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Nonempirical Investigation of Equilibrium Geometry and Electronic Structure of Kynurenine and 3-Hydroxykynurenine Molecule

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Abstract—By Hartree–Fock–Roothaan method with complete geometry optimization in the basis 6-31G* *ab initio* calculations of equilibrium geometry and electronic structure were performed for kynurenine $C_{10}H_{12}N_2O_3$ and 3-hydroxykynurenine $C_{10}H_{12}N_2O_4$ molecules in the singlet ground state and the first triplet excited state. The molecules in the triplet state can react at the oxygen of the carbonyl group adjacent to the aromatic ring by quite different pathway compared to the molecules in the ground singlet state.

Investigations of the biological effect and physicochemical characteristics of metabolites belonging to kynurenine path of tryptophan metabolism acquired an urgent practical importance for clinical medicine, in particular, for experimental medicine of neurodegeneration diseases. Any attempts to get insight into the mechanism of development of the diseases caused by distortions in this metabolism and selection of therapy strategy must base on the modern knowledge of the physicochemical properties of metabolites of this metabolism path. Just the knowledge of certain metabolite structure in the ground or excited state can infrequently suggest unusual way for devising pharmaceuticals..

The studies on tryptophan metabolism in biological systems under UV irradiation treat commonly the metabolites as existing in the ground singlet electronic state although the first excited triplet state also can be realized. The latter is characterized by another spatial structure of molecules under study and by appearance of new sterically accessible and potentially active toward protein addition sites. This study is dedicated to investigation of these problems for molecules of kynurenine $C_{10}H_{12}N_2O_3$ and 3-hydroxykynurenine $C_{10}H_{12}N_2O_4$ forming therefrom. The features of the electronic structure and the equilibrium geometry of the side branch of this metabolic path, neuroprotectant kynurenic acid, will be published later.

By Hartree–Fock–Roothaan method with complete geometry optimization in the basis 6-31G* [1] applying GAMESS sofrware [2] we carried out nonempirical calculations of equilibrium geometry and electronic structure for kynurenine and 3-hydroxykynurenine molecules in the ground singlet S (by restricted Hartree–Fock procedure, RHF) and in the first excited triplet state T (by unrestricted Hartree–Fock procedure, UHF) states. The corresponding total energies equal for kynurenine molecule to E_S –719.180332, E_T –719.099845 a.u., and for 3-hydroxykynurenine molecule to E_S –794.032678, E_T –793.954176 a.u. All calculations were performed on a claster for highly efficient calculations at the St. Petersburg University.

In Tables 1 and 2 are presented the data of quantum-chemical calculations for kynurenine and 3-hydroxykynurenine molecules, and in Table 3 are compiled the charges on atoms.

The analysis of changes in bond lengths and angles in the molecules of kynurenine and 3-hydroxykynurenine (Figs. 1, 2) in going from the singlet to triplet state shows that the spatial structure of these compounds suffers minor variations except for the bond lengths of C^4–C^9

Table 1. Bond angles in kynurenine and 3-hydroxykynurenine molecules in the singlet and triplet states

Angles, deg	Kynurenine		3-Hydroxykynurenine	
	singlet	triplet	singlet	triplet
$C^1C^6O^8(H^8)$	120.0	119.5	123.4	121.9
$C^3C^4C^9$	120.0	119.0	120.0	119.3
$C^5C^4C^9$	121.5	123.8	120.8	122.7
$C^4C^5N^7$	123.2	119.6	124.5	120.9
$C^4C^9C^{10}$	118.5	125.4	118.6	125.8
$C^4C^9O^{15}$	122.2	121.4	122.3	121.1
$C^6O^8H^{28}$	–	–	110.7	110.6
$H^{20}N^7H^{21}$	116.7	109.1	119.7	109.4
$C^9C^{10}C^{11}$	113.0	114.1	112.5	114.4
$C^{10}C^{11}C^{12}$	109.5	110.3	109.5	110.1
$C^{10}C^{11}N^{24}$	110.9	110.9	110.7	111.1
$H^{16}C^{10}H^{22}$	106.7	106.8	107.1	107.3
$C^{12}C^{11}N^{24}$	108.3	108.0	109.8	107.7
$C^{11}C^{12}O^{14}$	111.6	111.2	112.2	111.3
$O^{13}C^{12}O^{14}$	122.1	122.3	122.0	122.2
$H^{26}N^{24}H^{27}$	107.5	107.6	107.6	107.7

and C^9–O^{15} that respectively shortens by ~0.08 and elongates by ~0.15 E, and of C^5–N^7 that becomes longer by a ~0.05 Å. Therewith the lengths of the other bonds change no more than by ±0.03Å; the values of bond and torsion angles (apart those marked in Tables 1 and 2 altered by ~10 deg) remain constant within ±3 deg. An insignificant "turning" occurs of the carbon chain C^9–C^{10}–C^{11}–C^{12} from the figure surface in the direction of the viewer that is accompanied with some increase in the angle $H^{20}N^7H^{21}$ (by ~7–10 deg).

Table 2. Torsion angles in kynurenine and 3-hydroxykynurenine molecules in the singlet and triplet states

Angles, deg	Kynurenine		3-Hydroxykynurenine	
	singlet	triplet	singlet	triplet
$C^3C^4C^9O^{15}$	–178.6	–178.6	–175.5	–175.5
$C^5C^4C^9O^{15}$	2.0	2.0	4.5	4.5
$C^4C^9C^{10}C^{11}$	174.1	170.4	176.0	176.0
$C^9C^{10}C^{11}C^{12}$	–158.9	–158.9	–167.6	–167.6
$O^{14}C^{12}C^{11}N^{24}$	–54.0	–53.3	–42.0	–42.0

An interesting redistribution of charges on atoms in the molecules of kynurenine and 3-hydroxykynurenine occurred on transition from the singlet to the triplet state (Table 3). In both molecules this transition caused a considerable redistribution of the electron density to atoms C^5, C^9, and C^{10} (0.12, 0.27, and 0.07 a.c.u. respectively) from atoms C^4, N^7, and O^{15} (0.14, 0.05, and 0.27 a.c.u.). The charges on the other atoms of the molecules in question virtually did not change. The spin density on atomic nuclei that we calculated for the triplet state of kynurenine and 3-hydro-xykynurenine molecules were equal for both compounds and was on O^{15} 0.24 and on each of C^{1-6}, C^9 ~0.14 a.u.

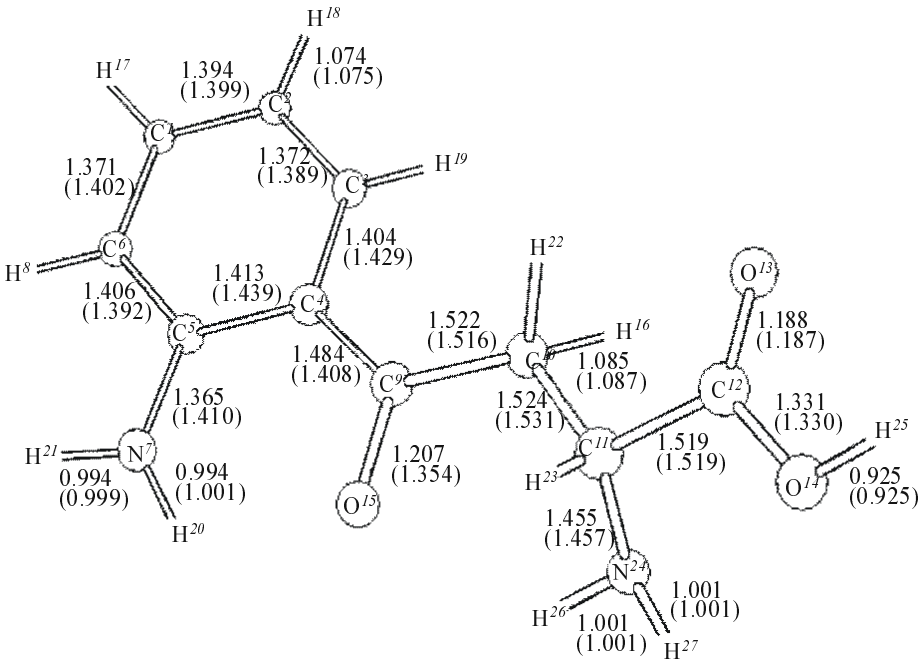

Fig. 1. Equilibrium geometry of kynurenine $C_{10}H_{12}N_2O_3$ molecule in the singlet and triplet (data in parentheses) states; figures indicate the distances in Å.

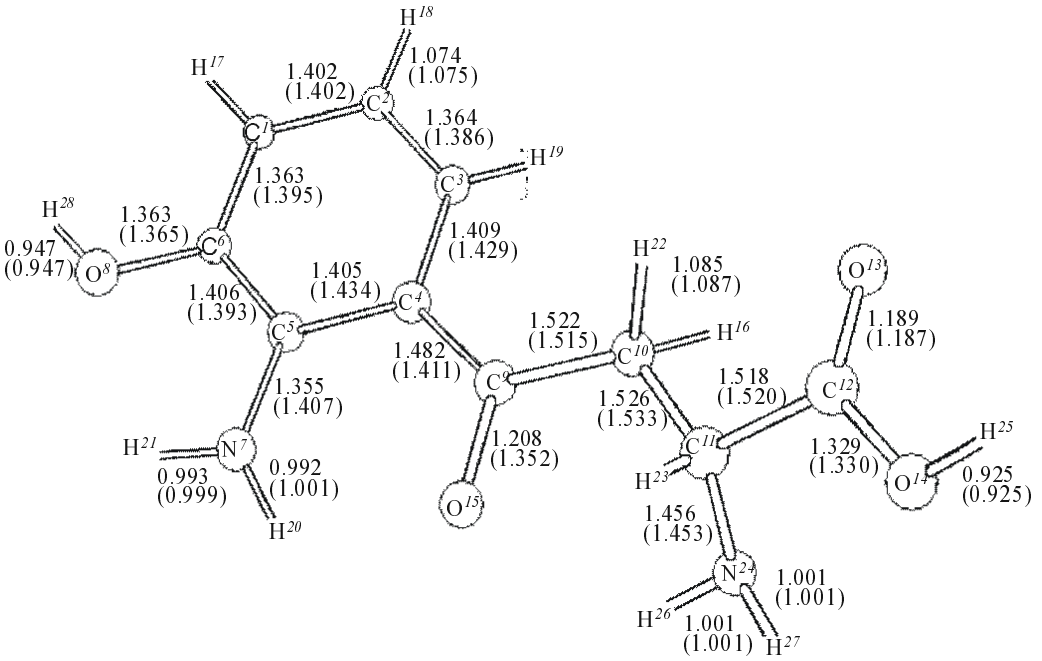

Fig. 2. Equilibrium geometry of 3-hydroxykynurenine $C_{10}H_{12}N_2O_4$ molecule in the singlet and triplet (data in parentheses) states; figures indicate the distances in Å.

The transition from the molecule of kynurenine to that of 3-hydroxykynurenine involving replacement of the C^6–H^8 bond by the C^6–O^8–H^{28} bond does not require significant changes in the geometry parameters of the molecules both in the singlet and the triplet states. The observed variations concern mainly the small changes in the bond lengths and angles neighboring to the substituted bond (Figs. 1, 2, and Tables 1, 2). The charges on atoms adjacent to the aromatic ring are more sensitive to this substitution (Table 3). Therewith the O^8–H^{28} bond turned out to be very similar to O^{14}–H^{25} bond by partly redistribution of electron density from the oxygen to the bond proper and to atom O^8. It is possible to indicate in the molecule of 3-hydroxykynurenine in the singlet (triplet) state the distances between oxygen atoms capable of participating in hydrogen bonds with the corresponding bonding sites of receptors: O^8–O^{15} 5.08 (5.10), O^8–O^{13} 8.79(8.79), O^8–O^{14} 9.74 (9.65)Å.

According to published data [3, 4, and references therein] proteins are bonded to the molecules of kynurenine and 3-hydroxykynurenine being in the ground electronic state at the N^{24} atom, and glucose adds to 3-hydroxykynurenine molecule at O^8 atom attached to the aromatic ring.

Yet our analysis of the free valence index in kynurenine and 3-hydroxykynurenine molecules when they are in excited triplet state reveals that in both molecules under study it amounts to 0.9 for O^{15} atom of the carbonyl bond C^9–O^{15} situated close to the aromatic ring, to 0.5 for C^9 atom, and ~0.3 for the carbons of the aromatic ring. These data together with the sterical accessibility of O^{15} revealed by calculations permit a conclusion on the presence in the kynurenine and 3-hydroxykynurenine molecules in the excited triplet state of a new reaction route through O^{15} atom.

The results of our quantum-chemical calculations show that in the kynurenine and 3-hydroxykynurenine molecules in the excited triplet state another radically new reaction route is possible via O^{15} atom of the carbonyl bond C^9–O^{15} neighboring to the aromatic ring.

Attention should be drawn to the fact that the "kynurenine" path of tryptophan metabolism is triggered in the body as reaction to stress, which in its turn is directly related to formation of oxygen free radicals [5]. Just these radicals are responsible for peroxide oxidation of lipids resulting in damages to cell membranes. Recent studies showed that excessive activation of the peroxide oxidation of lipids played an important role in development of numerous pathologic processes (radiation sickness, malignant growth, hypoxia, ischemia, arteriosclerosis, ageing) [5]. The route of tryptophan

metabolism leading to kynurenine as a key compound can by ring closure therein provide kynurenic acid acting as antioxidant (it prevents further active take up of oxygen radicals by transmitting a proton to a bond with O^- and thus terminates the oxidation process). Our calculations of the 3-hydroxykynurenine molecule with eliminated proton H^{28+} being in the singlet electronic state E_S –793.460988 a.u. with complete geometry optimization within the framework of the already described approach provided an estimation of the proton rupture energy from the difference in the total energies at ΔE 13.4 eV. It seems that 3-hydroxykynurenine depending on its concentration can operate either as an active antioxidant or as a generator of the oxidative stress observed at the ageing diseases and acute stress situations. This problem requires a special experimental analysis.

Besides two molecules of 3-hydroxykynurenine in a ground electronic state are able to form a chelate complex with a cation of a bivalent metal via O^8 and N^7 atoms located at the aromatic ring . In the excited electronic state two molecules of 3-hydroxykynurenine (kynurenine) can form a similar chelate complex through N^7 and O^{15} atoms. Similar chelate complexes with iron are known to be able to generate a cataract in mammals, and in insects they can function as additional screening eye pigments effecting changes in eye color at ageing.

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Table 3. Charges on atoms calculated by Mulliken method (a.c.u.) in molecules of kynurenine and 3-hydroxykynurenine in the singlet and triplet states

Atom	Kynurenine		3-Hydroxykynurenine	
	singlet	triplet	singlet	triplet
C^1	–0.159	–0.201	–0.244	–0.257
C^2	–0.249	–0.201	–0.236	–0.201
C^3	–0.185	–0.226	–0.200	–0.228
C^4	–0.172	–0.030	–0.167	–0.021
C^5	0.364	0.241	0.330	0.188
C^6	–0.267	–0.229	0.362	0.367
N^7	–0.937	–0.895	–0.955	–0.899
$H^8(O^8)$	0.198	0.191	–0.785	–0.785
C^9	0.586	0.317	0.585	0.308
C^{10}	–0.427	–0.366	–0.430	–0.360
C^{11}	–0.080	–0.109	–0.088	–0.105
C^{12}	0.798	0.802	0.802	0.800
O^{13}	–0.564	–0.560	–0.568	–0.560
O^{14}	–0.714	–0.711	–0.712	–0.719
O^{15}	–0.622	–0.353	–0.625	–0.346
H^{16}	0.220	0.214	0.219	0.272
H^{17}	0.210	0.200	0.200	0.194
H^{18}	0.205	0.201	0.206	0.204
H^{19}	0.226	0.213	0.223	0.215
H^{20}	0.434	0.363	0.440	0.361
H^{21}	0.371	0.359	0.406	0.390
H^{22}	0.223	0.230	0.229	0.224
H^{23}	0.199	0.207	0.203	0.198
N^{24}	–0.864	–0.852	–0.863	–0.857
H^{25}	0.469	0.470	0.469	0.470
H^{26}	0.377	0.362	0.374	0.370
H^{27}	0.360	0.363	0.360	0.363
H^{28}	–	–	0.462	0.460

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