

## Conformation and the Unique H-Bond of 2-(N,N-dimethylamino) Benzoic Acid in Gas Phase

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**Summary:** Only a few examples on strong neutral hydrogen bonds are known in the chemical literature. This computational organic chemistry study illustrates that the most stable conformer of the title amino acid in gas phase is (I). The conformational analysis of (I) around the O1-C1 bond leads to destabilizing the structure due to breaking the N H1-O1 hydrogen bond. However, this could not be used to estimate the hydrogen bond strength due to an unexpected interfering destabilizing factor that could not be quantified. Therefore, the hydrogen bond strength was estimated using a simulation model and the second order perturbation analysis. The B3LYP and the MP2 calculations predict the hydrogen bond in the gas phase to be stronger than 10 kcal/mol, which allows classifying it as a strong neutral hydrogen bond. To the best of our knowledge, this is the strongest neutral H-bond encountered that it is not a resonance assisted H-bond (RAHB). From a fundamental point of view, this example is a new addition to the hydrogen bond theory.

Keywords: N, N-dimethylanthranilic acid, DFT, ab-initio, conformational analysis, NBO.

### Introduction

The H-bond is one of the essential concepts in science due to its valuable role in chemistry and biology, which makes it one of the enduring active research topics. The quantum chemical calculations indicate that the strongest neutral H-bond can be found in the derivatives of malondialdehyde (12.4 kcal/mol) [1] and acetylacetone (12.0 kcal/mol) [2] (O...H-O hydrogen bonds), and the next strongest exists in Schiff bases derived from naphthaldehyde [3]. This computational study shows that N,N-dimethyl anthranilic acid (2-(N,N-dimethylamino) benzoic acid) is another unique example that incorporates within its structure a strong neutral H-bond.

The structure of the N,N-dimethyl anthranilic acid was studied by Dhaneshwar and Pant [4] using the X-ray crystallography. The analysis indicates that the acid exists in the solid state as the zwitterion form. The infrared analysis study carried out by Jose and coworkers [5-7] also supported this result, and they further proposed a neutral form in solution. The gas phase infrared spectrum of the acid, which is presented on the NIST website, shows a strong signal at nearly 1780 cm<sup>-1</sup> which is solid evidence that the compound exists in the gaseous state as the neutral molecule [8-11]. Other than these experimental studies, there has been virtually no theoretical treatment of the electronic structure characteristics, which is the subject of this study.

### Results and Discussion

#### *The Relative Stability of the Optimized Conformers*

Table-1 presents the energy calculations for the three conformers (Fig. 1). Entry 1 contains the

energies calculated based on the B3LYP/6-31G(d) method. The entries 2 and 3 include the energies that were obtained from single point calculations based on the previous geometries using the B3LYP/6-311+G(2d,p) and the MP2/6-311+G(2d,p) methods. The values within the brackets are the relative energies (kcal/mol) calculated with respect to conformer (I). All the calculations indicate that the order of the stability is (I)>(III)>(II), which is different from what is known about the unmethylated anthranilic acid (III>II>I) [12-15]. This new trend of the stability is attributed to the steric hindrance that results from the methyl groups and to the absence of the N-H1...O2 hydrogen bond (in anthranilic acid). But, why is conformer (III) slightly more stable than conformer (II)? The answer is hidden in the values of the intramolecular distances. The distance between the N atom and O2 in (III) (2.918 Å) is greater than the distance between N and O1 in (II) (2.822 Å) which implies that the electrostatic repulsion between N and O (two negatively charged atoms) should be less in (III). On the other hand, the distance between N and O1 in (I) is even less (2.641 Å) but in this case, the molecular stability is favored by the hydrogen bond (N H1-O1).

Table-1: The energies (Hartree) and the relative energies (between two brackets in kcal/mol).

Entry	Method	(I)	(II)	(III)
1	6-31G(d) <sup>a</sup>	-554.785536 (0.00)	-554.778574 (4.37)	-554.779802 (3.60)
2	6-311+G(2d,p) <sup>b</sup>	-554.960287 (0.00)	-554.953765 (4.09)	-554.955252 (3.16)
3	6-311+G(2d,p) <sup>c</sup>	-553.496963 (0.00)	-553.487757 (5.78)	-553.488706 (5.18)

<sup>a</sup>B3LYP/6-31G(d).

<sup>b</sup>B3LYP/6-311+G(2d,p)// B3LYP/6-31G(d).

<sup>c</sup>MP2/6-311+G(2d,p)// B3LYP/6-31G(d).

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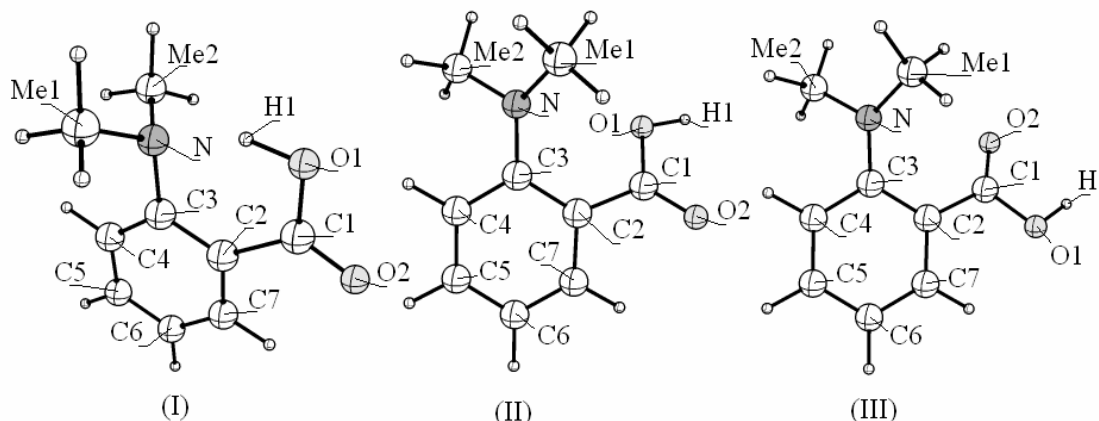


Fig. 1: The optimized structures of the three conformers.

#### The Conformational Analysis Around the C1-O1 Bond in (I)

A very general challenge in the study of intramolecular hydrogen bonds is quantifying the energy of the interaction. In intermolecular hydrogen bond molecular systems, the reference states are the separated components of the H-bond complexes [16]. In the cases of the structures that include intramolecular hydrogen bonds, this approach is unsuitable. Woodford [17] presented various descriptors of intramolecular hydrogen bonds. An acceptable strategy [18-22] compares the H-bonded structure with an open conformation, where the intramolecular hydrogen bond is broken.

In this regard, it was suggested to calculate the energy difference between conformer (I) and its rotamer that results from rotating the O1-C1 bond 180° (the new dihedral angle H1-O1-C1-C2= 180°) (Fig. 2). Initially, and in order to confirm that there is no other interfering interaction at this dihedral angle, this required measuring single point energy every 10°, and the results are presented in Table-2. Due to the molecular symmetry in conformer (I), the energy differences ( $\Delta E$ ) for the angle range 0°-180° were considered the same as that for the 190°-360° range and the results from the B3LYP/6-31G(d) calculations are presented in Fig. 3. It was expected that the point of the highest energy difference will appear at 180°, but, the data indicates that there is a stabilizing factor interfering after the 90° angle, which can only be the electrostatic interaction between H1 and O2 (Fig. 3). In addition to this, the values at the 90° angle are too high to describe a neutral hydrogen bond and it seems that there is an interfering destabilizing electronic factor, which is explained as an electrostatic repulsion between the

oxygen and the nitrogen lone pairs. Moreover, the curve that results for the 0°-90° angles is smooth and can not be decomposed to calculate the hydrogen bond energy. In this case, the other solution for estimating the hydrogen bond strength is the simulation model described in the next section.

(1) Changing the angle from 0-180°

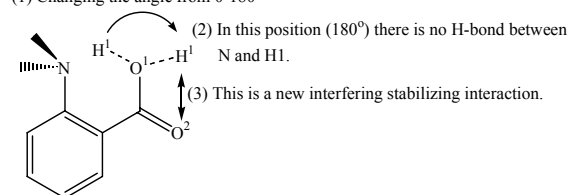


Fig. 2: The conformational analysis around O1-C1.

Table-2: The angle and the energy changes (kcal/mol) with respect to conformer (I).

Angle	$\Delta E^a$	$\Delta E^b$	$\Delta E^c$	Angle	$\Delta E^a$	$\Delta E^b$	$\Delta E^c$
0	0.00	0.00	0.00	100	24.11	23.55	24.76
10	1.11	1.23	1.27	110	22.99	22.38	23.67
20	4.10	4.44	4.59	120	21.07	20.51	21.84
30	8.13	8.60	8.90	130	18.64	18.18	19.52
40	12.31	12.77	13.21	140	15.99	15.72	17.02
50	16.10	16.42	17.01	150	13.49	13.41	14.65
60	19.31	19.39	20.13	160	11.44	11.53	12.72
70	21.81	21.66	22.55	170	10.11	10.32	11.45
80	23.50	23.16	24.19	180	9.65	9.90	11.02
90	24.29	23.82	24.94				

<sup>a</sup>B3LYP/6-31G(d).

<sup>b</sup>B3LYP/6-311+G(2d,p)// B3LYP/6-31G(d).

<sup>c</sup>MP2/6-311+G(2d,p)// B3LYP/6-31G(d).

#### Conformation of a Simulation Model and the Estimated H-bond

The structure in Fig. 4 was used to simulate the hydrogen bond strength in (I) based on the described equilibrium process. The direct relationship between the hydrogen bond strength and the charge

delocalization energy (M-1) allows estimation of the hydrogen bond strength for conformer (I).

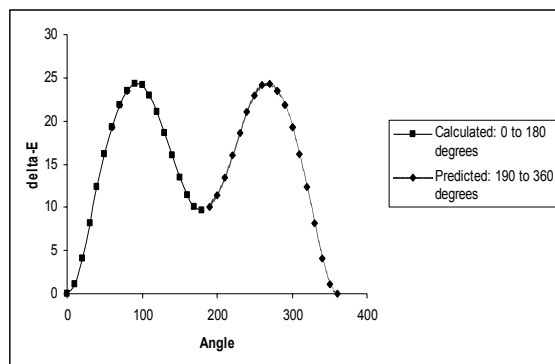


Fig. 3: A diagram presenting the relation between the H1-O1-C1-C2 dihedral angle (degrees) and the energy difference ( $\Delta E$ , Table-2) based on B3LYP/6-31G (d).

The second-order perturbation analysis (SOP) in this study provides with important evidence that the hydrogen bonding in conformer (I) is not a pure electrostatic interaction [23] but also includes electron density delocalization as presented in Table-3, which indicates that the N...H1-O1 interaction is strong and has covalent nature [24-26]. The estimated hydrogen bond energies of conformer (I) are similar to these calculated for malondialdehyde (12.4 kcal/mol) [1] and acetylacetone (12.0 kcal/mol) [2] and are slightly stronger than Schiff bases derived from 2-hydroxy-1-naphthaldehyde [3]. Based on the energy criteria discussed by Gilli [3], the hydrogen bond strength in conformer (I) is described as both strong and neutral hydrogen bond. In comparison with the previously known neutral H-bond systems, we attribute this unusually strong interaction to the unique molecular architecture of anthranilic acid which is essentially explained by two factors. The first is the original acidity of the carboxylic acid group which includes the highly polarized H-O bond. The second factor is the presence of the acidic hydrogen (H1-O1) in a close proximity to the basic tertiary nitrogen in a six-membered ring hydrogen-bond-based cycle.

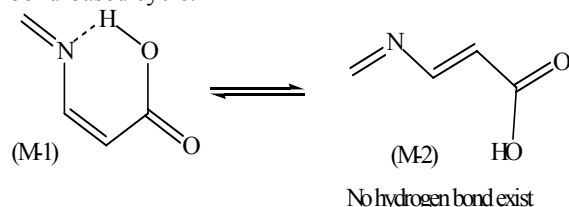


Fig. 4: A model used to simulate the hydrogen bond in conformer (I).

Table-3: The hydrogen bond strength (E) and the charge delocalization energies (CDE) (kcal/mol) in (M-1). Then, the charge delocalization energy and the estimated hydrogen bond in (I);  $E(I) = [CDE(I) \times E(M-1)] / CDE(M-1)$ .

Structure	6-31G(d) <sup>a</sup>	6-311+G(2d,p) <sup>b</sup>	6-311+G(2d,p) <sup>c</sup>
E (M-1)	7.73	6.74	7.03
CDE (M-1)	21.30	16.22	18.04
CDE (I)	31.85	25.66	32.09
E (I)	11.56	10.66	12.51

<sup>a</sup> B3LYP/6-31G(d).

<sup>b</sup> B3LYP/6-311+G(2d,p)// B3LYP/6-31G(d).

<sup>c</sup> MP2/6-311+G(2d,p)// B3LYP/6-31G(d).

## Experimental

All the calculations were performed using the Gaussian 03 suite of programs [27]. The geometries were optimized using the B3LYP/6-31G(d) method. The harmonic oscillator measure of aromaticity (HOMA) was calculated as described by Krygowski [28]. When its value is equal to 1 it means that the  $\pi$ -system is overlapping ideally, but when the value is equal to zero it means that the p-orbitals are not overlapping and the double bonds (and may be a conjugated lone pair) are fully localized. Using benzene as a reference, the 6-31G(d) basis set can produce a HOMA value equal to 0.979, which is very close to the ideal value (HOMA= 1). Taking into consideration the computer time and the obtained result, this makes the method suitable for qualitative analyses, which was the reason behind choosing it. Therefore, using more time consuming methods like B3LYP/6-311+G(2d,p) (HOMA= 0.996) and MP2/6-311+G(2d,p) (HOMA= 0.987) is not necessary. However, they were used to refine the energy as single point calculations. The calculated frequencies obtained are positive values which confirm that all the structures are true minima. The second order perturbation (SOP) calculations were executed using the standard NBO method [29]. The graphic interface ChemCraft was used through all the calculations.

## Conclusion

The calculations based on B3LYP/6-31G(d), B3LYP/6-311+G(2d,p)// B3LYP/6-31G(d), and MP2/6-311+G(2d,p)//B3LYP/6-31G(d) produced a homogeneous and a well-connected sets of data. The stability of conformer (I) over (II) and (III) is attributed to the H-bond that is absent in (II) and (III). Due to the structural nature of N,N-dimethyl-anthranilic acid, the conformational analysis could not be used directly to estimate the hydrogen bond strength, however, it provided with a further illumination into the importance of the H-bond in (I) in stabilizing the molecular electronic structure by moderating the electrostatic repulsion between the nitrogen and the carboxylate oxygen. Therefore, it was necessary to simulate the H-bond using a simpler

model with the aid of the second order perturbation analysis. The data indicate that the N...H1-O1 hydrogen bond is the strongest neutral H-bond that does not derive its strength from resonance, which is attributed to the unique molecular architecture of the amino acid.

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