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# A new structure of a serotonin salt: comparison and conformational analysis of all known serotonin complexes

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Four serotonin salt structures (serotonin adipate, $C_{10}H_{13}N_2O^+\cdot C_6H_9O_4^-$, is a previously unknown structure) were analysed to understand the influence of the anion on serotonin conformation. Hydrogen bonding alone favours a flat conformation, whereas additional stacking interactions between ions may possibly account for the nonplanar conformation. Since molecular conformation, stability and biological activity are interrelated, one can consider influencing the chemical and biological properties of serotonin by selecting an appropriate counter-ion for salt formation.

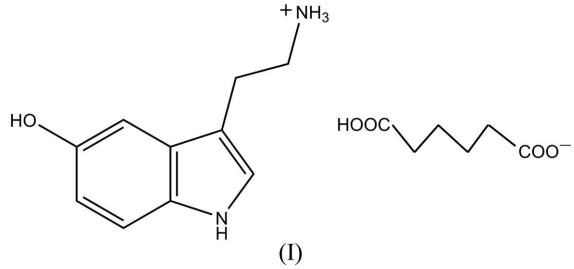
**Keywords: crystal structure; serotonin adipate; conformation; hydrogen bonding; stacking interactions; Hirshfeld surfaces.**

## 1. Introduction

Biologically active substances are at the focus of biological, pharmaceutical and chemical research. Serotonin, one of the most common neurotransmitters, is widely studied in relation to its effect on humans at different levels, from cellular up to mental (Mohammad-Zadeh *et al.*, 2008; Seo *et al.*, 2008; Berger *et al.*, 2009). Although serotonin plays a key role in some biological processes, its chemistry and crystallography have not been well studied.

Many biologically active compounds are crystallized with additional components as salts or cocrystals to improve stability or solubility or to decrease hygroscopicity (Almarsson & Zaworotko, 2004; Libbrecht, 2005; Schultheiss & Newman, 2009; Babu & Nangia, 2011; Brittain, 2012). Serotonin is not an exception. Its low thermal stability in solution can be overcome if a second component, like adipic acid, is added on crystallization. Serotonin adipate has been used in medical formulations in Russia and Eastern Europe as an analogue of serotonin creatinine sulfate monohydrate, but the crystal structure of the adipate salt remained unknown. Another interesting issue is that the conformation of serotonin creatinine sulfate monohydrate is different from that predicted theoretically for a 'free' serotonin molecule in the gas phase (Chothia, 1969; Pratuangdejkul, Jaudon *et al.*, 2006). It was worth investigating whether the conformation of serotonin in the adipate salt is the same as in creatinine sulfate, remembering that they are pharmacological analogues.

The aim of the present study was to crystallize serotonin adipate, (I), determine its crystal structure and analyse it in a comparison with all the other previously known crystal structures of serotonin (Karle *et al.*, 1965; Thewalt & Bugg, 1972; Aniy *et al.*, 1978), paying special attention to the interrelation between the crystalline environment of a molecule and the molecular conformation.




(I)

## 2. Experimental

### 2.1. Synthesis and crystallization

Serotonin adipate (purity not less than 98%, according to high-performance liquid chromatography data) was crystallized from an aqueous solution at 313 K. The crystals used in the diffraction experiments were almost transparent, with a light-brown tinge.

### 2.2. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 1. All H atoms were located in a difference Fourier map, and their positions and isotropic displacement parameters were refined freely.

## 3. Results and discussion

The crystal structure of serotonin adipate, (I) (Fig. 1), consists of sheets of molecules, in which chains of serotonin cations with protonated hydroxy and amino groups, linked *via* N—H···O hydrogen bonds (Table 2), alternate with chains formed by adipate anions, linked *via* O—H···O hydrogen bonds (Table 2). Additional O—H···O and N—H···O hydrogen bonds link serotonin cations to adipate anions, so that a two-dimensional network containing interconnected rings is formed (Fig. 2 and Table 2).

The serotonin conformations in four different known crystal structures (including the present structure of serotonin adipate) are compared in Fig. 3. The values of the bond

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**Table 1**
Experimental details.

| | |
|---|---|
| Crystal data | |
| Chemical formula | $C_{10}H_{13}N_2O^+\cdot C_6H_9O_4^-$ |
| $M_r$ | 322.36 |
| Crystal system, space group | Triclinic, $P\overline{1}$ |
| Temperature (K) | 298 |
| $a, b, c$ (Å) | 7.1582 (3), 10.5984 (7), 12.1715 (7) |
| $\alpha, \beta, \gamma$ (°) | 113.202 (6), 101.233 (4), 98.045 (4) |
| $V$ (Å$^3$) | 808.04 (8) |
| $Z$ | 2 |
| Radiation type | Mo $K\alpha$ |
| $\mu$ (mm$^{-1}$) | 0.10 |
| Crystal size (mm) | 0.15 × 0.12 × 0.05 |
| | |
| Data collection | |
| Diffractometer | Oxford Gemini Ultra R diffractometer |
| Absorption correction | Multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2008) |
| $T_{min}$, $T_{max}$ | 0.994, 1.000 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 10092, 3286, 1849 |
| $R_{int}$ | 0.061 |
| (sin $\theta/\lambda)_{max}$ (Å$^{-1}$) | 0.625 |
| | |
| Refinement | |
| $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ | 0.051, 0.121, 1.00 |
| No. of reflections | 3286 |
| No. of parameters | 296 |
| No. of restraints | 0 |
| H-atom treatment | All H-atom parameters refined |
| $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å$^{-3}$) | 0.16, −0.20 |

Computer programs: *CrysAlis PRO* (Oxford Diffraction, 2008), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), *OLEX2* (Dolomanov *et al.*, 2009), *Mercury* (Macrae *et al.*, 2008), *PLATON* (Spek, 2009), *CrystalExplorer* (McKinnon *et al.*, 1998; Spackman & McKinnon, 2002), *enCIFer* (Allen *et al.*, 2004) and *publCIF* (Westrip, 2010).

**Table 2**
Hydrogen-bond geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| O1—H1···O4$^{i}$ | 1.04 (3) | 1.53 (3) | 2.569 (2) | 172 (2) |
| N1—H1$A$···O3$^{ii}$ | 0.99 (3) | 1.80 (3) | 2.762 (3) | 163 (2) |
| N1—H1$B$···O5$^{iii}$ | 1.00 (3) | 1.80 (3) | 2.782 (3) | 166 (2) |
| O5—H5···O2$^{iv}$ | 0.84 (3) | 1.82 (3) | 2.647 (3) | 164 (3) |

Symmetry codes: (i) $x, y+1, z$; (ii) $-x, -y, -z+1$; (iii) $x, y-1, z$; (iv) $x, y, z+1$.

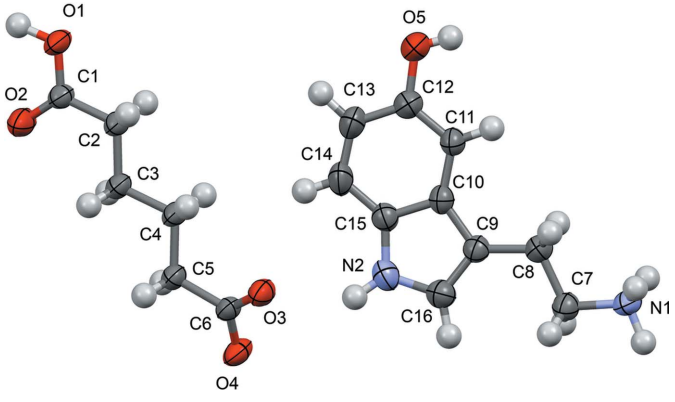


**Figure 1**
The molecular structure of serotonin adipate, (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level for non-H atoms. H atoms are shown as spheres of an arbitrary radius.

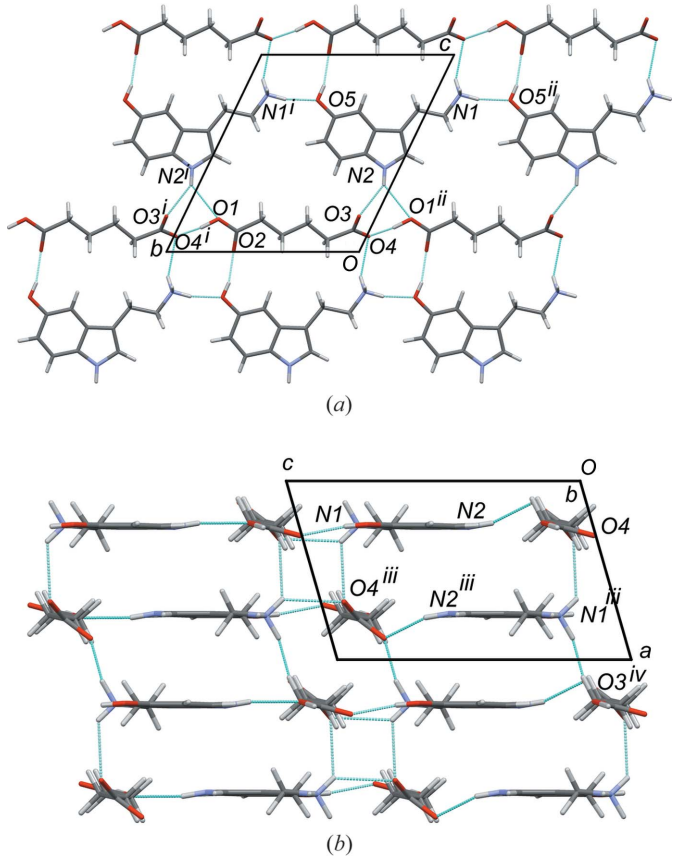


**Figure 2**
Fragments of the crystal structure of serotonin adipate, viewed in the *bc* and *ac* planes. Hydrogen bonds are shown as dashed lines. [Symmetry codes: (i) $x, y+1, z$; (ii) $x, y-1, z$; (iii) $-x+1, -y, -z+1$; (iv) $x+1, y, z$.]

lengths and angles are quite similar in all four structures. The torsion angles are rather close in three of the four compounds, in which the molecules are almost flat, but differ significantly in serotonin picrate, in which the side chain of serotonin is almost orthogonal to the planar bicyclic system (Fig. 3 and Table 3).

To understand the relationship between the molecular conformations and the crystalline environments, the molecular packing in the four structures was compared in relation to

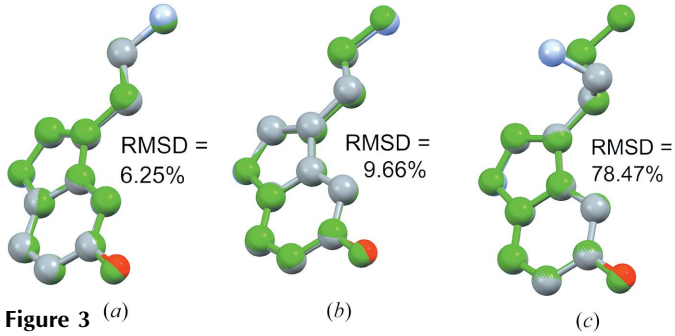


**Figure 3**
Serotonin conformations in different salts, showing overlay pictures of adipate (medium dark colour; green in the electronic version of the journal) with (*a*) oxalate, (*b*) creatinine sulfate and (*c*) picrate. The molecules are almost flat and identical in (*a*) and (*b*), but differ and are not flat in the case of (*c*).

**Table 3**
Geometric parameters of the serotonin molecule in different serotonin salts.

$\varphi_1$, $\varphi_2$, $\varphi_3$ and $\varphi_4$ are as defined in Fig. 4. Gp denotes the *+gauche*, Gm the *−gauche* and 'At' the *anti* conformation. The H atoms with similar values of the $\varphi_3$ torsion angle were chosen as HN1*A*. Serotonin picrate angles and distances can hardly be compared due to significant changes in dihedral angles. S.u. values are not given due to their absence in the original articles.

| Angle (°) | N1—C7—C8 | C7—C8—C9 | C8—C9—C16 | C8—C9—C10 | O5—C12—C11 | O5—C12—C13 |
|---|---|---|---|---|---|---|
| Adipate | 110.1 (2) | 113.9 (2) | 128.9 (2) | 124.5 (2) | 122.2 (2) | 116.0 (2) |
| Creatine sulfate | 108.0 | 111.1 | 131.3 | 124.6 | 121.9 | 115.9 |
| Oxalate | 115.4 | 113.9 | 129.7 | 123.4 | 121.4 | 118.1 |
| Picrate | 111.0 | 114.7 | 127.8 | 126.4 | 117.5 | 120.7 |

| Distance (Å) | N1—C7 | C7—C8 | C8—C9 | C9—C16 | C9—C10 | O5—C12 |
|---|---|---|---|---|---|---|
| Adipate | 1.483 (3) | 1.510 (3) | 1.490 (3) | 1.368 (3) | 1.427 (3) | 1.380 (3) |
| Creatine sulfate | 1.51 | 1.53 | 1.48 | 1.37 | 1.47 | 1.38 |
| Oxalate | 1.51 | 1.48 | 1.50 | 1.37 | 1.43 | 1.37 |
| Picrate | 1.49 | 1.51 | 1.50 | 1.37 | 1.44 | 1.39 |

| Dihedral angle (°) | Conformation of $\varphi_1\varphi_2$ | $\varphi_1$ | $\varphi_2$ | $\varphi_3$ | $\varphi_4$ |
|---|---|---|---|---|---|
| Adipate | AtAt | 178.7 | 177.2 | 60.0 | 4.0 |
| Creatinine | GpGp | 166.7 | 172.6 | 60.0† | 180.0† |
| Oxalate | GpAt | 171.7 | 179.7 | 63.9 | 174.2 |
| Picrate | GmGm‡ | −67.5 | −66.6 | 57.01 | 161.1 |

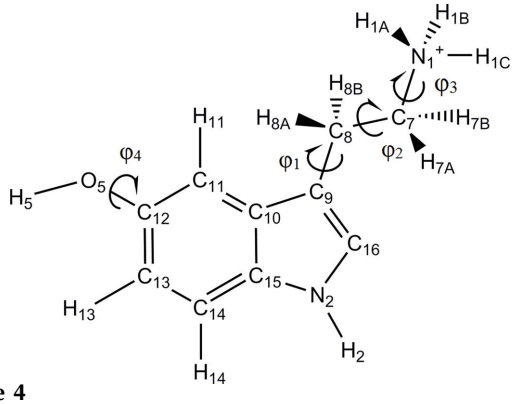


**Figure 4**
Definition of serotonin atom numbering and dihedral angles. The four torsion angles are defined as $\varphi_1$ (C10—C9—C8—C7), $\varphi_2$ (C9—C8—C7—N1), $\varphi_3$ (C8—C7—N1—$H_{N1A}$) and $\varphi_4$ (C11—C12—O5—H5).

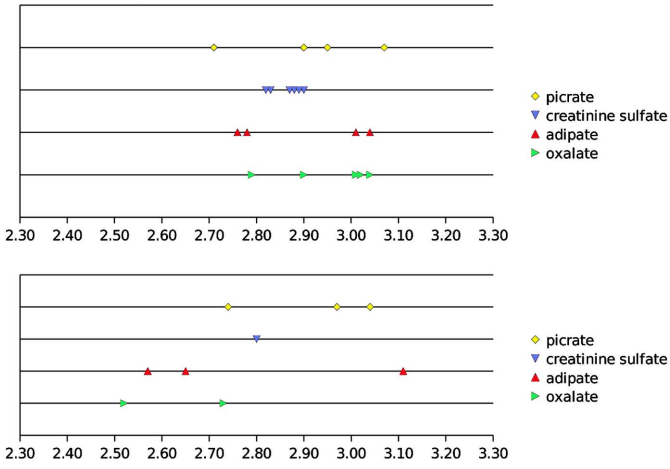


**Figure 5**
Hydrogen-bond-length distribution in serotonin complexes, showing (top) the N···O (and O···N) donor–acceptor distances (Å) and (bottom) the O···O donor–acceptor distances (Å).

intermolecular interactions. We start with discussing the hydrogen bonds, since they most often control crystal structures and the ability of molecules to change conformation. The geometric parameters of the hydrogen bonds are summarized in Table 2. In all four structures, the strengths of the hydrogen bonds are classified as moderate; donor–acceptor distances lie in the range 2.7–3.1 Å for N—H···O and O—H···N hydrogen bonds, and in the range 2.5–3.1 Å for O—H···O hydrogen bonds (Fig. 5).

Serotonin oxalate and serotonin adipate not only have similar geometric parameters of their hydrogen bonds but also

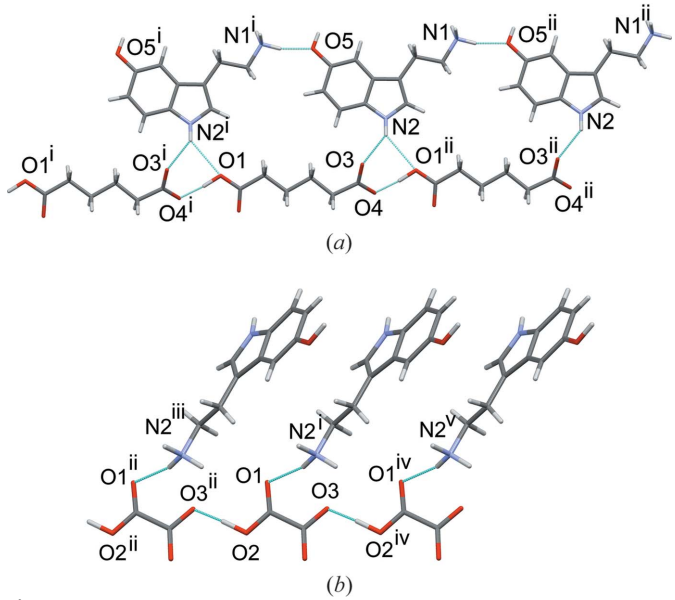


**Figure 6**
Chains of molecules in (*a*) serotonin adipate [symmetry codes: (i) $x, y+1, z$; (ii) $x, y-1, z$] and (*b*) serotonin oxalate [symmetry codes: (i) $-x+1, -y+2, -z+1$; (ii) $x, y+1, z$; (iii) $-x+1, -y+3, -z+1$; (iv) $x, y-1, z$; (v) $-x+1, -y+1, -z+1$].

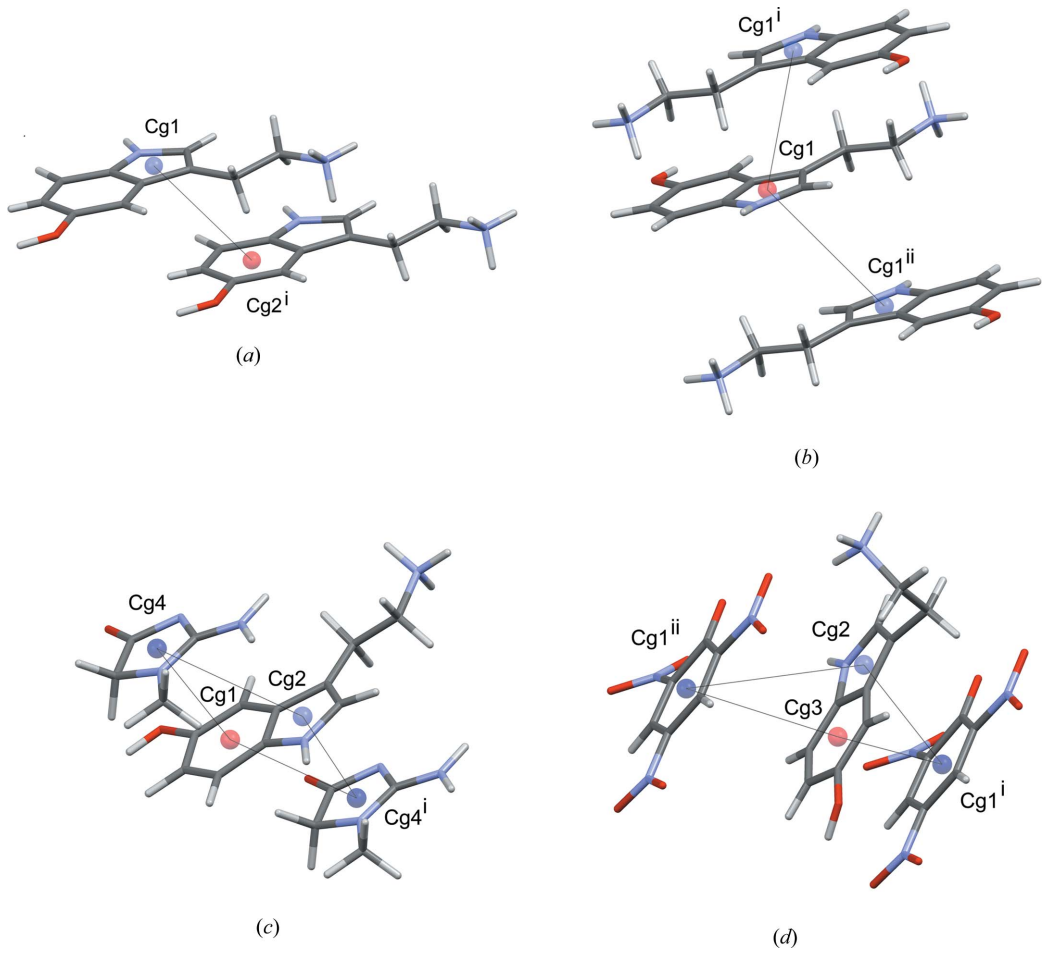


**Figure 7**
Stacking interactions in serotonin salts with (*a*) oxalate [symmetry code: (i) $x, y+1, z$], (*b*) adipate [symmetry codes: (i) $-x, -y, -z+1$; (ii) $-x+1, -y, -z+1$], (*c*) creatinine sulfate [symmetry code: (i) $x+\frac{1}{2}, y-\frac{1}{2}, z$] and (*d*) picrate [symmetry codes: (i) $-x, y-\frac{1}{2}, -z-\frac{1}{2}$; (ii) $-x, y+\frac{1}{2}, -z-\frac{1}{2}$]. *Cg* denotes ring centroids (indicated by large spheres).

similar structural motifs, with chains of oxalic and adipic acid molecules, respectively (Fig. 6).

Molecular conformation can also be affected by stacking interactions. In general, $\pi$–$\pi$ interactions of aromatic systems are possible in all four of these structures, but their strength should depend on the distances between the $\pi$-systems and their mutual orientation. (The geometric parameters which can be used to characterize the stacking of molecules are defined in the *Supplementary materials*, and their values are summarized in Supplementary Tables S1–S4.) The strongest interactions are shown in Fig. 7. In the following discussion, the term 'centroid' will be taken as referring to the geometric centre of a single cyclic system, *e.g.* the indole ring contains two such systems, one containing six atoms and the other five.

For serotonin oxalate, only the contact between centroid 1 (*Cg*1) and centroid 2 (*Cg*2), with a distance of 4.19 Å, gives any significant contribution to the stacking interaction, which is not likely to be strong for any pairs of neighbouring molecules, as far as one can judge from the interatomic distances (Fig. 7*a*).

The stacking interactions in serotonin adipate have some common features with those of serotonin oxalate, since the rings of neighbouring molecules are almost parallel to each other. The indole rings overlap only partially. All the other possible stacking interactions do not seem to be significant from an energetic point of view on the basis of their geometric parameters (see *Supplementary materials*).

Analysis of the stacking interactions in serotonin creatinine sulfate is more complicated. Theoretically, if creatinine were capable of adopting the enol form, the orientation and proximity of the aromatic rings would allow a strong $\pi$–$\pi$ interaction (Fig. 7*c*). Up to now, there has been no experimental evidence suggesting the existence of the enol form of creatinine in the crystalline state (du Pré & Mendel, 1955; Smith & White, 2001; Goswami *et al.*, 2006).

Karle *et al.* (1965) noted that the structural data for the creatinine sulfate complex are of poor quality, thus 'a discussion of individual bonds is not warranted since the refinement process was terminated before completion.' Therefore, using these data, we cannot fully rely on bond lengths to distinguish reliably between the ketone and enol forms. Many other structures containing creatinine (including aromatic systems) are known and they are invariably composed of the ketone form (du Pré & Mendel, 1955; Smith & White, 2001; Goswami

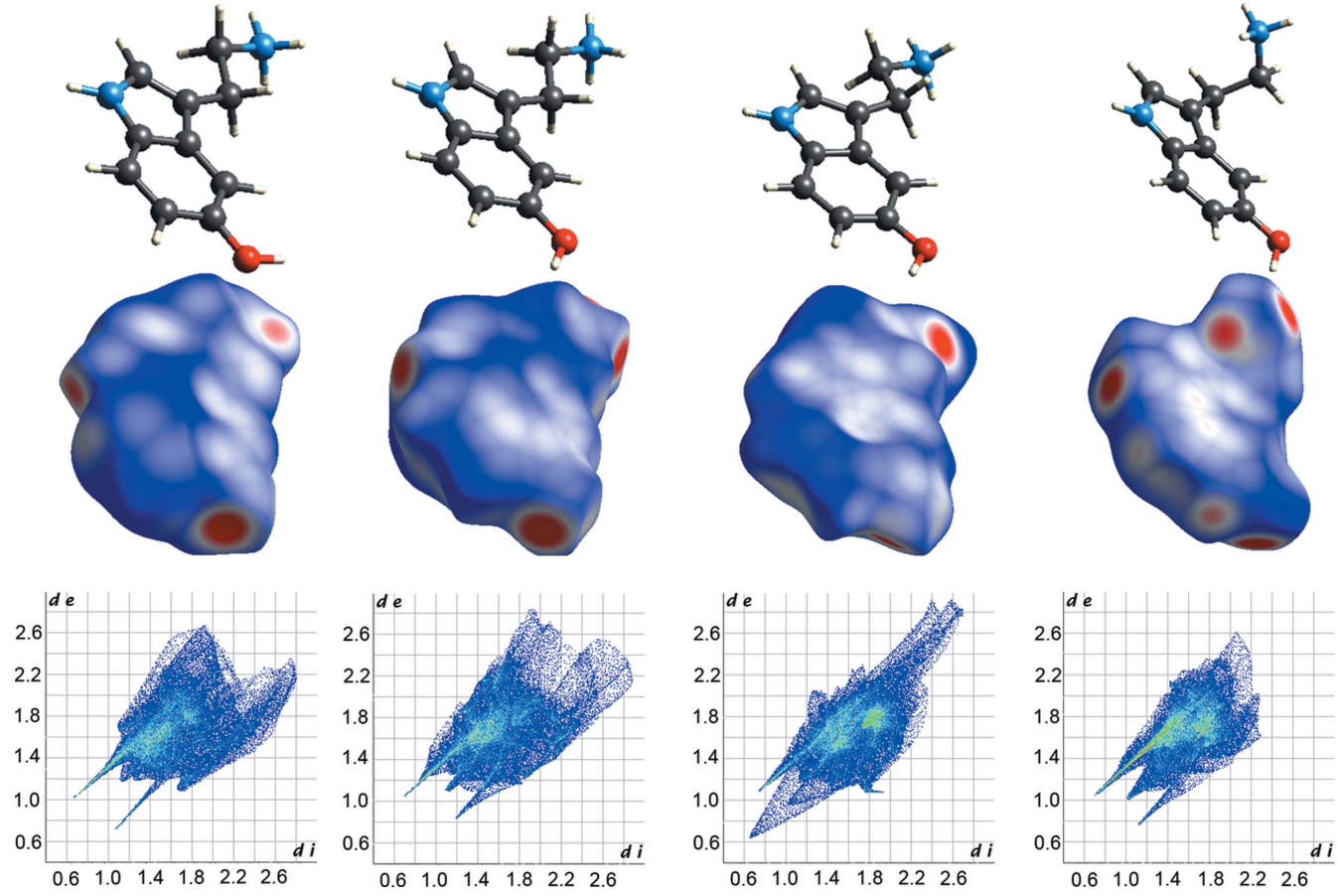


**Figure 8**
The molecular conformation (top row), Hirshfeld surfaces (middle) and fingerprint plots (bottom) for the serotonin molecule in various complexes. From left to right: adipate, oxalate, creatinine sulfate and picrate. Each molecule is shown with the Hirshfeld surface mapped with $d_{norm}$ [coloured between −0.500 (red in the electronic version of the journal) and 1.500 (blue)], where $d_{norm}$ is the normalized contact distance, which takes the van der Waals radii of the atoms into account.

*et al.*, 2006). Therefore, we conclude that $\pi$–$\pi$ interactions between the serotonin fragments in creatinine sulfate are likely to be absent. The only possible interaction is that of the indole $\pi$-system of serotonin with the conjugated $\pi$-system of the creatinine molecule. This interaction yields a lower stabilization energy than could be expected for related systems in which $\pi$–$\pi$ stacking interactions between aromatic rings exist. From the geometric criteria (see *Supplementary materials*), it can be assumed that the only serotonin structure that contains a strong $\pi$–$\pi$ stacking interaction is serotonin picrate, in which the whole indole system is involved in an interaction with another $\pi$-ring. Another point about intermolecular interactions is an additional donor–acceptor interaction with the indole $\pi$-system that can also influence the energy distribution in the crystal structure and complement the stacking interaction (see *Supplementary materials*).

Thus, only the structure of serotonin picrate has obvious $\pi$–$\pi$ interactions involving the indole $\pi$-system, and additionally $Y-X(-\mathrm{N}{=}\mathrm{O})\cdots\pi$ interactions, while the other three structures have only minor $\pi$–$\pi$ contributions to the overall intermolecular interaction.

Additional insight into the interactions between serotonin and its immediate crystalline environment can be obtained by analysing the Hirshfeld surfaces (McKinnon *et al.*, 1998; Spackman & McKinnon, 2002) (Fig. 8). It is quite obvious that three out of the four surfaces are quite similar to each other, while the last one, corresponding to another conformation, is significantly different. Some minor differences in the surfaces of serotonin adipate, oxalate and creatinine sulfate are related to the three-dimensional orientation of potentially reactive sites and the curviness of the surface. This can be explained by the difference in quality of the diffraction data.

Qualitative and quantitative differences in the Hirshfeld fingerprint plots are even more remarkable. The plot for serotonin adipate (bottom row of Fig. 8, leftmost plot) displays characteristics consistent with hydrogen bonding, similar to that in carboxylic acids: symmetric sharp features point to the lower left quadrant of the plot, the upper one corresponding to the hydrogen-bond donors and the lower one to the acceptors. $-NH_3^+$, NH in the indole ring and OH groups act as donors, while the only acceptor is the OH group (the O atom is an acceptor for another $NH_3^+$). The green colour shows that there are many more donor groups than acceptors (blue colour of another band). Another feature are the wings at the lower right ($\pi$-acceptor) and upper left (C—H donor) corners of the plot, corresponding to an 'aromatic' $C-H\cdots\pi$ inter-

action. The indole ring in serotonin acts as an acceptor for the $CH_2$ groups of adipic acid which lie above. Moreover, the $CH_2$ group of ethylamine donates an H atom in a C—H$\cdots\pi$ interaction with another molecule of serotonin. There are no indications of $\pi$–$\pi$ interactions in the region of $d_e = d_i = 1.8$ Å.

A very similar plot is calculated for serotonin oxalate (bottom row of Fig. 8, second plot from left). The same features characterizing the hydrogen bonding can be observed, namely the two symmetric bands at the lower left corner of the plot. More differences can be seen for the 'aromatic' interactions: there are no 'wings' typical of a C—H$\cdots\pi$ interaction; neither is there any evidence of $\pi$–$\pi$ stacking interactions. Another difference is the appearance of a significant number of widely spread dots in the upper right corner, which may indicate the presence of 'cavities' in the structure, and hence of a non-optimum packing.

The fingerprint plot calculated for serotonin creatinine sulfate (bottom row of Fig. 8, third plot from left) should be considered with care, given that the published data did not contain H-atom coordinates. In this work we calculated the H-atom positions using the *Mercury* feature 'Add missing H-atoms' (Macrae *et al.*, 2008). The unusual shape of the plot seems to be a consequence of the poor structural data. The features related to hydrogen bonding (such as the huge wing in the bottom left) cannot therefore be discussed. Nevertheless, a $\pi$–$\pi$ stacking interaction is independent of H-atom positions, and the fingerprint shows some evidence of such an interaction, which cannot be classified as 'strong' (Fig. 9).

The fingerprint plot of serotonin picrate (bottom row of Fig. 8, rightmost plot) gives evidence of a large number of hydrogen-bond donors, so that the colour of the lower left band is red at the position $d_e = 1.5$ Å and $d_i = 1.15$ Å. This can be explained by the existence of additional hydrogen bonds between the $NO_2$ group of the picrate and the C—H atoms of the indole ring. C—H$\cdots\pi$ interactions are absent. The presence of $\pi$–$\pi$ stacking interactions in this structure is also apparent. This can be better visualized by comparing the fingerprint plots of serotonin creatinine sulfate and serotonin picrate, in which C$\cdots$C contacts are considered as isolated (Fig. 9).

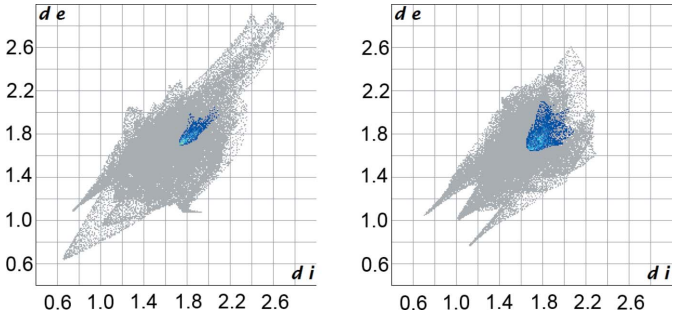


**Figure 9**
Hirshfeld fingerprint plots for the serotonin molecule in complexes with (left) creatinine sulfate and (right) picrate. Only C$\cdots$C interactions are highlighted. The highlighted surface area is 2.8% for the creatinine sulfate salt and 5.8% for the picrate salt.

To sum up this analysis of different interactions from hydrogen bonds to $\pi$–$\pi$ stacking using different techniques, we should discuss some key features that may cause conformational changes in serotonin. The hydrogen-bond motifs are quite different in almost all of these structures, so no clear correlation between molecular structure and hydrogen bonding is observed. C—H$\cdots\pi$ interactions apparently also do not play a key role. However, only one structure (the picrate salt) out of the four has a strong $\pi$–$\pi$ stacking interaction and this structure shows conformational changes. Thus, on the basis of the current evidence, it looks as though the flat conformation of serotonin may be obtained only in the absence of stacking interactions, even when the molecules form a hydrogen-bonded network.

We have not found any clear influence of water molecules on the conformational changes of serotonin in hydrates (serotonin creatinine sulfate monohydrate and serotonin picrate monohydrate), although it is very complicated to divide strictly the contribution of each molecule to the overall hydrogen-bond network and as a result establish its exact role in the whole structure. It should also be mentioned that, according to Karle *et al.* (1965) and Thewalt & Bugg (1972), these hydrates are stable under ambient conditions.

Another remarkable feature is that the conformation of serotonin in the present serotonin adipate structure differs from the most stable conformation predicted for a single molecule by adiabatic conformational analysis using quantum chemistry calculations: a 'free' serotonin molecule in cationic form should be nonplanar (Chothia, 1969; Pratuangdejkul, Jaudon *et al.*, 2006). It also differs from the serotonin conformations in all other known complexes, but the changes are not very significant among the 'flat' conformations. We should point out that some differences between serotonin adipate and serotonin creatinine sulfate that are described below can be noteworthy, but do not affect the overall conformation to any great extent.

The most significant difference between the adipate salt and the creatinine sulfate complex of serotonin is the orientation of the OH group (Table 3, $\varphi_4$), which is explained by forming the most energetically favourable hydrogen bond but, as mentioned above, it does not change the overall similarity of these structures. Depending on the values of the two dihedral angles, $\varphi_1$ and $\varphi_2$, serotonin can be in either a *+gauche* (Gp), *−gauche* (Gm) or *anti* (At) conformation (Figs. 3 and 4), and the serotonin conformers will be named hereinafter as, for example, GpAt when $\varphi_1$ corresponds to the *+gauche* conformation and $\varphi_2$ to the *anti* conformation. We will name as 'At' only those structures with dihedral angles very close ($\pm2^\circ$) to the ideal value of 180°, understanding that these angles can still be quite close to the other angles despite their different names. In this terminology, the serotonin conformation in the adipate salt is AtAt. The corresponding energy should be about 9 kcal mol$^{-1}$ (1 kcal mol$^{-1}$ = 4.184 kJ mol$^{-1}$) greater than that calculated for the most stable GmGp and GpGp conformations predicted for the 'free' molecule in the gas phase (Pratuangdejkul, Jaudon *et al.*, 2006). Three other conformations (GpGp, GmGm and GpAt) were reported for

serotonin in different crystalline environments, *viz.* for creatinine sulfate, picrate and oxalate, respectively. The GmGm and GmGp conformations were presumed to be stabilized by the interaction of the cationic group of serotonin ($NH_3^+$) with the $\pi$-system of the indole ring (Pratuangdejkul, Jaudon *et al.*, 2006). Interestingly, there are no such interactions in the known crystalline forms of serotonin. In the solid state, the conformation seems to be changed solely because of the stacking interactions.

We can suppose that the crystalline environment defines the molecular conformation. The calculated conformational energy difference between creatinine sulfate and picrate is only about 2 kcal mol$^{-1}$, while the difference in lattice energy is 274 kcal mol$^{-1}$ (Caillet *et al.*, 1977). Exact values aside, it is important to note the magnitude of the difference in conformational and lattice energies.

## 4. Conclusions

This work has shown the influence of different interactions on the molecular conformation of serotonin in the crystalline state. Three main conclusions may be drawn on the basis of the experimental data available so far: (i) the crystalline environment may define the conformation of serotonin molecules; (ii) 'flat' (thermodynamically unfavourable) conformations can be stabilized in the crystalline state if hydrogen bonds are the only intermolecular interactions; and (iii) additional stacking and donor–acceptor interactions change the molecular conformation dramatically, such that the molecules are no longer flat.

From these results we can suggest an intriguing theory that the intramolecular geometry of serotonin can be changed by varying the counter-ions in the crystal structures of its salts or molecular complexes. It is worth remembering that forming salts with different anions is a common technique for modifying the biological activity, pharmacological and therapeutic effect, and some physicochemical properties, such as p$K_a$, of the substance (Pratuangdejkul, Nosoongnoen *et al.*, 2006). We can also highlight that, according to one hypothesis (Akhrem *et al.*, 1978), the physiological effects of serotonin can be altered by varying its conformation. It is well documented that conformational polymorphs of one-component pharmaceutical crystals show pronounced differences in solubility and biological activity, potentially resulting from the retention of molecular conformation following dissolution, thus affecting subsequent substrate–receptor interactions in biochemical pathways (Leonidov, 1997). With an increased understanding of the effects of the crystalline environment on the conformation of biologically active molecules, one can imagine the possibility of explicitly inducing a desired conformation of the target molecule, thus leading to a specific augmentation in bioactivity. This prospect opens an avenue to advanced drug design, keeping these synergetic effects in mind.

It seems very promising to make an attempt at crystallizing serotonin salts with different anions and co-formers and to test the existence of a correlation between crystalline environment, molecular conformation and biological activity for a larger series of salts and complexes.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: YF3040). Services for accessing these data are described at the back of the journal.

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# supplementary materials

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# A new structure of a serotonin salt: comparison and conformational analysis of all known serotonin complexes

**Denis Rychkov, Elena V. Boldyreva and Nikolay A. Tumanov**

## Computing details

Data collection: *CrysAlis PRO* (Oxford Diffraction, 2008); cell refinement: *CrysAlis PRO* (Oxford Diffraction, 2008); data reduction: *CrysAlis PRO* (Oxford Diffraction, 2008); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: OLEX2 (Dolomanov *et al.*, 2009), *Mercury* (Macrae *et al.*, 2008), *PLATON* (Spek, 2009) and CrystalExplorer (McKinnon *et al.*, 1998; Spackman & McKinnon, 2002); software used to prepare material for publication: OLEX2 (Dolomanov *et al.*, 2009), *enCIFer* (Allen *et al.*, 2004) and *publCIF* (Westrip, 2010).

## 2-(5-Hydroxy-1*H*-indol-3-yl)ethanaminium 3-carboxypropanoate

*Crystal data*

$C_{10}H_{13}N_2O^+·C_6H_9O_4^-$
$M_r$ = 322.36
Triclinic, $P\overline{1}$
$a$ = 7.1582 (3) Å
$b$ = 10.5984 (7) Å
$c$ = 12.1715 (7) Å
$\alpha$ = 113.202 (6)°
$\beta$ = 101.233 (4)°
$\gamma$ = 98.045 (4)°
$V$ = 808.04 (8) Å$^3$
$Z$ = 2
$F(000)$ = 344
322.37
$D_x$ = 1.325 Mg m$^{-3}$
Mo $K\alpha$ radiation, $\lambda$ = 0.7107 Å
Cell parameters from 2039 reflections
$\theta$ = 1.9–26.3°
$\mu$ = 0.10 mm$^{-1}$
$T$ = 298 K
Plate, colourless
0.15 × 0.12 × 0.05 mm

*Data collection*

Oxford Gemini Ultra R diffractometer
Radiation source: Enhance (Mo) X-ray Source
Graphite monochromator
Detector resolution: 10.3457 pixels mm$^{-1}$
$\omega$ scans
Absorption correction: multi-scan (*CrysAlis PRO*; Oxford Diffraction, 2008)
$T_{min}$ = 0.994, $T_{max}$ = 1.000
10092 measured reflections
3286 independent reflections
1849 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.061
$\theta_{max}$ = 26.4°, $\theta_{min}$ = 1.9°
$h$ = −8→8
$k$ = −13→13
$l$ = −12→15

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.121
$S$ = 1.00
3286 reflections
296 parameters
0 restraints

| | |
|---|---|
| Primary atom site location: structure-invariant direct methods | $w = 1/[\sigma^2(F_o^2) + (0.0429P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| Secondary atom site location: difference Fourier map | $(\Delta/\sigma)_{max} < 0.001$ |
| Hydrogen site location: difference Fourier map | $\Delta\rho_{max} = 0.16$ e Å$^{-3}$ |
| All H-atom parameters refined | $\Delta\rho_{min} = -0.20$ e Å$^{-3}$ |

*Special details*

**Experimental**. CrysAlisPro, Agilent Technologies, Version 1.171.35.15 (release 03-08-2011 CrysAlis171 .NET) (compiled Aug 3 2011,13:03:54) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

**Geometry**. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

**Refinement**. Refinement of $F^2$ against ALL reflections. The weighted *R*-factor *wR* and goodness of fit *S* are based on $F^2$, conventional *R*-factors *R* are based on *F*, with *F* set to zero for negative $F^2$. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating *R*-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. *R*-factors based on $F^2$ are statistically about twice as large as those based on *F*, and *R*-factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| N1 | 0.2468 (4) | −0.1305 (3) | 0.7987 (2) | 0.0523 (6) |
| N2 | 0.2581 (3) | 0.0764 (2) | 0.4250 (2) | 0.0570 (6) |
| O1 | 0.2346 (2) | 0.81214 (18) | 0.16669 (15) | 0.0549 (5) |
| O2 | 0.3050 (3) | 0.65419 (18) | 0.00795 (17) | 0.0699 (5) |
| O3 | 0.1196 (2) | 0.08911 (16) | 0.18057 (15) | 0.0518 (4) |
| O4 | 0.3235 (2) | −0.01023 (16) | 0.07900 (15) | 0.0524 (4) |
| O5 | 0.2448 (3) | 0.5954 (2) | 0.7695 (2) | 0.0704 (6) |
| C1 | 0.2592 (3) | 0.6863 (2) | 0.1048 (2) | 0.0414 (5) |
| C2 | 0.2307 (4) | 0.5868 (2) | 0.1627 (2) | 0.0445 (6) |
| C3 | 0.2515 (4) | 0.4404 (2) | 0.0852 (2) | 0.0444 (6) |
| C4 | 0.2290 (4) | 0.3395 (2) | 0.1442 (2) | 0.0464 (6) |
| C5 | 0.2498 (4) | 0.1940 (2) | 0.0616 (2) | 0.0450 (6) |
| C6 | 0.2288 (3) | 0.0849 (2) | 0.1118 (2) | 0.0392 (5) |
| C7 | 0.2618 (4) | −0.1017 (3) | 0.6905 (2) | 0.0489 (6) |
| C8 | 0.2533 (4) | 0.0492 (3) | 0.7188 (2) | 0.0481 (6) |
| C9 | 0.2578 (3) | 0.0857 (2) | 0.6129 (2) | 0.0431 (6) |
| C10 | 0.2552 (3) | 0.2220 (2) | 0.6173 (2) | 0.0429 (6) |
| C11 | 0.2508 (3) | 0.3511 (3) | 0.7107 (2) | 0.0454 (6) |
| C12 | 0.2476 (3) | 0.4643 (3) | 0.6829 (2) | 0.0523 (6) |
| C13 | 0.2482 (4) | 0.4537 (3) | 0.5646 (3) | 0.0621 (7) |
| C14 | 0.2534 (4) | 0.3290 (3) | 0.4724 (3) | 0.0614 (7) |
| C15 | 0.2547 (3) | 0.2131 (3) | 0.4985 (2) | 0.0474 (6) |
| C16 | 0.2572 (3) | 0.0000 (3) | 0.4943 (2) | 0.0526 (6) |
| H1 | 0.261 (3) | 0.879 (3) | 0.124 (2) | 0.080 (8)* |
| H1A | 0.123 (4) | −0.117 (3) | 0.821 (3) | 0.094 (10)* |
| H1B | 0.249 (3) | −0.232 (3) | 0.775 (2) | 0.070 (8)* |
| H1C | 0.337 (4) | −0.072 (3) | 0.871 (3) | 0.099 (11)* |
| H2 | 0.236 (4) | 0.040 (3) | 0.342 (3) | 0.101 (11)* |

| | | | | |
|---|---|---|---|---|
| H2A | 0.325 (3) | 0.631 (2) | 0.245 (2) | 0.050 (6)* |
| H2B | 0.101 (3) | 0.584 (2) | 0.181 (2) | 0.071 (8)* |
| H3A | 0.156 (3) | 0.400 (2) | 0.003 (2) | 0.051 (6)* |
| H3B | 0.375 (3) | 0.448 (2) | 0.069 (2) | 0.060 (7)* |
| H4A | 0.101 (3) | 0.332 (2) | 0.162 (2) | 0.060 (7)* |
| H4B | 0.328 (3) | 0.380 (2) | 0.225 (2) | 0.070 (8)* |
| H5 | 0.254 (4) | 0.598 (3) | 0.841 (3) | 0.088 (11)* |
| H5A | 0.143 (3) | 0.154 (2) | −0.021 (2) | 0.059 (7)* |
| H5B | 0.370 (3) | 0.204 (2) | 0.044 (2) | 0.067 (8)* |
| H7A | 0.145 (3) | −0.172 (2) | 0.618 (2) | 0.054 (6)* |
| H7B | 0.382 (3) | −0.123 (2) | 0.675 (2) | 0.056 (7)* |
| H8A | 0.129 (3) | 0.064 (2) | 0.748 (2) | 0.069 (7)* |
| H8B | 0.359 (3) | 0.112 (2) | 0.791 (2) | 0.056 (7)* |
| H11 | 0.250 (3) | 0.360 (2) | 0.794 (2) | 0.051 (6)* |
| H14 | 0.249 (3) | 0.321 (2) | 0.395 (2) | 0.062 (7)* |
| H13 | 0.238 (3) | 0.540 (3) | 0.548 (2) | 0.067 (7)* |
| H16 | 0.252 (3) | −0.104 (3) | 0.453 (2) | 0.069 (8)* |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| N1 | 0.0699 (16) | 0.0382 (14) | 0.0561 (15) | 0.0199 (11) | 0.0242 (13) | 0.0224 (12) |
| N2 | 0.0695 (13) | 0.0595 (16) | 0.0422 (13) | 0.0134 (10) | 0.0188 (11) | 0.0213 (12) |
| O1 | 0.0824 (11) | 0.0379 (11) | 0.0620 (11) | 0.0245 (8) | 0.0337 (9) | 0.0296 (9) |
| O2 | 0.1189 (14) | 0.0511 (12) | 0.0653 (12) | 0.0333 (10) | 0.0526 (11) | 0.0340 (10) |
| O3 | 0.0702 (10) | 0.0449 (10) | 0.0571 (10) | 0.0217 (8) | 0.0327 (9) | 0.0294 (8) |
| O4 | 0.0643 (9) | 0.0426 (10) | 0.0717 (11) | 0.0251 (8) | 0.0336 (8) | 0.0352 (9) |
| O5 | 0.1139 (15) | 0.0494 (13) | 0.0589 (13) | 0.0287 (10) | 0.0290 (11) | 0.0293 (11) |
| C1 | 0.0473 (12) | 0.0350 (14) | 0.0469 (14) | 0.0126 (10) | 0.0168 (11) | 0.0198 (12) |
| C2 | 0.0528 (15) | 0.0377 (14) | 0.0511 (15) | 0.0154 (11) | 0.0183 (13) | 0.0242 (12) |
| C3 | 0.0544 (15) | 0.0345 (14) | 0.0503 (15) | 0.0126 (11) | 0.0160 (13) | 0.0229 (12) |
| C4 | 0.0590 (16) | 0.0359 (14) | 0.0552 (16) | 0.0157 (11) | 0.0218 (14) | 0.0264 (12) |
| C5 | 0.0599 (16) | 0.0354 (14) | 0.0475 (15) | 0.0137 (11) | 0.0199 (14) | 0.0225 (12) |
| C6 | 0.0451 (12) | 0.0313 (13) | 0.0423 (13) | 0.0067 (10) | 0.0103 (11) | 0.0186 (11) |
| C7 | 0.0565 (16) | 0.0475 (16) | 0.0502 (15) | 0.0154 (12) | 0.0207 (13) | 0.0250 (13) |
| C8 | 0.0571 (16) | 0.0412 (15) | 0.0470 (15) | 0.0109 (12) | 0.0152 (13) | 0.0199 (12) |
| C9 | 0.0448 (12) | 0.0440 (15) | 0.0450 (14) | 0.0125 (10) | 0.0147 (10) | 0.0220 (12) |
| C10 | 0.0435 (12) | 0.0472 (15) | 0.0423 (13) | 0.0099 (10) | 0.0131 (10) | 0.0232 (12) |
| C11 | 0.0542 (14) | 0.0466 (16) | 0.0425 (14) | 0.0148 (10) | 0.0180 (11) | 0.0235 (13) |
| C12 | 0.0635 (15) | 0.0442 (17) | 0.0502 (15) | 0.0137 (11) | 0.0151 (12) | 0.0213 (13) |
| C13 | 0.0840 (18) | 0.0558 (19) | 0.0565 (17) | 0.0152 (14) | 0.0174 (14) | 0.0358 (16) |
| C14 | 0.0804 (18) | 0.064 (2) | 0.0460 (16) | 0.0101 (13) | 0.0168 (14) | 0.0328 (16) |
| C15 | 0.0506 (13) | 0.0493 (16) | 0.0423 (14) | 0.0103 (10) | 0.0130 (11) | 0.0203 (13) |
| C16 | 0.0583 (15) | 0.0474 (18) | 0.0494 (16) | 0.0117 (11) | 0.0161 (12) | 0.0180 (14) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| N1—C7 | 1.483 (3) | C5—H5A | 1.02 (2) |
| N1—H1A | 0.99 (3) | C5—H5B | 0.93 (2) |
| N1—H1B | 1.00 (3) | C6—C5 | 1.508 (3) |

| | | | |
|---|---|---|---|
| N1—H1C | 0.90 (3) | C7—H7A | 1.02 (2) |
| N2—C16 | 1.381 (3) | C7—H7B | 0.95 (2) |
| N2—H2 | 0.89 (3) | C8—C7 | 1.510 (3) |
| O1—H1 | 1.04 (3) | C8—C9 | 1.490 (3) |
| O3—C6 | 1.245 (2) | C8—H8A | 1.03 (2) |
| O4—C6 | 1.271 (2) | C8—H8B | 0.96 (2) |
| O5—H5 | 0.84 (3) | C9—C16 | 1.368 (3) |
| O5—C12 | 1.380 (3) | C10—C9 | 1.427 (3) |
| C1—O1 | 1.305 (3) | C10—C11 | 1.402 (3) |
| C1—O2 | 1.217 (3) | C11—C12 | 1.371 (3) |
| C1—C2 | 1.493 (3) | C11—H11 | 0.99 (2) |
| C2—C3 | 1.511 (3) | C12—C13 | 1.400 (3) |
| C2—H2A | 0.98 (2) | C13—C14 | 1.367 (4) |
| C2—H2B | 1.00 (2) | C13—H13 | 1.02 (2) |
| C3—H3A | 0.98 (2) | C14—H14 | 0.91 (2) |
| C3—H3B | 0.94 (2) | C15—N2 | 1.377 (3) |
| C4—C3 | 1.512 (3) | C15—C10 | 1.411 (3) |
| C4—C5 | 1.520 (3) | C15—C14 | 1.385 (3) |
| C4—H4A | 0.98 (2) | C16—H16 | 1.00 (3) |
| C4—H4B | 0.99 (2) | | |

| | | | |
|---|---|---|---|
| N1—C7—C8 | 110.1 (2) | C8—C7—H7A | 111.4 (11) |
| N1—C7—H7A | 105.7 (12) | C8—C7—H7B | 113.9 (13) |
| N1—C7—H7B | 105.1 (13) | C9—C8—C7 | 113.9 (2) |
| N2—C15—C10 | 107.3 (2) | C9—C8—H8A | 111.8 (13) |
| N2—C15—C14 | 130.9 (2) | C9—C8—H8B | 110.9 (14) |
| N2—C16—H16 | 119.2 (15) | C9—C16—N2 | 109.9 (2) |
| O1—C1—C2 | 115.3 (2) | C9—C16—H16 | 130.8 (15) |
| O2—C1—O1 | 121.8 (2) | C10—C9—C8 | 124.5 (2) |
| O2—C1—C2 | 122.9 (2) | C10—C11—H11 | 120.5 (12) |
| O3—C6—O4 | 122.7 (2) | C11—C10—C15 | 119.0 (2) |
| O3—C6—C5 | 120.0 (2) | C11—C10—C9 | 133.4 (2) |
| O4—C6—C5 | 117.3 (2) | C11—C12—O5 | 122.2 (2) |
| O5—C12—C13 | 116.0 (2) | C11—C12—C13 | 121.8 (2) |
| C1—O1—H1 | 112.4 (14) | C12—O5—H5 | 112 (2) |
| C1—C2—C3 | 113.5 (2) | C12—C11—C10 | 118.4 (2) |
| C1—C2—H2A | 106.7 (12) | C12—C11—H11 | 121.1 (12) |
| C1—C2—H2B | 108.4 (13) | C12—C13—H13 | 118.1 (14) |
| C2—C3—C4 | 114.2 (2) | C13—C14—C15 | 118.3 (3) |
| C2—C3—H3A | 109.8 (12) | C13—C14—H14 | 120.9 (15) |
| C2—C3—H3B | 108.9 (14) | C14—C15—C10 | 121.8 (2) |
| C3—C2—H2A | 112.2 (12) | C14—C13—C12 | 120.7 (3) |
| C3—C2—H2B | 111.8 (14) | C14—C13—H13 | 121.1 (14) |
| C3—C4—C5 | 111.8 (2) | C15—N2—C16 | 108.7 (2) |
| C3—C4—H4A | 109.7 (13) | C15—N2—H2 | 124 (2) |
| C3—C4—H4B | 108.9 (14) | C15—C10—C9 | 107.5 (2) |
| C4—C3—H3A | 109.5 (12) | C15—C14—H14 | 120.7 (16) |
| C4—C3—H3B | 109.4 (14) | C16—N2—H2 | 126 (2) |
| C4—C5—H5A | 108.4 (12) | C16—C9—C10 | 106.5 (2) |

| | | | |
|---|---|---|---|
| C4—C5—H5B | 108.8 (15) | C16—C9—C8 | 128.9 (2) |
| C5—C4—H4A | 110.0 (13) | H1A—N1—H1B | 108 (2) |
| C5—C4—H4B | 110.4 (13) | H1A—N1—H1C | 102 (3) |
| C6—C5—C4 | 116.0 (2) | H1B—N1—H1C | 112 (2) |
| C6—C5—H5A | 106.4 (12) | H2A—C2—H2B | 103.7 (19) |
| C6—C5—H5B | 109.5 (15) | H3A—C3—H3B | 104.6 (19) |
| C7—N1—H1A | 112.9 (16) | H4A—C4—H4B | 106 (2) |
| C7—N1—H1B | 107.4 (14) | H5A—C5—H5B | 107 (2) |
| C7—N1—H1C | 115 (2) | H7A—C7—H7B | 110.1 (18) |
| C7—C8—H8A | 106.9 (13) | H8A—C8—H8B | 103.9 (19) |
| C7—C8—H8B | 108.9 (13) | | |

*Hydrogen-bond geometry (Å, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O1—H1···O4$^{i}$ | 1.04 (3) | 1.53 (3) | 2.569 (2) | 172 (2) |
| N1—H1*A*···O3$^{ii}$ | 0.99 (3) | 1.80 (3) | 2.762 (3) | 163 (2) |
| N1—H1*B*···O5$^{iii}$ | 1.00 (3) | 1.80 (3) | 2.782 (3) | 166 (2) |
| O5—H5···O2$^{iv}$ | 0.84 (3) | 1.82 (3) | 2.647 (3) | 164 (3) |

Symmetry codes: (i) *x*, *y*+1, *z*; (ii) −*x*, −*y*, −*z*+1; (iii) *x*, *y*−1, *z*; (iv) *x*, *y*, *z*+1.

*Geometric parameters of the serotonin molecule in different serotonin salts*

| Angle (°) | N1-C1-C2 | C1-C2-C3 | C2-C3-C4 | C2-C3-C5 | O5-C7-C6 | O5-C7-C8 |
|---|---|---|---|---|---|---|
| Adipate | 110.2 (2) | 113.9 (2) | 128.9 (2) | 124.5 (2) | 122.2 (2) | 116.0 (2) |
| Creatine sulfate | 108.0 | 111.1 | 131.3 | 124.6 | 121.9 | 115.9 |
| Oxalate | 115.4 | 113.9 | 129.7 | 123.4 | 121.4 | 118.1 |
| Picrate | 111.0 | 114.7 | 127.8 | 126.4 | 117.5 | 120.7 |
| | | | | | | |
| Distance (Å) | N1-C1 | C1-C2 | C2-C3 | C3-C4 | C3-C5 | O5-C7 |
| Adipate | 1.484 (4) | 1.510 (5) | 1.489 (4) | 1.37 | 1.427 (3) | 1.380 (3) |
| Creatine sulfate | 1.51 | 1.53 | 1.48 | 1.37 | 1.47 | 1.38 |
| Oxalate | 1.51 | 1.48 | 1.50 | 1.37 | 1.43 | 1.37 |
| Picrate | 1.49 | 1.51 | 1.50 | 1.37 | 1.44 | 1.39 |
| | | | | | | |
| Dihedral angle (°) | Conf $\varphi1\varphi2$ | $\varphi1$ | $\varphi2$ | $\varphi3$ | $\varphi4$ | |
| Adipate | AtAt | 178.7 | 177.2 | 60.0 | 4.0 | |
| Creatinine | GpGp | 166.7 | 172.6 | 60.0* | 180.0* | |
| Oxalate | GpAt | 171.7 | 179.7 | 63.9 | 174.2 | |
| Picrate | GmGm** | -67.5 | -66.6 | 57.01 | 161.1 | |

Notes: +*gauche* (Gp), -*gauche* (Gm) and *anti* (At) conformation. The H atoms with similar values of the $\varphi3$ torsion angle were choosen as HN11. (*) H atoms were calculated from *Mercury* `Edit structure′ (Macrae *et al.*, 2008). (**) In our view, it is more appropriate to name the creatinine sulfate conformation GmGm rather than GpGm (Pratuangdejkul, Jaudon *et al.*, 2006). Serotonin picrate angles and distances can hardly be compared due to significant changes in dihedral angles. S.u. values are not given due to their absence in the original articles.