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Electronegativity of the OMO-UMO quantum molecular states as fingerprint descriptors in the study of self-assembling of the aminoacid - magnetite nanoparticles

C. I. LEPADATU, D. C. CULITA, L. PATRON*
Institute of Physical Chemistry "Ilie Murgulescu", Splaiul Independentei 202, 060021 Bucharest, Romania

The assembly and the size of the hard core – shell nanoparticles are studied using QSAR procedures and namely the statistical correlation {Descriptors} – {Property}. The electronegativity X_i of the HOMO/LUMO quantum states defined as the contribution of the atoms in molecule $X_i = \Sigma_j \overline{C}^2_{ij} \chi_j(Q_j)$, 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, has been proved as being an appropriate tool to identify those atoms which mainly participate in the assembly of the molecules in the shell. For aminoacids (aspartic acid, glutamic acid, proline, tryptophan and arginine), it has been shown that the additional binding of the nitrogen atoms with the Fe ions at the edge of the core seems to influence the arrangement of the molecules in the shell and hence the size and shape as well as the contribution of the oxygen atoms to the saturation magnetism of the nanoparticles.

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1. Introduction

Magnetic nanoparticles are studied extensively due to their physical-chemical properties allowing their use in various fields, especially in hyperthermia treatment of cancer [1-6]. It is known that the magnetic nanoparticles are used in medicine under strict conditions on their size for their parenteral administration and magnetic manipulation during therapy [7].

We present in the following, several original methods of identifying factors that contribute to the magnetic nanoparticles assembling based on techniques CAMD (Computer Assisted Molecular Design) / QSPR (Quantitative Structure Property Relationship) techniques and the fingerprint descriptors using the electronegativity of the atoms in molecule.

In the present paper we use these procedures to a class of magnetite nanoparticles coated with aminoacids (aspartic acid, glutamic acid, arginine hydrochloride, proline, tryptophan) for which methods of synthesis and experimental estimates of the magnetism of saturation, and the average size of nanoparticles have recently been published [6, 8].

As we see below, with these procedures we can identify those atoms in the molecules of amino acids which mostly participate in the formation of response function, in this case, the average size of nanoparticles and the saturated magnetism. One obtains in this way information on how the aminoacid molecules are assembled in the one-layer shell. This information is useful for determining the conditions of synthesis to obtain nanoparticles with controlled size and dispersion.

2. Electronegativity descriptors for OMO/UMO quantum molecular states

We shall use in this paper new 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 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:

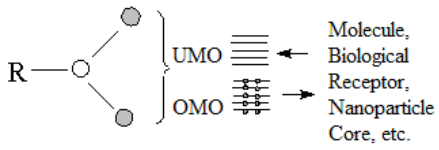


Fig. 1. Interaction between a molecule and another molecule or biological receptor.

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

$$X_i = \Sigma_j \overline{C}^2_{ij} \chi_j(Q_j) \quad (1)$$

where $\chi_i(Q_i)$ 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[9]

$$\chi(Q) = \frac{\partial E_n}{\partial Q} = -\frac{\partial E_n}{\partial N_n} = \chi_0 + \eta(Q)Q \quad (2)$$

where:

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

Q being the electrical 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 ≠ 1, as results of Slater rules for the screening constants.

Expressions (1) – (3) have been used to estimate the electronegativity of OMO/UMO states as 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 (1) – (3) 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 package used for molecular modeling and LCAOMO calculations for the molecules situated in the nanoparticle monolayer.

Elwindow program allows us to estimate the following descriptors: the electronegativity for each OMO/UMO state El = ELH + EC + EO + EN and separately, the sum of contributions of each atomic species (by summing $\overline{C}^2_{ij} \chi_j(Q_j)$ values of all atoms belonging to the same species) : ELH for hydrogen, EC – for carbon, EN - for nitrogen, EO – for oxygen, etc. For all descriptors in this paper, prefix H refers to the state HOMO and prefix L to the LUMO state.

3. Results and discussion

By using the electronegativities of OMO – UMO states we can obtain information on how the molecules from the nanoparticle monolayer interact with the atoms situated at the periphery of the core. This is possible, because every atom participates with c_{ij} mixing coefficient to the building of the wavefunction $\psi_i = \Sigma_j c_{ij} \varphi_j$ and with $\overline{C}^2_{ij} \chi_j(Q_j)$ the contribution to the electronegativity $X_i = \Sigma_j \overline{C}^2_{ij} \chi_j(Q_j)$ of a given OMO/UMO molecular state. In this case, such descriptors allow us to locate those atoms and to identify the molecular fragments or chemical groups involved responsible for a biological activity or chemical-physical property (1). We can design in this way, new structures from the identified molecular fragments or chemical groups for which the response function is predictable [10].

For this purpose, the chemical structures of amino acids used have been modeled (aspartic acid, glutamic acid, arginine hydrochloride, proline, tryptophan) and their molecular geometries and quantum molecular calculations performed using the software package MOPAC [11] that allows to get the electric charge on the atoms in molecule, mixing coefficients c_{ij}, atom contributions $\overline{C}^2_{ij} = \sum_{AO} \overline{c}^2_{ij}$, OMO/UMO levels, etc.). The fingerprint electronegativity descriptors can be calculated from the MOPAC output files using the Elwindow program earlier mentioned. These descriptors represent the chemical structures function, in our case the saturation magnetisation and the average size of the magnetite nanoparticles studied.

The electronegativities of all atomic species in the molecule, i.e. the sum of the atom contributions $\overline{C}^2_{ij} \chi_j(Q_j)$ from all UMO and OMO states are given in Table 1. For the most reactive quantum states of the molecules HOMO – Highest Occupied Molecular Orbitals and LUMO – Lowest Unoccupied Molecular Orbitals, the contributions, i.e. the sum $\overline{C}^2_{ij} \chi_j(Q_j)$ of the atomic species are given in Tables 2 and 3.

Table 1. Fingerprint descriptors for the all atomic species in molecule.

Aminoacid	ELH	EC	EO	EN
Aspartic acid	56.131	28.259	22.399	7.163
Glutamic acid	71.197	34.000	22.397	7.171
Proline	69.813	31.559	11.178	6.861
Tryptophan	94.171	65.663	11.141	16.671
Arginine	107.289	37.237	11.180	27.976

Table 2. Fingerprint descriptors for HOMO state.

Aminoacid	HELH	HEC	HEO	HEN
Aspartic acid	0.327	0.565	0.192	5.955
Glutamic acid	0.408	0.520	0.058	6.067
Proline	0.761	0.684	0.019	5.357
Tryptophan	0.067	4.189	0.008	2.378
Arginine	0.290	0.393	0.000	6.126

Table 3. Fingerprint descriptors for LUMO state.

Aminoacid	LELH	LEC	LEO	LEN
Aspartic acid	0.095	5.229	1.804	0.015
Glutamic acid	0.100	5.280	1.794	0.002
Proline	0.040	5.212	1.807	0.137
Tryptophan	0.018	5.381	0.005	0.506
Arginine	0.263	3.033	0.067	2.695

As may be seen in Tables 2 and 3, nitrogen atoms contribute mainly to the electronegativity of the HOMO state, in exchange carbon and oxygen atoms from aminoacids participate mainly to the LUMO electronegativity.

The fingerprint descriptors calculated for the aminoacids given in Tables 1-3 can be correlated by linear regression procedure with the chemical - physical properties of the magnetite - aminoacid nanoparticles.

Table 4. Physical properties for the magnetite – aminoacid nanoparticles.

Aminoacid	LELH	LEC
Aspartic acid	0.095	5.229
Glutamic acid	0.100	5.280
Proline	0.040	5.212
Tryptophan	0.018	5.381
Arginine	0.263	3.033

For the physical properties of the magnetite - aminoacid nanoparticles reported in Table 4 [6,13], where D represents the average size diameter of the nanoparticle and SM the saturation magnetisation, we can obtain linear regression equations of the type:

$$A = a_0 + a_1X_1$$

where A = SM, D and X_1 the fingerprint descriptors summarized in Tables 1-3.

The linear regression equations and the correlation coefficients $R^2(\%)$ obtained for the saturation magnetisation (SM) are given in Tables 5-7.

Table 5. Linear equation $SM = a_0 + a_1X_1$ for all atomic species in molecule (Table 1).

Descriptor X_1	$SM=a_0+a_1X_1$	$R^2(\%)$
ELH	SM(emu/g = 34.6 + 0.313 ELH	19.3
EC	SM(emu/g = 45.0 + 0.372 ELC	14.6
EO	SM(emu/g = 91.3 - 2.03 ELO	72.3
EN	SM(emu/g = 55.7 + 0.300 ELN	3.6

Table 6. Linear equation $SM = a_0 + a_1X_1$ for HOMO state (Table 2).

Descriptor X_1	$SM=a_0+a_1X_1$	$R^2(\%)$
HELH	0.095 SM(emu/g = 52.3 + 19.7 HELH	11.4
HEC	SM(emu/g = 55.9 + 2.95 HEC	10.8
HEO	SM(emu/g = 68.3 - 157 HEO	73.0
HEN	SM(emu/g = 80.0 - 3.94 HEN	18.3

As may be seen in Tables 5-6, the oxygen atoms of the aminoacid molecules are most involved in the saturation magnetisation, the correlation coefficient $R^2(\%) = 72.3$ for EO being very high compared with other values. This result seems to be interesting because it suggests that the oxygen atoms influence the saturation magnetisation most likely through a transfer of electron density from the HOMO state (HEO, $R^2(\%)=73$) to the Fe ions on the edge of magnetite core (see Fig. 1). This mechanism is confirmed by the results given in Table 7, where the poor correlation ($R^2(\%) = 9.1$) for LEO (LUMO state) shows that the reversed electron transfer cannot in principle take place.

Table 7. Linear equation $SM = a_0 + a_1X_1$ for LUMO state.

Descriptor X_1	**$SM=a_0+a_1X_1$**	**$R^2(\%)$**
LELH	SM(emu/g = 63.5 - 37.4 LELH	6.0
LEC	SM(emu/g = 62.8 - 0.67 LEC	0.2
LEO	SM(emu/g = 64.6 - 4.56 LEO	9.1
LEN	SM(emu/g = 58.3 + 1.94 LEN	2.3

In the case of the response function D (mean diameter, Table 1), according to the linear regressions summarized in Tables 8-9, practically all atoms in the aminoacids except oxygen ones participate in the function response.

Table 8. Linear equation $D = a_0 + a_1X_1$ for HOMO state.

Descriptor X_1	$D=a_0+a_1X_1$	$R^2(\%)$
HELH	D(nm) = 9.69 - 4.36 HELH	20.5
HEC	D(nm) = 6.41 + 1.30 HEC	76.9
HEO	D(nm) = 7.90 + 3.1 HEO	1.0
HEN	D(nm) = 15.0 - 1.35 HEN	77.8

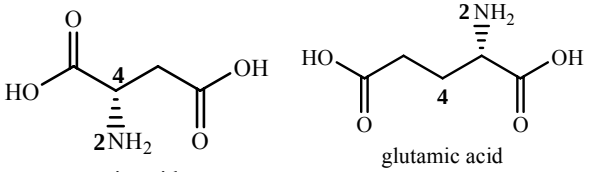
Table 9. Linear equation $D = a_0 + a_1X_1$ for LUMO state (Table 3).

Descriptor X_1	$D=a_0+a_1X_1$	$R^2(\%)$
LELH	D(nm) = 10.2 - 20.2 LELH	63.6
LEC	D(nm) = 0.09 + 1.65 LEC	46.7
LEO	D(nm) = 8.59 - 0.48 LEO	3.6
LEN	D(nm) = 8.80 - 1.09 LEN	26.3

This can be interpreted through the constant participation of all oxygen atoms form the aminoacid molecules in the formation of the shell by linking with iron ions at the edge of the magnetite core. In this case, from the statistical point of view, the linear regressions "exclude" those descriptors whose values do not vary in the studied class.

We shall examine in the following, only those atoms considered as heavy atoms (i.e. atoms other than hydrogen ones), namely nitrogen the atoms that participate mainly in the electronegativity of HOMO quantum state ($R^2(\%) = 77.8$, Table 8).

Fig. 2 shows the participation of the nitrogen atoms to the formation of HOMO molecular orbital $\psi_i = \Sigma_i c_{ii} \varphi_i$, the atom contribution $\overline{C}^2_{ij}$ being obtained with the quantum molecular calculations performed using the software package MOPAC earlier mentioned.

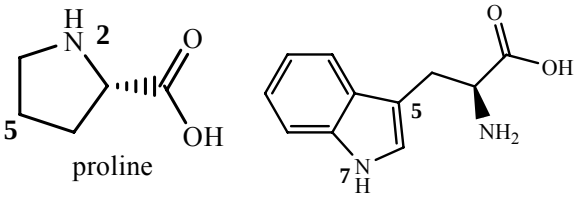


aspartic acid

2N: $\overline{C}^2_{ij} = 83.13\%$

glutamic acid

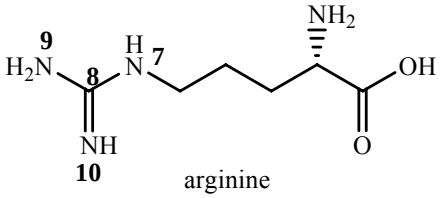
2N: $\overline{C}^2_{ij} = 84.60\%$



2N: $\overline{C}^2_{ij}$ = 78.06%

7N: $\overline{C}^2_{ij}$ = 23.86%

2N(-NH2): $\overline{C}^2_{ij}$ =1.28%



7N: $\overline{C}^2_{ij}$ = 33.60%

9N: $\overline{C}^2_{ij}$ = 34.44%

10N: $\overline{C}^2_{ij}$ = 29.75%

As can be seen, the nitrogen atoms participation in the formation of the HOMO state $\overline{C}^2_{ij}$ is very high. These results give us information about how the assembly of amino acid molecules takes place around the magnetite core (Fig. 3).

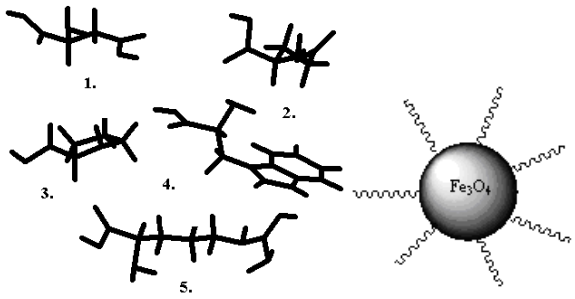


Fig. 3. Aminoacids molecules: 1. Aspartic acid 2.Glutamic acid 3. Proline 4. Tryptophan 5. Arginine.

For the first three amino acids (aspartic acid, glutamic acid and proline) the contribution of the nitrogen atoms is basically similar ($\overline{C}^2_{ij}$ ≈ 78 - 84%). In this case amino acids would bind the iron atoms at the edge of the magnetite core through Fe-COO and H_2N-Fe bonds, the last binding being mediated by the electron transfer from HOMO aminoacid state to the iron ions at the edge of the magnetite core.

Since the atom contribution of the nitrogen atoms to HOMO state for the first three amino acids is practically the same ($\overline{C}^2_{ij}$ ≈ 78 – 84%), and the molecular volumes take close values (V(Å^3) = 409 (aspartic acid); 465 (glutamic acid); 400 (proline), Hyperchem 7.52), it is expected that the mean size of the corresponding magnetite – aminoacid nanoparticles should be very close (D ≈ 6.87 – 8.72 nm, Table 4).

In exchange, for tryptophan the participation of the nitrogen atoms in the HOMO state is much lower (7N: $\overline{C}^2_{ij}$ = 23.86%; 2N (-NH2): $\overline{C}^2_{ij}$ = 1.28%), the linking of the tryptophan molecules to the magnetite core could be considered as being made virtually with –COO – Fe (magnetite) only, in agreement with the IR spectral data (6). This gives more freedom in the assembly of tryptophan molecules in the nanoparticle monolayer.

Taking into account of this and that the volume of tryptophan molecule is much larger (V (A^3) = 628 A^3, Hyperchem 7.52), one may explain why the average size of tryptophan – magnetite nanoparticles is obviously higher (D (nm) = 11.78, Table 4) if compared with D ≈ 6.87 - 8.72 nm for the first three aminoacids (see Table 4).

In the case of magnetite – arginine nanoparticles, the three nitrogen atoms contribute almost equally to HOMO state (7N: $\overline{C}^2_{ij}$ = 33.60%, 9N: $\overline{C}^2_{ij}$ = 34.44% , 10N: $\overline{C}^2_{ij}$ ≈ = 29.75%).

In this case, it might be that the arginine molecules are linked to the iron ions at the edge of the magnetite core through –COO – Fe bonds and addidional coordinative bonds with the three nitrogen atoms through electron transfer from arginine HOMO state to the Fe ions. In this case, the freedom in the assembly of arginine molecules in the nanoparticle shell is much lower. Taking into account the nearly linear shape of the arginine molecules (Figure 2) and the assumed nitrogen – Fe binding, one may explain why magnetite – arginine nanoparticles has the smallest average size (experimental D = 5.26 nm, Table 4), despite the fact that the volume of arginine molecule is appreciably high (589 A^3, Hyperchem 7.52).

4. Conclusions

The use of the electronegativity of HOMO/LUMO quantum molecular states as fingerprint descriptors has allowed for the magnetite nanoparticles containing aminoacid molecules in the shell (aspartic acid, glutamic acid, proline, tryptophan and arginine) to prove the additional binding of the nitrogen and oxygen atoms with the Fe ions at the edge of the magnetite core. Such chemical bindings seem to influence the arrangement the the molecules in the shell and hence the size and the shape as well as the saturation magnetism of the nanoparticles.

Because the electronegativity $X_i = \Sigma_j \overline{C}^2_{ij} \chi_j(Q_j)$ of the HOMO / LUMO molecular states are defined as the sum of contribution $\overline{C}^2_{ij} \chi_j(Q_j)$ from each atom, the proposed fingerprint descriptor may also be used to understand the participation of every atom in the chemical and physical properties.

Acknowledgments

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*Corresponding author: luminita_patron@yahoo.com