Structural-dynamic models of aspirin isomers in the condensed state

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Abstract. Structural-dynamic models of aspirin are proposed on the basis of non-empirical quantum calculations of geometrical and electronic structure. In this work, the parameters of the adiabatic potential are determined, and the interpretation of the vibrational states of the compound under study is proposed. Structural-dynamic models of its isomers are constructed, the signs of their spectral identification are revealed. The conformational structure of the molecules of the substance under study was analyzed. The choice of the method and the basis for calculating the fundamental vibration frequencies and band intensities in the IR and Raman spectra are substantiated. A method for estimating anharmonic vibrations using cubic and flat force constants is described. The article presents the results of a numerical experiment; the geometrical parameters of the molecules, such as the lengths of the valence bonds and the magnitudes of the angles between them, are determined. The frequencies of the vibrational states and the magnitudes of their integrated intensities are obtained. The interpretation of isomer vibrations is given and compared with the available experimental data. General regularities in the behavior of spectral bands of different isomers are shown. Frequencies that can be used to identify the isomer from the vibrational spectra of molecules are proposed. The calculation was carried out by the DFT/B3LYP density functional quantum method. It is shown that this method can be used to model the geometrical parameters of molecules and the electronic structure of various substituted benzoic acid. It allows to construct structural-dynamic models of the specified class of compounds on the basis of numerical calculations.
Keywords: aspirin, acetylsalicylic acid, benzoic acid, ortho substituted benzoic acid, isomers, vibrational spectra, IR spectra adiabatic potential, anharmonic displacement, hydrogen bond.

1. Introduction

Aspirin, acetylsalicylic acid is known in pharmacology as a compound with a wide range of applications in practical medicine. It can be attributed to orthosubstituted benzoic acid, for which the construction of structural and dynamic models is the subject of a number of scientific publications [7-9,12]. Note that aspirin, like all representatives of the class of carboxylic acids in real conditions, forms dimers, which are characterized by a complex structure of bands in the high-frequency range of the vibrational spectrum. Their interpretation is still a subject of scientific discussions. This is especially true for dimers of benzoic and pyridinecarboxylic acids. In [2,4,6], a technique for analyzing the anharmonic shift of the carboxyl

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fragment bands in monomers and dimers of carboxylic acids, based on quantum mechanical estimates of the adiabatic potential parameters of compounds, is proposed.

The purpose of this report is the construction of structural and dynamic models of possible aspirin isomers in the framework of this technique, the identification of signs of their spectral identification.

2. Mathematical model for estimating anharmonic vibrational states

To describe the anharmonic shift of vibrational states, we use the relation

$$E_{\nu} = \nu_s\left(n_s + 1/2\right) + \chi_{sr}\left(n_s + 1/2\right)\left(n_r + 1/2\right). \quad (1)$$

It is the solution of a model equation for the description of molecular oscillations in the framework of the second-order adiabatic perturbation theory [11].

$$2H^{(\nu)} = \nu_s(P_s^2 + (Q^s)^2) + \mu^{1/4}P_\alpha\mu^{-1/2}P_\beta\mu^{1/4} + \frac{1}{3}F_{srt}Q^sQ^rQ^t + \frac{1}{12}F_{srtu}Q^sQ^rQ^tQ^u\,. \quad (2)$$

The expressions for anharmonic constants χ_{sr} are proposed in publications [2,4,6].

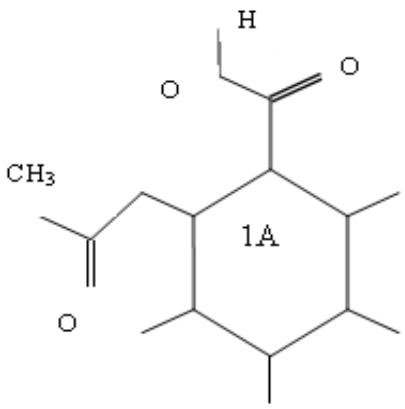
$$\chi_{ss} = \frac{1}{16}F_{ssss} - \frac{5}{48}\frac{\left(F_{sss}\right)^2}{\nu_s} + \frac{1}{32}\left(F_{ssr}\right)^2\left(\Omega(s;s;-r) - \Omega(s;s;r) - 12\Omega(r;r;r)\right)\left(1-\delta_{sr}\right) \quad (3)$$

$$\begin{aligned}\chi_{sr} = {} & \frac{1}{16}F_{ssrr} - \frac{1}{8}\left(F_{ssr}\right)^2\left(\Omega(s;s;-r) + \Omega(s;s;r)\left(1-\delta_{sr}\right)\right) + \\ & + \frac{3}{8}\left(F_{srt}\right)^2\left(\Omega(s;r;t) - \Omega(s;r;-t) + \Omega(s;-r;t) - \Omega(s;-r;-t)\right)\times\left(1-\delta_{sr}\right)\left(1-\delta_{st}\right)\left(1-\delta_{rt}\right) + \\ & + \frac{1}{2}L(a;sr)^2\left(\frac{1}{\left(\nu_s+\nu_r\right)} + \frac{1}{\left(\nu_s-\nu_r\right)}\right)\end{aligned} \quad (4)$$

In relations (1) - (4) $P_\alpha = L(\alpha;sr)Q^s\cdot P_r$; $L(\alpha;sr)$ – the constants of Coriolis,ν_s – harmonic frequencies (in cm-1);Q^s – dimensionless normal vibrational coordinates linearly related to Cartesian atomic displacements; F_{srt} и F_{srtu} – cubic and quartic force constants (parameters of adiabatic potential of a molecule), $\Omega(s; \pm r; \pm t) = (\nu_s \pm \nu_r \pm \nu_t)^{-1}$ – resonance functions, n_s – quantum numbers of the considered vibrational state.

The value of the anharmonic shift of a single band of fundamental oscillation is determined by the value of the anharmonic corrections $X_{ss} = 2\chi_{ss}$ and $X_s = \chi_{sr}/2$.

The set of fundamental oscillations of aspirin isomers presented in tables 1-5 can be divided into three groups: the oscillations of the benzene core (C_6H_4), vibrations of the carboxyl fragment and fragment $OCOCH_3$, which replaces the hydrogen atom of the hydroxyl fragment of salicylic acid (Figure 1). The torsional vibrations of this fragment could not be described by the possibilities of the Gaussian technology [10], therefore, the anharmonic shift of the bands was estimated using the scaling procedure with parameters from the publication [3, 5].



Изомер 1B: CH3 ↔ O

Изомер 2A: OH ↔ O

Изомер 2B: OH ↔ O; CH3 ↔ O

Figure 1. Molecular Diagrams of Aspirin Isomers.

3. Results and discussion

For the benzene fragment, the results of model calculations are presented in Table 1. They are completely consistent with those of the monograph [1] and the nonempirical quantum calculations presented in the publications [3,5]. We only note that the formation of a compound dimer affects only the intensity values of the bands in the IR and Raman spectra.

Table 1. Interpretation of benzene backbone vibrations in aspirin isomers

The form of vibration	$\nu_{эксп}$ [12]	$\nu_м$	Is1A		Is 1B		Is 2A		Is 2B		IR_Dimers			
			IR	Ram	IR	Ram	IR	Ram	IR	Ram	Is 1A	Is 1B	Is 2A	Is 2B
Q,γ,β	1610	1586	59	68	66	66	41	57	41	57	181	183	74	76
Q,γ,β	1583	1566	4.1	8.5	8.7	8.1	26	16	26	16	0.6	4.8	107	92
β,Q	1500	1465	71	8.6	101	9.8	78	10	78	10	124	178	147	177
β,Q	1448	1436	89	2.6	45	3.1	42	1.8	42	1.8	336	54	26	107
Q,β	1290	1292	12	11	21	15	9.3	11	9.3	11	115	66	275	182
β,Q		1259	15	0.9	33	5.2	0.4	2.5	0.4	2.5	59	30	30	76
β	1159	1149	98	35	24	16	251	31	251	31	267	539	265	112
β,Q_{CO}	1120	1116	91	2.5	71	6.4	55	0.4	55	0.4	24	45	12	151
γ,β	1052	1079	11	1.4	3.2	0.5	109	16	109	16	50	17	136	75
Q,β*	-	1037	27	17	24	25	121	8.9	121	8.9	23	25	14	15
γ	830	790	8.4	2.1	19	3.0	7.9	1.4	7.9	1.4	46	52	46	54
γ,γ_{OCO}	735	746	8.7	7.4	21	18	8.1	9.6	8.1	9.6	3.4	33	3.9	17
γ,β_{COC}*	623	658	21	9.7	28	2.7	9.6	11	9.6	11	49	7.1	17	5.5
ρ,χ	729	761	85	0.1	66	66	69	0.1	69	0.1	119	129	122	131
χ	694	709	50	0.6	8.7	8.1	42	0.8	42	0.8	11	9.7	12	76

The data presented in Table 2 confirm the conclusions made in [2] about the characteristics of fundamental vibrations of the carboxyl fragment.

Table 2. The interpretation of the fundamental vibrational states of carboxylic fragment in aspirin isomers

Isomer	Monomer				Dimer					
	$\nu_г$	$\nu_м$	IR	Ram	ν_h	$\nu_м$	IR	ν_h	$\nu_м$	Ram
$Q_{C=O}$										
Is 1A	1781	1721	408	42	1728	1671	1071	1676	1621	206
Is 1B	1777	1717	358	38	1732	1675	916	1677	1622	177
Is 2A	1805	1744	339	56	1752	1694	977	1706	1649	270
Is 2B	1820	1758	208	39	1764	1705	849	1719	1663	256
$\beta_{OH,}$ $Q_{CO,}$ Q_{CC}, β										
Is 1A	1389	1347	99	6.1	1463	1418	21	1521	1473	18
Is 1B	1394	1352	102	7.6	1462	1417	54	1520	1472	11
Is 2A	1363	1322	66	5.1	1456	1411	89	1492	1446	53
Is 2B	1358	1317	54	4.1	1451	1406	122	1485	1438	48
β,β_{OH}, Q_{CC},Q_{CO}										
Is 1A	1207	1172	175	31	1339	1299	886	1335	1295	79
Is 1B	1213	1178	166	38	1335	1295	830	1335	1295	101
Is 2A	1197	1163	153	22	1296	1258	594	1286	1249	77
Is 2B	1197	1163	95	13	1290	1252	523	1281	1243	69
γ_{OCO}										
Is 1A	642	626	36	2.8	663	647	18	660	644	8.9
Is 1B	653	637	28	2.7	650	635	7.1	649	633	12
Is 2A	642	627	57	0.1	665	649	58	663	647	6.1
Is 2B	641	625	91	0.7	670	654	101	665	669	4.5
χ_{OH}										
Is 1A	623	608	49	5.8	1006	979	192	959	933	0.5
Is 1B	624	609	53	5.5	1001	974	175	957	931	0.4
Is 2A	587	573	76	6.7	982	956	187	935	910	0.7
Is 2B	586	572	79	6.1	985	959	192	942	917	0.9

Note. Oscillation(vibration) frequency in cm^{-1}, intensity in IR – km/mol, in Raman – $Å^4$/aем

Let's consider the anharmonic shifts of the bands of valent vibrations of the carboxyl fragment OH bonds in aspirin dimers. The comparison of the results of model calculations in the anharmonic approximation of the theory of molecular vibrations, presented in table 3 for dimers of a number of carboxylic acids, gives grounds to talk about the characteristic of the bands of these oscillations in the frequency of form and intensity. It should be borne in mind that the proximity of the calculated values of the harmonic frequencies of valence bond oscillations OH and OH in dimers of carbonic acids can lead to a redistribution of intensities. This fact is illustrated by table 4, as a result of the capabilities of the numerical methods of Gaussian technology, if the energy gap between the vibrational states is less than 10 cm^{-1}. Note that by choosing the basis you can bypass this problem [2].

Table 5 gives a theoretical interpretation of the stretching(valent) vibrations of the $OOSH_3$ fragment of aspirin isomers. The bands, interpreted as deformation oscillations of this fragment, have, according to model calculations, low intensity in the IR and Raman spectra and are not of interest for problems of spectral identification. The manifestation of the oscillations of the methyl group (CH_3) in the IR and Raman spectra is well known [1].

To identify dimers, the intensity of the IR bands in the range of 1600-1100 cm^{-1} can be used (Table 1). For monomers, bands in the range below 1200 cm^{-1} are used.

Table 3. Interpretation of the valent vibrations of OH bonds of carboxyl fragment of aspirin

Compound	Monomer				Dimer							
	$\nu_г$	$\nu_м$	IR	Ram	ν_h	$\nu_м$	$\nu_{анг}$	IR	ν_h	$\nu_м$	$\nu_{анг}$	Ram
FA	3735	3549	49	78	3239	3091	2930	3239	3128	2988	2776	189
AA	3759	3571	51	102	3223	3076	2906	3122	3116	2977	2746	417
BA	3772	3577	99	137	3192	3048	2955	4639	3088	2951	2728	1070
SA	3757	3569	76	159	3199	3054	2890	4793	3096	2958	2722	1107
Is 1A	3749	3562	73	143	3197 *	3052	-	4998	3099	2961	-	1102
Is 1B	3753	3565	78	149	3223	3076	-	5315	3128	2987	-	1119
Is 2A	3777	3587	90	150	3214	3067	-	5613	3116	2977	-	1134
Is 2B	3777	3587	90	152	3213	3067	-	5676	3115	2975		1120

Note. Designation: FA, AA, BA, SA - formic, acetic, benzoic, salicylic acids, respectively.

Table 4. Interpretation of the valence vibrations of CH bonds of the benzene backbone of aspirin

$\nu_г$	$\nu_м$	Is 1A		Is 1B		Is 2A		Is 2B	
		IR	Ram	IR	Ram	IR	Ram	IR	Ram
Monomers									
3270	3120	7.2	58	6.3	120	7.6	56	5.5	117
3219	3072	4.1	115	8.0	18	1.4	99	1.2	100
3203	3056	12	163	5.6	121	15	187	9.6	16
3184	3039	5.3	81	11	156	4.8	81	14	185
Dimers									
3262	3112	14	136	0,2	196	14	131	0,3	184
3224	3077	17	193	224	198	2.5	188	4,8	190
3191*	3046	717	388	74	357	161	417	167	394
3173	3030	7.3	186	11	193	7.6	189	9,1	192

Table 5. Interpretation of the valent vibrations of the acetyl fragment of aspirin

$\nu_г$	$\nu_м$	IR	Ram	IR	Ram	$\nu_г$	$\nu_м$	IR	Ram	IR	Ram
		Monomer		Dimer				Monomer		Dimer	
$Q_{C=O}$ (1719 [12])						q_{CO} (1229 [12])					
1821	1759	203	22	496	27	1216	1181	169	32	954	8.9
1838	1776	341	39	669	61	1202	1167	127	39	464	4.1
1822	1759	271	11	579	21	1214	1180	307	3.7	1012	9.1
1842	1778	447	47	749	57	1191	1156	425	17	857	19
Q_{OC}						Q_{CC}					
1238	1202	640	29	457	129	938	913	27	2.1	46	6.1
1246	1212	508	32	585	137	937	912	29	2.5	65	5.8
1239	1203	313	48	570	127	938	913	34	1.5	46	5.1
1252	1215	369	37	676	147	936	911	36	2.7	66	5.3

According to the results of optimization of the geometry of the conformational models of aspirin (Fig. 1), the distance between the oxygen atoms of the carboxylic fragment and the fragment $OCOCH_3$ exceeds the value 2.5 Å. For the hydrogen atoms of the methyl group and the oxygen atoms of the carboxyl fragment, the distance is more than 3.1 Å. The effect of intramolecular interaction on the position of the bands of the fragment $OCOCH_3$ can be neglected, as evidenced by the data in Table 5.

4. Conclusion

The conducted numerical experiment for monomers and dimers of acetyl salicylic acid allows us to state that the manifestation of fundamental vibrations of the carboxyl fragment in the monomers and dimers of the compound has the same character as in various ortho-substituted ones of benzoic acid**.** The effect of the carboxyl fragment on the character of the substituent bands in the ortho position of the benzene backbone is determined by the interatomic distance between the atoms of the carboxyl fragment.

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