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# Cooperativity effects of H-bonding and charge transfer in an L-nitroarginine crystal with $Z' > 1$

**Alexandra O. Borissova,[a] Mikhail Yu. Antipin,[a] Harutyun A. Karapetyan,[b] Aram M. Petrosyan[b] and Konstantin A. Lyssenko*[a]**

[a] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5085; e-mail: kostya@xray.ineos.ac.ru*
[b] *Molecule Structure Research Center, National Academy of Sciences of Armenia, 375014 Yerevan, Armenia*

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**Detailed analysis of the charge density distribution function in the crystal of L-nitroarginine with two crystallographycally distinct molecules using Richard Bader's 'Atoms in Molecules' theory demonstrated the strengthening of hydrogen bonds owing to cooperativity effects and revealed the role of H-bonding in charge transfer in a structurally frustrated system.**

The phenomenon of cooperativity can be explained as follows: each individual H-bond taking part in a chain (either short or long) of interlinked H-bonds has higher energy than it would be in the absence of others.[1] 'Positive'[2] or 'negative'[3] cooperativity appears for a wide range of classical, ionic,[4] charge-assisted[5] and non-conventional[6] H-bonds.

To estimate the input of each interaction into the total energy of a system consisting of several H-bonded parts, one should compare the geometry and charge distribution in the hydrogen-bonded associate with those in the isolated moieties. However, the comparison of several crystal structures of similar model compounds is meaningless in this respect, as minor variations in a molecule (alkyl chain length, substitute at an aromatic ring, *etc.*) might lead to considerable differences in the crystal packing of a series of related compounds.[7] Thus, the thorough experimental investigation of the cooperativity effects demands a special sample, such as a molecular crystal with two or more crystallographically distinct molecules in an asymmetric unit ($Z' > 1$), where the medium polarity is the same for every moiety (*e.g.*, see ref. 8).

To analyse the competition (or synergy) of hydrogen bonds in detail, the crystal of L-nitroarginine can be used as a test material. With its multiple proton donors and acceptors,[9] the molecule is 'structurally frustrated',[10] and it crystallizes in the chiral low-symmetry group $P1$ with two independent molecules forming 3D H-bonded associates. The comparison of similar H-bonds in two independent molecules of L-nitroarginine would be a key to univocal evaluation of the H-bonds cooperativity.†

Two crystallographically distinct molecules of L-nitroarginine (**A** and **B**) (Figure 1) have an alkyl chain of different conformations. As this alkyl chain is rather long, a small variation in its conformation [the torsion angle N(1)–C(2)–C(3)–C(4) is 60.4° in the molecule **A** or 51.7° in the molecule **B**; C(4)–C(5)–N(2)–C(6) is 174.6° in **A** or 164.6° in **B**] does not cause a significant variation in the distance between carboxyl and nitroguanidine moieties.[11] Therefore, we can assess the influence of intermolecular interactions on the geometry of the independent molecules. To address this problem, we performed the topological analysis of the experimental (XRD) charge density distribution function [$\rho(r)$] within R. Bader's 'Atoms in Molecules' (AIM) theory.[12] In its frameworks, the presence of a bond critical point (3, –1) (bcp) and a corresponding bond path between two atoms is indicative of a bonding interaction. Furthermore, the energy of an interaction can be estimated with a high accuracy using the so-called Espinosa's correlation scheme.[13] As shown recently,[14] this approach is valid for weak interactions, *e.g.*, H···H and C–H···O contacts, as well as for moderate and strong H-bonds[3(a)] and some coordination bonds.[15] The possibility of quantitative description of the influence of intermolecular binding on molecular properties within this approach was shown in the investigation of pseudosymmetry in crystalline 3-isopropyl-4-thiomethyl-*N*6-benzoylsidnone imine with four independent molecules[8] and within the comparison of two polymorph forms of paracetamol.[16] Hence, it can be applied to examine the mutual influence of hydrogen bonds on charge density distribution within the crystallographically distinct species of L-nitroarginine.

The topological analysis of the experimental $\rho(r)$ function reconstructed from the high-resolution XRD data allowed locating the bcps and corresponding bond paths for all the covalent and hydrogen bonds expected on the basis of geometrical criteria. The topological parameters of the covalent bonds (see Online Supplementary Materials) are close to those in amino acids investigated earlier.[17]

The intramolecular hydrogen bond in the nitroguanidine fragment of L-nitroarginine N(5)–H(5NA)···O(3) (Figures 1 and 2) is considerably different in the **A** and **B** molecules: the N···O distance and the interaction energy obtained by means of Espinosa's correlation[13] is 2.5857(8) Å, 10.8 kcal mol$^{-1}$ and 2.5557(9) Å, 12.0 kcal mol$^{-1}$ in **A** and **B**, respectively. All bond lengths in the nitroguanidine moiety are listed in Table S1 (see

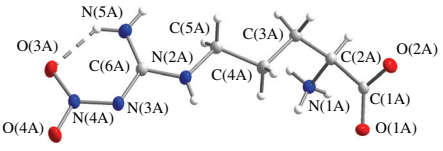


**Figure 1** General view of L-nitroarginine molecule in representation of atoms *via* thermal ellipsoids at a 80% probability level. The atomic numbers for the **A** moiety are shown.

† For details of X-ray diffraction data collection, conventional ($R = 0.0278$) and multipole ($R = 0.0211$) refinement and topological analysis of electron density function in the crystal of L-nitroarginine ($P1$, $Z = 2$), see Online Supplementary Materials.

CCDC 755512 contains 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. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

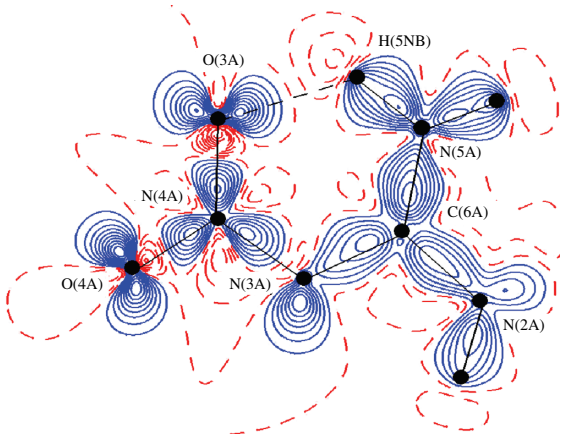


**Figure 2** Static DED distribution showing the nitroguanidine moiety. The contours are drawn with a 0.1 eÅ$^{-3}$ step, the negative contours are dashed, the positive contours are solid.

Online Supplementary Materials). One can attribute this variation of the H-bond strength to differences in the conformation of a six-membered H-bonded ring, but the latter is almost flat in both molecules [the torsion angles N(4)–N(3)–C(6)–N(5) are 4.89(9)° in **A** and 6.01(9)° in **B**]; hence, the reasons for this discrepancy should be further searched in the area of intermolecular interactions.

In the molecule **B** (Figure 3), only the proton donor atom N(5B) (of the amino group) is involved in the intermolecular N(5B)–H(5ND)···O(3A) bond [N···O 2.9418(8) Å, 4.9 kcal mol$^{-1}$]. In **A**, both the proton donor N(5A) and the proton acceptor O(3A) atoms participate in rather strong intermolecular interactions. Indeed, the oxygen atom is involved in the O(3A)···H(5ND)–

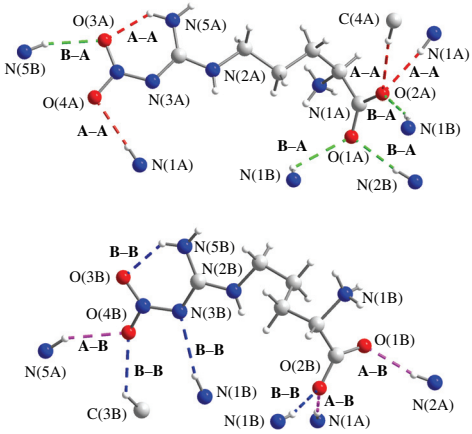


**Figure 3** Coordination environment of the molecules **A** and **B**, hydrogen bonds are dashed.

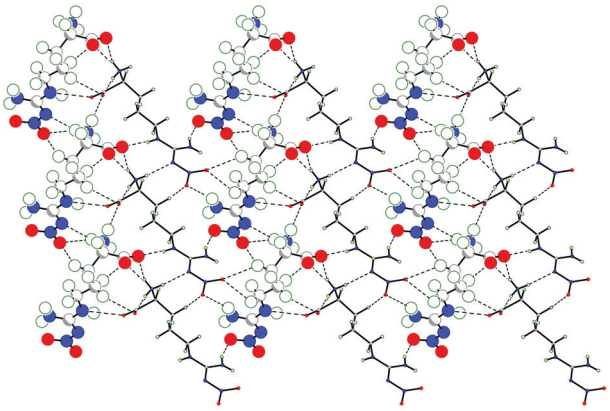

**Figure 4** Alternating **A**–**A** and **B**–**B** layers in the crystal packing of L-nitroarginine, large balls are **A** atoms, small balls are **B** atoms.

N(5B) bond (see above), the NH group in the N(5A)–H(5NA)··· O(4B) bond [N···O 3.0164(8) Å, 3.7 kcal mol$^{-1}$, Table 1]. At the same time, the intramolecular hydrogen bond in **B** is shorter than those in, *e.g.*, 2-nitroguanidine[18] (2.599 Å) and thiazole derivative of nitroguanidine[19] (2.610 Å), where the strong intermolecular interactions are absent. As a result, we can conclude that the presence of intermolecular interaction formed by a proton donor atom causes the strengthening of the intramolecular H-bond (cooperativity), while in the case of a proton acceptor atom intermolecular binding leads to the weakening of this H-bond (competition); the latter was proposed earlier for large H-bonded clusters[14(a),20] and small associates of organic molecules.[7] This concept is supported by the variation of oxygen and nitrogen charges ($Q$) obtained by integration of $\rho(r)$ within the atomic basins ($\Omega$) surrounded by the zero-flux surface:[12] the charges of the N(5A) and N(5B) atoms are nearly the same (–1.20 e and –1.19 e, respectively), those of the O(3A) and O(3B) atoms are slightly different (–0.43 e and –0.48 e, respectively) due to the formation of an additional H-bond in the case of the **A** molecule. Both the N–O bonds in nitro groups and the C–O bonds in carboxyl groups are influenced by the intermolecular H-bonds. The participation of oxygen atoms in the hydrogen bonding leads to the C=O bond elongation due to charge transfer through the H-bond, which is in good agreement with the variation of the charges.

Two H-bonded layers penetrating into each other can be distinguished in the crystal packing of L-nitroarginine (Figure 4). Both the **A** and **B** molecules are organized in separate corrugated layers linked by the hydrogen bonds of **A**–**B** and **B**–**A** type. The formation of **A**–**A** layers (Figure S2, see Online Supplementary Materials) is governed by two hydrogen bonds of moderate strength, namely, the N(1A)–H(1NA)···O(2A) and N(1A)–H(1NC)···O(4A) ones (Table 1). The layers are addi-

**Table 1** H-bond parameters.

| Bond[a] | $d$/Å | $\rho(r)$/eÅ$^{-3}$ | $\nabla^2\rho(r)$/eÅ$^{-5}$ | $V(r)$ (a.u.) | $H_e(r)$ (a.u.) | $E$/kcal mol$^{-1}$ | Type |
|---|---|---|---|---|---|---|---|
| N(2B)–H(2ND)···O(1A) | 2.8655(7) | 0.157 | 3.49 | –0.0230 | 0.0066 | 7.2 | **B**–**A** |
| N(1B)–H(1NF)···O(1A) | 2.9017(7) | 0.084 | 1.26 | –0.0082 | 0.0024 | 2.6 | **B**–**A** |
| N(1A)–H(1NA)···O(2A) | 2.8907(7) | 0.172 | 3.09 | –0.0234 | 0.0043 | 7.3 | **A**–**A** |
| N(1B)–H(1NF)···O(2A) | 2.8686(7) | 0.159 | 2.73 | –0.0205 | 0.0039 | 6.4 | **B**–**A** |
| N(5A)–H(5NB)···O(3A) | 2.5857(8) | 0.236 | 3.77 | –0.0345 | 0.0023 | 10.8 | intra (**A**) |
| N(5B)–H(5ND)···O(3A) | 2.9426(8) | 0.111 | 2.74 | –0.0156 | 0.0064 | 4.9 | **B**–**A** |
| N(1A)–H(1NC)···O(4A) | 2.9910(7) | 0.115 | 2.50 | –0.0151 | 0.0054 | 4.7 | **A**–**A** |
| N(2A)–H(2NA)···O(1B) | 2.7810(7) | 0.214 | 4.02 | –0.0321 | 0.0048 | 10.0 | **A**–**B** |
| N(1A)–H(1NB)···O(2B) | 2.7452(7) | 0.259 | 4.05 | –0.0391 | 0.0015 | 12.3 | **A**–**B** |
| N(1B)–H(1ND)···O(2B) | 2.8657(7) | 0.161 | 3.60 | –0.0238 | 0.0068 | 7.5 | **B**–**B** |
| N(5B)–H(5NE)···O(3B) | 2.5557(9) | 0.256 | 3.99 | –0.0384 | 0.0015 | 12.0 | intra (**B**) |
| N(5A)–H(5NA)···O(4B) | 3.0164(8) | 0.097 | 1.99 | –0.0118 | 0.0044 | 3.7 | **A**–**B** |
| N(1B)–H(1NE)···N(3B) | 3.3356(7) | 0.054 | 1.38 | –0.0066 | 0.0039 | 2.1 | **B**–**B** |

[a]For the atomic numbers for the **A** moiety, see Figure 1. The atomic numbers for the **B** moiety are the same marked by B instead of A. Hydrogen atoms have the same numbers as carbon/nitrogen atoms they are attached to and are marked by additional A–C letters for **A** moiety and D–F letters for **B** moiety.

tionally stabilized by the strong C–H···O binding formed by $CH_2$ groups neighboring to the H-bonded N(1) atom, namely, the C(4A)–H(4B)···O(2A) and C(3A)–H(3B)···O(4A) interactions with the energies of 1.8 and 2.9 kcal mol$^{-1}$, respectively. In turn, **B–B** layers (Figure S2) are formed by means of the chains linked by the N(1B)–H(1ND)···O(2B) bonds (Table 1). It is the only strong conventional hydrogen bond in the **B–B** layers, the others are weak N(1B)–H(1NE)···N(3B) H-bond (2.1 kcal mol$^{-1}$) and extremely strong non-conventional C(3B)–H(3E)···O(4B) bond (3.2 kcal mol$^{-1}$). The latter interactions should be treated as true H-bonds as they cause a red shift in IR spectra and lead to a consequent variation of the bond energy like the conventional hydrogen bonds.[21]

We estimated the input of **A–A**, **B–B**, **A–B**, **B–A** and all other interactions into the total energy of all intermolecular interactions, where **A–A** are the interactions between the two **A** molecules of L-nitroarginine, those between the two **B** molecules will be referenced as **B–B** interactions, and those between the **A** and **B** molecules **A–B** interactions (if the proton donor belongs to the **A** molecule) and **B–A** interactions (if the proton donor belongs to the **B** molecule). These types of interactions are crucially different in terms of charge transfer. While the **A–A** and **B–B** inputs are mainly polarizing, the **A–B** and **B–A** interactions are the channels of charge leaking from one molecule to another.

Most of the intermolecular interactions in the crystal of L-nitroarginine are of the **A–B** type. Their total energy is 33.2 kcal mol$^{-1}$, which is 32% of the sum of all the intermolecular interaction energies (103.2 kcal mol$^{-1}$ per two crystallographycally distinct molecules). The contributions of the **B–A**, **A–A** and **B–B** interactions are almost equal: 25.0 (24%), 20.9 (20%) and 19.1 (19%) kcal mol$^{-1}$, respectively. The total input of other interactions, namely, weak C···O, N···O, H···H and C···N ones, where interacting atoms belong to different molecules and no donor/acceptor atom can be distinguished, is considerably smaller: 5.0 kcal mol$^{-1}$ (5%). These interactions take part in charge transfer together with **A–B** and **B–A** ones, but the direction of transfer is unknown. The estimation of the charges of the **A** and **B** molecules (by the summation of all the corresponding atomic charges) showed that, within the accuracy obtained ('charge leakage' indicating the error of integration is 0.05 e), there is no charge transfer between the molecules. Thus, we cannot exclude the influence of intermolecular interactions on the charge distribution, but, in the test crystal, the difference between the contributions of the **A–B** and **B–A** types of interactions is too small to be discussed.

The interplay of hydrogen bonds may lead to both their strengthening and weakening, and the apparent interaction energy is the result of several effects acting together. The additional interactions of the proton acceptor manifest themselves in the negative cooperativity effect, the analogous interactions of the proton donor result in positive cooperativity leading to the amazing strengthening of hydrogen bond. The interplay of intermolecular hydrogen bonds influences the charge transfer between crystallographically distinct molecules, but the influence is not significant enough to be discussed.

Full details of the multipole refinement as well as the list of atomic charges, volumes, and laplacians are available as a supplementary material.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.09.006.

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