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Research Article

Theoretical B3LYP study of contrast agent metrizoate

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ABSTRACT

Metrizoic acid is a molecule used as meglumine metrizoate, sodium metrizoate contrast agent. 6 Isopak 44o* is a contrast medium containing a mixture of sodium, calcium, magnesium and N-methylglucamine salts of metrizoic acid. In order to determine the reactivity properties of metrizoic acid, melagnomie, anionic form of metrizoate, Metrisoate K, metrizoate-melagnomie salt, and Na-metrizoate, DFT calculations were made in gas and water phses at the level of B3LYP/LANL2DZ with the help of Gaussian 09 software. Some global chemical reactivity descriptors such as highest occupied molecular orbital energy, lowest empty molecular orbital energy, absolute hardness, chemical potential, softness, electronegativity, chemical potential, global electrophilicity and electrofugality were calculated. Moreover, nonlinear optical properties of the title compound were calculated too. In addition, thermodynamic properties of the molecules examined at different temperatures were calculated in gas and water phases. The findings of this study, obtained from extensive and time-consuming calculations and analyses, will be an important source of information for the preparation of the drug combination in the future.

Keywords: Metrizoate, DFT, B3LYP, quantum chemical calculations.

Kontrast maddesi metrizoatın teorik B3LYP incelemsi

ÖZ

Metrizoik asit, meglumin metrizoat, sodyum metrizoat kontrast maddesi olarak kullanılan bir moleküldür. 6 izopak 44o*, metrizoik asidin sodyum, kalsiyum, magnezyum ve N-metilglukamin tuzlarının bir karışımını içeren bir kontrast ortamıdır. Metrizoik asit, melagnomi, anyonik metrizoat formu, metrisoate K, metrizoate-melagnomie tuzu ve Na-metrizoate formunun reaktivite özelliklerini belirlemek için gaz ve su fazında B3LYP / LANL2DZ seviyesinde Gaussian 09 yazılımı yardımıyla DFT hesaplamaları yapıldı. En yüksek işgal edilen moleküler orbital enerji, en düşük boş moleküler orbital enerji, mutlak sertlik, kimyasal potansiyel, yumuşaklık, elektronegatiflik, kimyasal potansiyel, küresel elektrofiliklik, nükleojenite ve elektrofugalite gibi bazı küresel kimyasal reaktivite tanımlayıcıları hesaplandı. Ayrıca, bileşiğin lineer olmayan optik özellikleri de hesaplandı. Bunun yanında farklı sıcaklıklarda incelenen moleküllerin termodinamik özellikleri gaz ve su fazlarında hesaplandı. Kapsamlı ve zaman alan hesaplama ve analizlerden elde edilen bu çalışmanın bulguları, gelecekte ilaç kombinasyonunun hazırlanması için önemli bir bilgi kaynağı olacaktır.

Anahtar Kelimeler: Metrizoate, DFT, B3LYP, kuantum kimyasal hesaplamalar.

1. INTRODUCTION

The basic principle is the application of contrast agents in a way that changes the absorption of specific anatomical structures relative to the x-ray environment. Positive contrast agents are iodine or barium compounds, and negative contrast agents are gases. Positive contrast agents absorb more x-rays than tissues because of their higher density and higher atomic number, but gaseous contrast agents absorb fewer X-ray than tissues because of their low density, even though the effective atomic number may be higher.

The basic building block of iodized contrast agents is a benzene ring, which has three iodine molecules attached to positions 2, 4 and 6. Side chains at positions 3 and 5

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are modified with hydroxyl groups or other molecules that further define the properties of an agent. They can be classified into two groups as ionic and non-ionic contrast agents depending on whether they are dissociated in solution. Contrast agents can be classified according to osmality values. Those with ≥ 1400 mOsm/kg are classified as high osmolar, those with 780-800 mOsm/kg as low osmases and those with approximately 300 mOsm/kg are classified as iso-osmolar agents.

Three properties that define the physical properties of iodinated contrast agents-ionicity, osmolality and viscosity play a separate role in tolerance and adverse reaction profiles.[1]

Pattinson and co-workers[2] reported that sodium amidotrizoate showed certain advantages over the contrast media which they had previously used for angiocardiography. And also they found that high flow rates had been achieved with triosil 75% resulting in a great improvement in the quality of the angiocardiograms when small catheters had been used.

Emergency urography has been performed using either low osniolar nonionic (iohexol) or high osmolar ionic (metrizoat) contrast agent. In 56 percent of all children, the pain has increased after injection of contrast medium. The increase in pain occurs without any difference between the contrast agent and the degree of pain and the number of patients who experience an increasing pain.[3]

Ten radiographic contrast agents containing iodine have been tested to assess whether there are a rapid, continuous and reversible inhibition of thyroxine (T4) secretion from perfused canine thyroid lobes. All of four agents used for cholecystography (iocetamate, iodipamide, oglycamate and iotroxate) cause rapid inhibition of T4 secretion from TSH-induced perfused canine thyroid lobes, while amidotrizoate, metrizamide, metrizoate, iodamide, diodone and iodamide, significantly impressed. All cholecystographic agents have been reported to inhibit T4 deiodinases from canine thyroid and liver.[4]

In a double-blind, randomized, two-group study with 99 “high-risk” patients with essentially coronary artery disease, the nonionic contrast agent, amipak (metrizamide), have been compared to the ionic medium isopaque coronar (meglumine-Na-Ca-metrizoate) in inecardioangiography and they reported that the patients with a basal LVEDP above 15 mmHg, no significant change has occurred in LVEDP after left ventriculography with any of the 2 contrast media. It has been reported that no serious complications occurred.[5]

Cerebral computed tomography has been performed in 60 patients who applied for screening before and after contrast. Non-ionic contrast agent, iohexol, and an ionic contrast agent sodium metrizoate have been randomly administered to the patients as a contrast agent. Very minor side effects have been recorded with both iohexol and metrizoate, but iohexol causes much less discomfort than metrizoate. It has been reported that there is no difference in the development of normal intracranial structures.[6] Isopaque 44o* is a contrast medium which contains a mixture of the sodium, calcium, magnesium, and N-methylglucamine salts of metrizoic acid. Theoretical studies on the constructional features of metrizoate are seldom found in literature. In order to interpret molecular properties of metrizoic acid (MetA), melagnomie (Melag), anionic form of metrizoate (an-Met), metrisoate K (K-Met), metrizoate-melagnomie salt (Melag-Met), Na-metrizoate (Na-Met), theoretical studies are needed on the electronic and thermodynamic properties of molecules. B3LYP functional of quantum chemical calculation methods is widely used in studying both physical and chemical properties of molecules.[7]

In this study, thermodynamic properties and frontier molecular orbitals were theoretically calculated for the MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met. Polarizability, hyperpolarizability and some parameters related to HOMO and LUMO energies were investigated using B3LYP/LANLZDZ basis set.

2. CALCULATION METHODS

Structural parameters for each molecule were optimized for at the B3LYP method of Gaussian Program,[8] Becke’s three parameter hybrid functional combined with the gradient correlation functional of Lee, Yang and Parr (LYP), denoted B3LYP, in the computations using DFT/LANL2DZ level of theory, and the harmonic vibrational frequencies and zero-point vibrational energies (ZPVE) were computed at the same level. Throughout this paper, all calculations for B3LYP optimization of molecular geometry were carried out with B3LYP/LANL2DZ Opt. Freq. “Opt Freq” means that the frequency was calculated after optimization.

The values of the absolute electron negativity (χ), the chemical potential (μ_i), the absolute hardness (η), and the softness (σ, the inverse of the hardness), global electrophilicity (ω), nucleofugality (ΔE_n) and electrofugality (ΔE_e) related with the HOMO and LUMO energies can be determined by Equations (1-10).

$$\mu = -\chi \cong \left(\frac{E_{HOMO}+E_{LUMO}}{2}\right) \quad (1)$$

$$\eta = \frac{E_{LUMO}-E_{HOMO}}{2} \quad (2)$$

$$\sigma = \frac{\eta}{2} \tag{3}$$

$$\omega = \frac{\mu^2}{2\eta} \tag{4}$$

$$\Delta E_n = \frac{(\mu+\eta)^2}{2\eta} \tag{5}$$

$$\Delta E_e = \frac{(\mu-\eta)^2}{2\eta} \tag{6}$$

The complete equations (Equations (7)-(10)) for calculating the magnitude of total static dipole moment (μ), the mean polarizability ($<\alpha>$), the anisotropy of the polarizability ($\Delta\alpha$), the mean first hyperpolarizability (β) are defined as follows.

The total static dipole moment is

$$\mu = \left(\mu_x^2 + \mu_y^2 + \mu_z^2\right)^{1/2} \tag{7}$$

Mean polarizability is

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \tag{8}$$

The anisotropy of the polarizability $<\Delta\alpha>$:

$$\Delta\alpha = \left[\frac{(\alpha_{xx}-\alpha_{yy})^2 + (\alpha_{yy}-\alpha_{zz})^2 + (\alpha_{zz}-\alpha_{xx})^2 + 6(\alpha_{xz}^2+\alpha_{xy}^2+\alpha_{yz}^2)}{2}\right]^{1/2} \tag{9}$$

And the average hyperpolarizability is:

$$\beta = \left[(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2\right]^{\frac{1}{2}} \tag{10}$$

3. RESULT AND DISCUSSION

3.1. Frontier orbital

The optimized form, HOMO and LUMO contour plots for MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met molecules are shown in Figure 1. LUMO of MetA, an-Met, K-Met, Melag-Met, Na-Met consists of benzene ring and all the iodine atoms attached to benzene ring. HOMO of MetA consists of mainly spread benzene ring and N-methylacetamide group, HOMO of an-Met consists of mainly carboxylate group, HOMO of K-Met consists of benzoate group and iodine atoms, HOMO of Melag-Met consists of benzene ring and all the iodine atoms attached to benzene ring and N-methylacetamide group, and HOMO of Na-Met consist of two iodine atoms and N-methylacetamide group. The variation in the contribution to the HOMO was influenced by the neutral anionic and salt form.

The most widely used theory by chemists is the molecular orbital (MO) theory. From the Koopman's theorem, the ionization potential (*I*) and electron affinity (*EA*) are the Eigen value of the HOMO and LUMO with change of sign.[9]

It is important to reveal HOMO energy, LUMO energy, the electrophilicity index, chemical potential, electronegativity, hardness and softness in the Molecular Orbital framework. Based on density functional descriptors global chemical reactivity descriptors of compounds such as hardness, chemical potential, softness, electro negativity and electrophilicity index local reactivity has been calculated.[10]

The HOMO-LUMO energy gap (ΔE) along with computed global descriptors namely, absolute electron negativity (χ), the chemical potential (μ), the absolute hardness (η), and the softness (S), global electrophilicity nucleofugality (ΔE_n) and electrofugality (ΔE_e) of MetA, Melag, an-Met, K-Met, Melag-Met and Na-Met are reported in Table 1.

The molecule with the highest HOMO-LUMO energy gap will be the least prone to any external disruption and these orbital energies help to characterize the chemical reactivity and kinetic stability of the molecule. A small frontier orbital gap means that the molecule is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and it is also termed as soft molecule. The HOMO acts as an electron donor, and the LUMO acts as the electron acceptor. As presented in Table 1, the compound which have the lowest energetic gap is the anionic form of metrizoate (ΔE = 3.004 eV). This lower gap makes it the softest molecule. The compound that have the highest energy gap is the metrizoate-melagnomie (ΔE = 4.466 eV). The compound that has the highest HOMO energy is the anionic form of metrizoate (E_{HOMO} = -2.428 eV).

Which electrons are polarized or resists to deformation is measured with the magnitude of hardness (η). The values of η for MetA, Melag, an-Met, K-Met, Melag Met, Na-Met are 2.202, 3.399, 1.502, 2.170, 2.300, 2.233 in gas phase and 2.391, 3.633, 2.081, 2.214, 2.413

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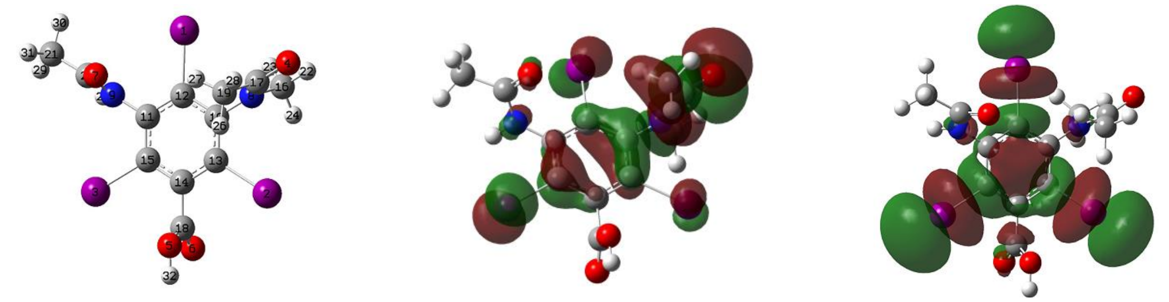
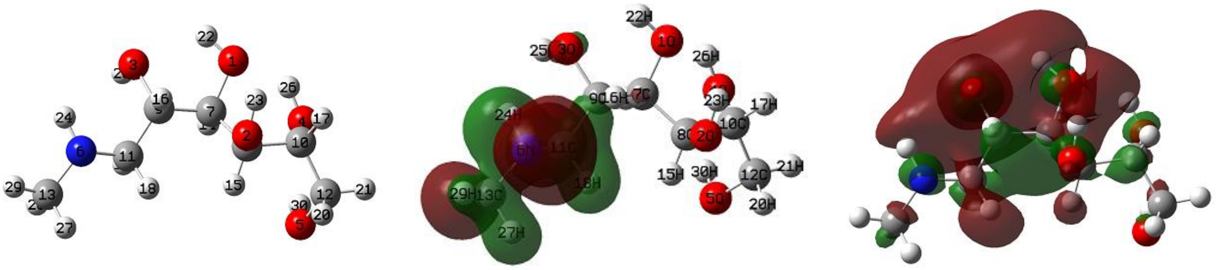
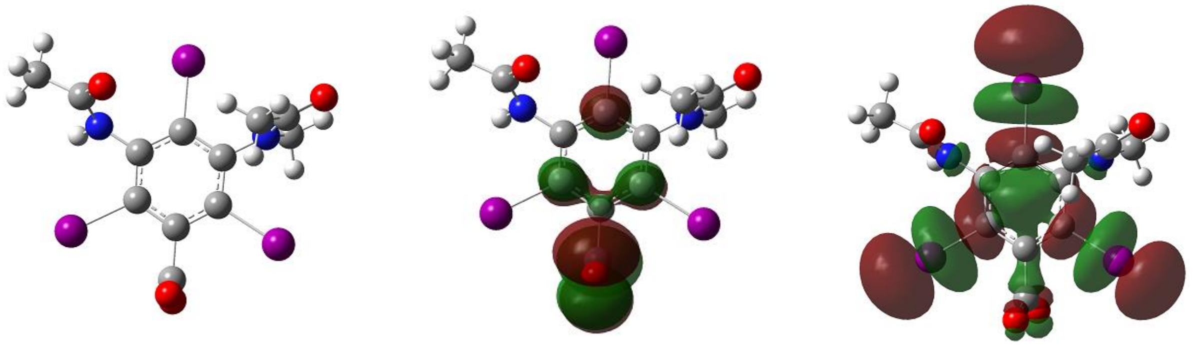


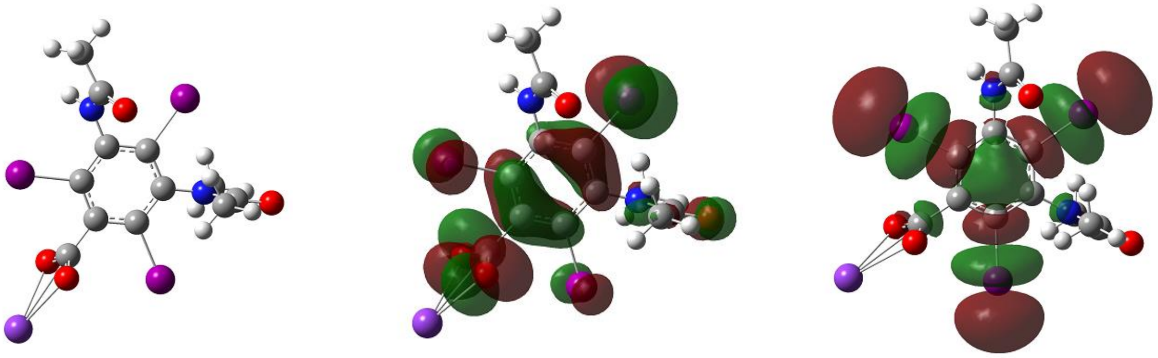
MetA-opt MetA-HOMO MetA-LUMO



Melag-opt Melag-HOMO Melag-LUMO



an-Met-opt an-Met-opt an-Met-LUMO



K-Met-opt K-Met-HOMO K-Met-LUMO

Figure 1. The optimized and HOMOs, LUMOs of molecules by using DFT/B3LYP/LANL2DZ basic set.

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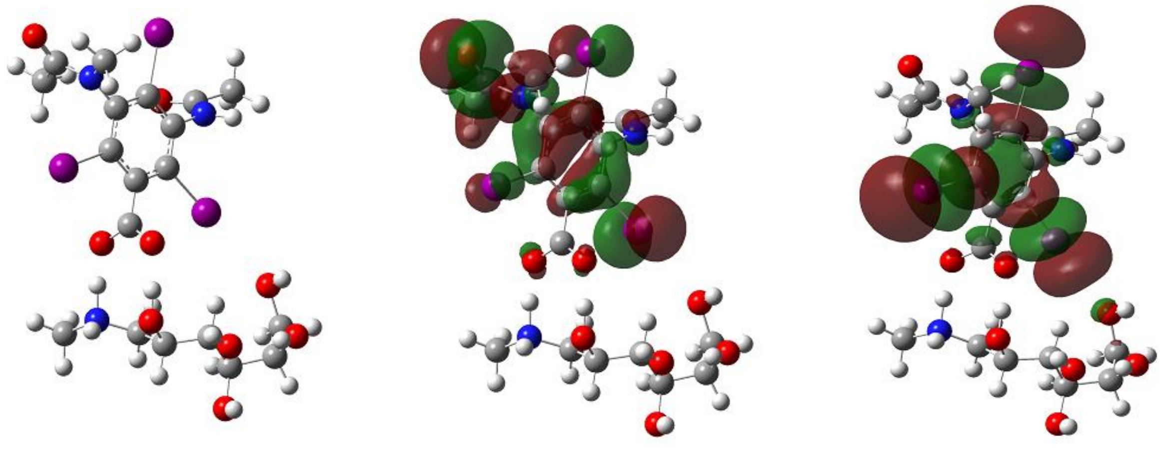
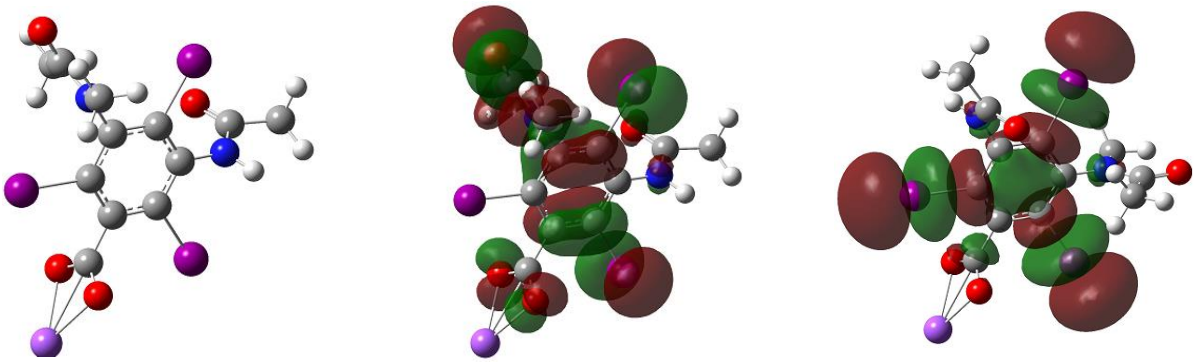


Melag-Met-opt Melag-Met-HOMO Melag-Met-LUMO



Na-Met-opt Na-Met-HOMO Na-Met-LUMO

Figure 1. (continuous)

and 2.264 in solvent phase, respectively. The results indicate that an-Met is relatively soft in gas phase and water phase. Increases in the hardness values of MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met going from the gas phase to the aqueous medium are 8.54%, 6.86%, 38.57%, 2.00%, 4.90% and 1.39%, respectively.

Physically, the escaping tendency of electrons from an equilibrium system is defined as chemical potential. The greater the electronic chemical potential means that the compound is the less stable or more reactive. The values of μ for MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met are -4.669, -2.492, -0.926, -3.989, -4.253 and -4.214 in gas phase, -4.725, -2.343, -4.141, -4.345, -4.517, -4.414 in solvent phase, respectively. The results indicates that chemical potential of the molecules under study in gas phase are less than in water phase except Melag. Decreases in the chemical potential values of MetA, an-Met, K-Met, Melag-Met, Na-Met going from the gas phase to the aqueous medium are 1.20%, 347.24%, 8.92%, 6.23% and 4.75%. In a study related with the electronic chemical potential of some of the reagents involved in Diels-Alder reactions, authors reported that the tetracyanoethylene molecule with a chemical potential of 7.04 eV acted as strong electron accepting molecules and the dimethylvinyl amine molecule with chemical potential of 1.85 eV acted as strong electron donating molecules.[10]

The electrophilicity index is a powerful tool to investigate the reactivity of organic molecules in polar reactions.[11] Molecules with an electrophilic index > 1.5 eV are classified as strong electrophiles, those with an electrophilic index between 0.8 and 1.5 are classified as medium electrophiles, and those less than 0.8 are marginal electrophiles.[12]

The values of ω for MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met, is 4.949, 0.913, 0.285, 3.666, 3.931, 3.976 in gas phase, 4.67, 0.755, 4.119, 4.264, 4.229, 4.303 in water phase, respectively. The results indicate that electrophilicity index of the molecules under study are higher in gas phase compared to water phase.

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Table 1. The calculated quantum chemical parameter values for gas and water phases

Molecule	**E_{HOMO} (eV)**	**E_{LUMO} (eV)**	**ΔE (eV)**	**μ (D)**	**MV (cm^3/mol)**	**TNC (e)**	**η (eV)**
MetA	-6.871	-2.467	4.405	5.7534	229.451	-3.530	2.202
Melag	-5.891	0.907	6.799	3.6635	151.934	-0.738	3.399
an-Met	-2.428	0.576	3.004	11.6898	261.558	-4.006	1.502
K-Met	-6.159	-1.819	4.341	13.6385	282.419	-4.181	2.170
Melag-Met	-6.553	-1.952	4.600	8.3651	359.370	-4.869	2.300
Na-Met	-6.447	-1.981	4.466	11.4035	257.500	-4.200	2.233
MetA*	-7.116	-2.334	4.781	7.2749	212.329	-3.646	2.391
Melag*	-5.975	1.290	7.265	4.8106	140.316	-0.814	3.633
an-Met*	-6.222	-2.060	4.163	17.4443	208.520	-4.258	2.081
K-Met*	-6.559	-2.131	4.427	15.7723	211.834	-4.272	2.214
Melag-Met*	-6.930	-2.105	4.826	10.1261	382.705	-5.039	2.413
Na-Met*	-6.678	-2.150	4.528	13.7972	278.837	-4.298	2.264

	σ (eV^{-1})	**χ (eV)**	**μ_i (eV)**	**Ω (eV)**	**ΔE_n (eV)**	**ΔE_e (eV)**	**SEZPE (eV)**
MetA	0.227	4.669	-4.669	4.949	1.381	10.720	-908.095
Melag	0.147	2.492	-2.492	0.913	0.121	5.105	-707.475
an-Met	0.333	0.926	-0.926	0.285	0.110	1.962	-907.585
K-Met	0.230	3.989	-3.989	3.666	0.762	8.740	-935.729
Melag-Met	0.217	4.253	-4.253	3.931	0.829	9.334	-1615.620
Na-Met	0.224	4.214	-4.214	3.976	0.879	9.307	-907.786
MetA*	0.209	4.725	-4.725	4.670	1.140	10.590	-908.125
Melag*	0.138	2.343	-2.343	0.755	0.229	4.914	-707.498
an-Met*	0.240	4.141	-4.141	4.119	1.019	9.301	-907.688
K-Met*	0.226	4.345	-4.345	4.264	1.026	9.716	-935.798
Melag-Met*	0.207	4.517	-4.517	4.229	0.918	9.953	-1615.475
Na-Met*	0.221	4.414	-4.414	4.303	1.021	9.850	-907.862

*Water Phase, ΔE: Energy gap, μ: Dipole moment, MV: Volume, TNC: Total negative charge, η: Hardness, σ: Softness, χ: Electronegativity, μ_i: Chemical potential, ω: Global electrophilicity, ΔE_n: Nucleofugality, ΔE_e: Electrofugality, SEZPE: Sum of electronic and zero point energy.

The electrophilicity index of MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met is greater than 1.5 eV, so they can be said to be strong electrophiles.

The electrophilicity index includes the tendency of an electrophile to obtain an extra electron density given around it, that is, the resistance to change the electron density with the given electron. Thus, a good electrophile is characterized by high electrophilicity index and low hardness parameter.

Another parameters proposed by Ayers and co-workers[13,14] are nucleofugality, ΔE_n and electrofugality, ΔE_e defining the quantify nucleophilic and electrophilic capabilities of a leaving group. As seen from Table 1, the values of nucleofugality and electrofugality of MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met are bigger in gas phase than that in water phase. The other properties such as molar volume, total negative charge, sum of zero point and electronic energy for gas and solvent phase are given in Table 1.

3.2. Thermodynamic analysis

The thermodynamic parameters were calculated using B3LYP method with the LANL2DZ basis set at the temperatures between 200 and 1000 K in gas phase and water phase for MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met.

The standard statistical thermodynamic functions such as heat capacity, entropy and enthalpy changes for Metrizoic acid (MetA), melagnomie (Melag), anionic form of metrisoate (an-Met), K-Metrizoate (K-Met), metrizoate-melagnomie salt (Melag-Met), Na-Metrizoate (Na-Met), in gas phase and water phase were obtained from the theoretical harmonic frequencies on the basis of vibrational analysis at B3LYP/LANL2DZ level. In order to determine the estimated precise value of thermodynamic functions, 0.96 rating factor was used. Figure 2 demonstrates the correlation graphs between various temperatures versus heat capacity, entropy, enthalpy for the methods of DFT level in gas and water phase. Figure 2 reveals that the heat capacities, entropy, and enthalpy changes increase with temperatures between 200 and 1000 K since the intramolecular vibrational intensities increase with temperature. [15]

The correlation equations between heat capacity, entropy, enthalpy and temperatures were fitted by parabolic formula. These thermodynamic data can provide useful information in determining the direction of chemical reactions in future studies.[16] Fitting equations for heat capacity, entropy and enthalpy and correlation coefficient in water medum are given in Table 2. For the title molecule, the equations are used to predict approximately the values of heat capacity at constant pressure, entropy and enthalpy for other range of temperature. The regression coefficient is also given in the parabolic equation.

3.3. Non-linear optical properties

Under the applied electric field, first order hyperpolarizability (third order tensor) can be defined by the 3 × 3 × 3 matrix. The Kleinman symmetry reduces the components of the 3D matrix to 10 components.[17] β components are defined as the coefficients in the Taylor series expansion of energy in the external electric field. The components of β are defined as the coefficients in the Taylor series expansion of the energy in the external electric field. When the external electric field is weak and homogeneous, this expansion is as in Equation (11).

$$E = E^{o} - \mu_{\alpha} F_{\alpha} - \frac{1}{2}\alpha_{\alpha\beta} F_{\alpha} F_{\beta} - \frac{1}{6}\beta_{\alpha\beta\gamma} F_{\alpha} F_{\beta} F_{\gamma} + \ldots \tag{11}$$

where E^{o} is the energy of the unperturbed molecules, F_a is the field at the origin, and m_a, a_{ab} and b_{abg} are the components of dipole moment, polarizability and the first order hyperpolarizabilities, respectively.

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The dipole moment is expected to be larger in solution than in the gas phase. Table 3 presents the dipole moments computed in the gas phase and in water at the level of B3LYP theory with LANL2DZ basis set. The values of the electric dipole moment (Debye) and dipole moment components are listed in Table 3. The total dipole moment of MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met is found to be 2.862, 1.893, 6.863, 3.703, 5.428 D for gas phase, and 2.862, 1.893, 6.863, 3.703, 5.428 D for water phase, respectively. As expected, the dipole moment is larger in water than in the gas phase.[18]

The first hyperpolarizability values calculated with Equations 11 and 12 for MetA, Melag, an-Met, K-Met, Melag-Met, Na-Met are presented in Figure 3. The first hyperpolarizability and the polarizability values calculated in atomic unit from Gaussian 09[8] output have been converted into electrostatic units (esu) (for hyperpolarizability 1 a.u. = 8.639 x 10^{-33} esu, for polarizability 1 a.u. = 0.1482 x 10^{-24} esu).

The first hyperpolarizability of MetA, Melag, an-Met, Melag-Met, Na-Met molecules are 3.25 10^{-30} esu, 0.46 10^{-30} esu, 17.28 10^{-30} esu, 2.91 10^{-30} esu, 10. 91 10^{-30} esu in gas phase, and they are 4.35 10^{-30} esu, 0.93 10^{-30} esu, 16.62 10^{-30} esu, 6.73 10^{-30} esu, 2. 13 10^{-30} esu in water phase.

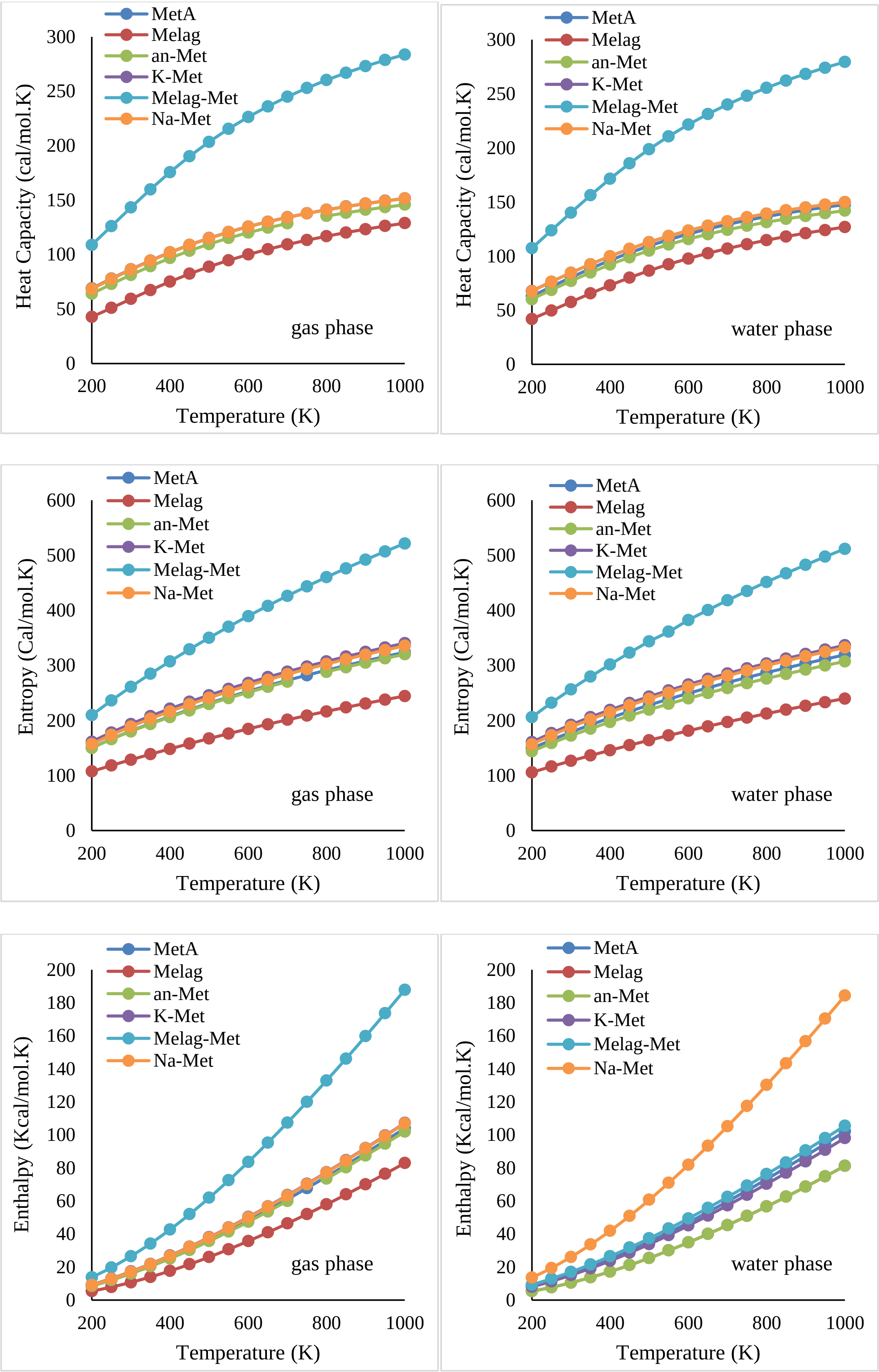

Figure 2. Thermodynamic properties at different temperatures at the B3LYP/LANL2DZ level of metrizoate.

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Table 2. Equation and correlation coefficient between temperatures and heat capacities, entropies, enthalpies for gas and water phases

	Gas Phase	**Water Phase**
Molecule	**Heat Capacity**	
MetA	$C = -0.0001T^2 + 0. 2228T + 24.592$ $R^2 = 0.9995$	$C = -0.0001T^2 + 0.2184T + 23.456$ $R^2 = 0.9997$
Melag	$C = -0.00009T^2 + 0. 215T + 3. 2548$ $R^2 = 0.9997$	$C = -0.00008T^2 + 0.2073T + 3.5785$ $R^2 = 0.9998$
an-Met	$C = -0.0001T^2 + 0. 2156T + 25.27$ $R^2 = 0.9996$	$C = -0.00009T^2 + 0.2107T + 22.153$ $R^2 = 0.9997$
K-Met	$C = -0.0001T^2 + 0. 2175T + 29.941$ $R^2 = 0.9995$	$C = -0.00009T^2 + 0.2119T + 29.506$ $R^2 = 0.9997$
Melag-Met	$C = -0.0002T^2 + 0. 4438T + 27.769$ $R^2 = 0.9997$	$C = -0.0002T^2 + 0.4264T + 28.981$ $R^2 = 0.9998$
Na-Met	$C = -0.0001T^2 + 0.219T + 29.295$ $R^2 = 0.9995$	$C = -0.00009T^2 + 0.2126T + 29.218$ $R^2 = 0.9997$
	Entropy	
MetA	$S = -0.0001T^2 + 0. 3318T + 89.462$ $R^2 = 0.9998$	$S = -0.00009T^2 + 0.3225T + 89.82$ $R^2 = 0.9998$
Melag	$S = -0.00005T^2 + 0. 2367T + 62.366$ $R^2 = 1.0000$	$S = -0.00005T^2 + 0.2299T + 62.068$ $R^2 = 1.0000$
an-Met	$S = -0.0001T^2 + 0. 3281T + 89.861$ $R^2 = 0.9998$	$S = -0.00009T^2 + 0.3093T + 87$ $R^2 = 0.9998$
K-Met	$S = -0.0001T^2 + 0. 3481T + 97.98$ $R^2 = 0.9998$	$S = -0.0001T^2 + 0.3403T + 98.568$ $R^2 = 0.9998$
Melag-Met	$S = -0.0001T^2 + 0.5655T + 104.08$ $R^2 = 0.9999$	$S = -0.0001T^2 + 0.5496T + 103.62$ $R^2 = 0.9999$
Na-Met	$S = -0.0001T^2 + 0.347T + 93.61$ $R^2 = 0.9998$	$S = -0.0001T^2 + 0.3398T + 94.637$ $R^2 = 0.9998$
	Enthalpy	
MetA	$H = 0.00005T^2 + 0.0596T - 9.0876$ $R^2 = 0.9998$	$H = 0.00005T^2 + 0.0571T - 5.7795$ $R^2 = 0.9998$
Melag	$H = 0.00005T^2 + 0. 035T - 4. 3754$ $R^2 = 0.9998$	$H = 0.00005T^2 + 0.0334T - 4.073$ $R^2 = 0.9998$
an-Met	$H = 0.00005T^2 + 0. 0588T – 5.9065$ $R^2 = 0.9998$	$H = 0.00005T^2 + 0.0545T - 5.5691$ $R^2 = 0.9998$
K-Met	$H = 0.00005T^2 + 0. 0643T – 6.2947$ $R^2 = 0.9998$	$H = 0.00005T^2 + 0.0622T - 5.8723$ $R^2 = 0.9999$
Melag-Met	$H = 0.0001T^2 + 0.0924T - 10.466$ $R^2 = 0.9998$	$H = 0.0001T^2 + 0.0893T - 9.8837$ $R^2 = 0.9998$
Na-Met	$H = 0.00005T^2 + 0.0639T – 6.4095$ $R^2 = 0.9998$	$H = 0.00005T^2 + 0.062T - 5.9832$ $R^2 = 0.9999$

Table 3. Dipole moment components and dipole moment of MetA, Melag, an-Met, K-Met, Melag-Met and Na-Met.

	Gas Phase				**Water Phase**			
Molecules	μ_x	μ_y	μ_z	μ	μ_x	μ_y	μ_z	μ
MetA	-1.981	-0.481	-0.984	2.264	-2.328	-0.349	-1.628	2.862
Melag	-0.890	0.794	-0.809	1.441	-1.103	1.124	-1.049	1.893
an-Met	-1.839	3.977	-1.398	4.599	-2.008	6.101	-2.418	6.863
Melag-Met	3.226	-0.038	0.650	3.291	2.532	2.127	-1.669	3.703
Na-Met	-3.881	1.715	-1.457	4.487	-4.661	1.664	-2.230	5.428

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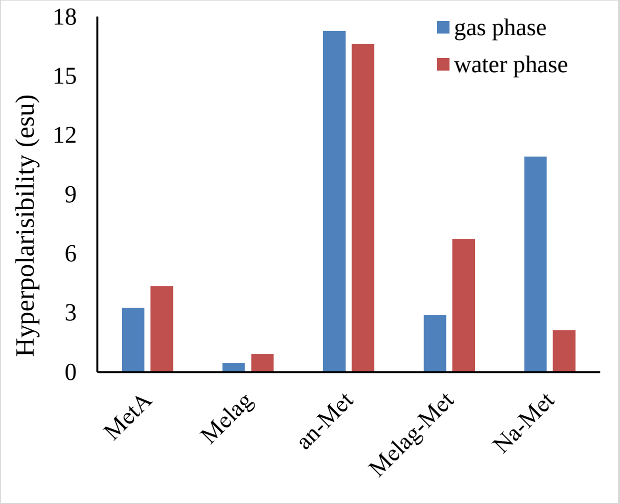

Figure 3. First hyperpolarizability *β* of MetA, Melag, an-Met, K-Met, Melag-Met and Na-Met (as values × 10^{-30} esu).

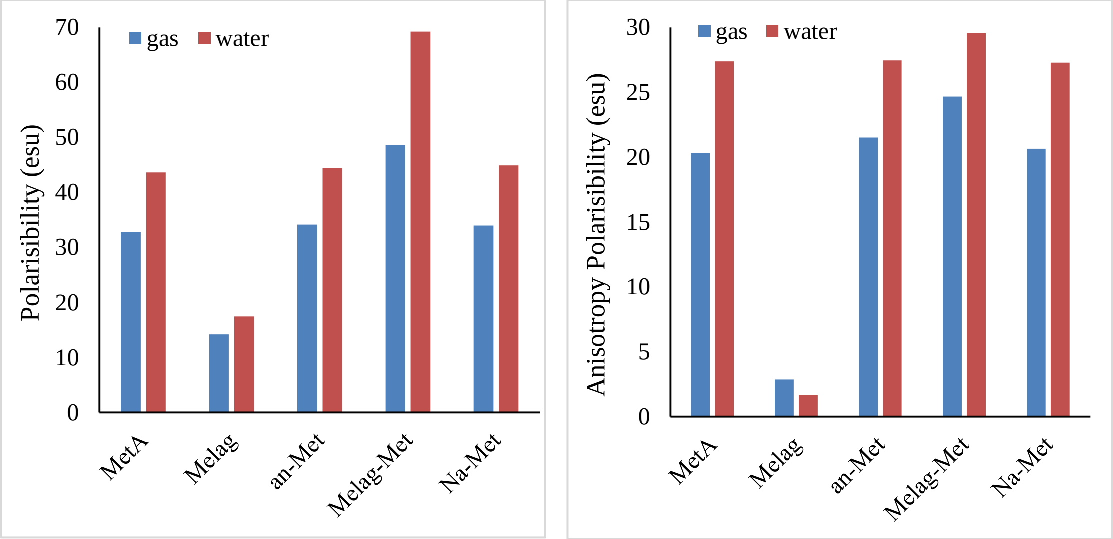

Figure 4. The average polarizability *α* (esu), the anisotropy of the polarizability *Δα* (esu), of MetA, Melag, an-Met, K-Met, Melag-Met and Na-Met calculated by B3LYP/LANL2DZ method (as values × 10^{-24} esu).

4. CONCLUSION

In the present work, the effect of the medium on the descriptors such as dipole moment and global reactivity was determined by B3LYP functional and LANL2DZ basis set. The HOMO-LUMO energy gap has been calculated to get the global reactivity descriptors such as η, μ, ω, electronic charge *ΔN* max, nucleofugality ΔE_n, electrofugality ΔE_e of the titled molecule. The value of the energy gap between the HOMO and LUMO of anionic form of metrisoate is very small 3.004 eV compared to other studied compounds, and this energy gap gives significant information about the reactivity of anionic form of metrizoate.

Conflict of interests

Authors declare that there is no a conflict of interest with any person, institute, company, etc.

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