MINDO-Forces Study on the Substituent Effect in the Keto-Enol Tautomerism of Acetyl Derivatives

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MINDO-Forces calculations with complete geometry optimization have been performed on acetaldehyde, vinyl alcohol and acetyl derivatives CH_3COX(X=H, F, OH, CN, NH_2, NO_2, CH_3, CF_3,OCH_3). It was found that acetaldehyde is more stable than vinyl alcohol by 10.451 kcal/mol. Thermodynamically, keto tautomers are more stable than their enol counterparts. This agrees with theoretical calculations. The electron releasing substituents tend to stabilize keto tautomers, while the electron withdrawing substituents tend to destabilize the keto tautomers, relative to the parent. Geometrical parameters, heats of formation, electron densities, Gibbs free energies and orbital energies (HOMO-LUMO) are reported.

Key words: Acetaldehyde; Vinyl Alcohol; Keto-Enol Tautomerism; Acetyl Derivative.

1. Introduction

Tautomerism refers to the equilibrium between two different structures of the same compound. It is a prototropic rearrangement in which a hydrogen at the α-position to a carbon-heteroatom double bond migrates to the heteroatom and forms a C-C double bond [1 – 4].

Processes involving proton transfer between interconversion tautomers are of fundamental importance in synthetic and mechanistic chemistry. This includes the keto-enol, imine-enamine, oxime-nitroso, hydrazo-azo, and phenol-keto isomerization [5].

Among these processes, the most common studied form of tautomerism is that between a carbonyl compound (keto form) and its enol form.

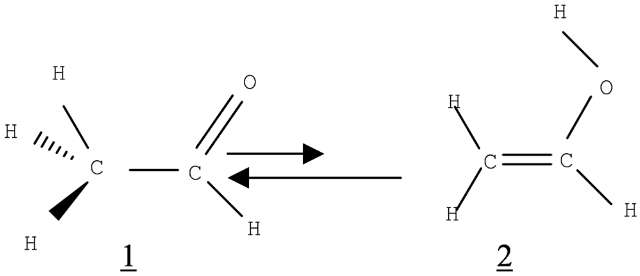
Acetaldehyde and vinyl alcohol are the prototypes for the keto/enol tautomersim.

$$\underset{\underline{\mathbf{1}}}{H_3C(CO)H} \rightleftarrows \underset{\underline{\mathbf{2}}}{H_2CCHOH}$$

Vinyl alcohol **2** is a transient intermediate in the very low-pressure pyrolysis of cyclobutanol [6, 7]. It has a half-life of 30 min, before undergoing a tautomeric rearrangement to acetaldehyde **1** which, by experimental estimate of heat formation, is by 13.2 kcal/mol more stable than vinyl alcohol. Ab initio molecular orbital calculations have been carried out on this tautomeric pair [8 – 13]. At the “G1” and MP4(fc)/6-311++G**//MP2(full)/6-31G* levels of theory, acetaldehyde **1** is found to lie 11.2 and 13.35 kcal/mol below vinyl alcohol **2** on the potential energy surface, respectively. Recent B3LYP and G2MP2 calculations [14] show that acetaldehyde **1** lies 10.4 and 11.1 kcal/mol below vinyl alcohol **2**, respectively.

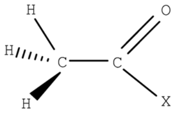
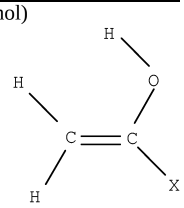
The effect of substituient on the carbonyl carbon position of the keto-enol tautomerism of acetaldehydes CH_3COX (X=H, BH_2, CH_3, NH_2, OH, F, Cl, CN, NC), was studied by Lien and Wu [1]. The natural bond orbital (NBO) analyses on the transition states show that the interaction of the lone pair electrons on the oxygen atom and the σ^* C-H bonds have a significant effect on their stabilities, which consequently affects the activation energies of tautomeric processes. Results show that in all cases the keto tautomers are thermodynamically more stable than their enol counterparts at all levels of theory. Also the magnitude of the energy barrier to the ketonization varies with the electronic nature of the substituent group and is in the order $CN > H > NC > BH_2 > CH_3 > Cl > F > OH > NH_2$.

Labbe and Perez [15] studied substituent effects on the keto-enol equilibria in 10 acetyl derivatives (CH_3COX, X= H, OH, CH_3, OCH_3, NH_2, $N(CH_3)_2$, OCHO, F, Cl, and Br). It was found that the electron donating groups, such as $N(CH_3)_2$, NH_2 and CH_3, lower the energy barrier, while the electron withdrawing groups push the energy barrier towards higher values with respect to X=H.



Scheme 1.

Table 1. Calculated heats of formation of acetyl derivatives and their enol counterparts.

	ΔH (kcal/mol)	
X		
H	− 43.645	− 33.194
F	−122.726	− 98.756
OH	−106.723	− 88.620
CN	− 26.418	− 22.546
NO_2	− 55.485	− 51.460
NH_2	− 55.085	− 48.751
CH_3	− 52.964	− 47.795
CF_3	−233.550	−230.470
OCH_3	− 96.979	− 79.084

In the present paper the keto-enol tautomerism for the parent acetaldehyde and its enol counterpart, together with the effect of the substituents (F, OH, CN, NH_2, NO_2, CH_3, CF_3, OCH_3) on the keto-enol tautomerism is reinvestigated by the MINDO-Forces MO method [16], whereby the molecular energy of the compounds obtained from the semiempirical MINDO/3 MO method [17] was completely minimized by Murtagh-Sargent technique [18]. The derivative of the energy was calculated according to Pulay's method [19]. The program allows the variation of the β-parameter with geometrical change in a consistent way. A full description of the program and its application is given in [16a].

2. Results and Discussion

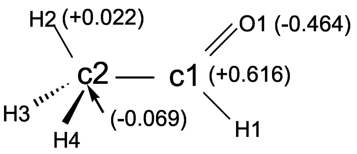
2.1. Parent Acetaldehyde and its Enol Counterpart

MINDO-Forces [16] calculations have been performed on acetaldehyde and its enol counterpart, and then on the substituted keto-enol tautomerism of acetyl derivatives.

The calculated heat of formation (Table 1) of acetaldehyde ($\Delta H_f = -43.645$ kcal/mol) is less than that of its enol counterpart ($\Delta H_f = -33.194$ kcal/mol), suggesting that the ketone is more stable than its enol counterpart. Thus ketone lies 10.451 kcal/mol below its enol counterpart, which agrees with the experimental results other theoretical calculations [5, 8 – 14].

The calculated electron densities of acetaldehyde and its enol counterpart are shown in Table 2.

In acetaldehyde **1**, the slight acidity of α-hydrogen due to the presence of the carbonyl carbon group, is shown through the slightly positive charge (+0.022) by these hydrogens (calculated from the electron density in Table 2).



1

The electron density distributions (Table 2) also predicts that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and the negative α-carbon [20 – 23].

The stability of ketone is also supported by thermodynamic calculations (Table 3), which show that the change in the Gibbs free energy (ΔG_r) of acetaldehyde and its enol is 10.157 kcal/mol. This almost agrees with the MP4 calculation ($\Delta G_r = 13.64$ kcal/mol) [1], which suggests that ketone is more stable than its enol counterpart, and the shift in equilibrium is to the ketone side (Scheme 1). This energy change will be taken as a reference for the acetyl derivatives in order to investigate the relative stability of the keto-enol system.

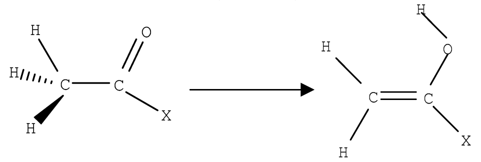
2.2. Effect of Substituents

The semiemperical MINDO-Forces method [16] was used to calculate fully the optimized geometries

Table 2. Calculated electron densities of acetyl derivatives and their enol counterparts (see Table 4 for numbering).

Comp.#	C_1	C_2	C_3	H_1	H_2	H_3	H_4	H_5	H_6	N	O_1	O_2	O_3	F_1	F_2	F_3
1	3.384	4.069		1.139	0.978	0.983	0.983				6.464					
3	3.045	4.083		0.950	0.988	0.950					6.496			7.488		
5	3.164	4.073		0.730	0.976	0.974	0.977				6.572	6.533				
7	3.422	4.060	4.029	0.989	0.973	0.989				5.048	6.483					
9	3.565	4.044		0.966	0.954	0.966				4.024	6.408	6.540	6.534			
11	3.347	4.087		0.991	0.974	0.991	0.918	0.918		5.275	6.500					
13	3.438	4.062	4.062	0.996	0.975	0.996	0.975	0.996	0.996		6.502					
15	3.548	4.056	2.781	0.959	0.960	0.959					6.426			7.469	7.394	7.469
17	3.182	4.072	3.576	0.977	0.972	0.977	1.054	1.070	1.070		6.571	6.479				
2	3.632	4.193		1.062	0.748	0.959	0.963				6.442					
4	3.194	4.426		0.931	0.740	0.900					6.462			7.347		
6	3.298	4.409		0.947	0.729	0.922	0.731				6.509	6.455				
8	3.611	4.244	3.928	0.962	0.751	0.955				5.097	6.443					
10	3.787	4.170		0.974	0.727	0.938				3.931	6.409	6.545	6.545			
12	3.502	4.308		0.958	0.750	0.949	0.915	0.915		5.208	6.494					
14	3.618	4.264	3.968	0.962	0.750	0.962	1.016	1.003	1.003		6.454					
16	3.812	4.125	2.710	0.958	0.734	0.922					6.422			7.468	7.425	7.425
18	3.304	4.407	3.575	0.943	0.734	0.923	1.051	1.075	1.075		6.502	6.409				

Table 3. Gibbs free energies of keto-enol tautomerism of acetyl derivatives and their enol counterparts.



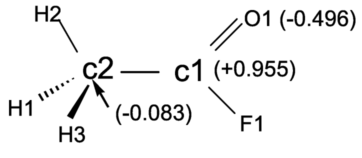
X	ΔG (kcal/mol)
H	10.157
F	24.056
OH	17.497
CN	0.895
NO_2	3.709
NH_2	5.974
CH_3	4.423
CF_3	2.957
OCH_3	17.493

of acetyl derivatives (CH_3COX, where X= H, F, OH, CN, NH_2, NO_2, CH_3, CF_3, OCH_3). The results of the optimized geometrical parameters are given in Table 4. All substituents cause a decrease in the bond angle C2C1O1 at which the substituent is attached, and an increase in the adjacent bond lengths (C1-C2 and C1-O1), except in the case of the substituent F, where the opposite holds [16e–g].

Effect of F

The substituent F in compound **3** (Table 2) decreases the electron density on carbon C1 and increases it on atoms C2 and O1, which suggests that F acts as electron releasing.

From the charge distribution of **3** obtained from the electron density (Table 2), it is shown that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and the negative α-carbon (C2) [20–23]



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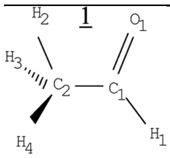
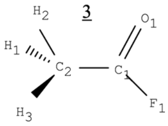
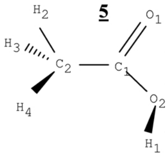
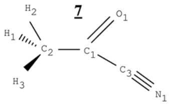
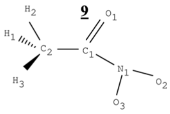
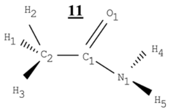
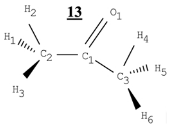
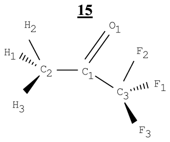
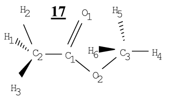
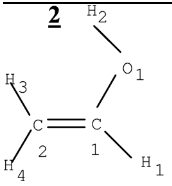
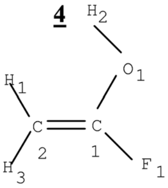
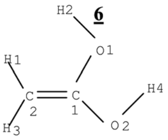
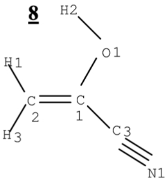
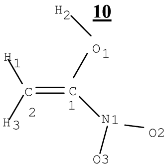
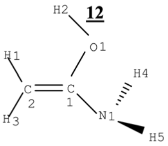
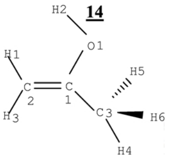
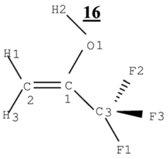
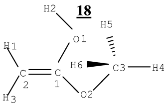
Calculation of the Gibbs energy (ΔG_r) for the F substituted keto-enol system (Table 3) shows that ΔG_r = 24.056 kcal/mol, which means that the reaction is non-spontaneous and shifts to the ketone side (Scheme 2).

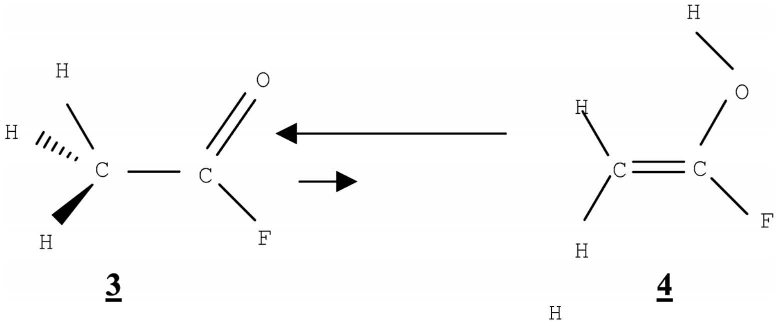
The stabilization effect of F on both the ketone **3** and its enol counterpart **4** (Table 5) is often confirmed by using isodesmic reactions [22–26]. A negative value indicates less stability and a positive value more stability. It can be seen that the ΔH_r values of the isodesmic reactions are positive for both **3** (ΔH_r = 20.602 kcal/mol) and **4** (ΔH_r = 10.754 kcal/mol). From these values, the compounds **3** and **4** are stabilized by F, but **3** is more stabilized than **4**. This explains the shift in equilibrium to the ketone side and agrees with ab initio calculation [1], in which the substituent F was found to lower the energy barrier of ketonization. i. e. increase the stability of ketone.

Effect of the OH Group

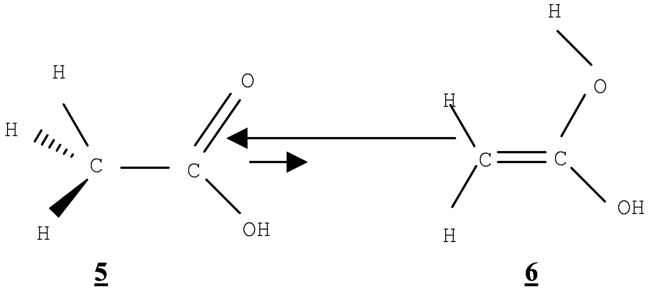
The OH substituent in **5** also behaves as an electron releasing group, which decreases the electron density

Table 4. Optimized geometrical parameters of acetyl derivatives and their enol Counterparts.

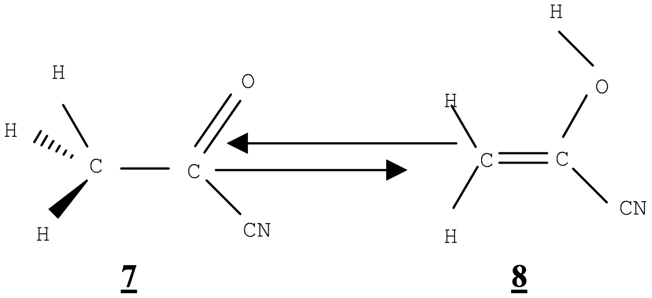
Molecule No. & Structure	Bond	Calculated Bond Length Å	Bond Angle	Calculated Angle Degree
1 	$O_1=C_1$	1.192	$<C_2C_1H_1$	111.5
	C_1-H_1	1.138	$<C_2C_1O_1$	127.3
	C_1-C_2	1.478	$<H_4C_2H_2$	106.3
	C_2-H_2	1.109	$<H_3C_2H_2$	106.3
	C_2-H_3	1.109	$<H_2C_2C_1$	114.4
3 	$O_1=C_1$	1.176	$<C_2C_1F_1$	96.8
	C_1-F_1	1.361	$<C_2C_1O_1$	134.6
	C_1-C_2	1.463	$<F_1C_1O_1$	128.6
	C_2-H_2	1.113	$<H_1C_2H_2$	106.2
	C_2-H_1	1.106	$<H_2C_2C_1$	111.2
5 	$O_1=C_1$	1.214	$<C_2C_1O_2$	105.7
	C_1-O_2	1.335	$<C_2C_1O_1$	124.3
	C_1-C_2	1.496	$<H_1O_2C_1$	119.3
	O_2-H_1	0.951	$<H_4C_2H_2$	104.8
	C_2-H_2	1.110	$<H_3C_2H_1$	105.0
	C_2-H_3	1.111	$<H_2C_2C_1$	112.3
7 	$O_1=C_1$	1.206	$<C_2C_1C_3$	121.1
	C_3-C_1	1.473	$<C_2C_1O_1$	119.8
	C_1-C_2	1.493	$<N_1C_3C_1$	178.2
	C_3-N_1	1.157	$<H_1C_2H_2$	106.0
	C_2-H_2	1.110	$<H_1C_2C_1$	112.6
	C_2-H_1	1.106	$<H_2C_2C_1$	113.2
9 	$O_1=C_1$	1.202	$<C_2C_1N_1$	121.2
	C_1-N_1	1.477	$<C_2C_1O_1$	120.8
	C_1-C_2	1.491	$<O_3N_1O_2$	133.2
	N_1-O_2	1.231	$<O_3N_1C_1$	113.5
	C_2-H_2	1.112	$<H_1C_2C_1$	113.6
	C_2-H_1	1.109	$<H_2C_2C_1$	110.6
11 	$O_1=C_1$	1.204	$<C_2C_1N_1$	121.8
	C_1-N_1	1.410	$<C_2C_1O_1$	120.7
	C_1-C_2	1.497	$<H_5N_1H_4$	105.2
	N_1-H_4	1.029	$<H_1C_2H_2$	105.4
	C_2-H_2	1.110	$<H_1C_2C_1$	113.0
	C_2-H_1	1.111	$<H_2C_2C_1$	113.4
13 	$O_1=C_1$	1.207	$<C_2C_1C_3$	122.0
	C_1-C_3	1.497	$<C_2C_1O_1$	118.8
	C_1-C_2	1.498	$<H_5C_3H_4$	105.5
	C_3-H_4	1.110	$<H_3C_2H_1$	106.0
	C_2-H_2	1.110	$<H_3C_2H_2$	105.5
	C_2-H_1	1.110	$<H_2C_2C_1$	113.9
15 	$O_1=C_1$	1.204	$<C_2C_1C_3$	123.7
	C_1-C_3	1.500	$<C_2C_1O_1$	121.5
	C_1-C_2	1.491	$<F_3C_3F_1$	110.1
	C_3-F_1	1.330	$<F_3C_3C_1$	102.7
	C_2-H_2	1.111	$<F_1C_3C_1$	102.7
	C_2-H_1	1.108	$<H_1C_2C_1$	112.2
			$<H_2C_2C_1$	111.6
17 	$O_1=C_1$	1.212	$<C_2C_1O_2$	111.5
	C_1-O_2	1.342	$<C_2C_1O_1$	122.5
	C_1-C_2	1.493	$<H_6C_3H_5$	105.9
	O_2-C_3	1.359	$<H_1C_2H_2$	104.5
	C_3-H_4	1.117	$<H_1C_2C_1$	114.7
	C_2-H_2	1.113	$<H_2C_2C_1$	111.3
2 	O_1-C_1	1.321	$<H_2O_1C_1$	112.3
	O_1-H_2	0.953	$<C_2C_1H_1$	123.4
	C_1-H_1	1.117	$<C_2C_1O_1$	128.8
	$C_1=C_2$	1.328	$<H_4C_2H_3$	112.2
	C_2-H_3	1.097	$<H_3C_2C_1$	124.5
4 	O_1-C_1	1.304	$<H_2O_1C_1$	114.1
	O_1-H_2	0.953	$<C_2C_1F_1$	118.9
	C_1-F_1	1.373	$<C_2C_1O_1$	133.5
	$C_1=C_2$	1.323	$<H_3C_2H_1$	114.4
	C_2-H_1	1.096	$<H_1C_2C_1$	120.7
6 	O_1-C_1	1.343	$<H_2O_1C_1$	112.4
	O_1-H_2	0.950	$<C_2C_1O_2$	120.1
	C_1-O_2	1.332	$<C_2C_1O_1$	123.0
	$C_1=C_2$	1.341	$<H_4O_2C_1$	115.8
	O_2-H_4	0.952	$<H_3C_2H_1$	112.5
	C_2-H_1	1.096	$<H_1C_2C_1$	121.3
8 	O_1-C_1	1.336	$<H_2O_1C_1$	112.2
	O_1-H_2	0.953	$<C_2C_1C_3$	124.6
	C_1-C_3	1.383	$<C_2C_1O_1$	124.6
	$C_1=C_2$	1.342	$<N_1C_3C_1$	179.8
	$C_3\ N_1$	1.162	$<H_3C_2H_1$	111.7
	C_2-H_1	1.097	$<H_1C_2C_1$	125.3
10 	O_1-C_1	1.338	$<H_2O_1C_1$	110.7
	O_1-H_2	0.954	$<C_2C_1N_1$	122.6
	C_1-N_1	1.459	$<C_2C_1O_1$	125.7
	$C_1=C_2$	1.338	$<O_3N_1O_2$	132.2
	N_1-O_2	1.226	$<O_2N_1C_1$	113.8
	C_2-H_1	1.098	$<H_1C_2C_1$	122.8
12 	O_1-C_1	1.338	$<H_2O_1C_1$	114.4
	O_1-H_2	0.951	$<C_2C_1N_1$	122.8
	C_1-N_1	1.386	$<C_2C_1O_1$	124.4
	$C_1=C_2$	1.341	$<H_5N_1H_4$	106.6
	N_1-H_4	1.025	$<H_4N_1C_1$	117.0
	C_2-H_1	1.098	$<H_3C_2H_1$	111.0
			$<H_1C_2C_1$	123.8
14 	O_1-C_1	1.339	$<H_2O_1C_1$	112.4
	O_1-H_2	0.952	$<C_2C_1C_3$	125.1
	C_1-C_3	1.491	$<C_2C_1O_1$	123.7
	$C_1=C_2$	1.344	$<H_4C_3C_1$	110.5
	C_3-H_4	1.113	$<H_3C_2H_1$	111.1
	C_2-H_1	1.096	$<H_1C_2C_1$	126.7
16 	O_1-C_1	1.338	$<H_2O_1C_1$	111.0
	O_1-H_2	0.953	$<C_2C_1C_3$	123.9
	C_1-C_3	1.469	$<C_2C_1O_1$	125.5
	$C_1=C_2$	1.341	$<F_2C_3F_1$	105.9
	C_3-F_1	1.337	$<F_1C_3C_1$	102.6
	C_2-H_1	1.098	$<H_1C_2C_1$	123.3
18 	O_1-C_1	1.341	$<H_2O_1C_1$	113.3
	O_1-H_2	0.950	$<C_2C_1O_2$	120.4
	C_1-O_2	1.339	$<C_2C_1O_1$	125.2
	$C_1=C_1$	1.341	$<C_3O_2C_1$	123.1
	O_2-C_3	1.352	$<H_5C_3H_4$	106.5
	C_3-H_4	1.123	$<H_1C_2C_1$	122.2
	C_2-H_1	1.097		



Scheme 2.



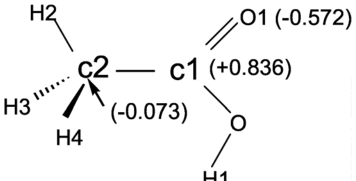
Scheme 3.



Scheme 4.

at C1 (the atom carrying the substituent) and increases it at the adjacent atoms C2 and O1 (Table 2), when compared with the parent **1**.

From the charge distribution of **5** it is seen that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and negative α-carbon (C2) [20–23].



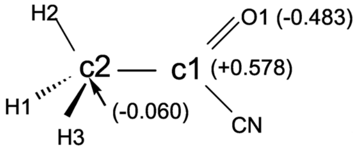
5

Thermodynamic calculations of ΔG_r (Table 3) for the OH substituted keto-enol system show that $\Delta G_r =$ 17.497 kcal/mol, which means that the reaction is non-spontaneous and the reaction shifts toward the ketone side (Scheme 3).

This is supported by the stabilization effect of OH group on both the ketone and its enol counterpart (Table 5). It can be seen that the ΔH_r of the isodesmic reaction is more positive for **5** ($\Delta H_r = 11.532$ kcal/mol) than that for **6** ($\Delta H_r = 0.765$ kcal/mol). This explain the shift in equilibrium to the ketone side. This agrees with ab initio calculations [1] in which OH substituent was found to lower the energy barrier of ketonization.

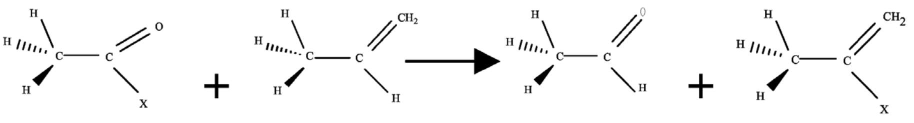
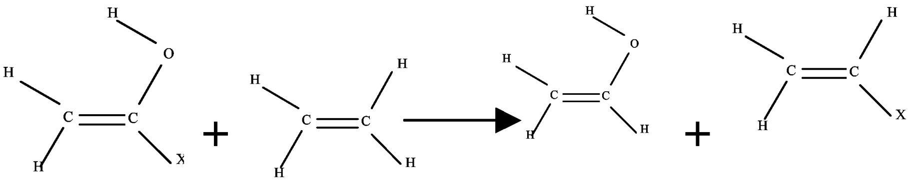
Effect of the CN Group

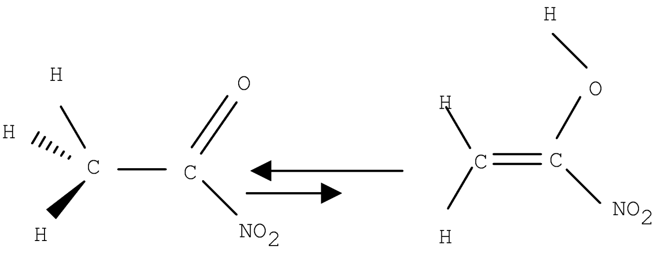
The CN substituent in **7** increases slightly the electron density on carbon C1 and decreases it on adjacent



7

Table 5. Evaluation of substituent effects on keto-enol tautomerism of acetyl derivatives and their enol counterparts via isodesmic reactions (ΔH_f in kcal/mol).

Isodesmic Reaction		
	F	20.602
	OH	11.532
	CN	5.621
	NO_2	2.730
	NH_2	9.321
	CH_3	5.213
	CF_3	0.705
	OCH_3	11.746
	F	10.754
	OH	0.765
	CN	4.997
	NO_2	0.995
	NH_2	3.500
	CH_3	2.075
	CF_3	0.176
	OCH_3	0.189



9 **10**

Scheme 5.

carbon C2 (Table 2) when compared with the parent **1**, i. e. behaves as weakly electron withdrawing.

From the charge distribution of **7** it is shown that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and the negative α-carbon (C2) [20–23].

This electrostatic attraction is less than that in the case of **3** and **5**, which indicates that the CN substituent is weakly stabilized by the ketone.

Thermodynamic calculations of ΔG_r (Table 3) for the CN substituted keto-enol system with a slightly positive value ($\Delta G_r = 0.895$ kcal/mol) indicate that the reaction is very slightly nonspontaneous (Scheme 4).

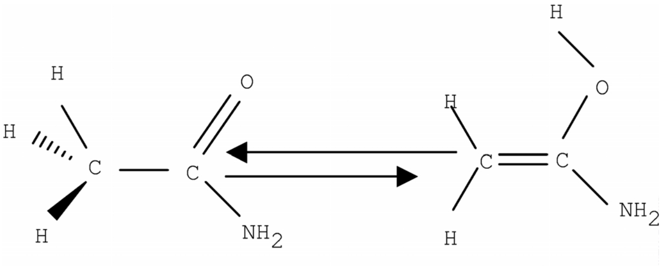
This is supported by the stabilizing effect of the CN group on both the ketone and its enol counterpart (Table 5), using an isodesmic reaction. It can be seen that the ΔH_r values for the isodesmic reactions of both **7** and **8** are positive ($\Delta H_r = 5.621$ kcal/mol for **7**, while $\Delta H_r = 4.997$ kcal/mol for **8**). From these two values, both **7** and **8** are stabilized by the CN group, but **7** is slightly more stabilized than **8**. This explains the shift to the ketone side ($\Delta G_r = 0.895$ kcal/mol). But the ΔG_r in the case of the substituent CN ($\Delta G_r = 0.895$ kcal/mol) is less than that in the parent **1** ($\Delta G_r = 10.157$ kcal/mol), which suggests that the substituent CN destabilizes the ketone.

This agrees with ab initio calculations [1], in which CN was found to increase the energy barrier of ketonization, i. e. destabilizes ketone relative to the parent **1**.

Effect of the NO_2 Group

The substituent NO_2 behaves as a strong electron withdrawing group in **9** (Table 2); this is reflected through an increase in the electron density at C1 and a decrease in the electron densities at the adjacent atoms C2 and O1, when compared with the parent **1**.

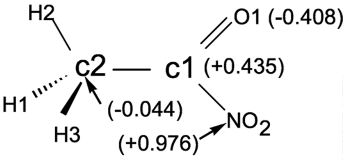
From the charge distribution of **9**, it can be seen that the carbonyl group is stabilized by electrostatic attraction between the carbonyl- and α-carbon, but it is less than that of F and OH substituents. Also the



11 **12**

Scheme 6.

electrostatic repulsion between the positive carbon C1 (+0.435) and the positive nitrogen atom in the NO_2 group (+0.976) destabilizes the carbonyl carbon.



9

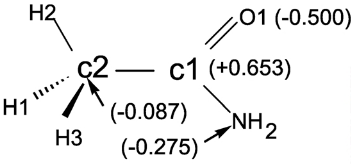
This result is confirmed by thermodynamic calculations (Table 3) of ΔG_r ($\Delta G_r = 3.709$ kcal/mol). This indicates that the reaction is non-spontaneous but not to a high degree (Scheme 5).

This result is also supported by isodesmic reactions (Table 5). It can be seen that $\Delta H_r = +2.730$ kcal/mol for ketone **9**, while $\Delta H_r = 0.995$ kcal/mol for enol **10**. This indicates that NO_2 slightly stabilizes ketone **9**, and the equilibrium shifts to the ketone side. But the value of ΔG_r in the case of the substituent NO_2 ($\Delta G_r = 3.709$ kcal/mol) is less than that in the parent **1** ($\Delta G_r = 10.157$ kcal/mol), which suggests that NO_2 destabilizes the ketone.

Effect of the NH_2 Group

The NH_2 substituent behaves as an electron releasing group in **11** (Table 2); this is reflected by a decrease in the electron density at C1 and an increase in the electron densities at the adjacent atoms C2 and O1, when compared with the parent **1**.

From the charge distributions of **11** it is shown that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and the negative α-carbon (C2) [20–23]. Also the electrostatic attraction between the positive carbon C1 (+0.653) and negative nitrogen atom (−0.275) in the NH_2 group increases the stability of the carbonyl carbon.



11

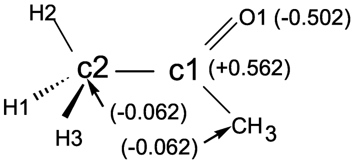
This stability is confirmed by thermodynamic calculation (Table 3) of ΔG_r, which yields a positive value ($\Delta G_r = 5.974$ kcal/mol), i.e. the reaction is nonspontaneous (Scheme 6).

This result is supported by isodesmic reactions (Table 5). It can be seen that ΔH_r of **11** and **12** is positive ($\Delta H_r = 9.321$ kcal/mol for **11**, while $\Delta H_r = 3.500$ kcal/mol for **12**). From these values follows that the NH_2 group stabilizes both compounds, but **11** more than **12**. This explains the shift to the ketone side.

Effect of the CH_3 Group

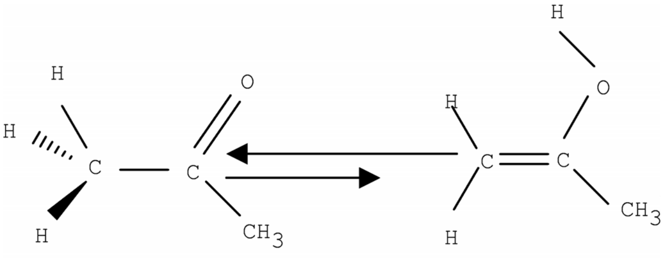
The substituent CH_3 behaves as a weak electron releasing group in **13** (Table 2), when compared with the parent **1**.

By the charge distributions of **13** it is shown that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and negative α-carbons (C2 and C in the CH_3 group) [20–23].



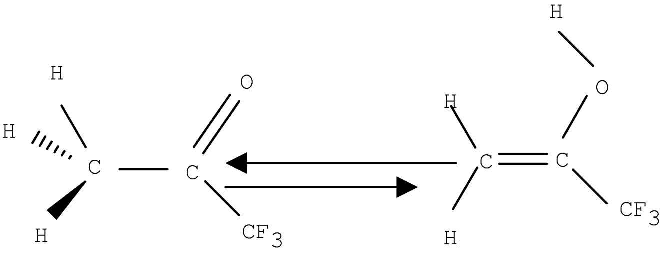
13

This electrostatic attraction is less than in OH and NH_2 as substituents, which may suggests less stabilization by the CH_3 substituent.



13 **14**

Scheme 7.



15 **16**

Scheme 8.

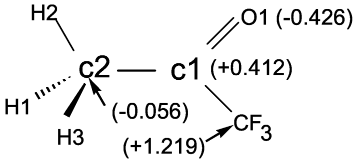
Calculation of the Gibbs energy ΔG_r (Table 3) shows that $\Delta G_r = 4.423$ kcal/mol, which means that the reaction is non-spontaneous (Scheme 7).

This result is confirmed by the isodesmic reactions (Table 5). It can be seen that the ΔH_r of **13** and **14** is positive ($\Delta H_r = 5.213$ kcal/mol for **13**, $\Delta H_r = 2.075$ kcal/mol for **14**). From these values follows that the CH_3 group stabilizes **13** and **14**, but **13** is more stabilized, which explains the shift in equilibrium to the ketone side.

Effect of the CF_3 Group

The CF_3 substituent behaves as a strong electron withdrawing group in **15** (Table 2); this is reflected by an increase in the electron density at C1 and a decrease at the adjacent atoms C2 and O1, when compared with the parent **1**.

From the charge distribution of **15** it is shown that the electrostatic attraction between the positive carbonyl carbon and negative α-carbon (C2) is less than that in the parent **1**. This indicates that the CF_3 substituent destabilizes ketone.



15

Also the electrostatic repulsion between the carbonyl carbon (+0.412) and the carbon atom in the CF_3 group (+1.219) destabilizes the carbonyl carbon.

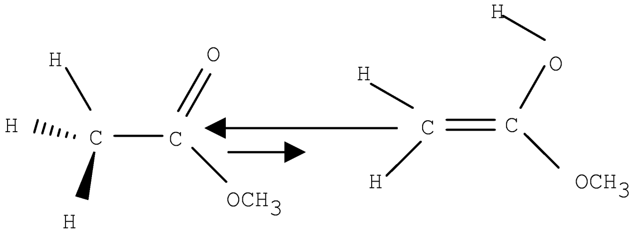
This is supported by thermodynamic calculations (Table 3), which show that ΔG_r is slightly positive ($\Delta G_r = 2.957$ kcal/mol). This indicates that the reaction is non-spontaneous, but not to a high degree (Scheme 8).

This is also confirmed by isodesmic reactions (Table 5). It can be seen that ΔH_r of **15** and **16** is slightly positive ($\Delta H_r = +0.705$ kcal/mol for **15**, $\Delta H_r = +0.176$ kcal/mol for **16**). From these two values it is seen that the CF_3 group is slightly stabilized in **15**, which indicates that the equilibrium is still slightly shifted to the ketone side. But the value of ΔG_r in case of the CF_3 substituent ($\Delta G_r = 2.957$ kcal/mol) is less than that in the parent **1** ($\Delta G_r = 10.157$ kcal/mol), which suggests that CF_3 destabilizes the ketone.

Effect of the OCH_3 Group

The OCH_3 substituent behaves as a strong electron releasing group in compound **17** (Table 2); this is reflected by a decrease in the electron density at C1 and an increase at the adjacent atoms C_2 and O_1, when compared with the parent **1**.

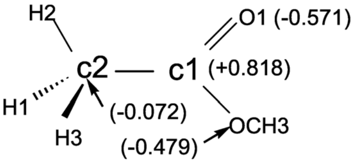
From the charge distributions of **17** it is shown that the carbonyl group is stabilized by electrostatic attraction between the positive carbonyl carbon and the neg-



17 **18**

Scheme 9.

ative α-carbon (C2), and also the attraction of the oxygen atom in the OCH_3 group (-0.479) [20–23].



17

This is supported by thermodynamic calculations (Table 3), which show that ΔG_r has a large positive value ($\Delta G_r = 17.493$ kcal/mol). This indicates that the reaction is non-spontaneous (Scheme 9).

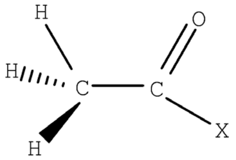
This result is confirmed by isodesmic reactions (Table 5). It can be seen that ΔH_r of **17** and **18** is positive ($\Delta H_r = 11.746$ kcal/mol for **17**, $\Delta H_r = 0.189$ kcal/mol for **18**). From these values follows that OCH_3 stabilizes **17** to a large extent, but **18** almost not. This explains the large positive value of ΔG_r ($\Delta G_r = 17.493$ kcal/mol) obtained from the present thermodynamic calculations. This agrees with ab initio calculations [15], in which OCH_3 was found to lower the energy of ketonization.

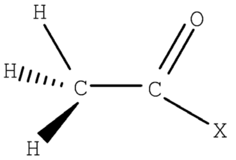
It can be seen from Table 3 that keto tautomers are thermodynamically more stable than their enol tautomers, in agreement with previous results [1, 5, 15, 27–33]. Also the strongly electron releasing substituents tend to stabilize the keto tautomers, while the strongly electron withdrawing substituents tend to destabilize the keto tautomers relative to the parent **1**, in agreement with previous results [1, 15].

2.3. Orbital Energies (HOMO and LUMO)

Introduction of a substituent into acetyl derivatives affects its orbital energies (HOMO and LUMO) relative to the parent. It can be seen from Table 6 that the energy gap (Eg) of the keto tautomers is greater than that of their enol counterparts, suggesting a stabilization of the keto tautomers. Also the strong electron releasing substituents (e.g. F, CH_3, OCH_3) cause an increase in the energy gap of keto tautomers relative to the parent **1**, suggesting a stabilization of the keto tautomers. While substituents with a strong electron withdrawing capacity (e.g. NO_2, CF_3) tend to decrease the energy gaps of the keto tautomers relative to the parent **1**, suggesting a destabilization of the keto tautomers. This agrees with previous work [1, 5, 15, 27–33].

Table 6. Calculated orbital energies (HOMO and LUMO) of acetyl derivatives and their enol counterparts (energy in eV). E_g = LUMO – HOMO.





X	HOMO	LUMO	E_g	HOMO	LUMO	E_g
H	−10.8742	0.8723	11.7645	− 9.4226	1.3098	10.7324
F	−12.3544	0.3139	12.6883	−10.3029	0.0972	10.4001
OH	−11.5596	0.9189	12.4785	− 8.9962	1.3047	10.3009
CN	−11.9023	−0.3351	11.5672	−10.0130	0.0522	10.0652
NO_2	−11.5989	−1.0781	10.5208	−10.6059	−0.8530	9.7529
NH_2	−10.6295	0.6702	11.2997	− 9.3215	1.0868	10.4083
CH_3	−10.8478	0.7092	11.5570	− 9.3464	1.0300	10.3764
CF_3	−11.9078	−0.4404	11.4674	−10.4419	−0.0669	10.3750
OCH_3	−11.5636	0.8499	12.4135	− 9.0132	1.2372	10.2504

3. Conclusion

It can be concluded that acetaldehyde is more stable than vinyl alcohol by 10.451 kcal/mol. The stability of the acetyl derivatives depends on the electronic nature of the substituent. Substituents with electron releasing capacity (e.g. F, OH, OCH_3) tend to stabilize the keto tautomers, while substituents with electron withdrawing capacity (e.g. NO_2, CF_3) tend to destabilize the keto tautomers compared to the parent **1**. Thermodynamically, the keto tautomers are more stable than their enol counterparts. These results were confirmed by Gibbs free energy calculations, isodesmic reactions and orbital energies.

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