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Vibrational Spectroscopy Investigation on Aspirin Using Semi-Empirical Calculations

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Abstract: Modern spectroscopic techniques are very effective and sensitive tools for the qualitative and quantitative analysis of many compounds and the results are well employed in the quality control laboratories of pharmaceutical firms. In the present work, the infrared spectroscopy is employed for the identification and assignment of the functional groups present in the medicinally important drug namely aspirin. The present investigation was undertaken to study the vibrational spectrum of the molecule completely and to identify the various normal modes with great wave number accuracy. The equilibrium geometries and harmonic frequencies of the compound aspirin were determined and analyzed using the semi-empirical methods AM1 and PM3. The differences between the observed and calculated wave number values in the molecule were marginal. Thermodynamic properties like entropy, heat capacity, zero point energy were calculated for the molecule.
Keywords: Aspirin, FTIR spectrum, semi-empirical, AM1, PM3.

INTRODUCTION

Predicting and understanding the properties and behavior of real material systems is of great importance both from technological and academic points of view. The theoretical problems associated with these systems are quite complex. Computational chemistry uses the results of theoretical chemistry, incorporated into efficient computer programs, to calculate the structure and properties of molecules and solids. The methods are based on theories which range from highly accurate, but suitable for small systems, to very approximate, but suitable for large systems. The accurate methods are called *ab initio* methods, as they are based entirely on theory from first principles. The less accurate methods, like MM1-4 methods are called empirical or semi-empirical, because some experimental results, often from atoms or related molecules are used with the theory. Semi-empirical methods represent a "middle road" between the mostly qualitative results available from molecular mechanics and the computationally time-consuming quantitative results available from *ab initio* methods. When used judiciously, semi-empirical methods like AM1, PM3 etc. can give great insight into structure and reactivity of even moderately large molecules[1-5].

Modern spectroscopic techniques are very effective and sensitive tools for the qualitative and quantitative analysis of many compounds and the results are well employed in the quality control laboratories of pharmaceutical firms. The infrared spectroscopy is employed here for the identification and assignment of the functional groups present in medicinally important drug aspirin. Aspirin is used in analgesics, anti-inflammatory drugs, antipyretics, anticoagulants and anti-rheumatics. Acetylsalicylic Acid is also known by trade name aspirin is introduced in the year 1899. It has attained a leading position world-wide in the prescription-free therapy of painful, inflammatory and feverish conditions. The origin of aspirin lies in the use of the bark of the willow tree. The acetyl derivative of salicylic acid is a white, crystalline, weakly acidic substance, with

melting point 137°C. The molecular formula and molecular weight of the aspirin is $C_9H_8O_4$ and 180.16 g/mol. Aspirin belongs to a class of medications called Non Steroidal Anti-inflammatory drugs (NSAIDs). Chemically NSAIDS are heterogeneous large groups of drugs which suppress inflammation in a manner similar to steroids, but less side effects of sedation, respiratory depression. They are effective in the relief of pain and fever.

The present investigation was undertaken to study the vibrational spectra of aspirin completely and to identify the various normal modes with greater wave number accuracy. For the analysis of the molecule, semi-empirical methods AM1and PM3 implemented in GAUSSIAN program have been used. Several thermodynamic parameters, zero-point vibration energies (ZPVEs), entropy $S_{vib}(T)$ have also been calculated for the molecule. The structure of the compound is presented in Fig. 1.

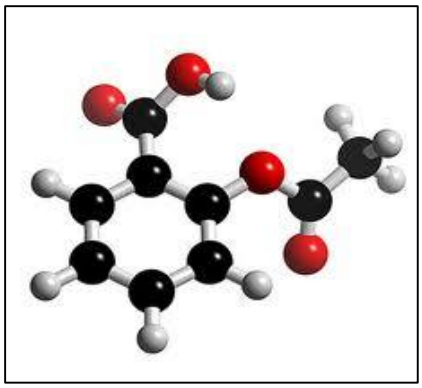

Fig. 1 Structure of aspirin

MATERIALS AND METHODS

High grade pure samples of aspirin were procured from a reputed pharmaceutical company, Sun Pharmaceutical Industries Limited, Mumbai, India and were used as such. The FTIR spectra have been recorded in the range 4000-400 cm^{-1} using PERKIN ELMER, FTIR Spectrometer at ACIC, St. Joseph's College, Tiruchirappalli. The FTIR module has globar and mercury vapor lamp as the sources and the interferometer chamber has Mylar beam splitters. The FTIR spectrometer has a resolution of 0.1cm^{-1}. It has the facilities of signal averaging, signal enhancement and baseline correction. Other spectral manipulations are also possible with multitasking OPUS software on the dedicated PC/INTEL-4. The FTIR spectrum of aspirin is presented in Fig 2.

RESULTS AND DISCUSSION

Molecular geometry

Full geometric optimization was carried out for the structure of aspirin at AM1 and PM3 levels of semi empirical methods using the Gaussian 03W chemical program package. The molecular parameters of aspirin are compared with the experimental values and are tabulated in **Table 1.** In this work, the calculated geometry using the semi-empirical methods consider only the gas phase, where the molecule is free of interactions, so we expected to find some differences with the experimental structure of the solid state.

Vibrational spectral analysis

The vibrational spectrum of a compound is the superposition of the absorption bands of specific functional groups. The functional groups present in the compound aspirin were identified and vibrational band assignment of the compound was made by comparing the spectra of similar compounds and also by observing the nature, shape and intensity of the vibrational bands in the spectra. The vibrational band assignment made on the title compound is presented in **Table 2.**

C=C Vibrations

The ring carbon - carbon stretching vibration occurs in the region 1625–1430cm^{-1} and is usually stronger. This occurs as two or three bands in the region due to skeletal vibration. In this case of substituted benzenes with groups, the vibrations produce the band at 1625-1590 cm^{-1} [6]. In the present compound aspirin, a very strong band at 1629 cm^{-1} is due to C=C stretching vibration.

A fairly weak band is observed in the region due to 1420–1400 cm^{-1} for substituted benzene due to C=C stretching vibration. In aspirin, these vibrations occur at 1454 cm^{-1} and 1412 cm^{-1}. Both the peaks are of medium intensity.

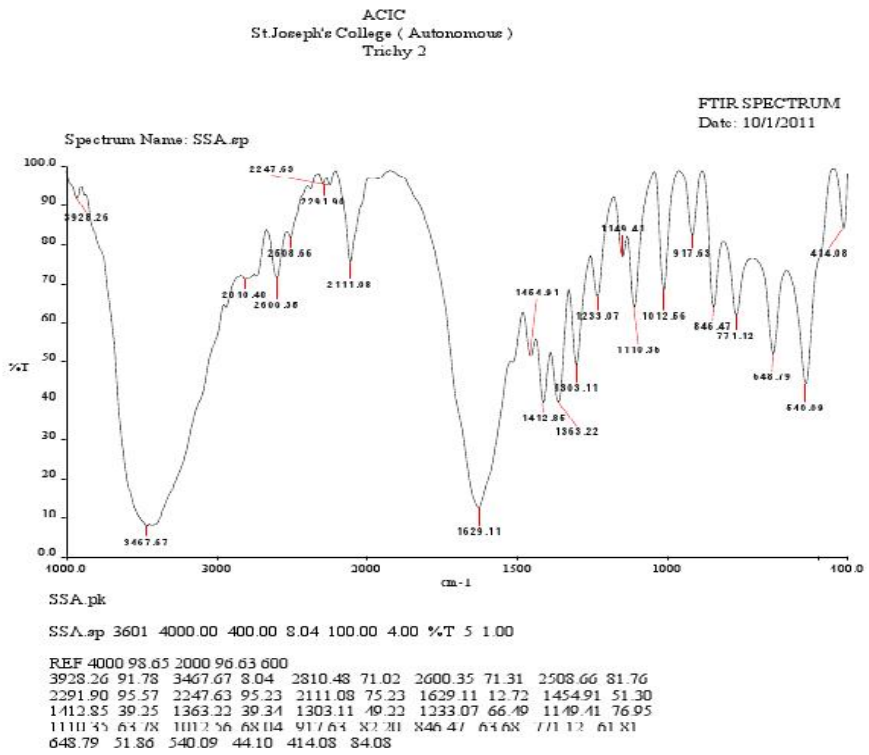

Fig. 2 FTIR Spectrum of aspirin

C=O Vibrations

Aromatic acids have a strong band at 570–545 cm^{-1} . This is due to the rocking vibration of the CO_2 group. Also the bending vibration of CO_2 groups result in a band at 620–610 cm^{-1}. The C=O stretching occurs around 1630 cm^{-1} for aromatic acids [7].

In the present investigation, the medium intensity band at 540 cm^{-1} is assigned to CO_2 rocking vibration. The bending of CO_2 group results in a medium intensity band at 648 cm^{-1}. Also a strong band due to C=O stretching vibration is formed at 1629 cm^{-1}.

O–H Vibrations

As a result of the presence of hydrogen bonding, carboxylic acid in the liquid and solid phase exhibit a broad band at around 3300-3500 cm^{-1}. Due to the O-H stretching vibration, carboxylic acids will observe vibrations in the region 2700-2500 cm^{-1}. The vibration 3467 cm^{-1} is very strong in intensity and it assigned to O-H stretching. Also weak vibration at 2810-2600 cm^{-1} belongs to O-H stretching vibration [8].

C-H Vibrations

In plane C-H deformations produce weak bands at around 1300-1000 cm^{-1} [9]. The vibrations at 1233, 1149, 1110, 1012 cm^{-1} belong to in plane C-H bending vibration. Aromatic C-H out of plane bending usually occurs in the range 960-900 cm^{-1} and 850-810 cm^{-1}. The vibrations at 917, 846, 771, 648 cm^{-1} belong to C-H out of plane deformation.

Table 1 Geometric parameters optimized in aspirin, bond length (A), bong angle (º)

Bond Length(AU)			**Bond Angle(deg)**		
Nature	**Calculated Value**		**Nature**	**Calculated Value**	
	AM1	**PM3**		**AM1**	**PM3**
O(1)-C(2)	1.2357	1.2158	O(1)=C(2)-O(3)	116.5093	116.4207
C(2)-O(3)	1.364	1.3558	O(1)=C(2)-C(4)	128.7887	128.578
C(2)-O(4)	1.4688	1.4857	O(3)-C(2)-C(4)	114.6668	114.9735
O(3)-H(4)	0.9723	0.9523	C(2)-O(3)-H(14)	109.2014	109.847
C(4)-C(5)	1.4014	1.3965	C(2)-C(4)-C(5)	119.5825	118.4405
C(4)-C(9)	1.4066	1.4025	C(2)-C(4)-(9)	121.3459	122.3765
C(5)-C(6)	1.3923	1.3896	C(5)=C(4)-C(9)	119.0669	119.1694
C(5)-H(15)	1.1022	1.0965	C(4)=C(5)-C(6)	120.4014	120.2547
C(6)-C(7)	1.3963	1.3921	C(4)=C(5)-H(15)	119.0456	119.7358
C(6)-H(16)	1.1003	1.0953	C(6)-C(5)-H(15)	120.5522	120.0084
C(7)-C(8)	1.3919	1.3888	C(5)-C(6)=C(7)	120.1707	120.3028
C(7)-H(17)	1.1011	1.0955	C(5)-C(6)=C(16)	119.8218	119.7735
C(8)-C(9)	1.4039	1.401	C(7)=C(6)-H(16)	120.0066	119.9225
C(8)-H(18)	1.1002	1.0964	C(6)-C(7)-C(8)	120.3383	120.2305
C(9)-O(10)	1.3863	1.3896	C(6)=C(7)-H(17)	119.964	119.9411
O(10)-C(11)	1.3941	1.3782	C(8)-C97)-H(17)	119.6959	119.7362
C(11)-C(12)	1.4835	1.497	C(7)-C(8)=C(9)	119.552	119.4418
C(11)-C(13)	1.227	1.2101	C(7)-C(8)-H(18)	121.0604	120.3591
C(12)-H(19)	1.1172	1.0973	C(19)=C(8)-H(18)	119.3756	120.1944
C(12)-H(20)	1.1169	1.0988	C(4)-C(19)=C(8)	120.451	120.5073
C(12)-H(21)	1.1217	1.0988	C(4)-C(9)-O(10)	120.9398	119.6526
			C(8)=C(9)-O(11)	118.1223	119.5127
C(9)-O(10)-C(11)		118.9036	118.6864		
O(10)-C(11)-C(12)		120.155	123.531		
O(10)-C(11)=C(13)		110.8313	107.6693		
C(12)-C(11)=O(13)		129.0018	128.7951		
C(11)-C(12)-H(19)		109.7417	111.2441		
C(11)-C(12)-H(20)		110.5717	111.0415		
C(11)-C(12)-H(21)		108.5145	110.2857		
H(19)-C(12)-H(20)		109.5566	108.1997		
H(19)-C(12)-H(21)		109.2032	107.9788		
H(20)-C(12)-H(21)		109.2267	107.9661		

Table 2 Infrared spectral assignment of aspirin

Observed frequency (cm-1)	Calculated Freq (cm-1)		Band Assignment
FTIR	**AM1**	**PM3**	
3467(VS)	3418	-	O-H stretching
1629(VS)	-	1614	C=C stretching
1454(M)	1468	-	C=C stretching
1412(M)	-	1442	C-O stretching
1363(M)	1399	1396	C-O stretching
1303(M)	1323	1302	C-O stretching
1233(W)	-	1243	C-H in plane deformation
1149(W)	1168	1152	C-H in plane deformation
1110(W)	1095	1115	C-H in plane deformation
1012(W)	1008	1015	C-H in plane deformation
917(VW)	916	913	C-H out plane deformation
846(W)	881	864	C-H out plane deformation
771(W)	797	772	C-H out plane deformation
648(M)	660	643	C-H bending vibration
540(M)	524	532	CO_2 in plane ring rocking
414(VW)	413	419	CO_2 out plane ring deformation

vs - very strong, s - strong, m - medium, w - weak, vw - very weak

Others Vibrations

Aromatic in plane ring deformation occurs in the range 555-495 cm^{-1} [8].The medium intensity band at 540 cm^{-1} belongs to aromatic in plane ring deformation or CO_2 rocking. The out of plane ring deformations produces a medium intensity band at 470-415 cm^{-1} [7]. In aspirin, the band occurs at 414 cm^{-1}.

The theoretical vibrational frequencies for the molecule aspirin calculated by semi-empirical AM1 and PM3 methods are presented in Tables 3 and 4. In the molecule aspirin, the aliphatic symmetric C=C stretching frequency assigned at 1629 cm^{-1} matches well with the calculated value at 1628cm^{-1} by PM3 method. For the same vibration the value at 1648cm^{-1} calculated by AM1 method shows slight deviation from experimental value. The CH bending and CO_2 rocking mode of vibrations assigned to frequencies 648 and 543cm^{-1} calculated by both the semi-empirical methods are in very good agreement with experimental results.

Other molecular properties

Using PM3 and AM1 semi-empirical method several thermodynamic properties of aspirin have been calculated. The values obtained for total energy, zero point energy, entropy computed using the PM3 and AM1 methods are projected in **Table 5**. The difference in the values calculated by both the methods is only marginal.

Table 3. Vibrational wavenumbers obtained for aspirin- at AM1 level: (Wave number (cm^{-1}); IR intensities (km mol^{-1}); reduced mass (amu); and force constants (m dyne A^{-1}))

Frequency	IR Intensity	Reduced Mass	Force constants
41	1.248	10.198	0.0100
52	1.057	9.773	0.0158
82	4.225	3.107	0.0124
92	0.859	4.012	0.0199
124	0.223	1.109	0.0100
145	1.793	4.569	0.0568
168	0.311	6.781	0.1132

251	2.006	3.976	0.1475
335	0.315	6.106	0.4043
368	4.233	5.461	0.4361
413	6.904	3.589	0.3612
444	6.298	3.656	0.4246
490	20.551	7.006	0.9920
524	17.448	2.811	0.4553
541	4.511	3.181	0.5495
543	102.75	1.191	0.2073
567	18.068	4.800	0.9089
642	39.59	5.626	1.3646
661	12.888	6.343	1.6308
705	27.900	4.935	1.4437
797	19.402	3.936	1.4732
826	44.650	1.365	0.5489
881	10.091	5.447	2.4923
916	1.451	1.746	0.8637
950	11.938	3.378	1.7972
983	3.729	1.579	0.8988
1009	0.926	1.730	1.0373
1043	3.1817	1.566	1.0032
1070	13.965	1.583	1.0678
1096	10.457	3.419	2.4198
1168	0.67477	1.338	1.0753
1183	3.982	1.242	1.0242
1199	4.085	1.125	0.9545
1288	4.322	1.329	1.2990
1323	21.819	3.903	4.026
1361	24.476	1.089	1.1893
1369	8.195	1.091	1.2045
1372	53.779	5.268	5.8403
1399	142.144	1.507	1.7387
1434	60.172	1.555	1.8856
1438	327.285	3.590	4.3768
1468	95.434	5.158	6.5529
1542	151.410	3.849	5.3898
1598	53.767	6.363	9.5768
1648	161.079	7.840	12.8484
1761	53.181	11.1091	20.318
1773	32.780	10.938	20.267
2079	256.493	10.3137	26.276
2090	460.817	12.753	32.828
3037	34.081	1.0898	5.924
3067	15.707	1.0928	6.656
3145	11.055	1.0285	5.992
3172	46.232	1.0792	6.399
3179	15.554	1.0772	6.413
3188	100.530	1.0793	6.462
3195	67.787	1.0876	6.541
3418	164.970	1.0631	7.321

Table 4. Vibrational wavenumbers obtained for aspirin- at PM3 level: (Wave number (cm^{-1}); IR intensities ($km\ mol^{-1}$); reduced mass (amu); and force constants (m dyne A^{-1}))

Frequency	IR Intensity	Reduced Mass	Force constants
3086	13.0302	1.0973	6.0847
3167	8.3139	1.0295	9.2983
3851	44.1378	1.0641	6.0857
40	0.7633	6.734	0.0062
42	4.004	4.699	0.005
57	2.355	6.481	0.0128
83	0.3599	1.274	0.0053
87	0.4468	2.614	0.0117
134	0.8055	4.470	0.0476
173	0.3015	7.083	0.1256
236	2.1062	4.267	0.1407
316	3.3625	5.971	0.3516
332	0.9686	4.0908	0.267
403	13.801	6.5728	0.629
419	7.732	3.9667	0.4112
436	12.791	4.3527	0.489
509	97.509	1.2330	0.1885
513	11.323	2.4352	0.3784
531	19.226	4.5866	0.7646
543	6.430	3.1991	0.5572
571	32.711	5.5052	1.0592
643	2.809	5.2683	1.2861
691	22.381	6.1406	1.7322
772	9.9853	2.8285	0.9953
785	35.346	1.3639	0.4961
808	5.785	4.9225	1.8964
864	7.944	2.8743	1.2643
913	3.008	2.1372	1.0511
966	3.1053	1.578	0.8684
970	11.112	2.2779	1.2636
991	6.4624	1.7107	0.9912
1003	4.4071	1.7782	1.0559
1015	0.8862	1.9267	1.1711
1099	0.2863	1.2523	0.8924
1115	1.5178	1.2126	0.8886
1152	0.2338	1.0308	0.8067
1200	0.369	1.2143	1.0309
1225	34.292	5.9012	5.2235
1243	36.0271	1.4113	1.2849
1302	10.7516	10.2514	10.2485
1321	201.722	2.0736	2.9479
1372	19.5595	2.6552	1.6497
1375	51.917	1.4801	1.2502
1381	29.0118	1.1124	2.3331
1396	178.978	2.0299	6.6838
1442	182.245	5.4525	9.7024
1563	75.606	6.734	10.8587
1628	29.285	7.0664	18.9498
1773	16.327	10.2202	19.2662
1789	30.654	10.2164	26.2145
1988	390.171	11.256	30.244
2003	356.171	12.7877	5.9739
3049	11.209	1.0903	5.9872
3053	4.7617	1.0899	6.0451
3062	66.2086	1.0938	6.1023
3073	13.684	1.0966	6.1311
3074	32.251	1.1009	6.1586

Table 5. Theoretically computed energies (a.u.), zero-point vibrational energies (kcal mol^{-1}), rotational constants (GHz), entropies (cal mol^{-1} K^{-1}) and Heat capacity (Kcal Mol^{-1} Kelvin^{-1}) for aspirin

Parameters	AM1	PM3
Entropy	109.442	112.868
Zero point energy	101.042	98.12
Rotational constants	1.0551	1.00928
	0.7562	0.7656
	0.4979	0.503
Energy		
Total	108.416	105.855
Translational	0.889	0.889
Rotational	0.889	0.889
Vibrational	106.638	104.077
Heat capacity	42.125	43.95

CONCLUSION

For a proper understanding of IR spectra, a reliable assignment of all vibrational bands is essential. For this purpose, the quantum chemical methods, ranging from semi empirical to DFT approaches, are invaluable tools, each method having its own advantages. The semi empirical calculations provide very fast, and in certain circumstances fairly good theoretical results, being applicable to large molecular systems. The Hartree-Fock *ab initio* methods are able to give good results provided a reasonable basis set and an appropriate correlation treatment are taken into account. On the other hand, DFT methods have evolved to a powerful quantum chemical tool for the determination of the electronic structure of molecules. Attempts have been made in the present work for predicting the vibrational frequencies for the compound aspirin. The equilibrium geometries and harmonic frequencies of the compound aspirin were determined and analyzed using the semi-empirical methods AM1 and PM3. The difference between the observed and calculated wave number values of most of the fundamental modes in the molecule is very small. Any discrepancy noted between the observed and calculated frequencies may be due to the fact that the calculations have been actually done on a single molecule in gaseous state contrary to the experimental values recorded in the presence of intermolecular interactions.

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