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QSAR STUDY OF TOXICITY OF AROMATIC NITRODERIVATIVES USING THE ELECTRONEGATIVITY OF OMO/UMO STATES AS FINGERPRINT DESCRIPTORS

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The present study considers a class of 28 aromatic nitroderivatives aiming at the interaction mechanism between the chemical substances and the biological receptor, the nature of these interactions and the possibility of identifying the active molecular fragments. A statistical analysis has been performed considering linear equations $\log A = a_0 + a_1X_1$, where $\log A = -\lg LC_{50}$ is the toxic activity and X_1 electronegativity for OMO/UMO quantum molecular states. The found results suggest that the interaction mechanism between the biological receptors and the nitroaromatics is based on the electron transfer from biological receptors to LUMO energy levels of the substances studied, the oxygen and nitrogen atoms from the LUMO states participating with 69.4% (oxygen) and 49.8% (nitrogen) to the toxic activity. These results confirm the Bailey's assumption on the ligand – biological receptor interaction mechanism and certify the OMO/UMO electronegativity as fingerprint descriptors for CADD and QSPR studies.

INTRODUCTION

The aromatic nitroderivatives are widely used as materials or as intermediates in the production of explosives, dyes, pesticides and organic synthesis. These chemicals appear as industrial waste and direct environmental pollutants, being relatively soluble in water. Currently, the aromatic nitroderivatives are mainly studied for their various toxic effects, such as narcosis, genetic mutations and carcinogenesis.[1-5]

The purpose of this paper is to establish which atoms of the nitroaromatics are responsible for their toxic activities, using as fingerprint descriptors the electronegativity of the MO (Molecular Orbital) states of these compounds. We chose this class of nitro compounds for obvious chemical reasons that the atoms responsible for the toxic activity are known.

In this way, we can check the quality of the descriptors used in this paper and the possibility to obtain additional information regarding the mechanism by which these atoms are involved in ligand receptor interaction responsible for the biological activity studied.

To identify these atoms, we have adopted a statistical QSAR procedure[6] in which the linear equation (1) contains a single descriptor only:

$$A = a_0 + a_i \cdot X_i \,, \qquad (1)$$

where A is the biological activity, a_i the statistical coefficients (weights) and X_i descriptors for the studied chemical compounds.

We shall use in this paper fingerprint descriptors based on electronegativity that describe the nature and the ability of the atoms in molecule to gain or to loose electron density.

Usually, the electronegativity of the atoms regards the valence shell partially filled with electrons, *i.e.* the outer atomic orbitals that are mostly involved in chemical bond formation.

Unlike an atom, the "valence shell" of a molecule can be considered as being composed of one layer filled with electrons (OMO – Occupied

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Molecular Orbital) and one unoccupied with electrons (UMO – Unoccupied Molecular Orbital).

The interaction of a molecule with a biological receptor in general or with another molecule may occur through the transfer of electrons in some OMO/UMO molecular states, as can be seen by the arrows in Fig. 1:

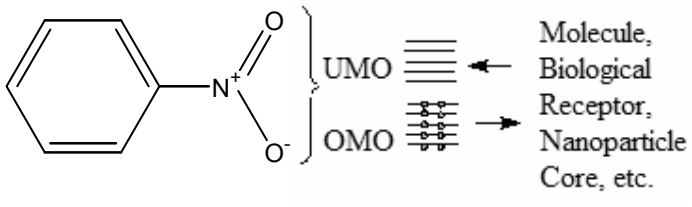

Fig. 1 – Interaction between a molecule and another molecule or biological receptor.

The electronegativity of OMO/UMO states described by the molecular orbitals $\psi_i = \Sigma_j c_{ij} \varphi_j$, where φ_j are the atomic orbitals and c_{ij} their mixing coefficients, can be estimated from the following expression:

$$X_i = \sum_j \overline{C}^2_{ij} \chi_j(Q_j), \qquad (2)$$

where $\chi_j(Q_j)$ represents the electronegativity of the atoms in molecule, Q_j their electrical charges and $\overline{C}^2_{ij}$ the contribution of "*j*" atom equal to the sum of the Mulliken partition coefficients of all its valence atomic orbitals $\overline{C}^2_{ij} = \sum_{AO} \overline{c}^2_{ij}$.

The electronegativity $\chi(Q)$ of each atom in the molecule can be estimated from the expressions obtained using Slater type atomic orbitals:[7, 8]

$$\chi(Q) = \frac{\partial E_n}{\partial Q} = -\frac{\partial E_n}{\partial N_n} = \chi_0 + \eta(Q)Q \qquad (3)$$

where:

$$\eta(Q) = \frac{1}{2}\frac{\partial^2 E_n}{\partial Q^2} = \frac{1}{2}\frac{\partial^2 E_n}{\partial N^2_n} = \eta_0 + \frac{3}{2}\frac{b^2 Q}{n^2}, \qquad (4)$$

Q being the electric charge on the atom in molecule, χ_0 and η_0 the electronegativity and hardness of the neutral atom (Q = 0), "*n*" the principal quantum number of the atomic valence shell and "*b*" a constant equal to 0.30 for $n = 1$ and 0.35 for $n \neq 1$, as results of Slater rules for the screening constants.

Such a process in which the molecular electronegativity descriptor plays the role of fingerprint descriptor has successfully been used in elucidating the mechanisms by which the (s, p) and (d^N) metal ions interact with biological receptors[8] and the identification of those atoms which participate in the assembly of aminoacid molecules into aminoacid - magnetic nanoparticles.[9]

RESULTS AND DISCUSSION

The toxic activity values of the aromatic nitroderivatives studied are shown in Table 1. The toxic activity expressed as -lg LC_{50} (LC – Lethal Concentration) is reported in literature[1, 10] for a fish species of the Cyprinids family (Fathead Minnow) present in freshwater.

Geometries of the 28 chemical structures presented in Table 1 were obtained by Molecular Mechanics (MM+) → MOPAC 2007 (RHF, PM3) (Molecular Orbital Package). The semiempirical quantomolecular calculations were performed using MOPAC 2007 (RHF, PM3).[11]

Expressions (3) – (4) have been used to estimate the electronegativity of OMO/UMO states as the contributions of the atoms in molecule, where χ_0 and η_0 represent the electronegativity and the hardness of the neutral atom (Q = 0). For the formulas (2) – (4), an in-house program named Elwindow has been written in order to calculate the electronegativities of the OMO/UMO quantum states by reading information (atomic species, electrical charges, mixing coefficients c_{ij}, atom contribution $\overline{C}^2_{ij}$, etc.) from the output files of MOPAC 2007 package used for molecular modeling and LCAOMO calculations for the molecules.

The following descriptors are obtained: EL – the total electronegativity of the molecule and the contribution of the atom species to the electronegativity of the quantum molecular, as follows: ELAT – heavy atoms (other than hydrogen atoms), ELH – hydrogen atoms, ELC – carbon, ELN – nitrogen, ELO – oxygen, EX – other heavy atoms.

Table 1

The values of the toxic activity for aromatic nitroderivatives

No.	Compounds	-lg LC_{50}	No.	Compounds	-lg LC_{50}
1	Nitrobenzene	3.02	15	2,4,6-Trinitrotoluene	4.88
2	1,2-Dinitrobenzene	5.45	16	2,3,6-Trinitrotoluene	6.37
3	1,3-Dinitrobenzene	4.38	17	2-Nitroaniline	3.70
4	1,4-Dinitrobenzene	5.22	18	2-Methyl-3-nitroaniline	3.48
5	1,3,5-Trinitrobenzene	5.29	19	2-Methyl-4-nitroaniline	3.24
6	2-Nitrotoluene	3.57	20	2-Methyl-5-nitroaniline	3.35
7	3- Nitrotoluene	3.63	21	2-Methyl-6-nitroaniline	3.80
8	4- Nitrotoluene	3.76	22	4-Methyl-3-nitroaniline	3.77
9	2,3-Dinitrotoluene	5.01	23	2,4-Dinitroaniline	4.07
10	2,4-Dinitrotoluene	3.75	24	2-Methyl-4,6-dinitroaniline	4.18
11	2,5-Dinitrotoluene	5.15	25	2-Methyl-3,6-dinitroaniline	5.34
12	2,6-Dinitrotoluene	3.99	26	3-Methyl-2,6-dinitroaniline	4.21
13	3,4-Dinitrotoluene	5.08	27	3-Methyl-2,4-dinitroaniline	4.26
14	3,5-Dinitrotoluene	3.91	28	4-Methyl-3,5-dinitroaniline	4.46

H prefix refers to the HOMO state and L prefix refers to the LUMO state. OC- prefix refers to electronegativity sum of all occupied molecular levels OMO and UN- prefix refers to electronegativity sum of all unoccupied levels UMO.

By using the fingerprint descriptors OMO-UMO, we can obtain information on how the molecules in the class studied interact with the active site of the biological receptor, allowing us to locate those atoms and to identify those molecular fragments or chemical groups involved in the formation of the biological response. We can design, in this way, new structures with predictable biological activity, using the identified molecular fragments or chemical groups. Statistical processing and correlation of descriptors with biological activity were performed using Minitab software release 13.31.

Tables 2-6 summarize the values for the fingerprint descriptors used in this paper.

Table 2

Total electronegativity for atoms of the aromatic nitroderivatives

Compound	-lg LC_{50}	EL	ELAT	ELH	ELC	ELO	ELN
1	3.02	100.845	60.790	40.055	34.311	7.604	18.875
2	5.45	121.569	89.352	32.217	33.781	17.825	37.746
3	4.38	122.006	89.355	32.651	33.964	17.595	37.796
4	5.22	121.717	89.000	32.717	33.766	17.666	37.568
5	5.29	135.411	110.366	25.045	33.587	20.019	56.759
6	3.57	122.584	67.899	54.685	40.308	8.727	18.864
7	3.63	122.602	67.906	54.697	40.351	8.683	18.871
8	3.76	122.677	67.883	54.794	40.312	8.670	18.901
9	5.01	114.936	90.792	24.143	39.709	13.366	37.717
10	3.75	115.342	90.913	24.429	39.899	13.200	37.814
11	5.15	115.047	90.608	24.439	39.762	13.264	37.582
12	3.99	115.030	90.910	24.121	39.933	13.281	37.695
13	5.08	111.143	86.909	24.34	38.299	15.576	33.034
14	3.91	115.177	90.562	24.616	38.497	14.285	37.779
15	4.88	119.787	111.547	8.240	39.500	20.070	51.977
16	6.37	127.423	111.133	16.291	39.148	20.251	51.734
17	3.70	116.855	69.538	47.317	34.070	8.566	26.901
18	3.48	97.238	73.304	23.934	40.104	6.559	26.641
19	3.24	97.307	73.125	24.182	38.693	7.535	26.897
20	3.35	97.552	73.341	24.211	40.092	6.507	26.741
21	3.80	96.909	72.961	23.948	38.702	7.476	26.783
22	3.77	97.346	73.366	23.980	40.081	6.550	26.735
23	4.07	117.415	92.979	24.436	33.643	12.987	46.349
24	4.18	102.317	94.196	8.122	39.763	12.991	41.442
25	5.34	109.722	93.512	16.210	39.519	13.162	40.831
26	4.21	112.902	96.737	16.166	39.623	12.917	44.197
27	4.26	112.890	96.802	16.088	39.678	13.174	43.950
28	4.46	101.899	93.822	8.077	39.614	13.280	40.928

Table 3

Total electronegativity OMO for atoms of the aromatic nitroderivatives

Compound	-lg LC_{50}	OC-EL	OC-ELAT	OC-ELH	OC-ELC	OC-ELO	OC-ELN
1	3.02	50.218	32.613	17.605	17.600	6.298	8.715
2	5.45	63.562	49.496	14.066	17.416	14.650	17.430
3	4.38	63.355	49.339	14.016	17.409	14.489	17.442
4	5.22	63.327	49.318	14.009	17.392	14.538	17.387
5	5.29	70.421	59.976	10.444	17.190	16.608	26.178
6	3.57	61.332	36.549	24.783	20.642	7.194	8.713
7	3.63	61.312	36.537	24.775	20.658	7.164	8.714
8	3.76	61.279	36.512	24.767	20.636	7.154	8.721
9	5.01	59.877	49.325	10.552	20.429	11.473	17.423
10	3.75	59.537	49.019	10.519	20.426	11.147	17.446
11	5.15	59.618	49.100	10.518	20.434	11.275	17.391
12	3.99	59.942	49.387	10.554	20.455	11.514	17.418
13	5.08	58.654	48.113	10.542	19.700	13.040	15.373
14	3.91	59.496	48.999	10.497	19.708	11.854	17.438
15	4.88	64.905	61.410	3.495	20.215	17.139	24.056
16	6.37	68.756	61.744	7.012	20.196	17.460	24.089
17	3.70	59.334	38.135	21.199	17.475	7.081	13.579
18	3.48	50.350	39.776	10.574	20.584	5.669	13.523
19	3.24	50.215	39.668	10.547	19.817	6.244	13.607
20	3.35	50.097	39.553	10.544	20.574	5.420	13.559
21	3.80	50.117	39.545	10.572	19.810	6.210	13.525
22	3.77	50.350	39.780	10.569	20.576	5.641	13.564
23	4.07	61.051	50.533	10.518	17.222	10.794	22.517
24	4.18	55.153	51.644	3.509	20.316	10.796	20.532
25	5.34	58.917	51.895	7.022	20.326	11.232	20.336
26	4.21	58.877	51.850	7.027	20.221	10.790	20.839
27	4.26	59.541	52.506	7.035	20.318	11.407	20.781
28	4.46	55.616	52.102	3.514	20.373	11.517	20.213

Table 4

Total electronegativity UMO for atoms of the aromatic nitroderivatives

Compound	-lg LC_{50}	UN-EL	UN-ELAT	UN-ELH	UN-ELC	UN-ELO	UN-ELN
1	3.02	50.627	28.177	22.450	16.711	1.306	10.160
2	5.45	58.007	39.856	18.151	16.366	3.175	20.316
3	4.38	58.650	40.016	18.634	16.555	3.106	20.354
4	5.22	58.390	39.682	18.708	16.374	3.127	20.181
5	5.29	64.990	50.389	14.601	16.397	3.411	30.581
6	3.57	61.252	31.349	29.903	19.666	1.532	10.151
7	3.63	61.291	31.369	29.922	19.693	1.520	10.157
8	3.76	61.398	31.370	30.028	19.676	1.515	10.179
9	5.01	55.059	41.467	13.592	19.280	1.893	20.294
10	3.75	55.804	41.894	13.910	19.473	2.053	20.368
11	5.15	55.429	41.508	13.921	19.328	1.989	20.191
12	3.99	55.088	41.522	13.566	19.478	1.767	20.278
13	5.08	52.489	38.796	13.693	18.599	2.536	17.661
14	3.91	55.682	41.563	14.119	18.790	2.431	20.342
15	4.88	54.882	50.137	4.745	19.285	2.931	27.922
16	6.37	58.667	49.388	9.278	18.952	2.791	27.645
17	3.70	57.521	31.403	26.118	16.595	1.486	13.323
18	3.48	46.888	33.528	13.360	19.520	0.890	13.118
19	3.24	47.091	33.457	13.634	18.876	1.291	13.290
20	3.35	47.454	33.788	13.666	19.518	1.087	13.182
21	3.80	46.792	33.416	13.376	18.892	1.266	13.259
22	3.77	46.997	33.586	13.411	19.505	0.909	13.171
23	4.07	56.364	42.446	13.918	16.421	2.193	23.832
24	4.18	47.164	42.552	4.613	19.447	2.194	20.910
25	5.34	50.806	41.617	9.188	19.193	1.930	20.494
26	4.21	54.026	44.887	9.139	19.402	2.126	23.359
27	4.26	53.349	44.296	9.053	19.360	1.767	23.169
28	4.46	46.283	41.720	4.563	19.241	1.763	20.716

Table 5

HOMO electronegativity for atoms of the aromatic nitroderivatives

Compound	-lg LC_{50}	HEL	HELAT	HELH	HELC	HELO	HELN
1	3.02	5.950	5.950	0.000	5.950	0.000	0.000
2	5.45	5.769	5.769	0.000	5.675	0.091	0.003
3	4.38	5.833	5.833	0.000	5.767	0.065	0.001
4	5.22	6.111	6.111	0.000	6.110	0.001	0.000
5	5.29	5.063	5.063	0.000	5.042	0.008	0.013
6	3.57	5.999	5.633	0.366	5.625	0.007	0.001
7	3.63	6.042	5.643	0.398	5.635	0.008	0.000
8	3.76	5.533	5.127	0.406	5.004	0.122	0.001
9	5.01	5.462	5.462	0.000	5.416	0.043	0.003
10	3.75	5.234	5.234	0.000	5.229	0.004	0.001
11	5.15	5.773	5.773	0.000	5.768	0.004	0.001
12	3.99	5.520	5.520	0.000	5.474	0.042	0.004
13	5.08	5.067	5.067	0.000	4.991	0.075	0.002
14	3.91	5.308	5.308	0.000	5.296	0.012	0.000
15	4.88	4.849	4.849	0.000	4.778	0.065	0.005
16	6.37	5.523	5.523	0.000	5.451	0.067	0.005
17	3.70	6.373	6.250	0.123	3.059	0.055	3.136
18	3.48	6.469	6.468	0.001	3.295	0.002	3.170
19	3.24	6.037	6.036	0.001	2.839	0.034	3.162
20	3.35	6.516	6.515	0.001	3.188	0.001	3.327
21	3.80	6.104	6.104	0.000	3.166	0.026	2.912
22	3.77	6.431	6.429	0.002	3.328	0.004	3.097
23	4.07	5.897	5.896	0.001	2.606	0.008	3.282
24	4.18	5.819	5.819	0.000	2.801	0.008	3.010
25	5.34	6.264	6.263	0.000	3.207	0.011	3.045
26	4.21	2.947	2.946	0.000	2.759	0.026	0.162
27	4.26	3.229	3.229	0.001	2.794	0.060	0.375
28	4.46	6.652	6.651	0.000	3.163	0.007	3.481

Table 6

LUMO electronegativity for atoms of the aromatic nitroderivatives

Compus	-lg LC_{50}	LEL	LELAT	LELH	LEC	LEO	LEN
1	3.02	6.525	6.525	0.000	4.608	0.211	1.707
2	5.45	5.989	5.987	0.002	4.662	0.313	1.013
3	4.38	6.554	6.554	0.000	4.948	0.350	1.255
4	5.22	6.267	6.267	0.000	4.295	0.469	1.503
5	5.29	6.291	6.291	0.000	5.276	0.002	1.012
6	3.57	6.435	6.355	0.080	4.839	0.293	1.223
7	3.63	6.766	6.749	0.017	4.560	0.420	1.769
8	3.76	6.750	6.618	0.133	4.605	0.389	1.624
9	5.01	5.873	5.873	0.000	4.669	0.172	1.032
10	3.75	6.154	6.154	0.000	4.981	0.052	1.120
11	5.15	5.749	5.749	0.000	4.521	0.076	1.153
12	3.99	5.944	5.943	0.001	5.291	0.147	0.505
13	5.08	5.697	5.695	0.002	4.637	0.273	0.785
14	3.91	6.305	6.305	0.000	4.912	0.106	1.286
15	4.88	6.172	6.172	0.000	5.285	0.040	0.847
16	6.37	5.165	5.164	0.001	4.680	0.167	0.317
17	3.70	7.211	7.159	0.052	4.315	0.444	2.400
18	3.48	6.091	6.090	0.001	4.824	0.211	1.055
19	3.24	6.557	6.557	0.000	4.427	0.187	1.944
20	3.35	6.194	6.194	0.000	4.432	0.013	1.749
21	3.80	6.895	6.895	0.000	4.311	0.215	2.370
22	3.77	6.172	6.171	0.001	4.741	0.214	1.216
23	4.07	6.696	6.695	0.000	4.535	0.005	2.156
24	4.18	6.305	6.305	0.000	4.528	0.007	1.770
25	5.34	4.694	4.693	0.001	4.339	0.044	0.310
26	4.21	6.648	6.647	0.001	4.880	0.046	1.721
27	4.26	5.829	5.829	0.001	4.972	0.143	0.714
28	4.46	5.753	5.752	0.001	5.140	0.154	0.458

From the statistical analysis of the linear regression $A = a_0 + a_1X_1$, the oxygen and nitrogen atoms seem to be notably involved in the toxic activity of the nitroaromatics. Indeed, the correlation coefficient values of R^2 (%) clearly certify this:

EL = 29.0; ELH = 14.1; ELAT = 57.8 → ELC 3.1, but ELO 69.4 and ELN 49.8, which obviously shows that among the heavy atoms (ELAT) only O and N atoms are mostly involved in the toxic response.

Going into details, now looking at the electronegativity as the sum of atomic electronegativity contributions for the occupied (OC-MO) or unoccupied (UN-MO) molecular states (Fig. 1), one may see that the oxygen and nitrogen atoms are most involved in the toxic activity:

OC-MO, R^2(%): ELH 14.8, ELC 2.3, ELO 70.8, ELN 45.5

UN-MO, R^2(%): ELH 13.5, ELC 4.0, ELO 55.2, ELN 52.3.

The mentioned atoms participate almost equally to the toxic activity, for both OC-MO and UN-MO molecular states. Such result would suggest that the interactions between ligand and receptor can occur through electron transfer in both directions: ligand (OC-MO) => receptor and ligand (UN-MO) <= receptor (Fig. 1).

If we now go further in detail, considering only the highest occupied state (HOMO) and lowest unoccupied (LUMO) molecular states, we have:

HOMO R^2(%): HELH 3.3, HELC 9.2, HELO 8.7, HELN 11.5

LUMO R^2(%): LELH 6.5, LELC 0.7, LELO 0.9, LELN 35.0.

The obtained results suggest that in the most reactive HOMO and LUMO molecular states, only the nitrogen atoms are actually involved in the ligand – receptor interaction. The correlation coefficient LELN, R^2 (%) = 35 for the LUMO state suggests that the electron transfer between the ligand and the biological receptor is of the type: receptor => ligand (Fig. 1).

Although the exact way by which the nitroaromatics exert a toxic effect is still unclear, the results allow us to assert that the oxygen and nitrogen atoms of $-NO_2$ groups are those who play an important role in the toxic response. The HOMO / LUMO molecular states suggest that the electron transfer from the biological receptor to the nitrogen atoms of the substances studied and the reducing process of the nitro group is therefore the primary mechanism of toxicity. The results obtained in this work using as fingerprint descriptors the electronegativity of OMO/UMO molecular states is consistent with Bailey's point of view.[12]

CONCLUSIONS

This paper determines by statistical correlation studies the nature of the atoms in chemical structures of the aromatic nitroderivatives responsible for the toxic activity.

An appropriate fingerprint descriptor used to study chemical compound – biological receptor interactions should be the electronegativity of OMO and UMO molecular states. The results suggest that the interaction mechanism between biological receptors and the nitroaromatic derivatives is based on the electron transfer from biological receptor to LUMO energy levels of the substances studied. Namely, oxygen and nitrogen atoms of $–NO_2$ groups are responsible for producing the toxic activity.

The electronegativity of the OMO/UMO molecular states has been proved as being a reliable fingerprint descriptor for QSAR/QSPR ans CADD studies.

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