THEORETICAL STUDIES OF DIFFERENT TAUTOMERS OF ANTI CANCER DRUG: DICHLOROACETATE

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ABSTRACT

The structure and relative energies of the tautomers of dichloroacetate are predicted using Hartree Fock method. The infrared spectra of two dominant tautomers are calculated in the density functional theory. Good agreement between calculated (DFT) and experimental harmonic vibrational frequencies is found. Assuming C_s point symmetry, vibrational assignments for the observed frequencies have been proposed. The spectra exhibit distinct features originating from low frequency vibrational modes caused by inter-molecular motion. Energy is minimum for DCA-2 tautomer. Dipole moment is large for DCA-1 tautomer and polar surface area is somewhat larger in caso of DCA-2. Local ionization potential map and lowest-unoccupied molecular orbital (LUMO) map has been drawn and analyzed. Linear regression data for both the tautomers has also been calculated, so clearly DCA1 is more correlated to experimental wavenumbers.

Keywords: Dichloroacetate, tautomers, MOPAC, Hartree-Fock, DFT, anti-cancer drug.

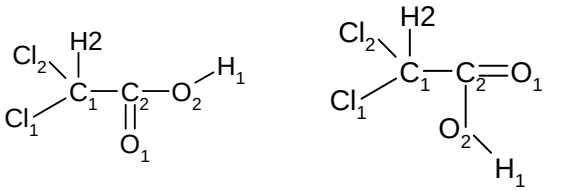
INTRODUCTION

Dichloroacetate (or DCA) is an analogue of acetic acid in which two of the three hydrogen atoms of the methyl group have been replaced by chlorine atoms (Anonymous, 2007). DCA is an odorless, colorless, inexpensive, relatively non-toxic, small molecule. Dichloroacetate (DCA), appears to suppress the growth of cancer cells without affecting normal cells, suggesting that it might not have the dramatic side effects of standard chemotherapies (Bennett *et al.*, 2007). DCA is also a metabolite in the biotransformation of several pharmaceuticals and has been administered orally and parenterally for decades as an investigational drug for the treatment of numerous cardiovascular and metabolic disorders (Stacpoole 1997 and Scott *et al.*, 1996).

In this paper, computational methods for two tautomers of DCA are reported used to find the tautomerization energy. The stabilities of both the two tautomers are examined and compared to each other. Vibrational modes and thermodynamics of both the tautomers are also calculated. Theoretical IR spectra are also drawn.

Computational methods

The AM1 and PM3 semi empirical approaches were performed as carried out in MOPAC program (Molecular Orbital programme, 1997) and the PRECISE keywords were used. Hartree Fock calculations were performed using Spartan' 06 program at the B3LYP (Here *et al.,* 1989) levels of theory with 6-31G* basis set (Florio *et al.,* 2001). The vibrational IR spectra were calculated at the HF/3-21 G levels of theory then starts from MMFF (Molecular Mechanics Force Field) conformer and AM1 geometry. We have transformed the harmonic force fields, determined initially in the Cartesian coordinates, were transformed to the force fields in the internal local coordinates.



Dichloroacetate (DCA-1)	Dichloroacetate (DCA-2)
Empirical Formula	$C_2H_2O_2Cl_2$
Molecular Weight	267.24

Fig. 1: Structure and formula of tautomers of Dichloroacetate (DCA)

RESULTS AND DISCUSSIONS

The experimental infrared spectrum and theoretically calculated infrared spectrum of both the tautomers are shown in figs. 2, 3 and 4 respectively.

The energy in au, energy(aqueous) in au, dipole moment in debye, weight in amu, area in $A^{\circ 2}$, polar surface area(PSA) in $A^{\circ 2}$, volume in $A^{\circ 3}$ for both the tautomers are presented in table 2. The values of bond lengths in A° and bond angles in degrees are presented in table 1.

Energy is minimum for DCA-2 tautomer. Dipole moment is large for DCA-1, so it means it has large separation of charge. Weight, area and volume are nearly equal in both the cases, but polar surface area is somewhat larger in case of DCA-2.

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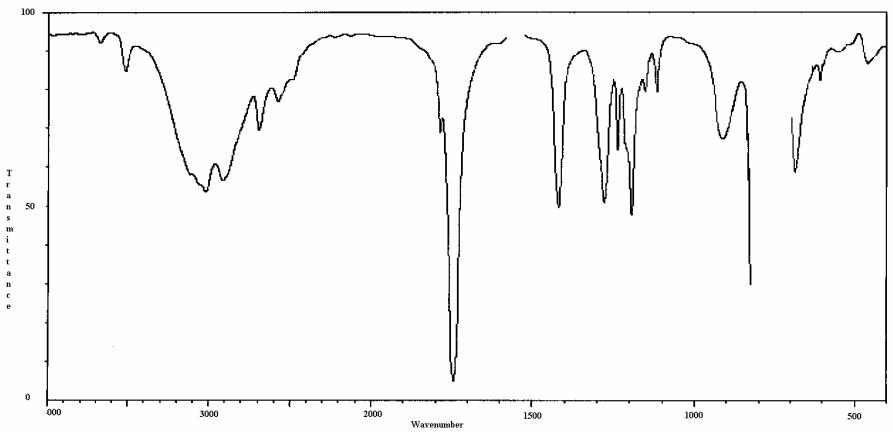

Fig. 2: IR spectrum (experimental) of DCA.

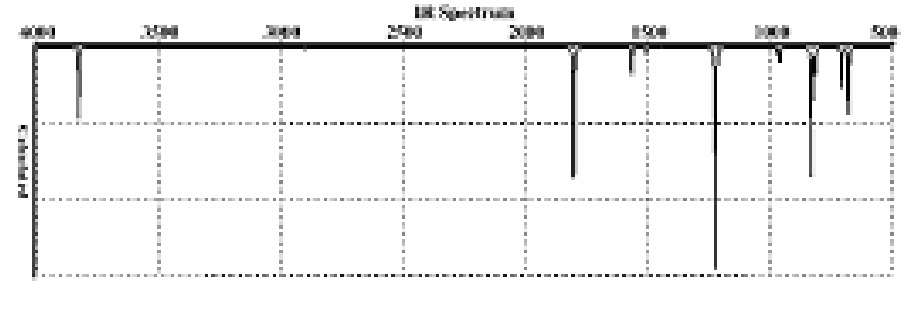

Fig. 3: IR Spectrum (Calculated) of DCA-1.

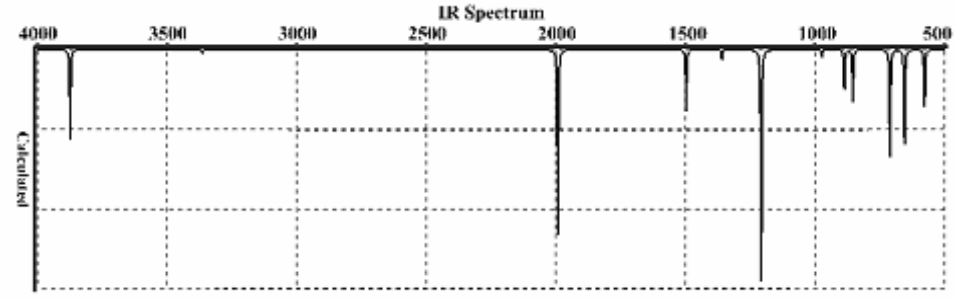

Fig. 4: IR Spectrum (Calculated) of DCA-2.

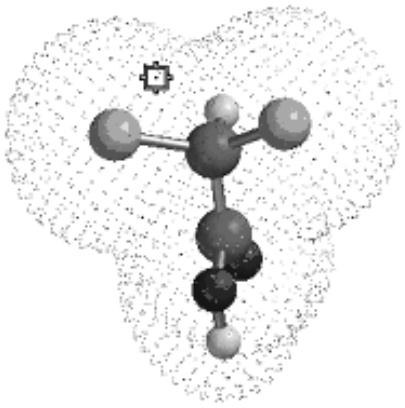

Fig. 5: Ionization potential map of DCA-1 tautomer.

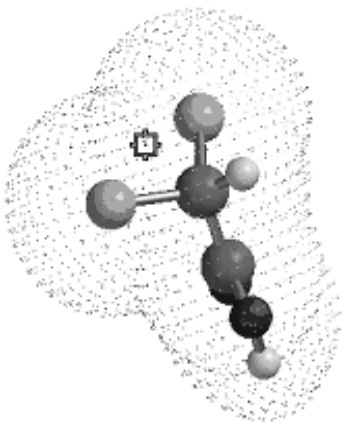

Fig. 6: Ionization potential map of DCA-2 tautomer.

Figs. 5 and 6 show electrostatic potential map for DCA-1 and DCA-2 tautomers respectively. The electrostatic potential map paints the value of the electrostatic potential onto an electron density surface to get a description of the electrostatic characteristics of target drug. By convention, colors toward red depict negative potential, while colors toward blue depict positive potential and colors between depict intermediate values of the potential. Thus, this drug has both, negative and positive well defined regions, which increase the interaction possibilities from the electrostatic point of view. Thus, especially when H-bonding (electrostatic in nature) is involved, the calculation of the electrostatic surfaces can be very useful to visualize the sites of interaction in both hosts and guests to predict their affinities (Delia Soto-Castro *et al* 2006). Areas showed by small box shows areas from which electron removal (ionization) is relatively easy; it means they are subjected to electrophillic attack.

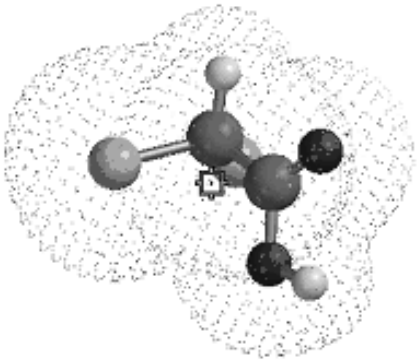

Fig. 7: LUMO map for DCA-1.

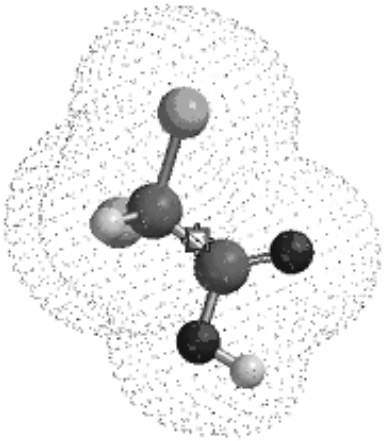

Fig. 8: LUMO map for DCA-2.

Figs. 7 and 8 show lowest unoccupied molecular orbital (LUMO) map for DCA-1 and DCA-2 tautomers respectively. Its maximum value for DCA-1 and DCA-2 is 15.23131 and 15.2270 respectively and are shown by boxes in figs. 7 and 8.

We can get information from computational vibrational spectra only when we compare it with experimental spectrum. The vibrational infrared frequencies for both the tautomers are shown in table 3. DCA contains 8 atoms so that it has 18 normal modes. The calculated normal modes are distributed among 13 a′ and 5 a′′ species of Cs symmetry group. The table 3 also shows that PED contributions for 18 normal modes. These assignments are partly based on the calculated frequencies. As table 3 is self-explanatory, we shall discuss here only some important points.

Table 1: Bond Length and bond angles of DCA-1 and DCA-2

SN	Bond Length in angstroms (DFT Calculated, Basis set 6-31G*)		
		DCA - 1	DCA - 2
1.	Cl1 – C1	1.775	1.765
2.	Cl2 – C1	1.776	1.791
3.	C1 – C2	1.518	1.517
4.	C1 – H2	1.094	1.075
5.	C2 – O1	1.348	1.357
6.	C2 – O2	1.357	1.348
7.	O2 – H2	0.982	0.969
	Bond Angles in degrees		
1.	Cl1-C1-Cl2	110.44	111.44
2.	Cl1-C1-H2	109.41	109.32
3.	Cl1-C1-C2	109.01	111.37
4.	Cl2-C1-H2	108.19	107.60
5.	Cl2-C1-C2	110.70	110.70
6.	O1-C2-C1	128.35	128.45
7.	O1-C2-O2	119.30	118.79
8.	C2-O2-H2	105.01	104.09
9.	C1-C2-O2	115.35	112.76
10.	C1-C2-O1	125.35	128.45

Table 2: Properties of DCA-1 & DCA-2 tautomers

SN	Property	DCA - 1	DCA - 2
1.	Energy in au	-1140.15349	-1140.15287
2.	Energy(aqueous) in au	-1140.16227	-1140.16123
3.	Dipole Moment in debye	2.67	2.27
4.	Weight in amu	128.942	128.942
5.	Area $A^{\circ 2}$	115.61	115.67
6.	PSA $A^{\circ 2}$	34.252	34.370
7.	Volume $A^{\circ 3}$	89.04	89.03
8.	Lowest energy conformation in kJ/mol	121.9231	121.923

In experimental IR spectrum strongest peak is at 1743cm^{-1} for C=O stretch but in calculated IR spectrum strongest peak is at 1221.233 cm^{-1} for DCA-1 and 1206.926 cm^{-1} for DCA-2 . In calculated IR spectrums we got number of

Table 3: Experimental and calculated frequencies and potential distribution in $C_2H_2O_2Cl_2$

Assignment	Experimental Frequencies (in cm^{-1})	Assignment	Frequencies (in cm^{-1})	
			DCA-1	DCA-2
			Hartree-Fock 3-21G*	Hartree-Fock 3-21G*
Species a'				
1	3616	OH str	3829.240	3874.037
2	2913	CH str	2899.654	3364.190
3	1743	C=O str	1801.228	1991.691
4	1419	OH bend + C-O str	1563.886	1496.708
5		OH i.p. def	1505.344	1404.495
6	1279	CH bend	1437.971	1358.692
7	1239	OH bend + C-O str	1221.233	1206.926
8	827	C-Cl str	956.310	886.106
9	807	CC str	827.456	853.201
10		C=O o.p.bend	812.016	709.811
11	607	C-Cl str	705.778	653.897
12		OCO bend	675.191	432.447
13		CCO bend	288.337	306.427

Assignment	Experimental Frequencies (in cm^{-1})	PED and Mode	Frequencies (in cm^{-1})	
			DCA-1	DCA-2
			Hartree-Fock 3-21G(*)	Hartree-Fock 3-21G(*)
Species a"				
1	913	OH o.p.def	967.785	972.309
2	459	C-O torsion	439.895	576.594
3		CH rocking	254.529	263.150
4		wagging	232.027	210.470
5			44.202	59.566

str- stretch; i.p.def- in plane deformation; o.p.bend – out of plane bend; o.p.def.- out of plane deformation

peaks between 1000 cm^{-1}-500 cm^{-1}. In experimental spectrum we got number of peaks between 1500 cm^{-1}-1000 cm^{-1}. In calculated IR spectrum we got less number of peaks because our calculations are based on a frozen molecule at 0K in a vacuum and do not take into account that the structure is vibrating at all. In experimental IR spectrum there is influence of the medium in which chemical species are found.

Polar surface area is a sum of surfaces of polar atoms (usually oxygen, nitrogen and attached hydrogen) in a molecule. This parameter has been shown to correlate very well with the human intestinal absorption, Caco-2 monolayer permeability, and blood-brain barrier penetration. Molecules with a polar surface area of greater than 140 angstroms squared are usually believed to be poor at permeating cell membranes. For molecules to penetrate the blood-brain barrier, PSA should be less than 60 $A^{\circ 2}$ (Ertl, 2000). PSA for DCA-1 and DCA-2 comes out to be 34.252 $A^{\circ 2}$ and 34.370 $A^{\circ 2}$.

Linear regression data for both the tautomers are shown in table 3, so it is clear from this table that DCA1 is more correlated to experimental wavenumbers

CONCLUSIONS

Attempts have been made in the present work for the proper frequency assignments for the DCA-1 and DCA-2 from the FT-IR spectra. Any discrepancy noted between the observed and the calculated frequencies may be because the calculations have been actually done on a single molecule in the gaseous state contrary to the experimental values recorded in the presence of intermolecular interactions. Also, difference is attributed due to neglect of anharmonicity and incomplete inclusion of electronic correlation effects. Therefore, the assignments made at higher levels of theory with only reasonable deviations from the experimental values, seem to be correct. For further agreement between computed

and experimental frequencies, the computed frequencies are often scaled by some specific factor.

All known bands in both the tautomers are reported. One aim of present study was to test which tautomer is more stable. The comparison with experiment is well for DCA1. Statistically also data's of DCA-1 tautomer is more near experimental one. PSA for DCA-1 is lower, so it is well for blood-brain barrier.

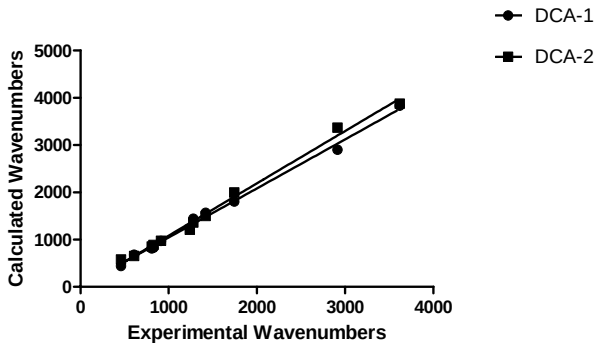

Fig. 9: Correlation between experimental wavenumbers and calculated wavenumbers

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Table 4: Linear regression data

	DCA - 1	DCA-2
Slope	1.038 ± 0.02408	1.107 ± 0.02970
Y-intercept when X=0.0	5.318 ± 41.41	-25.33 ± 51.08
X-intercept when Y=0.0	-5.125	22.89
1/slope	0.9638	0.9034
95% Confidence Intervals		
Slope	0.9831 to 1.092	1.040 to 1.174
Y-intercept when X=0.0	-88.35 to 98.99	-140.9 to 90.22
X-intercept when Y=0.0	-99.83 to 81.60	-85.90 to 121.2
Goodness of Fit		
r^2	0.9952	0.9936
Sy.x	75.28	92.86
Is slope significantly non-zero?		
F	1857	1389
DFn, DFd	1.000, 9.000	1.000, 9.000
P value	< 0.0001	< 0.0001
Deviation from zero?	Significant	Significant
Peak 1		
First X=	459.0	459.0
Last X=	3616	3616
Peak X=	3616	3616
Peak Y=	3350	3522
Area=	6.721e+006	7.064e+006
%Area=	100.0	100.0

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