



## Computational Investigation of Methamphetamine and its Halogenated Derivatives as the Main Source of Pain and Skin Itching

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### ABSTRACT

The structures and stability of methamphetamine and its halogenated derivatives as the main causes of increasing blood pressure, heart rate and arrhythmia chronic has been investigated via NMR, Frequencies Calculation and CHELPG analysis. The structures of methamphetamine and halogenated derivatives were designed primarily using of Chem. Bio Draw and their geometry has been optimized at the MP2/6-31G computational level. Frequencies calculations have been carried out to confirm that the structures obtained correspond to energetic minima. According to the obtained thermodynamic parameters, the Gibbs free energy ( $\Delta G$ ) and standard enthalpies ( $\Delta H$ ) of all these molecules are positive and they have unstable structure. Moreover the Natural Bond Orbital (NBO) analysis has provided the detailed insight into the type of hybridization and the nature of bonding in these molecules.

**Key words:** Methamphetamine; NMR; CHELPG; Computational

### INTRODUCTION

Methamphetamine is a variant of amphetamine which has been synthesized in Japan in 1893 by Nagayoshi Nagai from the chemical ephedrine precursor<sup>1-3</sup>. Methamphetamine has one more methyl group in comparison to amphetamine; it is a stimulant and addictive substance that is a stronger central nervous system stimulant than amphetamines<sup>4</sup>. At the room temperature,

methamphetamine is a clear and colorless liquid with an odor characteristic of geranium leaves and it has a chiral center with two enantiomers; in contrast, the amphetamine hydrochloride salt is odorless with a bitter taste<sup>5-9</sup>.

Methamphetamine causes increasing in blood pressure, heart rate and arrhythmia chronic which cause weight loss, tooth decay, hallucinations, pain, and skin itching.

Methamphetamine effects on the body depending on the dosage and duration of its use. In low doses, it can cause an elevated mood and increases the heart rate, blood pressure and body temperature, as well as dilate the pupil. On the other side, in high doses, it can result in heart problems, liver or kidney failure, seizures and even coma<sup>10,11</sup>. Moreover the animal studies show that increasing the concentration of injected methamphetamine decreased dopamine release from the striatum which leads to auto-phagocytosis of the neuritis and apoptosis of neurons in the striatum<sup>12-19</sup>.

In recent decades, an increase in methamphetamine use has been associated with increased disability and death. So understanding the exact structure of methamphetamine and its derivative has attracted more attention in order to find the exact mechanism of methamphetamine acting in the body<sup>20-24</sup>.

In this work, the structure of methamphetamine and halogenated derivatives has been investigated via NMR, MP2/6-31G, NBO Calculations and CHELPG analysis and their HOMO and LUMO energies have been calculated in order to find the reactivity of these compounds. Moreover the formation energies and Gibbs free energies of these compounds calculated via Gaussian software<sup>25, 26</sup>.

### Computational Methods

The structures of methamphetamine and halogenated derivatives were designed primarily using Chem. Bio Draw 12.0 (Figure 1). The geometry of the systems has been optimized at the MP2/6-31Gof computational level<sup>27-29</sup>. Frequencies calculations have been carried out to confirm that the structures obtained correspond to energetic minima. All the calculations of all systems are done in the gas phase by density functional theory (DFT) using MP2 method and the standard 6-31G basis set using Gaussian09 (Gaussian 09, Revision A.02). The total energy, electronic and nuclear energies were calculated for the three studied compounds, as well as HOMO, LUMO energies and the difference between them ( $\Delta E$ ). Finally obtained results were compared to other derivatives. Mulliken charges on the atoms, dipole moments, and geometry parameters such as bond lengths were

also determined by the same method. The energy barrier for rotation around the tow bond in the methamphetamine molecule is also assessed using Gaussian software<sup>30-36</sup>.

## RESULTS AND DISCUSSION

### Geometries

The structures of methamphetamine and halogenated derivatives were designed using of Chem. Bio Draw 12.0 and the obtained results were compared to other derivatives (Figure 1). The optimization, NBO, NMR and CHELPG calculations of the whole systems are done by density functional theory (DFT) using MP2 method and the standard 6-31G basis set using Gaussian09<sup>37,38</sup>.

The optimized geometrical parameters, such as Dipole moment (Debye), nitrogen charge, structure formation energy (HF: kcal/mole), enthalpies ( $\Delta H$ ) and Gibbs free energy ( $\Delta G$ ) are listed in Table 1. As shown in Table 1, the chlorine derivative has the lowest  $\Delta G$  is 99.7307677 Kcal/mol and the methamphetamine molecule has the largest  $\Delta G$  is 121.29689 Kcal/mol. The Cl-mta molecule has the lowest  $\Delta H$  is 148.321687 Kcal/mol and the methamphetamine molecule has the largest  $\Delta H$  is 153.048689 Kcal/mol. Therefore, the formation of chlorinated derivatives requires less energy<sup>39, 40</sup>.

### Rotation energy barrier

The energy barrier for rotation around the tow bond in the methamphetamine molecule is also assessed using Gaussian software and the results are represented in Table 2 and Figure 2.

As shown in Table 2 rotation -61.3182 degree around the N10-C11 bond has the lowest energy state is the most stable for methamphetamine<sup>41, 42</sup>.

### Energies

Various energies such as the equilibrium energy, HOMO-LUMO band gap corresponding to methamphetamine and halogenated derivatives after the geometry optimization are summarized in Table 1. The HOMO and LUMO energies are so important since the basic electronic parameters related to the energy level of frontier orbitals in a molecule and their resulting energy gap. Also both

Table 1. Occupancy of natural orbitals (NBOs), hybrids, geometry and molecular properties and CHELPG of methamphetamine and halogenated derivatives calculated by the MP2 method with 6-31G(d) basis set

Symbol	charge of nitrogen	ΔG	ΔH	Energy of band gap (kcal/mol)	E (kcal/mol)	Dipole Moment(D)	NBO <sup>a</sup>	Occupancy	Hybrides	Energy	Length(A)	ΔV(V2-V1)	ΔV Mulliken(j/c)	ΔV chelpg(j/c)
H - Mta <sup>a</sup>	-0.733586	121.29689	153.048689	-34.7199	-288.62	1.8026	$\sigma_{C_8-N_{10}}$	1.98698	$0.63(sp^{3.26})_{C_8} + 0.77(sp^{2.10})_{N_{10}}$	-0.92443	1.4869	-	-	-2.7023
							$\sigma_{N_{10}-C_{11}}$	1.99244	$0.77(sp^{2.25})_{N_{10}} + 0.62(sp^{3.02})_{C_{11}}$	-0.92104	1.4814	3.6798	7.00171	10.1753
							$\sigma_{N_{10}-H_{23}}$	1.98244	$0.83(sp^{3.45})_{N_{10}} + 0.55s_{H_{23}}$	-0.78029	1.0229	17.315	13.857	18.665
							CR(1) N <sub>10</sub>	1.99947	s	-	-	-	-	-
							LP(1) N <sub>10</sub>	1.94561	$sp^{5.87}$	11.12596	-	-	-	-
F - Mta <sup>a</sup>	-0.187612	108.21653	148.468523	-132.8053	3.2036	3.2036	$\sigma_{C_8-N_{10}}$	1.98535	$0.61(sp^{3.64})_{C_8} + 0.78(sp^{2.1})_{N_{10}}$	-0.94874	1.4990	-	0.01284	-
							$\sigma_{N_{10}-C_{12}}$	1.99001	$0.78(sp^{2.25})_{N_{10}} + 0.62(sp^{3.45})_{C_{12}}$	-0.95038	1.5309	3.5866	0.46059	1.79231
							$\sigma_{N_{10}-F_{11}}$	1.99082	$0.55(sp^{10.59})_{N_{10}} + 0.83(sp^{6.88})_F$	-0.89069	1.4857	8.3551	0.71270	0.29949
							CR(1) N <sub>10</sub>	1.99929	s	-	-	-	-	-
							LP(1) N <sub>10</sub>	1.96317	$sp^{2.52}$	15.51138	-	-	-	-
Cl - Mta <sup>a</sup>	-0.563892	99.7307677	148.321687	-90.26672	3.1577	3.1577	$\sigma_{C_8-N_{10}}$	1.98704	$0.61(sp^{3.85})_{C_8} + 0.79(sp^{1.97})_{N_{10}}$	-0.56116	1.5036	-	0.01850	-
							$\sigma_{N_{10}-C_{11}}$	1.99135	$0.79(sp^{2.17})_{N_{10}} + 0.61(sp^{3.45})_{C_{11}}$	-0.94942	1.4935	3.6049	1.41210	2.39221
							$\sigma_{N_{10}-Cl_{12}}$	1.98347	$0.67(sp^{10.35})_{N_{10}} + 0.73(sp^{10.5})_{Cl_{12}}$	-0.69326	1.9068	3.5873	0.18880	0.64844
							CR(1) N <sub>10</sub>	1.99943	s	-	-	-	-	-
							LP(1) N <sub>10</sub>	1.96222	$sp^{2.85}$	15.48764	-	-	-	-

<sup>a</sup> LP(n)A is a valence lone pair orbital (n) on A atom and CR is 1c core.

HOMO and LUMO are the main orbital take part in chemical stability<sup>43-46</sup>.

As shown in Table 1, the F-mta molecule has the largest energy gap is -132.8053 Kcal/mol and the methamphetamine molecule has the lowest energy gap is -34.7199Kcal/mol. Therefore, fluorinated derivative is less reactive in comparison to methamphetamine because the role of a nucleophile to share electrons<sup>47-49</sup>.

### NMR

In this section, the NMR shielding tensors, isotropic shielding ( $\sigma_{iso}$ ) and anisotropic shielding ( $\sigma_{aniso}$ ),  $\sigma_{11}$ ,  $\sigma_{22}$ ,  $\sigma_{33}$  of methamphetamine and its halogenated derivate has been investigated using MP2/6-31G level in the gas phase. Hamiltonian Chemical shielding is given by following equation (Mehring,1983)<sup>50</sup>:  $H=\gamma\sigma B_0^!$ .

Where  $\gamma$  is magneto-gyric ratio,  $B_0$  is magnetic field and  $I$  is nuclear spin operator. The  $\sigma$  in this equation called NMR chemical shielding tensor whose elements describe the size of chemical shielding as a function of molecular orientation with respect to the external magnetic field.

Quantum chemical calculations yield chemical shielding tensors in the principal axis

system with the order of  $s_{33} > s_{22} > \sigma_{11}$  hence, Eqs. (1) And (2) are used to convert the calculated chemical shielding tensors to the absolute isotropic ( $\sigma_{iso}$ ) and anisotropic ( $\Delta\sigma$ ) chemical shielding parameters:

$$\sigma_{iso} = (\sigma_{11} + \sigma_{22} + \sigma_{33})/3 \quad \dots(1)$$

$$\Delta\sigma = \sigma_{33} - (\sigma_{11} + \sigma_{22})/2 \quad \dots(2)$$

The shielding tensor asymmetry parameter ( $\eta$ ) is given by equation 3.

$$\eta = \frac{|\sigma_{22} - \sigma_{11}|}{|\sigma_{33} - \sigma_{iso}|} \quad \dots(3)$$

The span ( $\Omega$ ) describes the maximum width of the powder pattern and the skew ( $\kappa$ ) describes the amount and orientation of the asymmetry of the tensor<sup>43, 50-52</sup>.

$$S_{pan} = \Omega = \sigma_{11} - \sigma_{33}; \Omega \geq 0$$

$$Skew: \quad \kappa = \frac{3(\sigma_{22} - \sigma_{iso})}{\Omega}; (-1 \leq \kappa \leq +1)$$

Table 3 presents the computed chemical

**Table 2: The calculated energy barrier and dipole moment of rotation around bonds  $N_{10}-C_{11}$  and  $C_6-C_7$**

Rot1( $C_8-N_{10}-C_{11}-H_{26}$ )			Rot2( $C_5-C_6-C_7-C_8$ )		
Angstroms and Degrees	E(k(Cal/mol))	Dipole moment	Angstroms and Degrees	E(k(Cal/mol))	Dipole moment
-76.3181	-1.93521	1.5846	-96.2876	-1.3394	1.5217
-61.3182	-2.28435	1.6619	-81.2875	-1.62046	1.7067
-46.3181	-2.00311	1.7511	-66.2877	-1.66513	1.8218
-31.3181	-1.21214	1.8158	-51.2877	-1.49703	1.8153
-16.3184	-0.35071	1.7985	-36.2877	-1.17443	1.7328
-1.3184	0	1.6636	-21.2876	-0.75589	1.617
13.6819	-0.36922	1.5272	-6.2877	-0.32937	1.4923
28.682	-1.13101	1.5213	8.7123	-0.07455	1.3835
43.682	-1.90245	1.5765	23.7123	0	1.2813
58.682	-2.27939	1.6655	38.7124	-0.10837	1.2157
73.6819	-2.05387	1.7711	53.7124	-0.49905	1.2172
88.6818	-1.29089	1.8653	68.7124	-0.96265	1.303
103.6817	-0.3839	1.7596	83.7124	-1.36337	1.3993

Table3: Computed chemical shifts for selected atoms

Structure	Atom number	$\sigma_{11}$	$\sigma_{22}$	$\sigma_{33}$	$\sigma_{iso}$	$\Delta\sigma$	$\eta$	$\kappa$	Charge
H-Mta*	C7	146.9847	160.9234	181.079	162.9957	27.12495	0.770805	-0.18234	-0.31273
F-Mta*		147.1365	163.0539	188.8494	166.3466	33.7542	0.707352	-0.236811634	-0.32932
Cl-Mta*		148.4062	162.8184	186.8326	166.0191	31.2202	0.692445	-10.844	-0.32798
H-Mta*	C8	136.8285	148.4067	171.1291	152.1214	28.5115	0.609133	-0.3249	0.02915
F-Mta*		126.9628	133.0718	163.9976	141.3441	33.9803	0.269671	-0.670096774	-0.00713
Cl-Mta*		118.6898	127.4056	165.5425	137.2126	42.4948	0.307654	1.639551	-0.00343
H-Mta*	C9	167.2129	184.2486	204.6426	185.368	28.91185	0.883843	-0.08972	-0.45397
F-Mta*		180.1229	188.042	205.7572	191.3074	21.67475	0.548041	-0.382152038	-0.46953
Cl-Mta*		174.704	188.2307	205.31	189.4149	23.8427	0.850998	-6.07815	-0.46198
H-Mta*	N	197.0117	224.9498	279.6787	233.8801	68.69795	0.61002	-0.32408	-0.73359
F-Mta*		-400.716	-40.8172	261.5734	-59.9866	482.34	1.119228	0.086832433	-0.18761
Cl-Mta*		-274.858	20.7531	267.3612	4.4186	394.4139	1.124242	1.016999	-0.56389
H-Mta*	C11	155.5817	159.7533	204.3224	173.2191	46.6549	0.134121	-0.82882	-0.23831
F-Mta*		133.8418	152.6714	198.9021	161.8051	55.6455	0.507577	-0.421164673	-0.26106
Cl-Mta*		122.0069	143.4918	201.1619	155.5535	68.4125	0.471073	-5.10898	-0.25977
H-Mta*	H17	24.6718	31.9568	35.7524	30.79367	7.4381	1.469125	0.314911	0.161477
F-Mta*		24.5395	31.8223	35.6076	30.65647	7.4267	1.470936	0.315997326	0.166793
Cl-Mta*		24.4303	31.7162	35.9324	30.693	7.8592	1.390598	-1.94299	0.170266
H-Mta*	H18	27.9644	30.0751	33.804	30.6145	4.78425	0.661765	-0.27711	0.160793
F-Mta*		27.2003	29.1569	32.6975	29.6849	4.5189	0.649472	-0.288146693	0.203244
Cl-Mta*		27.9728	29.2671	32.4583	29.8994	3.8384	0.505803	1.215115	0.200161
H-Mta*	H19	28.2291	30.9838	33.5421	30.91833	3.93565	1.049903	0.036966	0.174737
F-Mta*		26.5702	30.5448	34.2974	30.4708	5.7399	1.038677	0.028729682	0.193684
Cl-Mta*		26.5414	30.1423	34.4971	30.3936	6.1552	0.877519	-0.42479	0.202707
H-Mta*	H20	26.0701	30.7593	37.9129	31.58077	9.4982	0.74054	-0.20809	0.157462
F-Mta*		26.3046	30.1412	38.2827	31.57617	10.0598	0.572069	-0.359398402	0.156771
Cl-Mta*		26.1879	30.5716	38.2559	31.6718	9.8762	0.665801	-0.38022	0.162089
H-Mta*	H21	27.009	30.2733	39.1423	32.14153	10.50115	0.466278	-0.46193	0.153787
F-Mta*		26.9275	30.9158	38.7752	32.20617	9.85355	0.607137	-0.326739367	0.164108
Cl-Mta*		26.7877	30.4159	39.473	32.2255	10.8712	0.500614	-0.39114	0.163566
H-Mta*	H22	29.1459	30.3661	37.9655	32.4925	8.2095	0.222949	-0.7233	0.143134
F-Mta*		26.4801	30.396	36.8549	31.24367	8.41685	0.697868	-0.245114123	0.195033
Cl-Mta*		26.9462	31.3367	36.356	31.5463	7.2146	0.912843	-0.36039	0.188213
H-Mta*	H24	25.5249	27.9229	38.3388	30.59553	11.6149	0.309688	-0.62572	0.162492
F-Mta*		24.6873	28.0878	34.3382	29.03777	7.95065	0.641551	-0.29529992	0.208249
Cl-Mta*		24.9937	27.479	35.2048	29.2258	8.9684	0.415672	0.620178	0.207114
H-Mta*	H25	25.8083	30.0883	37.3398	31.0788	9.3915	0.683597	-0.25769	0.169746
F-Mta*		26.8157	28.7303	37.1739	30.90663	9.4009	0.305492	-0.630320905	0.178455
Cl-Mta*		25.5696	28.5438	37.8828	30.6654	10.8261	0.412087	-0.77634	0.188893
H-Mta*	H26	25.192	29.7145	37.603	30.8365	10.14975	0.683666	-0.27121	0.127256
F-Mta*		25.226	29.1398	34.5117	29.62583	7.3288	0.801045	-0.157025319	0.17304
Cl-Mta*		25.7331	28.0734	35.49	29.7655	8.5868	0.408822	-0.37564	0.166762

\*Mta=methamphetamine

The isotropic chemical shielding  $\sigma_{iso}$  parameters are average of parameters,  $\sigma_{11}$ ,  $\sigma_{22}$  and  $\sigma_{33}$ .

shift for selected hydrogen, nitrogen and carbon atoms. According to this table, isotropic shielding value ( $\sigma_{\text{iso}}$ ) for N atom of F-meta molecule is a negative value, because F is electronegative. N of Cl-Mta molecule has the lowest isotropic shielding and the highest anisotropic shielding value, respectively, because Cl is electronegative and large atom.

### NBO analysis

Population analysis is a mathematical way of partitioning a wave function or electron density into charges on the nuclei, bond orders, and other

related information. A full NBO analysis is obtained in Gaussian when using the POP=NBO keyword.

Natural bond analysis provides an efficient way to study intra and intermolecular bonding and interaction among bonds, and also provides a convenient basis for investigating charge transfer or conjugative interactions in molecular systems.

NBOs are an orthonormal set of localized "maximum occupancy" orbitals whose leading N/2 members (or N members in the open-shell case) give the most accurate possible Lewis-like

**Table 4: Second-order interaction energy (E2, kcal/mol) between donor and acceptor orbitals in methamphetamine and halogenated derivatives**

thyl-1 -phenylpropan-2-amine				b: N-fluoro-N-methyl-1 -phenylpropan-2-amine				c: N-chloro-N-methyl-1 -phenylpropan-2-amine					
Acceptor NBO (j) <sup>a</sup>	E(2) <sup>b</sup>	E(0)-E(i) <sup>c</sup> a.u.	F(i,j) <sup>d</sup> a.u.	Donor NBO (i)	Acceptor NBO (j) <sup>a</sup>	E(2) <sup>b</sup>	E(0)-E(i) <sup>c</sup> a.u.	F(i,j) <sup>d</sup> a.u.	Donor NBO (i)	Acceptor NBO (j) <sup>a</sup>	E(2) <sup>b</sup>	E(0)-E(i) <sup>c</sup> a.u.	F(i,j) <sup>d</sup> a.u.
$\pi^* \text{C}2\text{-C}3$	44.1	0.46	0.128	$\pi \text{C}1\text{-C}6$	$\pi^* \text{C}2\text{-C}3$	43.0	0.47	0.12	$\pi \text{C}1\text{-C}6$	$\pi^* \text{C}2\text{-C}3$	43.3	0.47	0.127
$\pi^* \text{C}4\text{-C}5$	39.2	0.47	0.122	$\pi \text{C}1\text{-C}6$	$\pi^* \text{C}4\text{-C}5$	38.9	0.48	0.12	$\pi \text{C}1\text{-C}6$	$\pi^* \text{C}4\text{-C}5$	39.1	0.48	0.122
$\text{R} \text{Y}^*(3) \text{C}2$	1.87	1.15	0.045	$\pi \text{C}2\text{-C}3$	$\pi^* \text{C}1\text{-C}6$	39.7	0.48	0.12	$\pi \text{C}1\text{-C}6$	$\text{R} \text{Y}^*(3) \text{C}2$	1.88	1.16	0.046
$\text{R} \text{Y}^*(3) \text{C}5$	1.75	1.18	0.045	$\pi \text{C}2\text{-C}3$	$\pi^* \text{C}4\text{-C}5$	39.7	0.48	0.12	$\pi \text{C}1\text{-C}6$	$\text{R} \text{Y}^*(3) \text{C}5$	1.83	1.19	0.046
$\pi^* \text{C}1\text{-C}6$	38.0	0.48	0.120	$\pi \text{C}4\text{-C}5$	$\pi^* \text{C}1\text{-C}6$	42.9	0.47	0.12	$\pi \text{C}1\text{-C}6$	$\sigma^* \text{C}7\text{-C}8$	4.64	0.88	0.062
$\pi^* \text{C}4\text{-C}5$	41.9	0.47	0.125	$\pi \text{C}4\text{-C}5$	$\pi^* \text{C}2\text{-C}3$	42.7	0.46	0.12	$\pi \text{C}1\text{-C}6$	$\sigma^* \text{C}7\text{-H}19$	1.88	0.98	0.042
$\text{R} \text{Y}^*(3) \text{C}1$	1.74	1.17	0.044	$\text{LP}(1) \text{N}10$	$\text{R} \text{Y}^*(3) \text{C}8$	1.16	1.57	0.03	$\pi \text{C}2\text{-C}3$	$\pi^* \text{C}1\text{-C}6$	39.9	0.47	0.123
$\text{R} \text{Y}^*(3) \text{C}4$	1.79	1.16	0.044	$\text{LP}(1) \text{N}10$	$\pi^* \text{C}4\text{-C}5$	0.53	0.75	0.01	$\pi \text{C}2\text{-C}3$	$\pi^* \text{C}4\text{-C}5$	40.2	0.48	0.124
$\pi^* \text{C}1\text{-C}6$	42.8	0.47	0.127	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}7\text{-C}8$	1.36	1.15	0.03	$\pi \text{C}2\text{-C}3$	$\text{R} \text{Y}^*(3) \text{C}1$	1.73	1.17	0.044
$\pi^* \text{C}2\text{-C}3$	42.0	0.46	0.125	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}8\text{-C}9$	7.76	1.15	0.08	$\pi \text{C}2\text{-C}3$	$\text{R} \text{Y}^*(3) \text{C}4$	1.77	1.16	0.044
$\text{R} \text{Y}^*(3) \text{C}3$	1.77	1.15	0.044	$\text{LP}(1) \text{N}10$	$\sigma^* \text{N}10\text{-F}11$	0.72	0.80	0.02	$\pi \text{C}4\text{-C}5$	$\pi^* \text{C}1\text{-C}6$	43.2	0.47	0.127
$\text{R} \text{Y}^*(3) \text{C}6$	0.89	1.31	0.033	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}12\text{-H}24$	1.42	1.26	0.03	$\pi \text{C}4\text{-C}5$	$\pi^* \text{C}2\text{-C}3$	42.5	0.46	0.125
$\text{R} \text{Y}^*(3) \text{C}8$	0.71	1.42	0.029	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}12\text{-H}26$	7.13	1.23	0.08	$\pi \text{C}4\text{-C}5$	$\text{R} \text{Y}^*(3) \text{C}3$	1.76	1.15	0.044
$\sigma^* \text{C}5\text{-H}16$	0.72	1.18	0.026	$\text{LP}(1) \text{F}11$	$\text{R} \text{Y}^*(2) \text{N}10$	0.91	2.63	0.04	$\pi \text{C}4\text{-C}5$	$\text{R} \text{Y}^*(3) \text{C}6$	0.88	1.33	0.033
$\sigma^* \text{C}7\text{-C}8$	2.64	1.02	0.047	$\text{LP}(1) \text{F}11$	$\sigma^* \text{C}9\text{-N}11$	0.64	1.80	0.03	$\text{LP}(1) \text{N}10$	$\text{R} \text{Y}^*(3) \text{C}8$	1.04	1.50	0.036
$\sigma^* \text{C}7\text{-H}17$	0.5	1.11	0.021	$\text{LP}(1) \text{F}11$	$\sigma^* \text{C}13\text{-H}26$	0.55	1.95	0.02	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}7\text{-C}8$	1.85	1.13	0.041
$\sigma^* \text{C}8\text{-C}9$	10.1	1.02	0.091	$\text{LP}(2) \text{F}11$	$\sigma^* \text{C}9\text{-N}11$	1.49	1.30	0.04	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}8\text{-C}9$	7.62	1.13	0.083
$\sigma^* \text{C}9\text{-H}21$	0.87	1.11	0.028	$\text{LP}(2) \text{F}11$	$\sigma^* \text{N}11\text{-C}13$	0.70	1.32	0.02	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}11\text{-H}24$	1.39	1.25	0.037
$\sigma^* \text{C}11\text{-H}24$	0.92	1.12	0.029	$\text{LP}(3) \text{F}11$	$\sigma^* \text{C}9\text{-H}21$	0.88	1.30	0.03	$\text{LP}(1) \text{N}10$	$\sigma^* \text{C}12\text{-H}26$	7.31	1.22	0.085
$\sigma^* \text{C}11\text{-H}25$	2.15	1.12	0.044	$\text{LP}(3) \text{F}11$	$\sigma^* \text{N}11\text{-C}13$	1.36	1.15	0.03	$\text{LP}(2) \text{Cl}$	$\sigma^* \text{C}8\text{-N}$	1.03	1.12	0.030
$\sigma^* \text{C}11\text{-H}26$	10.9	1.1	0.099	$\text{LP}(3) \text{F}11$	$\sigma^* \text{C}13\text{-H}26$	0.96	1.29	0.03	$\text{LP}(3) \text{Cl}$	$\sigma^* \text{C}8\text{-N}$	0.88	0.96	0.026

<sup>a</sup>Starred label (\*) denotes antibonding, and Ry corresponds to the Rydberg NBO orbital.

<sup>b</sup>E(2) means energy of hyper conjugative interaction (stabilization energy).

<sup>c</sup>Energy difference between donor and acceptor i and j NBO orbitals.

<sup>d</sup>F(i, j) is the Fock matrix element between i and j NBO orbitals.

description of the total N-electron density (Theoretical Chemistry Institute of the University of Wisconsin).

Table 1 lists the calculated occupancies of natural orbitals for methamphetamine and its halogenated derivate as well as calculated Natural bond hybrids.

For each electron donor (*i*) and acceptor (*j*), the stabilization energy *E*(2) associated with the delocalization *i*→*j* is estimated as:

$$\Delta E_{i \rightarrow j}^{(2)*} = -n_{\sigma} \frac{\langle \sigma_i | \hat{F} | \sigma_j^* \rangle^2}{\epsilon_j^* - \epsilon_i}$$

Where *F* is the effective orbital Hamiltonian and  $\langle \sigma_i | \hat{F} | \sigma_j^* \rangle^2$  is the Fock matrix of element *i* and *j*

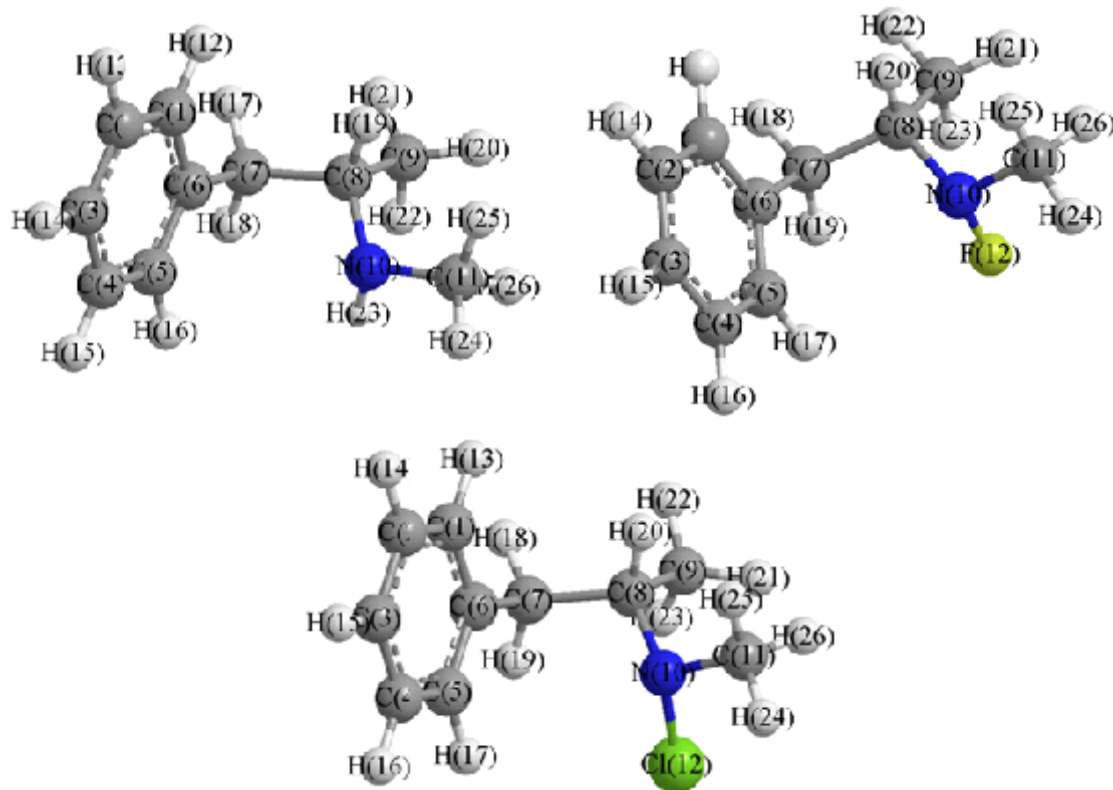


Fig. 1: Optimized structure of (a) methamphetamine (b) fluorine derivatives (c) Chlorine derivatives

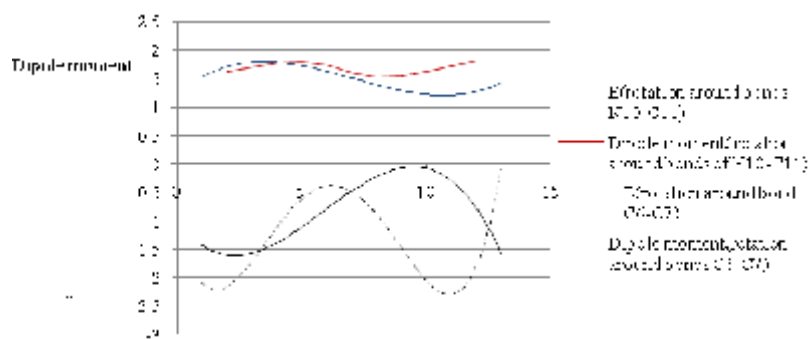


Fig. 2: Potential energy and dipole moment verses degrees changing

NBO orbitals,  $\varepsilon_i^*$  and  $\varepsilon_i$  are the energies of  $i$  and  $j^*$  NBOs and  $\eta_c$  is the population of the donor  $\sigma$  orbital.

Table 4 lists the selected values of second order perturbation theory analysis of Fock matrix at MP2/6-31G level of theory as well as the selected values of the calculated second order interaction energy (E2) between donor–acceptor orbitals in methamphetamine and halogenated derivatives. According to these results, the strongest interactions are the electron donations from a  $\pi_{C-C}$  to the antibonding acceptor  $\pi_{C-C}$  orbitals. According to calculations, the nitrogen atom forms three single bond (sigma bond) with two carbon atoms  $C_8$  and  $C_{11}$  ( $\sigma_{C_8-N_{10}}$  and  $\sigma_{N_{10}-C_{11}}$ ), and a hydrogen atom  $H_{23}$  ( $\sigma_{H_{23}-N_{10}}$ ), a lone pair orbital (Lp), and a CR orbital. As seen from Table 3, the LP hybrid is an  $sp^{5.87}$  for the H-MTa molecule,  $Sp^{2.52}$  hybrid for the F-Mta molecule, and  $Sp^{2.85}$  for the Cl-Mta molecule.

#### Charges from Electrostatic Potentials using a Grid (ChelpG)

In this method, the molecular electrostatic potential is observable and is used for ChelpG population analysis method. Though the molecular electrostatic potential is observable (can be measured) in the population analysis, it is computed from the wave function of the system. The most notable disadvantage of ChelpG is that it does not work well for large systems, especially those with “inner” atoms since the molecular electrostatic potential is a surface characteristic (Ramachandran et al., 2008).<sup>53</sup> The results of

ChelpG are collected in Table 1. As it can be seen in this table,  $\sigma_{C_8-N_{10}}$  of these molecules has the lowest  $\Delta V$  chelpg is -2.7023j/c in the H-Mta, -1.79231 j/c in the F-Mta, and -2.39221 j/v in the Cl-Mta.

#### CONCLUSION

In the present work, the theoretical analyses of methamphetamine and its halogenated derivatives have been performed and the Dipole moment ( $\mu$ ) and energy of structure formation (HF) of these molecules have been obtained. According to these results F-Mta\* has lowest and methamphetamine has highest dipole moment and HF.

Also according to the obtained thermodynamic parameters, it has been found that the amount of Gibbs free energy ( $\Delta G$ ) and standard enthalpies ( $\Delta H$ ) of methamphetamine and its halogenated derivative are positive value, therefore methamphetamine and its halogenated derivative are unstable structure. Also the chemical shifts have been calculated using quantum mechanics.

Moreover the Natural Bond Orbital (NBO) analysis has provided the detailed insight into the type of hybridization and the nature of bonding in methamphetamine and its halogenated derivative. Finally the Charges from Electrostatic Potentials Were also calculated and the results compared to different derivatives.

#### REFERENCES

- Nagai, T.; Kamiyama, S. *International Journal of Legal Medicine*. **1988**, *101*(3), 151-159.
- Lineberry, T.W. *Mayo Clinic Proceedings*. **2006**, *81*(1), 77-84.
- Meredith, C.W.; Jaffe, C.; Ang-Lee, K.; Saxon A.J. *Harvard Review of Psychiatry*. **2005**, *13*(3), 141-154.
- Molitor, F.; Truax, S.; Ruiz, J. *West J Med*. **1998**, *168*, 93–97.
- Chang, L.; Alicata, D.; Ernst, T. *Addiction*. **2007**, *102*(Supple 1), 16–32.
- Mollaamin, F.; Monajjemi, M. *Physics and Chemistry of Liquids*. **2012**, *50*(5), 596–604
- Monajjemi, M.; Rajaeian, E.; Mollamin, F.; Naderi, F.; Saki, S. *Physics and Chemistry of Liquids*. **2008**, *46*, 299-306.
- Mollaamin, F.; Varmaghani, Z.; Monajjemi, M. *Physics and Chemistry of Liquids*. **2011**, *49*(3), 318–336
- Monajjemi, M.; Honarparvar, B. H.; Haeri, H.; Heshmat, M. *Russian Journal of Physical Chemistry C*. **2006**, *80*(1), S40-S44.
- Westfall, D.P.; Westfall, T.C. *Miscellaneous Sympathomimetic Agonists*. In Brunton LL, Chabner BA, Knollmann BC. *Goodman & Gilman's Pharmacological Basis of Therapeutics* (12th ed.). New York: McGraw-Hill. **2010**. ISBN 978-0-07-162442-8.



11. Chomchai, C.; Na Manorom, N.; Watanarungsan.P.;Yossuck P.; Chomchai S. *Southeast Asian J. Trop. Med. Public Health*. **2010**, *35* (1): 228–231. PMID 15272773.
12. Ricaurte, G.A.; Schuster, C.R.; Seiden, L.S.*Brain Research*. **1980**, *193*, 153–163.
13. Wagner, G.C.; Ricaurte, G.A.; Johanson, C.E.; Schuster, C.R.; Seiden, L.S. *Neurology*. **1980**, *30*, 547–550.
14. Villemagne, V.; Yuan, J.; Wong, D.F.; Dannals, R.F.; Hatzidimitriou, G.; Mathews, W.B.; Ravert, H.T.;Musachio, J.; McCann, U.D.; Ricaurte, G.A. *The JournalofNeuroscience*.**1998**, *18*, 419–427.
15. Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Franceschi, D., Sedler, M., Gatley, S.J., Miller, E., Hitzemann, R., Ding, Y.S. *The Journal of Neuroscience* **2001**, *21*, 9414.
16. Monajjemi, M.; Mollamin,F. *Journal of Computational and Theoretical Nanoscience*, **2012**, *9*(12) 2208-2214 .
17. Mollamin,F.; Monajjemi, M.; MehrzadJ. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2014**, *22*: 738-751,
18. Monajjemi, M.; Robert Wayne, Jrand James E. Boggs, *Chemical Physics*. **2014**, *433*, 1-11.
19. Ghalandari, B.; Monajjemi, M.; Mollaamin, F. *Journal of Computational and Theoretical Nanoscience*. **2011**, *8*: 1212-1219.
20. Monajjemi, M.;FarahaniN.; Mollaamin,F. *Physics and Chemistry of Liquids*. **2012**, *50*(2), 161-172.
21. Mollaamin, F.; Najafpour, J.;Ghadami, S.;Ilkhani, A. R.;Akrami, M. S.;Monajjemi, M. *J. Comput. Theor .Nanosci*. **2014**, *11*, 1290-1298
22. Monajjemi, M.; Mollaamin, F.;Karimkeshteh, T. *J. Mex. Chem. Soc*. **2005**, *49*(4), 336-340.
23. ahanA.;Monajjemi, M. *ActaBiotheor*. **2011**, *59*, 291–312.
24. Monajjemi, M.; Mollaamin,F. *J Clust Sci*. **2012**, *23*, 259–272
25. Monajjemi, M.; Khaleghian, M. *J Clust Sci*. **2011**, *22*, 673–692
26. Monajjemi, M.; Faham R.;Mollaamin,F. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2012**, *20*, 163-169.
27. Møller,C.; Plesset, M. S. *Phys. Rev*.**1934**, *46*, 0618-22
28. Frisch, M.J.; A.Pople, J. S.; Binkley, J.J. *Chem. Phys*. **1984**, *80*, 3265.
29. Frisch, M. J. et al. *Gaussian 09, Revision A.02*, **2009**. *Gaussian, Inc., Wallingford CT, 2009*. *Gaussian, Inc., Wallingford CT*.
30. Monajjemi,M.; JafariAzan M.; Mollaamin F. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2013**, *21*(6), 503–515.
31. Yahyaei,H.;Monajjemi, M.;Aghaie,H., Zare K. *Journal of Computational and Theoretical Nanoscience*. **2013**, *10*(10), 2332-2341.
32. Monajjemi, M.; Boggs, J.E. *J. Phys. Chem A*. **2013**, *117*, 1670.
33. Ardalan, T.;Ardalan,P.;Monajjemi, M. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2014**, *22*, 687–708,
34. Monajjemi, M. *Chemical Physics*. **2013**, *425*, 29-45.
35. Yahyaei,h.;Monajjemi, M. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2014**, *22*, 346-361.
36. Monajjemi, M.; Lee, V. S.; Khaleghian, M.; Honarparvar, B.;Mollaamin,F. *J. Phys. Chem. C*. **2010**, *114*, 15315-15330.
37. Monajjemi, M. Karachi, N.;Mollaamin, F. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2014**, *22*, 643-662.
38. Monajjemi, M. *Struct Chem*. **2012**, *23*, 551-580.
39. Monajjemi, M.; Heshmat, M.; Haeri,H. *H.Biochemistry (Moscow)*. **2006**, *71*, S113-S122.
40. Monajjemi, M.;Sobhanmanesh, A.; Mollaamin, F. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2013**, *21*, 47-63.
41. Monajjemi, M.;Baheri, H.; Mollaamin, F. *Journal of Structural Chemistry*. **2011**, *52*(1), 54-59.
42. Monajjemi, M.;SeyedHosseini, M.; Mollaamin, F. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2013**, *21*, 381-393.
43. Gunasekaran, S.; Balaji, R. A.; Kumaresan, S. *Can. J. Anal. Sci. Spectrosc*. **2008**, *53*, 149.
44. Monajjemi, M.;Yamola, H.; Mollaamin, F. *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2014**, *22*, 595–603.
45. Mollaamin,F.;Monajjemi, M. *Journal of Computational and Theoretical Nanoscience*. **2012**, *9*(4), 597-601.
46. Monajjemi, M.; Chegini,H.; Mollaamin,F.;

- Farahani, P.; *Fullerenes, Nanotubes, and Carbon Nanostructures*. **2011**, *19*, 469-482.
47. Monajjemi, M.; Falahati, M.; Mollaamin, F. *Ionics*. **2013**, *19*, 155-164.
48. Mollaamin, F.; Shahani pour, K.; Ilkhani.; A. R.; Sheckari, Z.; Monajjemi, M. *Russian Chemical Bulletin, International Edition*. **2012**, *61*(12), 2193-2198.
49. Monajjemi, M.; Afsharnezhad, S.; Jaafari, M.R.; Abdolahi, T.; Nikosade, A.; Monajjemi, M. *Russian Journal of physical chemistry A*. **2007**, *2*, 1956-1963.
50. Mehring, M. *Principles of High Resolution NMR in Solids*. Springer, Berlin. **1983**.
51. Monajjemi, M.; Razavian, M.H.; Mollaamin, F.; Naderi, F.; Honarparvar, B. *Russian Journal of Physical Chemistry A*. **2008**, *82* (13), 2277-2285.
52. Defalque, R.J.; Wright, A.J. *Bull. Anesth. Hist.* **2011**, *29*(2): 21-24, 32.
53. Ramachandran, K.I.; Deepa Gopakumar, Krishnan Namboori. *Springer Berlin Heidelberg*. **2008**, 253-255.