Solvent Effects on the Contrast Agent Iomeprol with Density Functional Theory

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Abstract

Contrast compounds, also called contrast agents or contrast media are substances that temporarily change the way X-rays or other imaging tools interact with the body. Iomeprol is a nonionic monomeric iodinated contrast medium. Optimized geometries of Iomeprol, HOMO-LUMO energy, energy gap, global chemical indices, total energy, nonlinear optical and Natural Bond Orbital (NBO) analysis in the gas phase and in solvents (chloroform, acetic acid, ethanol, DMF, DMSO and water) were obtained based on Density Functional Theory with B3LYP/lanl2dz basis set. The results revealed that the solvents have an effect on the optimized and some chemical parameters (hardness, electronegativity, electrophilicity index, nucleofugality,..). It was observed \( E_{\text{HOMO}} \) values become more negative and \( E_{\text{LUMO}} \) values become more positive due to the increase dielectrical constant of the solvent. It was observed that Iomeprol had a highest stability, harder and less reactive in the water phase. In the NBO analysis, interaction between donor and acceptor electrons was effected with the dielectric constant of the solvent.

Keywords: Density Functional Theory, Gaussian 09, HOMO-LUMO, Stabilisation Energy, Iomeprol.

Yoğunluk Fonksiyonel Teorisi ile Kontrast Madde Iomeprol Üzerinde Çözücü Etkileri

Öz

Kontrast madde olarak da adlandırılan kontrast bileşikleri, X-ışınlarının veya diğer görüntüleme araçlarının vücutla etkileşimi için geçici olarak değiştirilen maddeye dair. Iomeprol, mononik bir monomik iodo kontrast ortamdır. Iomeprol, HOMO-LUMO enerji, enerji aralığı, global kimyasal indeksler, toplam enerji, doğrusal optik ve Natural Bond Orbital (NBO) analizi (karbon dioksit, asetik asit, etanol, DMF, DMSO ve su) bağlanısında elde edildi. Sonuçlar, çözücülerin ve bazı kimyasal parametreler (kınayıcılık, elektronegatiflik, elektrofilik indeksi, nükleofüliftle...) üzerinde etkileri gözlemlendi. Iomeprol, su fazında en yüksek sabitlere sahip, daha sert ve daha az aktif olduğu belirlendi. Ayrıca NBO analizinde, alıcı ve verici elektro))^4

Anahtar Kelimeler: Yoğunluk Fonksiyonel Teorisi, Gaussian 09, HOMO-LUMO, Stabilizasyon Enerjisi, Iomeprol.

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1. Introduction

Contrast agents are iodine-containing solutions and the most commonly used in radiology today. Iodinated contrast agents can be used pretty much anywhere in the body and administered as intravenously, intratraherially, intraheccally and intraabdominalhly [1].

A structure in the human body can be made visible by radiation only if its attenuation of radiation differs from that of its surroundings. The attenuation difference between the different structures is an important effect of the contrast agent, which enhances the attenuation difference between different body structures with different concentrations in the diverse body parts in question. Since the contrast agent is distributed to both the extracellular area and to a lessor extent the intracellular area, it touches all plasma proteins and all cells of the body. Therefore, undesirable adverse reactions may occur [2]. Although serious or life-threatening reactions can occur, they are usually safe and side effects are usually mild and self-limiting [1].

Contrast agents are classified as ionicmonomers, ionic dimers, nonionic monomers, nonionic dimers and are different in terms of carboxyl and hydroxyl groups and osmolality. In imaging studies, iodinated contrast media are used commonly [3].

Iomeprol is a new nonionic, hydrosoluble, monomeric iodinated, injectable contrast agent with very low molecular toxicity for diagnostic radiologic examinations and Bracco synthesized and developed it. Chemically, Iomeprol is characterized as N1,N1-bis-(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)methylamino]-2,4,6-triido-1,3-benzenedicarboxamide [4]. Formulations of iodine do not contain chelants and are characterised by the lowest osmolality, chemotoxicity and viscosity of all the available nonionic, monomeric contrast agent at alike iodine concentrations [5]. Since Iomeprol does not have chelating agent, it causes undesirable hemodynamic and electrophysiological effects less with its lowered ionized calcium in myocardial capillary and interstitial fluid with chelating elements. However, this did not provide advantage over Iomeprol when compared with other nonionic agents in clinical trials [6]. The contrast enhancing potency of Iomeprol is caused by the iodine-trisubstituted benzene ring4. When compared to nonionic contrast agents, it is reported that water solubility is higher with Iomeprol [3]. The 3 high-hydrophilic side-chain groups in structure cause water solubility [4]. Iomeprol is higly soluble in water and forms stable formulation. For this reason, Iomeprol is used for diagnostic procedures because of its many concentrations [7].

Iomeprol has equal diagnostic efficacy and tolerability profile, which is similar to other nonionic contrast agents. Iomeprol is suitable for use in diagnostic imaging like others of its class [3].

2. Material and Method

Gaussian 09 package was used for all calculations [8]. The molecular structure geometries and electronic structure were visualized by GaussView 5.0 program [9]. Optimization for geometry was made by using hybrid 3-parameter exchange function of Becke and nonlocal correlation functional of Lee, Yang, and Parr (B3LYP) [10]. The population analysis has also been performed by the natural bond orbital method at B3LYP/lanl2dz level of theory using natural bond orbital (NBO) program with Gaussian 09.

3. Results and Discussion

The ionization potentials (IP) and electron affinities (EA) of the molecule in the gas phase and in solvents are calculated with the use of Koopman’s Hypothesis, including the HOMO and LUMO energy orbitals respectively using the following expressions:

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

Figure 1, presents optimised structure, the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and electron density of Iomeprol in the gas phase computed at the DFT/B3LYP level with the lanl2dz basis set. It can be observed from Figure 1, HOMO are formed from benzene ring and group attached to N atom, benzene ring. LUMO are composed of benzene and iodine groups attached to benzene ring.

HOMO that is an electron donor shows the ability to give electron, the higher the $E_{HOMO}$, the easier it is for HOMO to give electrons; and LUMO that is an electron acceptor shows the ability to receive electron. If $E_{LUMO}$ is lower, it is the easier to accepts electrons for the LUMO [11].

![Figure 1. Optimized structure, HOMO, LUMO and total electron density map of Iomeprol](image)

In Koopman’s hypothesis, ionization potentials (IP) and electron affinities (EA) of the molecule are related with $E_{HOMO}$ and $E_{LUMO}$. The electron affinity (EA) and ionization potential (IP) measure the tendency of compounds to gain or lose an electron [12]. The energy of frontier orbitals are presented in Figure 2. The higher the $E_{HOMO}$, the easier it is to remove an electron to form an ion.

In the Figure 2, the solvents are arranged in ascending order of dielectric constant with their respective values for $E_{HOMO}$ and $E_{LUMO}$ and near five molecular orbital energies close to frontier orbitals in eV unit.
The kinetic stability, chemical reactivity, optical polarizability and chemical hardness-softness of a molecule are determined with the use of energy gap between $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$[14]. According to energy gap value, the order of stability of the molecule is more in the water > DMSO > DMF > ethanol > acetic acid > chloroform > gas phase. Interestingly, the order of stability for Iomeprol molecule increases with an increase in polarity of the solvents.

$E_{\text{HOMO}}, E_{\text{LUMO}}$, hardness, softness, electronegativity, chemical potential, electrophilicity index, nucleofugality, electrofugality, maximum electrons transferred in a chemical reaction in Iomeprol are shown in Table 1.

Chemical hardness is given by half of the energy band gap as shown in the equation 4 [15].

$$\eta = \frac{IP - EA}{2} \quad (4)$$

As seen in Table 1, Iomeprol molecule in the water phase has slightly the highest value of chemical hardness (2.381) is considered to be harder and more stable than in the rest of the solvents, followed by DMSO, DMF, ethanol, acetic acid and chloroform. This indicates that Iomeprol in chloroform is less stable than in the rest of the solvents.

Electrophilicity index ($\omega$) refers to the measurement of energy decrease because of maximal electron flow between donor and acceptor. Global electrophilicity index ($\omega$) is predicted by employing electronegativity and chemical hardness parameters in the equation [16, 13].

$$\omega = \frac{\mu^2}{2\eta} \quad (6)$$

High electrophilicity shows a good electrophile, and small electrophilicity shows a good nucleophile. As seen in Table 1, electrophilicity index increases with an increase in the dielectric constant of the solvents.

As seen in Table 1, Iomeprol molecule in the water phase has slightly the highest value of chemical hardness (2.381) is considered to be harder and more stable than in the rest of the solvents, followed by DMSO, DMF, ethanol, acetic acid and chloroform with chemical hardness. This indicates that Iomeprol in chloroform is less stable than in the rest of the solvents.

Electron polarizability (i.e. chemical softness ($S$)) refers to the capacity of an atom or an atom group to have electrons can be formulated with the equation 5.

$$S = \frac{1}{2\eta} = \left(\frac{\partial^2 N}{\partial E^2}\right)_{V(r)} = \left(\frac{\partial N}{\partial \mu}\right)_{V(r)} \quad (5)$$

Figure 2. Frontier orbital energies for Iomeprol

We find that the inclusion of solvents causes the HOMO values become more negative and LUMO values become more positive due to the increase dielectric constant.

In Figure 2, it can be observed that it is more difficult to remove an electron from water > DMSO > DMF > ethanol > acetic acid > chloroform > gas phase to form an ion. Similarly, it is more difficult to add an electron in terms of their EAs to the molecule in gas phase > chloroform > acetic acid > ethanol > DMF > DMSO > water.

Compounds with large $E_{\text{HOMO}}$-$E_{\text{LUMO}}$ gap value given with equation 3 tend to have higher stability [13].

$$E_{\text{gap}} = E_{\text{LUMO}} - E_{\text{HOMO}} = IP - EA \quad (3)$$

| Solvent ($\varepsilon$) | $E_{\text{HOMO}}$ | $E_{\text{LUMO}}$ | $\Delta E$ | $\eta$ | $S$ | $\chi$ | $\mu$ | $\omega$ | $\Delta N_{\text{max}}$ | $\Delta E_a$ | $\Delta E_e$ |
|--------------------------|-----------------|-----------------|-----------|------|----|------|------|------|-----------------|-------------|-------------|
| Gas                      | -6.746          | -2.199          | 4.548     | 2.274| 0.220| 4.472| -4.472| 4.399| 1.967           | 1.063       | 10.008      |
| Chloroform (4.81)        | -7.018          | -2.287          | 4.731     | 2.366| 0.211| 4.652| -4.652| 4.574| 1.967           | 1.105       | 10.409      |
| Acetic acid (6.15)       | -7.034          | -2.294          | 4.740     | 2.370| 0.211| 4.664| -4.664| 4.589| 1.968           | 1.110       | 10.437      |
| Ethanol (24.55)          | -7.069          | -2.310          | 4.759     | 2.379| 0.210| 4.689| -4.689| 4.621| 1.971           | 1.121       | 10.500      |
| DMF (36.71)              | -7.073          | -2.312          | 4.761     | 2.380| 0.210| 4.692| -4.692| 4.625| 1.971           | 1.123       | 10.507      |
| DMSO (46.68)             | -7.074          | -2.313          | 4.761     | 2.381| 0.210| 4.693| -4.693| 4.626| 1.971           | 1.123       | 10.510      |
| Water (80.1)             | -7.077          | -2.314          | 4.763     | 2.381| 0.210| 4.695| -4.695| 4.629| 1.972           | 1.124       | 10.515      |

$\varepsilon$: Dielectric constant, $\Delta E$: Energy gap, $\eta$: Hardness, $S$: Softness, $\chi$: Electronegativity, $\mu$: Chemical potential, $\omega$: Nucleofugality, $\Delta E_e$: Electrofugality

Table 1. Chemical Parameters for Iomeprol

Electrophilicity index, $\Delta N_{\text{max}}$: The maximum number of electrons transferred in a chemical reaction, $\Delta E_a$: Nucleofugality, $\Delta E_e$: Electrofugality
Electric dipole polarizability (measurement of linear response of an infinitesimal electric field (F) representing second-order variation energy) is an important property used in determining the polarizability of a molecule or compound [17].

Mean polarizability (\(\langle \alpha \rangle\)), anisotropic polarizability (\(\Delta \alpha\)) and \(\kappa\) anisotropy, which are large experimental interest quantities in the theory of optoelectronic and intermolecular forces, of the molecule in gas and in various solvents were computed and reported in Table 2.

Table 2. Polarizability (\(\langle \alpha \rangle\)), Anisotropic Polarizability (\(\Delta \alpha\)), \(\kappa\) Anisotropy of the Optimized Iomeprol Molecule in the Gas Phase and Different Solvents

| Solvent (e) | \(\langle \alpha \rangle\) (Esu) | \(\langle \Delta \alpha \rangle\) (Esu) | \(\langle \Delta \alpha \rangle\) (Ure times) | \(\kappa\) |
|------------|----------------|-----------------|----------------|---|
| Gas        | 300            | 18.619          | 8.718          | 0.018 |
| Chloroform (4.81) | 368          | 22.495          | 10.533         | 0.017 |
| Acetic acid (6.15) | 374          | 22.858          | 10.703         | 0.017 |
| Ethanol (24.55) | 388          | 23.765          | 11.127         | 0.016 |
| DMF (36.71) | 390           | 23.873          | 11.178         | 0.016 |
| DMSO (46.68) | 390           | 23.918          | 11.199         | 0.016 |
| Water (80.1) | 391           | 23.989          | 11.232         | 0.016 |

It can also be observed that ongoing from non-polar to polar solvent the polarizability of Iomeprol increases as the polarity of the solvents decreases whereas the anisotropic polarizability increases with an increase in the polarity of the solvents. Consequently, the polarity of the solvents plays an important role in determining the values of the non-linear optical properties of Iomeprol. Urea is commonly used as a reference material in NLO studies. The calculated \(\Delta \alpha\) value for urea with the B3LYP/6-311++G(d,p) level is 2.13568262.10^{-24} esu [18]. As seen in Table 2, the anisotropy of polarizability values for the title compound are approximately ten times greater than those of urea for gas and all solvents.

Hyperpolarizability is of boundary molecular orbital energies that aid in the use of intramolecular charge transfer to account for hyperpolarizability. In this study, the values of the first hyperpolarizability were obtained using the following equations:

The first order hyperpolarizability (\(\beta\)) such as \(\beta_{\text{vec}}\) (\(\beta\) vector), \(\beta_{\parallel}\) (\(\beta\) parallel) and \(\beta_{\text{tot}}\) (\(\beta\) total) is the nonlinear optical activity measurement. It is a 3rd rank tensor and may be described with a 3×3 matrix and using Kleinman's symmetry, the 3D matrix is reduced to 27 components and 10 components. 10 components of this matrix that is called as \(\beta_{\text{xxx}}, \beta_{\text{xyy}}, \beta_{\text{yyz}}, \beta_{\text{zxx}}, \beta_{\text{xyz}}, \beta_{\text{yzx}}, \beta_{\text{zxy}}, \beta_{\text{zyz}}, \beta_{\text{zzz}}\) are provided output of GAUSSIAN calculations [19-21].

As the experimental first hyperpolarizability of Iomeprol values in the literature are not reported, it is hard to determine which basis set computes reliable \(\beta\) values. As the polarizability values \(\alpha\) and the 1st hyperpolarizability \(\beta\) of Gaussian 09 are reported as atomic units (a.u.), the computed values were converted into electrostatic units (esu) (\(\alpha\): 1 a.u. = 0.1482×10^{-24} esu; \(\beta\): 1 a.u. = 8.6393×10^{-33} esu). \(\beta_{\text{xxx}}, \beta_{\text{xyy}}, \beta_{\text{yyz}}, \beta_{\text{zxx}}, \beta_{\text{xyz}}, \beta_{\text{yzx}}, \beta_{\text{zxy}}, \beta_{\text{zyz}}, \beta_{\text{zzz}}\) matrix element are given in Table 3 and the total including the hyperpolarizability \(\beta_{\text{tot}}\) which may be computed with the equation given below:

Here,

\[
\beta_{\text{tot}} = \beta_{\text{xxx}} + \beta_{\text{xyy}} + \beta_{\text{yyz}} + \beta_{\text{zxx}} + \beta_{\text{xyz}} + \beta_{\text{yzx}} + \beta_{\text{zxy}} + \beta_{\text{zyz}} + \beta_{\text{zzz}}
\]

Table 3: \(\beta\times10^{-30}\) (esu), \(\beta\) (a.u.) Components and Values Calculated Using DFT Levels of Theory for Iomeprol

| Solvent (e) | \(\beta_{\text{xxx}}\) (a.u.) | \(\beta_{\text{xyy}}\) (a.u.) | \(\beta_{\text{yyz}}\) (a.u.) | \(\beta_{\text{zxx}}\) (a.u.) | \(\beta_{\text{xyz}}\) (a.u.) | \(\beta_{\text{yzx}}\) (a.u.) | \(\beta_{\text{zxy}}\) (a.u.) | \(\beta_{\text{zyz}}\) (a.u.) | \(\beta_{\text{zzz}}\) (a.u.) |
|-------------|-----------------|-----------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Gas         | -53.80          | -89.30          | -92.67          | -101.90       | -103.07       | -103.57       | -104.33       |
| Chloroform  | -96.50          | -128.77         | -134.12         | -149.15       | -151.11       | -151.94       | -153.26       |
| Acetic Acid | 6.54            | 48.58           | 53.67           | 67.03         | 68.71         | 69.42         | 70.55         |
| Ethanol     | -95.94          | -2.83           | 9.86            | 44.13         | 48.48         | 50.30         | 53.19         |
| DMF         | 6.27            | -65.98          | -73.66          | -93.24        | -95.73        | -96.78        | -98.47        |
| DMSO        | -16.07          | 8.45            | -7.37           | -4.49         | -4.14         | -3.99         | -3.73         |
| Water       | -79.96          | -121.50         | -125.53         | -135.42       | -136.61       | -137.11       | -137.94       |
| Ethanol     | 12.97           | 32.52           | 34.42           | 38.69         | 39.26         | 39.51         | 39.93         |
| DMF         | 2.60            | 63.84           | 70.78           | 88.64         | 90.83         | 91.76         | 93.24         |
| DMSO        | 25.30           | 55.53           | 58.98           | 68.02         | 69.13         | 69.56         | 70.14         |

\(\beta_{\text{total}}\) (a.u.)

\[
\beta_{\text{total}} = \beta_{\text{xxx}} + \beta_{\text{xyy}} + \beta_{\text{yyz}} + \beta_{\text{zxx}} + \beta_{\text{xyz}} + \beta_{\text{yzx}} + \beta_{\text{zxy}} + \beta_{\text{zyz}} + \beta_{\text{zzz}}
\]
In Table 3, it is seen that the calculated β values of Iomeprol using B3lyp/lan2dz level (the β of Iomeprol for gas, chloroform, acetic acid, ethanol, DMF, DMSO, water) are 1.72x10^{-30} esu., 1.28x10^{-30} esu., 1.30x10^{-30} esu., 1.40x10^{-30} esu., 1.41x10^{-30} esu., 1.42x10^{-30} esu., 1.44x10^{-30} esu, respectively. The first polarizability values obtained using B3lyp/lan2dz level for Iomeprol are the largest value in gas phase and the lowest value in chloroform. Similarly β_{total} -first hyperpolarizability value is very important key factors to identify NLO properties of molecular systems. In all phase, the first hyperpolarizability values for the title compound are approximately two times greater than those of urea (β_{total}, value for urea with the B3LYP/6-311++G(d,p) level is 7.2228469891.10^{11} esu [18]). Due to the obtained results, the Iomeprol molecule has bigger first hyperpolarizability than urea. So, it may be an attractive matter for the nonlinear optical applicants.

NBO analysis emphasizing the intermolecular orbital interaction’s role in charge transfer is done by considering all probable interactions among the donor and receiver NBOs and by predicting energetic significance with second-order perturbation theory. For donor NBO (i) and acceptor NBO (j), the stabilization energy E(2) attributed to electron delocalization between the donor and the receiver is predicted below:

\[ E^{(2)} = q_i \frac{(F_{ij})^2}{\varepsilon_j - \varepsilon_i} \]  

(8)

where \( F_{ij} \) is the o-diagonal NBO Fock matrix element, \( q_i \) is the orbital occupancy, and \( \varepsilon_i, \varepsilon_j \) are diagonal elements conjugative interactions in molecular system [22].

Delocalization of electron density between occupied Lewis type (bond or lone pair) NBO orbitals and formally unoccupied (antibonding or Rydberg) non Lewis NBO orbital’s correspond to a stabilizing donor-acceptor inter-action. The molecular interaction is formed by the orbital overlap between.

When \( E^{(2)} \) value becomes large, it shows that the interaction between electron donors and acceptors is intensive, and when the donation tendency from electron donors to electron acceptors is more, the extent of conjugation of the whole system is larger [23].

Table 4: Second-order perturbation theory analysis of Fock matrix in NBO basis for Iomeprol are listed in Table 4 and 5, and 6 which incudes only energy fort he other studied solvent.

The energies for the interaction n3(1s) → π^*(C15-C19) , n3(1s) → π^*(C16-C19) and n3(1s) → (C17-C20) 7.72, 7.83 and 7.49 kcal/mol, respectively demonstrate the intramolecular hyperconjugative interaction between the iodine atoms and benzene ring is strong in the ground state for Iomeprol in gas phase. The energies for the interaction n3(1s) → π^*(C15-C18), n3(1s) → π^*(C16-C19) and n3(1s) → (C17-C20) becomes 7.81, 7.59 and kcalmol^{-1}, respectively in water phase (Table 5). The energies for the interaction are 20.81 and 19.22 kcalmol^{-1} for n2(Oa) → σ*(N12-C25), and σ*(C14-C25); 20.87 and 19.18 kcalmol^{-1} for n2(Oa) → σ*(N14-C26) and (C17-C20); 24.14 kcalmol^{-1} for n2(Oa) → σ*(N12-C30). The highest energies for the interaction are seen as 57.29 kcalmol^{-1} for n1(N12) → σ*(O10-C30) in gas phase.
### Table 5. Second-order Perturbation Theory Analysis of Fock Matrix in NBO Basis for Iomeprol for Water Phase

| Item NO | Donor (i) | Type | Occup. | ED(j) | Acceptors (j) | Occup. | ED(j) | E(2) kcal/mol | E(j)-E(i) a.u. | F(i,j) a.u. |
|---------|------------|------|--------|-------|---------------|--------|-------|---------------|--------------|------------|
| 1       | I′-C_{18}  | σ    | 1.965  | -0.519 | C_{15}-C_{19}  | σ*     | 0.048 | 0.478         | 7.49          | 1          |
| 1       | I′-C_{18}  | σ    | 1.965  | -0.519 | C_{17}-C_{20}  | σ*     | 0.039 | 0.483         | 7.24          | 1          |
| 2       | I_{2}-C_{19} | σ    | 1.964  | -0.518 | C_{15}-C_{18}  | σ*     | 0.048 | 0.478         | 7.54          | 1          |
| 2       | I_{2}-C_{19} | σ    | 1.964  | -0.518 | C_{16}-C_{20}  | σ*     | 0.039 | 0.484         | 7.26          | 1          |
| 3       | I_{3}-C_{20} | σ    | 1.967  | -0.524 | C_{16}-C_{19}  | σ*     | 0.039 | 0.490         | 7.14          | 1          |
| 3       | I_{3}-C_{20} | σ    | 1.967  | -0.524 | C_{17}-C_{18}  | σ*     | 0.039 | 0.490         | 7.17          | 1          |
| 28      | N_{14}-H_{39} | σ    | 1.983  | -0.672 | O_{7}-C_{26}   | π*     | 0.030 | 0.436         | 5.1           | 1          |
| 30      | C_{15}-C_{18} | π    | 1.668  | -0.306 | C_{16}-C_{19}  | π*     | 0.387 | -0.014         | 19.27         | 0.29        |
| 30      | C_{15}-C_{18} | π    | 1.668  | -0.306 | C_{17}-C_{20}  | π*     | 0.393 | -0.016         | 22.87         | 0.29        |
| 33      | C_{16}-C_{19} | π    | 1.662  | -0.302 | C_{15}-C_{18}  | π*     | 0.400 | -0.022         | 22.61         | 0.28        |
| 33      | C_{16}-C_{19} | π    | 1.662  | -0.302 | C_{17}-C_{20}  | π*     | 0.393 | -0.016         | 19.51         | 0.29        |
| 38      | C_{17}-C_{20} | π    | 1.670  | -0.304 | C_{15}-C_{18}  | π*     | 0.400 | -0.022         | 19.83         | 0.28        |
| 38      | C_{17}-C_{20} | π    | 1.670  | -0.304 | C_{16}-C_{19}  | π*     | 0.387 | -0.014         | 23.19         | 0.29        |
| 39      | C_{17}-C_{26} | σ    | 1.959  | -0.672 | N_{14}-C_{22}  | σ*     | 0.023 | 0.297         | 6.04          | 0.97        |
| 50      | C_{27}-H_{40} | σ    | 1.983  | -0.526 | O_{4}-C_{23}   | σ*     | 0.032 | 0.211         | 5.01          | 0.74        |
| 52      | C_{28}-H_{42} | σ    | 1.983  | -0.528 | O_{5}-C_{24}   | σ*     | 0.032 | 0.210         | 4.99          | 0.74        |
| 57      | C_{30}-C_{31} | σ    | 1.977  | -0.646 | N_{12}-C_{29}  | σ*     | 0.025 | 0.274         | 5.76          | 0.92        |
| 59      | C_{31}-H_{48} | σ    | 1.972  | -0.526 | O_{9}-C_{30}   | π*     | 0.294 | -0.022         | 5.15          | 0.5         |
| 90      | I_{1}       | 3     | 1.933  | -0.279 | C_{15}-C_{18}  | π*     | 0.400 | -0.022         | 7.81          | 0.26        |
| 93      | I_{2}       | 3     | 1.931  | -0.277 | C_{16}-C_{19}  | π*     | 0.387 | -0.014         | 7.89          | 0.26        |
| 96      | I_{3}       | 3     | 1.942  | -0.287 | C_{17}-C_{20}  | π*     | 0.393 | -0.016         | 7.39          | 0.27        |
| 98      | O_{4}       | 2     | 1.967  | -0.337 | C_{23}-C_{27}  | σ*     | 0.029 | 0.346         | 5.36          | 0.68        |
| 100     | O_{3}       | 2     | 1.968  | -0.342 | C_{24}-C_{28}  | σ*     | 0.029 | 0.344         | 5.37          | 0.69        |

* Avrupa Bilim ve Teknoloji Dergisi
**Table 6. Interaction Energies of Iomeprol for Different Solvent**

| Donor (i) | Type | Acceptor | Type | Gas | Chloroform | Acetic Acid | Ethanol | DMF | DMSO | Water |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| I3-C18 | σ | C15-C19 | σ* | 7.45 | 7.48 | 7.48 | 7.49 | 7.49 | 7.49 | 7.49 |
| I3-C18 | σ | C17-C20 | σ* | 7.16 | 7.22 | 7.22 | 7.23 | 7.23 | 7.23 | 7.24 |
| I2-C19 | σ | C15-C18 | σ* | 7.5 | 7.53 | 7.53 | 7.54 | 7.54 | 7.54 | 7.54 |
| I2-C19 | σ | C16-C20 | σ* | 7.19 | 7.24 | 7.25 | 7.26 | 7.26 | 7.26 | 7.26 |
| I3-C20 | σ | C16-C19 | σ* | 7.12 | 7.13 | 7.13 | 7.14 | 7.14 | 7.14 | 7.14 |
| I3-C20 | σ | C17-C18 | σ* | 7.15 | 7.17 | 7.17 | 7.17 | 7.17 | 7.17 | 7.17 |
| N13-H3 | σ | O6-C25 | π* | 5.12 | 5.16 | 5.24 | 5.25 | 5.25 | 5.25 | 5.25 |
| N14-H39 | σ | O7-C26 | π* | 5.08 | 5.09 | 5.1 | 5.1 | 5.1 | 5.1 | 5.1 |
| C15-C18 | π | C16-C19 | π* | 18.87 | 19.18 | 19.2 | 19.26 | 19.27 | 19.27 | 19.27 |
| C15-C18 | π | C17-C20 | π* | 23 | 22.9 | 22.9 | 22.9 | 22.9 | 22.9 | 22.9 |
| C16-C19 | π | C15-C18 | π* | 22.73 | 22.64 | 22.63 | 22.61 | 22.61 | 22.61 | 22.61 |
| C16-C19 | π | C17-C20 | π* | 19.03 | 19.4 | 19.4 | 19.4 | 19.4 | 19.4 | 19.4 |
| C16-C23 | σ | N13-C21 | σ* | 5.85 | 5.96 | 5.97 | 5.99 | 5.99 | 5.99 | 5.99 |
| C17-C18 | σ | N12-C15 | σ* | 4.92 | 5.0 | 5.0 | 19.83 | 19.83 | 19.83 | 19.83 |
| C17-C20 | π | C15-C18 | π* | 19.64 | 19.79 | 19.8 | 19.83 | 19.83 | 19.83 | 19.83 |
| C17-C20 | π | C16-C19 | π* | 23.5 | 23.26 | 23.24 | 23.20 | 6.03 | 23.19 | 23.19 |
| C17-C26 | σ | N14-C22 | σ* | 5.87 | 6.0 | 6.01 | 5.03 | 5.01 | 6.04 | 6.04 |
| C27-H20 | σ | O2-C23 | σ* | 5.0 | 5.01 | 5.01 | 5.01 | 5.01 | 5.01 | 5.01 |
| C30-C31 | σ | N12-C29 | σ* | 5.49 | 5.69 | 5.75 | 5.76 | 5.76 | 5.76 | 5.76 |
| C31-H18 | σ | O2-C30 | π* | 4.98 | 5.09 | 5.14 | 5.15 | 5.15 | 5.15 | 5.15 |
| I1 | 3 | C15-C18 | π* | 7.72 | 7.79 | 7.8 | 7.81 | 7.81 | 7.81 | 7.81 |
| I2 | 3 | C16-C19 | π* | 7.83 | 7.87 | 7.87 | 7.88 | 7.88 | 7.88 | 7.88 |
| I3 | 3 | C17-C20 | π* | 7.49 | 7.41 | 7.41 | 7.39 | 7.39 | 7.39 | 7.39 |
| O4 | 2 | C23-C27 | σ* | 5.69 | 5.43 | 5.37 | 5.38 | 5.38 | 5.38 | 5.38 |
| O5 | 2 | C24-C28 | σ* | 5.67 | 5.46 | 5.39 | 5.38 | 5.38 | 5.38 | 5.38 |
| O6 | 2 | N13-C25 | σ* | 20.81 | 19.68 | 19.59 | 19.37 | 19.35 | 19.34 | 19.32 |
| O6 | 2 | C16-C25 | σ* | 19.22 | 18.24 | 18.16 | 17.96 | 17.93 | 17.93 | 17.91 |
| O7 | 2 | N14-C26 | σ* | 20.87 | 19.77 | 19.68 | 19.47 | 19.44 | 19.43 | 19.42 |
| O7 | 2 | C17-C26 | σ* | 19.18 | 18.26 | 18.18 | 17.99 | 17.97 | 17.96 | 17.94 |
| O8 | 2 | C27-H40 | σ* | 5.71 | 5.8 | 5.8 | 5.8 | 5.8 | 5.8 | 5.8 |
| O9 | 2 | C28-H42 | σ* | 5.66 | 5.79 | 5.8 | 5.8 | 5.8 | 5.8 | 5.8 |
| O10 | 2 | N12-C30 | σ* | 24.14 | 22.43 | 22.3 | 21.99 | 21.96 | 21.96 | 21.92 |
Table 6 shows that the variation of the first hyperpolarizability of Iomeprol for different solvents. Seen as for n1(N12) → σ*(O16-C30) interaction in gas phase being 57.29 kalmol⁻¹ increases with the polarity of the solvents increases. The order of this interaction is more in chloroform > acetic acid > ethanol > DMF > DMSO > water (Table 6). The same order are observed for n1(N13) → σ*(O16-C23) interaction. These interaction are 40.51, 82.56, 83.67, 85.92, 86.17 and 86.27 kalmol⁻¹ in gas, chloroform, acetic acid, ethanol, DMF, DMSO and water. n1(N14) → σ*(O7-C26) interaction energies are 33.44, 70.19, 72.49, 77.75, 78.33, 78.56, 78.56 kalmol⁻¹.  

4. Conclusions and Recommendations  
The molecular structures and quantum chemical parameters of the Iomeprol in different solvents were studied by employing the B3LYP with the 6-311G(d) basis set. To understand the effects of solvents on structural, electronic and non-linear optical properties of Iomeprol molecule, extensive computational study of the HOMO, LUMO, HOMO-LUMO energy gap, ionization potential, electron affinity, chemical hardness, chemical softness, chemical potential, electronegativity, electrophilicity index, polarizability, anisotropic polarizability, hyperpolarizability were calculated. Quantum chemical parameters for Iomeprol in different solvents were investigated by determining the polarizability α and the hyperpolarizability β by employing the same methods.  

It was determined in the study that the energy gap hardness increases with the increase of dielectric constant of the solvent interaction energy. The polarizability and the anisotropic polarizability increases with the increase in the dielectric constant of the solvents while κ anisotropy decreases as the polarity of the solvents increases. The title molecule may be an attractive in the future nonlinear optical materials studies according to anisotropic polarizability and hyperpolarizability values. In the NBO analysis, it was observed interaction between donor and acceptor electrons change with the change of dielectric constant of the solvent.  

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