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LETTER

The C=N…C—X σ-Hole Interaction Acts as a Conformational Lock

Zhenfeng Zhang,‡*[a] Li Wang‡[b] and Xiaopeng Xuan [a]

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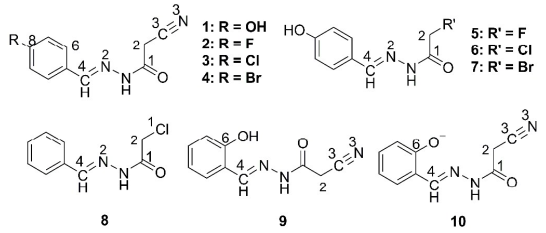
An interesting C=N…C–X conformation lock, which determines the linear alignment of the C=N and C–X fragments, has been found for the first time and is rationalized by the density functional theory calculations. Second-order perturbation theory analysis based on the NBO method further reveals that the nature of the C=N…C–X interaction is mainly the lp(C=N)→σ*(C–X) interaction.

Conformations of single molecules are primarily dominated by noncovalent interactions[1-4]. The interaction dictating molecular conformation is frequently referred to as a conformation lock. The usual type of conformation lock is hydrogen bonding.[1-2] There are also other types of noncovalent interactions[3-4] which can serve as a conformation lock, where the bridging atom is not a H but a member of group IV, V, VI or VII. These interactions usually share certain structural features: there is a positive region on the extension of the σ-bonds in the acceptor segment, which is frequently called a σ-hole,[5-8] or (and) a positive region above groups, such as C=O and C≡N etc, which is sometimes denoted a π-hole. Whether σ-hole or π-hole, one of the positive regions is drawn toward either a lone pair or a π-bond, thus leading to two intramolecular segments to lie close to one another. Given that molecule conformation influences supramolecular assembly of any crystal, the physical properties of materials,[9] and the reactivity and selectivity of the reactions,[10] It is of vital importance to explore molecule conformation and the conformation lock.

(E)-N'-benzylidene-2-cyanoacetohydrazides are interesting model molecules with C=N and $CH_2C≡N$ groups separated by rotatable chemical bonds (Scheme). The former, C=N, can serve as an electron-donor (N lone pair), and the latter, C≡N, can generate two positive regions, one on the neighboring atom C2 (σ-hole), and one above itself (π-hole). Would the $CH_2C≡N$ group generate a σ-hole interaction or a competitive π-hole interaction with the C=N group ? Once one of the two interactions occurs, it would lock up the molecule conformation. Therefore, here the σ-hole (or the π-hole) interaction is expected to be an effective and reliable instrument for conformation control. As far as our knowledge extends, the C=N…C—CN conformation lock has not been studied in the literature. Thus, we have designed and synthesized a series of such model compounds, and examined their X-ray crystal structures. Due to the strong electron-withdrawing ability of the C≡N group, the σ-hole on C2 becomes more positive. Thus, it is



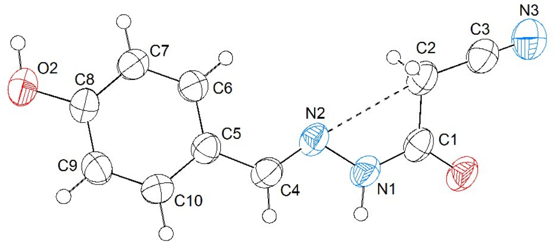


Fig. 1 Structure of 2-cyano-N'-[(1E)-(4-hydroxyphenyl)methylidene]-acetohydrazide, **1**, showing both experimentally and theoretically the linear alignment of the cyanomethyl to the imino group, and the underlying C=N…C-CN interaction; the distances N2…C2 from experimental and DFT calculations are 2.761 and 2.764 Å, respectively.

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[a] *School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, P. R. China.*
E-mail: zzf@htu.cn; Fax: +86 373-3326336;
Tel: +86 373-3326335
[b] *The first affiliated hospital of Xi'an Medical University, Xi'an,710000, China*

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‡ L. Wang and Z. Zhang contributed equally to this work.

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probable for the imino (C=N) lone pair to approach the σ-hole of the intramolecular $CH_2C≡N$ fragment. Interestingly, this expectation is confirmed first by the X-ray crystal structure of **1** (Fig. 1). As shown in Fig. 1, the cyanomethyl group adopts a linear alignment to the imino fragment, the conformation allows the N2 lone pair to approach the σ-hole of the $CH_2C≡N$ group. The distance of 2.761(2) Å between C2 and N2 is significantly shorter than the sum of van der Waals radii, 3.25 Å. The characteristic geometry suggests a C=N…C—CN σ-hole interaction. Molecular electrostatic potentials (Fig. 2) of **1** have further confirmed its existence. As illustrated in Fig. 2, there is a red negative region above imino atom N2 corresponding to the N lone pair, and a blue positive region (the σ-hole) on the extension of the N≡C—C bond.

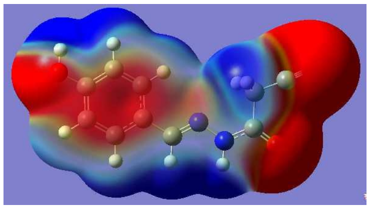

Fig. 2 wb97xd/6-311+g(d,p) electrostatic potential at 0.001 a.u. isosurface of electron density for the 2-cyano-N'-[(1E)-(4-hydroxyphenyl)-methylidene]acetohydrazide, **1**. The blue region represents the positive part of the electrostatic potential, and the red region the negative part of the electrostatic potential.

Recent studies have shown the existence of N…C interactions.[11-13] However, the works on this subject still remain theoretical, and the reported N…C interactions occur only intermolecularly. Computational study shows that the N…C interactions can occur between electron-donor, such as NH_3 or C≡N, and electron-acceptor CH_3X (X = CN, OH, F), and that the amino (or cyano) atom N was found to lie along the C—X bond. Here the C=N…C—CN interaction in **1**, though different in electron-donor, is very similar with the C≡N…CH_3CN and H_3N…CH_3OH interactions.

Considering that the natural bond orbital (NBO) theory[14,15] is quite useful for quantitatively analyzing intramolecular interactions,[16] in order to characterize the C=N…C—CN conformation lock via orbital interactions, the density functional theory (DFT) calculations were conducted on the molecule **1** at the WB97XD[17]/6-311+G(d,p) levels using the crystal coordinates. The optimized geometries were further used for the NBO analysis with NBO version 3.1[18] incorporated in the GAUSSIAN 09[19] package. The result shows that the optimized conformation is in good agreement with the crystallographically determined structure **1** (Fig. 1), suggesting that the linear orientation of the C=N to C−CN unit is caused not by crystal packing but by a certain intramolecular noncovalent interaction between imino and cyanomethyl fragments. The NBO analysis further shows that there are three intramolecular orbital interactions, A, B, C (Table 1) involved in the C=N…C—CN interaction, out of which only the strongest interaction A is shown in Fig. 3. As shown in Fig. 3 and the table 1, the lone pair on the imino atom N2 interacts with the σ*-antibonding orbital of the C2—CN bond, with a concomitant second-order stabilization energy of E(2) = 1.03 kcal.mol^{-1}. The total orbital interaction energy that attributed to the C=N…C—CN interaction is 2.49 kcal.mol^{-1}. The result has theoretically confirmed that the orbital interactions, though not strong, are the decisive factors for the linear alignment of the cyanomethyl and imino fragments.

Table 1 Stabilization energies for selected NBO pairs in **1-8, 10**, as given by second-order perturbation theory analysis of the Fock Matrix in the NBO basis, obtained from WB97XD/6-311+G(d,p).

compounds	Pair name	donor NBO	acceptor NBO	E(2) energy (kcal.mol^{-1})
1	A	lp (N2)	σ* (C2—CN)	1.03
	B	lp (N2)	σ* (C2—C1)	0.76
	C	σ (C4=N2)	RY* (C2)	0.70
2	A	lp (N2)	σ* (C2—CN)	1.00
	B	lp (N2)	σ* (C2—C1)	0.75
	C	σ (C4=N2)	RY* (C2)	0.69
3	A	lp (N2)	σ* (C2—CN)	1.00
	B	lp (N2)	σ* (C2—C1)	0.75
	C	σ (C4=N2)	RY* (C2)	0.69
4	A	lp (N2)	σ* (C2—CN)	1.00
	B	lp (N2)	σ* (C2—C1)	0.75
	C	σ (C4=N2)	RY* (C2)	0.70
5	A	lp (N2)	σ* (C2—F1)	1.54
	B	lp (N2)	σ* (C2—C1)	0.54
6	A	lp (N2)	σ* (C2—Cl1)	1.52
	B	lp (N2)	σ* (C2—C1)	0.65
7	A	lp (N2)	σ* (C2—Cl1)	1.66
	B	lp (N2)	σ* (C2—C1)	0.67
8	A	lp (N2)	σ* (C2—Cl1)	1.50
	B	lp (N2)	σ* (C2—C1)	0.65
10	A	lp (N2)	σ* (C2—CN)	1.47
	B	lp (N2)	σ* (C2—C1)	1.00

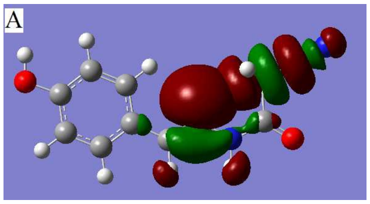

Fig. 3 Dominant orbital interaction A, lp (N2)→σ* (C2—C3≡N3), corresponding to the C=N…C–CN interaction in **1**.

Given that the C=N…C—CN conformation lock works in **1**, it is very probable to find this kind of interaction in analogues, **2**-**8**. In order to verify our expectation, we have conducted the geometry optimization on molecules **2**-**8** using the same method as **1**. Interestingly, the optimized molecule conformations and the main geometry parameters are in perfect accordance with those in **1** (Fig. 1); each of the cyanomethyl or halogenmethyl groups in **2**-**8** adopts a linear alignment to the imino fragment; the distance between C2 and N2 ranges from 2.722 to 2.741 Å. Molecular electrostatic potentials show that the conformations are fixed by the C=N…C—X (X = CN, Cl, Br) σ-hole interaction. As typical representatives, the molecular electrostatic potentials of **7** and **8** are shown in Fig. 4. From this figure, it can be easily found that there exists a stronger C=N…CH_2X σ-hole interaction where the red negative region above N2 (N lone pair) interacts with the blue positive region (the σ-hole) on atom C2. The results are in good agreement with data from the second-order perturbation theory analysis in NBO Basis. NBO analysis shows that there are three orbital interactions in **2**-**4** and two in **5**-**8**

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involved in the C=N…C—X interaction (Table 1). The total orbital interaction energy that attributed to the C=N…C—X interaction is in the range of 2.15～2.49 kcal.mol^{-1}, which is enough strong to stabilize the molecule conformation. The results reveal that the C=N…C—X (X = CN, F, Cl, or Br) conformation lock does work universally in N'-[(1E)-phenylmethylidene]acetohydrazides.

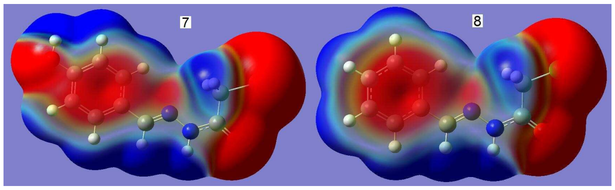

Fig. 4 wb97xd/6-311+g(d,p) electrostatic potential at 0.001 a.u. isosurface of electron density for compounds N'-(4-hydroxybenzylidene)-2-bromoaceto-hydrazide, **7**, and N'-benzylidene-2-chloroacetohydrazide, **8**. The blue region represents the positive part of the electrostatic potential, and the red region the negative part of the electrostatic potential.

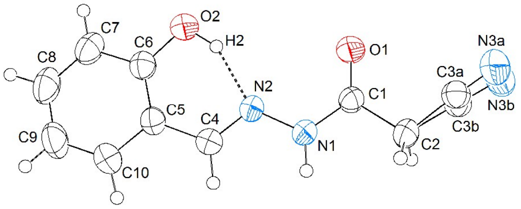

Fig. 5 Crystal structure of 2-cyano-N'-[(1E)-(2-hydroxyphenyl)methylidene]-acetohydrazide, **9**, showing formation of the O2—H2…N2 hydrogen bond (the stabilization energy is 25.81 kcal.mol^{-1} according to NBO calculations) which is competitive with the C=N…C–CN conformation lock.

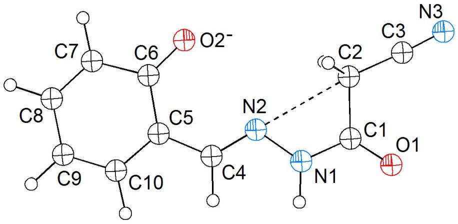

Fig. 6 structure of 2-((2-(2-cyanoacetyl)hydrazono)methyl)phenol oxygen anion, **10**, optimized at WB97XD/6-311+G(d,p) level, showing the existence of the C=N…C—CN conformation lock; the distances N2…C2 is 2.670 Å.

In the C=N…C—X (X = CN, F, Cl, or Br) interaction, the imino unit acts as an electron-donor (lone pair), and the cyanomethyl (or halogenmethyl) as an electron-acceptor. If a strong and competitive electron-acceptor, such as the C6-OH in **9**, is imported, a strong O—H…N=C hydrogen bond would be expected to be formed, thus probably preventing the formation of the C=N…C—CN interaction. Consequently, the molecule conformation should undergo a great change. Keeping our motivation in mind, we also crystallized compound **9**. The crystal structure of **9** is illustrated in Fig. 5. As shown in this Figure, the C6-OH group does form a strong O—H…N=C hydrogen bond, the O2—H2…N2 distance being only 1.76 Å, and the associated angle 152°. According to NBO calculations, the total orbital interaction energy involved in the O—H…N=C interaction is up to 25.81 kcal.mol^{-1}. Due to the formation of the strong H-bond, the relatively weak C=N…C—CN interaction has been prevented. As a result, the plane O1\C1\C2\C3\N3 rotates about 180° around the N1—C1 axis with respect to that in **1**-**4**. From this point of view, the O2—H2…N2 hydrogen bond can be considered as an “obstacle” to the C=N…C—CN conformation lock.

If the above “obstacle” doctrine is true, once the “obstacle” in **9** is destroyed by basification, the C=N…C—CN conformation lock should come into action, and are expected to be stronger than those in **1**-**4**. In view of this, we also conducted a geometry optimization on the phenolic oxygen anion **10**. Interestingly, the C=N…C—CN conformation lock does come back ! As shown in Fig. 6, the linear alignment of the cyanomethyl to the imino is locked by the C=N…C—CN interaction, the distance between N2 and C2 being 2.670 Å, which is markedly shorter than ones in **1**-**4**. This reveals that once the O2—H2…N2 hydrogen bond is no longer in existence, the C=N…C—CN conformation lock is then in operation in the phenolic oxygen anion **10**. NBO analysis shows that the stabilizing energies of the orbital interactions, A and B, involved in the C=N…C—CN conformation lock in **10** are 1.47 and 1.00 kcal.mol^{-1}, respectively. So far, these examples from both sides have proved that the C=N…C—X conformation lock exists universally in N'-[(1E)-phenylmethylidene]acetohydrazides, and the lock can be opened by a strong intramolecular H-bond, such as the O2—H2…N2 in **9**. This suggests that the conformation of these compounds can be modified by pH adjustment.

In addition to the C=N…C—CN conformation lock, there are four intermolecular hydrogen bonds involved in the crystal packing of **1**, one of N—H…O, one of O—H…N, and two of C—H…O types (Fig. 7). The distances N1—H1…O1, O2—H2…N3, C2—H2B…O1 and C2—H2A…O2 are 1.96, 1.86, 2.33 and 2.58 Å, respectively, and the corresponding angles 171, 171, 168 and 127°, respectively. These hydrogen bonds synergistically constitute a complicated 3D structure, the formation of which can be easily understood in the following way (Fig. 7). The molecules related by n-glide plane form a zig-zag [101] chain via a strong O—H…N hydrogen bond; such chains related by antiparallel are laterally linked into a (-301) sheet by N—H…O and C2—H2A…O2 hydrogen bonds; these parallel sheets are finally interconnected into a 3D structure via a C2—H2B…O1 hydrogen bond.

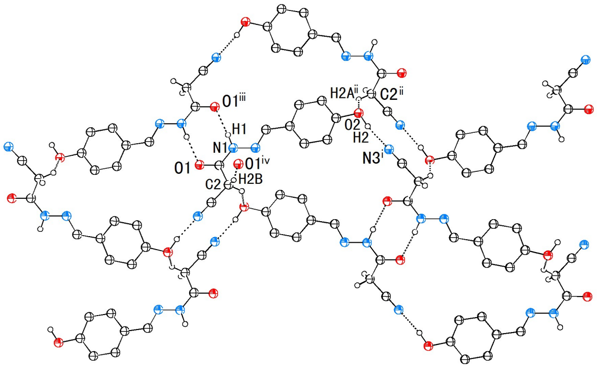

Fig. 7 The part packing diagram of 1, showing formation of a (-301) sheet. Symmetry codes: (i) -3/2+x, 3/2-y, -1/2+z; (ii) 1/2-x, -1/2+y, 3/2-z; (iii) 2-x, 1-y, 2-z; (iv) -1+x, y, z.

In conclusion, the work has revealed an interesting σ-Hole C=N…C–X conformation lock existing universally in N'-[(1E)-phenylmethylidene]acetohydrazides. Ab initio calculations

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provided effective support to the interaction; second-order perturbation theory analysis of the Fock Matrix on the NBO basis has confirmed that the conformation lock is in nature intramolecular charge transfer from the C=N lone pair into the σ*(C—X) antibonding orbital. We believe that the present work may be the first study on conformation effect of C=N…C–X σ-Hole interaction.

Experimental

Synthesis of 1 and **9**.

To a solution of ethyl cyanoacetate (0.2 mol) in anhydrous ethanol (50mL), were added hydrazine (80%, 0.25 mol), the reaction mixture was stirred at room temperature. The precipitate was filtered off, washed with anhydrous ethanol and dried to give pure cyanoacetohydrazide (12 g). As intermediate, cyanoacetohydrazide (0.1 mol) was dissolved in anhydrous ethanol (50 mL), and then 4-hydroxy or 2-hydroxybenzaldehyde (0.1 mol) was added. The reaction mixture was refluxed for 20 min, and then cooled to room temperature. The solid was collected by filtration, washed with ethanol, and dried to yield the compound **1** or **9** (15 g) as a crystalline solid. Crystals **1** and **9** suitable for an X-ray analysis were obtained by slow cooling of a hot acetonitrile solution of the corresponding product.

Crystal data of compounds 1 and 9

1: $C_{10}H_9N_3O_2$, M = 203.20, Monoclinic, P21/n, a = 4.7366(4), b = 11.1769(10), c = 18.9660(18) Å , α = 90, β = 97.015(2), γ = 90°, V = 996.55(15) Å^3, Z = 4, T = 296(2) K, Dc = 1.354 g.cm^{-3}; 5454 reflections collected, 1767 unique (Rint = 0.026), 1289 observed with $I > 2\sigma(I)$; final R = 0.0345, wR2 = 0.0866, goodness-of-fit S = 1.01.

9: $C_{10}H_9N_3O_2$, M = 203.20, Monoclinic, P21/n, a = 4.5944(3), b = 9.3525(4), c = 22.972(3) Å , α = 90, β = 94.883(2), γ = 90°, V = 983.50(15) Å^3, Z = 4, T = 296(2) K, Dc = 1.372 g.cm^{-3}; 14740 reflections collected, 2971 unique (Rint = 0.035), 1796 observed with $I > 2\sigma(I)$; final R = 0.0496, wR2 = 0.1400, goodness-of-fit S = 1.01.

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Table of contents entry

The C=N…C—X σ-hole interaction determines the linear alignment of the cyanomethyl or halogenmethyl group to the imino unit.