Modeling the Solid-state Vibrational Spectroscopic Properties of Morphine-based Formulations With Hybrid Meta Density Functional Theory

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***Abstract*—Solid state vibrational spectroscopic properties of morphine sulphate pentahydrate were studied combining experimental and theoretical approaches. Experimental studies involved a Fourier Transform infrared spectroscopic (FT IR) study of the title compound with the attenuated total reflection (ATR) technique. From theoretical side, a detailed study of the main possible constituents of the investigated molecular crystals: neutral morphine molecule and *N*-protonated morphine-H^+ cation was carried out, employing meta hybrid density functional theory (DFT) approach with the M06-2X exchange-correlation functional, using 6-311G(*d,p*) basis set. Potential energy surfaces (PES) of the studied systems were explored in details, paying particular attention to the intramolecular torsional flexibility. In both cases, four stable minima on the explored PES were located. Subsequently, harmonic vibrational analyses were carried out for each minimum, with the method of diagonalization of the mass-weighted Hessian matrices. Experimental data strongly suggest the presence of hydrogen sulphate anionic species in the investigated solid phase. Accounting for the stoichiometry of the compound, it is suggested that both neutral (unprotonated) morphine along with the *N*-protonated morphine-H^+ cation could be present in the solid state as well. The agreement between experimental and theoretical spectra in the regions of appearance of bands due to morphine (or *N*-protonated morphine-H^+ cation) intramolecular vibrational modes is remarkable. Thus, the present theoretical calculations enable solid theoretical support to the empirical assignments of the spectral bands and the present work could serve as a starting point for further studies of spectroscopic manifestations of morphine incorporation into specific drug dosage forms.**

Keywords—morphine; morphine sulphate pentahydrate; IR spectra; solid-state spectroscopy; computational chemistry; density functional theory; computational vibrational spectroscopy

I. INTRODUCTION

Usage of modeling and/or simulation tools for virtual prediction of material properties of the active pharmaceutical ingredient (API) and excipients prior to experimental work is a major step forward in the design, development and optimization of the new drug dosage forms (DDF), that should result with reduced cycle time and costs at minimal possible levels.

In this context, in-depth understanding of the intermolecular interactions between the excipients present in the specific DDF and the API is crucial. In numerous studies of a wide variety of intermolecular interactions of this type, vibrational spectroscopies (infrared as well as Raman) have been used as valuable tools to judge on the character and strength thereof, as the intramolecular vibrational modes are rather sensitive probes to changes in the intermolecular environment and molecular surrounding in general. To be able to monitor the changes in the spectral features of a given API upon its incorporation into specific DDF, one has to make certain comparisons with the situation encountered in a free or reference system containing the same molecule.

Efficient treatment of pain, especially of moderate-to-severe chronic pain is still a major medical challenge. Clinically, morphine (Fig. 1) remains the most used opioid analgesic drug currently available and it is recommended as the drug of choice for treatment of moderate and severe pain by the World Health Organization [1]. Having in mind the problems associated with the conventional oral DDF, development of modified release morphine formulations is desirable in order to achive reduced toxicity, improved efficacy, life quality and patient compliance [2].

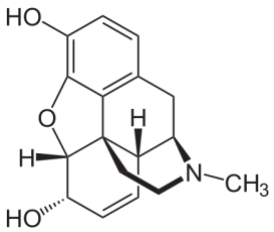

Fig. 1. Structural formula of morphine.

The two most widely used "classical" forms of morphine are morphine sulphate pentahydrate and morphine hydrochloride. Aside from the medical significance of the title compound that has been extensively studied, available literature data related to the detailed analysis of the vibrational spectra of the two most commonly encountered forms of the API are limited [3,4]. To bridge the gap between the understanding of its affinities towards incorporation into specific DDF and the properties of starting (reference system), in the present study we aim to provide theoretically-based in-depth understanding of vibrational spectroscopic properties of solid-phase morphine sulphate pentahydrate, combining a state-of-the-art quantum chemical computational technique, based on meta hybrid density functional theory approach, and experimental Fourier Transform infrared spectroscopy (FT-IR).

II. Computational Details

A. General Theoretical Methodology

Preliminary investigations of the potential energy surface (PES) of morphine molecule, as well as of the *N*-protonated morphine-H^+ were carried out at several semiempirical levels of theory, based on AM1 [5], PM3 [6] and PM6 [7] model Hamiltonians, as well as with density functional tight binding approach (DFTB [8,9]). As the free morphine molecule as well as its *N*-protonated derivative possess certain conformational flexibility, mainly with respect to torsional motions of the two O-H groups, such preliminary investigations of the PESs appeared to be rather cost-effective from a computational aspect. Starting from the minima located on these preliminary explored PESs, further, productive geometry optimizations of the two explored systems were carried out employing hybrid meta density functional theory (DFT). This was done using Schlegel's gradient optimization algorithm [10], computing the second derivative matrix at the starting point of each search for the stationary points on the explored PES. Subsequently to location of the stationary points on the studied PESs, harmonic vibrational analyses were performed. Computation and sequential diagonalization of the mass-weighted second-derivative matrices (Hessians) enabled calculations of harmonic vibrational frequencies and deriving conclusions concerning the character of the particular stationary point on the corresponding PES. Absence of imaginary frequencies (negative eigenvalues of the Hessian) indicated that a true minimum is in question (instead of a saddle point on the PES).

B. The Hybrid Meta Density Functional Theory Approach

The productive calculations for the purpose of the present study have been carried out with the hybrid meta exchange-correlation functional M06-2X developed by the Truhlar's group [11]. This member of the class of M06 functionals is characterized with a high nonlocality (it contains a double amount of nonlocal exchange – 2*X*). The local part of M06-2X functional (similarly as in the case of M06) depends on spin density ρ_σ, reduced spin density gradient x_σ and spin kinetic energy density τ_σ:

$$x_\sigma = \frac{|\nabla\rho_\sigma|}{\rho_\sigma^{4/3}}; \quad \sigma = \alpha, \beta \tag{1}$$

$$\tau_\sigma = \frac{1}{2}\sum_i^{occup.} |\nabla\Psi_{i\sigma}|^2 \tag{2}$$

The Kohn-Sham (KS) SCF equations were solved iteratively for each particular purpose of the present study, using an "ultrafine" (99, 590) grid for numerical integration (99 radial and 590 angular integration points). The rather flexible but still cost-effective Pople-type 6-311G(*d*,*p*) basis set was used for orbital expansion.

All calculations were performed with the Gaussian09 series of programs [12].

C. Experimental

Fourier-transform infrared (FT-IR) spectra of morphine sulphate pentahydrate were recorded using the attenuated total reflection method, on a Varian 660 FT-IR spectrometer. Spectra were recorded at room temperature, using MIRACLE ZnSe ATR module with low-pressure micrometer clamp. Working resolution was 4 cm^{-1}. 16 spectra were accumulated and averaged for production purposes.

III. Results and Discussion

In the present study, we aim to contribute to a more in-depth understanding of vibrational spectroscopic properties of morphine and its derivatives as API in specific DDF. We hereby focus on the interpretation of solid-state vibrational spectra of morphine sulphate pentahydrate. As the crystal structure of this compound is not known, any effort to predict the spectral features by e.g. 3D periodic DFT calculation is a priori hampered. Still, since the title compound is known to form molecular crystals, though certain structural deformations are indeed expected to be induced by the solid phase incorporating it into a crystal structure, still these perturbations are moderate ones and valuable insights may be gained from studies of the corresponding free molecular species. Still, this task is far from trivial. This is particularly true in the case of molecular systems that possess high conformational flexibility. The presently studied system exerts substantial conformational flexibility with respect to rotation of side OH groups and therefore it can potentially exist in several different conformations. Also, one should keep in mind that the current experimental data have been collected for morphine sulphate pentahydrate. On the basis of fundamental chemical principles one can straightforwardly suppose that the most probable form in which morphine incorporates into the crystal structure is in protonated form, as a closed-shell cation. We further denote this form by morphine-H^+. As the most probable protonation site is the ammine nitrogen atom, we consider the *N*-protonated form in the present study.

A. Structure and Energetics

The structures corresponding to real minima located on the M06-2X/6-311G(*d*,*p*) PES of free morphine molecule are shown in Fig. 2. Table I, on the other hand, compiles the computed energies and the corresponding zero-point vibrational corrections.

As can be seen from Fig. 2, in the minimum a), the side OH groups are directed oppositely to the furanoid ring oxygen

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atom. This minimum does not have intramolecular O-H…O contacts. Minima b) and c), on the other hand, have one such contact, while in the minimum d) both O-H groups are directed towards the O atom within the furanoid ring. Inspection of both the total and ZPVE-corrected energy values listed in Table I indicates that minimum d) is the most stable one, while a) is the least stable. Such order of stability is in relation to the existence of the mentioned intramolecular O-H…O contacts, which are also evidenced in the spectroscopic properties of the conformers, discussed further in the paper.

TABLE I. TOTAL ENERGIES, ZERO-POINT VIBRATIONAL CORRECTIONS TO THE TOTAL ENERGIES (ZPVE), AND THE ZPVE-CORRECTED ENERGY VALUES FOR MINIMA LOCATED ON THE M06-2X/6-311G(*D,P*) PES OF FREE MORPHINE MOLECULE. (E_{TOTAL} AND $E_{CORR.}$ EXPRESSED IN HARTREES, AND ZPVES IN HARTREES/PARTICLE).

Minimum	E_{total}	**ZPVE**	$E_{corr.}$
a	-939.483479	0.338027	-939.145452
b	-939.489856	0.338394	-939.151462
c	-939.494127	0.338805	-939.155323
d	-939.497242	0.338931	-939.158311

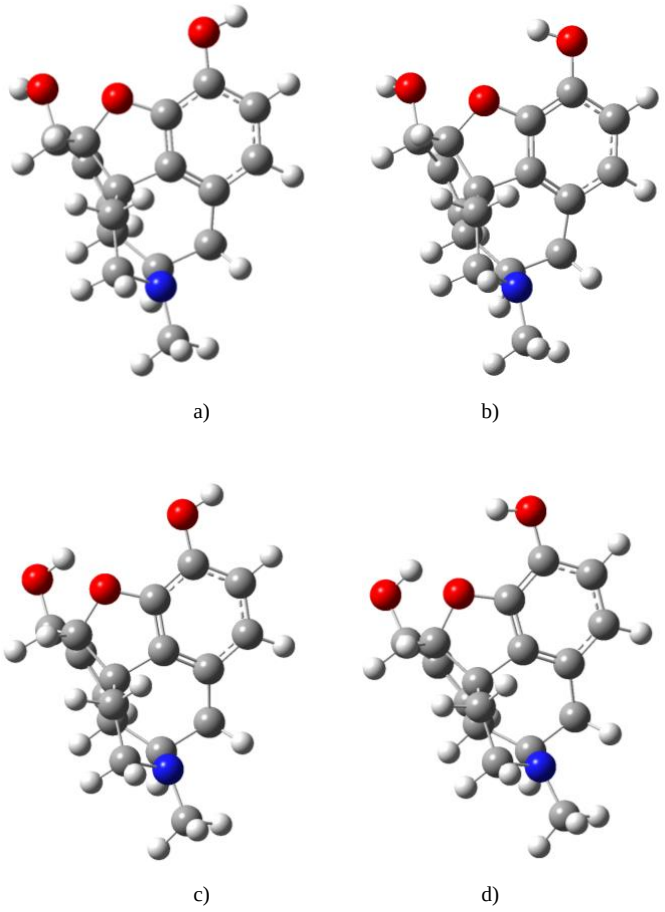

Fig. 2. The true (real) minima located on the M06-2X/6-311G(*d,p*) PES of free morphine molecule.

The structures corresponding to real minima located on the M06-2X/6-311G(*d,p*) PES of *N*-protonated morphine-H^+ molecule are shown in Fig. 3. The computed energies and the corresponding zero-point vibrational corrections are listed in Table II.

Closer inspection of geometrical features of the morphine-H^+ conformers shows that upon protonation at the N-site, the N-H group tilts towards the benzenoid ring, forming a N-H…π contact, which may be classified as a very weak intramolecular hydrogen bond of N-H…π type. This tilting, on the other hand, induces certain strain in the N-containing ring, which, on the other hand, appears to affect the molecular neighborhood. The overall effect of this strain propagation affects the side O-H group in minimum a) which is significantly tilted in comparison to the situation in the analogous minimum located in the case of free morphine molecule (Fig. 2 a). In the case of morphine-H^+, this minimum is also characterized with an intramolecular O-H…O contact with the O atom within the furanoid ring. The other minima at the *N*-protonated morphine-H^+ PES are in a sense analogous to those located in the case of free (non-protonated) morphine. In this case, also the order of stability is different and it is the structure a) that corresponds to the lowest-energy minimum among those shown in Fig. 3. Tilting of the O-H group towards the O atom in the furanoic ring is accompanied with deformations in the corresponding cyclohexenoid ring to which this group is connected.

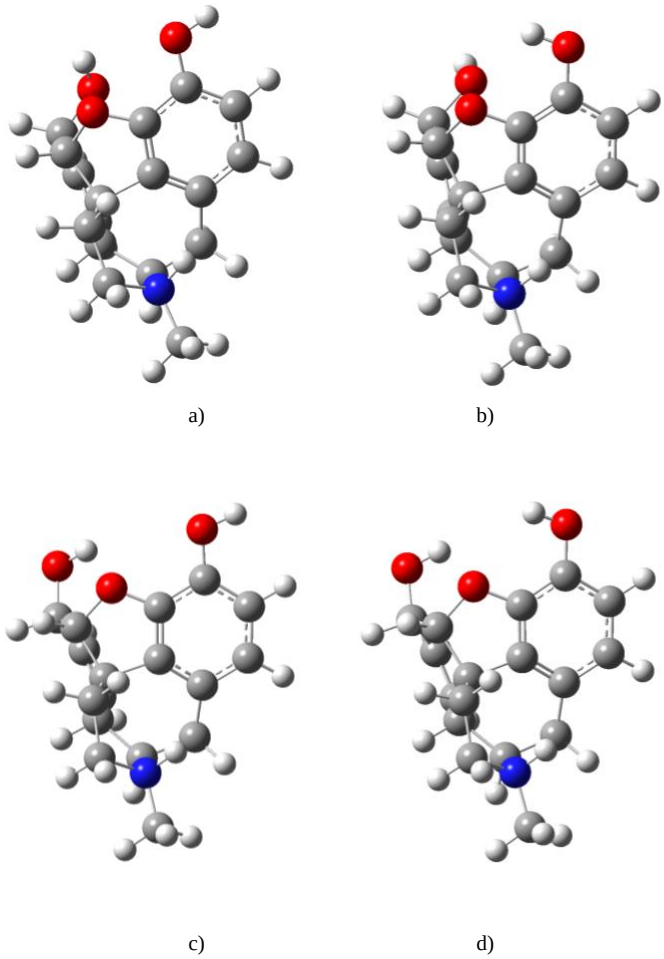

Fig. 3. The true (real) minima located on the M06-2X/6-311G(*d,p*) PES of free *N*-protonated morphine-H^+ molecule.

The overall energy ordering thus results from a subtle competition between the energetic of the intramolecular hydrogen bonding contacts (of the "conventional" O-H…O, as well as of the "unconventional" N-H…π type) and the intramolecular strain. A more detailed analysis of these aspects on the basis of natural bond orbital theory [13] and Bader analysis [14] is in progress.

TABLE II. TOTAL ENERGIES, ZERO-POINT VIBRATIONAL CORRECTIONS TO THE TOTAL ENERGIES (ZPVE), AND THE ZPVE-CORRECTED ENERGY VALUES FOR MINIMA LOCATED ON THE M06-2X/6-311G(*D,P*) PES OF N-PROTONATED MORPHINE-H^+ MOLECULE. (E_{TOTAL} AND $E_{CORR.}$ EXPRESSED IN HARTREES, AND ZPVES IN HARTREES/PARTICLE).

Minimum	E_{total}	ZPVE	$E_{corr.}$
a	-939.881177	0.354793	-939.526384
b	-939.879410	0.354466	-939.524944
c	-939.878468	0.354343	-939.524126
d	-939.879874	0.354272	-939.525603

B. Vibrational Spectroscopic Properties

The primary focus of the present study is on modeling of the vibrational spectroscopic properties of the title compound. One of the most widely used forms thereof is the corresponding sulphate salt, crystallizing as crystallohydrate (morphine sulphate pentahydrate).

In this context, we aim to provide a theoretical support to the empirical assignment of the solid-state infrared spectra of this compound, and also to get a more in-depth insight into the vibrational spectroscopic properties of the key ingredient of a wide variety of formulations based on morphine. Since all the calculations have been based on double harmonic approximation, we have corrected the raw (as-computed) harmonic vibrational normal mode frequencies with a single scaling factor 0.957 throughout the whole spectral range. In this way, both the systematic deficiencies of the theoretical method used as well as the inherent anharmonicities of the vibrational modes are at least partially accounted for.

Theoretical infrared spectra computed for the four conformers of the free neutral morphine molecule (those shown in Fig. 2) at the M06-2X/6-311G(*d,p*) level of theory are shown in Fig. 4. Fig. 5, on the other hand, shows the theoretical infrared spectra computed for the four conformers of the *N*-protonated morphine-H^+ cation (those shown in Fig. 3) at the same level of theory. In Fig. 6 and 7, experimental FT-IR spectra of a solid state sample of morphine sulphate pentahydrate are shown. Fig. 6 actually shows the complete (as-recorded) absorption spectrum, in which contributions from all molecular/ionic species are present, while Fig. 7 has been generated from 6 by eliminating the regions with notable contributions from the anionic (supposedly hydrogensulphate) species, and rescaling the ordinate axis.

As mentioned before, the crystal structure of the title compound is not known. Accounting, however, for the morphine molecular structure, as well as the behavior of similar organic molecular systems in solid phase, we make the following assumptions concerning the most probably crystal structure of the studied system (which are, as will be seen further, completely consistent with our experimental spectroscopic data). Due to the basic character of the amine segment of morphine molecule, interaction with sulfuric acid is expected to lead to its protonation, and transformation to morphine-H^+ cation (morphonium cation). Since further protonation of single morphine molecule does not appear to be possible, one possibility for solid phase formation is that the crystal is built up by morphine-H^+ cations and hydrogen sulphate (HSO_4^-) anions, together with crystalline water. Another possibility would be, of course, packing in which the sulphuric acid undergoes a complete deprotonation, leading to presence of sulphate (SO_4^{2-}) anions in the crystal structure, along with the crystalline water. Our experimental infrared spectroscopic data, however, seem to indicate presence of hydrogen sulphate anionic species in the solid phase. The empirical formula of morphine sulphate pentahydrate is usually written in the form $(C_{17}H_{19}NO_3)_2{\cdot}H_2SO_4{\cdot}5H_2O$, so that the stoichiometry of the solid phase would also allow for the presence of only sulphate (SO_4^{2-}) anions and morphine-H^+ cations, *i.e.* $[(C_{17}H_{19}NO_3)H]_2SO_4{\cdot}5H_2O$. We discuss the alternative possibilities below, in the context of analysis of vibrational spectroscopic data.

The highest frequency region of the spectrum contains bands due to X-H vibrational modes (morphine O-H and C-H, protonated morphine-H^+ O-H, N-H and C-H as well as crystalline water O-H). Since the computations have been done for free morphine (or protonated morphine-H^+) molecule, having in mind that the solid state packing of any of the forms of this compound could involve interactions with crystalline water molecules, aside from the complexities arising due to the inherent torsional flexibility of neutral and protonated morphine, direct comparison between theory and experiment is unfortunately hampered in the case of this spectral region. However, inspection of the spectral pattern in the region above 2000 cm^{-1} indicates a specific sequence of bands with a sharp "Evans hole"-like feature appearing at about 2790 cm^{-1}. The overall spectral appearance in this region is characteristic for systems containing strongly hydrogen-bonded groups, such as hydrogen sulphate anions [15].

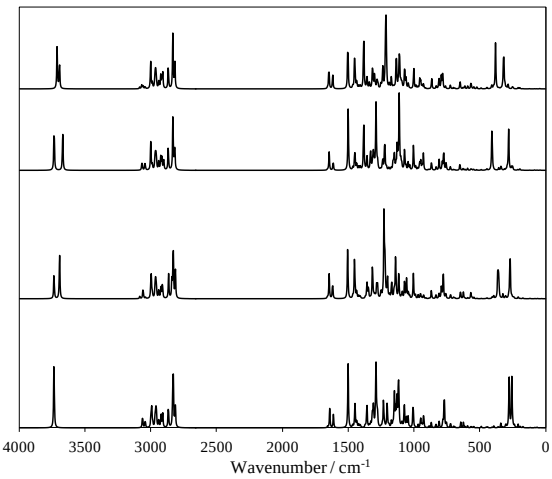

Fig. 4. Theoretical infrared spectra of the four conformers of the free neutral morphine molecule (a, b, c and d in Fig. 2, from the downmost curve uppwards) calculated at the M06-2X/6-311G(*d,p*) level of theory.

More detailed conclusions concerning this spectral region will be possible if partial deuteration studies are carried out and also if more details concerning the crystal structure of the studied compound are known. However, even the basic spectroscopic findings for the protiated compound, presented here, strongly indicate the presence of hydrogen sulphate anionic species in the solid phase, or, at least, existence of some X-H fragment participating in a strong hydrogen bonding interaction.

Considering the overall stoichiometry of the compound, existence of hydrogen sulphate species in the solid phase along with the considered protonation possibilities of the morphine molecule, indicate that both protonated and neutral morphine molecules could exist in the solid state structure of morphine sulphate pentahydrate.

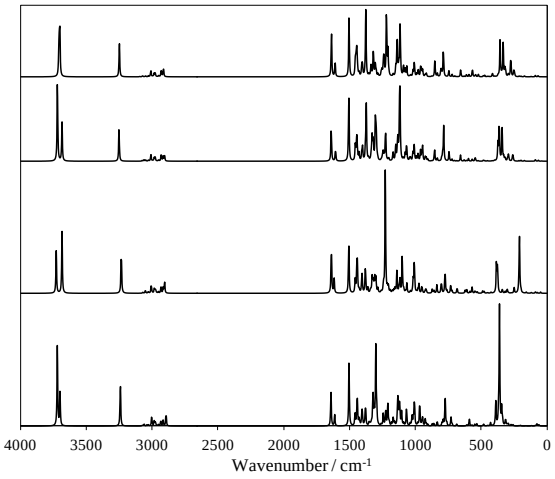

Fig. 5. Theoretical infrared spectra of the four conformers of the *N*-protonated morphine-H^+ molecule (a, b, c and d in Fig. 3, from the downmost curve uppwards) calculated at the M06-2X/6-311G(*d,p*) level of theory.

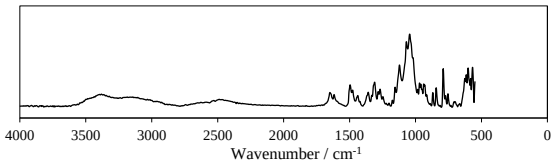

Fig. 6. Experimental ("raw", *i.e.* as-recorded) solid-state FT-IR spectrum of morphine sulphate pentahydrate (the wavenumber axis has been constructed in a manner that allows a direct comparison with the theoretical spectra).

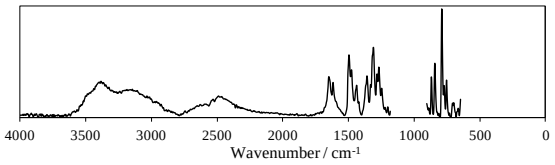

Fig. 7. Experimental solid-state FT-IR spectrum of morphine sulphate pentahydrate with removed contributions from sulphate species (the wavenumber axis has been constructed in a manner that allows a direct comparison with the theoretical spectra; the ordinate axis has also been scaled).

As can be seen from Fig. 4 and Fig. 5, meta hybrid density functional theory predicts that in the case of free neutral and *N*-protonated morphine species, this spectral region could be used to discriminate between the possible conformers, once the IRPDM or similar experimental data become available. On the basis of DFT computations presented in this paper, one could also generate Boltzmann-averaged IR spectra of both of the mentioned species, which could allow for a direct comparison with experimental gas-phase data. In the experimental solid-state spectra, this spectral region contains a broad absorption feature, which is pretty much structureless at first sight. Obviously, the bands due to morphine intramolecular O-H stretching modes are overlapped with the bands arising from the O-H stretching vibrations of crystalline water. Due to the existence of various intra- and intermolecular hydrogen bonds with various strengths, these bands actually span the region down to the area where bands due to morphine intramolecular C-H stretching motions are expected to appear. As morphine and its protonated analogue contain both aliphatic-like and aromatic-like C-H bonds, bands due to these modes are actually expected both above and below 3000 cm^{-1}.

The previously outlined assumption, on the basis of spectral appearance in the O-H stretching region, that the investigated solid state system contains hydrogen sulphate anionic species is further supported by the presence of high-intensity bands at about 1050 cm^{-1} (due to the antisymmetric S-O stretching motions within the $HOSO_3$ anion), lower-intensity band at ~ 980 cm^{-1} (due to the symmetric S-O stretching) and also by the intense band at ~ 600 cm^{-1} (due to the $HOSO_3$ bending motions). All of these bands show notable substructure, due to the superposition with the bands arising from the organic fragment (supposedly neutral morphine and protonated morphine-H^+). To be able to provide a clearer theoretically-supported assignment of bands due to morphine in the studied solid phase, in Fig. 7 we have presented a spectrum derived from the "raw" (original) one by eliminating the regions with notable contributions from the anionic (supposedly hydrogensulphate) species appearing at about 1050 and 600 cm^{-1}, and rescaling the ordinate axis.

Even a simple visual inspection of the theoretical and experimental spectra in the frequency region below 2000 cm^{-1} show remarkable agreement in the overall spectral pattern. On the basis of that, relying on the harmonic normal mode analysis by meta hybrid density functional theory, we were able to provide a theoretically-supported empirical assignment of bands appearing in this region.

The highest-frequency bands appearing in the region below 2000 cm^{-1} (appearing in the region from ~ 1650 to 1450 cm^{-1}) may be attributed to the C-C stretching vibrations originating from the aromatic segments within the morphine molecule. Of course, bands due to bending modes of crystalline water are expected to appear here as well, and the band appearing at about 1615 cm^{-1}, as well as certain shoulders of the 1650 cm^{-1} band most probably originate exactly from crystalline water bending modes.

In the spectral region from 1500 – 1200 cm^{-1}, according to theoretical calculations, bands due to a wide variety of intramolecular C-H and O-H bending modes in the case of neutral morphine (C-H, N-H and O-H bending modes in the case of protonated morphine-H^+) are expected to appear. Generally, within the mentioned spectral region, the intramolecular morphine N-H and O-H bendings are expected to appear at lower frequencies than the C-H bending ones. Of course, having in mind that we deal with a crystalline hydrate, this spectral region is expected to contain bands due to HOH bending modes of crystalline water as well. Also, hydrogen sulphate O-H bendings are expected to appear somewhere around 1400 cm^{-1}.

According to theoretical hybrid meta DFT results, in the region around 1120 cm^{-1} bands due to the intramolecular C-O stretching modes of the morphine moieties are expected to appear, which are superimposed on the bands due to antisymmetric stretching mode of the hydrogen sulphate species. In this region bands due to morphine CCC bending modes are expected as well. Somewhat below, at ~ 1060 cm^{-1}, bands due to morphine C-N stretching mode with moderate intensity should appear, probably masked with the symmetric S-O stretching mode.

We assign the bands in the region from ~ 1040 cm^{-1} to 1000 cm^{-1} to the C-C stretching motions localized within the aliphatic-like (sp^3 carbons) fragments within morphine

molecule. The CH_3-N stretching motion within morphine gives rise to a band at ~ 980 cm^{-1}. The bands in the region below 1000 cm^{-1} are, according to theoretical computations, due to complex intramolecular motions within morphine moieties, involving out-of-plane C-H deformations in the aromatic fragments as well. Below 720 cm^{-1}, the bands are assigned to the out-of-plane CC deformations, with significant contributions from out-of-plane C-H deformations in the case of certain modes. These bands are superimposed on the band due to S-O deformation mode due to hydrogen sulphate anionic species.

IV. Conclusions

In the present paper, we present the results from a combined FT-IR spectroscopic and theoretical study of morphine sulphate pentahydrate. Theoretical study has been based on meta hybrid DFT approach, at M06-2X/6-311G(*d*,*p*) level of theory. In summary, the main results and conclusions consist of the following. Experimental data strongly suggest that hydrogen sulphate anionic species, participating in strong intermolecular interactions of hydrogen bonding type are present in the investigated solid state system. Besides that, accounting for the compound's stoichiometry, the possibility that the solid phase contains both neutral morphine molecule and *N*-protonated morphine-H^+ cation is outlined. In the spectral regions where bands due to intramolecular modes of the two previously mentioned molecular/cationic systems are expected, theoretical results are in remarkable agreement with the experiment. Thus, a solid theoretical background for the empirical band assignments is provided. In parallel, the gained knowledge concerning vibrational spectroscopic properties of the currently studied reference morphine solid-state formulation could serve as a starting point for further spectroscopic study of other formulations thereof, especially in the context of its incorporation into specific drug dosage forms.

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