Theoretical Investigation of the Modeling of Indole –dichlormethane Hydrogen Bonding in Different Solvents

Jamelah S. Al-Otaibi

Princess Noura Bint AbdulRahman University: Princess Nourah bint Abdulrahman University

Y.Sheena Mary (✉ marysheena2018@rediffmail.com)

Researcher, Thushara, Neethinagar-64, Kollam <https://orcid.org/0000-0002-9082-3670>

Y.Shyma Mary

Thushara

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Abstract

Theoretical vibrational spectra of indole (IND) and its binary combination with dichloromethane (DC) in various solvents were computed to track the impact of molecular interactions on drug spectral characteristics. When transitioning from plain drug to complexes, 3561.26 cm^{-1} mode of the IND displays a substantial shift in peak location. The 3561.26 band shows (~ 15.58) red shift upon dilution. The geometry of drug and IND-DC complex in various solvents was calculated using quantum chemical calculation utilizing DFT.

Introduction

Intermolecular interactions are crucial to comprehending the mechanism of variety chemical and physical phenomena [1–3]. Hydrogen bonding is one of the most significant intermolecular interactions and it can be monitored by utilizing theoretical methods to examine the solute-solvent interactions in systems. Hydrogen bonds are important in stabilization of proteins' secondary and tertiary structures, as well as providing significant hints to molecular recognition [4]. Hydrogen bond forms can be seen in several biomolecules, which are critical for controlling processes in living systems. Spectroscopic studies of weakly bound intermolecular complexes provide a plethora of data on their dynamics which is use for for more complete study of a variety of macroscopic phenomena [5]. Raman and IR spectra are significant experimental tools for probing intermolecular interactions. Because Raman spectroscopic techniques may extract both structural and dynamic information, they are suitable for monitoring hydrogen bonding [6]. The hydrogen bonding interaction in a range of binary mixes with different hydrogen donor solvents has been examined, resulting in a variety of alterations in spectrum characteristics [7, 8].

Indoles are found in a wide range of bioactive substances, medicines and pharmaceuticals [9–12] which is a favoured scaffold in drug development because of its unique structural features and biodynamic capabilities, which gives a rich possibility for the identification of novel medications [13]. Natural indoles have been utilized to treat a variety of cancers all around the world [14]. It has the unusual property of imitating the structure of several enzymes and allowing for reversible binding [15, 16]. The existence of a rich in electron pyrrole moiety that can exploit noncovalent interactions with others by forming hydrogen bonding in NH and ring system makes the indole with outstanding capabilities in medicinal field [17–19]. Compounds containing an indole moiety have been demonstrated to efficiently reduce diabetes [20]. As a result indole's design and selective function have been the focus of recent research [21]. A theoretical investigation of indole derivative as multitarget drugs against cancer and bacterial infections was published by Gupta et al. [22]. In the present work, interaction of indole with DC under different solvents is reported.

Methods

The Gaussian16 program was used to do all theoretical calculations with the functional CAM-B3LYP/6-311++G(d)(6D,7F) and Gaussview [23, 24]. Using DFT functional, geometrical parameters and

wavenumbers of IND and its complex with DC were determined and the properties with different solvents are also calculated. We estimated the drug's solvated structures in addition to the gas phase computations. For solvent effect, the polarizable continuum model was utilized [25].

Results

Structures and energies

In the complex, IND-DC (Fig. 1), where the Cl atoms are attached to H10(NH), two relatively weaker hydrogen bonds (Cl ...H10-N1) were formed with bond lengths of 2.8375 and 3.795Å. The DC to IND other interacting distances are: N1-H18 = 2.8147, N1-Cl21 = 3.5080, C2-H18 = 2.7405, C5-H18 = 1.9063, H10-C17 = 3.2546 and H12-Cl21 = 3.2962Å. Interaction of DC to the π -ring and NH bond of IND affect the vibration modes of IND [6]. The bond lengths, 1N-2C, 1N-10H, 2C-3C, 2C-5C show deviations of -0.001Å in the IND-DC complex (table 1). However in other IND-DC solvents significant variations are seen [26]. The angles C2-N1-H10 and C7-N1-H10 show slight change of 0.138 and 0.2098 upon complexation with DC. In solvent phases also there are changes in angles for some angles. The binding energy : $E = E_{IND-DC} - E_{IND} - E_{DC}$ [27, 28]. The binding energy in the gaseous phase is -14.28 kcal/mol while in the solvents, the energy is changed from - 9.26 to -9.55 kcal/mol.

Table 1

Geometrical parameters of IND and it's complexes

(a) Bond lengths of IND and it's complex in different solvents

	IND	IND-DC				
		Gaseous	water	Ethanol	Methanol	DMSO
R(1,2)	1.3762	1.3772	1.3746	1.375	1.3749	1.3747
R(1,7)	1.3781	1.3778	1.3757	1.3759	1.3758	1.3759
R(1,10)	1.0065	1.0079	1.0087	1.0088	1.0088	1.0088
R(2,3)	1.4136	1.4146	1.4163	1.4163	1.4163	1.4163
R(2,5)	1.3959	1.3975	1.3985	1.3985	1.3985	1.3985
R(3,4)	1.4356	1.4354	1.4357	1.4357	1.4357	1.4357
R(3,6)	1.4018	1.4017	1.4032	1.403	1.403	1.4031
R(4,7)	1.3619	1.3621	1.3647	1.3645	1.3645	1.3646
R(4,11)	1.0805	1.0804	1.0808	1.0808	1.0808	1.0808
R(5,8)	1.3822	1.3832	1.3843	1.3841	1.3842	1.3841
R(5,12)	1.086	1.0859	1.0859	1.0859	1.0859	1.0859
R(6,9)	1.3815	1.382	1.3831	1.3831	1.3831	1.383
R(6,13)	1.0861	1.086	1.0863	1.0863	1.0863	1.0863
R(7,14)	1.0806	1.0805	1.0806	1.0806	1.0806	1.0806
R(8,9)	1.4066	1.4064	1.4078	1.4076	1.4077	1.4078
R(8,15)	1.0856	1.0856	1.0856	1.0856	1.0856	1.0856
R(9,16)	1.0855	1.0855	1.0856	1.0857	1.0857	1.0857

(b) Changes in Bond lengths

IND		Change in bond lengths of IND-DC				
		Gaseous	water	Ethanol	Methanol	DMSO
R(1,2)	1.3762	-0.001	0.0016	0.0012	0.0013	0.0015
R(1,7)	1.3781	0.0003	0.0024	0.0022	0.0023	0.0022
R(1,10)	1.0065	-0.0014	-0.0022	-0.0023	-0.0023	-0.0023
R(2,3)	1.4136	-0.001	-0.0027	-0.0027	-0.0027	-0.0027
R(2,5)	1.3959	-0.0016	-0.0026	-0.0026	-0.0026	-0.0026
R(3,4)	1.4356	0.0002	-0.0001	-0.0001	-0.0001	-0.0001
R(3,6)	1.4018	0.0001	-0.0014	-0.0012	-0.0012	-0.0013
R(4,7)	1.3619	-0.0002	-0.0028	-0.0026	-0.0026	-0.0027
R(4,11)	1.0805	0.0001	-0.0003	-0.0003	-0.0003	-0.0003
R(5,8)	1.3822	-0.0001	-0.0021	-0.0019	-0.002	-0.0019
R(5,12)	1.086	0.0001	0.0001	0.0001	0.0001	0.0001
R(6,9)	1.3815	0.0000	-0.0016	-0.0016	-0.0016	-0.0015
R(6,13)	1.0861	0.0001	-0.0002	-0.0002	-0.0002	-0.0002
R(7,14)	1.0806	0.0001	0	0	0	0
R(8,9)	1.4066	0.0002	-0.0012	-0.001	-0.0011	-0.0012
R(8,15)	1.0856	0	0	0	0	0
R(9,16)	1.0855	0	-0.0001	-0.0002	-0.0002	-0.0002

(c) Bond angles of IND and it's complex in different solvents

	IND	IND-DC				
		Gaseous	water	Ethanol	Methanol	DMSO
A(2,1,7)	109.1689	109.0844	109.1749	109.1689	109.171	109.1694
A(2,1,10)	125.4538	125.3158	125.4936	125.5007	125.5019	125.4944
A(7,1,10)	125.3772	125.587	125.284	125.3071	125.3017	125.2863
A(1,2,3)	107.2839	107.3128	107.3707	107.3562	107.3598	107.3676
A(1,2,5)	130.3998	130.3631	130.3865	130.3965	130.3893	130.3869
A(3,2,5)	122.3163	122.323	122.2429	122.2472	122.2509	122.2455
A(2,3,4)	106.8763	106.8436	106.7759	106.7832	106.7809	106.7786
A(2,3,6)	118.7999	118.7635	118.81	118.8109	118.8062	118.8136
A(4,3,6)	134.3238	134.3928	134.4141	134.4059	134.4129	134.4078
A(3,4,7)	106.9992	106.9985	106.8859	106.8986	106.8957	106.8921
A(3,4,11)	126.9066	126.9218	126.981	126.971	126.974	126.9662
A(7,4,11)	126.0942	126.0795	126.1331	126.1304	126.1303	126.1418
A(2,5,8)	117.4824	117.437	117.4969	117.4848	117.4866	117.4876
A(2,5,12)	121.3206	121.2207	121.1568	121.1943	121.183	121.1824
A(8,5,12)	121.197	121.3413	121.3448	121.3198	121.3293	121.3285
A(3,6,9)	119.1336	119.1762	119.1664	119.1606	119.1618	119.1579
A(3,6,13)	120.2866	120.2774	120.3018	120.2994	120.3009	120.2948
A(9,6,13)	120.5798	120.5464	120.5318	120.54	120.5373	120.5472
A(1,7,4)	109.6716	109.7606	109.7918	109.7928	109.7923	109.7916
A(1,7,14)	120.3332	120.2516	120.1666	120.1648	120.1624	120.1516
A(4,7,14)	129.9952	129.9871	130.0416	130.0423	130.0453	130.0568
A(5,8,9)	121.2122	121.2205	121.2213	121.23	121.2259	121.2279
A(5,8,15)	119.4064	119.3808	119.3719	119.3683	119.371	119.3767
A(9,8,15)	119.3815	119.3982	119.4062	119.4014	119.4027	119.395
A(6,9,8)	121.0556	121.0796	121.0618	121.0662	121.0682	121.0669
A(6,9,16)	119.7251	119.6964	119.7178	119.7106	119.7105	119.7211
A(8,9,16)	119.2193	119.224	119.2204	119.2232	119.2212	119.212

(d) Changes in Bond angles

	IND	IND-DC				
		Gaseous	water	Ethanol	Methanol	DMSO
A(2,1,7)	109.1689	0.0845	-0.006	0	-0.0021	0
A(2,1,10)	125.4538	0.138	-0.0398	-0.0469	-0.0481	-0.0406
A(7,1,10)	125.3772	-0.2098	0.0932	0.0701	0.0755	0.0909
A(1,2,3)	107.2839	-0.0289	-0.0868	-0.0723	-0.0759	-0.0837
A(1,2,5)	130.3998	0.0367	0.0133	0.0033	0.0105	0.0129
A(3,2,5)	122.3163	-0.0067	0.0734	0.0691	0.0654	0.0708
A(2,3,4)	106.8763	0.0327	0.1004	0.0931	0.0954	0.0977
A(2,3,6)	118.7999	0.0364	-0.0101	-0.011	-0.0063	-0.0137
A(4,3,6)	134.3238	-0.069	-0.0903	-0.0821	-0.0891	-0.084
A(3,4,7)	106.9992	0	0.1133	0.1006	0.1035	0.1071
A(3,4,11)	126.9066	-0.0152	-0.0744	-0.0644	-0.0674	-0.0596
A(7,4,11)	126.0942	0.0147	-0.0389	-0.0362	-0.0361	-0.0476
A(2,5,8)	117.4824	0.0454	-0.0145	-0.0024	-0.0042	-0.0052
A(2,5,12)	121.3206	0.0999	0.1638	0.1263	0.1376	0.1382
A(8,5,12)	121.197	-0.1443	-0.1478	-0.1228	-0.1323	-0.1315
A(3,6,9)	119.1336	-0.0426	-0.0328	-0.027	-0.0282	-0.0243
A(3,6,13)	120.2866	0.0092	-0.0152	-0.0128	-0.0143	-0.0082
A(9,6,13)	120.5798	0.0334	0.048	0.0398	0.0425	0.0326
A(1,7,4)	109.6716	-0.089	-0.1202	-0.1212	-0.1207	-0.12
A(1,7,14)	120.3332	0.0816	0.1666	0.1684	0.1708	0.1816
A(4,7,14)	129.9952	0.0081	-0.0464	-0.0471	-0.0501	-0.0616
A(5,8,9)	121.2122	-0.0083	-0.0091	-0.0178	-0.0137	-0.0157
A(5,8,15)	119.4064	0.0256	0.0345	0.0381	0.0354	0.0297
A(9,8,15)	119.3815	-0.0167	-0.0247	-0.0199	-0.0212	-0.0135
A(6,9,8)	121.0556	-0.024	-0.0062	-0.0106	-0.0126	-0.0113
A(6,9,16)	119.7251	0.0287	0.0073	0.0145	0.0146	0.004
A(8,9,16)	119.2193	-0.0047	-0.0011	-0.0039	-0.0019	0.0073

Electronic and spectroscopic properties

Table 2
Chemical descriptors (eV)

	E_{HOMO}	E_{LUMO}	Energy gap	Hardness	Chemical potential	Electrophilicity index
IND	-8.8898	-4.9521	3.9377	1.9689	-6.9210	12.1640
IND-DC gaseous	-8.1358	-4.9644	3.1714	1.5857	-6.5501	13.5284
IND-DC Water	-8.1247	-4.9698	3.1549	1.5775	-6.5473	13.5868
IND-DC Ethanol	-8.1257	-4.9679	3.1578	1.5789	-6.5468	13.5729
IND-DC Methanol	-8.1255	-4.9685	3.1570	1.5785	-6.5470	13.5772
IND-DC DMSO	-8.1252	-4.9687	3.1565	1.5783	-6.5469	13.5787

The HOMO and LUMO of IND-DC are – 8.1358 and – 4.9644 eV while that of IND is -8.8898 and – 4.9521 eV (Table 2). Energy gap of IND-DC show a lowering effect (from 3.9377 to 3.1714 eV) and due to solvation there is further decrease in HOMO-LUMO energy gap values. Significant changes are observed for the IND-DC complex for hardness and chemical potential values in comparison with that of IND. The electrophilicity index of IND-DC and its solvated values increases in comparison with that of bare IND. These shows the reactivity changes in the system [29]. The HOMO and LUMO are localized on IND with interchange in polarity while in all complexes, HOMO is over the DC and LUMO is over the IND [30, 31]. This shows strong charge transfer from DC to IND (Fig. 2).

In the potential surface plots (Fig. 3), rings show yellow - negative electrostatic potentials, electrophilic regions, and H atom of NH show blue, stronger positive potential, nucleophilic region. These are the most reactive sites in the molecule. Chlorine atoms also contribute to reactive sites in the systems [32–34]. Due to complexation with DC, the dipole moment of the drug changes from 2.1478 to 0.7353 Debye while in all solvents, the dipole moment increases from that of IND-DC value but less than that of IND. All the polarizability components are increasing order except for the first order polarizability in the case of methanol solvent (Table 3). Hence complexation of IND increases the NLO activity [35–37].

Table 3
NLO parameters

	Dipole Moment (Debye)	Polarizability ($\times 10^{-23}$ esu)	First order Polarizability ($\times 10^{-30}$ esu)	Second order Polarizability ($\times 10^{-37}$ esu)
IND	2.1478	1.190	0.907	2.131
IND-DC (gaseous)	0.7353	1.622	1.347	6.812
IND-DC (Water)	1.7971	2.137	3.529	6.516
IND-DC (Ethanol)	1.5877	2.110	3.320	6.643
IND-DC (Methanol)	1.6252	2.119	0.964	6.625
IND-DC (DMSO)	1.6726	2.128	3.433	6.595

The IND charges, C2 and C5 decreases by an amount 0.02359 and 0.01944e while the H10 and H12 increases by 0.01403 and 0.01487e due to complexation with DC (table S1). In solvents also, these charges show deviations from the pristine values with significant variations. All these show the charge transfer due to complexation with DC.

The theoretically predicted IR and Raman spectra of all complexes are depicted in Figs. 4 and 5. The NH stretching mode of parent is 3561.26, which is red shifted in DC complex by an amount of 15.58 and due to solvation, the red shift increases to lower wavenumbers which shows the hydrogen bonding of drug with DC (tables S2 and S3). Also the parent molecule's vibrational modes at 1650.12, 1609.24, 1541.59, 1506.04, 1464.94, 1337.64 show lowering of wavenumber value in the DC complex and such lowering increases with salvation. Different vibrational modes of IND undergo red and blue shift due to DC complexation. All these shifts show the interaction between IND molecule and DC due to hydrogen bonding [6].

Conclusion

DFT simulations were used to investigate intermolecular interactions between IND and DC molecule. The influence of hydrogen bonding was used to monitor hydrogen bonding in IND and DC systems. Distinct solvents have different properties, which are also reported. The binding strengths revealed that IND-DC was linked to the ring and NH and was stable with a considerable effect on the parent's vibrations. Overall the study is a great example of using theoretical modeling to monitor extremely weak hydrogen bonds.

Declarations

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Conflict of interest:

The authors declare no competing interests.

Data availability:

All data are available on request to the corresponding author

Code availability:

N/A

Author's contributions:

Conceptualization, Y.Sheena Mary; Methodology, Y.Shyma Mary; Writing original draft, Jamelah S.Al-Otaibi, Y.Sheena Mary; Writing-review and editing, Jamelah S.Al-Otaibi, Y.Sheena Mary, Y.Shyma Mary

Ethics approval

The manuscript is prepared in compliance with the Ethics in Publishing Policy as described in the Guide for Authors

Consent to participate

The manuscript is approved by all authors for publication

Consent for publication

The consent for publication was obtained from all participants

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Figures

Figure 1

Optimized geometry of IND-DC

Figure 2

HOMO-LUMO plots of (a) IND and IND-DC (b) gaseous (c) water (d) ethanol (e) methanol (f) DMSO solvents

Figure 3

MEP and ESP plots of (a) IND and IND-DC (b) gaseous (c) water (d) ethanol (e) methanol (f) DMSO solvents

Figure 4

Theoretical IR spectra of (a) IND (b) IND-DC in solvents

Figure 5

Theoretical Raman spectra of (a) IND (b) IND-DC in solvents

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