

Interplay of the intramolecular N–H...N bond and π -stacking interaction in 2-(2'-tosylaminophenyl)benzimidazoles

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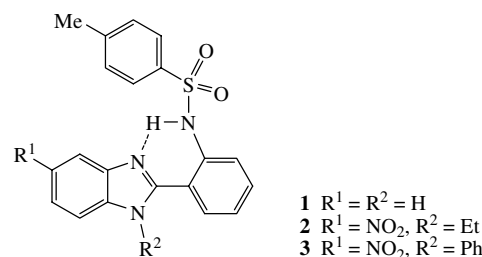
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The competition of the intramolecular N–H...N bond and π -stacking was analysed and energy input of both interactions was estimated within topological analysis of electron density distribution function in the crystal of 1-ethyl-2-(2'-tosylaminophenyl)-5-nitrobenzimidazole.

An uncommon example of competition of the intramolecular H-bond and π -stacking interaction between tolyl and benzimidazole rings was recently discovered based on the experimental and theoretical analysis of 2-(2'-tosylaminophenyl)-benzimidazole **1**.¹ It was shown that, in the solid state, a molecule is characterised by a conformation in which the N–H...N bond is slightly weakened due to the formation of stacking interaction between the phenyl and benzimidazole rings, whereas the above π -stacking interaction was not observed in a gas phase according to the spectral data.¹ Although such a conformation in a crystal of **1** can solely be the consequence of the crystal packing effects, one can propose that it is the general feature of this system. In addition, a CSD search for molecules with an aryl–SO₂–X–aryl fragment showed that intramolecular aryl–aryl separation is usually rather high.²

In order to estimate the role of such an unusual competition of intramolecular H-bond and π -stacking in the stabilization of **1**, we have undertaken the X-ray diffraction (XRD) investigation[†] of two similar compounds, namely 1-ethyl-2-(2'-tosyl-



aminophenyl)-5-nitrobenzimidazole **2** and 1-phenyl-2-(2'-tosylaminophenyl)-5-nitrobenzimidazole **3** (Figure 1).

Competition (or synergy) between intramolecular H-bonding and π -stacking interactions defines adoption of stable structures of guanine–cytosine and adenine–thymine dimers and of DNA where according to ref. 4 stacking interactions make a larger contribution to the stabilization energy than H-bonding.

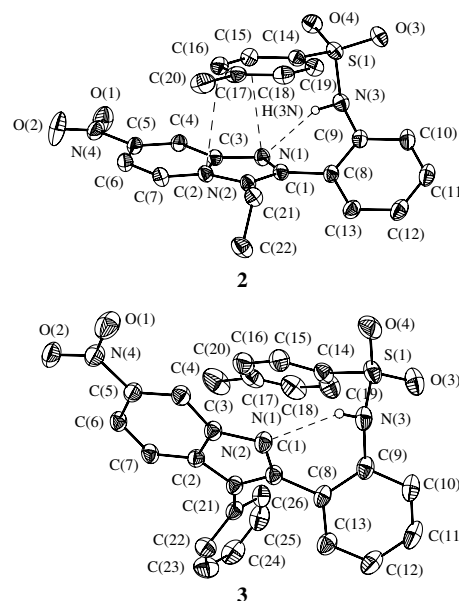


Figure 1 The general view of molecules **2** and **3** in thermal ellipsoids at the 50% probability level. The parameters of H-bonds N(1)...N(3), H(3N)...N(1) (Å) and N(3)H(3N)...N(1) (°): 2.774, 2.082, 137.6 in **2** and 2.780, 2.137, 139.6 in **3**.

[†] *Crystallographic data.* Crystals of **2** (C₂₂H₂₀N₄O₄S, *M* = 436.48) are monoclinic, space group *C2/c*, at 120(2) K: *a* = 24.4279(9), *b* = 12.6434(5) and *c* = 16.5779(6) Å, β = 125.325(2)°, *V* = 4177.4(3) Å³, *Z* = 8, *d*_{calc} = 1.388 g cm^{−3}, μ (MoK α) = 0.193 cm^{−1}, *F*(000) = 1824. Crystals of **3** (C₂₆H₂₀N₄O₄S, *M* = 484.53) are triclinic, space group *P1̄*, at 200(2) K: *a* = 9.184(2), *b* = 10.653(2) and *c* = 11.743(2) Å, α = 87.83(3)°, β = 86.88(3)°, γ = 85.39(3)°, *V* = 1142.9(4) Å³, *Z* = 2, *d*_{calc} = 1.408 g cm^{−3}, μ (MoK α) = 0.184 cm^{−1}, *F*(000) = 504. Intensities of 47519 (**2**) and 5293 (**3**) reflections were measured with a Bruker AXS Smart 1000 CCD and Syntex P2₁ diffractometers and 18052 (**2**) and 4979 (**3**) independent reflections [*R*_{int} = 0.0332 (**2**) and 0.0207 (**3**)] were used in further refinement. The refinement converged to *wR*₂ = 0.0982 and GOF = 1.001 for all independent reflections [*R*₁ = 0.0493 was calculated against *F* for 10362 observed reflections with *I* > 2 σ (*I*)] for **2** and to *wR*₂ = 0.0910 and GOF = 1.001 for all independent reflections [*R*₁ = 0.0373 was calculated against *F* for 3828 observed reflections with *I* > 2 σ (*I*)] for **3**. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 601832 and 601833. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2007.

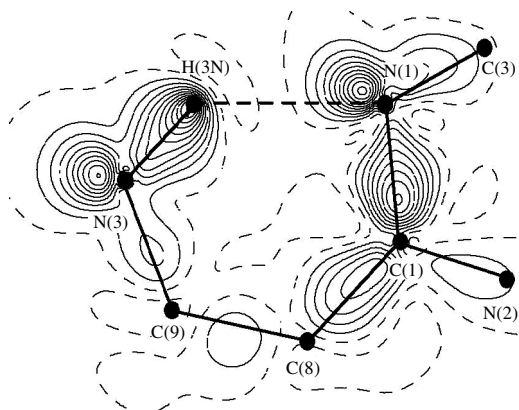


Figure 2 The section of DED in the N(3)H(3N)N(1) plane. The contours are drawn with 0.1 eÅ⁻³ step, the negative contours are dashed. The deviations of C(9), C(8) and C(1) atoms from the N(3)H(3N)N(1) plane are equal to 0.522, 0.520 and 0.081 Å.

According to XRD, the geometry of **2** and **3** in the crystal is rather similar to that of **1** (Figure 1). In all structures, the H-bonded six-membered ring is considerably non-planar with the torsion angle N(1)C(1)C(8)C(9) (ϕ) equal to 28.6,¹ 36.3 or 35.9° in **1**, **2** or **3**, respectively. In turn, the non-planarity of two aromatic fragments causes the weakening of the N–H...N bond: the N(1)...N(3) distance increases up to 2.773(1) or 2.780(2) Å in **2** or **3** against 2.755(1) Å in **1**. The variation of ϕ and the N(1)...N(3) distance in **1–3** can be a consequence of steric repulsion due to the exchange of H atom at N(2) by an alkyl or aryl fragment. Indeed, the B3LYP/6-311G* calculation of **2** demonstrated that, in the isolated molecule, the value of ϕ is also considerably higher (32.9°) than the corresponding one in **1** (14.4°).¹

Taking into account that the barrier of rotation around the C(1)–C(8) bond in **2** and **3** is low,^{1,4} we can propose that the variation of ϕ and the weakening of the N–H...N bond in **1–3** can solely be the consequence of crystal packing effects. On the other hand, the analysis of intramolecular distances in **2** and **3** shows the probable presence of π -stacking interaction between phenyl and benzimidazole rings. Indeed, in both compounds, the shortened contacts between the above rings occur [the shortest distances are 3.426(1) Å for C(2)...C(16) in **2** and 3.216(1) Å for N(1)...C(15) in **3**]. Although the intramolecular N...C contact is shorter in **3**, the mutual disposition of rings is more favourable for π -stacking interaction in **2** (the corresponding dihedral angle is 8 or 27.3° in **2** or **3**, respectively). Thus, we can propose the presence of intramolecular π -stacking interaction at least in **2** from the geometrical point of view.

A comparison of the bond lengths and angles in benzimidazole and tolyl rings in a crystal and an isolated molecule clearly shows that, despite of the probable stacking interaction, they are nearly identical. The only difference is the systematic decrease of the

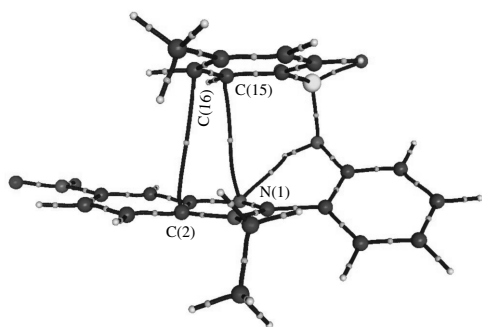


Figure 3 The bond paths and critical point (3, -1) (denoted by small balls) in the crystal of **2**.

S(1)N(3)C(9) angle in crystals of **1** and **2** [116.1 and 118.3(5)°, respectively] as against corresponding values in the isolated molecules [124.2 and 124.8°, respectively]. In addition, note that, in the crystal of a similar benzoxazole⁵ where the H-bonded six-membered ring is almost planar (ϕ is 5.2°) and thus there is no intramolecular π -stacking, the corresponding SNC angle is equal to 128°, which is typical of such compounds.^{6,7} The S(1)N(3)C(9) angle in **3** (121°) can serve as an additional indication of the presence of π -stacking interaction.

Despite of all the above geometrical features of the presence of π -stacking interaction in 2-(2'-tosylaminophenyl)benzimidazoles in the solid state, we cannot exclude that the shortening of interplane distance do not lead to charge transfer and attractive interaction. As the example of such situations, [2.2]paracyclophane and its derivatives can be mentioned.⁸

During the last decade, an estimation of the atom...atom interaction nature using experimental and/or theoretical analysis of the electron density distribution function $\rho(r)$ within Bader's 'Atom in Molecule' theory (AIM) has been commonly used.⁹ There is a number of examples of analysis of the nature of so-called 'forced' intramolecular interactions.^{8,10}

Thus, to evaluate reliability of the above geometrical criteria for analysis of the forced C...C and C...N contacts in this system, we have undertaken the topological analysis of charge density distribution function in the crystal and isolated molecule of **2**.[‡]

The principal characteristics of charge density distribution in the crystal of **2** are close to expected.¹² In particular, as it can be seen from the deformation electron density (DED) map in the area of the N–H...N bond, the charge accumulation is observed for all chemical bonds and nitrogen electron lone pairs (Figure 2).

The critical point (CP) search and consequent calculation of bond paths have revealed that CP (3, -1) are located not only in case of all expected chemical bonds but also in case of the intramolecular N–H...N bond and two shortened contacts C(15)...N(1) and C(16)...C(2) (Figure 3). Thus, we can undoubtedly conclude that, in the crystal, the observed conformation is stabilised by stacking between benzimidazole and phenyl rings. In contrast, in the isolated molecule, the only intramolecular interaction observed is the N–H...N bond.

In addition to the above intramolecular interaction the CP search in a crystal revealed that some of C–H...O, C–H...N and H...H contacts also correspond to the attractive interactions. Taking into account that, within the topological analysis of $\rho(r)$, it is possible to estimate the energy of weak interactions,¹³ it was intriguing to compare the relative inputs of stacking and N–H...N interaction in the stabilization of the conformation in a crystal and isolated molecule of **2**. The comparison of topological parameters in CP (3, -1) for the N–H...N bond clearly shows that, in the crystal, it is somewhat weakened [$\rho(r)$ is equal to

[‡] The multipole refinement was carried out for **2** within the Hansen–Coppens formalism^{11(a)} using the XD program package.^{11(b)} Before the refinement C–H and N–H bond distances were normalised to the values obtained in the B3LYP/6-311G(d,p) calculation. The level of multipole expansion was octopole for carbon, nitrogen, oxygen and sulfur atoms and dipole for hydrogen atoms. The refinement was carried out against F and converged to $R = 0.0381$, $wR = 0.0387$ and $GOF = 1.316$ for 10192 merged reflections with $I > 3\sigma(I)$. All bonded pairs of atoms satisfy the Hirshfeld rigid-bond criteria.^{11(c)} The average value of difference of the mean square displacement amplitudes along the bond was 6×10^{-4} Å². The residual electron density was no more than 0.135 eÅ⁻³. Analysis of topology of the $\rho(r)$ function was carried out using the WINXPRO program package.^{11(d)} *Ab initio* calculations of **2** were performed with the Gaussian 98 program package at the B3LYP level of theory. Topological analysis of the $\rho(r)$ function was performed using the MORPHY 98 program, basing on the wave functions obtained from the B3LYP calculations.

0.16 eÅ⁻³ against 0.21 eÅ⁻³ in an isolated molecule] and, as a result, the N–H...N bond energy estimated within the Espinosa correlation scheme^{13(b)} decreased from 7.21 to 6.47 kcal mol⁻¹.

In turn, the stacking interaction in a crystal is considerably weaker: $\rho(r)$ values and energy of both contacts are equal to ca. 0.03 eÅ⁻³ and 0.67 kcal mol⁻¹, respectively. The latter values are close to those found for intermolecular stacking in a crystal of 3-amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine where the energy of C...C [3.317(1) Å] and N...C [3.47(1) Å] interactions is equal to 0.74–0.85 kcal mol⁻¹.¹⁴ Thus, the stacking interaction is much weaker than H-bond. On the other hand, the calculated value of H-bond energy in the isolated molecule is approximately equal to the sum of energies of π -stacking interaction and NH...N bond in the crystal (7.81 kcal mol⁻¹). The whole energy of intramolecular interactions in **2** is nearly constant because the weakening of H-bond is compensated by π -stacking interaction formation.

It should be noted that an analysis of atomic charges obtained by means of integration of $\rho(r)$ within the atomic basin has revealed that charges in the pairs of atoms involved in stacking interaction are of the same sign and equal to –0.7, –0.06 e for N(1), C(15) and 0.21, 0.06 e for C(2), C(16), respectively. Thus, we can conclude that the electrostatic component of stacking interaction in **2** is not the dominant one although the polarization of **2** during the transfer from solution to a crystal can be a possible reason of the stacking interaction appearance.

As regards the crystal packing according to CP search there are some weak contacts, namely: eight C–H...O contacts with the average energy^{13(b)} 1.71 kcal mol⁻¹, one C–H...N contact with the energy 1.80 kcal mol⁻¹, two C...C contacts formed by alkyl groups with the average energy 1.19 kcal mol⁻¹ and ten H...H-contacts with the average energy 1.19 kcal mol⁻¹. The summation of all contact energies, as it was shown previously, serves as estimation of crystal energy¹⁵ and is equal to 17.54 kcal mol⁻¹ in **2**.

Taking into account the above atomic charges as well as that aromatic rings, which are involved in stacking interactions both in **1** and **2** do not participate in any shortened intermolecular contacts, we can propose that appearance of stacking interaction in **1–3** is a consequence of medium polarity in a crystal rather than of ‘specific solvation’.

Thus, it means that such an unusual interplay of intramolecular π -stacking interaction and N–H...N bond in 2-(2'-tosylaminophenyl)benzimidazoles is not an accident and, probably, can be a general feature of this type of compounds in a solid state and polar medium.

We can propose that such (or similar) systems have great importance as possible reversible molecular switchers,¹⁶ which can enhance the intramolecular charge transfer, will be governed by the medium polarity change.

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