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 ortho substituted 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
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

\[ E_v = v_s(n_s + 1/2) + \chi_{sr}(n_s + 1/2)(n_r + 1/2) \]  

(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].

\[ 2H^{(v)} = v_s(P_s^2 + (Q^s)^2) + \mu^{1/4}P_a\mu^{1/4}P_b\mu^{1/4} + \frac{1}{3}F_{sr}Q'Q'' + \frac{1}{12}F_{srut}Q'Q'Q'' . \]  

(2)

The expressions for anharmonic constants \( \chi_{sr} \) are proposed in publications [2,4,6].

\[ \chi_{ss} = \frac{1}{16}F_{ssss} - \frac{5}{48}(F_{ss})^2v_s + \frac{1}{32}(F_{ss})^2(\Omega(s,s;\pm r) - \Omega(s,s;r) - 12\Omega(r,r,r)(1 - \delta_{sr})) \]  

(3)

\[ \chi_{sr} = \frac{1}{16}F_{srss} - \frac{1}{8}(F_{ss})^2(\Omega(s,s;\pm r) + \Omega(s,s;r)(1 - \delta_{sr})) + \frac{3}{8}(F_{ss})^2(\Omega(s,s;\pm t) - \Omega(s,s;r) - 12\Omega(r,r,s)(1 - \delta_{sr})(1 - \delta_{rt})) + \frac{1}{2}L(s,s;r) \]  

(4)

In relations (1) - (4) \( P_\alpha = L(\alpha;sr)Q' \cdot P_\alpha; L(\alpha;sr) \) – the constants of Coriolis, \( \nu_s \) – harmonic frequencies (in cm\(^{-1}\)); \( Q' \) – dimensionless normal vibrational coordinates linearly related to Cartesian atomic displacements; \( F_{sr} \) and \( F_{srut} \) – cubic and quartic force constants (parameters of adiabatic potential of a molecule), \( \Omega(s; \pm r; \pm t) = (\nu_s \pm \nu_r \pm \nu_t) \) – 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 \( \chi_{ss} = 2\chi_{ss} \) and \( \chi_{sr} = \chi_{sr}/2 \).

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\(_6\)H\(_4\)), vibrations of the carboxyl fragment and fragment COCH\(_3\), 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].
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.

![Molecular Diagrams of Aspirin Isomers](image)

**Figure 1.** Molecular Diagrams of Aspirin Isomers.

| The form of vibration | \(\nu_{\text{asc}}\) | \(\nu_{\text{st}}\) | Is 1A | Is 1B | Is 2A | Is 2B | IR_Dimers |
|-----------------------|----------------|----------------|------|------|------|------|-----------|
| \(Q,\gamma,\beta\)    | 1610 | 1586          | 59   | 68   | 66   | 66   | 41 57    | 41 57    | 181 183 | 74 76 |
| \(Q,\gamma,\beta\)    | 1583 | 1566          | 4.1  | 8.5  | 8.7  | 8.1  | 26 16    | 26 16    | 0.6     | 4.8 107 | 92   |
| \(\beta,\gamma\)     | 1500 | 1465          | 71   | 8.6  | 101  | 9.8  | 78 10    | 78 10    | 124 178 | 147 177 |
| \(\beta,\gamma\)     | 1448 | 1436          | 89   | 2.6  | 45   | 3.1  | 42 1.8   | 42 1.8   | 364 36   | 26 107 |
| \(Q,\beta\)         | 1290 | 1292          | 12   | 1   | 21   | 15   | 9.3 11   | 9.3 11   | 115 66   | 275 182 |
| \(\beta,\gamma\)     | 1259 | 1586          | 15   | 0.9  | 33   | 5.2  | 0.4 2.5  | 0.4 2.5  | 59 30    | 30 76   |
| \(\beta\)           | 1159 | 1149          | 98   | 35   | 24   | 16   | 251 31   | 251 31   | 267 539  | 265 112 |
| \(\beta,\gamma\)     | 1120 | 1116          | 91   | 2.5  | 71   | 6.4  | 55 0.4   | 55 0.4   | 24 45    | 12 151  |
| \(\gamma,\beta\)    | 1052 | 1079          | 11   | 1.4  | 3.2  | 0.5  | 109 16   | 109 16   | 50 17    | 136 75  |
| \(Q,\beta^*\)       | -    | 1037          | 27   | 17   | 24   | 25   | 121 8.9  | 121 8.9  | 23 25    | 14 15   |
| \(\gamma\)         | 830  | 790           | 8.4  | 2.1  | 19   | 3.0  | 7.9 1.4  | 7.9 1.4  | 46 52    | 46 54   |
| \(\gamma,\beta,\gamma\) | 735  | 746           | 8.7  | 7.4  | 24   | 18   | 8.1 9.6  | 8.1 9.6  | 3.4 33   | 39 17   |
| \(\gamma,\beta,\gamma\) | 623  | 658           | 9.7  | 2.7  | 28   | 2.7  | 9.6 11   | 9.6 11   | 49 7.1   | 17 5.5  |
| \(\rho,\chi\)     | 729  | 761           | 85   | 0.1  | 66   | 6.6  | 69 0.1   | 69 0.1   | 119 129  | 122 131 |
| \(\chi\)           | 694  | 709           | 50   | 0.6  | 8.7  | 8.1  | 42 0.8   | 42 0.8   | 11 9.7   | 9.7 12   |

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 |
|--------|---------|-------|
|        | νг      | νм     | IR | Ram | νг | νм | IR | Ram |
|        | Q_{C=O} | β_{OH,Q_{C=O},Q_{CC},β} | γ_{OCO} | β_{OH} | Q_{C=O} | γ_{OH} |
| 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 |

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

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\textsubscript{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\textsubscript{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\textsuperscript{-1} can be used (Table 1). For monomers, bands in the range below 1200 cm\textsuperscript{-1} are used.
Table 3. Interpretation of the valent vibrations of OH bonds of the carboxyl fragment of aspirin

| Compound | Monomer | Dimer |
|----------|---------|-------|
|          | (ν<sub>r</sub>, ν<sub>s</sub>) | (IR, Ram) | (IR, Ram) | (IR, Ram) | (IR, Ram) | (IR, 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       | 3777, 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 | - |
| Is 1B    | 3755, 3565 | 78, 149 | 3223, 3076 | 3128, 2987 | - | 1119 |
| Is 2A    | 3777, 3587 | 90, 150 | 3214, 3067 | 3116, 2977 | - | 1134 |
| Is 2B    | 3777, 3587 | 90, 152 | 3213, 3067 | 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

| ν<sub>r</sub> | ν<sub>s</sub> | Is 1A | Is 1B | Is 2A | Is 2B |
|--------------|--------------|-------|-------|-------|-------|
|              |              | 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         | 71    | 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 valence vibrations of the acetyl fragment of aspirin

| ν<sub>r</sub> | ν<sub>s</sub> | IR | Ram | IR | Ram | IR | Ram |
|--------------|--------------|----|-----|----|-----|----|-----|
| Monomer      | Dimer        |    |     |    |     |    |     |
|              |              |    |     |    |     |    |     |
| 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<sub>cc</sub> (1219 [12])

| Q<sub>cc</sub> | Q<sub>CC</sub> |
|----------------|--------------|
| 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 OCOCH₃ 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 OCOCH₃ 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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