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Scientific paper

Theoretical B3LYP Study on Electronic Structure of Contrast Agent Iopamidol

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Abstract

Nonionic low-osmolar contrast agents are thought about safe for intravenous or intra-arterial administration. Iopamidol is one of the contrast agents used for diagnostic clinical computed tomography (CT) protocols last four decades years. The molecular structure of Iopamidol was calculated by the B3LYP density functional model with the LANL2DZ basis set by the Gaussian program. The natural bond orbital analysis in terms of the hybridization of atoms and the electronic structure of the title molecule have been analyzed by using the data obtained from the quantum chemical results. First-order hyperpolarizability (βtot), the dipole moment (μ) and polarizability (α) and anisotropic polarizability (Δα) of the molecule have been reported. HOMO and LUMO energies and parameters related to energies, and dipole moment, polarizability and hyperpolarizability show minor dependences on the solvent polarity. The hardness of Iopamidol decreases with increasing solvent polarity. The stability of the Iopamidol contrast agent with the hyper conjugative interactions, charge delocalization has been analyzed using natural bond orbital analysis. In addition, thermodynamic properties were obtained in the range of 200–1000 K.

Keywords: Quantum chemical calculations; DFT; B3LYP; lopamidol; gaussian program; electronic structure.

1. Introduction

Iodinated X-ray contrast agents (ICM) are often used to enable the medical imaging of soft tissues like organs and blood vessels.[1] The nonionic, water-soluble, low-osmolar contrast agents such as Iopamidol with the 1-N,3-N-bis(1,3-dihydroxypropan-2-yl)-5-[[(2S)-2-hydroxypropanoyl]amino]-2,4,6-triiodobenzene-1,3-dicarboxamide IUPAC name is widely used for intravascular administration.[2,3] It has very wide diagnostic applications, including the central nervous system, the cardiovascular apparatus, and the urinary tract.[4] Iopamidol, a clinically approved X-Ray contrast agent, exhibits high water solubility and low toxicity.[4,5] For this reason, it can be safely administered intravenously at very high doses like 400 mg/ml.[4] This contrast agent was eliminated through the kidneys with a half-life of 2 hours.[2]

The molecule of Iopamidol contains a high number of mobile protons on amide and alcohol moiety exchanging with water. This contributes to a reduction in the MR signal density of the water proton. So, Iopamidol commonly used for CT, may be also considered as a contrast agent for Magnetic resonance imaging (MRI) applications.[4]

The geometry, dipole moment, polarizability, hyperpolarizability, and other molecular properties can be affected by the polarity of the solvent due to variable interactions with the highest occupied and lowest unoccupied molecular orbitals (HOMO-LUMO)[6,7] and so the polarity of the solvent can influence the stability and reactivity of the molecule.[8] They can be obtained by quantum chemical calculation without laboratory measurements, thus saving time and equipment, reducing safety and disposal concerns. So, investigation of the theoretical properties of the molecules has recently attracted the attention of scientists and quantum chemical calculation has been widely used to study reaction mechanisms.[9]

Bellich et all discussed the structure of Iopamidol for three different crystalline phases. In the anhydrous and monohydrate crystal forms, they reported that Iopamidol molecules are shown conformation of the long branches emerging from the triiodobenzene ring, while the pentahydrate phase had anti-conformation. IR and Raman spectroscopic studies, conducted in conjunction with quantum chemical calculations on three crystal forms, revealed that distinctly different spectral properties can be attributed, in particular, to different molecular structures.[10]

The Density Functional Theory (DFT) calculations eventually lead to a good understanding of molecular properties and a detail of the molecular characteristics and interactions.[8] Thermodynamic properties such as enthalpy, entropy, and Gibbs free energy are important to understand the stability of molecules at different temperatures and pressures, which can be easily explained using DFT with the Gaussian 03 program.[11,12]

DFT has recently gained popularity as a cost-effective general procedure for studying the physical properties of molecules. Unlike the Hartree-Fock theory, DFT gives a good electron correlation through electron density functions in the self-consistent Kohn-Sham procedure and complex operations. Descriptions for systems requiring electron correlation in the traditional ab initio approach is, therefore, a cost-effective and reliable method.[13,14,15]

Descriptors such as Chemical hardness, chemical potential, polarizability, and softness known as global reactivity descriptors based on density functional theory have found great utility in field selectivity as well as in predicting the reactivity of atoms and molecules, therefore this work presents the quantum chemical studies of the effects of solvents on molecular properties of Iopamidol such as the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), energy gap (ΔE), electronegativity (χ), electron affinity (A), global hardness (μ), softness (S), ionization potential (I), the fraction of electrons transferred and the total energy (ΔN_{max}), nucleofugality (ΔE_n) electrofugality (ΔE_e). These molecular properties of Iopamidol were computed by the B3LYP density functional model with the LANL2DZ basis set by the Gaussian program in the gas phase and in solvents (chloroform, acetic acid, ethanol, DMF, DMSO and water). This study was conducted to report the media effect of Iopamidol on dipole moment, polarizability, first-order hyperpolarizability and chemical reactivity, the stability of Iopamidol in different solvent systems and the development of new pharmaceutical and (bio) chemical products derived from Iopamidol.

2. Theory and Computational Details

DFT (density functional theory) methods have become very popular in recent years were used in this study. The fundamental base of DFT is the use of electronic density instead of the wave function for calculating the energy constitutes. All calculations were done by GAUSSIAN 09W software package,[16] using the B3LYP functional[9] and the LANL2DZ basis set.[17] The B3LYP, a version of the DFT method, uses Becke's three-parameter functional (B3) and includes a mixture of HF with DFT exchange terms associated with the gradient corrected correlation function of Lee, Yang, and Parr(LYP)[9]. The geometry of the Iopamidol contrast agent under investigation was determined by optimizing all the geometrical variables without any symmetry constraints. In solvents with different dielectric constants such as water, DMSO, DMF, ethanol, acetic acid and chloroform, the Solubility on Density Model applied in Gaussian 09 was used for all calculations. The SMD model is highly parameterized, uses the original polarizable continuity model (PCM), and the charge density of the dissolved molecule interacts with the dielectric environment of the solvent via the surface tension at the solvent-solvent boundary.

3. Results and Discussion

In the case of electronic response, the main effects caused by the solvent medium[18] (i) change of wave function due to change in structure perturbing environment, (ii) change of geometric structure (iii) change of response properties, and (iv) altering the dynamics of the excitation processes.

Optimized structure, the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO) and electron density of Iopamidol in the gas phase calculated at the DFT/B3LYP level with the LANL2DZ basis set was given in Figure 1. As seen from Figure 1, HOMO and LUMO are formed from mainly benzene ring and iodine group attached to benzene ring.

A large $E_{HOMO} - E_{LUMO}$ gap means high kinetic stability and low chemical reactivity due to energetically unfavorable to add electrons to a high-lying LUMO. Meanwhile, a molecule with a small $E_{HOMO} - E_{LUMO}$ gap is more polarizable, is generally associated with a high chemical reactivity-low kinetic stability and is termed as a soft molecule.[19] The solvent medium changes the properties of solvated molecules and sometimes significantly affects the dynamics of the processes. Ten molecular orbital energy near E_{HOMO} and E_{LUMO} to study the photo-physics and kinetic stability of Iopamidol compounds were shown in Figure 2 in different phases such as gas, chloroform, acetic acid, ethanol, DMF, DMSO and water. E_{HOMO} and five molecular orbital energy near HOMO of Iopamidol for –6.80, –6.85, –6.95, –6.98, –7.10, –7.16 eV. E_{LUMO} and five molecular orbital energy near LUMO of Iopamidol for gas phase are –2.19, –1.51, –1.46, –1.12, –0.95, –0.41 eV.

The highest occupied molecular orbital (HOMO) which is the outermost orbital filled by electrons and the lowest unoccupied molecular orbital (LUMO) represent-

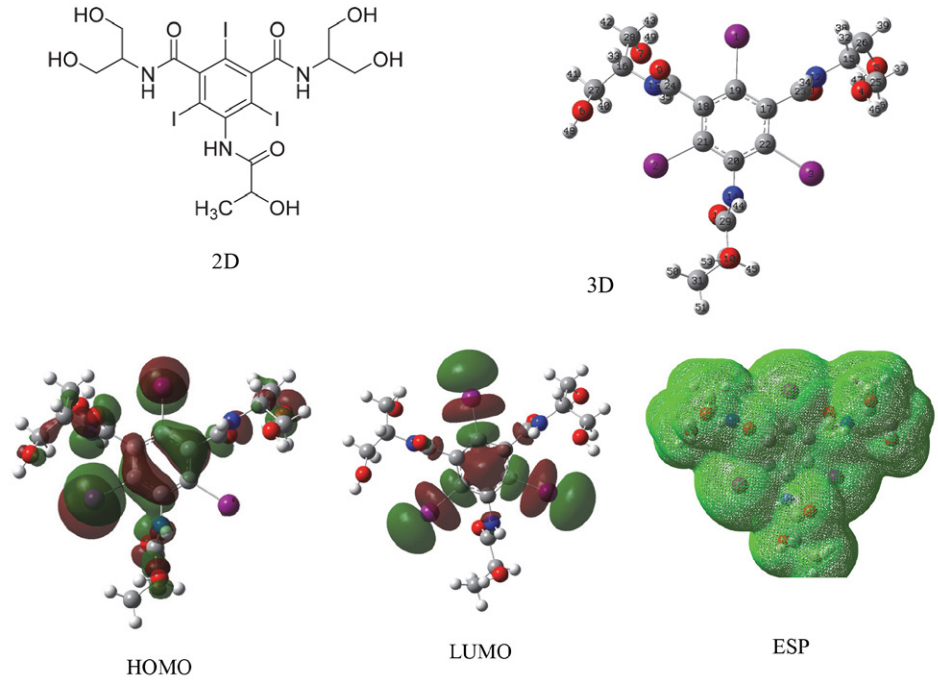

Figure 1. Optimized Structure, HOMO, LUMO and electron density of Iopamidol

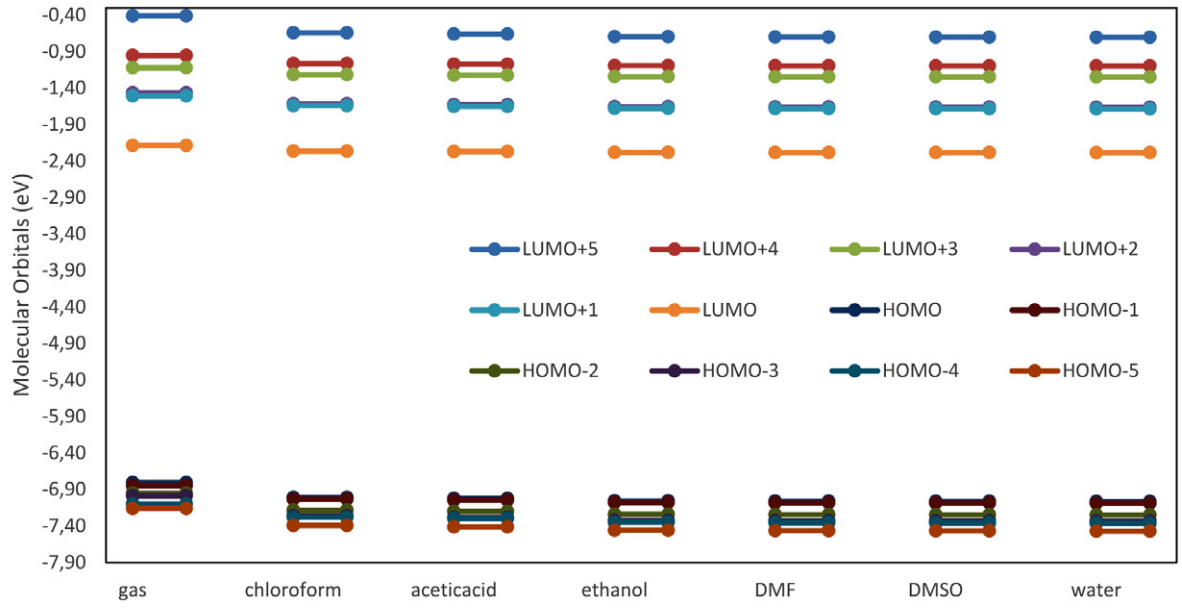

Figure 2. Frontier orbital energies for Iopamido

ing the first empty inner most orbital unfilled by electrons called frontier orbitals are the main orbitals taking part in a chemical reaction.[20]

The HOMO-LUMO energy band gap is a very important parameter for the determination of molecular electrical properties and an indication of molecular chemical stability. The quantum molecular descriptors such as ionization potential, electron affinity, chemical reactivity, kinetic stability, polarizability, chemical hardness and softness, and electronegativity, electrofugality, nucleofugality can be calculated by using the gap between E_{HOMO} and E_{LUMO}.

E_{HOMO} and E_{LUMO} values and E_{HOMO} and E_{LUMO} band gap values, computed with the B3LYP / LANL2DZ level, and additionally, chemical potential, electron affinity, electronegativity chemical hardness, softness and electrophilicity, electrofugality, nucleofugality index parameters, found using the computed HOMO and LUMO energy values, were summarized in Table 1.

Table 1. Parameters related with E_{HOMO} and E_{LUMO}.

	E_{HOMO}	E_{LUMO}	ΔE	η	S	χ	μ	Ω	ΔN_{max}	ΔE_n	ΔE_e
Gas	–6.80	–2.19	4.62	2.31	0.22	4.50	–4.50	4.38	1.95	1.04	10.03
Chloroform	–7.01	–2.26	4.75	2.37	0.21	4.64	–4.64	4.53	1.95	1.08	10.35
Acetic acid	–7.02	–2.27	4.75	2.38	0.21	4.65	–4.65	4.54	1.95	1.08	10.37
Ethanol	–7.06	–2.28	4.77	2.39	0.21	4.67	–4.67	4.57	1.96	1.09	10.43
DMF	–7.06	–2.28	4.78	2.39	0.21	4.67	–4.67	4.57	1.96	1.09	10.43
DMSO	–7.06	–2.28	4.78	2.39	0.21	4.67	–4.67	4.57	1.96	1.09	10.44
Water	–7.06	–2.29	4.78	2.39	0.21	4.67	–4.67	4.57	1.96	1.09	10.44

The highest occupied molecular orbitals (HOMO) and the lowest empty molecular orbitals (LUMO), called boundary molecule orbitals (FMOs), are the main orbitals involved in the chemical reaction. The energy gap formed between HOMO and LUMO indicates the chemical stability of the molecules and is a critical parameter for determining the molecular electrical transport properties as well as the properties of the molecules. The highest HOMO value of –6.80 eV was found in the gas phase followed by –7.01, –7.02, –7.06, –7.06, –7.06, –7.06 in chloroform, acetic acid, ethanol, DMF, DMSO and water phases indicate that the molecule will be best electron donor in the gas phase. So, it was observed that the negative value of the HOMO increased with the increase of dielectric constants of the solvents. They reported that the inclusion of solvents for Iopamidol causes the HOMO values to become more negative.[21]

The lowest LUMO energy of –2.29 eV was found to be in water indicating that the molecule will be the best accept electron in water compare to the gas phase and other solvents. The energy gap is used in determining molecular electrical transport properties. The largest HOMO-LUMO gap of 4.78 eV was found in water solvent which implies higher kinetic stability and less chemical reactivity[22] followed by 4.78 eV and the other studied solvents and found 4.62 eV in the gas phase.

The electronic chemical potential as seen in Equation 1 is defined as the energy changes of the system with respect to the electron number N at a fixed external potential v(r), i.e., the potential created by the nuclei.[23, 24] The electronic chemical potential is associated with the feasibility of a system to exchange electron density with the environment at the ground state.

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \quad (1)$$

When the finite difference approximation is used the following simple expression is obtained:

$$\mu \approx -\frac{(I+A)}{2} \quad (2)$$

Where, I is the ionization potential and A is the electron affinity of an atom or molecule. The ionization potential and the electron affinity can be approached by the frontier HOMO and LUMO energies as by E_{HOMO} and as by E_{LUMO} according to Koopmans theorem[25] and Kohn–Sham formalism[26] within the DFT, as a result, the electronic chemical potential can be expressed as:

$$\mu \cong \left(\frac{E_{HOMO}+E_{LUMO}}{2}\right) \quad (3)$$

Accordingly, the electronic chemical potential allows the establishment of the flux direction of the Global Electron Density Transfer[27] along in a polar reaction. Likewise, in a polar reaction having two molecules, such as A and B, with uA < uB, the electron density flux will occur from molecule B, which has the higher, towards molecule A, which has the lower. So, in such a reaction A will act as the electron-acceptor, whereas, B will act as the electron-donor, i.e., the nucleophile. The larger electronic chemical potential difference means global Electron Density Transfer presents a low polar character. Iopamidol molecule in solvent acts as a more electron acceptor molecule than in the gas phase. The chemical potential of the molecule was found to be increased as the dielectric constants of the solvents increased from the gas phase. The chemical potentials of the Iopamidol in chloroform, acetic acid, ethanol, DMF, DMSO, water are –4.64, –4.65, –4.67, –4.67, –4.67, –4.67 eV, respectively.

Pearson proposed the hard and soft acids and bases (HSAB) principle in an acid/base reaction.

In 1963, Pearson established a classification of Lewis acids and bases into hard and soft.[28–30] Within the conceptual DFT, Parr defined, in 1983, a quantitative expression for the chemical hardness, which can be expressed as the changes of the electronic chemical potential of the system with respect to the electron number N at a fixed external potential v(r).[18]

$$\eta = \left(\frac{\partial u}{\partial^2 N}\right)_{v(r)} = \left(\frac{\partial E^2}{\partial^2 N}\right)_{v(r)} \quad (4)$$

The resistance of a molecule to exchange electron density with the environment is defined as the chemical hardness and when the finite difference approximation is applied, the following simple expression is obtained:

$$\eta \approx -\frac{(I-A)}{2} \quad (5)$$

With the substitution of I by E_{HOMO} and A by E_{LUMO} can be expressed as:

$$\eta \cong \left(\frac{E_{LUMO}+E_{HOMO}}{2}\right) \quad (6)$$

Also the chemical hardness, chemical potential of the molecule was found to be increased, the chemical softness of the molecule was found to be decreased as the dielectric constants of the solvents increased from gas phase to water and was confirmed to decrease as the dielectric constant of the solvents increased from ethanol to water.

According to Parr and co-workers, global molecular electrophilicity (ω_{mol}) and global molecular nucleophilicity (ε_{mol}) index were defined and they were calculated based on molecular hardness and molecular electronegativity of the studied compounds with the help of the following equations, respectively.

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

The electrophilicity index measures the property of a molecule to accept electrons. Nucleophile molecule is characterized by a lower value of μ, ω; and conversely electrophile molecule is characterized by a high value of μ, ω. Organic molecules having a value of more than 1.5 is classified as strong electrophiles, the value between 0.8 and 1.5 eV is classified as moderate electrophiles, smaller than 0.8 eV is said as marginal electrophiles.[31] Terrier classified high reactivity of the species that he studied as super electrophiles.[32] So, the electrophilicity index of Iopamidol in the gas phase and different solvents of more than 1.5 eV is classified as super electrophilic. The electrophilicity index of Iopamidol increases with the increase of the dielectric constant of the solvent.

The maximum number of electrons that an electrophile can obtain is given by the following formula.[33]

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (8)$$

The maximum charge transfer that is completely determined by the electronic chemical potential of the molecule measures the stabilization in energy when the system acquires an additional electronic charge (ΔN) from the environment.[34–36] The maximum charge transfer ΔN_{max} to the electrophile means the ability of the system to obtain additional electronic charge from the medium defining the charge capacity of the molecule.

The maximum amount of electronic charge (ΔN_{max}) can define the donor and acceptor electron charge of molecules. The ΔN_{max} <0 indicates the molecule acts as an electron donor.[37] In gas and solvent phase, Iopamidol are electron acceptors and can have significant power of electron affinity. The ΔN_{max} index of Iopamidol increases as follow: gas < chloroform < acetic acid < ethanol =DMF =DMSO < water at the B3LYP/ LANL2DZ basis set. According to these results, it can be easily predicted that Iopamidol has the biggest ΔN_{max} in water for the studied solvents.

Ayers and co-workers[38,39] have proposed nucleophilic and electrophilic capabilities of a leaving group as nucleofugality (ΔE_n) and electrofugality (ΔE_e) and defined as follows:

$$\Delta E_n = EA + \omega = \frac{(\mu+\eta)^2}{2\eta} \quad (9)$$

$$\Delta E_e = IP + \omega = \frac{(\mu-\eta)^2}{2\eta} \quad (10)$$

Electrofugality values of Iopamidol in gas chloroform, acetic acid, ethanol, DMF, DMSO and water are 10.03, 10.35, 10.37, 10.43, 10.43, 10.44, 10.44, respectively. As seen from the result electrophilic capabilities of a leaving group for Iopamidol are the highest in the water phase.

The electronic transitions of Iopamidol were calculated by time-dependent DFT in the gas phase Theoretical results were used for the interpretation of experimental absorption bands. The experimental (λmax) and calculated (λDFT) wavelengths of maximum absorption are 241nm[40] and 242.11 nm which was marked as HOMO-15→LUMO, HOMO-11→LUMO+1, HOMO-10→LUMO+1, HOMO-7→LUMO+1, HOMO-6→LUMO+1, HOMO-6→LUMO+2, HOMO-5→LUMO+1, HOMO-2→LUMO+2, HOMO-2→LUMO+4, HOMO-1→LUMO+5, HOMO→LUMO+1, HOMO-1→LUMO+4 transitions which contributions are –0.20018, 0.17061, 0.14008, –0.12374, 0.19838, 0.25823, 0.21063, –0.11627, 0.18419, –0.17126, –0.12012, 0.12035.

Electric dipole polarizability which is a measure of the linear response of an infinitesimal electric field (F) and represents second-order variation energy is an important property used in determining the polarizability of a molecule or compound.[41]

$$\alpha = -\frac{\partial^2 E}{\partial F_a \partial F_b} \quad (11)$$

Where, the α_{xx}, α_{yy} and α_{zz} quantities are the principal values of polarizability tensor. Polarizability (α) which is the measure of distortion of a molecule in an electric field, the anisotropy of the polarizability <Δα> and Kappa were calculated using the following equation, respectively:

$$\alpha = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (12)$$

$$\Delta\alpha = \left[\frac{(\alpha_{xx}-\alpha_{yy})^2+(\alpha_{yy}-\alpha_{zz})^2+(\alpha_{zz}-\alpha_{xx})^2+6(\alpha_{xz}^2+\alpha_{xy}^2+\alpha_{yz}^2)}{2}\right]^{1/2} \quad (13)$$

$$\kappa = \frac{\alpha_{xx}{}^2+\alpha_{yy}{}^2+\alpha_{zz}{}^2}{6<\alpha>^2} \quad (14)$$

In unsubstituted aromatic molecules, the π electrons in a direction perpendicular to the plane do not contribute to the polarizability in a direction perpendicular to the plane, only sigma bonds in the vertical direction contribute to the polarization of the molecules. Since the anisotropy j becomes zero for the spherical symmetric charge distribution, it gives a measure of the spherical symmetry deviations. The calculated polarizability <α>, the anisotropy of the polarizability <Δα> and Kappa for Iopamidol molecules are listed in Table 2.

The variation of <α> is in the atomic units and <Δα> in esu ($\times 10^{-24}$) for Iopamidol molecule are given. The result shows that the lowest polarizability and anisotropic polarizability values obtained were 296 au and 21.77 × 10^{-24} esu in the gas phase. It was observed that polarizability and anisotropic polarizability increases with an increase in the polarity of the solvents while the kappa decreases as the polarity of the solvents increases.

$$\begin{aligned} \beta_{tot} &= \left(\beta_x^2+\beta_y^2+\beta_z^2\right)^{1/2} \\ \beta_x &= \beta_{xxx}+\beta_{xyy}+\beta_{xzz} \\ \beta_y &= \beta_{yyy}+\beta_{xxy}+\beta_{yzz} \\ \beta_z &= \beta_{zzz}+\beta_{xxz}+\beta_{yyz} \end{aligned} \quad (15)$$

The , and refer to the components of hyperpolarizability along *x, y* and *z* components of molecular dipole moment.

It can be seen from Table 3, the calculated β values of Iopamidol using B3LYP/ LANL2DZ level (the β of Iopamidol for gas, chloroform, acetic acid, ethanol, DMF, DMSO, water) are 1.48 × 10^{-30} esu., 2.55 × 10^{-30} esu., 2.69 × 10^{-30} esu., 1.87 × 10^{-30} esu., 3.04 × 10^{-30} esu., 3.06 × 10^{-30} esu., 2.94 × 10^{-30} esu., respectively. The first polarizability values obtained using B3LYP/LANL2DZ level for Iopamidol are the largest value in DMSO and the lowest value in gas phase.

4. Thermodynamic Properties

The total contribution of the electronic, translational, rotational and vibrational energies to the entropy (S) and heat capacity (Cv), as well as the rotational constants and zero-point vibrational energies (ZPVE) of Iopamidol in the gas phase and different solvents were presented in Table 4.

It can be observed in Table 4 that the specific heat capacity of Iopamidol was found to increase with an increase in the polarity of the solvent except in acetic acid solution. The highest entropy value of 240.311 cal/mol was found in the gas phase followed by 235.989, 235.189, 234.749 cal/mol in chloroform, acetic acid, ethanol solution. It was observed that as the dielectric constant of the solvents was increased from chloroform to water the entropy was found to be slightly decreased, while, entropy was found to increase slightly in DMF, DMSO, water. The zero-point vibrational energy (ZPVE) decreases except in acetic acid solution with the increase of dielectric constant.

Based on vibrational analysis at B3LYP/LANL2DZ level, the standard statistical thermodynamic functions: heat capacity (C^0P,m), entropy (S^0m), and enthalpy changes (H^0m),

for the Iopamidol, are obtained from the theoretical harmonic frequencies in gas and solvent phases and presented in Figure 3. It can be observed that these thermodynamic functions are increasing with temperature ranging from 200 to 1000 K because molecular vibrational intensities increase with temperature.[42]

Table 5, demonstrates the correlation of heat capacity at constant pressure, entropy, enthalpy respectively, for

Table 2. Polarizability (⟨α⟩), anisotropic polarizability (Δα), Kappa (κ) of the optimized Iopamidol molecule in the gas phase and different solvents.

Polarisibility	Gas	Chloroform	Acetic acid	Ethanol	DMF	DMSO	Water
<a> (au)	296	365	371	386	387	388	389
(<Δα> (esu) 10^{-24}	21.77	25.64	25.95	26.69	26.78	26.82	26.88
κ	0.02646	0.02341	0.02315	0.02254	0.02247	0.02244	0.0224

Table 3. β × 10^{-30} (esu), βx, βy, βz, in (a.u.) components and values calculated using DFT levels of theory for Iopamidol.

	Gas	Chloroform	Acetic Acid	Ethanol	DMF	DMSO	Water
β_x	76.7636	173.4901	177.5463	184.9257	185.4881	185.5127	83.0876
β_y	–87.2752	–224.2531	–240.4815	71.3396	–286.2781	–288.0864	273.9023
β_z	57.6274	83.6470	85.2293	88.1287	88.4319	88.5943	184.1473
β_{total}	1.48	2.55	2.69	1.87	3.04	3.06	2.94

Table 4. Thermodynamic properties of the optimized Iopamidol molecule in the gas phase and different solvents.

Positions	Vibrational Cv	Total	Rotational S	Vibrational	Total
Gas	117.731	123.692	38.531	155.952	240.311
Chloroform	117.758	123.720	38.536	151.624	235.989
Acetic acid	117.751	123.713	38.536	150.823	235.189
Ethanol	117.760	123.722	38.536	150.384	234.749
DMF	117.764	123.726	38.536	150.414	234.779
DMSO	117.766	123.728	38.536	150.426	234.791
Water	117.769	123.731	38.536	150.453	234.818
	Rotational Constants (GHz)			ZPVE (Kcal/Mol)	
Gas	0.08199	0.06561	0.04052	249.87778	
Chloroform	0.08118	0.06626	0.04031	249.85006	
Acetic acid	0.08114	0.06629	0.04030	249.86599	
Ethanol	0.08109	0.06635	0.04029	249.84713	
DMF	0.08109	0.06636	0.04029	249.84051	
DMSO	0.08109	0.06636	0.04029	249.83742	
Water	0.08108	0.06637	0.04029	249.83212	

For Cv Electronic: 0.000, Translational: 2.981, Rotational: 2.981 For S Electronic: 0.000, Translational: 45.829

Table 5. Correlation of heat capacity, entropy and enthalpy with temperature for Iopamidol molecule

Iopamidol			
Gas	$C = -0.0002T^2 + 0.3841T + 28.257$ $R^2 = 0.9996$	$S = -0.0001T^2 + 0.5054T + 106.3$ $R^2 = 0.9997$	$H = 9E\text{-}05T^2 + 0.0865T - 9.6639$ $R^2 = 0.9998$
Chloroform	$C = -0.0002T^2 + 0.3846T + 28.184$ $R^2 = 0.9996$	$S = -0.0001T^2 + 0.5085T + 101.17$ $R^2 = 0.9999$	$H = 9E\text{-}05T^2 + 0.0866T - 9.7776$ $R^2 = 0.9998$
Acetic acid	$C = -0.0001T^2 + 0.3412T + 41.995$ $R^2 = 0.996$	$S = -9E\text{-}05T^2 + 0.44T + 122.2$ $R^2 = 0.9977$	$H = 0.0001T^2 + 0.0712T - 4.8992$ $R^2 = 0.999$
Ethanol	$C = -0.0002T^2 + 0.362T + 31.162$ $R^2 = 0.9997$	$S = -0.0001T^2 + 0.4743T + 105.21$ $R^2 = 0.9999$	$H = 6E\text{-}05T^2 + 0.1283T - 14.295$ $R^2 = 0.999$
DMF	$C = -0.0002T^2 + 0.3847T + 28.152$ $R^2 = 0.9996$	$S = -0.0001T^2 + 0.5086T + 99.937$ $R^2 = 0.9999$	$H = 9E\text{-}05T^2 + 0.0867T - 9.8173$ $R^2 = 0.9998$
DMSO	$C = -0.0002T^2 + 0.4077T + 19.679$ $R^2 = 0.9988$	$S = -0.0001T^2 + 0.5129T + 98.095$ $R^2 = 0.9999$	$H = 8E\text{-}05T^2 + 0.1063T - 14.192$ $R^2 = 0.9997$
Water	$C = -0.0002T^2 + 0.3917T + 26.68$ $R^2 = 0.9997$	$S = -0.0001\ T^2 + 0.5086\ T + 99.973$ $R^2 = 0.9999$	$H = 9E\text{-}05T^2 + 0.0828T - 9.2518$ $R^2 = 0.9998$

the methods of DFT/LANL2DZ level. The correlation equations between heat capacities, entropies, enthalpy changes and temperatures were fitted by quadratic formulas, and the corresponding fitting factors (R2) for these thermodynamic properties are 0.9996, 0.9997, and 0.9998 respectively for gas-phase; 0.9996, 0.9999, 0.9998 respectively for chloroform. All the thermodynamic data supply helpful information for further study on the Iopamidol. All thermodynamic calculations were done in the gas phase in solution such as chloroform, acetic acid, ethanol, DMF, DMSO, water.

The net atomic charges of the Iopamidol contrast agent in various solvents using the Mulliken Population Analysis (MPA) method were given in Table 6. MPA values in different solvents were evidence of charge transfer and polarization.[43]. The significant influences of the solvents on the atomic charges are observed from the calculation. As seen from Table 6, the atomic charges increase with the increase of solvent polarity from acetone to water.

All carbon atoms making a bond with iodine atom in the benzene ring have a negative charge and the negative charge of the carbon atom bonded iodine atom increase with the increase of polarity of the solvent. The charge of C_{19} atom of Iopamidol in gas, chloroform, acetic acid, ethanol, DMF, DMSO, and water phases is –0.7531, –0.7667, –0.7680, –0.7711, –0.7715, –0.7717, –0.7719 ē. The rest of the carbon atoms in the benzene ring have positive excess charges accumulation and the positive charge of the carbon atom in the benzene ring increase with the increase of polarity of the solvent. The charges of nitrogen atoms are the negative and negative value of the charge decreases with the increase of polarity of the solvent. The charge of

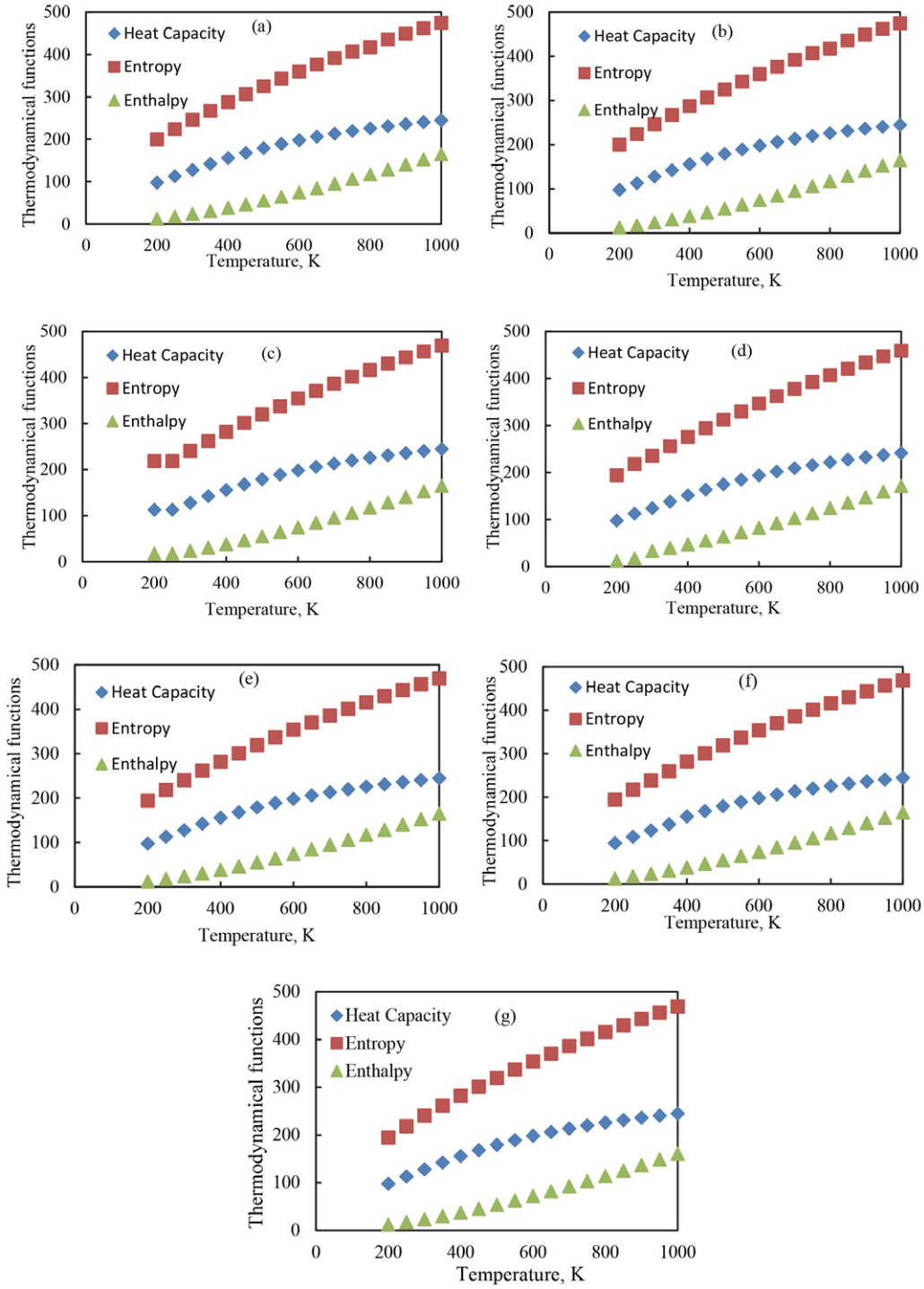

Figure 3. Correlation graph of heat capacity, entropy and enthalpy with temperature for Iopamidol molecule

N_{12} atom of Iopamidol in gas, chloroform, acetic acid, ethanol, DMF, DMSO, and the water phase is –0.3366, –0.3298, –0.3293, –0.3280, –0.3278, –0.3278, –0.3277 ē. The charge of N_{13} atom is –0.3473, –0.3406, –0.3397, –0.3376, –0.3373, –0.3372, –0.3371 ē. All oxygen atoms belonging to the hydroxyl group and carbonyl group for Iopamidol have neagative charge, and the negative charge of both oxygen atoms increases with the increase of polarity of the solvent.

Selected second-order perturbation energies (E (2) kcal/mol) with values greater than 5 kcal/mol

for Iopamidol in gas phase were presented in Table 7, and Table 8 includes only energies for the other studied solvents and gas phase. The energies for the interaction

Table 6. Some Mulliken Atomic charges (e) of Iopamidol in various solvents.

	Gas	Chloroform	Acetic acid	Ethanol	DMF	DMSO	Water
I_1	0.1672	0.1899	0.1919	0.1970	0.1976	0.1978	0.1982
I_2	0.1792	0.1868	0.1878	0.1904	0.1907	0.1909	0.1911
I_3	0.1704	0.1910	0.1927	0.1967	0.1972	0.1974	0.1977
O_4	–0.5147	–0.5337	–0.5353	–0.5390	–0.5394	–0.5396	–0.5398
O_5	–0.4972	–0.5264	–0.5290	–0.5352	–0.5359	–0.5363	–0.5367
O_6	–0.4761	–0.5177	–0.5210	–0.5290	–0.5299	–0.5303	–0.5309
O_7	–0.5135	–0.5409	–0.5428	–0.5473	–0.5479	–0.5481	–0.5484
O_8	–0.3082	–0.3494	–0.3529	–0.3616	–0.3626	–0.3630	–0.3636
O_9	–0.2577	–0.3129	–0.3176	–0.3290	–0.3303	–0.3309	–0.3317
O_{10}	–0.5047	–0.5291	–0.5307	–0.5343	–0.5347	–0.5348	–0.5351
O_{11}	–0.2612	–0.3174	–0.3220	–0.3330	–0.3343	–0.3349	–0.3357
N_{12}	–0.3366	–0.3298	–0.3293	–0.3280	–0.3278	–0.3278	–0.3277
N_{13}	–0.3473	–0.3406	–0.3397	–0.3376	–0.3373	–0.3372	–0.3371
N_{14}	–0.5198	–0.5101	–0.5092	–0.5068	–0.5065	–0.5064	–0.5062
C_{17}	0.5775	0.5957	0.5971	0.6001	0.6004	0.6005	0.6007
C_{18}	0.5511	0.5666	0.5679	0.5710	0.5714	0.5715	0.5718
C_{19}	–0.7531	–0.7667	–0.7680	–0.7711	–0.7715	–0.7717	–0.7719
C_{20}	0.8067	0.8134	0.8139	0.8153	0.8155	0.8155	0.8156
C_{21}	–0.7098	–0.7287	–0.7303	–0.7343	–0.7348	–0.7350	–0.7353
C_{22}	–0.7149	–0.7283	–0.7296	–0.7325	–0.7328	–0.7330	–0.7332

Table 7. Selected second-order perturbation energy (E (2) kcal/mol) with values greater than 10 kcal/mol (except for iodine interaction) for Iopamidol in gas phase.

Donor (i)	Type	Occupancy	ED(j)	Acceptor	Type	Occupancy	ED(j	E(2) kcal/mol	E(j)-E(i) a.u	F(i,j) a.u
C_{17}-C_{22}	π	1.67185	–0.74673	C_{18}-C_{19}	π *	0.39117	–0.00725	18.95	0.29	0.067
C_{17}-C_{22}	π	1.67185	–0.74673	C_{20}-C_{21}	π *	0.39095	–0.00959	22.39	0.29	0.073
C_{18}-C_{19}	π	1.67060	–0.29565	C_{17}-C_{22}	π *	0.39611	–0.00844	23.39	0.29	0.074
C_{18}-C_{19}	π	1.67060	–0.29565	C_{20}-C_{21}	π *	0.39095	–0.00959	19.16	0.29	0.067
C_{20}-C_{21}	π	1.65835	–0.29446	C_{17}-C_{22}	π *	0.39611	–0.00844	19.73	0.29	0.068
C_{20}-C_{21}	π	1.65835	–0.29446	C_{18}-C_{19}	π *	0.39117	–0.00725	23.60	0.29	0.074
I_1	LP3	1.94231	–0.27742	C_{18}-C_{19}	π *	0.39117	–0.00725	7.31	0.27	0.043
I_2	LP3	1.93293	–0.26730	C_{20}-C_{21}	π *	0.39095	–0.00959	7.83	0.26	0.044
I_3	LP3	1.93545	–0.27219	C_{17}-C_{22}	π*	0.39611	–0.00844	7.81	0.26	0.044
O_8	LP2	1.86415	–0.29057	N_{12}-C_{23}	σ*	0.06954	0.42301	16.06	0.71	0.097
O_8	LP2	1.86415	–0.29057	C_{17}-C_{23}	σ*	0.06831	0.35615	18.75	0.65	0.100
O_9	LP2	1.86542	–0.25360	N_{13}-C_{24}	σ*	0.07259	0.42608	21.11	0.68	0.109
O_9	LP2	1.86542	–0.25360	C_{18}-C_{24}	σ*	0.07486	0.35976	19.38	0.61	0.099
O_{11}	LP2	1.87731	–0.25037	N_{14}-C_{29}	σ*	0.07966	0.41160	23.83	0.66	0.113
O_{11}	LP2	1.87731	–0.25037	C_{29}-C_{30}	σ*	0.08219	0.33581	19.06	0.59	0.095
N_{12}	LP1	1.65078	–0.27471	O_8-C_{23}	σ*	0.20853	0.18886	24.37	0.46	0.098
N_{12}	LP1	1.65078	–0.27471	O_8-C_{23}	π*	0.17216	0.23265	12.69	0.51	0.075
N_{13}	LP1	1.66817	–0.26134	O_9-C_{24}	σ*	0.25871	0.09976	39.60	0.36	0.109
N_{14}	LP1	1.66817	–0.26134	O_{11}-C_{29}	π*	0.21432	0.10625	33.67	0.38	0.103

LP3(I_1) → π*(C_{18}-C_{19}), LP3(I_2) → π*(C_{20}-C_{21}) and LP3(I_3) → π* (C_{17}-C_{22}) 7.31, 7.83 and 7.81 kcal mol^{-1}, respectively demonstrate the intramolecular hyperconjugative interaction between the iodine atoms and benzene ring in the ground state for Iopamidol in gas phase.

The interaction energy from the I_1 electron pairs corresponds to conjugation with the antibonding molecular orbitals of the neighboring C_{20}-C_{21} whereas, these interaction energies correspond to conjugation with the antibonding molecular orbitals of the neighboring LP3(I_1) → π*C_{17}-C_{19} with the stabilization energy 7.41, 7.42, 7.43 kcal/mol in chloroform, acetic acid, and ethanol, respectively, and 7.44 kcal/mol in DMF, DMSO, water. The interaction LP3(I_2) → π*(C_{20}-C_{21}) in gas phase shifted to LP3(I_2) → π*(C_{18}-C_{21}) in studied solvents and LP3(I_3) → π*(C_{17}-C_{22}) was shifted to LP3(I_3) → π*(C_{20}-C_{22}) in studied solvents.

Table 8. Interaction energies of Iopamidol in gas phase and in different solvents.

Donor	Type	Acceptor	Type	Gas	Chloroform	Acetic Acid	Ethanol	DMF	DMSO	Water
				E(2) kcal/mol						
I_1-C_{19}	σ	C_{17}-C_{22}	σ*	7.06	7.10	7.11	7.12	7.12	7.12	7.12
I_1-C_{19}	σ	C_{18}-C_{21}	σ*	7.07	7.05	7.05	7.06	7.06	7.06	7.06
I_2-C_{21}	σ	C_{18}-C_{19}	σ*	7.15	7.16	7.16	7.16	7.17	7.17	7.17
I_2-C_{21}	σ	C_{20}-C_{22}	σ*	7.12	7.19	7.19	7.21	7.21	7.21	7.21
I_3-C_{22}	σ	C_{17}-C_{19}	σ*	7.11	7.17	7.39	7.19	7.19	7.19	7.19
I_3-C_{22}	σ	C_{20}-C_{21}	σ*	7.13	7.21	7.22	7.23	7.24	7.24	7.24
C_{17}-C_{19}	π	C_{18}-C_{21}	π*		22.60	22.58	22.53	22.53	22.53	22.52
C_{17}-C_{19}	π	C_{20}-C_{22}	π*		19.17	19.17	19.17	19.17	19.17	19.17
C_{17}-C_{22}	π	C_{18}-C_{19}	π*	18.95						
C_{17}-C_{22}	π	C_{20}-C_{21}	π*	22.39						
C_{18}-C_{19}	π	C_{17}-C_{22}	π*	23.39						
C_{18}-C_{19}	π	C_{20}-C_{21}	π*	19.16						
C_{18}-C_{21}	π	C_{17}-C_{19}	π*		19.64	19.64	19.63	19.63	19.63	19.63
C_{18}-C_{21}	π	C_{20}-C_{22}	π*		22.71	22.67	22.60	22.59	22.59	22.58
C_{18}-C_{24}	σ	N_{13}-C_{16}	σ*		6.25	6.26	6.29	6.30	6.30	6.30
C_{20}-C_{21}	π	C_{17}-C_{22}	π*	19.73						
C_{20}-C_{21}	π	C_{17}-C_{19}	π*	23.60		23.53	23.53	23.53	23.53	23.53
C_{20}-C_{22}	π	C_{18}-C_{21}	π*		23.53	19.52	19.61	19.62	19.62	19.63
C_{20}-C_{22}	π	C_{18}-C_{19}	π*		19.48					
I_1	LP3	C_{17}-C_{19}	π*		7.41	7.42	7.43	7.44	7.44	7.44
I_1	LP3	C_{18}-C_{19}	π*	7.31						
I_2	LP3	C_{18}-C_{21}	π*		7.90	7.90	7.90	7.90	7.90	7.90
I_2	LP3	C_{20}-C_{21}	π*	7.83						
I_3	LP3	C_{17}-C_{22}	π*	7.81						
I_3	LP3	C_{20}-C_{22}	π*		7.65	7.66	7.69	7.69	7.69	7.69
O_8	LP2	O_5-H_{47}	σ*	9.35	14.20	14.52	15.38	15.48	15.52	15.59
O_8	LP2	N_{12}-C_{23}	σ*	16.06	13.76	13.59	13.17	13.12	13.10	13.06
O_8	LP2	C_{17}-C_{23}	σ*	18.75	18.21	18.14	17.97	17.95	17.94	17.93
O_9	LP2	N_{13}-C_{24}	σ*	21.11	20.05	19.96	19.74	19.72	19.71	19.69
O_9	LP2	C_{18}-C_{24}	σ*	19.38	18.35	18.26	18.05	18.03	18.02	18.00
O_{11}	LP2	N_{14}-C_{29}	σ*	23.83	22.61	22.51	22.27	22.24	22.23	22.21
O_{11}	LP2	C_{29}-C_{30}	σ*	19.06	18.02	17.93	17.72	17.70	17.69	17.67
N_{12}	LP1	O_8-C_{23}	σ*	24.37	72.52	75.67	82.43	83.14	83.44	83.90
N_{12}	LP1	O_8-C_{23}	π*	12.69						
N_{13}	LP1	O_9-C_{24}	σ*	39.60	81.88	83.09	85.07	85.29	85.37	85.50
N_{14}	LP1	O_{11}-C_{29}	σ*		15.95	17.47	21.64	22.15	22.37	22.73
N_{14}	LP1	O_{11}-C_{29}	π*	33.67	16.10	14.84	12.02	11.73	11.61	11.41

The stabilization energy for the interaction LP1(O_8) → σ*(N_{12}-C_{23}) and LP2(O_8) → σ*(O_5-H_{47}) increases with the increase of the dielectric constant of the solvent whereas the stabilization energy for the interaction LP2(O_8) → σ*(N_{12}-C_{23}) and LP2(O_8) → σ*(C_{17}-C_{23}) decreases with the increase of the dielectric constant of the solvent.

5. Conclusions

The ground state molecular geometries, polarizability, anisotropic polarizability, hyperpolarizability, and frontier orbital energies of Iopamidol were theoretically investigated in gas, chloroform, acetic a4cid, ethanol, DMF, DMSO, and water phase to understand the structure–property relationship of the molecular structure of Iopamidol in terms of solvent effects.

From the obtained results by using the DFT calculations, it was obtained that the dipole moment, electrophilicity index, polarizability and first-order hyperpolarizability of Iopamidol was gradually increased with the increase of dielectric constant of the solvent.

Likewise, the largest HOMO-LUMO gap was found in water solvent and this means higher kinetic stability and less chemical reactivity with increasing polarity of solvents. Therefore, quantum chemical calculations aid the understanding of the structure- property relationship of molecules.

Solvent effects on thermodynamic properties of the optimized geometry of the molecule were investigated and reported. The variation of solvent influences the structural, electronic, and molecular properties of the Iopamidol and will be useful in the design and development of Iopamidol as a contrast agent.

The NBO analysis has provided a detailed in-sight into the type of hybridization and the nature of bonding in Iopamidol. he stabilization energy for the interaction $LP1(O_8) \rightarrow \sigma^*(N_{12}\text{-}C_{23})$ increases with the increase of the dielectric constant of the solvent whereas the stabilization energy for the interaction $LP2(O_8) \rightarrow \sigma^*(N_{12}\text{-}C_{23})$ decreases with the increase of the dielectric constant of the solvent. The negative charge of carbon atoms attached to the iodine atom in the benzene ring increase with the increase of polarity of the solvent. The rest of the carbon atoms in the benzene ring have positive and positive charge density with the increase of polarity of the solvent.

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Povzetek

Neionske kontrastne snovi z nizko osmolalnostjo veljajo za varne pri intravenozni in intraarterialni aplikaciji. Iopamidol je eno od kontrastnih sredstev ki se uporablja za diagnostično računalniško tomografijo (CT) že štiri desetletja. Molekulsko strukturo Iopamidola smo izračunali s funkcionalnim modelom B3LYP in baznim setom LANL2DZ določenim z Gaussovim programom. Analizo veznih orbital, hibridizacijo atomov in elektronsko strukturo molekule smo izvedli s podatki dobljenimi iz kvantno kemijskih izračunov. V članku podajamo vrednosti za hiperpolarizabilnost prvega reda (βtot), dipolni moment (μ), polarizabilnost (α) in anizotropno polarizabilnost (Δα) molekule. Energije HOMO in LUMO in parametri povezani z energijami, dipolnim momentom, polarizabilnostjo in hiperpolarizabilnostjo so le malo odvisni od polarnosti topila. Trdota Iopamidola se zmanjšuje z naraščanjem polarnosti topila. Analizirali smo stabilnost kontrastnega sredstva Iopamidol s hiperkonjugativnimi interakcijami in izračunali K.