Interaction Energies of Neurotransmitter with Cations-(Dopamine-Li+, Na+, K+): Density Functional Theory Calculations

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The energy minima of systems made of dopamine molecule with lithium, sodium and potassium cations have been determined with the help of quantum chemical computations the B3LYP density functional theory level of computation and the standard 6-311++G(d,p) basis set. Different coordination sites for metal ions on several dopamine conformers were considered. Several structures close in energy and the most stable form corresponds to a bidentate complex in which the cation interacts with two oxygen atoms of hydroxyl group of dopamine and optimized structures indicate that Li+, Na+ and K+ prefer a bidentate coordination, bonding with both oxygen atoms of hydroxyl group of dopamine and formation of 5 membered ring.

Key Words: Dopamine, Density functional theory, Quantum chemical computations, Li+, Na+, K+.

INTRODUCTION

Neurotransmitters are small molecules that liberated by a presynaptic neuron into the synaptic cleft and cause a change in the postsynaptic membrane potential. Neurotransmitters action receptors, which are *trans* membrane proteins that have an extra cellular site that binds the neurotransmitter and suffers some conformational change. Each neurotransmitter has a particular biosynthetic pathway, but can be divided into three principal classes, since they share some enzyme or metabolic pathway.

The first class is made up of acetylcholine alone, the second classes are the biogenic amines, are molecules formed by an amino acid losing a hydroxyl or carboxyl group. The third class is made up amino acids presences.

Dopamine is a biogenic amino compound and acts as a monoamine neurotransmitter. Dopaminergic neurons are widely distributed through out the brain in three important dopamine systems. A decreased brain dopamine concentration is a contributing factor in Parkinson's disease, while an increase in dopamine concentration has a role in the development of schizophrenia.

The metal-dopamine equilibrium systems are themselves fairly complex[1]. In the physiological pH range, dopamine coordinates to the metal ion like amino acid, but bonding of one or both phenolic hydroxyl groups cannot be excluded. The stabilities of mixed ligand complexes of dopamine and some amino acids were determined[2].

Lithium, sodium and copper ion affinities of the most common amino acids have been measured[3-6]. The development of, the initio Hartree-Fock including configuration interaction and density functional methods, in conjunction with the increasing power of computers, offers reliable new tools also in this area. In particular, the density functional methods have been proven to be very efficient for the prediction of different molecular properties and metal ion affinity[6-10].

Interaction between the Cu^+ and glycine, cysteine and serine employing HF, MP_2 and $B_3LYP/6-31G^*$ methods also were done[11,12].

Interaction of Li^+ cation with small molecules like H_2O and NH_3 with $6-311++G^{**}$ basis set has been considered[13-15]. As it is evident from previous studies, the metal-amino complexes have been widely examined, but no work exists on the interaction between metal cations and dopamine.

In the present work, interaction between Li^+, Na^+ and K^+ ion with dopamine was investigated. The computed properties included the preferred coordination site of the metal cation and the geometrical structure of the complexes and their vibrational frequencies.

COMPUTATIONAL DETAILS

The computations have been performed with the Gaussian 2003 package[16]. For establish the best basis set, dopamine have been optimized with different basis sets using the hybrid Beckes[17] and Lee *et al.*[18].

Interaction energy Ej considered as the negative of the enthalpy for the process:

$$B + M^+ \rightarrow BM^+$$
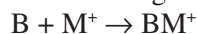
That has been calculated as:

$$E_1 = E(B \ldots M^{n+}) - [E(B) + (E(M^{n+})]$$
$$E = E_{cley} + E_{VIB}$$

where E_{clc} is the electronic energy obtained from the SCF computation and E_{vib} includes the zero point energy and temperature correction[19] from 0-298 K.

The geometry of vibrational frequencies has been computed to characterize the stationary points.

RESULTS AND DISCUSSION

Choice of basis sets: Very few works have been devoted to theoretical determination of metal ion affinity. The computations for dopamine have been performed within the formalism of density functional theory (DFT) with different basis sets. Results are shown in Table-1 (energies in Hartree and relative energies in Kcal/mol). The best compromise between computational cost and reliability of the results is reached with the $B_3LYP/6-311++G^{**}$ level of theory. Present results also confirmed selection of basis set by metal ion affinities for glycine with lithium, sodium and potassium[13]. The results show that differences of minimum energy in basis set $6-311++G^{**}$ with other basis set is noticeable. Therefore, we have chosen to use the hybrid B_3LYP functional coupled with $6-311++G^{**}$ basis set to determine metal interaction of dopamine.

TABLE-1
DOPAMINE GEOMETRIES OPTIMIZATION AT 298 K USING
HYBRID B_3LYP FUNCTIONAL WITH DIFFERENT BASIS SET

Method	Energy (Hartree)	Relative energy (Kcal/mol)
6-311++G**	-516.8166485	–
6-311+G*	-516.7864550	18.95
6-311++G*	-516.7717343	28.15
6-311++G	-516.7132200	64.87
6-311+G	-516.6741300	89.40
6-31G**	-516.6472370	106.30
6-31G*	-516.6470370	106.40
6-311G	-516.6365000	113.00
6-311G*	-516.6148253	126.65
6-31G	-516.5040420	196.16
6-21G	-516.4321040	241.34

Coordination mode: In principle, the metal cation can coordinate with dopamine in four different positions. (1) on ammonia nitrogen, (2) on hydroxyl oxygen (2 position, O_7 and O_9), (3) on both oxygen of hydroxyl group in bicoordinated mode. All of possible metal coordination modes in compounds **I-IV** (Fig. 1) to dopamine have been explored. Results from B_3LYP/6-311++G** full energy minimization of complexes dopamine-metal are shown in Tables 2-4.

TABLE-2
ENERGIES (HARTREE) AND RELATIVE ENERGIES (Kcal/mol) OF THE OPTIMIZED
CONFORMATIONS (B_3LYP/6-311++G**) FOR COMPLEXES OF DOPAMINE-Li^+ AT 298 K

Structure	Energy (Hartree)	Relative energy (Kcal/mol)
III	-524.197362	0
IV	-524.172430	15.675
II	-524.172300	15.720
I	-524.172390	15.660

TABLE-3
ENERGIES (HARTREE) AND RELATIVE ENERGIES (Kcal/mol) OF THE OPTIMIZED
CONFORMATIONS (B_3LYP/6-311++G**) FOR COMPLEXES OF DOPAMINE-Na^+ AT 298 K

Structure	Energy (Hartree)	Relative energy (Kcal/mol)
III	-678.971380	0
II	-678.954994	10.280
IV	-678.946824	15.412
I	-678.946022	15.920

The vibrational analysis indicates that all these structures are minimum. B_3LYP/6-311++G** absolute (E in Hartree) and relative energies (ΔE in Kcal/mol) at 298 K.

TABLE-4
ENERGIES (HARTREE) AND RELATIVE ENERGIES (kcal/mol) OF THE OPTIMIZED
CONFORMATIONS (B₃LYP/6-311++G**) FOR COMPLEXES OF DOPAMINE-K⁺ AT 298 K

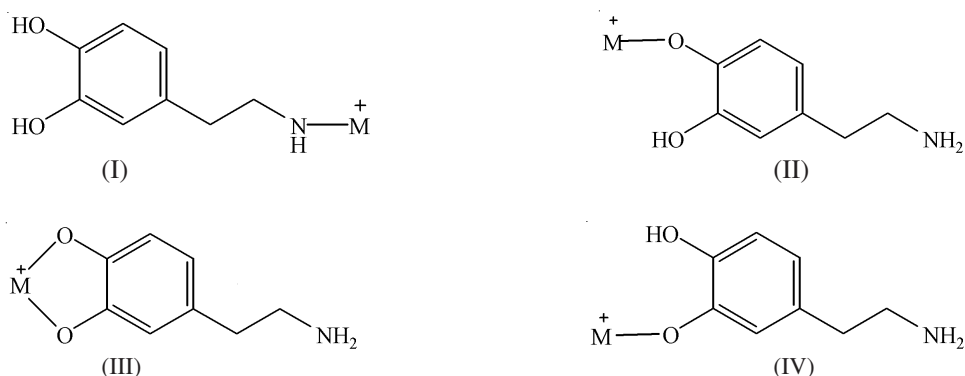| Structure	Energy (Hartree)	Relative energy (Kcal/mol)
III	-1116.6254713	0
II	-1116.6254712	0.00063
IV	-1116.6114846	8.78000
I	-1116.6114169	8.82000

Fig. 1.

The results of Tables 2-4 show that (**1**) The interaction energies of the metalated dopamine are systematically increased with atomic number of metal. So, interaction energies increases in the following order; K-dopamine > Na-dopamine > Li-dopamine. This increasing is due to larger dipole moments for metalated dopamine with heavy atoms. (**2**) The results also show that formation of 5-membered rings has the most stability (Fig. 1). Dopamine acts as bidentate ligand and coordinated to metal by 2 oxygen atom of hydroxyl groups. Lithium is a hard acid and linked to a hard base, therefore coordination of lithium to 2-oxygen atoms that acts as a hard base, preferred. (**3**) With increased atomic number of metal differences of interaction energies decrease. It is due to larger size of metal is softer than small size and can coordinate to nitrogen atom and in 5-membered ring have strain.

The geometries of isolated dopamine and in the complexes differ considerably. Results of Tables 5-7 shows bond lengths and angles among complexes and isolated dopamine. These results also show that all most important bond length changes take place in the 5-membered ring. In structure of (**III**) bond lengths of C_1-N_2, C_1-C_3, C_3-C_4 and C_5-C_6 didn't variable but bond lengths of C_6-C_8, C_6-O_7, C_8-O_9, M-O_7 and M-O_9 changed until the to be closely and formed a 5-membered ring. Also bond angles among complexes in structure of (**III**) confirmed formation of 5-membered ring. Bond distances of complexes shows similar results for alkali metals. Difference between the longest bond and shortest bond distance for Li-dopamine, Na-dopamine and K-dopamine consequence show 1.183, 1.398 and 1.381 Å, respectively.

TABLE-5
SELECTED GEOMETRICAL PARAMETERS FOR OPTIMIZED
Li^+-DOPAMINE COMPLEXES AT B_3LYP/6-311++G** LEVEL

Structure	Dopamine	Dop-Li$^+$(III)	Dop-Li$^+$(IV)	Dop-Li$^+$(II)	Dop-Li$^+$(I)
C_1-N_2	1.4624	1.4509	1.4496	1.4494	1.4495
C_1-C_3	1.5476	1.5565	1.5553	1.5552	1.5553
C_3-C_4	1.5113	1.5079	1.5076	1.5076	1.5076
C_5-C_6	1.3915	1.3836	1.3897	1.3896	1.3897
C_6-O_7	1.3667	1.4050	1.4059	1.4055	1.4059
C_6-C_8	1.4045	1.3887	1.3954	1.3954	1.3954
C_8-O_9	1.3676	1.4056	1.3653	1.3651	1.3653
C_8-O_{10}	1.3905	1.3836	1.3895	1.3893	1.3894
M-N_2	–	–	–	–	2.5479
M-O_7	–	1.8836	–	1.8530	–
M-O_9	–	1.8786	1.8470	–	–
Bond angle (º)					
C_3-C_1-N_2	115.9614	116.0145	116.4245	116.4279	116.423
C_5-C_6-O_7	123.1730	123.7947	118.0135	118.0092	122.320
C_6-O_7-M	–	110.9511	90.3204	119.7418	–
O_7-M-O_9	–	87.2490	–	–	–
M-O_9-C_8	–	110.9365	–	–	–
C_{10}-C_8-O_9	123.5695	124.2459	126.7541	126.7574	126.276
C_1-N_2-M	–	–	–	–	122.345

TABLE-6
SELECTED GEOMETRICAL PARAMETERS FOR OPTIMIZED
Na^+-DOPAMINE COMPLEXES AT B3LYP/6-311++G** LEVEL

Structure	Dopamine	Dop-Na$^+$(III)	Dop-Na$^+$(IV)	Dop-Na$^+$(II)	Dop-Na$^+$(I)
C_1-N_2	1.4624	1.4523	1.4470	1.4529	1.4533
C_1-C_3	1.5476	1.5549	1.5604	1.5543	1.5450
C_3-C_4	1.5113	1.5113	1.5085	1.5091	1.5089
C_5-C_6	1.3915	1.3870	1.3990	1.3881	1.3890
C_6-O_7	1.3667	1.3988	1.3667	1.3718	1.3714
C_6-C_8	1.4045	1.3917	1.4179	1.3944	1.4027
C_8-O_9	1.3676	1.3994	1.3527	1.4031	1.3885
C_8-O_{10}	1.3905	1.3868	1.3973	1.3830	1.3910
M-N_2	–	–	–	–	2.6731
M-O_7	–	2.2548	–	2.1962	–
M-O_9	–	2.2512	2.7508	–	–
C_3-C_1-N_2	115.9614	116.0575	116.0447	–	–
C_5-C_6-O_7	123.1730	122.4141	123.9712	–	–
C_6-O_7-M	–	116.1801	–	–	–
O_7-M-O_9	–	72.9393	–	–	–
M-O_9-C_8	–	134.5316	121.7572	-	–
C_{10}-C_8-O_9	123.5695	122.8426	124.4780	–	–
C_1-N_2-M	–	–	–	–	–

TABLE-7
SELECTED GEOMETRICAL PARAMETERS FOR OPTIMIZED
K^+-DOPAMINE COMPLEXES AT $B_3LYP/6-311++G^{**}$ LEVEL

Structure	Dopamine	Dop-K^+(III)	Dop-K^+(IV)	Dop-K^+(II)	Dop-K^+(I)
C_1-N_2	1.4624	1.4534	1.4909	1.4534	1.4902
C_1-C_3	1.5476	1.5539	1.5386	1.5539	1.5388
C_3-C_4	1.5113	1.5089	1.5127	1.5089	1.5129
C_5-C_6	1.3915	1.3886	1.3914	1.3886	1.3914
C_6-O_7	1.3667	1.3945	1.3604	1.3945	1.3599
C_6-C_8	1.4045	1.3927	1.4087	1.3927	1.4089
C_8-O_9	1.3676	1.3676	1.3589	1.3952	1.3588
C_8-O_{10}	1.3905	1.3882	1.3907	1.3882	1.3907
M-N_2	–	–	–	–	2.7385
M-O_7	–	2.6427	–	2.6426	–
M-O_9	–	2.6366	2.7480	–	–
C_3-C_1-N_2	115.9614	116.0868	115.1570	116.0845	115.2287
C_5-C_6-O_7	123.1730	122.1303	123.6058	122.1254	123.6161
C_6-O_7-M	–	121.3775	–	121.3678	–
O_7-M-O_9	–	61.4439	–	121.4125	–
M-O_9-C_8	–	121.4226	119.2538	–	–
C_{10}-C_8-O_9	123.5695	122.5390	123.9212	122.5348	123.9264
C_1-N_2-M	–	–	–	–	163.4288

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