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Theoretical Study of Tautomerism of N-(Pyridine-2yl)Acetamide by Density Functional Theory(DFT)

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ABSTRACT

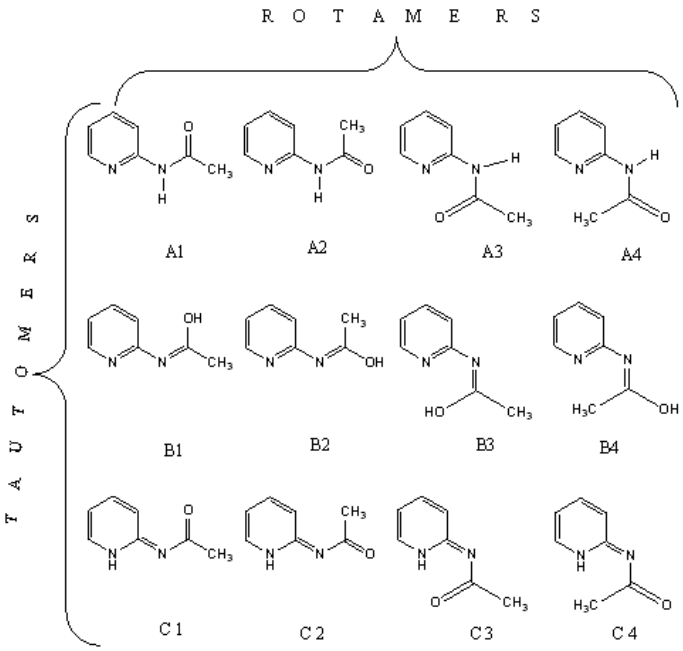
The geometries of various rotamers, tautomers and isomers of N-(pyridine -2yl)acetamide have been studied using the density functional theory (DFT) method at the level of B3LYP employing 6-311++G(d,p) basis set. We report the enthalpies, Gibbs free energy, entropy, relative stability and tautomeric equilibrium constants for the title compound isomers at 298.15 K in gas phase. The most stable A4 is taken as reference to obtain the relative energetic stability of other rotamers. Calculated values for the equilibrium between these some tautomers show that pK_T value is negative values. If the pK_T was positive, equilibrium moved from right towards the lift and when it was negative, equilibrium moved from left towards the right.

Introduction

The hindered rotation around an amide CAN bond is one of the well-known and carefully studied phenomena in organic chemistry [1–3]. The partial double bond character of the CAN bond arises through conjugation of the lone pair at the N-center with the carbonyl moiety. This leads to planarity at the amide nitrogen center and an unusually high, for a formal single bond, rotation barrier, which causes the generation of distinct s-E and s-Z isomers, often detectable through their separate sets of signals in NMR spectra. Similar features have been observed in other, related structures, such as carbamates [4–8] and ureas [9–12], which have also become subject of considerable interest. Carbamoyl chlorides, on the other hand, have received less attention [13–16], even though they are common precursors in the preparation of both carbamates and ureas. However, as a class of compounds, they have not been the subject of any theoretical studies.

The present work reports the results of a systematic theoretical examination of N-(pyridine -2yl)acetamide of tautomers. N-(pyridine-2-yl)acetamide can theoretically exist in three tautomeric structures, each of which can exit in four preferred rotameric forms: (i) the acaylamino form A (rotamers: A1, A2, A3 and A4); (ii) the hydroxyimino form B(rotamers: B1, B2, B3 and B4) and (iii) the acylimino form C(rotamers: C1, C2, C3 and C4) (seheme1). In this work, density functional theory (DFT) calculations have been carried out at the B3LYP/6-311++G (d,p) level of theory. Hence we undertook a theoretical study on a class of structures A, B and C rotamers and tautomers to achieve the following:

1. Optimize the rotamers arising through rotation around the C(=O)-N bond and calculate the corresponding gas-phase equilibrium constants
2. Optimize the tautomers arising through the proton transfer from the amino to the keto group of oxygen atom and calculate the corresponding gas-phase equilibrium constants.
3. To calculate the amino ↔ imino tautomeric (hydroxyimino form B to acylimino form C) equilibrium constants. In addition to calculate the equilibrium constants of geometrical isomers of Z and E forms of hydroxyimino tautomers and acylimino tautomers.(see scheme 1)



Scheme: 1. Possible tautomeric forms of N-(pyridin-2-yl)acetamide { A1 ,A2, A3 and A4 =N-(pyridin-2-yl)acetamide; B1 and B3 = (Z)-N-(pyridin-2-yl)acetamidic acid; B2 and B4 = (E)-N- (pyridin-2-yl)acetamidic acid ; C1 and C2= (6E)-N-(pyridine-2(H)-ylidene)acetamide ;C3 and C4 = (6Z)-N-(pyridine-2(H)-ylidene)acetamide}

In the present paper, we report the entropy, Gibbs free energy, relative stability and tautomeric equilibrium constants for the title compound isomers at 298.15 K in gas phase. After having predicted the relative stability of tautomers, we have found the tautomeric equilibrium constants with respect to the more stable tautomers of the acaylamino form A, the hydroxyimino form B and the acylimino form C in the gas phase.

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Table 1. The relative energies and thermodynamic properties of N-(pyridin-2-yl)acetamide tautomers at DFT/6-311++G(d,p) level. The relative energies and thermodynamic properties compared to the most stable isomer A4 and the energies in brackets in kcal mol^{-1}

Tautomers	Energy(E) (a.u)	Enthalpy(H) (a.u)	Free energy(G) (a.u)	Entropy(S) cal mol^{-1}
A1	-472.502993 (2.69)	-472.360847 (-2.83)	-472.404423 (-2.91)	91.713
A2	-472.498358 (5.60)	-472.356138 (-5.79)	-472.399496 (-6.00)	91.255
A3	-472.490350 (10.62)	-472.348663 (-10.48)	-472.392634 (-10.31)	92.544
A4	-472.507276 (0.00)	-472.365361 (0.00)	-472.409061 (0.00)	91.974
B1	-472.465841 (26.00)	-472.324574 (-25.59)	-472.368232 (-25.62)	91.888
B2	-472.474098 (20.82)	-472.332924 (-20.35)	-472.375740 (-20.91)	90.114
B3	-472.464980 (26.54)	-472.323625 (-26.19)	-472.367491 (-26.09)	92.324
B4	-472.487749 (12.25)	-472.346377 (-11.91)	-472.389686 (-12.16)	91.152
C1	-472.487203 (12.60)	-472.345129 (-12.70)	-472.389073 (-12.54)	92.487
C2	-472.487203 (12.60)	-472.345126 (-12.70)	-472.389062 (-12.55)	92.471
C3	-472.497570 (6.09)	-472.356973 (-5.26)	-472.398846 (-6.41)	88.130
C4	-472.497580 (6.08)	-472.356007 (-5.87)	-472.399054 (-6.28)	90.601

Table 2. Calculated Enthalpy change (ΔH), Free Energy change (ΔG), Entropy change (ΔS) and equilibrium constants (Keq) and pK_T for N-(pyridin-2-yl)acetamide DFT/6-311++G (d,p) level for all tautomers

equilibrium	ΔE (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)	ΔS (cal/mol K)	K	pKT
rotamers						
A4 ↔ A1	2.6861	2.8310	2.9087	-0.261	0.0073	2.1323
A4 ↔ A2	5.5929	5.7842	5.9987	-0.719	3.9968x10^{-5}	4.3976
A4 ↔ A3	10.6133	10.4722	10.3022	0.57	2.7948 x10^{-8}	7.5524
B4 ↔ B1	13.7396	13.6738	13.4549	0.736	1.3638 x10^{-10}	9.8636
B4 ↔ B2	8.5612	8.4370	8.7462	-1.038	3.8657 x10^{-7}	6.4117
B4 ↔ B3	14.2796	14.2689	13.9196	1.172	6.2238 x10^{-11}	10.2042
C4 ↔ C1	6.5079	6.8221	6.2596	1.886	2.5728 x10^{-5}	4.5888
C4 ↔ C2	6.5079	6.8240	6.2665	1.87	2.5430 x10^{-5}	4.5939
C4 ↔ C3	0.0063	-0.6058	0.1304	-2.471	0.8024	0.0956
Tautomers						
A1 ↔ B1	23.3133	22.7617	22.7102	0.175	2.2321 x10^{-17}	16.6485
A2 ↔ B2	15.2234	14.5670	14.9071	-1.141	1.1749 x10^{-11}	10.9282
A3 ↔ B3	15.9218	15.7116	15.7775	-0.22	2.7029 x10^{-12}	11.5662
A4 ↔ B4	12.2534	11.9126	12.1580	-0.822	1.2180 x10^{-9}	8.9128
B1 ↔ C1	-13.4049	-12.8985	-13.0779	0.599	387974494	-9.5872
B2 ↔ C2	-8.2235	-7.6569	-8.3597	2.357	134706.237	-6.1284
B3 ↔ C3	-20.4506	-20.9262	-19.6756	-4.194	2.6685 x10^{14}	-14.4239
B4 ↔ C4	-6.1691	-6.0429	-5.8785	-0.551	20424.6717	-4.3094
A1 ↔ C1	9.9084	9.8632	9.6323	0.774	8.6603 x10^{-8}	7.0613
A2 ↔ C2	6.9999	6.9101	6.5474	1.216	1.5827 x10^{-5}	4.7998
A3 ↔ C3	-4.5287	-5.2146	-3.8981	-4.414	721.2946	-2.8576
A4 ↔ C4	6.0843	5.8697	6.2795	-1.373	2.4878 x10^{-5}	4.6034
Geometrical isomerism(E-Z)						
B1(Z) ↔ B2(E)	-5.18	-5.24	-4.71	-1.774	2.8405 x10^{3}	-3.4528
C3(Z) ↔ C1(E)	6.51	7.43	6.13	4.357	3.2076 x10^{-5}	4.4938

Computational methods

Density functional theory calculations are thus an attractive source of new and precise molecular descriptors, which can, in principle, express all the electronic and geometric properties of molecules and their interactions. So, in this work, because of the considerably large size of the studied molecules, density functional theory (DFT) method at the level of B3LYP employing 6-311++G(d,p) basis set was performed to complete geometrical optimization.

The geometries of all tautomers investigated (scheme 1) were completely optimized with the Gaussian 09 [17] program and visualized with the GaussView V. 3.09 [18] packages. Following the geometry optimizations, analytical frequency calculations were proceeded at the DFT/6-311++G (d,p) level, using following standard procedures, to obtain the thermochemical properties. All geometries were assumed as C1 point group with no special symmetry constrain imposed.

Results and Discussion

Energies and Relative Stability

The relative stabilities, enthalpies Gibbs free energies and entropies for the tautomers of N-(pyridin-2-yl)acetamide are given in Table 1, among the 12 tautomers, four are (rotamers: A1 ,A2, A3 and A4) the caylamino form A, four are (rotamers: B1,B2,B3 and B4) the hydroxyimino form B and four are (C1,C2,C3 andC4) the acylimino form C. The most stable A4 is taken as reference to obtain the relative energetic stability of other tautomers. It can be seen from the results that among three rotamers of the hydroxyimino form B (B1, B2 and B3) have highest energy, with relative energy about 20-27 kcal mol^{-1}, because of the possibility of migration of hydrogen atoms. According to relative energy the order of stability is A4 > A1 > A2 > C4 ≈ C3 > A3 > B4 > C1 = C2 > B2 > B1 > B3.

Tautomeric equilibrium constants

Rotamers equilibrium constants

In order to confirm the predominance of one tautomeric form to another, we have considered the three tautomeric equilibria, (i) rotamers equilibrium constants: between the rotamers of all three forms (A, B and C forms) with respect to their stable isomer (ii) the acaylamino form A to the hydroxyimino form B and similarly acaylamino form A to the acylimino form C of all rotamers and (iii) geometrical isomerism (E-Z) (see seheme1).

The B3LYP/6-311++G(d,p) calculated tautomeric equilibrium constants with respect to the most stable tautomers of the acaylamino form A, the hydroxyimino form B and the acylimino form C in the gas are listed in Table 2. The tautomeric equilibrium between tautomers a and b is described as

$$a \underset{\longleftarrow}{\overset{K_T}{\longrightarrow}} b \qquad (3)$$

Equilibrium constants for each species were calculated by using the following equation

$$K_T = e^{-(\Delta G/RT)} \qquad (4)$$

where K_T is the tautomeric equilibrium constant between the tautomers, the gas constant R is 1:987 $x10^{-3}$ kcal/mol; and the temperature T is 298.15 K. The quantity ΔG is the difference between the Gibbs free energies of the given tautomer with respect to the most stable one, $\Delta G = \Delta G_{(b)} - \Delta G_{(a)}$; $\Delta G_{(a)}$ and $\Delta G_{(b)}$ are Gibbs free energies of each tautomer (a or b) and they are given in Table 2. If the enthalpy and entropy terms are known we can calculate the Gibbs free energy of each molecule, ΔG and K_T value. The Gibbs free energy of each tautomer at a given temperature T can be expressed as

$$\Delta G_{(i)} = \Delta H_{(i)} - T\Delta S_{(i)} \qquad (5)$$

where i = a, b. The differences in enthalpy ΔH, entropy ΔS and free energy ΔG between the two tautomeric species was determined from the temperature dependence of K_T

$$\Delta G = - RT \ln K_T \qquad (6)$$

The pK_T values of the studied molecules were calculated by means of the following equation

$$pK_T = \frac{\Delta G}{2.303RT} \qquad (7)$$

From table 2, the calculated values for the equilibrium between the rotamers A4 and A1 of acaylamino form show that the rotamer A4 is more dominant than the rotamer A1, with a pK_T value of 0.0073. The rotamer A4 is also a more dominant rotamer than the rotamers of A2 and A3 and the order of the stability of acaylamino form rotamers is 4 > 1 > 2 > 3. Predicted equilibrium constants for the hydroxyimino form B rotamers equlibria B4 and B2 show that the rotamer B4 is more dominant than the rotamer B2, with a pK_T value of 6.4117. The rotamer B4 is also a more dominant rotamer than the rotamers of B1 and B3. Rotamer B3 is not present in detectable amounts. The order of the stability of acaylamino form rotamers is 4 > 2 > 1. Calculations also show that the rotamers of acylimino form C, the equlibria between C4 and C3 show that the form rotamer C4 is more dominant than the rotamer C3, with a pK_T value of 0.0956. The rotamer C4 is also a more dominant rotamer than the rotamers of C1 and C2 and the order of the stability of acaylamino form rotamers is 4 > 3 > 1 > 2.

Equlibria between acaylamino form, hydroxyimino form and acylimino form

The calculated tautomeric enthalpies, Gibbs energies, and equilibrium constants for the amino↔ imino tautomerization reactions in gas phase are shown in Table 2. Calculated values for the equilibrium between the tautomers of acaylamino form A (rotamers) and hydroxyimino form B (rotamers) show that the A4 is more dominant than the B4, with pK_T value of 8.9128. The remaining equlibria between A1↔B1, A2↔B2 and A3↔B3 are not present in detectable amounts. In the case of the equlibria between hydroxyimino form (B) and acylimino form (C) are different from between acaylamino form (A) and hydroxyimino form (B) tautomers. Calculated values for the equilibrium between these tautomers show that with pK_T value are negative values. If the pK_T was positive, equilibrium moved from right towards the lift and when it was negative, equilibrium moved from left towards the right.

For the equilibrium between acaylamino form (A) and acylimino form (B) tautomers, some *pKT* were positive and other one negative; that determine the privileged direction of equilibrium (Table 2).

Geometrical isomerism (E-Z)

Hydroxyimino form (B) and acylimino form (C) tautomers N-(pyridin-2-yl)acetamide may exist as two geometrical isomers with respect to the alkyl group [B1 and B3 = (Z)-N-(pyridin-2-yl)acetamidic acid; B2 and B4 = (E)-N- (pyridin-2-yl)acetamidic acid ; C1 and C2= (6E)-N-(pyridine-2(H)-ylidene)acetamide ; C3 and C4 = (6Z)-N-(pyridine-2(H)-ylidene)acetamide; Scheme 1] . The calculated tautomeric enthalpies, Gibbs energies, and equilibrium constants for the E - Z geometrical isomerism reactions in gas phase are shown in Table 2. The (*Z*) isomers have been computed to be the most stable species, which is apparently due to the absence of intramolecular repulsion between hydrogen atoms of the N atom and hydrogens of the methyl in these isomers. The larger difference in the $Z \leftrightarrow E$ isomerization Gibbs energies were found with acylimino form (C) tautomers.

Conclusions

For N-(pyridin-2-yl)acetamide, tautomerization in gas was studied using DFT at the B3LYP/6- 311++G (d,p) basis set. In this work we calculated relative stability, the constants of equilibrium for different rotamers and tautomers of N-(pyridin-2-yl)acetamide. According to our calculations, the most stable form is A4 rotamer. According to relative energy the order of stability is A4 > A1 > A2 > C4 ≈ C3 > A3 > B4 > C1 = C2 > B2 > B1 > B3.

From equilibrium constant values, some pK_T were positive and other negative; that determine the privileged direction of equilibrium. If the pK_T was positive, equilibrium moved from right towards the lift and when it was negative, equilibrium moved from left towards the right.

For the E - Z geometrical isomerism reaction, the larger difference in the $Z \leftrightarrow E$ isomerization Gibbs energies were found with acylimino form (C) tautomers.

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