Influence of atomic bonds on the properties of the laxative drug sodium picosulphate

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Abstract

In this work, the influence of the different S═O, S−O, N⋯H, O⋯H, Na⋯O bonds present in the structures of the powerful laxative drug, sodium picosulphate in gas and aqueous solution phases were studied combining the density functional theory (DFT) calculations with the experimental available infrared, 1H NMR and UV-visible spectra. The structural, topological, electronic and vibrational properties were investigated in both media by using the hybrid B3LYP/6-31G* method and the integral equation formalism variant polarised continuum model (IEFPCM). Here, the characteristics of the S═O, S−O, N⋯H, O⋯H, Na⋯O bonds were completely revealed by using atomic charges, natural bond orbital (NBO) and atoms in molecules (AIM) studies. The infrared, 1H NMR, 13C NMR and UV-visible spectra are in reasonable concordance with those experimental available in the literature. The vibrational analysis of sodium picosulphate was performed considering C3V symmetries for both SO42− groups and the complete assignments of the 126 vibration modes were reported in gas phase and aqueous solution together with their corresponding force fields. In addition, the reactivities of sodium picosulfate increase in solution due to their ionic characteristic which probably justifies their behaviour as a stimulant cathartic and their easy metabolic conversion, as reported in the literature.

Keywords: Pharmaceutical science, Theoretical chemistry, Inorganic chemistry
1. Introduction

The sodium salts containing $\text{SO}_4^{2-}$ or $\text{SO}_3^{2-}$ groups in their structures are employed as reactive in numerous and important industries, as was reported by Periasamy et al. [1]. Structurally, two modes of coordination in particular, monodentate or bidentate, are expected for these groups in different compounds [2, 3, 4]. Normally, those sodium salts when are linked to different organic rings present interesting biological activities which due to their ionic characteristic are highly used in the pharmaceutical industry to facilitate the incorporation of drugs to the human organism or as an intermediate in the preparation of other drugs [4]. For these reasons, the structures and properties of pharmaceutical drugs containing those salts are of great interest to their identifications by using different spectroscopic techniques, such as the vibrational spectroscopy and also, to know and predict their reactivities and behaviours in the different media in which they are present. The aim of this work is to study the structural and vibrational properties of anhydrous sodium picosulphate or picosulfate, a stimulant laxative drug orally administered to patients in preparations for colonoscopy [5, 6, 7, 8], taking into account that, so far, these properties were not reported. Actually, the control and the quantitative analysis of this drug are performed by using the high performance liquid chromatographic (HPLC) because this technique is one of the most studied [9, 10]. The chemical name of this compound is the 4,4′-(2-pyridinylmethylene) bisphenol bis (hydrogen sulfate) (ester) disodium salt. This salt itself is pharmacologically inactive but it is converted by bacterial hydrolase in the human organism to the pharmacologically active metabolite, bis(p-hydroxyphenyl)-2-pyridylmethane [6]. Here, we have reported a detailed study on the structural and vibrational properties of sodium picosulphate combining the DFT calculations with the experimental available FTIR, NMR and UV-visible spectra in gas phase and in aqueous solution taking into account that this salt is soluble in water. The initial structures of this salt in these two media were optimized by using the hybrid B3LYP/6-31G* level of theory [11, 12]. After that, NBO [13, 14] and AIM [15, 16] calculations were performed in order to investigate the characteristics of the different pyridinyl and phenyl rings and of the Na–O, S=O and S–O bonds together with their topological properties. The force fields for the compound in the two media were computed by using a generalized valence force field (GVFF) [17, 18] and the normal modes calculations with the Molvib program [19]. Then, the complete assignments of the 126 vibration normal modes predictable for sodium picosulphate were reported in both media using the potential energy distribution (PED). In this paper, the structural, topological and vibrational properties for sodium picosulphate together with their vibrational assignment are reported for the first time. This way, the sodium picosulphate salt could be easily identified in different media by means of the vibrational spectroscopy.
2. Methodology

The initial anhydrous sodium picosulfate (APS) structure was modelled by using the GaussView program [20] taking into account a $C_{3v}$ symmetry for the two sulfate groups, in accordance with the experimental structure observed for the potassium borosulfate [2]. After that, the Cartesian coordinates were optimized in gas and aqueous solution phases using the hybrid B3LYP/6-31G* method [11, 12] with the Gaussian 09 program [21]. The influence of the solvent on their properties were studied by using the self-consistent reaction field (SCRF) method together with the IEFPCM model at the same level of theory [22, 23]. The volume variation that experiment the salt in water was also computed using the Moldraw program [24] whiles the solvation energy involved in this process was calculated using the solvation model [25]. Both stable structures represent minima in the potential energy surface because all the frequencies are positive. Fig. 1 show the optimized structure of sodium picosulfate together with the numbering of the atoms while the detailed identification of the pyridinyl and phenyl rings is presented in Fig. 2. The characteristics of the three rings and of the Na–O, S=O and S–O bonds were investigated by using the atomic charges, bond orders, molecular electrostatic potentials (MEP) surface, stabilization energies, topological properties which were computed in both media with the NBO 3.1 and AIM2000 programs [14, 16]. Here, the MEP surface of the salt in the gas phase was built with the aid of the GaussView program [20] while the corresponding values were obtained using the

![Fig. 1. Theoretical molecular structure of anhydrous sodium picosulfate and the atoms labelling.](image-url)
Merz-Kollman (MK) charges [26]. Additionally, the frontier molecular orbitals and some descriptors were calculated in order to predict the reactivity and behaviours in the two media studied [27, 28, 29, 30, 31, 32, 33]. On the other hand, the Molvib program [19] was used to transform the force fields initially expressed in Cartesian coordinates to natural internal coordinates. After that, the Potential Energy Distribution (PED) were computed from the scaled quantum mechanics (SQM) force fields in both media using the same level of theory in order to perform the complete assignments considering the PED contributions ≥ 10%. The ¹H-NMR and ¹³C-NMR spectra in aqueous solution were predicted by using the GIAO method [34] while the time dependent density functional theory (TD-DFT) calculations were employed to predict the electronic spectra in solution at the same level of theory.

3. Results and discussion

3.1. Geometrical parameters in both media

The calculated total energies, dipole moments, volume variation and solvation energy for APS in gas and aqueous solution phases can be seen in Table 1. The results show a notable increase in the dipole moment value from 11.06 D in gas phase to 15.14 D in solution while the volume in solution increase from 471.2 Å³ in gas phase to 484.5 Å³ in solution showing a volume variation of 13.3 Å³. Fig. 3 shows that in solution an additional change in the direction of the dipole moment is observed due to the separation between the pairs of SO₄²⁻ and Na⁺ ions. As was above mentioned the volumes in both media were calculated with the Moldraw program [24] using the B3LYP/6-31G* method. Thus, the expansion of the volume observed in solution is attributed to the calculated high corrected solvation energy value (-254.38 kJ/mol) as a consequence of the hydration of this salt with the water.
molecules. Note that the corrected solvation energy has higher value than the corresponding uncorrected because the total non electrostatic terms due to the cavitation, dispersion and repulsion energies, computed with the IEFPCM [22, 23] and SM [25] models were added.

So far, the crystalline and molecular structure of APS were not experimentally determined and, for this reason, the calculated geometrical parameters for the three rings of APS in both media were compared with those experimental values observed by Sun et al. [35] for Bis[μ−1,2-diphenyl-N,N’-bis-(di-2-pyridyl-methyl-eneamino)ethane-1,2-diimine]disilver(I) bis-(hexa-fluorido-phosphate) acetonitrile disolvate because it compound have similar pyridyl and phenyl rings in their structure. On the other hand, the calculated parameters for the SO₄²⁻ groups were compared with those experimental recently reported for a new sulfate salt, sodium magnesium sulfate deca-hydrate, Na₂Mg(SO₄)₂.10 H₂O by Leduc et al. [36] because it compound present two sulfate groups linked to sodium atoms, such as APS. These comparisons were performed by means of the root-mean-square deviation (RMSD) values which are summarized in Table 2 together with the geometrical parameters for APS in both media. Regarding the results we clearly observed that in general the calculations in gas phase predicted higher values for the bond lengths and angles related to the pyridyl and phenyl rings than for the SO₄²⁻ groups while in solution are most notable the increase in the bond lengths

| E (hartree) | μ (D) | V (Å³) |
|------------|-------|--------|
| −2471.27   | 11.06 | 471.2  |
| −2471.36   | 15.14 | 484.5  |
| ΔG_u#      | ΔG_ne | ΔG_c  |
| −236.07    | 18.31 | −254.38 |
| ΔV (Å³)=13.3 |        |        |

Table 1. Calculated total (E) and relative energies (ΔE), dipole moments, volume variation and solvation energy for anhydrous sodium picosulphate in gas and aqueous solution phases.
corresponding to the SO$_4^{2-}$ groups, as expected due to the affinity of these groups with the water. The exhaustive analysis show that from the four S–O bonds in the sulphate groups three S=O bonds present lower and similar values, showing clearly their double bond character, while the remain S1–O3 and S2–O4 distances have higher values, confirming this way, the $C_{3v}$ symmetry considered for these groups. In solution, important changes in the S=O and S–O distances are observed, thus, whereas two S–O bonds are enlarged the other two are shortened, as shown Table 2. Other very important observation is the remarkable increase in solution of both O-Na distances evidencing the ionic characteristics of these bonds, as expected due to the presence of two SO$_4^{2-}$ groups and two Na$^+$ cations in the structure of APS.

Fig. 3. Dipole moment directions for the anhydrous sodium picosulfate salt in gas phase (top) and in aqueous solution (bottom) showing the corresponding magnitudes and orientations of their vectors.
Table 2. Comparison of calculated geometrical parameters for the anhydrous with the corresponding experimental ones.

| B3LYP/6-31G* | Gas  | PCM  | Experimental
|--------------|------|------|-------------|
| Parameter    |      |      | Exp b | Exp c      |
| Bond lengths (Å) |      |      |       |            |
| C25-O3       | 1.388| 1.401|       |            |
| C26-O4       | 1.387| 1.402|       |            |
| C12-C13      | 1.534| 1.530|       |            |
| C12-C14      | 1.532| 1.531|       |            |
| C12-C15      | 1.528| 1.530|       |            |
| C13-C16      | 1.402| 1.402| 1.372 |            |
| C16-C21      | 1.392| 1.394| 1.361 |            |
| C21-C25      | 1.396| 1.393| 1.369 |            |
| C25-C23      | 1.394| 1.392| 1.361 |            |
| C23-C18      | 1.395| 1.395| 1.371 |            |
| C18-C13      | 1.401| 1.402| 1.375 |            |
| C14-C17      | 1.400| 1.403| 1.372 |            |
| C17-C22      | 1.394| 1.394| 1.361 |            |
| C22-C26      | 1.394| 1.393| 1.369 |            |
| C26-C24      | 1.396| 1.392| 1.361 |            |
| C24-C19      | 1.392| 1.395| 1.371 |            |
| C19-C14      | 1.401| 1.400| 1.375 |            |
| C15-N11      | 1.342| 1.344| 1.347 |            |
| N11-C28      | 1.337| 1.343| 1.324 |            |
| C28-C29      | 1.394| 1.392| 1.381 |            |
| C29-C27      | 1.393| 1.394| 1.369 |            |
| C27-C20      | 1.393| 1.392| 1.365 |            |
| C20-C15      | 1.401| 1.401| 1.361 |            |
| O5-Na43      | 2.151| 2.263|       | 2.518      |
| O6-Na44      | 2.156| 2.263|       | 2.518      |
| S1-O3        | 1.810| 1.720|       | 1.488      |
| S1-O5        | 1.500| 1.493| 1.481 |            |
| S1-O7        | 1.461| 1.472| 1.463 |            |
| S1-O8        | 1.460| 1.472| 1.477 |            |
| S2-O4        | 1.807| 1.719| 1.488 |            |
| S2-O6        | 1.500| 1.493| 1.481 |            |
| S2-O9        | 1.461| 1.472| 1.463 |            |
| S2-O10       | 1.459| 1.472| 1.477 |            |

(Continued)
Table 2. (Continued)

| Parameter | Gas  | PCM  | Exp<sup>b</sup> | Exp<sup>c</sup> |
|-----------|------|------|----------------|----------------|
| RMSD      | 0.132| 0.095|                |                |

Dihedral angles (°)

|                  |      |      |      |      |
|------------------|------|------|------|------|
| C12-C13-C16      | 118.4| 118.9| 120.9|      |
| C12-C13-C18      | 123.3| 122.5| 121.3|      |
| C12-C14-C17      | 119.5| 118.3| 120.9|      |
| C12-C14-C19      | 122.0| 123.1| 121.3|      |
| C12-C15-N11      | 118.1| 118.4|      |      |
| C12-C15-C20      | 120.1| 119.3|      |      |
| O7=S1=O8         | 118.7| 115.6|      | 109.6|
| O7=S1=O5         | 114.9| 114.7|      | 109.6|
| O8=S1=O5         | 115.3| 115.0|      | 109.3|
| O3-S1=O8         | 94.9  | 105.7|      | 108.9|
| O9=S2=O10        | 118.6| 115.6|      | 109.6|
| O9=S2=O6         | 114.8| 114.8|      | 109.6|
| O6=S2=O10        | 115.3| 114.9|      | 109.3|
| O4-S2=O6         | 94.7  | 96.9  |      | 108.9|
| S1-O5-Na43       | 103.8| 104.4|      | 87.4  |
| S2-O6-Na44       | 103.9| 104.3|      | 87.4  |
| **RMSD**         | **9.4** | **8.2** |      |      |

Dihedral angles (°)

|                  |      |      |      |      |
|------------------|------|------|------|------|
| C15-C12-C13-C18  | −39.3| −41.3|      |      |
| C15-C12-C14-C19  | 72.2 |      | 96.0 |      |
| C14-C12-C15-C20  | 119.8|      | 139.4|      |
| C14-C12-C15-N11  | −59.2|      | −41.2|      |
| C25-O3-S1=O5     | 177.2|      | 172.6|      |
| O3-S1=O5-Na43    | 0.0  |      | −2.6 |      |
| C26-O4-S2=O6     | 176.7|      | 178.4|      |
| O4-S2=O6-Na44    | −0.4 |      | −0.7 |      |
| **RMSD**         | **19.8** | **18.4** |      |      |

<sup>a</sup>This work.
<sup>b</sup>[35].
<sup>c</sup>[36].
3.2. NPA charges, bond orders and MEP surface studies

The ionic nature of APS is clearly evidenced by the geometrical parameters principally due to the two \( \text{SO}_4^{2-} \) groups and the two \( \text{Na}^+ \) cations which suggest the importance to study the charge distributions on their structures in both media and, besides the nature of the different bonds. For these reasons, we have studied two charge’s types which are the natural population atomic (NPA) and the MK charges [26], the bond orders expressed by the Wiberg indexes and the molecular electrostatic potentials (MEPs). With the MK charges it is possible to calculate the MEP surface values in the two media while their surfaces mapped have permitted to observe the electrophilic and nucleophilic regions by their different colorations. All these properties are presented in Table 3. First, analyzing the charges we observed that both charges predicted higher positive values on the two S atoms than the two Na atoms but, in general, the values observed in the NPA charges are very different from those MK charges. For instance, the NPA charges on all the S, O and H atoms in both media are higher than the other ones while on the N atoms are observed lower NPA values. In relation to the charges on the C atoms with hybridizing sp\(^2\), we observed negative signs on five C atoms belonging to the phenyl R1 and R2 rings, these are those rings linked to the \( \text{SO}_4^{2-} \) groups while in the pyridyl rings R3 only three C atoms have negative signs because the N atoms of these rings are also predicted by the calculations with negative signs. On the other hand, both charges predicted negative signs on the C12 atoms with hybridizing sp\(^3\) in both media. Both charges reveal clearly the characteristics ionic of the two sulphate groups and the two Na atoms.

When the MEP surface values in both media are analyzed we observed a decreasing in the negative values according to the following order: \( \text{S} > \text{Na} > \text{O} > \text{C} > \text{H} \) where the MEP values on the O atoms linked to the rings, these are the C25-O3 and C26-O4 bonds, decreasing their values in solution while the remain O atoms belonging to the \( \text{SO}_4^{2-} \) groups exhibit increase in their corresponding MEP surface values. Obviously, the decrease and increase in the MEP surface values are strongly related to the MK charges, as observed in Table 3.

In relation to the bond orders, clearly Table 3 evidence the low bond order values observed in the two Na atoms being lower in solution, this way, the ionic behaviour of these atoms in both media is confirmed. In relation to the O atoms of both \( \text{SO}_4^{2-} \) groups we observed that the O5 and O6 atoms present the lower values because they are linked to the S and Na atoms and their values slightly decrease in solution by the same reason before explained. Regarding the values for the C atoms, we observed that those with hybridizing sp\(^2\), the C13, C14 and C15 atoms, have the higher values while the C25 and C26 atoms which are linked to O atoms present the lower values, as expected due to the ionic characteristics of both \( \text{SO}_4^{2-} \) groups. The Wiberg bond index matrix in the NAO basis in gas phase shows bond order...
Table 3. Atomic MK and NPA charges, Molecular electrostatic potentials (MEP) and bond orders (Wiberg indexes) for anhydrous sodium picosulfate in both media at B3LYP/6-31G* level of theory.

| Atoms | MK Gas | PCM | NPA Gas | PCM | MEP Gas | PCM | Wiberg index |
|-------|--------|-----|---------|-----|---------|-----|--------------|
| 1S    | 1.137  | 1.141| 2.537   | 2.564| −58.941 | −58.949| 4.210        |
| 2S    | 1.137  | 1.140| 2.539   | 2.564| −58.948 | −58.958| 4.210        |
| 3 O   | −0.759 | −0.703| −0.847  | −0.841| −22.284 | −22.274| 1.759        |
| 4 O   | −0.752 | −0.713| −0.846  | −0.842| −22.291 | −22.283| 1.763        |
| 5 O   | −0.661 | −0.669| −1.055  | −1.065| −22.332 | −22.341| 1.489        |
| 6 O   | −0.662 | −0.673| −1.055  | −1.066| −22.339 | −22.350| 1.488        |
| 7 O   | −0.484 | −0.502| −0.925  | −0.944| −22.345 | −22.363| 1.670        |
| 8 O   | −0.479 | −0.508| −0.918  | −0.942| −22.345 | −22.364| 1.679        |
| 9 O   | −0.489 | −0.504| −0.926  | −0.945| −22.352 | −22.373| 1.667        |
| 10 O  | −0.476 | −0.500| −0.917  | −0.941| −22.353 | −22.373| 1.681        |
| 11 N  | −0.559 | −0.579| −0.478  | −0.459| −18.363 | −18.367| 3.074        |
| 12 C  | −0.215 | −0.521| −0.291  | −0.294| −14.721 | −14.720| 3.958        |
| 13 C  | −0.052 | 0.124 | 0.026   | 0.028| −14.733 | −14.728| 2.003        |
| 14 C  | 0.179  | 0.296 | 0.029   | 0.024| −14.739 | −14.737| 4.040        |
| 15 C  | 0.575  | 0.757 | 0.242   | 0.233| −14.696 | −14.698| 3.988        |
| 16 C  | −0.043 | −0.122| −0.217  | −0.215| −14.742 | −14.736| 3.947        |
| 17 C  | −0.233 | −0.231| −0.220  | −0.218| −14.746 | −14.745| 3.949        |
| 18 C  | −0.071 | −0.202| −0.226  | −0.227| −14.746 | −14.739| 3.934        |
| 19 C  | −0.105 | −0.272| −0.205  | −0.204| −14.751 | −14.749| 3.938        |
| 20 C  | −0.418 | −0.520| −0.262  | −0.265| −14.730 | −14.731| 3.944        |
| 21 C  | −0.380 | −0.286| −0.255  | −0.249| −14.744 | −14.737| 3.940        |
| 22 C  | −0.288 | −0.209| −0.257  | −0.250| −14.752 | −14.747| 3.939        |
| 23 C  | −0.336 | −0.243| −0.253  | −0.248| −14.742 | −14.736| 3.949        |
| 24 C  | −0.290 | −0.210| −0.255  | −0.245| −14.749 | −14.748| 3.949        |
| 25 C  | 0.575  | 0.478 | 0.284   | 0.280| −14.686 | −14.678| 3.905        |
| 26 C  | 0.505  | 0.430 | 0.290   | 0.279| −14.691 | −14.689| 3.905        |
| 27 C  | 0.105  | 0.136 | 0.193   | 0.195| −14.719 | −14.720| 3.943        |
| 28 C  | 0.297  | 0.288 | 0.034   | 0.032| −14.703 | −14.706| 3.927        |
| 29 C  | −0.367 | −0.377| −0.279  | −0.280| −14.729 | −14.731| 3.943        |
| 30 H  | 0.064  | 0.127 | 0.252   | 0.256| −1.118   | −1.114 | 0.939        |
| 31 H  | 0.120  | 0.133 | 0.234   | 0.236| −1.111   | −1.105 | 0.947        |
| 32 H  | 0.146  | 0.136 | 0.231   | 0.232| −1.115   | −1.113 | 0.948        |
| 33 H  | 0.132  | 0.161 | 0.256   | 0.255| −1.118   | −1.111 | 0.937        |
| 34 H  | 0.126  | 0.201 | 0.252   | 0.249| −1.124   | −1.123 | 0.938        |

(Continued)
values of 0.460 for the S1–O3 and S2–O4 bonds indicating higher polarizations of these two bonds in relation to the other ones. This way, these bonds show different characteristics than the other ones, as will see later.

The study of the MEP surface mapped surfaces of APS in both media at the B3LYP/6-31G* level of theory show strong blue colorations on the two Na atoms

![Fig. 4. Calculated electrostatic potential surfaces on the molecular surface of anhydrous sodium picosulfate in gas phase. Color ranges, in au: from red −1.186 to blue ++1.186. B3LYP functional and 6-31G* basis set. Isodensity value of 0.005.](image-url)
and green on remain atoms, this way, Fig. 4 support the nature electrophilic of this salt in both media. Note that the green colour indicated inert sites, as expected because they correspond to the three rings. Obviously, the blue colour on both Na atoms indicate probable sites reacting with potential biological nucleophiles. Evidently, the mapped surfaces could in part explain the laxative property observed for APS in solution.

3.3. NBO and AIM analysis

The above studies have showed the ionic characteristics of APS in both media but the study of the interactions between the involved SO$_4^{2-}$ and Na$^+$ ions is also important in relation to their stabilities in both media. Hence, the stabilization energies and the topological parameters were calculated by using the NBO [14] and AIM [16] programs. Table 4 shows the main delocalization energy for APS in gas and in aqueous solution phases at B3LYP/6-31G* level of theory. Three important $\Delta E_{\pi\pi\pi^*}$, $\Delta E_{\sigma\pi^*}$ and $\Delta E_{\sigma\sigma^*}$ charge transfers are observed in both media and other two $\Delta E_{\sigma\pi^*}$ and $\Delta E_{\sigma\sigma^*}$ charge transfers with lower values are also observed. The most important delocalization energy values are transitions from bonding orbitals C=Co or C=N bonds to antibonding orbitals C=C, C=N or S=O bonds observed on the three rings and from the lone pairs of the O atoms of both SO$_4^{2-}$ groups to antibonding orbitals S=O bonds. Notice that the two $\Delta E_{\sigma\pi^*}$ charge transfers are only observed in gas phase. Obviously, the total $\Delta E_{Total}$ contribution reveals the high stability of APS in both media, but specifically in solution, as expected due to their ionic characteristics.

The Bader’s theory [15] is very interesting to explain the characteristics of inter and intra-molecular interactions in different compounds by using their topological properties which can be calculated with the AIM2000 program [16]. Thus, the electron density distribution, $\rho(r)$, the Laplacian values, $\nabla^2 \rho(r)$, the eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) of the Hessian matrix and, the $\lambda_1/\lambda_3$ ratio calculated in the bond critical points (BCPs) reveal the interaction’s types. Hence, the interaction is of hydrogen bonds or ionic interaction when $\lambda_1/\lambda_3 < 1$ and $\nabla^2 \rho(r) > 0$ [37]. Here, these parameters for APS in both media at B3LYP/6-31G* level of theory are presented in Table 5. The values of those parameters in the BCPs show clear differences among the S-O bonds of both SO$_4^{2-}$ groups in both media, as observed in Table 5. For instance, three S-O bonds of each SO$_4^{2-}$ group show $\rho(r)$ values between 0.29 and 0.26 a.u. with $\nabla^2 \rho(r) > 0$ and high values indicating that these interactions are highly polar covalent and are called closed-shell interactions while the S1–O3 and S2–O4 bonds present $\rho(r)$ values relatively high (0.3 and 0.1 a.u.) and negative of $\nabla^2 \rho(r)$ values (-0.2 and -0.1 a.u.) demonstrating that these interactions are called shared interaction which are typical of covalent bonds. On the other hand, in gas phase are observed other eight closed-shell interactions ($\nabla^2 \rho (r) > 0$) of which four are ionic with low $\rho(r)$ and high $\nabla^2 \rho(r)$ (Na43⋯O3,
Table 4. Main delocalization energy (in kJ/mol) for anhydrous picosulfate in gas and in aqueous solution phases at B3LYP/6-31G* level of theory.

| Delocalization          | Gas    | PCM    |
|-------------------------|--------|--------|
| $\pi$N11-C15 $\rightarrow$ $\pi^*$C20-C27 | 53.80  | 55.26  |
| $\pi$N11-C15 $\rightarrow$ $\pi^*$C28-C29 | 115.16 | 112.15 |
| $\pi$C13-C18 $\rightarrow$ $\pi^*$C16-C21 | 85.10  | 84.52  |
| $\pi$C13-C18 $\rightarrow$ $\pi^*$C23-C25 | 88.91  | 90.04  |
| $\pi$C14-C17 $\rightarrow$ $\pi^*$C19-C24 | 83.77  |        |
| $\pi$C14-C17 $\rightarrow$ $\pi^*$C22-C26 | 85.48  |        |
| $\pi$C14-C19 $\rightarrow$ $\pi^*$C17-C22 | 85.10  | 84.52  |
| $\pi$C14-C19 $\rightarrow$ $\pi^*$C24-C26 | 115.16 | 112.15 |
| $\pi$C16-C21 $\rightarrow$ $\pi^*$C13-C18 | 82.01  | 84.14  |
| $\pi$C16-C21 $\rightarrow$ $\pi^*$C23-C25 | 87.65  | 88.74  |
| $\pi$C17-C22 $\rightarrow$ $\pi^*$C14-C19 | 83.77  | 84.52  |
| $\pi$C17-C22 $\rightarrow$ $\pi^*$C22-C26 | 86.86  |        |
| $\pi$C19-C24 $\rightarrow$ $\pi^*$C14-C17 | 81.30  | 80.13  |
| $\pi$C19-C24 $\rightarrow$ $\pi^*$C22-C26 | 81.38  | 80.13  |
| $\pi$C20-C27 $\rightarrow$ $\pi$N11-C15 | 119.34 | 117.54 |
| $\pi$C20-C27 $\rightarrow$ $\pi^*$C28-C29 | 71.94  | 70.85  |
| $\pi$C22-C26 $\rightarrow$ $\pi^*$C14-C17 | 82.93  |        |
| $\pi$C22-C26 $\rightarrow$ $\pi^*$C19-C24 | 79.42  |        |
| $\pi$C23-C25 $\rightarrow$ $\pi^*$C13-C18 | 81.30  | 80.13  |
| $\pi$C23-C25 $\rightarrow$ $\pi^*$C13-C18 | 81.30  | 80.13  |
| $\pi$C24-C26 $\rightarrow$ $\pi^*$C14-C19 | 81.55  | 83.26  |
| $\pi$C24-C26 $\rightarrow$ $\pi^*$C17-C22 | 82.93  | 83.26  |
| $\pi$C28-C29 $\rightarrow$ $\pi^*$N11-C15 | 68.55  | 67.46  |
| $\pi$C28-C29 $\rightarrow$ $\pi^*$C20-C27 | 95.01  | 95.09  |
| $\Delta ET_{\pi\rightarrow\pi^*}$ | 1532.92 | 1538.93 |
| LP(2)O5 $\rightarrow$ $\sigma^*$S1-O7 | 59.52  | 62.28  |
| LP(2)O5 $\rightarrow$ $\sigma^*$S1-O8 | 57.93  | 60.53  |
| LP(2)O5 $\rightarrow$ $\sigma^*$S1-O3 | 116.16 | 102.66 |
| LP(2)O6 $\rightarrow$ $\sigma^*$S2-O9 | 59.60  | 59.23  |
| LP(2)O6 $\rightarrow$ $\sigma^*$S2-O10 | 57.85  | 59.23  |
| LP(2)O6 $\rightarrow$ $\sigma^*$S2-O4 | 115.70 | 102.24 |
| LP(2)O7 $\rightarrow$ $\sigma^*$S1-O5 | 70.81  | 64.58  |
| LP(2)O7 $\rightarrow$ $\sigma^*$S1-O8 | 76.16  | 75.20  |
| LP(2)O7 $\rightarrow$ $\sigma^*$S1-O3 | 185.13 | 153.40 |
| LP(2)O8 $\rightarrow$ $\sigma^*$S1-O5 | 71.94  | 64.62  |
| LP(2)O8 $\rightarrow$ $\sigma^*$S1-O7 | 76.66  | 75.78  |

(Continued)
Na\textsubscript{43}⋯O5, Na\textsubscript{44}⋯O4, Na\textsubscript{44}⋯O6) and the other ones are H bond interactions (O7⋯H36, N11⋯H33, N11⋯H34 and O9⋯H37) with very low $\rho(r)$ and $\nabla^2 \rho(r)$ values. In solution, the number of H bond interactions is notably reduced from 4 to 1 and, where in some cases, the $\rho(r)$ and $\nabla^2 \rho(r)$ values increase (S⋯O) while in other ones decrease (Na⋯O, N−H), as observed in Table 5. These analyses clearly support: (i) the high stabilities of APS in both media, (ii) the ionic nature of APS and, (iii) the different characteristics of the S−O bonds belonging to the SO\textsubscript{4}\textsuperscript{2−} groups and of Na−O bonds present in sodium picosulfate.

### Table 4. (Continued)

| Delocalization | Gas   | PCM   |
|----------------|-------|-------|
| $LP(3)O8 \rightarrow \sigma^*S1-O3$ | 188.60 | 155.83 |
| $LP(2)O9 \rightarrow \sigma^*S2-O6$ | 70.51  | 64.41  |
| $LP(2)O9 \rightarrow \sigma^*S2-O10$ | 76.03  | 75.32  |
| $LP(3)O9 \rightarrow \sigma^*S2-O4$ | 183.96 | 153.65 |
| $LP(2)O10 \rightarrow \sigma^*S2-O6$ | 72.06  | 64.66  |
| $LP(2)O10 \rightarrow \sigma^*S2-O9$ | 76.87  | 75.57  |
| $LP(3)O10 \rightarrow \sigma^*S2-O4$ | 188.64 | 154.87 |
| $LP(1)N11 \rightarrow \sigma^*C15-C20$ | 42.26  |   |
| $\Delta ET_{LP\rightarrow\sigma^*}$ | **1804.13** | **1664.52** |
| $\sigma S1-O3 \rightarrow \pi^*C23-C25$ | 61.15  |   |
| $\sigma S2-O4 \rightarrow \pi^*C22-C26$ | 69.97  |   |
| $\Delta ET_{\pi\rightarrow\pi^*}$ | **131.12** |   |
| $\sigma S1-O5 \rightarrow \sigma^*S1-O7$ | 71.23  | 92.25  |
| $\sigma S1-O5 \rightarrow \sigma^*S1-O8$ | 70.85  | 93.04  |
| $\sigma S2-O6 \rightarrow \sigma^*S2-O9$ | 71.60  | 92.59  |
| $\sigma S2-O6 \rightarrow \sigma^*S2-O10$ | 70.39  | 92.33  |
| $\Delta ET_{\pi\rightarrow\sigma^*}$ | **284.07** | **370.21** |
| $\pi^*N11-C15 \rightarrow \pi^*C20-C27$ | 1075.84 | 1116.56 |
| $\pi^*N11-C15 \rightarrow \pi^*C28-C29$ | 884.44  | 748.55  |
| $\pi^*C23-C25 \rightarrow \pi^*S1-O3$ | 158.13  |   |
| $\pi^*C23-C25 \rightarrow \pi^*C13-C18$ | 1107.11 |   |
| $\pi^*C24-C26 \rightarrow \pi^*S2-O4$ | 184.21  |   |
| $\pi^*C24-C26 \rightarrow \pi^*C14-C19$ | 1078.31 |   |
| $\Delta ET_{\sigma^*\rightarrow\sigma^*}$ | **3067.39** | **3285.76** |
| $\Delta E_{Total}$ | **6819.63** | **6859.42** |
Table 5. Analysis of the topological properties for sodium picosulfate in both media by using the B3LYP/6-31G* method.

| Parameter | S1⋯O3 | S1⋯O5 | S1⋯O7 | S1⋯O8 | Na43⋯O3 | Na43⋯O5 | O7⋯H36 | N11⋯H33 | N11⋯H34 | S2⋯O4 | S2⋯O6 | S2⋯O9 | S2⋯O10 | Na44⋯O4 | Na44⋯O6 | O9⋯H37 |
|-----------|-------|-------|-------|-------|---------|---------|--------|--------|--------|-------|-------|-------|-------|---------|---------|--------|
| ρ(r_2)    | 0.1544| 0.2682| 0.2865| 0.2872| 0.0267  | 0.0140  | 0.0084 | 0.1549 | 0.2683 | 0.2863 | 0.2874 | 0.0268 | 0.0314 | 0.0076  |
| ∇²ρ(r_2)| -0.0910| 1.0500| 1.0644| 0.1920| 0.2235  | 0.0273  | 0.0462 | 0.0304 | 0.0940 | 0.6999 | 1.0466 | 1.0669 | 0.1882 | 0.2204 | 0.0292  |
| λ_1       | -0.2328| -0.4872| -0.4884| -0.0348| -0.0438 | -0.0047 | -0.0137| -0.0062| -0.2330| -0.493 | -0.4869| -0.4887| -0.0351| -0.0432| -0.0063  |
| λ_2       | -0.2211| -0.4999| -0.4395| -0.4398| -0.0325| -0.0012 | -0.0122| -0.0016| -0.2215| -0.4206| -0.4399| -0.4403| -0.0328| -0.0400| -0.0036  |
| λ_3       | 0.3629 | 1.5688| 1.9768| 1.9927| 0.2544  | 0.3079  | 0.0333 | 0.0721 | 0.3605 | 1.5698 | 1.9734 | 1.9960 | 0.2561 | 0.3037 | 0.0391  |
| | | | | | | | | | | | | | | | |
| Distance (Å) | 1.810 | 1.500 | 1.461 | 1.460 | 2.191   | 2.151   | 2.743  | 2.376  | 2.742  | 1.807  | 1.500  | 1.461  | 1.459  | 2.190  | 2.156  | 2.665  |

| Parameter | S1⋯O3 | S1⋯O5 | S1⋯O7 | S1⋯O8 | Na43⋯O3 | Na43⋯O5 | N11⋯H33 | S2⋯O4 | S2⋯O6 | S2⋯O9 | S2⋯O10 | Na44⋯O4 | Na44⋯O6 |
|-----------|-------|-------|-------|-------|---------|---------|--------|-------|-------|-------|-------|---------|---------|
| ρ(r_2)    | 0.1800| 0.2716| 0.2833| 0.2835| 0.0201  | 0.0247  | 0.0088 | 0.1804| 0.2715| 0.2833| 0.2835| 0.0202  | 0.0247  |
| ∇²ρ(r_2) | -0.2020| 0.7773| 0.9332| 0.9353| 0.1252  | 0.1551  | 0.0302 | -0.2033| 0.7852| 0.9340| -0.9330| 0.1262  | 0.1554  |
| λ_1       | -0.2623| -0.4560| -0.4741| -0.4744| -0.0236| -0.0312 | -0.0073| -0.2630| -0.4560| -0.4743| -0.4741| -0.0237 | -0.0312 |
| λ_2       | -0.2476| -0.4409| -0.4367| -0.4353| -0.0227| -0.0290 | -0.0031| -0.2481| -0.4412| -0.4363| -0.4355| -0.0228 | -0.0290 |
| λ_3       | 0.3081| 1.6743| 1.8440| 1.8451| 0.1715  | 0.2154  | 0.0410 | 0.3079| 1.6757| 1.8446| 1.8427| 0.1728  | 0.2157  |
| | | | | | | | | | | | | | | | |
| Distance (Å) | 1.720 | 1.493 | 1.472 | 1.472 | 2.316   | 2.263   | 2.617  | 1.719 | 1.493 | 1.472 | 1.472 | 2.313   | 2.263   |
3.4. Frontier orbital and quantum molecular descriptors studies

Since long time it is highly known that the gap values can predict the reactivity of a drug in different media by using the frontier orbitals [27, 28]. On the other hand, their behaviours in different media can also be predicted by using diverse descriptors such as, the chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S), global electrophilicity index (ω) and global nucleophilicity index (E) descriptors [29, 30, 31, 32, 33]. In this work, we have calculated for APS in both media the gap values and those descriptors at B3LYP/6-31G* level of theory. These parameters in both media can be seen in Table 6 together with the corresponding equations and compared with those observed for drugs with potential antimicrobial activity, as the 1,3-benzothiazole tautomers [33] and with antiviral properties as cidofovir and brincidofovir [38]. These compounds have different rings and groups, as can be observed in Fig. 5. Analyzing the gap values, we observed that the thione form of 1,3-benzothiazole is the most reactive than the other ones while the reactivity decrease according to the following order: thione > brincidofovir > sodium picosulfate > thiol > cidofovir. When the descriptors are deeply analyzed, we observed that the most reactive thione present

Table 6. Calculated HOMO and LUMO orbitals, energy band gap, chemical potential (μ), electronegativity (χ), global hardness (η), global softness (S) and global electrophilicity index (ω) for sodium picosulfate in gas phase and in aqueous solution.

| Frontier orbitals (eV) | Sodium picosulfate | thione | thiol<sup>b</sup> | Cidofovirc | brincidofovirc<sup>c</sup> |
|------------------------|--------------------|--------|-------------------|------------|--------------------------|
|                        | Gas                | PCM    | Gas               | PCM        | Gas                      |
| HOMO                   | −5.912             | −6.100 | −6.4443           | −6.4066    | −6.8847                  | −6.9012                  | −5.9366                  | −5.5435                  |
| LUMO                   | −1.949             | −2.173 | −2.7918           | −2.8545    | −2.6194                  | −2.6679                  | −0.6401                  | −1.772                   |
| GAP                    | −3.963             | −3.927 | −3.6525           | −3.5521    | −4.2653                  | −4.2333                  | −5.2965                  | −3.7715                  |

| Descriptors (eV)       |                     |        |                   |            |                          |
|------------------------|----------------------|--------|-------------------|------------|--------------------------|
| χ                      | −1.9815              | −1.9635| −1.8263           | −1.7761    | −2.1327                  | −2.1167                  | −2.6483                  | −1.8858                  |
| μ                      | −3.9305              | −4.1365| −4.61805          | −4.63055   | −4.7521                  | −4.7846                  | −3.2884                  | −3.6578                  |
| η                      | 1.9815               | 1.9635 | 1.8263            | 1.7761     | 2.1327                   | 2.1167                   | 2.6483                   | 1.8858                   |
| S                      | 0.2523               | 0.2546 | 0.2738            | 0.2815     | 0.2345                   | 0.2362                   | 0.1888                   | 0.2651                   |
| ω                      | 3.8983               | 4.3572 | 5.8388            | 6.0364     | 5.2943                   | 5.4076                   | 2.0416                   | 3.5474                   |
| E;                     | −7.7883              | −8.1220| −8.4337           | −8.2241    | −10.1345                 | −10.1272                 | −8.7087                  | −6.8979                  |

S = ½ηω, ω = μ²/2η; E = μ*η.

χ = - (E(LUMO) − E(HOMO))/2; μ = (E(LUMO) + E(HOMO))/2; η = (E(LUMO) − E(HOMO))/2;

<sup>a</sup>This work.<br><sup>b</sup>From [33];<sup>c</sup>From [38].
the higher electrophilicity index while cidofovir has the most low index. Apparently both parameters are related to the presence of strong charged groups, as the $\text{NO}_2^-$ and S–H groups that in the thiol form due to the presence of an H bond decreases their reactivity, as compared with the thione form. Brincidofovir has slightly higher reactivity than picosulfate and much higher than cidofovir due to the presence of a $\text{PO}_4^{3-}$ group and of a Na atom, here, evidently the presence of a group with higher charge increase the reactividad in brincidofovir. Probably, a high nucleophilicity index together with a high electrophilicity index reduce the reactivity of a drug, as observed for cidofovir because the separation between both indexes is of approximately 4–3 eV while in the most reactive thione that separation is about 3–2 eV. Sodium picosulfate presents reactivity similar to brincidofovir probably due to the presence of two $\text{SO}_4^{2-}$ groups and of the two Na atoms in their structure. The other parameters such as, global hardness ($\eta$) and softness ($S$) are in very good concordance with the order of reactivity, as expected because both descriptors are calculated directly from the gap values.

3.5. NMR study

The $^1$H- and $^13$C-NMR chemical shifts for APS in gas phase and in aqueous solution phases were calculated by using the GIAO method [34] at the B3LYP/6-31G* level of theory and the results are presented in Table 7 and Table 8, respectively. Here, the $^1$H- NMR chemical shifts were compared with the
corresponding experimental available for APS in DMSO-d$_6$ from [39] and with the predicted by Spinus-Web [40] by means of the RMSD values. The comparison of the calculated $^{13}$C-NMR chemical shifts was performed with those $^{13}$C-NMR predicted by Banfi and Patiny [41] and Castillo et al. [42] by means of the RMSD values, as observed in Table 7. Notice that a better correlation is observed for the H nuclei (1.54–1.39 ppm) than the C nuclei (9.14–8.73 ppm), as expected because the calculations were performed using the B3LYP/6-31G* calculations in gas phase and in aqueous solution while the experimental $^1$H-NMR spectrum was registered in DMSO-d$_6$ solution. In aqueous solution, the presences of the SO$_4^{2-}$ groups and of Na atoms evidently have certain influence on the chemical shifts of both nuclei because APS has a higher affinity in water than DMSO.

3.6. Vibrational study

The structures of APS in the two media using the B3LYP/6-31G* level of theory were optimized with $C_1$ symmetries and both structures have 126 normal vibration modes which present activity in both IR and Raman spectra. The available experimental IR spectrum for the monohydrated sodium picosulphate in the solid phase was taken from [43] and can be seen in Fig. 6 compared with the predicted

| H atom | Sodium picosulfate$^a$ | Pred.$^b$ | Exp.$^c$ |
|--------|------------------------|-----------|----------|
|        | Gas        | PCM       |          |          |
| 30-H   | 5.15       | 5.55      | 5.51     | 2.50     |
| 31-H   | 7.38       | 7.43      | 7.51     | 7.08     |
| 32-H   | 7.40       | 7.27      | 7.51     | 7.20     |
| 33-H   | 8.63       | 7.68      | 7.51     | 8.52     |
| 34-H   | 8.32       | 7.56      | 7.51     | 7.74     |
| 35-H   | 7.43       | 7.34      | 7.27     | 7.22     |
| 36-H   | 7.58       | 7.63      | 7.08     | 7.24     |
| 37-H   | 7.69       | 7.46      | 7.08     | 7.70     |
| 38-H   | 7.19       | 7.31      | 7.08     | 5.57     |
| 39-H   | 7.14       | 7.49      | 7.08     | 3.34     |
| 40-H   | 7.74       | 7.68      | 7.69     | 7.72     |
| 41-H   | 9.11       | 9.02      | 8.53     | 8.53     |
| 42-H   | 7.28       | 7.22      | 7.21     | 7.05     |
| RMSD   | 1.39       | 1.54      | 1.44     |

$^a$This work GIAO/B3LYP/6-31G* Ref. to TMS.
$^b$From [39].
$^c$From [40].
The vibrational assignments for APS in both media were performed with the SQMFF procedure \[17, 18\] by using the Molvib program [19] and taking into account the PED contributions $\geq 10\%$. The symmetry coordinates used in the determination of the force fields were similar to those reported for compounds containing analogous rings and groups \[2, 3, 4, 30, 31\] for this reason, they were not presented here. On the other hand, the scale factors used are those reported by Rauhut and Pulay and defined for the 6-31G* basis set [17, 18]. Table 9 shows the observed and calculated wavenumbers and assignments for anhydrous sodium picosulfate in both media. Obviously, we observed higher quantity of bands in the experimental spectrum due to the vibration modes of the water molecule, hence, the broad IR bands at 3639 and 3458 cm$^{-1}$ are clearly attributed to the OH stretching modes. Note that the very intense band predicted by the calculations in gas phase at 606 cm$^{-1}$ and assigned easily to the symmetric $\delta_s$SO$_3$ deformation

### Table 8. Calculated $^{13}$C chemical shifts ($\delta$ in ppm) for sodium picosulfate in gas phase and in aqueous solution.

| C atoms | Sodium picosulfate$^a$ | Pred.$^b$ |
|---------|-------------------------|----------|
|        | Gas                     | PCM      |
| 12-C    | 71.06                   | 71.33    | 40.95 |
| 13-C    | 144.70                  | 144.35   | 141.23 |
| 14-C    | 143.99                  | 144.06   | 141.23 |
| 15-C    | 167.12                  | 168.38   | 162.39 |
| 16-C    | 134.27                  | 134.69   | 126.66 |
| 17-C    | 133.04                  | 133.64   | 126.66 |
| 18-C    | 131.64                  | 134.19   | 126.66 |
| 19-C    | 134.88                  | 135.96   | 126.66 |
| 20-C    | 127.53                  | 127.24   | 118.43 |
| 21-C    | 127.54                  | 128.19   | 121.75 |
| 22-C    | 126.30                  | 127.48   | 121.75 |
| 23-C    | 127.23                  | 127.93   | 121.75 |
| 24-C    | 127.05                  | 128.47   | 121.75 |
| 25-C    | 154.03                  | 153.24   | 151.67 |
| 26-C    | 154.77                  | 153.15   | 151.67 |
| 27-C    | 138.95                  | 138.53   | 136.80 |
| 28-C    | 153.28                  | 154.58   | 149.33 |
| 29-C    | 124.73                  | 124.23   | 123.37 |

**RMSD** 8.73 9.14

$^a$This work GIAO/B3LYP/6-31G* Ref. to TMS.

$^b$From [41, 42].
mode in solution decrease significantly their intensity probably due to that the $\Delta E_{\sigma^*}$ charges transfers related to the O atoms of these groups decrease from 1804.13 kJ/mol in gas phase to 1664.52 kJ/mol in solution, as observed in Table 4. This variation can also be attributed to the topological properties of the S–O bonds because in solution two of these bonds are enlarged while the other two shortened, as observed by AIM calculations (Table 5). The predicted Raman spectra for APS in both media by using the same method of calculation are compared in Fig. 7. We present below a brief discussion of the assignments for some groups.

3.7. Band Assignments

3.7.1. $SO_4^{2-}$ groups

Normally, the asymmetric and symmetric stretching and bending modes of these groups for a tetrahedral structure are expected between 1150 and 320 cm$^{-1}$ [1, 44, 45, 46] while in potassium borosulfate, where three sulphate groups have C$_{3v}$ symmetries, the antisymmetric and symmetric modes were assigned to the bands at 1375 and 884 cm$^{-1}$. Here, the broad and intense band between 1342 and 1146 cm$^{-1}$, centred at 1258 cm$^{-1}$, obviously is assigned to the four antisymmetric stretching modes expected for both $SO_4^{2-}$ groups while the corresponding symmetric modes are assigned to the intense IR band at 892 cm$^{-1}$, as indicated in

![Fig. 6. Experimental available infrared spectra of sodium picosulfate hydrate (upper) taken from [43] and the corresponding anhydrous predicted in gas phase (medium) and in aqueous solution (bottom) by using B3LYP/6-31G* level of theory.](image-url)
Table 9. Observed and calculated wavenumbers (cm\(^{-1}\)) and assignments for anhydrous sodium picosulfate in both media.

| Experimental\(^a\) | B3LYP/6-31G* Method\(^b\) | Gas phase | Aqueous solution |
|------------------|--------------------------|-----------|------------------|
| **IR**           | **SQM\(^b\)** | **Assignments** | **SQM\(^b\)** | **Assignments** |
| solid            | SQM\(^b\) | Assignments | SQM\(^b\) | Assignments |
| 3639w            |       | νOH H\(_2\)O |       | νOH H\(_2\)O |
| 3458m            |       | νOH H\(_2\)O |       |               |
| 3100 sh          | 3103  | tC19-H34   | 3100  | tC18-H33     |
|                  | 3096  | tC21-H36   | 3097  | tC21-H36     |
|                  | 3091  | tC18-H33   | 3096  | tC29-H42     |
|                  | 3084  | tC29-H42   | 3095  | tC24-H39     |
|                  | 3072  | tC20-H35   | 3086  | tC23-H38     |
|                  | 3069  | tC22-H37   | 3085  | tC20-H35     |
| 3068w            | 3068  | νC24-H39   | 3083  | tC19-H34     |
|                  | 3068  | tC23-H38   | 3074  | tC27-H40     |
|                  | 3058  | tC27-H40   | 3072  | tC17-H32     |
| 3047w            | 3049  | tC16-H31   | 3070  | tC16-H31     |
|                  | 3045  | tC17-H32   | 3059  | tC22-H37     |
| 2999w            | 3041  | tC28-H41   | 3057  | tC28-H41     |
| 2915w            | 2932  | tC12-H30   | 2950  | tC12-H30     |
| 1653m            | 1606  | tC16-C21   | 1600  | tC16-C21,tC23-C18 |
| 1616m            | 1593  | tC27-C20   | 1592  | tC28-C29,tC20-C15 |
| 1600 sh          | 1586  | tC24-C19,tC14-C17 | 1583  | tC18-C13,tC13-C16 |
| 1560 sh          | 1579  | tC18-C13,tC13-C16 | 1580  | tC14-C17,tC26-C24 |
| 1541 sh          | 1577  | tC29-C27   | 1571  | tC29-C27,tC15-N11 |
| 1529s            | 1560  | tC19-C14,tC26-C24 | 1562  | tC19-C14,tC22-C26 |
| 1495m            | 1502  | βC16-H31   | 1498  | βC16-H31,tC21-C25 |
| 1462m            | 1479  | βC24-H39   | 1476  | βC28-H41,βC20-H35 |
| 1454m            | 1476  | βC28-H41,βC20-H35 | 1471  | βC24-H39 |
| 1438w            | 1436  | βC29-H42   | 1429  | βC29-H42     |
| 1420             | 1420  | tC23-C18   | 1416  | pC12-H30     |
| 1405             | 1355  | pC12-H30,βC17-H32,βC19-H34 | 1396  | βC17-H32 |
| 1347 sh          | 1324  | βC28-H41   | 1345  | pC12-H30     |
| 1301s            | 1306  | βC22-H37   | 1302  | βC19-H34     |
| 1271 sh          | 1295  | tC25-C23,tC21-C25 | 1298  | tC25-C23     |
|                  | 1284  | tC22-C26   | 1281  | tN11-C28     |
| 1258 vs          | 1274  | ν\(_e\)SO\(_3\)(2) | 1266  | tN11-C28     |
|                  | 1272  | ν\(_e\)SO\(_3\)(1) | 1246  | tC19-C14,pC12-H30 |

(Continued)
| Experimental B3LYP/6-31G* Method* | IR Gas phase | Aqueous solution |
|-----------------------------------|-------------|------------------|
| IR                               | SQM Assignments | SQM Assignments |
| solid 1226s                       | νN11-C28     | 1240 νC15-N11    |
| 1239                              | νC15-N11     | 1192 νC25-O3     |
| 1234                              | ρC12-H30,υC19-C14 | 1190 νSO3(1)   |
| 1196sh                            | νC25-O3      | 1190 νSO3(2)     |
| 1183 sh                           | νC26-O4      | 1185 νC26-O4     |
| 1186                              | νC20-C15,νC12-C15 | 1184 νC12-C15   |
| 1177                              | νSO3(1)      | 1176 νC12-C13    |
| 1175                              | νSO3(2)      | 1159 βC21-H36    |
| 1166 sh                           | υC12-C13     | 1158 βC22-H37    |
| 1163                              | βC23-H38     | 1152 νC12-C14,υC24-C19 |
| 1130 sh                           | νSO3(2),υC26-O4 | 1143 νSO3(2)   |
| 1121w                             | νC12-C14     | 1143 βC27-H40    |
| 1151                              | βC27-H40     | 1142 νSO3(1)     |
| 1105                              | βC21-H36,βC18-H33 | 1101 βC23-H38   |
| 1086s                             | βC29-H42,υC17-C22 | 1089 νC17-C22   |
| 1073 sh                           | υC17-C22     | 1088 νC27-C20    |
| 1033m                             | αC28-C29     | 1043 νC29-C27    |
| 1009w                             | βR1(1)       | 1016 βR1(1)      |
| 996                               | βR1(3)       | 1012 γC27-H40    |
| 995                               | βR1(2)       | 994 βR1(3)       |
| 993                               | βR1(2)       | 992 βR1(2)       |
| 979w                              | γC18-H33     | 980 γC28-H41     |
| 965w                              | γC28-H41     | 972 γC18-H33     |
| 952w                              | γC16-H31     | 963 γC19-H34     |
| 892s                              | νSO3(2)      | 959 γC16-H31     |
| 892s                              | νSO3(1)      | 951 νSO3(1)      |
| 942                               | γC24-H39     | 950 νSO3(2)      |
| 933                               | γC17-H32     | 947 γC17-H32     |
| 900                               | γC20-H35     | 911 γC20-H35     |
| 871m                              | γC22-H37     | 888 γC24-H39     |
| 868                               | γC23-H38     | 875 γC23-H38     |
| 842m                              | δC13C12C15   | 856 δC13C12C15   |
| 826 sh                            | γC19-H34     | 836 γC23-H38,γC24-H39 |
| 830                               | γC26-O4      | 831 γC23-H38     |

(Continued)
Table 9. (Continued)

| IR | Gas phase | B3LYP/6-31G* Method | Aqueous solution |
|----|-----------|---------------------|------------------|
| solid | SQM<sup>b</sup> Assignments | SQM<sup>b</sup> Assignments |
| 828 | γC21-H36 | 829 | γC21-H36 |
| 824 | γC19-H34 | 822 | γC24-H39 |
| 811 | γC22-H37 | 816 | γC22-H37 |
| 783m | δC13C12C14 | 806 | δC13C12C14 |
| 762m | γC29-H42 | 769 | γC29-H42 |
| 747w | tR<sub>1</sub>(3) | 752 | tR<sub>1</sub>(3) |
| 731w | tR<sub>1</sub>(2) | 729 | tR<sub>1</sub>(2) |
| 718w | tR<sub>1</sub>(1) | 711 | tR<sub>1</sub>(1) |
| 676 sh | βR<sub>3</sub>(3),βR<sub>3</sub>(3) | 681 | βR<sub>3</sub>(3) |
| 660m | βR<sub>3</sub>(1),βR<sub>3</sub>(1) | 644 | βR<sub>3</sub>(1) |
| 650w | βR<sub>3</sub>(3) | 642 | βR<sub>3</sub>(1) |
| 630 sh | βR<sub>3</sub>(2) | 631 | βR<sub>3</sub>(2) |
| 625w | βR<sub>3</sub>(3) | 626 | νS1-O3 |
| 610w | βR<sub>3</sub>(2) | 621 | βR<sub>3</sub>(2) |
| 598m | γSO<sub>3</sub>(2) | 596 | δSO<sub>3</sub>(1) |
| 581w | δSO<sub>3</sub>(1) | 565 | δSO<sub>3</sub>(1) |
| 575 sh | tR<sub>1</sub>(1) | 566 | δSO<sub>3</sub>(1) |
| 560 sh | tR<sub>1</sub>(2) | 563 | δSO<sub>3</sub>(2) |
| 528 sh | δSO<sub>3</sub>(1) | 523 | δSO<sub>3</sub>(1) |
| 524 | δSO<sub>3</sub>(2) | 522 | δSO<sub>3</sub>(2) |
| 521w | δSO<sub>3</sub>(1) | 518 | δSO<sub>3</sub>(2),γC26-O4 |
| 514 | δSO<sub>2</sub>(2),γC26-O4 | 514 | δSO<sub>2</sub>(1),γC25-O3,γC13-C12 |
| 500 sh | tR<sub>3</sub>(3),γC15-C12 | 498 | tR<sub>3</sub>(3) |
| 477 | tR<sub>2</sub>(2) | 473 | tR<sub>2</sub>(2) |
| 458 sh | tR<sub>2</sub>(1) | 468 | tR<sub>2</sub>(1) |
| 429 sh | βC25-O3 | 441 | βC25-O3 |
| 421w | βC26-O4 | 435 | βC26-O4 |
| 412 | tR<sub>3</sub>(1) | 415 | tR<sub>3</sub>(1) |
| 405w | tR<sub>3</sub>(3) | 408 | tR<sub>3</sub>(2) |
| 398w | tR<sub>3</sub>(2) | 407 | tR<sub>3</sub>(3) |
| 380 | νO6-Na44 | 373 | νS1-O3 |
| 366 | ρSO<sub>3</sub>(1) | 355 | ρSO<sub>3</sub>(1) |
| 333 | νS2-O4 | 342 | ρSO<sub>3</sub>(1) |
| 313 | νS1-O3 | 322 | ρSO<sub>3</sub>(2) |
| 303 | ρ′SO<sub>3</sub>(1) | 310 | ρ′SO<sub>3</sub>(1) |

(Continued)
Table 9. Notice that in solution these stretching modes are shifted toward lower wavenumbers, as expected because these modes are strongly affected by the hydration, as was previously analyzed. Here, the symmetric bending modes are predicted by calculations at higher wavenumbers (600–596 cm⁻¹) than the corresponding antisymmetric modes (525–514 cm⁻¹) and; for this reason, they

| Experimental | B3LYP/6-31G* Method |
|--------------|----------------------|
| IR Gas phase | Aqueous solution     |
| solid SQM    | Assignments          | solid SQM    | Assignments          |
| 294 ρ'sO₃(2) | 298 ρ'sO₃(2)          |
| 280 λO₅-Na₄₃| 257 βC₁₁-C₁₁          |
| 268 ρSO₃(2) | 248 υO₅-Na₄₃,βS₁O₅Na₄₃|
| 264 δS₁O₅Na₄₃| 230 υO₅-Na₄₃          |
| 244 βC₁₁-C₁₁| 226 υO₆-Na₄₄          |
| 234 ρ'sO₃(2),βC₁₁-C₁₁| 215 βC₁₁-C₁₁         |
| 206 βC₁₁-C₁₂,βC₁₁-C₁₂| 206 βC₁₁-C₁₂        |
| 179 tr₃(1),tR₃(2) | 181 tr₃(2),tR₃(1)    |
| 169 tr₃(2),υO₅-Na₄₃| 155 δC₂₂O₃S₁         |
| 145 tr₃(2),ρSO₃(2) | 131 δS₁O₅Na₄₃        |
| 134 δC₂₂O₃S₁ | 120 δS₂O₆Na₄₄         |
| 92 δC₁₂C₁₂C₁₅| 86 δC₂₂O₄S₂           |
| 72 γC₂₂O₃   | 71 δC₂₂O₄S₂           |
| 67 δC₂₂O₄S₂,δC₁₂C₁₂C₁₅| 67 τₐC₂₂O₃   |
| 50 τNa₄₄-O₆ | 60 τNa₄₄-O₅           |
| 49 τNa₄₃-O₅ | 59 τNa₄₄-O₆           |
| 47 τNa₄₃-O₅,τₐC₁₂C₁₂C₁₅| 57 τₐC₂₂O₃   |
| 39 twSO₃(2) | 51 τₐC₂₂O₃            |
| 37 twSO₃(1) | 47 τₐC₂₂O₃,τₐC₁₂C₁₂C₁₅|
| 32 τₐC₁₂C₁₂ | 35 twSO₃(2)           |
| 26 τₐC₁₁-C₁₂ | 29 γC₁₁-C₁₂            |
| 21 τₐC₁₁-C₁₂ | 27 τₐC₁₂-C₁₂            |
| 13 τₐC₂₂O₄   | 19 twSO₃(1)            |
| 11 γC₁₁-C₁₂ | 18 τₐC₁₁-C₁₂,τₐC₁₂-C₁₂C₁₅|
| 4 τₐC₂₂O₃   | 15 τₐC₂₂O₄             |

Abbreviations: κ, stretching; β, deformation in the plane; γ, deformation out of plane; wag, wagging; τ, torsion; βR, deformation ring τR, torsion ring; ρ, rocking; tw, twisting; δ, deformation; a, antisymmetric; s, symmetric; (1), glucopyranose Ring1; (2), glucopyranose Ring2.

*This work.

*From scaled quantum mechanics force field.

*From [43].
were assigned to the band and shoulder at 598 and 591 cm\(^{-1}\), respectively. In solution, all these modes are predicted between 565 and 514 cm\(^{-1}\) because are influenced by the hydration. The four rocking and the two twisting modes expected for both sulphate groups are clearly predicted in gas phase in the 303–268 and 39–37 cm\(^{-1}\) regions, respectively and, both modes were not assigned because in the IR spectrum were recorded bands only up to 398 cm\(^{-1}\). This vibrational analysis shows clearly the influence of the different S–O bonds of the sulphate groups on the positions of the IR bands and, in particular, in aqueous solution support the shifting of the bands related to these groups as a consequence of the hydration.

3.7.2. Pyridinyl and phenyl rings modes.

The thirteen expected C–H stretching modes are predicted in gas phase between 3103 and 2932 cm\(^{-1}\) where the C12–H30 bond related to the C atom with hybridization sp\(^3\), is predicted to lower wavenumbers than the other ones. Thus, the bands observed between 3100 and 2915 cm\(^{-1}\) are clearly assigned to those vibration modes. In solution, these modes are predicted slightly to higher wavenumbers, as observed in Table 9 probably due to that these H atoms are involved in gas phase to two N⋯H and two O⋯H bonds while in solution only the N⋯H is observed. The in-plane C–H deformation modes are assigned to the bands
observed between 1495 and 1086 cm\(^{-1}\) because they are predicted by SQM calculations in this region while the corresponding out-of-plane CH deformation modes are assigned according to calculation between 1009 and 762 cm\(^{-1}\). These modes are not affected by the hydration because they undergo few shifted in solution. The C=C stretching modes of both phenyl rings are predicted by the SQM/B3LYP/6-31G* calculations between 1606 and 1560 cm\(^{-1}\) while the C–C stretching modes between 1420 and 1044 cm\(^{-1}\), hence these modes are assigned according to calculations. On the other hand, the two expected C–N stretching modes belonging to the pyridinyl ring are predicted at 1271 and 1239 cm\(^{-1}\) while in solution are predicted to higher wavenumbers. This observation can be attributed to the two N⋯H bonds observed only in gas phase while in solution only one of them is observed. Moreover, two transitions observed by NBO calculation justify the shifting observed in solution, they are the \(\Delta ET_{\pi\rightarrow\pi^*}\) and \(\Delta ET_{\pi\rightarrow\pi^*}\) charge transfers (see Table 4). The deformation and torsion modes for both pyridinyl and phenyl rings are predicted by SQM calculations in the expected regions [4, 28, 29, 30, 31, 32] and only some deformation modes were assigned because the torsion modes are predicted in the lower wavenumbers region where there are not observed bands. The assignments for the remaining skeletal modes can be seen in Table 9.

**3.8. Force fields**

The force constants for APS in both media were first calculated in Cartesian coordinates from their corresponding force fields by using the SQM procedure and later they were transformed to internal coordinates with the Molvib program [17, 18, 19]. These constants are summarized in Table 10 compared with those reported for CrO\(_2\)(SO\(_3\)F)\(_2\) [3] and benzisoxazole methane sulfonic acid sodium salt (BOSNa) [4] and, with those calculated in this work for K\(_5\)[B(SO\(_4\)]\(_4\)]. Analyzing first the force constants values for APS in both media we observed that practically the \(f(\nu C-C)_{A6}\), \(f(\nu C-C)\) and \(f(\nu C-H)\) constants change slightly in solution, especially the latter increase because the H bonds decrease in this media, as suggested by the above studies. The other constants change notably due to the structural changes that experiment the both SO\(_4^{2-}\) groups and the Na⋯O bonds in solution. When the constants for APS are compared with those observed for CrO\(_2\)(SO\(_3\)F)\(_2\) [3] the values are higher in this chromyl compound because their three S=O bonds have double bound character while the high value observed in the \(f(\nu S-F)\) constant is due to the presence of the F atom instead of other O atom. On the other hand, the \(f(\nu S=O)\) constant is higher in APS than that calculated for BOSNa because only three S=O bonds have this species while that a higher value is observed in their \(f(\nu C-N)\) constant due to that the N atoms are linked to C and O atoms instead of two C atoms, as in APS and, besides these bonds belong to a five member ring instead of a six member ring, as in APS. However, the \(f(\nu Na-O)\) constant values
are practically similar in these compounds while in \( \text{K}_5\text{[B(SO}_4\text{)]}_4 \) the presence of the most electropositive K atom increase notably the constant value in this borate compound. Moreover, the presence of five sulphate groups evidently increase the values of the\( f(\nu\text{SO}) \) and\( f(\nu\text{S−O}) \) constants, as compared with that observed in APS. Obviously, this study also support the differences in the S=O, S−O and Na⋯O bonds and their modifications in solution.

### 3.9. Electronic spectrum

The electronic spectrum for APS in aqueous solution was predicted by B3LYP/6-31G* calculations and their comparison with the experimental available UV-visible spectrum reported for the sodium picosulphate hydrate [47] can be seen in Fig. 8. A strong band at 262.54 nm is observed in the experimental spectrum while in the predicted spectrum is calculated at 234.50 nm which can be easily assigned to the \( \pi\rightarrow\pi^* \) and \( \pi^*\rightarrow\pi^* \) interactions due to the C=C and C−N bonds because the calculations predicted these interaction with higher energy values, as observed by

### Table 10. Comparison of scaled internal force constants for sodium picosulfate in both media with those calculated for compounds with similar groups.

| Force constant          | B3LYP/6-31G\( ^{\text{a,a}} \) | B3P86/6-31G\( ^{\text{a,a}} \) |
|-------------------------|-------------------------------|-------------------------------|
|                         | Picosulfate                  | CrO\(_2\)(SO\(_3\)F\(_2\))\(^{\text{b}} \) | BOSNa\(^{\text{c}} \) | K\(_5\)[B(SO\(_4\)]_4 \) |
|                         | Gas   | PCM | Gas | Gas | Force constant | Gas | Gas |
| \( f(\nu\text{SO}) \)  | 8.25  | 7.79 | 10.6 | 7.27 | \( f(\nu\text{SO}) \) | 8.7 |
| \( f(\nu\text{S−X}) \) | 1.65  | 2.37 | 4.7  | 6.48 | \( f(\nu\text{S−O}) \) | 4.3 |
| \( f(\nu\text{C−C}) \)  | 6.50  | 6.51 | 6.48 | 8.17 | \( f(\nu\text{C−C}) \) | 8.17 |
| \( f(\nu\text{C−N}) \)  | 7.03  | 6.87 | 5.72 | 5.72 | \( f(\nu\text{Na−O}) \) | 1.42 |
| \( f(\nu\text{C−H}) \)  | 5.18  | 5.21 | 0.82 | 1.91 | \( f(\delta\text{S−O−C}) \) | 0.40 |
| \( f(\nu\text{Na−O}) \) | 0.88  | 0.52 | 0.52 | 0.52 | \( f(\nu\text{K−O}) \) | 1.42 |
| \( f(\nu\text{C−H}) \)  | 5.18  | 5.21 | 0.82 | 1.59 | \( f(\nu\text{S−O}) \) | 2.0 |
| \( f(\delta\text{O−S−O}) \) | 1.72  | 1.59 | 1.6  | 1.6  | \( f(\delta\text{S−O−C}) \) | 0.40 |
| \( f(\delta\text{S−O−C}) \) | 0.87  | 0.95 | 0.95 | 0.95 | \( f(\delta\text{S−O−B}) \) | 0.40 |
| \( f(\delta\text{C−C}) \)  | 1.83  | 1.93 | 1.6  | 1.6  | \( f(\delta\text{S−O−C}) \) | 0.40 |
| \( f(\delta\text{S−O−Na}) \) | 2.56  | 1.33 | 2.56 | 1.33 | \( f(\delta\text{S−O−B}) \) | 0.40 |

Units are mdyn Å\(^{-1}\) for stretching and mdyn Å rad\(^{-2}\) for angle deformations, A6, pyridinyl and phenyl Rings.

\(^{\text{a}}\) This work.

\(^{\text{b}}\) From [3].

\(^{\text{c}}\) From [4] for benzisoxazole methane sulfonic acid sodium salt (BOSNa); X = (O,F).
NBO analysis (Table 4). Here, the presence of shoulders in the experimental spectrum could be attributed to the quantity observed of these interactions as a consequence of the three six member’s rings in the structure of APS. Table 11 shows the positions and intensities of the observed bands in the experimental spectrum and in the predicted by the TD-DFT calculations.

**Table 11.** TD-DFT calculated visible absorption wavelengths (nm) and oscillator strengths (f) for sodium picosulfate in aqueous solution.

| Energy Transition (eV) | λ(nm) | f     | λ(nm)     | Assignment         |
|------------------------|------|-------|-----------|---------------------|
| B3LYP6-31G* a          |      |       |           |                     |
| 5.9557                 | 208.18 | 0.1042 | 157.00 sh | π→π* (C=C)          |
| 5.2871                 | 234.50 | 0.1413 | 262.54 s  | π→π* (C-N)          |
| 5.1603                 | 240.26 | 0.1700 | 268.80 sh | π*→π* (C=C)         |

aThis work.
4. Conclusions

In this work, the theoretical molecular structures of anhydrous sodium picosulfate with chemical formula C_{18}H_{13}NNa_{2}O_{8}S_{2}, was optimized in gas and aqueous solution phases by using the B3LYP/6-31G* method. The influences of the solvent on their properties were studied with the IFEPCE and SM models. The AIM results show clearly the presence of the S═O, S―O, Na⋯O, N⋯H and O⋯H bonds with different characteristics, thus, in each sulphate group is observed one covalent S―O bond where the O atoms are linked to the C atoms, three highly polar covalent S═O bonds and two ionic Na―O bonds. Besides, in gas phase are predicted two N⋯H and O⋯H bonds while in solution disappear one N⋯H bond and the two O⋯H bonds. The nature of those bonds belonging to the two C-O-SO_{3}-O-Na groups and, evidenced by AIM calculations, have notable influence on the NPA and MK charges, MEP values, reactivities, descriptors, vibration normal modes and force constants in both media. On the other hand, the high stabilities of sodium picosulfate are supported by the NBO in both media and evidenced by the strong band observed in the electronic spectrum in solution. Here, the force fields using the B3LYP/6-31G* method and the complete assignments of the 126 vibration normal modes expected for sodium picosulfate in both media are presented. The predicted infrared, ^1H-NMR and UV-visible spectra are in reasonable concordance with the corresponding available experimental spectra. In addition, the frontier orbitals show the high reactivities of sodium picosulfate in both media which is approximately comparable to brincidofovir, an antiviral drug used against the Ebola disease.

Declarations

Author contribution statement

Davide Romani: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Isabel Salas Tonello: Performed the experiments.

Silvia A. Brandán: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This work was supported by CIUNT (Consejo de Investigaciones, Universidad Nacional de Tucumán).
Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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