

IR spectra of paracetamol

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Abstract

Paracetamol is a very popular medication used to treat pain and fever. IR spectra of paracetamol have been measured for powder crystals. Ab initio calculations of its equilibrium geometry and vibrational spectra were carried out for spectrum interpretation. Differences between the experimental IR spectra of crystalline samples have been analyzed. Variations of molecular structure from the isolated state to molecular crystal were estimated based on the difference between the optimized molecular parameters of free molecules and the experimental bond lengths and angles evaluated for the crystal forms of the title compounds. The role of hydrogen bonds in the structure of molecular crystals of paracetamol is investigated.

Keywords: Pharmaceuticals; Ab initio calculation; Molecular crystals; Hydrogen bond; Intermolecular interaction

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Introduction

Paracetamol (acetaminophen) is widespread pharmaceuticals with anti-fever activities. The biological activity and the pharmaceutical properties of drugs are strongly dependent on their structure. The structural formulas and some physicochemical properties of these compounds have been known for decades. Detailed investigations of their crystal forms, however, were started in recent years. For paracetamol, three polymorphic modifications were described (Haisa *et al.*, 1974; Haisa *et al.*, 1976; Nichols and Framp-ton, 1998; Szelagiewicz *et al.*, 1999). Molecular spectroscopy methods, in particular, experimental IR spectroscopy, have long been successfully employed for structure investigations of complex molecular compounds. These techniques are especially effective when used in combination with direct methods of structural analysis in hydrogen bond investigations.

At present, few works reporting the IR spectra of paracetamol are available. Thus IR spectra have been published

for three of its crystal modifications, and an assignment of the most intense bands has been suggested (Szelagiewicz *et al.*, 1999). The first and, to the best of our knowledge, the single spectroscopic work with full quantum-chemical calculation of the structure and vibrational spectrum of paracetamol appeared in 1998 (Binev *et al.*, 1998). The vibrational spectrum calculated with a good (DFT/SDD) basis set and with appropriate scaling of frequencies was successfully correlated with the experimental IR spectrum of paracetamol. Full spectrum assignment was made based on the calculation using the shapes of normal vibrations in accordance with the potential energy distribution over internal coordinates.

The aim of the present work is theoretical and experimental spectroscopic investigation of free molecules and molecular crystals of paracetamol to gain insight into the structure and role of hydrogen bonds in their molecular crystals.

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Materials and methods

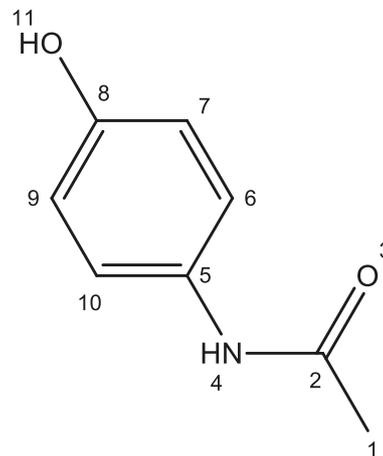
Paracetamol commercial samples were purified by recrystallization from an ethanol solution. The orthorhombic modification of paracetamol was obtained from a melt according to the procedure described in (Politov *et al.*, 2001).

IR spectra were recorded on a ShemadzuIRPrestige-21 with mid-near-far infrared measurement range Fourier Transformed IR spectrometer (resolution 4 cm^{-1}) for KBr pellets (2 mg sample with 500 mg KBr). Attempts were made to monitor the intermolecular interactions in solutions according to changes in the spectra. For spectrum measurements in the near IR range (400 cm^{-1} - 4000 cm^{-1}), was used. Diffuse scattering spectra of paracetamol powders were recorded, which were subsequently converted into absorption spectra. Ab initio calculation of equilibrium geometry and normal vibration frequencies for paracetamol molecules was carried out using the Gaussian-94/DFT program.

Results and discussions

Ab initio quantum-chemical calculation of the structure and vibrational spectra of paracetamol molecules was carried out in a density functional theory (DFT) approximation using hybrid (B3LYP) potentials (Becke, 1993). The DFT method provides the best agreement with experiment for vibrational frequencies and is considered to be the most suitable technique for spectrum calculations of moderately large molecules (Johnson *et al.*, 1993). The standard 6-31G* basis set was used. For geometry optimization for paracetamol, the Cartesian atomic coordinates obtained from structure determination of the monoclinic modification were specified as initial data (Haisa *et al.*, 1976). The optimized geometry of paracetamol with the OH group replaced by the ethyl fragment was given as the initial structure for geometry optimization of clonazepam. Frequency assignment for normal vibrations was fulfilled by analyzing atomic displacements in Cartesian coordinates, by calculating the potential energy distribution over internal coordinates (bond lengths and angles, dihedral angles, and coordinates of bond departure from the molecular plane), and by calculating the potential and kinetic energy distribution over the molecular fragments $-\text{CH}_3$, $-\text{C}=\text{O}$, $-\text{NH}$, $-\text{C}_6\text{H}_4$, and $-\text{O}-\text{H}$ (for paracetamol) or $-\text{CH}_2\text{CH}_3$ (for clonazepam), or over larger fragments: phenyl, amide, and $-\text{O}-\text{H}$ or $-\text{CH}_2\text{CH}_3$. Optimization gave planar conformations (with the phenyl and amide fragments lying in the same plane) for both molecules (Fig. 1). The calculated normal vibration frequencies and their assignment are given in Table 1. Due to dissolution, bioavailability and absorption, the molecular form and crystal form of paracetamol impart differences in physicochemical and pharmacological properties.

Theoretical spectra of paracetamol:



Structure of paracetamol

The X-H high-frequency vibrations above 2900 cm^{-1} (Table 1) are completely localized on the corresponding molecular fragments of paracetamol namely, on $-\text{OH}$, $-\text{NH}$, $-\text{C}_6\text{H}_6$, $-\text{CH}_3$, and $-\text{CH}_2\text{CH}_3$. The nearly free rotation of the methyl group noted (Wilson and Struct, 1997) for the monoclinic modification of crystalline paracetamol is evidently also due to the minor changes in the parameters of the methyl fragment in the molecular crystal compared to the free methyl group.

The frequencies in the range 1682 cm^{-1} - 1530 cm^{-1} are due to the stretching vibrations of the phenyl ring; the highest frequency is completely localized on the phenyl ring in both molecules, and the other frequencies are mixed with the vibrations of the amide fragment. The largest contribution to the potential energy of these mixed vibrations is from the variation of the NCH bond angle in the plane of the molecule. For lower frequencies from this range, the contributions from the amide and phenyl fragments are approximately the same. Based on the potential energy distribution over the internal coordinates, these vibrations are in a certain sense attributable to the band that is interpreted in experimental spectroscopy as the second band of the amide group. It should be noted, however, that none of the vibrations in this range is localized on the amide fragment.

In the range 1500 cm^{-1} - 1300 cm^{-1} , the C-C stretching vibrations of the phenyl group are mixed with the deformation vibrations of the amide methyl fragments are also mixed with the deformation vibrations of the ethyl group. The potential energy of the low frequencies of this range has a contribution from the variation of the CO and CN bonds, but this contribu-

tion is too low (20%) to assign any of these frequencies to the stretching vibrations.

The vibrations in the range 1291 cm^{-1} - 950 cm^{-1} are in-plane deformation vibrations of the C–H bonds of the phenyl ring, which are mixed [except the 1155 (1154) cm^{-1} frequencies with the stretching and deformation vibrations of the amide-fragment. Starting from 952 cm^{-1} for paracetamol, one can observe the out-of-plane deformation vibrations of the phenyl C–H bonds; these are mixed with the deformation vibrations of the C–C bonds accompanied by the departure of the carbon atoms from the plane of the phenyl ring. Some of these are completely localized on the phenyl fragment, while the others are mixed with the deformation and out-of-plane vibrations of the amide group. The frequencies below 600 cm^{-1} correspond to the in-plane and out-of-plane (alteration of the dihedral angles between the planes of the phenyl and amide groups) vibrations of molecules and are not localized on any fragments.

Thus, our calculations enabled us to assign the calculated frequencies within the framework of the group frequency-concept, which is conveniently used for interpreting the experimental data.

The calculated frequencies of free paracetamol molecules are similar to the frequencies in the experimental spectra. Therefore, one can conclude that the calculated molecular parameters (bond lengths and angles, dihedral angles, and force con-

stants) are similar to the corresponding parameters of free molecules.

Our DFT calculation is slightly better in reproducing the experimental frequencies of paracetamol than the calculation of (Binev *et al.*, 1998). The maximal divergence of the unscaled frequencies is 435 cm^{-1} in [14] and 96 cm^{-1} in our calculation. It seemed useful to give our assignment of the calculated normal vibration frequencies for paracetamol (Table 1), although it does not differ fundamentally from (Binev *et al.*, 1998)

For the spectra of solutions, the assignment of the experimental 3600 cm^{-1} and 3438 cm^{-1} absorption bands (ABs) to the OH and NH stretching vibrations in paracetamol. The weak ABs above 3000 cm^{-1} are also unambiguously assigned to the C–H stretching vibrations of the phenyl ring, and the stronger bands above 2800 cm^{-1} are attributed to the stretching vibrations of the methyl and ethyl groups (Fig. 2, 1, 2; Table I).

The intermolecular interactions are most conspicuous in this spectral region because of the displacement and broadening of the absorption bands caused by hydrogen bonding. Interpreting the spectral region above 2500 cm^{-1} is complicated by the presence of overtones and composite frequencies. In view of the Fermi resonance, the intensity of these bands may be anomalously high. The presence of harmonic frequencies in great numbers in the spectra of paracetamol is

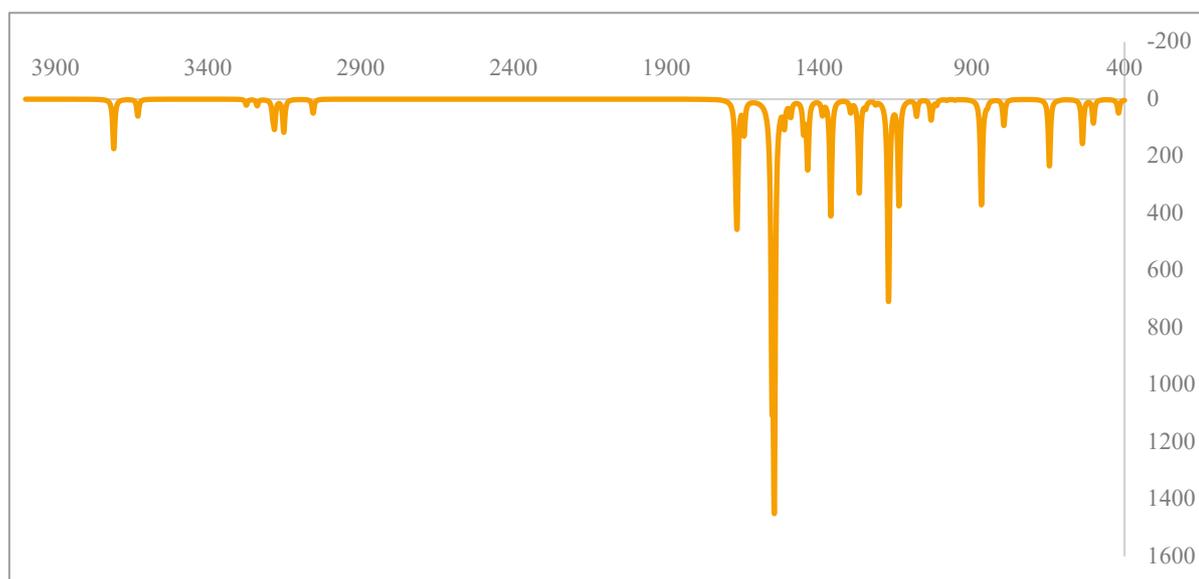


Fig. 1. Theoretical IR of paracetamol

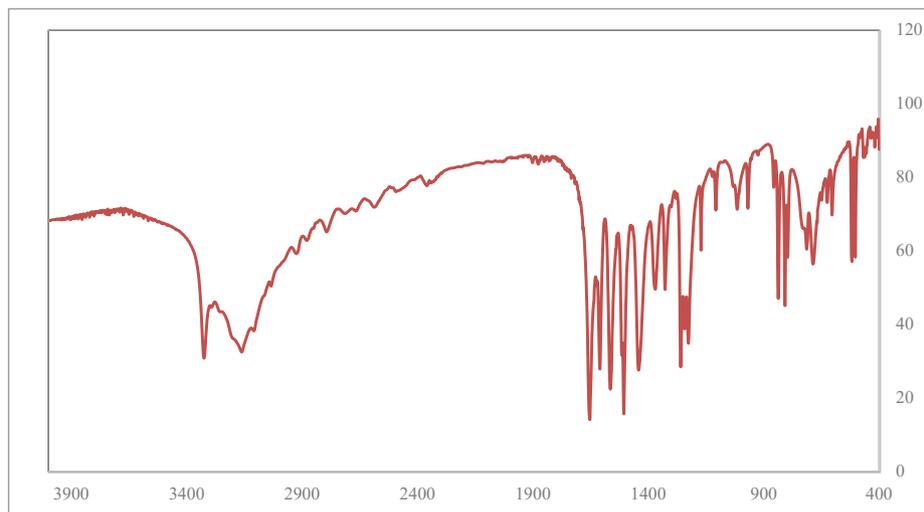


Fig. 2. Experimental IR of ACE

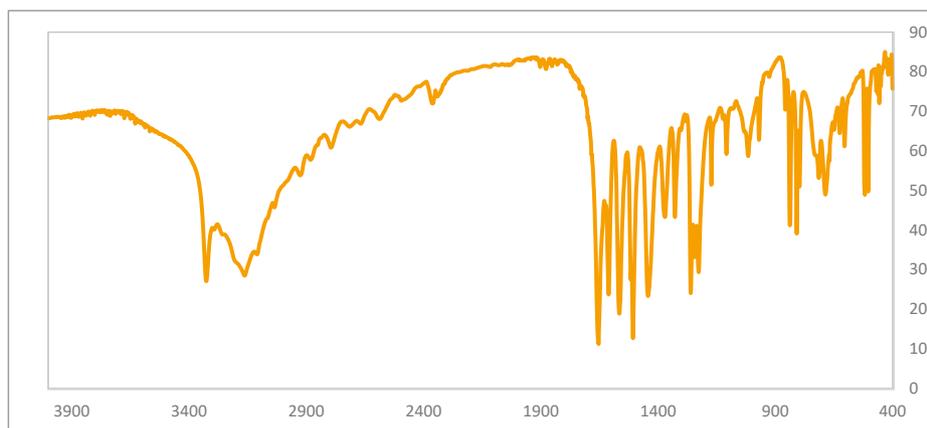


Fig. 3. Experimental IR of Fast

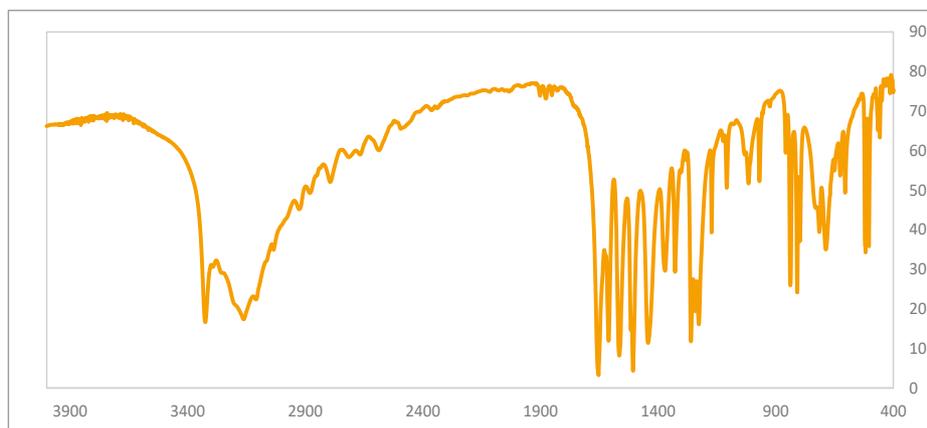


Fig. 4. Experimental IR of Napa

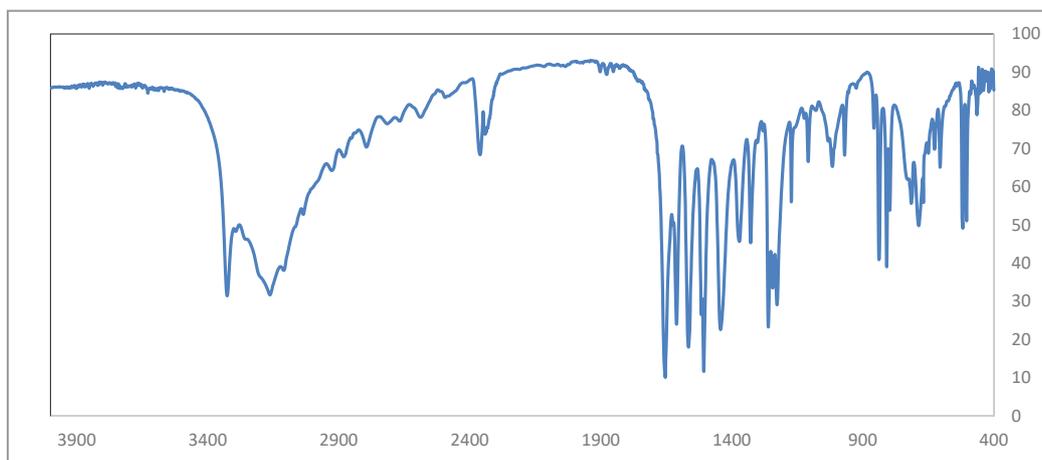


Fig. 5. Experimental IR of Glasco paracetamol

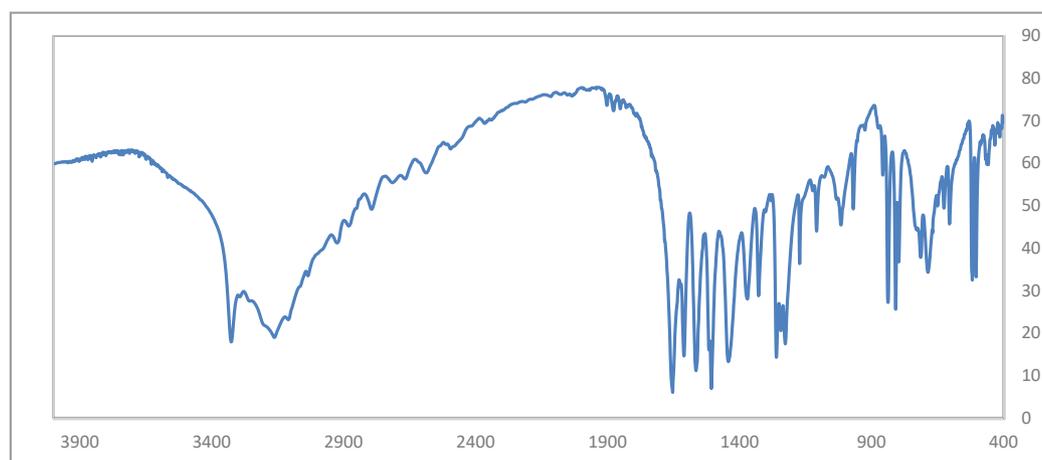


Fig. 6. Experimental IR of Tamen

also confirmed by the experimental spectra of the crystalline powders in the near IR region (Fig. 4).

According to our calculation, the intense 1683 cm^{-1} band of a paracetamol solution and the 1679 cm^{-1} band of a clonazepam solution (nonpolar solvents in both cases) correspond to the first band of the amide group, more than 57% of their potential energy reflecting the state of the C=O bond. In the spectra of the two crystal modifications of paracetamol and crystalline clonazepam, the frequency of this vibration is 20 cm^{-1} - 30 cm^{-1} lower than that in the spectra of the molecular forms. For the monoclinic modification of paracetamol, this is a single vibration band (1654 cm^{-1}); for the orthorhombic modification, there are two bands (1667 cm^{-1} and 1656 cm^{-1}).

In the range 1625 cm^{-1} - 1000 cm^{-1} , the spectra of the solutions and crystal forms of paracetamol (Fig. 3, 1, 3, 4) differ mainly in the relative intensity and in the number of absorption bands, while the position of the fundamental bands changes insignificantly and the experimental spectra are rather close to the theoretical spectra (Table I).

Below 1000 cm^{-1} , the spectra of solutions could not be obtained for any of compounds because of solvent absorption and the narrow spectral ranges of solvent transparency, leading to unreliable spectrum subtraction. Therefore in the range 1000 cm^{-1} - 400 cm^{-1} , Fig. 3 shows only the spectra of the crystal forms of the compounds. The assignment of the relevant absorption bands in the spectra of the crystalline samples based on the assignments in the theoretical spectra

Table I. Comparison of theoretical and experimental vibrational frequencies of paracetamol

Serial No.	Types of Vibration	Theoretical (cm ⁻¹)	Experimental (cm ⁻¹)
1	V _{OH}	3710	3325
2	V _{NH}	3631	3292
3	V _{PhH}	3275	3254
4	V _{PhH}	3240	3198
5	V _{PhH}	3184	3162
6	V _{CH3}	3153	3107
7	V _{CH3}	3056	3062, 3034
8	V _{Ph(C=C)}	1669	1654
9	V _{C=O}	1668	1610
10	V _{C=O+CNC+Ph}	1452	1564, 1506
11	V _{CH3}	1438	1440
12	V _{Ph(C=C)}	1389	1369
13	V _{PhH}	1362	1328
14	V _{NH(Bening)}	1297	
15	V _{C-O}	1269	1260
16	V _{NCH(Bening)}	1215	1243
17	V _{CN}	1173	1226
18	V _{Ph(Ring)}	1139	1172
19	V _{CH3}	1081	1108
20	V _{Ph(Ring deformation)}	1033	1015
21	V _{Ph(Ring deformation)}	863	808
22	V _{Ph(Ring deformation)}	795	796
23	V _{Ph(Ring deformation)}	646	686
24	V _{Ph(Ring deformation)}	538	517
25	V _{Ph(Ring deformation)}	501	503

seems to be quite correct because of good agreement between the theoretical and experimental frequencies (Table I).

Spectral features indicative of intermolecular interactions. The molecular crystals of paracetamol are suitable model systems for investigating intermolecular interactions. The paracetamol molecule includes two potential donor (N-H and O-H) and two acceptor (C=O and H-O) groups. The

OH group is both proton donor and acceptor (-NH...OH...O=C-), while the NH group is a proton donor alone.

The difference between the optimized parameters of the free paracetamol and the experimental bond lengths and angles of their crystal forms is associated with the presence of hydrogen bond systems in the crystals of these compounds (Haisa

et al., 1974; Haisa *et al.*, 1976; Yuasa and Akutagava, 1996; Nichols and Frampton, 1998; Szlagiewicz *et al.*, 1999; Hendriksen *et al.*, 1998; Naumov *et al.*, 1998; Wilson and Struct, 1997; Wilson *et al.*, 1997; Wilson and Kristallogr, 2000; Boldyreva *et al.*, 2000; Boldyreva *et al.*, 2002).

The difference between the spectra of crystalline powders and those of diluted solutions of paracetamol, which is especially conspicuous in the region of the X–H stretching vibrations, is a spectral indication to the presence of a system of hydrogen bonds in paracetamol and clonazepam crystals.

The large shifts of these frequencies compared to the spectra of solutions, as well as the complex shape of the absorption contours, point to the presence of a system of strong hydrogen bonds (NH...O and OH...O) in the molecular crystals of both modifications of paracetamol and NH...O in the molecular crystals of clonazepam. This agrees with the results of diffraction studies (Haisa *et al.*, 1974; Haisa *et al.*, 1976; Yuasa and Akutagava, 1996; Nichols and Frampton, 1998; Hendriksen *et al.*, 1998; Naumov *et al.*, 1998; Wilson and Struct, 1997; Wilson *et al.*, 1997; Wilson and Kristallogr, 2000; Boldyreva *et al.*, 2000; Boldyreva *et al.*, 2002) including studies at reduced temperatures and elevated pressures.

The lowering of the ν_{XH} frequency due to hydrogen bonding compared to the spectrum of the free molecule is a direct measure of hydrogen bond strength. Therefore, one can assume that in the monoclinic modification of paracetamol, the O–H...O hydrogen bonds ($\Delta\nu_{\text{VOH}} = 440 \text{ cm}^{-1}$) are slightly stronger than those in the orthorhombic modification ($\nu_{\text{VOH}} = 400 \text{ cm}^{-1}$). This agrees with the conclusions based on the diffraction analysis of the geometrical parameters of hydrogen bonds (Boldyreva *et al.*, 2002; Boldyreva *et al.*, 2002).

Similarly, from the shifts of the ν_{NH} frequencies ($\Delta\nu_{\text{NH}} = 110 \text{ cm}^{-1}$) one can assume that in both crystal modifications of paracetamol, the N–H...O hydrogen bonds are approximately equal in stability and are less stable than the N–H...O hydrogen bonds in clonazepam crystals ($\Delta\nu_{\text{NH}} = 153 \text{ cm}^{-1}$). As intermolecular hydrogen bonding in the latter is only possible to NH groups, one would expect that the NH stretching vibration frequency will decrease more drastically compared to the spectrum of the free molecule. Indeed, in the crystal forms of paracetamol, the ν_{NH} frequency has a 44 cm^{-1} smaller shift than in clonazepam crystals relative to the position of this frequency in the molecular state that is free from hydrogen bonds.

The C=O bond length was calculated to be 1.226 Å (Fig. 1) for the optimized structure of free paracetamol and clonazepam molecules, 1.235 Å for monoclinic paracetamol, and 1.241 Å for crystalline clonazepam. The larger C=O bond length and the correspondingly decreased $\nu_{\text{C=O}}$ frequency unambiguously indicate that hydrogen bonding leads to a redistribution of electron density.

In the spectra of both crystalline modifications of paracetamol and crystalline clonazepam, the frequencies in the range 1660 cm^{-1} –1640 cm^{-1} , reflecting the state of the C=O bond (denoted for simplicity $\nu_{\text{C=O}}$), are 20 cm^{-1} –30 cm^{-1} lower than in the spectra of the molecular form. This is another indication to strong intermolecular interactions involving the C=O bond in crystals.

We traced the effect of intermolecular interactions on the $\nu_{\text{C=O}}$ frequency in the spectra of DMSO solutions of paracetamol and clonazepam. The $\nu_{\text{C=O}}$ frequency was slightly shifted in both paracetamol and clonazepam solutions depending on the solution concentration; it was roughly the same—around 1670 cm^{-1} , which is lower than in the molecular form and higher than in crystal forms. Probably, the formation of hydrogen bonds between the S=O group of DMSO and the NH and OH groups of paracetamol, as well as the NH group of clonazepam, also leads to an electron density redistribution on the C=O bond, which is manifested as the decreased $\nu_{\text{C=O}}$ frequency.

The larger shift of $\nu_{\text{C=O}}$ in the monoclinic form of paracetamol versus the orthorhombic form relative to the same frequency in a molecule that is free from hydrogen bonds also points to stronger hydrogen bonds in the monoclinic modification of paracetamol.

Conclusion

The calculated molecular parameters (bond lengths and angles, dihedral angles and force constants) are similar to the corresponding parameters of free molecules. The intermolecular interactions are most conspicuous in this spectral region because of the displacement and broadening of the absorption bands caused by hydrogen bonding. The difference between the spectra of crystalline powders and those of diluted solutions of Paracetamol which is especially clear in the region of X–H stretching vibrations, is a spectral indication to the presence of a system of hydrogen bonds in paracetamol. The $\nu_{\text{C=O}}$ frequency was slightly shifted in Paracetamol solutions depending on the solution concentration; it was roughly the same around 1670 cm^{-1} which is lower than in the molecular form and higher than in crystal forms.

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