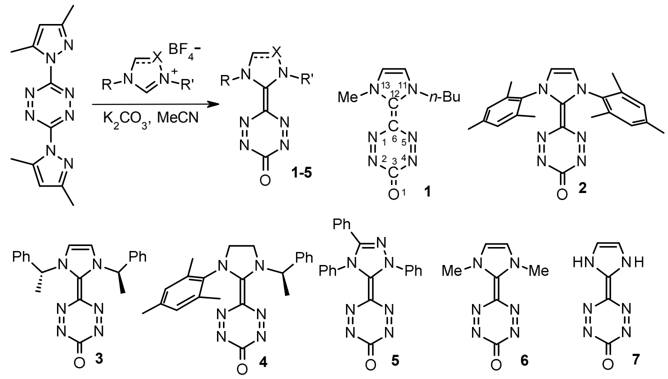
Detailed structural and computational investigations have been carried out to elucidate the unprecedented structural properties of NHC-derived tetrazinones. The provocative structural contradictions featured by this class of molecules as emerged from single crystal X-ray diffraction studies include the non-coplanar core ring system with an inter-ring C-C single bond indicating aromaticity but a pattern of bond alteration consistent with an overall quinoidal structure. Combination of periodic and gas-phase calculations identified two key factors affecting the overall structure. The first is a strong tendency to avoid cross-conjugation resulting in a coupled aromatic-quinoidal system whereas the second is the steric demand of the substituents determining the conformational behaviour of the rings. The peculiar electron distribution yields remarkably large polarizations and dipole moments for these molecules which can be a key in their potential applications.

Introduction

The chemistry of tetrazines has gained increased attention in the past few decades[1] mostly due to their applications in organic synthesis,[2] crop protection[3] and materials science.[4] Their basic structural feature, the electron deficient heterocyclic core, is the key to their most extensively utilized transformation, the 'inverse electron demand' Diels–Alder reaction, that provides an attractive route to pyridazines,[5] pyrroles,[6] pyrazoles,[7] and other condensed[8] and strained[9] heterocyclic ring systems. This reactivity has also been actively exploited recently in natural product synthesis[10] and bioconjugation studies.[11] The electron deficient nature of the heteroaromatic ring makes tetrazines susceptible also to nucleophilic attack. There are several reports on the addition of nucleophiles onto the ring[12] or substitution of leaving groups (LG), such as chloro, methylthio, or dimethylpyrazolyl with nitrogen, oxygen, or sulfur nucleophiles.[13] Although the analogous introduction of carbon nucleophiles would also be of synthetic importance, there are only a very limited number of known examples utilizing potassium cyanide, malonates[14], or cross-coupling reactions.[15] The reaction of appropriately substituted tetrazines with nucleophilic heterocyclic carbenes (NHC) has also been described previously (Scheme 1).[16] Quite unexpectedly this transformation furnished a so far unprecedented compound class whose structure could formally be described by a quinoidal central core. The proposed quinoidal structure has also been partly corroborated by the analysis of the X-ray structure of **2**, the observed bond lengths suggesting the presence of C=O and N=N bonds. At the same time the C-C bond between the tetrazine and imidazoline rings was found to be significantly longer than a C=C bond with bond distance of 1.464(11) Å and we have observed a significant deviation of the N-C-C-N angle from planarity (43.4°) which also contradicts the continuous conjugation between the heterocyclic rings. This unique finding prompted us to launch a more detailed examination addressing the following questions: i) are the same structural features present in other similar tetrazine derivatives; ii) is the observed deviation from coplanarity a result of crystal packing or is it an inherent feature of this molecule class?



Scheme 1. NHC-derived tetrazines that are part of this study. Compounds **1-5** were synthesized while compounds **6-7** were used in modeling studies. The numbering of key atoms followed in this study is shown for **1**. Double bonds are drawn for the quinoidal mesomers. Dashed line in the five-membered rings indicates possible variance in the order of this bond.

To answer these questions a series of analogous tetrazines has been prepared (Scheme 1) bearing sterically and electronically diverse heterocyclic substituents such as imidazoline (**1-3**), imidazolidine (**4**) and triazoline (**5**). In case of the imidazoline derivatives the size and flexibility of the N-substituent also varied from the small and flexible alkyl chains (**1**) through the bigger but still quite flexible benzylic groups (**3**) to the bulky and less flexible mesityl group (**2**). The synthesis of **1-5** was achieved by the reproduction of the earlier published procedures.[16] The solid state structure of the molecules was determined by means of single crystal X-ray diffraction. The combined structural findings were further verified by crystallographic database search as well as high level computational studies detailed below.

Results and discussion

An extensive search in the Cambridge Structural Database[17] has been carried out to identify similar structures. Our strategy was to recognize the main structural motif of the NHC-derived tetrazine core, *i.e.* the linked five- and six-membered rings with a carbonyl group at the six-membered ring in para position. First we sought non-metallic compounds featuring the linked rings composed of only carbon atoms. The number of hits was 114. Most of these molecules are bridged and/or steroid compounds. The closest relatives of our molecules are naphthoquinone derivatives (LIQQOS, LIQQUY, LIQRAF).[18] However in these molecules the inter-ring bonds are definitely double C-C bonds. In the subsequent, more focused searches we have included strategically positioned N atoms in the queries. Surprisingly no hit has been obtained for molecules featuring any 1,2,4,5-tetrazine-3-on derivative attached to a C_5 ring and one hit has been found for molecules with an imidazole ring connected to a C_6 ring bearing the required carbonyl function. Finally 6 hits have been scored for a query where 1,2,4,5-tetrazine-3-on or its hydrogenated derivative is connected to a 1,3-azole ring. Note that among them there is 2 published by us. The rest of the group consists of two 1,2,4,5-tetrazinan-yl derivatives where the rings have an angle of approximately 90°, and three coplanar oxoverdazyl derivatives (AGUJAO,[19] QIZBAD and QIZBIL[20]). This screening clearly indicates that compounds 1-5 indeed represent a unique tetrazine structure.

Based on classic valence bond theory considerations the structure of these unique tetrazines might be described with different resonance structures. The two typically anticipated mesomeric forms (**A**, **B**) are depicted in Figure 1. Resonance form **A** portrays the quinoidal arrangement of the electrons while in resonance form **B** both the tetrazine and the imidazole retain their formal aromatic character, which in turn leads to charge separation and a zwitterionic nature. For discussion purposes it should be mentioned that one can also envisage resonance form **C**, which carries the same allocation of valence electrons in the five-membered ring as **B** but in which the formal distribution of π-electrons in the tetrazine part is quinoidal-like. The characteristic features of mesomeric form **A** include formal C−O and N−N double bonds as well as an exocyclic C−C double bond that would favor the coplanar arrangement of the two heterocycles. On the other hand in mesomeric form B the C−O bond as well as the C−C bond are single, resulting in elongated distances and the possibility of non-coplanarity. In mesomeric form C the formal C−O and N−N double bonds coexist with a formally single C−C bond connecting the two ring systems.

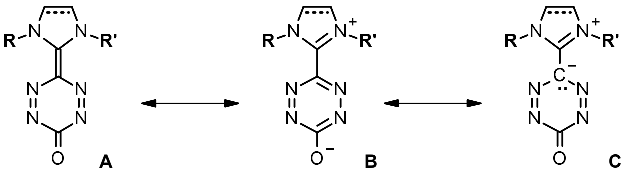


Figure 1. Possible mesomeric representations of the prepared tetrazines. Dashed line in the imidazole rings indicates potential variance in the order of this bond.

The most important structural properties of compounds **1-5** as measured in their crystalline form are collected in Table 1. The first striking feature of our compounds is that in all cases the two core heterocycles show a significant deviation from coplanarity in the solid state, with torsion angles ranging from 35.5° to 50.2°. In parallel, the C−C bond length varies between 1.453-1.481 Å, a range that is markedly longer than a typical C−C double bond. On the other hand, in all cases the C–O bonds have a strong double bond character with the observed atomic distances varying between 1.199-1.235 Å. This unique combination of structural features (*i.e.* the double bond character of the C−O bond points to a quinoidal structure, whereas the elongated C−C bond and non-coplanarity suggest zwitterionic structure) prompted us to explore crystal packing interactions as a possible origin of this structural peculiarity.

Table 1. Key geometry parameters extracted from the X-ray structures of **1**-**5**. Distances are in Å, angles are in degree. See Scheme 1 for numbering of the atoms.

	1	**2**	**3**	**4**	**5**
(N13−C12−C6−N1)[a]	37.6	43.4	43.2	41.6	-38.1
(N11−C12−C6−N5)[a]	41.5	35.9	43.2	50.2	-35.4
τ[b]	40.22	40.23	42.37	46.68	36.93
d(C6−C12)	1.481	1.464	1.457	1.467	1.453
d(C3−O1)	1.223	1.235	1.199	1.216	1.215

[a] Dihedral angles defined by the listed atoms [b] Angle between the planes of the tetrazine and imidazole rings. The plane of a ring is defined as the least-square plane of the atoms constituting the ring.

Analysis of the secondary interactions shows that there are weak C−H ••• O hydrogen bonds between the carbonyl group and suitable hydrogens for all compounds. However, these weak interactions cannot be responsible for the significant distortions of the skeletons from planarity if the inter-ring bond is a double bond. Further insight has been obtained from a systematic computational investigation. In structure **3** the aromatic rings are in parallel orientation (see Figure 2) but the distance of their centroids is more than 4.9 Å, hence we can exclude any appreciable π−π interaction. We have calculated both the crystal and gas-phase structures of the molecules and also considered simplified model structures in order to separate the contribution of the bulky ligands from that of the electronic structure of the core tetrazine-imidazole system.

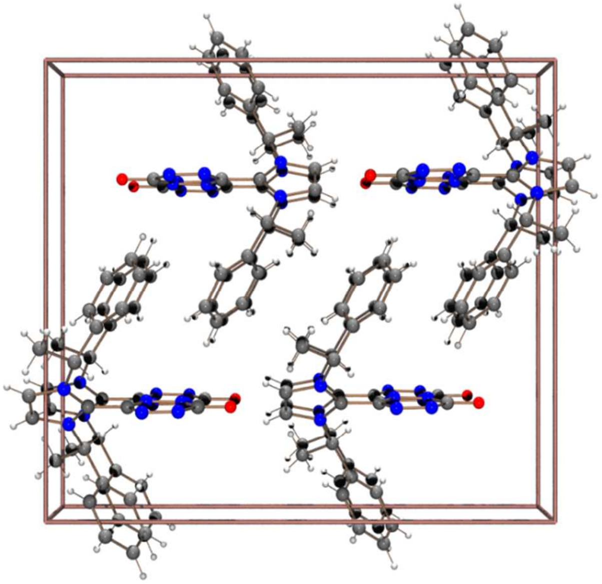


Figure 2. Crystal packing of **3** view normal to (100).

From the perspective of the present study the most important structural parameters are the angle between the planes of the two connecting rings,[21] and the length of the bond between them. Their calculated and experimental values in the solid state are collected in Table 2.

Table 2. Structural parameters of the molecules in their crystal form. Angles[a] (τ) are in degree, distances[b] (d) between the five-membered and tetrazine rings are in Å.

Compound	τ			dC-C		
	BLYP	BLYP+D3	exp.	BLYP	BLYP+D3	exp.
1	40.0	41.1	39.0	1.461	1.464	1.481
2	39.5	39.5	40.2	1.456	1.457	1.464
3	53.9	52.4	42.1	1.463	1.466	1.457
4	45.1	45.6	46.7	1.470	1.468	1.467
5	37.3	37.5	36.8	1.453	1.455	1.453

[a]Angle between the planes of the tetrazine and imidazole rings as defined in Table 1. [b]Length of the C-C bond between the tetrazine and five-membered rings.

Table 2 shows that the calculations predict a distinctly rotated ring conformation for all the molecules in agreement with experiment. In fact, the optimized structures nicely reproduce the experimental structures. The largest discrepancy can be observed for molecule **3**, but even in this case the agreement is still good and the deviation from coplanarity is clearly captured by the calculation. We can also notice that the dispersion corrections affect marginally the geometry of the molecules in the crystals. The theoretical inter-ring bond distances are longer than the length of a typical C−C double bond in accordance with the experimental findings and they actually indicate an sp^2−sp^2 single bond between the two rings. One can conclude that the calculations have reproduced the experimentally observed structural peculiarities and in particular the pronounced tilting of the heterocyclic rings in each molecule together with the elongated inter-ring bonds. These observed structural features are in sharp contrast with an overall quinoidal electronic structure which would imply planar conformations.

In order to determine the importance of crystal packing effects we have also optimized the molecules in gas-phase. Two model compounds (**6** and **7**) have also been considered. In **6** the R and R' substituents of the imidazole ring are methyl groups, whereas in molecule **7** they are hydrogens. Table 3 compares the calculated molecular and crystal geometries.

Table 3. Comparison of calculated structural parameters of the molecules in gas-phase and in crystalline form obtained using the BLYP functional. Angles[a] (τ) are in degree, distances (d) between the tetrazine and the five-membered rings are in Å.

molecule	τ		dC-C	
	gas-phase	crystal	gas-phase	crystal
1	18.4	40.0	1.446	1.461
2	34.4	39.5	1.444	1.456
3	25.4	53.9	1.460	1.463
4	27.8	45.1	1.447	1.470
5	25.4	37.3	1.438	1.453
6	16.7		1.458	
7	0.0		1.421	

[a]See Table 1 for definition.

Table 3 shows that the rotated ring-structure is preserved in the gas-phase albeit to a moderately reduced extent. The bond between the two rings is slightly shortened. We note that τ is somewhat sensitive to the employed functional and more accurate functionals further enhance the torsion between the tetrazine and the five membered rings.[22] The slightly shorter gas-phase inter-ring bonds suggest a small increase in the double bond character in line with the reduced tilting. Still we can conclude that all synthetized molecules (**1-5**) prefer a distorted structure to the expected planar one. In addition we also see that the extent of the torsion in gas-phase clearly depends on the steric demand of the N-substituents at the immediate vicinity of the tetrazine ring. Molecule **2** with the bulkiest mesitylene groups has the largest τ value (34°), while **7** is planar. This suggests that the most likely reason for the torsion is the repulsion between the N-substituents of the five-membered rings and the tetrazine ring. Further insight could be obtained by inspecting the rotational potential as a function of the torsional angle around the inter-ring bond. Figure 3 displays the change of the energy as a function of the torsion angle around the bond connecting the two rings for molecules **1**, **2**, **6** and **7**. These molecules represent a series featuring N-substituents of varying steric demand. In this group **2** has the bulkiest substituent mesitylene whereas the combination of n-butyl and methyl groups in **1** poses limited steric bulk. The two methyl groups represent even less steric demand in **6** whereas the smallest steric constraints can be found in **7** with two H substituents.

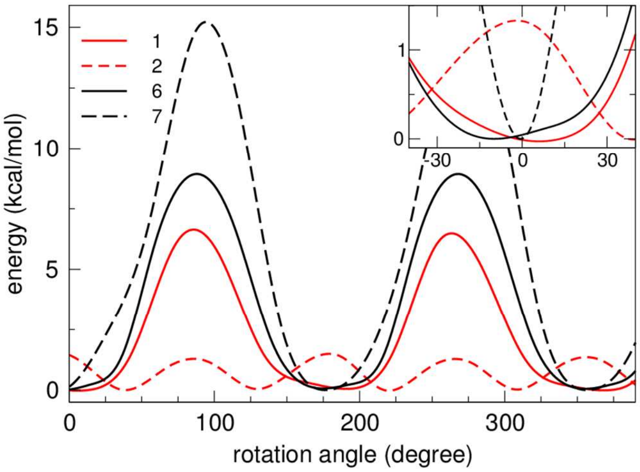


Fig. 3. Fig. 3. Rotational potentials around the inter-ring bond. The curves have been generated by systematically varying τ defined in Table 1. Inset: The same curves plotted around τ=0˚."

The rotational potential of **2** clearly shows that its preferred structure is a tilted conformation, although transformation to the planar arrangement requires only ~2 kcal/mol. The small barriers are attributed to the highly destabilized conformer states by the bulky mesitylene groups. For molecules **1** and **3-6** we obtained somewhat larger values for the difference between the optimal and planar conformations although with different number of local minima and maxima between the optimal conformers.[22] In particular, molecule **1** has only two maxima and two minima along a full rotation with a ca. 6.5 kcal/mol barrier as seen in Figure 3. The position of the minima indicates that its equilibrium structure is only slightly tilted (see also Table 3 and inset in Figure 3). Compound **6** displays similar behaviour: it prefers a planar arrangement due to the largely reduced steric hindrance. The torsional barriers are also very similar. Curiously, the methyl-hydrogen exchange (**6** vs. **7**) increases further the torsion potential between the favored fully planar conformers. This quite stiff torsion potential can be attributed to the H-bonds formed between the tetrazine N lone pairs and the imidazole hydrogens in the coplanar conformer. The inter-ring bond distances in **6** and **7** are still quite long: 1.439 Å and 1.421 Å, respectively, which implies only very limited double bond character. In fact, the corresponding calculated bond orders[23] are around 1.2, which clearly indicates single inter-ring bonds. We can therefore conclude that the main reasons behind the non-planar structures of **1-5** are ligand repulsion and the single bond character of the inter-ring C−C bond with soft torsional potential.

An important and unexpected outcome of the calculations is that the single bond character of the inter-ring bond is quite independent of the torsion of the central ring system. We also found that the C−O group on the tetrazine ring keeps its double bond character in all investigated conformers as shown by its bond lengths (1.21 Å). Similarly, the N−N distances in the tetrazine ring fall between 1.28-1.29 Å in all molecules indicating double bond character.[22] The structural peculiarities of **1-5** identified in crystalline and molecular state were also seen in molecules **6** and **7**. In view of these observations we conclude that the apparent conflict of the quinoidal vs. dipolar aromatic structure is present also in the planar two-ring core system.

To shed additional light on this interesting problem further analysis of the electronic structures has been conducted. We have found that all molecules (**1-7**) feature very large calculated dipole moment (12.8-14.0 D). This points to a zwitterionic electron structure in all cases. Indeed, a significant polarization can be seen along the O1−C3−C6−C12 line of the rings as shown in Figure 4, where the electrostatic potential of molecule **1** is plotted. It clearly shows that the imidazole group represents a partially positive region in the molecule whereas around the tetrazine ring the electrostatic potential is negative. Similar charge distributions can be observed for the other molecules.[22] The large dipole moments can be interpreted with an idealized fictitious two-charge system. Indeed, the 12.8-14.0 D range is equivalent to two unit point charges with opposite sign separated by 2.7-2.9 Å distance which is comparable with the distance of the ring centers of the core. This remarkable feature convincingly shows that the two core rings are responsible for the zwitterionic nature.

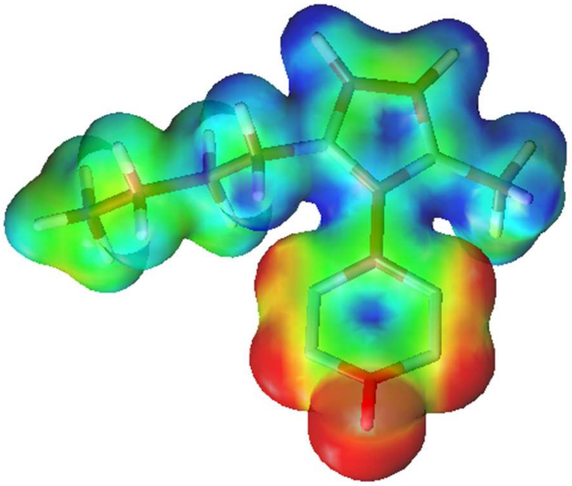


Fig. 4. Molecular electrostatic potential mapped onto the total electron density surface generated with a contour value of 0.02 au for molecule **1**. Blue and red colors indicate positive (0.1 au.) and negative (-0.1 au.) regions, respectively. The other colors show transient regions.

We have then tested if aromaticity can be located in the studied molecules. To this end we have selected a magnetic criterion, the nucleus independent chemical shift (NICS) index.[24] This quantity corresponds to the negative of the magnetic shielding computed at a given point. In the present case we calculated it at the center of the rings. Large negative values indicate aromaticity, whereas positive values can reveal antiaromatic character.[25] In Table 4 we have collected the NICS values computed to the center of the tetrazine and the five-membered (azole) ring.

Table 4. NICS values computed for the tetrazine and the five-membered rings for molecules **1**-**7**.

molecule	NICS	
	5-membered ring	tetrazine ring
1	-12.6	3.2
2	-11.1	3.4
3	-12.1	2.0
4	-4.9	3.1
5	-8.6	3.1
6	-12.5	3.3
7	-11.5	5.3

Inspection of Table 4 reveals that molecules **1**-**3** and **5**-**7** preserved the aromatic character of their five-membered heterocyclic precursors. Molecule **4** has a saturated five-membered ring, 1,3-imidazolidine therefore it has a small negative NICS value. In contrast, the tetrazine rings in **1**-**7** are definitely not aromatic: instead a very weak antiaromatic character can be assigned to them. This is clearly in accordance with the structural observations, and we can conclude that the tetrazine rings feature a quinoidal-like structure. The stability provided by the strong aromatic character of the imidazole or triazole rings together with the delocalization in the tetrazine ring can be an important driving force in avoiding the expected long-range quinoidal π-electron distribution. Cross conjugation[26] via the inter-ring double bond would probably destabilize the delocalized electron states within the rings. In case of **4** the delocalization in the imidazolidine ring would be also destabilized by the cross-conjugation with the inter-ring double bond.

The combined results of the quantum chemical studies thus fully corroborate the experimentally determined structures and provide the explanation of their uniqueness. The electron distribution and the resulting bond lengths in the tetrazine rings show a quinoidal-like character as depicted for mesomeric form **A** in Figure 2, while the electron distribution and bond lengths in the five-membered rings are “aromatic” as in form **B** in Figure 2. The resolution of this superficial contradiction lies in the lack of aromaticity in the tetrazine ring. Thus the two-ring core of the molecules accommodates a remarkable π-electron distribution giving rise to a linked dipolar aromatic - quinoidal system as depicted for mesomeric form **C** in Figure 1, avoiding possible cross-conjugation between the rings. Although the fact that aromaticity decreases as we replace the carbon atoms of benzene with nitrogens, has been apparent in the different chemical reactivity of tetrazines, to our knowledge this is the first case when a nonaromatic tetrazine moiety has been preferred over an aromatic form. This indicates that the latter structure would be less stable, presumably due to the necessary long distance charge separation.

Experimental

Single crystal X-ray diffraction

Diffraction intensity data collection was carried out at 293(2) K on a Bruker-Nonius MACH3 diffractometer equipped with a point detector using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by SIR-92 program[27] and refined by full-matrix least-squares method on F^2, with all non-hydrogen atoms refined with anisotropic thermal parameters using the SHELXL-97 package.[28] Publication material was prepared with the WINGX-suite.[29] The hydrogen atoms were located geometrically and refined in the rigid mode. All structure determinations gave acceptable checkcif results. In case of structure **3** the asymmetric unit contains half of the molecule. Crystals of compound **1** were rather weakly diffracting ones. The applied X-ray radiation does not make it possible to determine the absolute configuration of stereogenic centers in structures **3** and **4**. However, in our case it was not necessary as the starting material was optically pure. Crystallographic experimental details along with packing diagrams and figures are collected in the Electronic Supplementary Information. The crystallographic calculations were performed using the PLATON[30] and MERCURY[31] programs.

Computational details

The periodic calculations have been performed using the CP2K program package.[32] It employs a hybrid Gaussian and plane-wave method. The molecular crystal models have been constructed by using the crystallographic cell parameters and the atomic positions were fully optimized. Gaussian basis set of double-ζ + polarization quality (DZVP)[33] has been employed to expand the electronic orbitals, while the one-electron densities have been represented on a plane-wave set characterized by a 300 Ry energy cutoff. Additional test computations using a much larger basis set of TZV2P quality showed that the structural parameters are sufficiently converged (see ESI). Only valence electrons have been treated explicitly, whereas the interactions between the valence electrons and the ionic cores were described by the Goedecker−Teter−Hutter pseudopotentials.[34] We have employed the BLYP exchange-correlation functional[35] with and without the Grimme D3 corrections[36] (labeled as BLYP+D3 and BLYP, respectively) in order to see the role of dispersion in the periodic structures.

The individual (gas-phase) molecules have been fully optimized by the Gaussian 09 program.[37] We have employed the BLYP and the dispersion-corrected, range-separated hybrid ωB97X D exchange-correlation functional[38] with the 6-31G(d) basis set.[39] Test calculations showed that the calculated electronic and structural parameters show small sensitivity to a large variety of functionals and basis sets (see ESI). In particular we have verified that switching from BLYP to ωB97X D functional does not alter the qualitative features of the optimized structures. This allows the direct comparison of the periodic and gas-phase calculations and the application of high-level exchange-correlation functional (ωB97X D).[40]

CCDC 1003465-1003469 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.

Conclusions

The single crystal structure of a series of tetrazine derivatives bearing an NHC-derived substituent showed a unique pattern of bond lengths and torsional angles irrespective of the nature and substitution of the five-membered ring attached to the tetrazine core. A search in the Cambridge Structural Database has also confirmed the uniqueness of the structural features of this novel compound class. The seemingly contradicting features of the molecules included a C−O bond of strong double bond character at one end of the tetrazine and a non-coplanar five-membered ring on the other end of the tetrazine ring attached through a C−C bond of very weak double bond character. Structural studies helped exclude crystal packing effects as the reason behind the unusual structural data. Systematic computational investigation revealed that the unique structural features are present both in the crystalline and gas phase. Computational studies also demonstrated that the steric demand of the N-substitution on the five-membered ring has a clear and direct influence on the conformational equilibria of these molecules but the apparent conflict between the quinoidal and aromatic electron distribution is not affected. The calculations suggest that the two-ring core of the molecules can be described as a coupled aromatic (azole) – quinoidal (tetrazine) system which also explains their unique structure. The driving force behind this electron distribution is to avoid cross-conjugation and large charge separation between the two rings. The easy synthetic access to the compound class and its unusual structural and electronic features might open up new avenues in chemical reactivity and applications in materials science that are being explored.

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Notes and references

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Electronic Supplementary Information (ESI) available: Crystallographic data and figures including packing diagrams for compounds **1**-**5** and results of QM calculations including calculated coordinates and pictures of molecular electrostatic potentials for compounds **1**-**7**. See DOI: 10.1039/b000000x/

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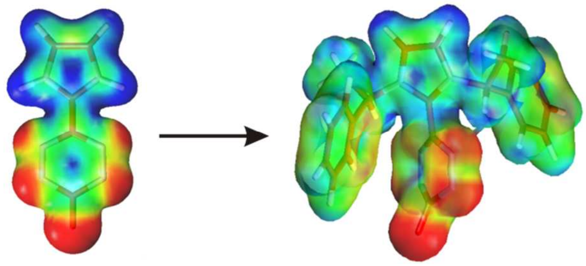

Combined experimental and theoretical investigations helped to elucidate the mechanisms responsible for the unique structural and electronic properties of NHC-substituted tetrazinone compounds.