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AM1 Theoretical Analysis on the Effect of Some Substituents (X) at Carbonyl Carbon Position of the Formamide-Formamidic Acid Tautomerization System. (X = F, Cl, Br, I, CN, NO_2, CH_3 and CF_3)

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Abstract

Heats of formation, entropy changes, free energy changes and equilibrium constant values at 25 °C were calculated by the use of AM1 semiempirical quantum chemical method. The calculations were performed on unsubstituted formamide-formamidic acid tautomeric system, as well as on substituted systems. The equilibrium constant value for the unsubstituted system was found to be 2.21×10^{-9}. It is found that the tautomerization equilibria for the substituted systems, for all of the substituents employed in this work, have lower equilibrium constant values compared to that obtained for the unsubstituted system. These values were found to be several orders of 10 less, depending upon the substituent. Geometrical parameters (bond lengths and bond angles) were, also, reported for all of the compounds studied in this work. The results were compared to the available experimental values, and to those obtained from ab initio and DFT obtained at different levels of theory.

Keywords: AM1, formamide, isodesmic reactions, tautomerization, dipole moment, semiempirical methods

1. Introduction

Tautomerism in formamide has attracted scientists because it is the simplest model for peptide bond, which is of considerable importance in many biologically active compounds like proteins, enzymes, nucleic acid bases and DNA base pairs.[1–8] A comprehensive literature survey (theoretical and experimental) about formamide-formamidic acid tautomeric system showed that almost all of the work done was related to the geometry of the formamide and formamidic acid forms,[2,9,10] tautomerism energy barrier in gas phase, in water or other solvents, or in the presence of another formamide molecule (self-assisted process), proton transfer in formamide dimer.[2,11–21] None of the previous work was related to the effect of substituents at the carbonyl carbon position on the tautomerization reaction of formamide-formamidic acid. Lim and Francl[22] have used ab initio LCAO-MO SCF method to calculate the optimized geometry and rotation barrier about C–N bond for formamide, acetamide, cyanoformamide, fluoroformamide and chloroformamide. Also, Langley et al.[23] have worked on cynoformate and ethynyl formate, where they calculated the optimized geometry, relative energies, thermodynamic and some other properties by the use of ab initio methods. Another work was dedicated to the effect of some substituents at the amide nitrogen position,[24,25] where the aim of the study was to investigate the effect of these substituents on the stability of their corresponding amide conformers.

2. Computational Methods

Theoretical calculations were carried out by the use of MOPAC2007 program.[26] This program is written in FORTRAN-90/95-Language, it supports AM1[27,28] and other semiempirical methods. The default self-consistent method in this program is RHF. For geometry optimization, Baker's EigenFollowing (EF) procedure is used as

default. In this procedure, an approximate geometry is selected then the forces acting on the system are calculated, from which, a new geometry is calculated. The cycle is continued until reaching an equilibrium geometry, where the energy is minimum, and the net forces acting on every atom become nearly zero or vanish. The program has many capabilities. Heats of formation, entropies, partition functions, heat capacities, vibrational frequencies, force constants, isotopic substitution effect, transition state location, solvent effects, and may other properties can be calculated. In this work, all structures were optimized to a gradient norm of less than 0.02.

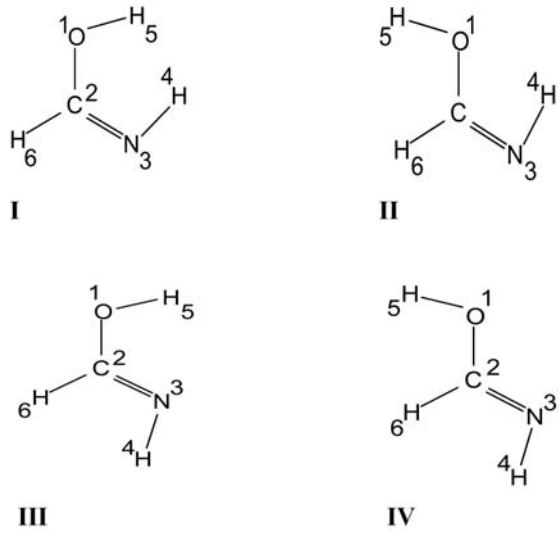
3. Results and Discussion

3. 1. The Unsubstituted Formamide/ Formamidic Acid Tautomeric Pair

The geometrical parameters obtained for formamide, together with some other theoretical and experimental values obtained from the literature are shown in Table 1. Almost all of the theoretical work about the geometry of formamide is compared to some of the few experimental results that are available in the literature.[29–33]

From a look at these numbers, it can be clearly seen that the bond lengths obtained from this work (AM1) are equal or very near to one of those obtained either theoretically or experimentally. For example, the O1C2 bond length is very near to the result obtained by microwave where the difference is 0.004 Å. If the bond angles are considered, the largest difference is found in the O1C2N3 bond angle where it was 3.0° from the result obtained by microwave method. This difference is the same as that obtained by RB3LYP/6-311++G** method. The difference in the other bond angles to the nearest experimental value is even smaller, where it was 1.2° and 2.1° in the case of H4N3C2 and H5N3C2 bond angles, respectively.

In formamide, the amino group angle is a result of balance of delocalization of the lone pair of nitrogen between the nitrogen atom and the rest of the molecule,[17] the resonance stabilization of formamide molecule is maximum when the molecule is planar, and this presumable stabilization would be lost when the amino group is rotated by 90°.[35] This supports the result obtained in this work where the dihedral angles obtained are all 0.00 or 180.0 which indicates planar formamide molecule with C_S symmetry. The equilibrium positions of atoms in structures are determined by the electrostatic repulsive and attractive forces between them, which are determined by the charge distribution on these atoms and the interatomic distances.[19,36,37] Different formamidic acid (enol) forms of formamide are obtained by changing the orientation of the O1H5 and the N3H4 bonds. This produces structures I to IV as shown in Scheme 1 below:



Scheme 1

The change in the orientation of these bonds resulted in a change in the number of the attractive and repulsive forces, which affects the stability of these enol forms. Atoms O1, C2, and N3 maintain their position in these

Table 1. Geometrical parameters of formamide obtained by AM1 compared to those obtained by other theoretical and experimental results, bond lengths are in Å and bond angles are in degrees.

	AM1 (This Work)	RB3LYP/6 -311++G**[a]	QCISD/6- 31++G**[a]	MP2/6 -311++G**[b]	X-ray[c]	Microwave[d]	Electron Diffraction[e]
O1C2	1.243	1.212	1.224	1.216	1.239	1.219	1.211
C2N3	1.367	1.361	1.363	1.369	1.326	1.352	1.367
H4N3	0.986	1.010	1.007	1.009	1.01	1.098	1.12
H5N3	0.990	1.007	1.004	–	1.01	1.002	1.021
H6C2	1.114	1.103	1.100	–	1.09	1.002	1.021
O1C2N3	121.9	121.9	124.5	124.7	124.9	124.7	124.9
H4N3C2	121.2	121.4	121.3	–	119	120.0	120.0
H5N3C2	120.6	119.5	119.4	117.5	118	118.5	118.5
H6C2O1	123.1	–	–	–	–	–	–

Ref: [a] 14, [b] 4, [c] 34, [d] 30, [e] 31.

structures (I to IV), and the forces between them are attractive forces because they carry opposite charges, Table 2.

Table 2. Charge distribution on the atoms of the enol tautomers of formamide

	O1	C2	N3	H4	H5	H6
I	–0.307	0.0660	–0.311	0.144	0.212	0.196
II	–0.316	0.0480	–0.271	0.159	0.221	0.158
III	–0.274	0.0706	–0.341	0.164	0.233	0.147
IV	–0.247	0.0384	–0.257	0.153	0.215	0.0980

It can be seen from a look at structure IV that it contains two forces of repulsion, one is between H4 and H6, and the other is between H5 and H6. The H4–H6 repulsion force is replaced by attraction force between O1 and H4 in structure II. Also, the H5–H6 repulsion force is replaced by H5–N3 attractive force in structure III. This makes these two structures more stable compared to structure IV, and their energy is similar because one force of repulsion is replaced by one force of attraction in each case. The two forces of repulsion in structure IV (H5–H6 and H4–H6) are replaced by two forces of attraction and one force of repulsion in structure I, resulting in a net gain of one attraction force. These forces are O1–H4 and N3–H5 attractive forces, and H4–H5 repulsion force. The result of this is greater stability in structure I compared to structures II, III and IV. From the calculations in this work it is found that the heats of formation (in kJ/mol) were –138.4, –132.7, –131.0 and –97.9 for structures I, II, III and IV, respectively. This type of interaction between the nitrogen and OH groups is found in 2-pyridone but is not present in 4-pyridone.[38,39] It is also found between structures III and IV in formamide tautomers as illustrated by Schlegel et al.[36] but there is no investigation mentioned about the other two tautomers (I and II). The energy difference between structures III and IV in this work is found to be 33.05 kJ/mol where it is reported to be about 37.66 kJ/mol by Schlegel and his coworkers. A theoretical study on formamide tautomers[40] by the use of density functional theory (B3LY/6-311++G(3df,2pd)) found that the stability order of the enol forms of formamide was IV < II < I < III. This order of stability is different from the one obtained in this study but agrees with the information that the least stable tautomer is structure IV. The transformation between these structures (I–IV) is found to be achieved easier by intramolecular bond rotation rather than by proton transfer.[40]

It is noticed that the repulsion between H4 and H5 in structure I leads to an opening of the O1C2N3 angle, where it is found to be 130.2°. This angle is found to be 129.2°, 129.3° and 130.2° at RHF/3-21G, RHF-6-31G(d) and MP2(Full)/6-31G(d) levels of calculations, respectively, and it is in the range between 119.1–124.5 for structures II, III and IV.[19] In this work the O1C2N3 angle was 122.2° in structure II, 121.5° in structure III and 116.7° in structure IV. The twist angles obtained for formamidic acid I were all 0.00 or 180.00, (±0.04°). These angles indicate that these structures are perfectly planar with C_S point group of symmetry. This result was obtained in many works.[19,40] No experimental results about the geometry of these structures (I, II, III and IV) are found in the literature. Also, substituted formamidic acid has not been observed spectroscopically.[36] The geometric parameters for the most stable formamidic acid I obtained in this work, together with those obtained from some other theoretical work,[19,40] are presented in Table 3.

Table 3. Geometrical parameters of formamidic acid I as obtained by AM1 compared to those obtained by other theoretical methods (bond lengths are in Å and bond angles are in degrees).

	AM1 (This Work)	B3LYP/6-311++G (3df,2pd)[a]	RHF/3-21G[b]	RHF/6-1G(d)[b]	MP2 (Full) /6-1G(d)[b]
O1C2	1.381	1.356	1.373	1.339	1.363
C2N3	1.277	1.259	1.246	1.246	1.273
H4N3	0.997	1.021	1.013	1.007	1.026
H5O1	0.967	0.966	0.976	0.952	0.980
H6C2	1.111	1.086	1.068	1.075	1.087
O1C2N3	130.2	129.7	129.2	129.3	130.2
H4N3C2	117.9	113.6	117.6	113.5	112.2
H5O1C2	111.2	110.1	114.2	111.2	108.8
H6C2O1	108.4	109.6	109.3	110.1	109.5

Ref.: [a] 40, [b]19.

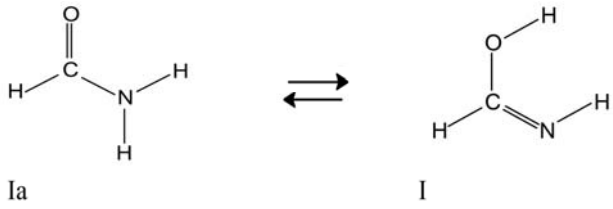
Compared to the other results, the bond lengths and bond angles obtained by AM1 calculations are within the range of those obtained by DFT, RHF and MP2 shown in Table 3. The largest bond length difference is found in the H6C2 bond length compared to that obtained by MP2(Full)/6-1G(d), where this difference was 0.024 Å. Also, the largest bond angle difference is found in H6C2O1 angle compared to that obtained by RHF/3-21G, and it was 0.9°. This means that the results obtained by AM1 calculations in this work are in good agreement with those previously obtained by the above theoretical methods.

Most of the work on formamide and formamidic acid before 1997 was reviewed in the work done by Fogarasi and Szalay.[21] Also, in their work they showed that the geometry of formamide is affected by both basis set and electron correlation. It is found that these two factors work in opposite directions. The former prefers planar structure whereas the latter prefers nonplanarity. They obtained exactly planar structure at the highest level of theory where large basis set (CCSD(T)/ccPTVZ) was employed. Markova and Enchev[16] obtained a nonplanar structure for formamide at MP2/6-31+G(d) level, where they found that the amino group is turned 5.5° from the plane of the molecule. As the aim of this work is to analyze the

effect of substituents on tautomerism, it is recommended to consult the geometrical details of formamide and formamidic acid, reviewed elsewhere.[2,4,14,16,21,25,40]

The heat of formation of formamide Ia is found to be –187.41 kJ/mol. It is more stable than formamidic acid I by 49.01 kJ/mol. So, the tautomerization reaction in Scheme 2 is endothermic. The energy difference between formamide and the most stable formamidic acid is found to be 51.04 kJ/mol as obtained by Schlegel and coworkers at HF/6-31G* level,[36] 48.5 kJ/mol at MP2/6-311++G** level[4] and 49.10 kJ/mol at MP4/6-311++G(3df,2p) level.[16] Also, this energy difference is calculated by the use of 11 different combinations of methods and basis sets.[18] The values obtained were in the range of 48.83 and 59.58 kJ/mol. These values are in good agreement with the value obtained in this work (49.01 kJ/mol).

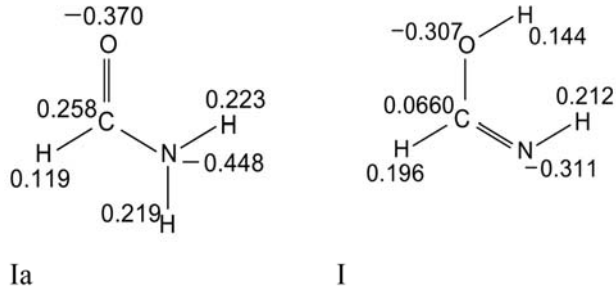
The calculated entropy values for the formamide Ia and formamidic acid II were found to be 252.19 and 250.85 J/molK respectively. The entropy change was small and in the favor of formamide because it is negative. The entropy of formamide was calculated to be 256.24 J/molK at RHF/6-31+G*//RHF/6-31+G* by other workers.[41] The free energy (ΔG) for the tautomerization reaction in Scheme 2 at 25 °C is calculated to be 49.41 kJ/mol, $\Delta G = \Delta H - T\Delta S$. This positive free energy indicates that the tautomerization reaction is spontaneous in the reverse direction (Scheme 2).



Scheme 2

Free energy change value of 51.60 kJ/mol is obtained by highly accurate G2MP2/6-31+G* method[2] and 53.39 kJ/mol by HF/6-31G** method.[18] Other workers have obtained a value of 51.50 kJ/mol at the QCISD/6-31++G** level,[42] 57.28 kJ/mol by DFT at the B3LY/6-311++G** level,[14] 57.3, 56.6, and 54.9 kJ/mol by use of DFT method, and 55.1, 49.8 and 51.3 by use of MP2 ab initio method[15] using different basis sets. Obviously, the result obtained in this work (49.41 kJ/mol) is nearer to those obtained by ab initio method. The results obtained by DFT seem to be high compared to the result obtained in this work and to those obtained by MP2, HF and QCISD methods. This indicates that the results obtained in this work (semiempirical AM1) are in good agreement with those obtained by other ab initio methods. This conclusion was also reported by Ventura and Rama[20] on their, comparative study on gas-phase structure and acidity of formohydroxamic acid and formamide.

The extra stability of formamide Ia over formamidic acid I is explained by the well-known resonance stabilization model.[21,35,43,44] This extra stability could also be explained by charge distribution on the atoms of both tautomers obtained from this work (Scheme 3). From the charge distribution on the atoms in both structures, it can be clearly seen that the opposite charges are larger in magnitude in formamide Ia, which results in larger attraction forces compared to those in formamidic acid I. This suggests that the former (I) is more stable than the latter (II), which makes the equilibrium inclined in the reverse direction. The concept of atomic charges is used to explain the stability of *cis* and *trans* conformers of *N*-substituted formamides for methyl and fluoromethyl substituents.[24]



Scheme 3

The calculated equilibrium constant value at 25 °C, employing the relation $\ln K = -\Delta G/RT$, was 2.21×10^{-9}. An energy barrier for the formamide/formamidic acid tautomerization reaction of 187.86 kJ/mol was obtained by Kalia et al.[2] By using Arrhenius equation, $k = A_o \exp(-E_a/RT)$, neglecting the statistical factor (A_o), the rate constant, k, for the formamide/formamidic acid tautomerization reaction is calculated to be 1.26×10^{-33}, which is a very low value, indicating a very slow tautomerization reaction. So, both thermodynamics and kinetics work point in the same direction; ΔG predicts a nonspontaneous reaction and the rate constant predicts a very slow reaction in the forward direction.

3. 2. Effect of Substituents

Introduction of substituents onto formamide and formamidic acid molecules affects the bond lengths and bond angles. The computed equilibrium structures (bond lengths and bond angles) obtained from this work are reported in Table 4 for substituted formamide and in Table 5 for substituted formamidic acid molecules.

From an inspection of the bond lengths in susbstituted formamide molecules (Table 4), it can be seen that they were slightly affected by substitution compared to those in the unsubstituted formamide. All of the changes in bond lengths were 0.009 Å or lower. Regarding the

Table 4. Calculated bond lengths (Å), bond angles and dihedral angles (degree) of the X-substituted formamides.*

X-Formamide	F	Cl	Br	I	CH_3	CF_3	CN	NO_2	H
O1C2	1.240	1.238	1.238	1.239	1.248	1.237	1.243	1.234	1.243
C2N3	1.373	1.366	1.363	1.362	1.375	1.360	1.370	1.360	1.367
H4N3	0.987	0.988	0.989	0.989	0.985	0.989	0.987	0.992	0.986
H5N3	0.988	0.991	0.992	0.992	0.989	0.991	0.990	0.992	0.990
X6C2	1.354	1.757	1.956	2.09	1.508	1.578	1.459	1.574	1.114
O1C2N3	126.59	123.89	122.83	122.10	119.83	124.87	122.24	126.62	121.94
H4N3C2	121.12	121.59	121.86	121.80	121.19	120.92	121.60	121.66	121.18
H5N3C2	118.41	118.84	119.23	119.77	119.75	119.68	119.04	118.22	120.60
X6C2O1	116.36	120.97	123.06	124.42	121.98	119.68	121.35	116.62	123.09
H4N3C2O1	179.93	–179.98	180.00	179.93	179.89	179.47	179.93	0.00	0.040
H5N3C2O1	0.079	–0.007	0.00	0.055	0.077	0.36	0.040	180.00	0.024
X6C2O1N3	0.020	180.00	180.00	0.030	0.090	–179.70	0.001	180.00	–0.010

* X is the substituent (atom number 6) attached to the carbonyl carbon.

Table 5. Calculated bond lengths (Å), bond angles and dihedral angles (degree) of the X-substituted formamidic acids.*

X-Formamide acid	F	Cl	Br	I	CH_3	CF_3	CN	NO_2	H
O1C2	1.384	1.388	1.387	1.382	1.393	1.380	1.392	1.385	1.381
C2N3	1.291	1.284	1.280	1.277	1.287	1.278	1.286	1.284	1.277
H4N3	0.996	0.997	0.998	0.998	0.997	0.997	0.998	0.998	0.997
H5O1	0.967	0.968	0.969	0.969	0.967	0.969	0.968	0.970	0.967
X6C2	1.345	1.718	1.910	2.052	1.503	1.560	1.444	1.538	1.111
O1C2N3	132.73	129.52	128.98	129.40	127.05	131.19	128.92	130.91	130.20
H4N3C2	114.89	116.38	117.19	117.84	116.54	117.38	116.44	116.20	117.79
H5O1C2	110.16	110.00	110.39	110.95	110.85	110.34	109.94	109.20	111.21
X6C2O1	103.20	108.39	110.31	110.69	108.79	107.69	108.98	106.73	108.39
H4N3C2O1	0.00	0.00	0.00	0.00	0.00	0.135	0.00	0.00	0.00
H5O1C2N3	0.00	0.00	0.00	0.00	0.00	–0.400	0.00	0.00	0.00
X6C2O1N3	180.00	180.00	180.00	180.00	180.00	–179.76	179.99	180.00	180.00

* X is the substituent (atom number 6) attached to the carbonyl carbon. In these two tables (Table 4 and 5) the last coulumn showing the geometrical parameters of the unsubstituted compounds is added to facilitate the comparison.

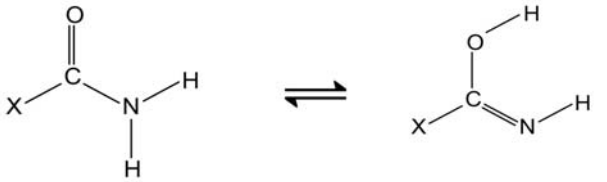
bond angles, the most affected bond angle was O1C2N3, where this angle was increased with all of the substituents. The largest increase was with the NO_2, F and CF_3 substituents. This increase was 4.68, 4.65 and 2.93 degrees, respectively. The increase in the case of all other substituents was 2 degrees or lower.

The most affected bond, in the case of formamidic acid (Table 5) was the C2N3 bond. This was with the F substituent. The length of this bond was increased by 0.014 Å. The increase in the case of the other substituents was found to be in the range from 0.00 to 0.009 Å. The H4N3C2 bond angles have decreased with all susbstiutents, except with the I substituent, where it was slightly increased by, 0.050 degree. The decrease in this bond angle was the largest where it was 2.90 degrees. The decrease in the other angles was 1.59 degrees or lower. All of the H5O1C2 bond angles have decreased by the substituents, and the largest decrease was in the case of NO_2 substituent. This decrease was by 1.27 degrees. The O1C2N3 bond angle was decreased by some of the substituents and increased by the others. The largest change was in the case of CH_3 substituent, where this angle was decreased by 3.15 degrees.

Obviously, the O1C2 bond has double bond character in formamide compounds, where it is significantly shorter than the C2N3 bond, which has a single bond character. This situation is reversed in the formamidic acid compounds. This is, of course, due to tautomerization.

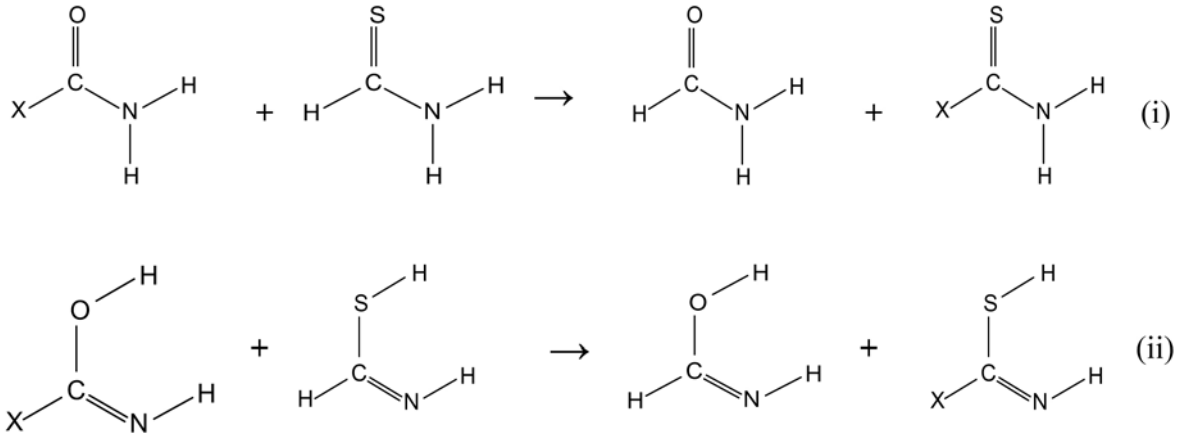
The dihedral angles within the part of the molecule, other than the substituent, in all of the substituted formamide and formamidic acid, were 0.00 or 180.00 with small fluctuation from planarity in some substituents with less than ±0.5 degree. This indicates that the planarity of the molecules was not affected by the substitution. So, all of the substituted and unsubstituted formamamide and formamidic acid molecules have C_S point group of symmetry. The mirror plane bisects the HC6H and FC6F angle and passes through the rest of the atoms in the case of CH_3 and CF_3 substituents respectively.

The spontaneity of the tautomerization reaction in either direction can be guessed from the free energy chan-



Scheme 4

ge, ΔG, for the reaction in Scheme 4, where ΔG is calculated from the equation, $\Delta G = \Delta H - T\Delta S$. Negative ΔG value indicates spontaneity of the reaction in the forward direction, whereas positive value indicates spontaneity in the reverse direction. Also, isodesmic reactions are frequently used to show the effect of substituents on the stability of substances, in this case, on the stability of the substituted formamide and formamidic acid forms of the tautomerization reaction in Scheme 4. Positive ΔH value of the isodesmic reaction indicates stabilization effect, while negative ΔH value indicates a destabilization effect.[38,45–47] The general equations of the isodesmic reactions for the formamide and formamidic acid forms appear in reactions (i) and (ii), respectively.



The heats of formation of halide-substituted compounds in this work can be compared together because of the periodic relation between the halides. The strength of a covalent bond is determined not only by the orbital overlap but also, to a large degree, by the energy of the valence electrons.[48] In the halide-substituted formamides, the extent of overlap would be considered similar because it is between the same type of orbitals, p-orbital of the halide atom and the sp^2 hybrid orbital of the carbonyl carbon. The energy of the valence shell electrons, and consequently, the bond strength and bond energy, generally, follow the same order as the ionization energy.[49] Accordingly, in the halide-substituted formamides, the bond strength follow the order F–C > Cl–C > Br–C > I–C which is the same as the ionization energy order for halides. Lower heats of formation indicate stronger bonds and more stable molecules. The heats of formation, obtained in this work, for halide-substituted formamides were –396.12, –213.95, –151.75, and –100.71 kJ/mol for the F, Cl, Br and I substituents, respectively. It can be seen that lower heat of formation is associated with more stable molecule and stronger C–X bond, as expected from the ionization energy order. The same observation is noticed for the substituted formamidic acid compounds where the heats of formation were found to be –319.33, –133.91, –81.18, and –44.39 kJ/mol for the F, Cl, Br, and I substituents, respectively.

3. 2. 1. Effect of Fluorine Atom Substituent

The calculated heats of formation of F-substituted formamide and formamidic acid were found to be –396.12 and –319.33 kJ/mol, respectively. Also, the calculated entropy for the former was 271.78 J/molK and that for the latter was 270.00 J/molK. Accordingly, the free energy change (ΔG) at 25 °C for the tautomerization reaction in Scheme 4 is calculated to be 77.32 kJ/mol. This value is positive which means that the equilibrium favors the reverse direction. This result is also found from the calculations of the enthalpy changes of the isodesmic reactions for the F-substituted formamide (i) and formamidic acid (ii). The enthalpy change (ΔH) for the former reaction was found to be 43.78 and that of the latter was 43.36 kJ/mol. These values are positive, so they indicate that substitution stabilized both formamide and formamidic acid, but the former is more stabilized because it has a higher ΔH value. This means that the reactants are more stabilized than the products, or, the reaction is spontaneous in the reverse direction. This agrees with the positive ΔG value obtained for this reaction.

3. 2. 2. Effect of Chlorine Atom Substituent

The heat of formation of Cl-substituted formamide was –213.95 kJ/mol, and that of Cl-substituted formamidic acid was –133.91 kJ/mol. So, the enthalpy change for the tautomerization reaction (Scheme 4) is 80.04 kJ/mol. The entropy values were 281.50 and 280.23 J/molK for the Cl-substituted formamide and formamidic acid, respectively. Therefore, the entropy change for the tautomerization reaction is –1.27 J/molK. Accordingly, Δ*G* at 25 °C is calculated to be 80.42 kJ/mol. This positive free energy value indicates that the tautomerization reaction is spontaneous in the reverse direction, or favors the Cl-formamide. The enthalpy change (Δ*H*) for the Cl-substituted formamide isodesmic reaction (i) was 2.33 kJ/mol, and that of Cl-substituted formamidic acid (ii) was –14.09 kJ/mol. So, the Cl-substitution stabilized formamide and destabilized the formamidic acid, which means that the reverse tautomerization reaction is favored according to the results of the isodesmic reactions. This supports the result obtained by the positive Δ*G* value.

3. 2. 3. Effect of Bromine Atom Substituent

The heats of formation of Br-substituted formamide and formamidic acid were –151.75 and –81.18 kJ/mol, respectively. The entropy for the former was 293.01 and that of the later was 292.38 J/molK. Therefore, the calculated Δ*G* at 25 °C is 70.76 kJ/mol. The enthalpy of the isodesmic reaction for the Br-substituted formamide (i) was –10.26 and that for the Br-substituted formamidic acid (ii) was –29.79 kJ/mol. These negative values indicate that both Br-substituted formamide and formamidic acid were destabilized, but the latter was destabilized more because it has more negative value. This means that the equilibrium favors the Br-substituted formamide and the reaction is spontaneous in the reverse direction as also suggested by the positive Δ*G* value.

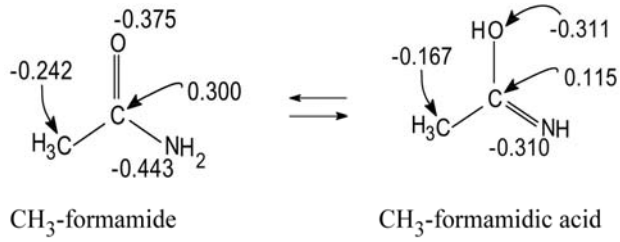
3. 2. 4. Effect of Iodine Atom Substituent

The heat of formation of I-substituted formamide was found to be –100.71 kJ/mol and its entropy value was 300.41 J/molK. Also, the heat of formation of I-substituted formamidic acid was –44.39 kJ/mol and its entropy value was 299.92 J/molK. From these data, the calculated Δ*G* at 25 °C is 56.46 kJ/mol, which is positive, indicating that the reverse reaction is the favorable. Enthalpy changes of the isodesmic reactions also support this result, where the enthalpy change for the I-substituted fomamide (i) was –14.95 kJ/mol and that of formamidic acid (ii) was –31.10 kJ/mol. These values indicate that iodine substitution destabilized both formamide and formamidic acid, but the latter is destabilized more because it has more negative value. So, again, the reverse reaction is favorable.

3. 2. 5. Effect of CH_3 Substituent

The calculated heats of formation of methyl-substituted formamide and that of its corresponding formamidic acid were found to be –212.30 and –156.89 kJ/mol, respectively. The entropy values were 281.02 J/molK for the former and 280.10 for the latter. So, the free energy change (Δ*G*) at 25 °C is calculated to be 55.68 kJ/mol. The positive value of Δ*G* indicates that the reactants are favorable over the products and the reaction is spontaneous in the reverse direction. The enthalpies of the isodesmic reactions support this result also, where they were 3.03 kJ/mol for the substituted formamide (i) and –1.02 kJ/mol for the substituted formamidic acid reaction (ii). The positive value of the formamide isodesmic reaction indicates that the formamide is stabilized by methyl susbstitution, and the negative value for the substituted formamidic acid indicates that formamidic acid is destabilized by methyl substitution. Therefore, the isodesmic reactions also support the result obtained by the free energy change.

One more evidence is to be given here to support the spontaneity of the tautomerization reaction (Scheme 4) in the reverse direction, which is the charge distribution (Scheme 5).



Scheme 5

It is apparent from the charge distribution that the forces are all attractive forces in both forms because the charges on atoms have opposite signs, but they are larger in magnitude in the methyl-substituted formamide compared to the methyl-substituted formamidic acid, which makes the former more stable and the equilibrium favors the reverse direction.

3. 2. 6. Effect of CF_3 Substituent

The heat of formation of trifluoromethyl formamide and trifluoromethyl formamidic acid obtained in this work were –826.59 and –761.21 kJ/mol, respectively. The entropy values were 316.27 and 329.04 J/molK for the former and the latter, respectively. From these data, the calculated Δ*G* at 25 °C is found to be 61.57 kJ/mol. In the case of this substiuent, the entropy change was positive, i.e. in favor of the products, but it is not big enough to overcome the effect of the energy factor which strongly favors the reactant. The enthalpy change for the isodesmic reac-

tion of trifluoromethyl-substituted formamide was 11.56 kJ/mol and that of trifluoromethyl-substituted formamidic acid reaction was 9.44 kJ/mol. Both of these values are positive which means that substitution stabilized both formamide and formamidic acid, but the former is stabilized more because its corresponding isodesmic reaction has higher enthalpy change. The result of this is that free energy change and isodesmic reaction results both suggest that the reactant (trifuorosubstituted formamide) is more stable and the equilibrium is shifted in the reverse direction.

3. 2. 7. Effect of CN Substituent

In this substituent group it is again found that the results of the free energy change and isodesmic reactions favor the CN-substituted formamide. The calculated ΔG at 25 °C was calculated to be 65.17 kJ/mol. This value is positive which favors reverse reaction. The isodesmic reaction enthalpy change for the CN-substituted formamide was –8.60 kJ/mol and that of the CN-substituted formamidic acid isodesmic reaction was –14.17 kJ/mol. These values indicate that both tautomers have been destabilized upon CN-substitution but the formamidic acid was destabilized more, which means that the equilibrium prefers the reverse direction, as suggested from the positive free energy change.

3. 2. 8. Effect of NO_2 Substituent

The calculated heats of formation of NO_2-substituted formamide and formamidic acid were –140.04 and –43.93 kJ/mol, respectively. The calculated entropies were found to be very close to each other, being 295.92 for substituted formamide and 295.90 J/molK for the substituted formamidic acid. According to these data, the calculated ΔG at 25 °C is found to be 96.12 kJ/mol. This is positive, therefore the equilibrium is shifted backwards. The calculations of the isodesmic reaction enthalpies showed that the formamide was stabilized and formamidic acid was destabilized upon NO_2-substitution. These enthalpies were 5.26 and –9.16 kJ/mol for the former and for the latter, respectively. This again suggests that the backward reaction is favorable as suggested by the positive free energy changes.

3. 3. Entropy Changes in Tautomerization Reactions

The free energy change (ΔG) is a combination of energetic (ΔH) and entropic ($T\Delta S$) factors. Forward reaction is energetically favorable when the energy factor is negative, and entropically favorable when the entropy factor is positive. In all of the halide substituents in this work it is found that both factors favor the reverse reaction where all of the ΔH values obtained were positive and all entropy change (ΔS) values were negative.

The entropy changes have small values. This is probably because the reaction is tautomerization reaction. In this type of reactions there is no big structural changes between the reactants and products, as the number of bonds is conserved and most of the atoms maintain their positions. This results in similarity between vibrational, rotational, translational and electronic contributions to the total entropy in both reactants and products, which make the entropy difference (ΔS) between them small. So, it can be concluded that in the tautomerization reactions the direction of spontaneity is mainly determined by energetic factor not by entropic factor.

3. 4. Dipole Moments

The change in dipole moment upon substitution can be understood from the polarity of the substituent and the direction of its dipole moment vector relative to that of the unsubstituted molecule. In this work, halides can be compared to each other. The electron-withdrawing ability, or, the inductive effect follows the order F > Cl > Br > I. The inductive effect is weakened as the distance from the position of substitution increases.[50] In this work, the dipole moments for the halide-substituted formamides were found to be 3.86, 3.62, 3.51, and 3.42 D for the F, Cl, Br, and I substituents, respectively. Obviously, higher electron-withdrawing substituent further polarizes the formamide molecule. This is because the dipole moment vector for the rest of the molecule remains unchanged, resulting in larger dipole moment values for the substituents with larger inductive effect. The same observation was found for the substituted formamidic acids where the dipole moments were 2.99, 2.23, 2.04, and 1.84 D for the F, Cl, Br, and I substituted formamidic acids, respectively.

The geometry of the substituent is also important in determination of the direction and magnitude of the dipole moment vector of that substituent relative to the rest of the molecule. In this work, the dipole moment obtained for CH_3 and CF_3 substituted formamides were 3.75 and 3.73, respectively. The hybridization of the carbon atom in these two substituents is sp^3, therefore, in CF_3 substituent, for example the effect of two of the fluorine atoms is decreased by the effect of the third due to the sp^3 orientation in space. The same effect is obtained in the case of CH_3 substituent. Taking the FCF and HCH bond angles into account, the dipole moments obtained for these two molecules were similar. The dipole moment obtained for the NO_2-substituted formamide molecule was 4.84. This group is planar (sp^2) as found from the dihedral angles, which makes the dipole moment vector due to this substituent large enough to produce a relatively large dipole moment molecule.

The charge re-distribution upon introduction of a substituent is another way to look at the magnitude of the dipole moment vector introduced by a substituent. Higher inductive effect substituent accommodates more negative

charge, leaving the atom attached to it more positive. This results in larger magnitude of the dipole moment vector due to that substituent and, therefore, molecule with higher dipole moment is produced. In the case of formamide substitution, the charges calculated on carbon and halide atoms, respectively, were 0.428 and –0.128 for F substituent, 0.325 and –0.076 for Cl substituent, 0.257 and –0.013 for Br substituent, 0.174 and 0.090 for I substituent. Obviously, the dipole moment vector, that is due to the substituent, is the largest in the case of F substituent and decrease down the group following the inductive effect order. The same effect was also observed for the halide substitution of the formamidic acid.

3. 5. Equilibrium Constants

The equilibrium constant values (K) were calculated form the values of the free energy change for the tautomerization reactions according to the equation, $\ln K = -\Delta G/RT$. The temperature was 25 °C. The values obtained are listed in Table 6.

Table 6. Calculated equilibrium constant values for the formamide/formamidic acid tautomerization reactions obtained for different substituents.

X	K
H	2.21×10^{-9}
F	2.84×10^{-14}
Cl	8.13×10^{-15}
Br	4.00×10^{-13}
I	1.28×10^{-10}
CH_3	1.75×10^{-10}
CF_3	1.63×10^{-11}
CN	3.82×10^{-12}
NO_2	1.45×10^{-17}

The calculated equilibrium constant value for the unsubstituted tautomerization system obtained by DFT (B3LYP) and MP2 ab initio method using 6-311++g(2d,2p) basis set were 2.4×10^{-10} and 1.03×10^{-9}, respectively.[15] Obviously, the value obtained in this work (2.21×10^{-9}) is in a very good agreement with the one obtained by MP2 calculation method. The same comparison can be made in the case of methyl-substituted formamide, where Sklenak and his co-workers have calculated equilibrium constant values of 5.62×10^{-10} at B3LYP/6-31G**//B3LYP/6-31G**, 1.87×10^{-10} at MP2(full)/6-31G** and 2.52×10^{-10} at CCSD(T)/6-311G**//MP2 (full)/6-31G**.[46] The equilibrium constant value obtained in this work in the case of methyl substituent was 1.754×10^{-10}, which is in a very good agreement with those obtained by MP2 ab initio calculation method.

Substituents with different electronic properties have been employed in this work: strong electron withdrawing groups (CN, NO_2, CF_3) and electron donating groups (I, Br, Cl, F, CH_3) with different donation abilities.[24,38,45] From Table 6 can be seen that all of the equilibrium constant values for the tautomerization reactions have decreased upon substitution, compared to that of the unsubstituted tautomeric system. This means that all of the substituents have pushed the equilibrium more in the reverse direction relative to the unsubstituted tautomeric system.

The net effect of the substituents was the same, but to different extents, depending on the nature of the substituent. The substituents have different effects on the formamide and formamidic acid forms due to structural differences. Also, other factors like σ effects, dipolar interactions between the substituent and the carbonyl group,[38,45] overlap between the nitrogen atom lone pair and the substituent lone pair, which is important in the case of halo-substituents.[22] All of these factors influence the orbital energies, which, ultimately, influence the enthalpy change (ΔH) for the tautomerization reaction. This enthalpy change was found to be largely positive in all substituents. Since the entropic factor was minor in tautomerization reactions as discussed above, this enthalpy change (energy factor) is the crucial factor for determination of ΔG and, consequently, the equilibrium constant.

4. Conclusion

It is found that the tautomerization reactions were pushed in the reverse direction with all of the substituents compared to the unsubstituted tautomeric system. This was found from the calculated values of the equilibrium constants. These reactions were governed, to a large extent, by energetic factor, where the entropic factor was minor as shown by the calculations of ΔG for individual substituents. The decrease in equilibrium constant values was in several orders of 10, ranging from 10^{-10} down to 10^{-17}, depending on the nature of the substituent. In order to understand the nature of the changes that happen upon substitution, it would be a valuable and complementary work to have a kinetic study on the tautomerization reactions in this work, and calculate the activation energies and rate constants in each case and then draw conclusions.

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Povzetek

Tvorbene toplote, spremembe entropije in proste energije ter ravnotežne konstante pri 25 °C so bile izračunane s pomočjo AM1 semiempiričnih kvantno kemijskih metod. Izračuni so bili izdelani za nesubstituiran tavtomerni sistem formamid-formamidna kislina ter tudi za substituirane analoge. Ravnotežna konstanta za nesubstituiran primer je bila 2.21 $\times 10^{-9}$. Ugotovljeno je bilo, da imajo ravnotežja substituiranih tavtomernih oblik v vseh raziskanih primerih manjše ravnotežne konstante (glede na nesubstituiran sistem). Vrednosti so bile manjše za več redov 10, pač odvisno od substituentov. Podani so tudi geometrijski parametri (dolžine vezi in koti med njimi) za vse spojine, raziskane v tem delu. Opisana je tudi primerjava rezultatov eksperimentalnih vrednosti s teoretičnimi, dobljenimi z ab initio in DFT metodami na različnih nivojih teorije.