Theoretical Study of the Effect of Different α-Substituents on the Acetaldimine-Vinylamine Tautomeric System

Hamzeh S. M. Al-Omari

Chemistry department, College of Science, University of Mutah, Karak, Jordan

Reprint requests to Dr. H. A.-O.; e-mail: hamzehs@mutah.edu.jo

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The Acetaldimine-Vinylamine tautomeric system has been studied by employing the MNDO semi-empirical method. The imine structure was found to be energetically favorable, as indicated by the calculated heats of formation, Gibbs free energy, LUMO and HOMO, and charges. The substitution of F, Cl, CN, CH_3, CF_3, NO_2 and BH_2 at the α-position was found to affect the geometrical parameters. F and Cl substituents are found to favor the imine formation, while CF_3, NO_2, CN_2 and BH_2 favor the amine formation. The proton transfer in this tautomeric system is found to be easier ($\Delta H =$ 5.224 kcal/mol) than that in the keto-enol tautomeric system ($\Delta H = 11.1$ kcal/mol).

Key words: Imine-enamine; Tautomerization; Acetaldimine; Vinylamine; MNDO.

1. Introduction

Tautomerism is a fundamental process in many organic systems; it involves inter-conversion between two chemically related structures through a proton transfer. One of these structures usually predominates the other, depending on many factors. Imine/enamine and keto/enol systems are famous examples on tautomerism. Many theoretical studies that are related to these and other systems are available in [1 – 7].

An extensive theoretical work has been made on the imine/enamine tautomeric system employing different levels of theory, the results of which emphasize the extra stability of the imine over the enamine system [1, 8].

The energy difference between the parent acetaldimine **1** and vinylamine **1a** tautomers depends strongly on the employed level of theory. For example, Smith and Radom [9] reported an energy difference of 4.31 kcal/mol (18 kJ/mol) at MP4/6-311G**//HF/6-31+G* in favor of the imine **1**, which reduces to 2.0 kcal/mol at C1SD/6-31G* [10], while vinylamine **1a** is the more stable form at HF/4-31G [11]. An experimental difference in the heat of formation of 2 kcal/mol is reported by Fraser and Banville [12]. However, this direction of stability can be reversed to obtain a more stable enamine **1a** by the use of different substituents depending, on their electronic nature [13].

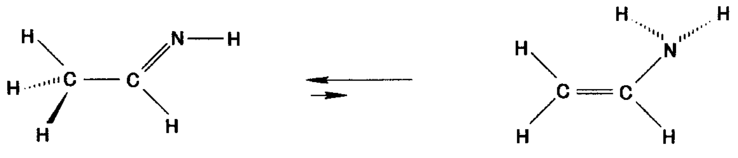
2. Results and Discussion

The calculated heats of formation of imine and enamine together with the geometrical parameters are given in Tables 1 and 2, respectively.

2.1. Parent Imine and it's Enamine Counterpart

2.1.1 Acetaldimine (imine) $CH_3CH=NH$

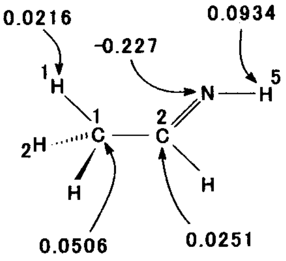
The anti conformer of acetaldimine **1** is found to be energetically the most stable one. It is found to be by 0.300 kcal/mol more stable than the other well-know syn conformer **1b**. Close analysis to the charges and distances in both of these two conformers signals higher repulsion between the H1 and H5 in the syn conformer **1b** that is due to the smaller H1-H5 distance (2.50 Å), where that distance in the case of the



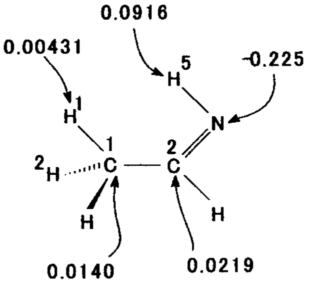
1 **1a**

Table 1. Calculated heats of formation, (ΔH_f) for the parent and substituted acetaldemines and their vinylamines, and the thermodynamic functions for tautomerization processes.

X	ΔH_f (kcal/mol) (Imine)	ΔH_f (kcal/mol) (Enamine)	$\Delta H_{reaction}$ (kcal/mol)	ΔS /mol·K)	ΔG (103kcal (kcal/mol)
H	8.911	14.135	5.224	−0.021	5.230
F	−35.445	−35.358	0.0871	0.266	0.00786
Cl	0.579	3.757	3.178	−0.022	3.185
CH_3	3.614	3.709	0.0952	1.059	−0.220
NO_2	27.011	25.221	−1.789	−0.813	−1.370
CN	42.857	41.117	−1.741	1.189	−2.095
BH_2	15.226	11.155	−4.071	−1.218	−4.434
CF_3	−138.892	−140.536	−1.644	0.743	−1.865



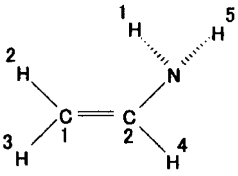
1
Anti



1b
Syn

anti conformer **1** is 3.62 Å. Also the attraction is higher between H1 and N in the anti conformer **1** due to it's smaller H1-N distance (2.62 Å) than that in the syn conformer **1b** 2.76 Å.

Most of the theoretical work emphasises that the anti conformer is more stable than the syn conformer. This is well-reviewed by Lammmertsma and Prasad [2]. However, Smith and Radom [9] have used the syn conformer in their calculations. Lammertsma and Prasad have found a difference of 0.9 kcal/mol at the MP4/6-311++G**//MP2/6-31G* level of calculation in favor of the anti acetaldemine conformer stability. Some other authors found a value of ca. 2 kcal/mol [12, 14, 15].



1a

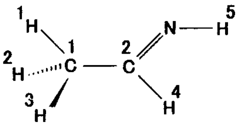
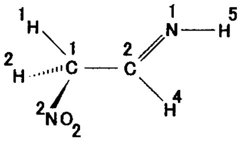
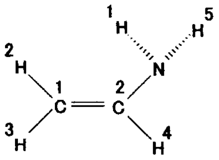
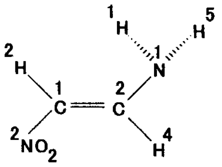
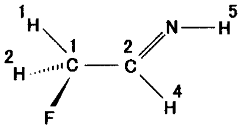
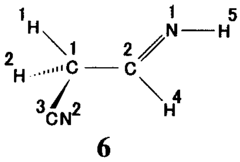
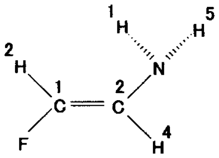
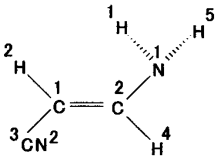
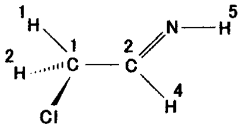
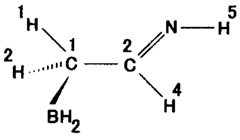
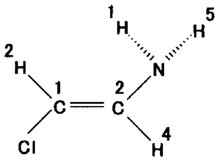
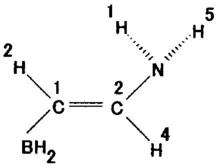
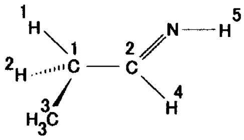
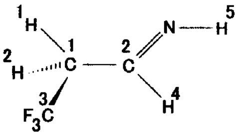
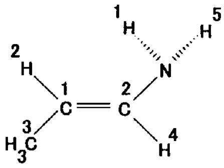
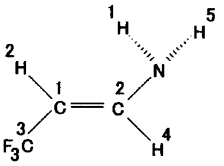
2.1.2 Vinylamine (CH_2=$CHNH_2$)

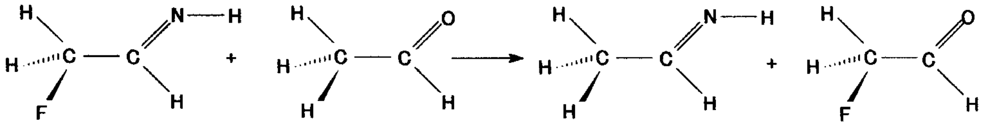
Several conformations of the enamine **1a** have been tested for their stability. It was found that the most stable conformer is the one where the H2, C1, C2, N, H3 and H4 atoms are located in one plane and H1 and H5 are located by 31 ° below that plane with pyramidal geometry (Table 2) around the nitrogen atom, which is consistent with the spectroscopic observations [16]. This structure is found to be by 0.057 kcal/mol more stable than the one where H5 and H1 are 17° below the plane, as found by Lammertsma and Prasad [1].

2.1.3 Acetaldimine-Vinylamine Tautomerization

The free energy change (ΔG) at constant temperature depends on two factors, the energy change (ΔH) and the entropy change (ΔS) through the relation ($\Delta G = \Delta H - T\Delta S$). Spontaneous processes are encouraged by a positive entropy change and negative energy change. In the imine/enamine tautomerism both of these factors are found to favor nonspontaneous processes or predominance of the imine over the enamine in the equilibrium. The small and negative entropy change ($-0.021 \cdot 10^{-3}$ kcal/mol.K) can't be overcome by a negative energy change, where the energy change was 5.224 kcal/mol, which makes ΔG positive and so the tautomarization process was non spontaneous. The free energy change (ΔG) as calculated at 298 K was found to be 5.230 kcal/mol. This could be attributed to the extra stability of the imine over enamine. This stability is indicated by the lower heat of formation of the imine (8.911 kcal/mol) relative to that of the enamine (14.135 kcal/mol), which means that the imine is 5.224 kcal/mol more stable than the enamine. Smith and Radom [9] have calculated an energy difference of 14 kJ/mol (3.3 kcal/mol) between the acetaldimine and vinylamine at 298 K at the MP4/6-311+G** level. Lias et al. [17] reported an experimental value of 21 kJ/mol (5.02 kcal/mol), which is near

Table 2. Optimized geometrical parameters (bond lengths in Å and bond angles in degrees) calculated by MNDO for the unsubstituted and substituted acetaldimines and their corresponding vinylamines.

 **1**	H1C1, 1.108; C1C2, 1.505; C2N, 1.287; NH5, 1.006; C2H4, 1.103. H1C1C2, 113.48; C1C2N, 121.51; C2NH5, 113.72; H4C2C1, 114.36; H3C1C2, 109.70.	 **5**	H1C1, 1.114; C1C2, 1.515; C2N1, 1.285; N1H5, 1.005; C2H4, 1.101. H1C1C2, 113.62; C1C2N1, 119.08; C2N1H5, 114.28; H4C2C1, 115.73; N2C1C2, 109.57.
 **1a**	H2C1, 1.088; C1C2, 1.346; C2N; 1.421; NH5, 1.008; C2H4, 1.098. H1C1C2, 124.90; C1C2N, 125.31; C2NH5, 110.40; H4C2C1, 120.97; H3C1C2, 121.37.	 **5a**	H2C1, 1.092; C1C2, 1.363; C2N1; 1.398; N1H5, 1.003; C2H4, 1.099. H2C1C2, 124.60; C1C2N1, 122.30; C2N1H5, 113.86; H4C2C1, 123.59; N2C1C2, 122.49.
 **2**	H1C1, 1.121; C1C2, 1.534; C2N, 1.284; NH5, 1.006; C2H4, 1.101. H1C1C2, 111.74; C1C2N, 119.64; C2NH5, 114.02; H4C2C1, 115.16; FC1C2, 111.44.	 **6**	H1C1, 1.12; C1C2, 1.517; C2N1, 1.286; N1H5, 1.006; C2H4, 1.102. H1C1C2, 112.05; C1C2N, 120.34; C2NH5, 113.94; H4C2C1, 114.81; C3C1C2, 111.81.
 **2a**	H2C1, 1.097; C1C2, 1.363; C2N; 1.417; NH5, 1.008; C2H4, 1.097. H1C1C2, 124.78; C1C2N, 122.96; C2NH5, 110.38; H4C2C1, 122.22; FC1C2, 121.49.	 **6a**	H2C1, 1.094; C1C2, 1.359; C2N1; 1.409; N1H5, 1.005; C2H4, 1.098. H2C1C2, 122.52; C1C2N1, 123.98; C2N1H5, 112.22; H4C2C1, 121.75; C3C1C2, 123.08.
 **3**	H1C1, 1.107; C1C2, 1.507; C2N, 1.286; C2H4, 1.101; NH5, 1.006. H1C1C2, 114.35; C1C2N, 120.04; C2NH5, 113.98; H4C2C1, 115.03; ClC1C2, 109.76.	 **7**	H1C1, 1.118; C1C2, 1.505; C2N, 1.287; NH5, 1.006; C2H4, 1.103. H1C1C2, 111.75; C1C2N, 121.19; C2NH5, 113.66; H4C2C1, 114.75; BC1C2, 116.89.
 **3a**	H2C1, 1.085; C1C2, 1.349; C2N; 1.416; NH5, 1.007; C2H4, 1.097. H1C1C2, 127.31; C1C2N, 123.52; C2NH5, 110.96; H4C2C1, 122.05; ClC1C2, 121.22.	 **7a**	H2C1, 1.097; C1C2, 1.366; C2N; 1.401; NH5, 1.003; C2H4, 1.100. H2C1C2, 119.48; C1C2N, 124.76; C2NH5, 113.87; H4C2C1, 121.53; BC1C2, 124.57.
 **4**	H1C1, 1.114; C1C2, 1.513; C2N, 1.287; NH5, 1.006; C2H4, 1.103. H1C1C2, 111.28; C1C2N, 121.10; C2NH5, 113.64; H4C2C1, 114.82; C3C1C2, 113.56.	 **8**	H1C1, 1.113; C1C2, 1.513; C2N, 1.286; NH5, 1.005; C2H4, 1.101. H1C1C2, 111.67; C1C2N, 119.82; C2NH5, 114.06; H4C2C1, 115.28; C3C1C2, 113.56.
 **4a**	H2C1, 1.095; C1C2, 1.352; C2N; 1.420; NH5, 1.007; C2H4, 1.098. H2C1C2, 121.03; C1C2N, 124.38; C2NH5, 110.64; H4C2C1, 121.98; C3C1C2, 125.37.	 **8a**	H2C1, 1.092; C1C2, 1.356; C2N; 1.404; NH5, 1.004; C2H4, 1.099. H2C1C2, 122.05; C1C2N, 123.49; C2NH5, 112.90; H4C2C1, 122.59; C3C1C2, 125.03.



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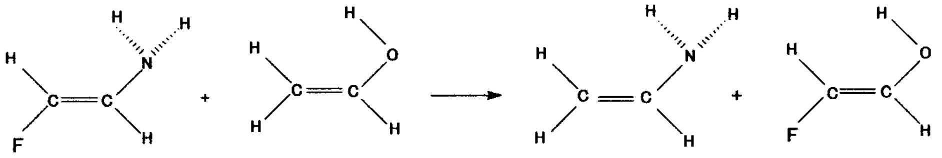
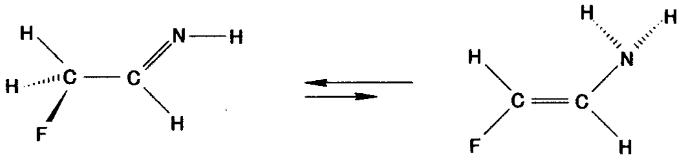
(1)



2a

(2)



2 **2a**

(3)

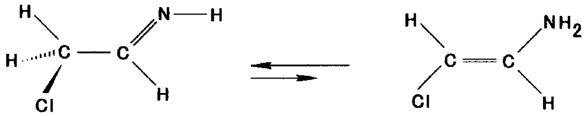
to the value obtained in this work (5.224 kcal/mol). This energy gap (5.224 kcal/mol) is smaller than that in the keto-enol system (11.1 kcal/mol) [13], suggesting that the functional group NH_2 of enamine is a better π-donor than the OH group in enols. Hence it reduces the energy difference from 11.1 kcal/mol to 5.224 kcal/mol. That is to say, tautomerization in the case of imine-enamine system takes place easier than that in the keto-enol system.

The energy gap E_g between the LUMO and HOMO for the imine tautomer (12.154 eV) is found to be greater than that of the enamine (10.392 eV), suggesting that the imine tautomer is electronically more stable than the enamine due to the larger E_g [18]. The small positive charge (0.02162) on H1 (compound 1) indicates that the imine is slightly acidic, but this would not be sufficient to drive the equilibrium in favor of enamine formation [19].

2.2. *Effect of Substituents*

The calculated heats of formation and the geometrical parameters of the substituents F, Cl, CH_3, OH, CN, CF_3, NO_2, and BH_2 are given in Tables 1 and 2, respectively. All substituents have some effects on the geometrical parameters, especially at the position where the substituent is attached. This agrees with previous results [19].

The changes on the rest of the molecule were minor or nil (Table 2).



3 **3a**

The stabilization effect of a substituted imine or enamine is evaluated by using the isodesmic reactions. Stabilization is indicated by a positive heat of reaction while a negative heat of reaction, indicates a destabilization of the reactant by the substituent [19, 20].

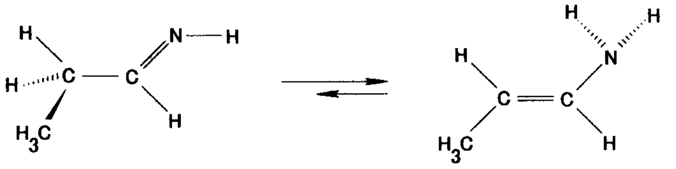
2.2.1 F and Cl Substituents

The calculated heat of formation of fluorine-substituted imine (−35.445 kcal/mol) (Table 1) is slightly less than that of enamine (−35.358 kcal/mol), suggesting a slight stabilization of the imine. This is also supported by the isodesmic reactions (1) and (2).

The calculated ΔH for the imine **2** (1) (0.645 kcal/mol) is more positive than that of the enamine **2a** (2) (0.358 kcal/mol), suggesting a slight stabilization of imine.

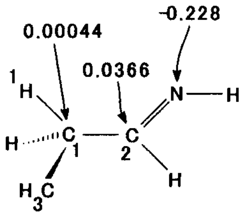
This slight stabilization in the case of F-substituted imine is also supported by a slight positive Gibbs free energy ($\Delta G = 0.00786$ kcal/mol), suggesting a very slightly nonspontaneous process (3)

For a Cl substituent, the stabilization of imine is more pronounced than for an F substituent. The difference in energy between imine **3** and enamine **3a**



4 **4a**

(4)



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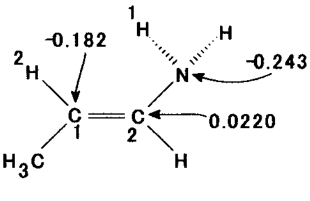
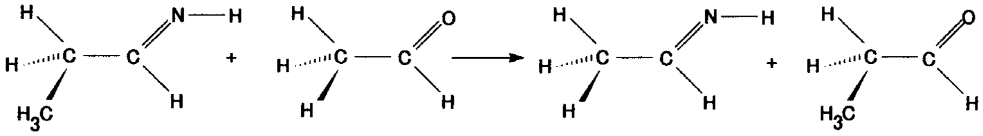


4a



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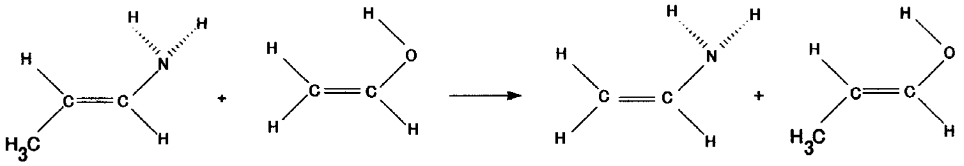
(5)



4a

(6)

(3.175 kcal/mol) suggests a stabilization of **3**. Also, the calculated ΔH for the isodesmic reaction of the imine **3** (1.029 kcal/mol) is more positive than that of the enamine **3a** (0.572 kcal/mol) suggesting a stabilization of imine. This is supported by the calculated Gibbs free energy ($\Delta G = 3.185$ kcal/mol), which indicates that imine **3** is more stable than enamine **3a**.

2.2.2. CH_3 Substituent

The energy difference between the CH_3 substituted imine **4** and enamine **4a** is small and positive (0.0952 kcal/mol, Table 1) but the entropy change was found to be positive ($\Delta S = 1.059$ cal/mol.K) which makes the free energy change for the tautomeric process negative ($\Delta G = -0.220$ kcal/mol) at room temperature. This makes the tautomerization process spontaneous (4).

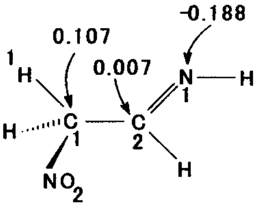
A close look at the charges indicates that the substituted enamine **4a** is more stable than the substituted imine **4** because of the relatively large electrostatic attraction between the charges on C1(−0.182) and C2(0.0220) in compound **4a** compared to the repulsion between the same carbons in compound **4**.

The isodesmic reactions (5) and (6) show that the CH_3-substituent destabilizes both the imine and enamine, both having negative values of ΔH, but it is more positive for the enamine **4a** ($\Delta H = -0.311$ kcal/mol) than that of imine **4** ($\Delta H = -0.376$ kcal/mol), suggesting a slight stabilization of enamine **4a**. This indicates a spontaneous process in (4) above.

2.2.3. NO_2, CN, BH_2, and CF_3 Substituents

These substituents show negative Gibbs free energies (Table 1), suggesting a destabilization of imine **1**. This destabilization is more pronounced in the case of CN and BH_2 substituents, which was mentioned in previous work [13].

The charge distribution may give an alternative explanation for the destabilization of the imine by the latter substituents.



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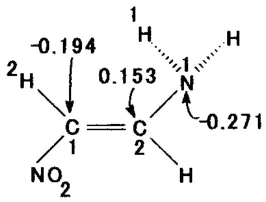
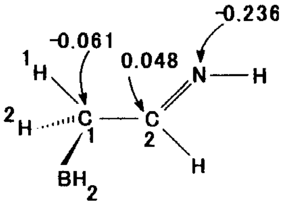
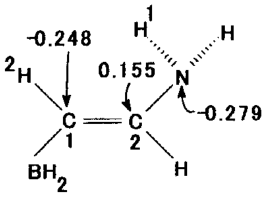


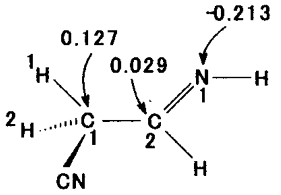
5a



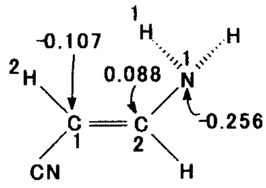
7



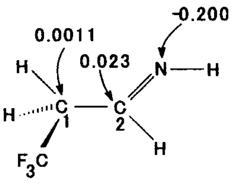
7a



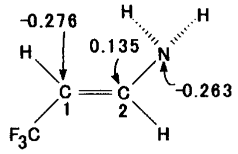
6



6a



8



8a

For the NO_2 substitutent (imine **5** and enamine **5a**), the electrostatic attraction between the positive charge on C2(0.007) and negative charge on N1(−0.188) in compound **5** is less than that in compound **5a**, and also the repulsion between the two positive carbons, C1 and C2 in compound **5**, while there is an electrostatic attraction between the same carbons in case of the enamine, **5**, suggesting a stabilization of compound **5a**, that is to say NO_2 substituent stabilizes enamine **5a**.

In the case of the CN substituent, the electrostatic repulsion between the two positive carbons C1(0.127) and C2(0.029) in compound **6** destabilizes the imine while the electrostatic attraction between the negative charge on C1 (−0.107) and positive charge on C2(0.088) in compound **6a** stabilizes the enamine. Also the attraction between C2(0.088) and N1 (−0.256) in compound **6a** is greater than that in compound **6**, suggesting stabilization of the former one.

For the substituent BH_2, the electrostatic attraction between C1(−0.248) and C2(0.155) in compound **7a** is greater than that in compound **7**, suggesting a stabilization of the enamine **7a**. The attraction between C2 and N in the emamine **7a** is larger than that in the imine **7**, which also supports the stabilization of enamine **7a** over the imine **7**.

For CF_3 substituent, the large attraction between C1(−0.276) and C2(0.135) in the enamine **8a** compared to the repulsion between C1(0.0011) and C2(0.023) in the imine **8**, and on the other hand the large attraction between C2(0.135) and N(−0.263) in the enamine **8a** compared to a smaller attraction between C2(0.023) and N(−0.200) in the imine **8** make the enamine **8a** more stable than the imine **8**.

For substituents with an empty π-orbital (BH_2) or $\pi*$ orbital (CN,NO_2,CF_3), to accept the π electron density from the C=C double bond the 'pull and push' effect becomes operative, leading to a further stabilization of the enamine form. This agrees with previous results [22]. Also the charge distribution explanation was mentioned previously [19, 21].

3. Conclusion

It can be concluded that acetaldimine lies below vinylamine by 5.224 kcal/mol. The F and Cl substituents stabilize acetaldimine, while NO_2, CF_3, CN and BH_2 destabilize the acetaldimine.

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