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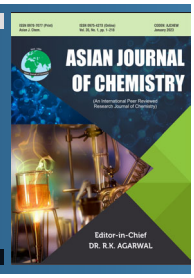

Computational Insights on Solvation and Hydrogen Bonding Studies of Indomethacin

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Over a long time, non-steroidal anti-inflammatory drugs (NSAIDs) play a vital role in medical field. Indomethacin is a NSAID mainly used against inflammation and pain. But the poor solubility of indomethacin limits its therapeutic usage. Hydrotropy is a solubilization technique used to enhance the drug solubilization. Microscopic solvent effect is considered to be a part of hydrotropy in which hydrogen bond (H-bond) networks are formed with an isolated molecule with solvent molecules such as water. A comprehensive theoretical investigation was performed under density functional theory (DFT) to explore the isolated and monohydrated indomethacin complexes. The geometries were optimized on B3LYP method with 6-311G (2d,2p) basis set. The interaction energies of hydrated indomethacin complexes were computed by correcting the basis set superposition error. Natural bond orbital (NBO) study was performed in order to deepen the knowledge on O-H···O and C-H···O type H-bonds. A linear relationship between H-bond length and the stabilization energy ($E^{(2)}$) was observed in the solvated indomethacin complexes with a correlation coefficient of 0.8346. It identifies maximum $E^{(2)}$ (95.33 Kcal/mol) in INDO-12 complex. The molecular electrostatic potential mapping (MESP) for the optimized structures was also analyzed.

Keywords: Indomethacin, Hydrotropy, Hydrogen bond, Molecular electrostatic potential mapping.

INTRODUCTION

Therapeutics is a branch of medicine concerned with the treatment of disease. Non-steroidal anti-inflammatory drugs (NSAIDs) are recognized as the members of therapeutic medicine, which aim to minimize pain, reduce inflammation, lower fever and avoid blood clots. Indomethacin (also known as indocin and indometacin) with molecular formula $C_{19}H_{16}ClNO_4$ is a chemically synthesized NSAID derived from indole structure [1]. Even though the pharmacological function of indomethacin is not completely known, it is believed that it functions by decreasing secretion of prostaglandins in the human body [2]. Prostaglandins are the molecules responsible for the fever and suffering linked to inflammation. Prostaglandin levels are decreased by indomethacin because it inhibits the cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes [3]. This generates prostaglandins thereby relieves pain, reduce inflammation and bring down a high temperature. Indomethacin is also used to treat the symptoms of gout, long-term musculoskeletal pain issues and paints at joints, firmness and swelling related to arthritis along with neurodegenerative illness [4].

Currently, indomethacin is administrated as oral drug and also given as rectal and intravenous routes. Good quality aqueous solubility is considered as a prime prerequisite of an oral route drug. At the same time, poor aqueous solubility of these types of oral active drugs like indomethacin (0.937 mg/L) appears to be one of the main challenges, which posts questions about their insufficient rate of solution formation, proper absorption, bioavailability and clinical response [5]. The poor solubility of indomethacin in water leads to local drug concentrations, which causes formation of ulcer in the tissues that weakens its therapeutic usage.

Hydrotropy is a unique and well-accepted solubilization technique used to improve drug solubility. This method explains the increase in solubility of one solute as a result of addition of another solute [6]. Rossi *et al.* [7] studied the inclusion of cyclodextrins, which are a family of naturally existing or chemically synthesized non-covalent, cyclic molecules with indome-

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thacin through Raman spectroscopy along with quantum chemical and molecular simulation techniques. They tried to improve the aqueous solubility of indomethacin drug along with its chemical solidity and biological availability. Recently, Liu & Zhang [8] attempted to use various dopants such as silicon, carbon, aluminium and gallium doped boron nitride nanosheet as carrier for poorly soluble drugs like indomethacin. They identified that silicon doped boron nitride nanosheet was found to be appropriate as an indomethacin carrier and the solubility of doped boron nitride nanosheet-indomethacin complex can be adjusted by doping.

Indomethacin shows a good antitumor activity against COX-2. Almeida *et al.* [9] studied porphyrin- and chlorin–indomethacin complexes through DFT studies and the reaction mechanism of indomethacin compounds was evaluated to compare their stability in solution. In photodynamic therapy, non-toxic photosensitizers are administrated to the disease sites. Huang *et al*. [10] designed a new photosensitizer with indomethacin by using zinc(II) phthalocyanine to target COX-2 tumor cells and improved the efficacy of photodynamic therapy through reduction in the aggregation of photosensitizers and achieved a better tumor targeting.

As a part of hydrotropy, Alsalhi & Chan [5] analyzed the hydrotropic effect on indomethacin and carbamazepine with twelve amino acids and concluded that tryptophan showed better solubilization compared to other amino acids because of the existence of π-π stacking. It was found that the amino acid side chains are considered to be crucial in deciding the degree of solubilization of the in-soluble rugs. Similarly, Parkan *et al*. [11] computationally approached the indomethacin-amino acids complexes including tryptophan and phenylalanine through DFT calculations and analyzed the importance of these interactions. During the exposure to natural as well as artificial light, drugs interact with ultraviolet radiation right from their manufacture even after intake, which results in photo-toxic and photo-allergic reactions that cause some adverse effects.

Porta *et al*. [12] investigated the photo-assisted mechanism behind few drugs including indomethacin by employing solvent effect with water and studied their structural photo-activity relationships. Laguna *et al.* [13] used DFT method to study the copper(II)-indomethacin component in solvent such as ethanol and water molecules in the first solvation sphere and tried to offer vital understanding of the action mechanism of poor soluble drugs through UV-visible spectrophotometry.

Some NSAIDs together with indomethacin are found to be potentially secure, undemanding and cost-effective candidates used in the host-directed treatments for tuberculosis by decreasing lung pathology and mediating the immune system reaction of the host [14]. Chakraborty *et al*. [15] analyzed indomethacin computationally through the drug repurposing techniques for deadly SARS-CoV-2 infections. It is interesting to observe the effectiveness of indomethacin in opposition to COVID-19 infection is found to be slightly higher than the famous drugs such as remdesivir, hydroxychloroquine and lopinavir which proves the rising potential of indomethacin with its impressive antiviral characteristic against SARS-CoV-2.

In view of the increasing the solubility of indomethacin thereby improving its clinical performance, Xu *et al*. [16] performed co-crystallization of indomethacin with nicotinamide and saccharin. This study used DFT calculations and terahertz spectroscopy to characterize the indomethacine-nicotinamide and indomethacine-saccharin co-crystal units and check their thermodynamic stability. Polyvinylpyrrolidone (PVP) is a water-soluble, biodegradable polymer prepared and generally plays a vital role in controlled release of poorly water–soluble drugs like indomethacin and improving their bioavailability and used as excipient for amorphous drug dispersions. Xiang & Anderson [17] used molecular dynamics method to examine the molecular interactions existing between amorphous structures of indomethacin in PVP and also studied the formation of hydrogen bonds in isolated indomethacine units and between indomethacin and PVP, which had been considered as a critical component of solubility enhancement.

In the ground of hydrotropy, with an intention to increase the drug solubilization of poorly soluble drugs, microscopic solvent effect plays a vital role. Microscopic solvent effect (also known as microsolvation) refers to the binding of a small number of water molecules in suitable positions of a specified solute. This demonstrates individual solute-solvent interactions that can be predominantly essential while H-bonds are formed between the solvent and solute molecules [18]. The present study aims to perform density functional quantum chemical studies were carried out to explore the structural influence and effect of single water added at all possible sites of indomethacin (capable of forming H-bonds) and 20 different monohydrated complexes was obtained and labelled as INDO-n, where n = 1,2,3....20.

COMPUTATIONAL METHODS

Initially, the structure of indomethacin has been retrieved from the NCBI PubChem database [19]. The DFT with Becke's three parameter exact exchange functional (B3) [20] combined with gradient-corrected correlation functional of Lee–Yang–Parr (LYP) [21] have been used to optimize the indomethacin and its monohydrated compounds with 6-311G (2d,2p) basis set. The Boys and Bernardi counter poise method [22] was used to compute the interaction energies of the optimized structures with the help of the following equation

$$E_{int}(corr) = E_{AB}(AB) - [E_A(AB) + E_B(AB)] \quad (1)$$

where $E_{AB}(AB)$ represents complex's energy; $E_A(AB)$ is the energy of monomer A and $E_B(AB)$ is the energy of B. The H-bond stabilization energy ($E^{(2)}$) has been computed under Natural Bond Orbital (NBO) analysis by using eqn. 2:

$$E^{(2)} = q_i \frac{F^2(i,j)}{\varepsilon_i - \varepsilon_j} \quad (2)$$

here, q_i represents the orbital occupancy of the i^{th} donor; ε_j and ε_i are the diagonal elements; and F(i,j) is the NBO Fock matrix off diagonal element. The Gaussian 09W program [23] has been employed to perform the computational studies.

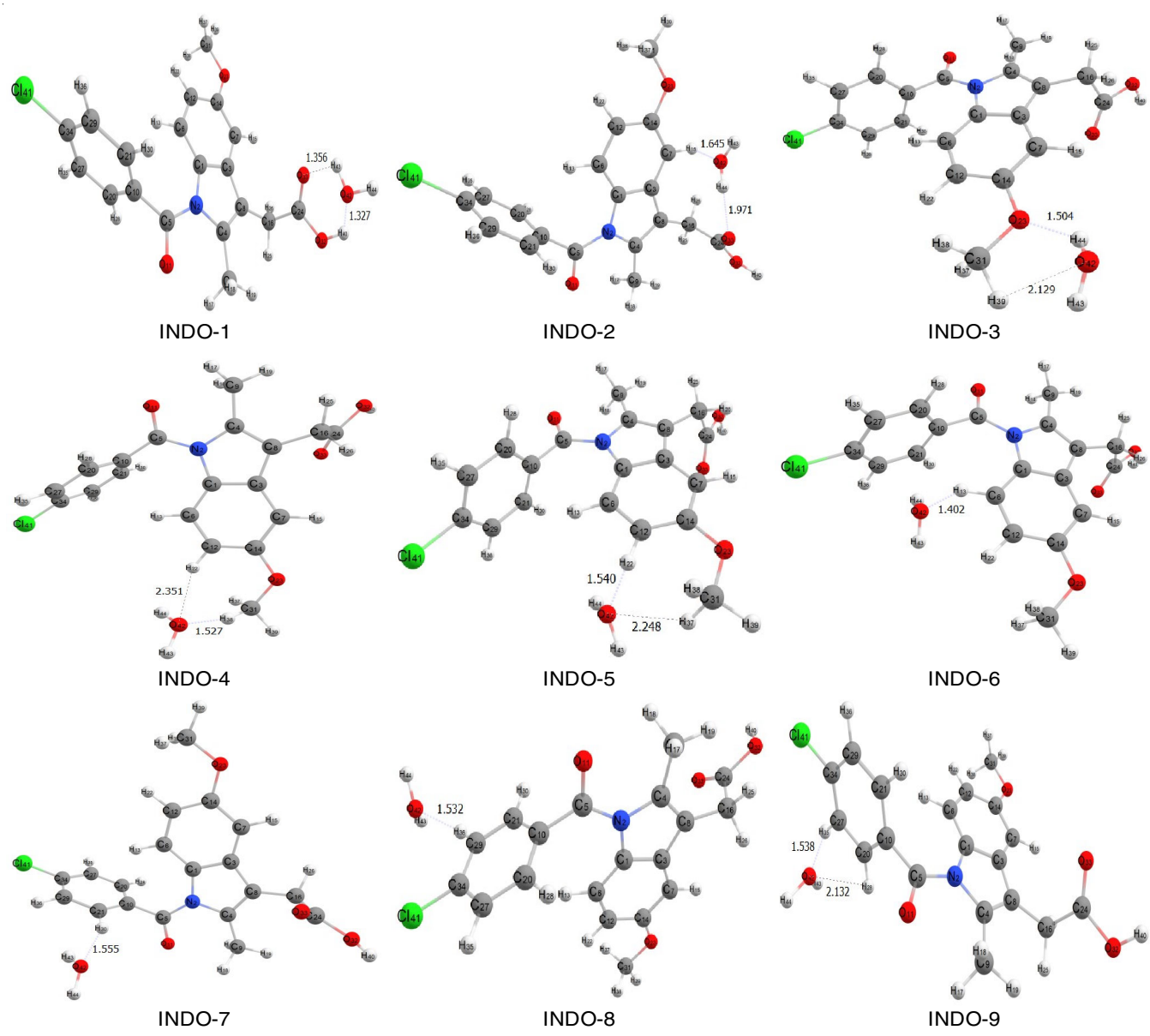
RESULTS AND DISCUSSION

Fig. 1 shows the optimized structures of INDO-n, where n = 1,2,3....20 complexes (with atom numbering) that are optimized at B3LYP/6-311G(2d,2p) level of theory and the bond lengths are represented in Å. The calculated structural parameters of bare indomethacin in gas phase with available theoretical results [24,25] are presented in Table-1. It is significant to observe that R(C24-O32), R(C24-O33) belong to carboxylic acid group of indomethacin and the associated angle θ(O33-C24-O32) agreed well with the previous values. The θ(C4-N2-C1) of indomethacin is smaller by approximately 2º. The dihedral angles which involve carbonyl oxygen and benzylic carbon atoms is found to be increased by 46º and the dihedral angle C4-N2-C5-O11 is smaller by 26.8º. Important deviations are observed in other geometrical parameters as shown in Table-1. These differences may be attributed to the estimation of the geometrical parameters at different levels of theory.

TABLE-1
SELECTED GAS PHASE MOLECULAR GEOMETRICAL PARAMETERS (BOND LENGTHS (Å), BOND ANGLES AND DIHEDRAL ANGLES (°) OF INDOMETHACIN COMPUTED AT B3LYP/6-311G (2d,2p) LEVEL OF THEORY

Geometrical parameters	Indomethacin	Previous
C16-C24	1.513	1.520 [24]
C24-O32	1.357	1.35 [24]
O32-H40	0.981	0.97 [24]
C24-O33	1.225	1.21 [24]
C1-C3	1.402	1.34 [24]
C1-N2	1.399	1.27 [24]
C3-C8	1.414	1.34 [24]
C4-C8	1.372	1.35 [24]
C4-N2	1.382	1.28 [24]
N2-C5	1.412	1.27 [24]
O33-C24-O32	123.2	123.94 [24]
C4-N2-C1	107.9	109.54 [24]
C4-N2-C5-O11	2.6	29.49 [25]
O11-C5-C10-C21	89.3	43.32 [25]

Fig. 1 can be referred for atom labeling.



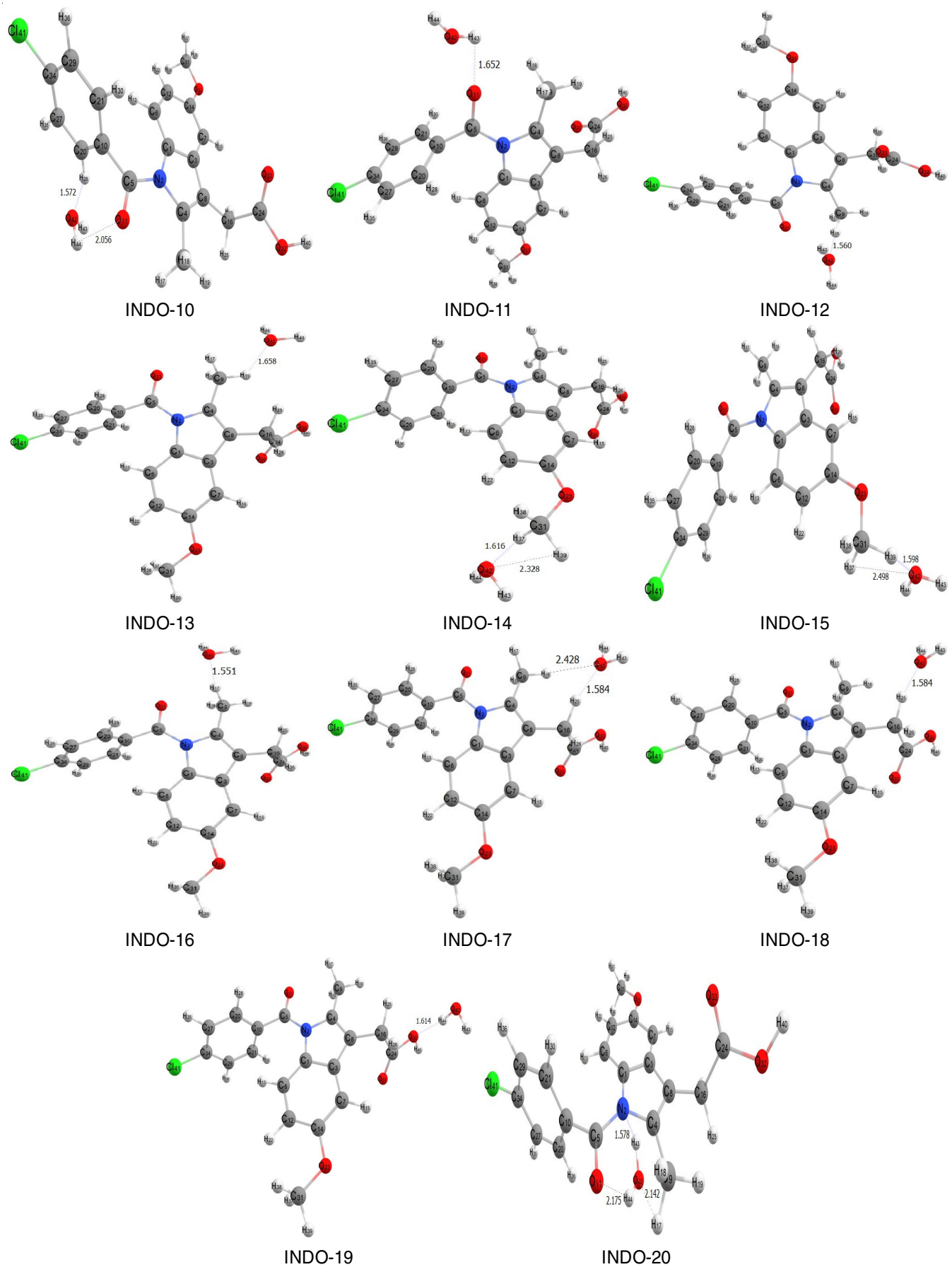


Fig. 1. Optimized structures of the indomethacin...1W (INDO-n, n = 1, 2, 3....20) complexes at B3LYP/6-311G(2d,2p) level of theory

The solvation of indomethacin results decrease in the energy value compared to its bare counterpart, which paves way to the increased system stability. When the water molecule interacts with the site belonging to methylene hydrogen (H25) of indomethacin at O16, the system (INDO-17) appears to be the most stable structure. In this structure, the oxygen atom of water forms bidentate H-bonds; one with methylene hydrogen (H25) connected at C16 and other with one of the three methyl hydrogens (H19) connected at C9 at 1.584 and 2.428 Å, respectively. But at the same time, when the water molecule joins at the same methylene moiety building interaction with H26 (INDO-18) forms two C-H···O H-bonds by involving O42 in bidentate mode. It is significant to observed that compared to the most stable structure (INDO-17), it stands at third place in the order of stability of complexes with relative energy of 14.12 Kcal/mol.

Apart from INDO-17 and INDO-18, bidentate H-bonds were also found in INDO-1 complex where the water molecule acts as bridge between carbonyl oxygen and hydroxyl hydrogen of carboxylic acid group by creating strongest hydrogen bonds at 1.356 and 1.327 Å, respectively with maximum interaction energy of 95.33 Kcal/mol. INDO-4 and INDO-5 also posses bidentate H-bonds taking sixth and second places, respectively in the stability order with relative energies 15.88 and 8.28 Kcal/mol having dipole moments 3.174 and 2.304 debye, respectively. In INDO-10, the water molecule finds a place in between carbonyl oxygen of the carboxamide group (O11 @ C5) and one of the chlorophenyl hydrogens (H28) of indomethacin and acts as viaduct between them through two H-bonds as shown in Fig. 1 with interaction energy and dipole moment 47.37 Kcal/mol and 3.176 debye, respectively. Apart from INDO-10, hydration of indomethacin at its chlorophenyl hydrogens yielded three more structures *via* INDO-n, (n = 7, 8 and 9). These structures were identified with stronger C-H···O H-bonds formed approximately at 1.5 Å and the stability order is found to be INDO-7 > INDO-8 > INDO-10 > INDO-9.

In INDO-20, where the water forms three H-bonds as a bridge among carbonyl oxygen (O11 connected at C5 – 2.175 Å), carboxamide nitrogen and one of the methyl hydrogens (H17 connected @ C9 – 2.142 Å) having interaction energy 69.51 Kcal/mol. Out of three existing H-bonds of INDO-20 complex, it is evident that the strongest H-bond is created with carboxamide nitrogen (as a unique O-H···N interaction out of all the other monohydrated indomethacin complexes) at the shortest distance of 1.578 Å. In INDO-2 complex, water acts a link between carboxylic oxygen and indolic hydrogen (H15 connected @ C7) having 32.66 Kcal/mol interaction energy. Bidentate H-bonds are traced in the other complexes formed with indolic hydrogens H22 (INDO-5) and H13 (INDO-6) also. In INDO-5, water molecule makes a viaduct between H22 and H37 (Fig. 1) through H-bonds formed at 1.54 and 2.248 Å with interaction energy 21.09 Kcal/mol and dipole moment 2.304 debye. Unpredictably, in INDO-6, both the indolic hydrogens are bridged by water molecule through H-bonds formed at 1.592 and 2.55 Å with Rx....y at 2.351 and 2.88 Å, respectively. In INDO-3, one of the methyl hydrogens (H39) is bridged with methoxy oxygen (O23 connected at C14) through bidentate H-bonds having relative energy of 51.71 Kcal/mol.

During the selection of hydration sites at methyl hydrogens (H17, H18 and H19 connected at C9) of indomethacin, three different structures were obtained and taken as INDO-12, INDO-13 and INDO-16. In INDO-12, water molecule is attached with H18 by forming C-H···O H-bond at 1.56 Å with interaction energy of 13.11 Kcal/mol with dipole moment 1.643 debye. In the other two structures INDO-13 and INDO-16, only single C-H···O H-bond is formed at 1.658 and 1.551 Å, respectively. When considering the complexes hydrated at methoxy hydrogens H37 (INDO-14), H38 (INDO-4) and H39 (INDO-15), INDO-15 is the most stable compound with 19.03 Kcal/mol interaction energy. Herein, a bifurcated H-bond is formed where oxygen of water molecule donates electrons to two methoxy hydrogens H37 and H39 through C-H···O H-bonds at 1.598 and 2.498 Å, respectively. It is interesting to observe that almost a similar structure with analogous bifurcated H-bond was obtained when tried to attach the water molecule at H37 (INDO-14) but with slightly different H-bond lengths at 1.616 and 2.328 Å, respectively. Even though INDO-15 registers itself as an energetically stronger complex, INDO-14 with comparatively stronger H-bonds records higher interaction energy of 38.73 Kcal/mol. The calculated interaction energies are presented in Table-2, which shows that the INDO-12 complex possess the maximum interaction energy with a strongest C-H···O H-bond at 1.56 Å. The next stable structure INDO-9 has interaction energy 77.76 Kcal/mol which is associated with two C-H···O H-bonds present at 1.535 and 2.132 Å.

TABLE-2
ENERGETICAL PARAMETERS (TOTAL ENERGY E (Hartree), RELATIVE ENERGY ΔE (kcal/mol), INTERACTION ENERGY E_{int} (kcal/mol)) AND DIPOLE MOMENT μ_m (debye) OF THE INDOMETHACIN AND INDOMETHACIN...1W COMPLEXES CALCULATED AT B3LYP/6-311G (2d,2p) LEVEL OF THEORY

Complex	E	ΔE	$-E_{int}$	μ_m
Indomethacin	-1549.8500	–	–	1.372
INDO-1	-1626.1546	83.96	13.11	2.149
INDO-2	-1626.2574	19.45	32.66	2.701
INDO-3	-1626.2060	51.71	65.08	0.769
INDO-4	-1626.2631	15.88	17.59	3.174
INDO-5	-1626.2752	8.28	21.09	2.304
INDO-6	-1626.2431	28.43	36.99	1.718
INDO-7	-1626.2544	21.33	33.46	1.767
INDO-8	-1626.2441	27.80	40.47	2.219
INDO-9	-1626.1854	64.63	77.76	4.325
INDO-10	-1626.2348	33.63	47.37	3.176
INDO-11	-1626.2495	24.41	35.33	2.133
INDO-12	-1626.2863	1.32	95.33	1.643
INDO-13	-1626.2558	20.46	17.24	3.047
INDO-14	-1626.2343	33.95	38.73	3.111
INDO-15	-1626.2632	15.81	19.03	3.775
INDO-16	-1626.2422	28.99	22.90	2.477
INDO-17	-1626.2884	0.00	11.95	3.906
INDO-18	-1626.2659	14.12	26.43	3.985
INDO-19	-1626.2641	15.25	27.52	2.171
INDO-20	-1626.1997	55.66	69.51	1.544

The NBO analysis can be viewed as a method for evaluating the impacts of hybridization and co-valency in intermolecular interactions [26], and it will be useful for revealing

the hidden information concerning the nature of H-bonds. It highlights the variation in charge densities in proton donors and acceptors including the bonding and anti-bonding orbitals. The NBO study was carried out for the monohydrated indomethacin complexes to understand the characteristics of the existing H-bonds. It is also known to be a consistent tool for analyzing the H-bonds, which reflects the alterations in the length of H-bonds as a result of changes in the fundamental chemical characteristics. Mostly C-H···O and O-H···O (only one O-H···N) H-bonds are formed in the Indomethacin...1W complexes. The oxygen and nitrogen atoms of indomethacin act as donor and X-H (X = O, C) as acceptor involving in the charge transfer interactions in the hydrated indomethacin complexes. The stabilization energies $E^{(2)}$ of inter-molecular H-bond interactions computed through B3LYP/6-311G(2d,2p) level of theory are presented in Table-3.

The H-bonds observed in the hydrated indomethacin complexes show that for the C-H···O interactions, the length of H-bonds vary from 1.402 to 2.498 Å. For O-H···O type H-bonds, the lengths vary between 1.327 and 2.175 Å. The shortest H-bond has been formed in INDO-1 complex (O-H···O bond at 1.327 Å) with next larger one is identified in the same complex (O-H···O bond at 1.356 Å). The strong interaction between donor and acceptor bonding orbitals is ensured by the large value of $E^{(2)}$. In various monohydrated indomethacin complexes, seven O-H···O interactions were identified whose stabilization energies varies from 0.59 to 47.21 Kcal/mol. In this juncture, the strongest interaction was observed between hydrogen belongs to carboxylic group of indomethacin and water molecule with stabilization energy 47.21 Kcal/mol in INDO-1. Herein, the water oxygen acts as donor and contributes lone pairs to O-H anti-bond orbital of carboxylic moiety in indomethacin.

The other three O-H···O H-bonds appeared in INDO-1, INDO-2 and INDO-19 complexes with stabilization energies were 15.61, 1.83 and 5.22 Kcal/mol, respectively where the indomethacin carboxylic oxygen acts as donor and the O-H bond of water acts as acceptor. The remaining two O-H···O interactions where indomethacin oxygens offer lone pair electrons to water O-H anti-bond orbital also record lower stabilization energies compared to the H-bonds involving oxygen atom of water offering electrons. This shows that water oxygen is ready to donate electrons to indomethacin than its oxygen atoms and the resultant H-bonds are found to be strong.

In hydrated indomethacin complexes, the C-H···O interactions surpasses all the other H-bonds and found to be the most occurring non-bonding interactions that exist when water oxygen lone pairs offer electrons to indomethacin C-H anti-bonding orbital with stabilization energies varying from 0.23 to 29.51 Kcal/mol. In particular, the lowest value $E^{(2)}$ (0.23 Kcal/mol) was observed in INDO-20 complex with comparatively longest H-bonds formed between indomethacin's methyl

TABLE-3
HYDROGEN BOND LENGTH R (Å) AND THE STABILIZATION ENERGIES $E^{(2)}$ (kcal/mol) OF INDOMETHACIN...1W COMPLEXES CALCULATED AT B3LYP/6-311G (2d,2p) LEVEL OF THEORY

Complex	H-Bond (X-H···Y)	$R_{H\cdots Y}$	$R_{X\cdots Y}$	<X-H···Y	$E^{(2)}$
INDO-2	C7-H15···O42	1.645	2.089	97.65	3.10
	O42-H44···O33	1.971	2.650	128.23	1.83
INDO-3	O42-H44···O23	1.504	1.862	95.45	7.38
	C31-H39···O42	2.219	2.477	94.96	0.29
INDO-4	C31-H38···O42	1.527	2.574	157.47	28.40
	C12-H22···O42	2.351	3.074	122.57	0.29
INDO-5	C12-H22···O42	1.540	2.454	137.69	19.21
	C31-H37···O42	2.248	2.977	121.94	0.58
INDO-6	C6-H13···O42	1.402	2.351	142.42	29.51
INDO-7	C21-H30···O42	1.555	2.179	109.88	2.60
INDO-8	C29-H36···O42	1.532	2.178	111.43	4.53
INDO-9	C27-H35···O42	1.538	1.850	87.88	2.38
INDO-10	C20-H28···O42	1.572	2.030	97.87	1.38
	O42-H44···O11	2.056	2.574	111.73	0.71
INDO-11	O42-H43···O11	1.652	1.957	94.30	2.76
INDO-12	C9-H18···O42	1.560	2.644	169.54	22.70
INDO-13	C9-H19···O42	1.658	2.489	128.35	11.25
INDO-14	C31-H37···O42	1.616	2.117	100.91	3.24
	C31-H39···O42	2.328	2.117	65.21	0.40
INDO-15	C31-H39···O42	1.598	2.415	126.44	12.79
	C31-H37···O42	2.498	2.415	72.92	0.21
INDO-16	C9-H17···O42	1.551	2.448	134.66	14.87
INDO-17	C16-H25···O42	1.584	2.654	164.11	21.15
INDO-18	C16-H26···O42	1.541	2.268	117.68	10.04
	C16-H25···O42	2.292	2.268	74.91	0.40
INDO-19	O42-H44···O32	1.614	2.180	112.92	5.22
INDO-20	C9-H17···O42	2.142	2.513	96.46	0.23
	O42-H43···N2	1.578	2.185	116.42	6.29
	O42-H44···O11	2.175	2.987	143.83	0.59

Fig. 1 can be referred for labeling of atoms.

hydrogen and water oxygen (at 2.142 Å), between the carbonyl oxygen of the carboxamide group of indomethacin and water hydrogen (2.175 Å), which is attributed due to the minimum energy transfer effect. In addition to the O-H···O and C-H···O H-bonds, a unique O-H···N interaction is noticed in INDO-20 with stabilization energy 6.25 kcal/mol where lone pairs of indomethacin's nitrogen offer electrons to the anti-bonding orbital of water. The stability order among the hydrated complexes at methyl hydrogens based on total energy (INDO-12 > INDO-16 > INDO-13) is well supported by the stability order predicted based on stabilization energies with 22.7, 14.87 and 11.25 kcal/mol, respectively. A good correlation was obtained among $E^{(2)}$ and length of H-bonds in the monohydrated indomethacin complexes and shown in Fig. 2.

Highest occupied molecular orbitals (HOMO-electron donor regions) measures the ionization potentials. *i.e.* electron donor character of a complex. Lowest unoccupied molecular orbital (LUMO) represents the electron acceptor regions that

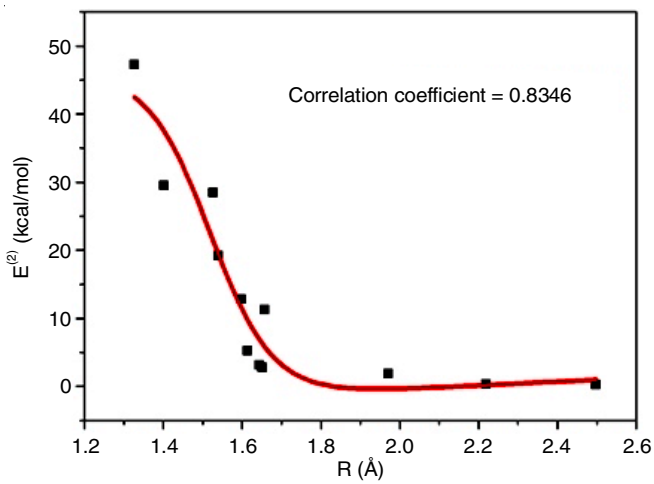


Fig. 2. Correlation between the stabilization energy ($E^{(2)}$) and H-bond lengths of indomethacin...1W complexes calculated at B3LYP/6-311G-(2d,2p) level of theory

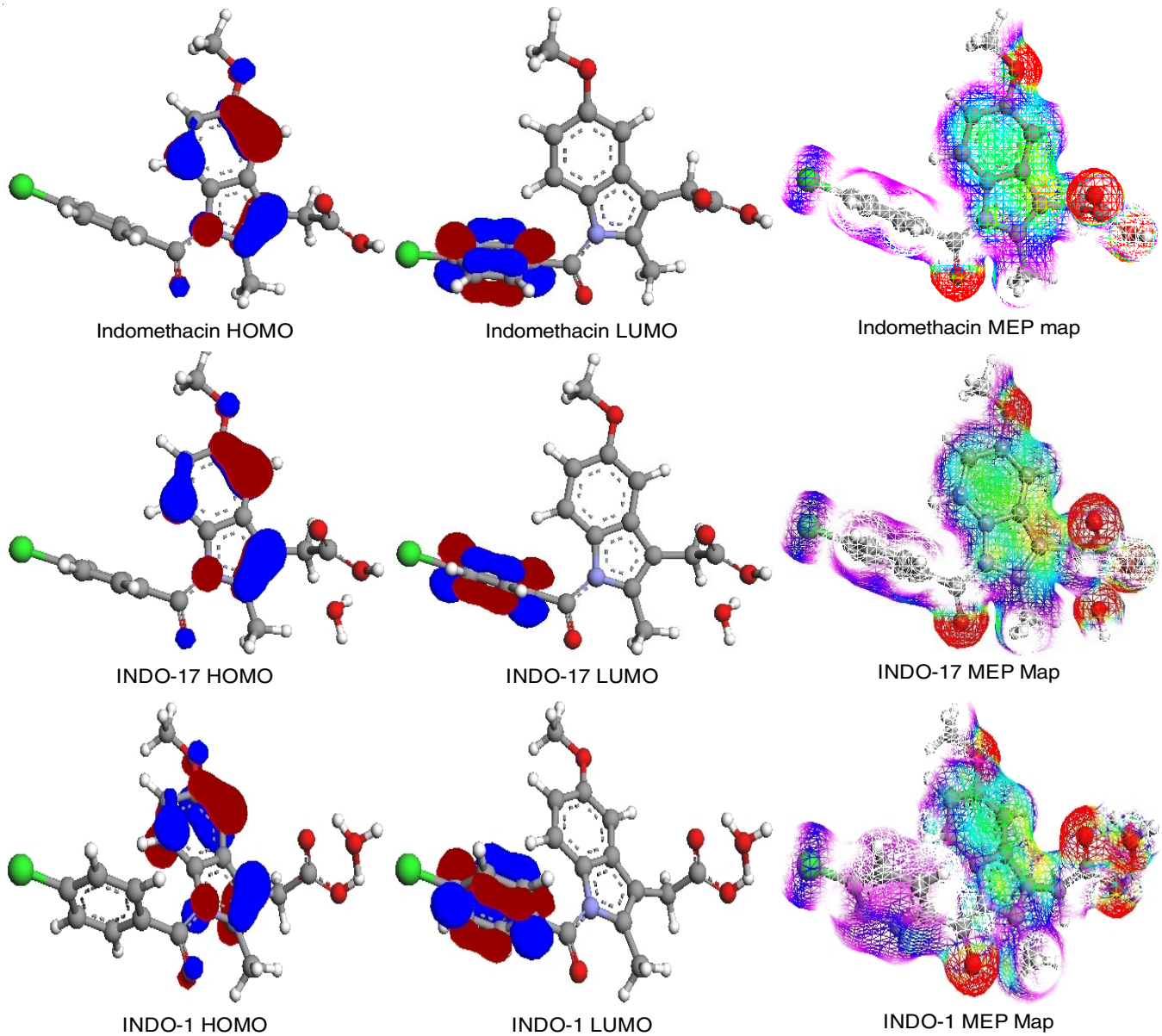


Fig. 3. HOMO, LUMO orbitals and MEP map of isolated indomethacin, most and least stable Indomethacin...1W complexes

determine the electron affinity. The higher values of HOMO show the greater electron donating ability of the complexes. The lower LUMO values indicate the ability of electron acceptance. The nature of HOMO-LUMO plot for isolated, most and least stable indomethacin...1W compounds are presented in Fig. 3. The HOMO density is located at indole ring in all the three structures. The minimum contribution of five memebered ring with nitrogen has also been observed. The LUMO is localized on the chlorophenyl group of indomethacin in isolated as well as in hydrated complexes, which shows that the water molecule doesn't involve orbital contamination.

The molecular electrostatic potential (MEP) is a three dimensional illustration of the charge distribution in a molecule and considered to be extremely good for describing the non-covalent interactions especially H-bonds. The MEP surface for the isolated indomethacin, the most and least stable indomethacin...1W complexes were also obtained for the optimized structures and are presented in Fig. 3. In indomethacin and its most and least stable hydrated complexes, more electronegative area is composed of oxygen atoms of indomethacin (O11, O23 and O32). The lighter shades (towards blue) represent the electron insufficiency and are marked near chlorine atom establishing this area as less electronegative. The green colour in Fig. 3 indicates the electron less regions with zero electrostatic potential.

Conclusion

The DFT B3LYP method has been used to optimize the isolated and 20 monohydrated indomethacin complexes. The optimized geometrical parameters were comparable with the previous results except a few. As expected, the NBO study revealed the hydrated complexes having shorter (stronger) H-bonds with higher stabilization energy except a few inconsistencies with small variations. NBO study describes the process of decrease in stabilization energy through the development of more than one H-bonds irrespective of the stronger H-bonds as observed in INDO-20 with 3 H-bonds. Apart from O-H···O and C-H···O H-bonds, the NBO study shows that the exclusive O-H···N H-bond exist as a result of the orbital overlap involving the nitrogen lone pairs as electron donor and the anti bonding orbital of O-H bond as acceptor in INDO-20 complex. The HOMO-LUMO analysis shows that the HOMO is concentrated on indole ring and the LUMO is localized at chlorophenyl ring of indomethacin. The MEP mapping showed that the electronegative area is located at the oxygen atoms and chlorine atom of indomethacin was identified as less electronegative region.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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