Acta Cryst. (1977). A33, 885–889

On the Conformational Varieties of 5-Methoxy-*N*,*N*-Dimethyltryptamine and Serotonin in Crystalline Environment

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(*Received* 7 *May* 1977; *accepted* 10 *June* 1977)

Conformational energy maps obtained from quantum-mechanical computations for two indolalkylamines (5-methylbufotenine and serotonin) indicate preferred conformers which do not correspond to those observed in some crystals containing these molecules. Moreover, two different conformations are observed for serotonin in two different mixed crystals [serotonin creatinine sulphate (hydrated) and serotonin picrate]. These facts suggest an influence of the crystalline environment upon intramolecular conformation. The intermolecular lattice energy has been computed for the experimental crystals and a number of hypothetical ones, obtained by varying the conformation of the indolalkylamine molecule. The results obtained establish complete agreement with the experimental observations: for the three crystals considered, the lattice energy is much lower when use is made of the corresponding observed conformation and these differences between the lattice energies largely overcompensate the variations of the intramolecular conformational energy, thus explaining the role of the lattice energy in the determination of the conformations observed in the crystals.

1. Introduction

In a recent paper (Caillet, Claverie & Pullman, 1976), we have inaugurated a study of the crystal structure of pharmacological compounds composed of a conjugated heterocyclic ring with an attached ethylamine side chain. Our aim was to explain the occurrence in the crystal of conformers different from those predicted as the preferred ones for the free molecule.

In this type of molecule the essential problem concerns the mutual orientation of the side chain and the ring. It is generally defined by two torsion angles (Pullman, 1977) τ_1 [C(2)–C(3)–C(10)–C(11)] and τ_2 [C(3)–C(10)–C(11)–N^+(12)] indicated in Fig. 1 for serotonin and 5-methoxy-*N*,*N*-dimethyltryptamine. We recall that with the usual convention, the torsion angle about *B*–*C* in the sequence *A*–*B*–*C*–*D* is the angle through which the far bond *C*–*D* is rotated relative to the near bond *A*–*B*. The *cis*-planar position of *A*–*B* and *C*–*D* corresponds to $\tau = 0°$. The torsion angles are considered positive for a right-handed rotation: if one looks along *B*–*C*, *C*–*D* rotates clockwise relative to *A*–*B*.

Alternatively, the positive angles are defined as 0° to 180°, measured for a clockwise rotation and negative angles as 0° to −180°, measured for a counterclockwise rotation.

In the previous paper (Caillet, Claverie & Pullman, 1976) we have studied the molecule of adrenaline, which exists in the crystalline state as a planar-*trans* conformer with $\tau_1 = -3°$ and $\tau_2 = 179°$, while the most stable conformation predicted for the free compound corresponds to $\tau_1 = 90°$ and $\tau_2 = 60°$, *i.e.* a perpendicular-*gauche* conformation.

We have shown that the crystalline 'unusual' conformation has associated with it a strong stabilization due to the lattice intermolecular energy, which overcomes the loss of conformational energy with respect to the theoretically most stable conformer of the isolated molecule.

In the present paper, we extend our study to two indolalkylamines: 5-methoxy-*N*,*N*-dimethyltryptamine (Falkenberg & Carlström, 1971), which is a 5-methylated bufotenine, and serotonin (Fig. 1). The cationic head of the former has two methyl groups and

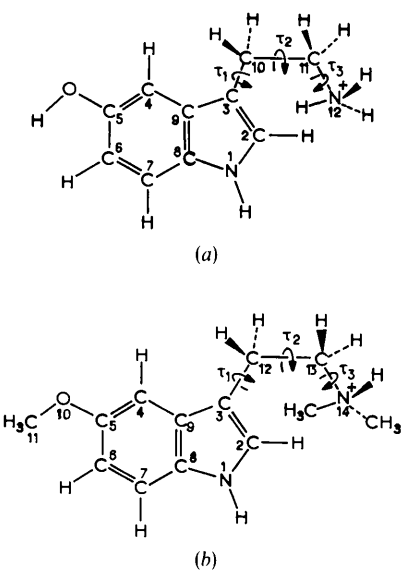

Fig. 1. Torsion angles. (*a*) Serotonin. (*b*) 5-Methoxy-*N*,*N*-dimethyltryptamine.

one H attached to the N atom and thus involves a third torsion angle τ_3 which can be introduced in the calculation of the conformation energy. In the present work, we have not studied the variation of this angle which was kept fixed at its experimental value of $\tau_3 = 52{\cdot}33°$.

The case of serotonin is particularly interesting because this molecule is found in two different crystals in two different conformations: the crystal of serotonin picrate monohydrate (Thewalt & Bugg, 1972) which with $\tau_1 = +115{\cdot}3°$ and $\tau_2 = -66{\cdot}72°$ presents an almost perpendicular-*gauche* conformation, and the crystal of serotonin creatinine sulphate complex (Karle, Dragonette & Brenner, 1965) which with $\tau_1 = 13{\cdot}3°$ and $\tau_2 = 172{\cdot}55°$ presents an almost planar-*trans* conformation of the side chain with respect to the ring.

2. Method

The computations on the crystal lattice energies have been carried out with the procedure utilized previously in our study on the crystal structure of adrenaline (Caillet, Claverie & Pullman, 1976; Caillet & Claverie, 1974, 1975). Its description will therefore not be repeated here.

The only new element is represented by the Cl^- ion in the structure of 5-methoxy-*N*,*N*-dimethyltryptamine. The parameters utilized for this ion are: van der Waals radius 1·81 Å, parameter K for the depth of the potential well = 2·4.

3. Results and discussion

The methodology consists of calculating the minimum energy of the crystal with different assumed conformations for the molecule under investigation, with different parameters for the crystal cell or for the positions of the molecules in the cell.

Some comments are appropriate concerning the minimization procedures: indeed, our previous work (Caillet & Claverie, 1975; Caillet, Claverie & Pullman, 1976) has indicated the possibility that several local energy minima exist whenever the molecules of the crystal are not very simple. As a consequence, the result of a minimization may depend on the initial configuration chosen, since this configuration may belong to one or another among the various potential wells of the energy hypersurface. This problem is not important for an experimentally observed crystal geometry, since we need only to check that this geometry corresponds with reasonable accuracy to a minimum of our theoretically calculated energy. But the problem is more serious for a hypothetical geometry, *i.e.* when considering a molecular conformation which is not the one observed in the crystal: then, we do not know *a priori* which relative configuration of the molecules would give the lowest energy for the hypothetical crystal, and we can only try several initial configurations and choose the lowest among the energy minima thus obtained (Caillet, Claverie & Pullman, 1976). But performing several minimization processes becomes very expensive when one is dealing with large molecules embedded in mixed crystals such as adrenaline or the indolalkylamines considered here. Therefore, in the present work, we performed only one minimization process for every hypothetical crystal (the initial geometry being built by using for the *indole part* of the molecule the same position as in the experimental crystal). Thus, we cannot be sure that the minima found for these hypothetical crystals are the absolute ones, but the more thorough treatment performed previously for adrenaline gives us confidence concerning at least the qualitative relevance of the results obtained from a single minimization process for every hypothetical crystal.

A. 5-Methoxy-N,N-dimethyltryptamine

A_1. Crystalline conformation: approximately planar-trans

The crystalline conformation of 5-methoxy-*N*,*N*-dimethyltryptamine corresponds to the torsion angles

Table 1. *Results of energy minimizations for 5-methoxy-N,N-dimethyltryptamine*

The different energies are expressed in kcal/mole of the complex. The direction cosines of the rotation axes are given with respect to an orthonormal coordinate system defined from the lattice cell **a**, **b**, **c**. The reference positions chosen are the experimental ones.

A_1 Crystalline conformation $\tau_1 = 17{\cdot}2°$, $\tau_2 = 179{\cdot}2°$

Cell parameters	$a = 17{\cdot}71$ Å		
	$b = 22{\cdot}23$		
	$c = 5{\cdot}90$		
Rotation angle	6·59°		
Rotation axis	−0·58	Translation	0·26 Å
	0·48		0·02
	−0·66		−0·57

A_2 PCILO global minimum conformation $\tau_1 = 120°$, $\tau_2 = 180°$

Cell parameters	$a = 16{\cdot}06$ Å		
	$b = 25{\cdot}88$		
	$c = 8{\cdot}20$		
Rotation angle	33·45°		
Rotation axis	−0·67	Translation	−0·84 Å
	−0·73		0·25
	0·03		1·97

A_3 Secondary PCILO minimum $\tau_1 = 120°$, $\tau_2 = 60°$

Cell parameters	$a = 17{\cdot}08$ Å		
	$b = 20{\cdot}68$		
	$c = 10{\cdot}21$		
Rotation angle	54·6°		
Rotation axis	0·05	Translation	−1·12 Å
	−0·59		0·05
	−0·80		−0·71

Conformation	Total lattice energy	Conformational energy with respect to A_2	Lattice energy + conformational energy
A_1	−181·6	+3	−178·6
A_2	−143·24	0	−143·24
A_3	−134·95	+0·5	−134·4

$\tau_1 = 17{\cdot}2°$ and $\tau_2 = 179{\cdot}2°$. The molecule is left free to move in the cell, the angular parameters of which are kept constant. The minimum energy is evaluated to be $-181{\cdot}6$ kcal/mole. The molecules are very slightly displaced from the experimental position (Table 1).

Table 2. *Detailed geometrical results of the energy minimizations concerning serotonin*

The direction cosines of the rotation axis and the translation coordinates are given with respect to an orthonormal coordinate system defined from the experimental lattice cell **a**, **b**, **c**. Since $\gamma = (\mathbf{a},\mathbf{b}) = 90°$, we have chosen as basis vectors $\mathbf{a}/a$, $\mathbf{b}/b$ and $\mathbf{c}' = (\mathbf{a}/a) \times (\mathbf{b}/b)$ (vector product).

Experimental crystalline conformation of serotonin creatinine sulphate (hydrate) complex, $\tau_1 = 13{\cdot}3°$, $\tau_2 = 172{\cdot}6°$ (planar-*trans* = *t*)

Cell parameters	$a = 10{\cdot}75$ Å	$\alpha = 90{\cdot}2°$
	$b = 9{\cdot}70$	$\beta = 99{\cdot}2$
	$c = 35{\cdot}26$	$\gamma = 90{\cdot}0$

	Serotonin	Creatinine	Sulfate
Rotation angle	0	0	0
Translations	0	0	0
	0	0	0
	0	0	0

PCILO conformation, serotonin creatinine sulphate complex, $\tau_1 = 140°$, $\tau_2 = -20°$

Cell parameters	$a = 10{\cdot}76$ Å	$\alpha = 90{\cdot}0°$
	$b = 9{\cdot}70$	$\beta = 99{\cdot}3$
	$c = 35{\cdot}26$	$\gamma = 90{\cdot}3$

	Serotonin	Creatinine	Sulphate
Rotation angle	1·87°	0·19°	1·55°
Rotation axis	0·0	0·0	0·0
	0·43	0·16	−0·99
	0·90	−0·98	−0·16
	0·02	0·0	−0·02
Translations	−0·004 Å	0·0 Å	0·003 Å
	0·01	0·0	−0·01

Perpendicular-*trans* ($\perp t$) conformation, serotonin creatinine sulphate complex, $\tau_1 = 90°$, $\tau_2 = 180°$

Cell parameters	$a = 10{\cdot}76$ Å	$\alpha = 90{\cdot}0°$
	$b = 9{\cdot}69$	$\beta = 99{\cdot}3$
	$c = 35{\cdot}26$	$\gamma = 90{\cdot}54$

	Serotonin	Creatinine	Sulphate
Rotation angle	6·54°	0·05°	0·93°
Rotation axis	0·0	0·0	0·0
	−0·2	0·1	0·4
	0·98	0·99	−0·92
Translations	0·01 Å	0·0 Å	−0·01 Å
	−0·01	0·0	0·01
	0·006	0·0	−0·005

Perpendicular-*gauche* ($\perp g$) serotonin creatinine sulphate complex, $\tau_1 \simeq 90°$, $\tau_1 \simeq 60°$

Cell parameters	$a = 10{\cdot}76$ Å	$\alpha = 89{\cdot}75°$
	$b = 9{\cdot}71$	$\beta = 99{\cdot}64$
	$c = 35{\cdot}26$	$\gamma = 88{\cdot}48$

	Serotinin	Creatinine	Sulphate
Rotation angle	7·10°	1·87°	0·79°
Rotation axis	0·0	0·0	0·0
	0·71	−0·21	0·31
	−0·70	0·97	−0·95
Translations	−0·02 Å	0·02 Å	−0·001 Å
	0·01	0·004	−0·01
	−0·03	0·04	−0·01

Table 2 (*cont.*)

Experimental crystalline conformation in serotonin picrate monohydrate, $\tau_1 = 112{\cdot}5$, $\tau_2 = -66{\cdot}6°$ (perpendicular-*gauche*: $\perp g$)

Cell parameters	$a = 14{\cdot}17$ Å	$\alpha = 90{\cdot}5°$
	$b = 6{\cdot}90$	$\beta = 101{\cdot}9$
	$c = 18{\cdot}75$	$\gamma = 89{\cdot}7$

	Serotonin	Picrate
Rotation angle	0·68°	0·32°
Rotation axis	0·0	0·0
	−0·7	−0·2
	0·7	0·90
Translations	−0·003 Å	+0·001 Å
	−0·002	0·003
	−0·001	0·002

PCILO conformation, serotonin picrate monohydrate, $\tau_1 = 140°$, $\tau_2 = -20°$

Cell parameters	$a = 14{\cdot}17$ Å	$\alpha = 90{\cdot}0°$
	$b = 6{\cdot}91$	$\beta = 101{\cdot}3$
	$c = 18{\cdot}75$	$\gamma = 88{\cdot}9$

	Serotonin	Picrate
Rotation angle	2·95°	0·12°
Rotation axis	0·0	0·0
	−0·8	−0·98
	−0·58	−0·43
Translations	−0·001 Å	0·0 Å
	−0·001	0·001
	−0·01	0·002

Perpendicular-*trans* ($\perp t$) conformation, serotonin picrate monohydrate, $\tau_1 = 90°$, $\tau_2 = 180°$

Cell parameters	$a = 14{\cdot}16$ Å	$\alpha = 90{\cdot}2°$
	$b = 6{\cdot}90$	$\beta = 101{\cdot}1$
	$c = 18{\cdot}75$	$\gamma = 88{\cdot}76$

	Serotonin	Picrate
Rotation angle	1·95°	1·02°
Rotation axis	0·0	0·0
	0·91	−0·02
	−0·39	0·99
Translations	0·01 Å	−0·01 Å
	0·0	−0·001
	0·02	−0·01

Planar-*trans* conformation (= *t*), serotonin picrate monohydrate, $\tau_1 \simeq 0$, $\tau_2 \simeq 180°$

Cell parameters	$a = 14{\cdot}17$ Å	$\alpha = 91{\cdot}2°$
	$b = 6{\cdot}91$	$\beta = 103{\cdot}17$
	$c = 18{\cdot}75$	$\gamma = 88{\cdot}04$

	Serotonin	Picrate
Rotation angle	4·96°	0·67°
Rotation axis	0·0	0·0
	0·63	0·24
	0·77	0·97
Translations	0·001 Å	−0·002 Å
	−0·01	0·005
	0·003	−0·005

A_2. *Perpendicular-trans conformation (approximately)*

The second conformation which we study corresponds to the global energy minimum for the free molecule as obtained by PCILO calculations (Pullman, Courrière & Berthod, 1974): the side chain is appreciably inclined with respect to the ring with $\tau_1 = 120°$ and $\tau_2 = 180°$. The energy minimum obtained is

$-143{\cdot}2$ kcal/mole with a relatively important displacement of the molecule with respect to its initial position.

A_3. Perpendicular-gauche conformation ($\tau_1 \simeq 120°$, $\tau_2 = -60°$)

A local energy minimum of the PCILO conformational map corresponds to $\tau_1 = 120°$ and $\tau_2 = -60°$. In this case also, the side chain is inclined with respect to the plane of the ring. The rotation angle is more important than in the preceding case (Table 1). The minimum obtained is -135 kcal/mole. Here also, the displacement is important with respect to the initial position.

As in our previous paper (Caillet, Claverie & Pullman, 1976), the present results indicate that the stabilization due to the lattice energy of the crystal is larger than the destabilization of the isolated molecule in the same conformation: this fact appears clearly in the last part of Table 1.

B. Serotonin

Serotonin is particularly interesting because it exists in two different conformations in two different crystals. The detailed results concerning the various minimizations performed are given in Tables 2 (geometries) and 3 (energies).

B_1. Planar-trans conformation ($\tau_1 \simeq 13{\cdot}3°$, $\tau_2 = 172{\cdot}6°$) ($=t$)

This conformation is adopted by the serotonin molecule in the crystal of serotonin creatinine sulphate complex. The energy minimum obtained with this input data is -451 kcal/mole without displacement of the molecules of the complex.

B_2. Perpendicular-gauche conformation ($\tau_1 \simeq 90°$, $\tau_2 \simeq 60°$) ($\perp g$)

This conformation is the experimental one in the crystal of serotonin picrate monohydrate. The minimum obtained is -177 kcal/mole.

In these two cases, the displacements of the molecules are very small and the experimental position corresponds to the energy minimum.

B_3. Conformer corresponding to the PCILO minimum for the free molecule (Pullman, Courriere & Berthod, 1974) ($\tau_1 = +140°$, $\tau_2 = -20°$; $\tau_1 = -140°$, $\tau_2 = +20°$)

On the conformational energy map of free serotonin obtained by the PCILO method, the global minimum is obtained for $\tau_1 = +140°$ and $\tau_2 = -20°$, but since the molecule is quasi-symmetrical with respect to the plane of the indole ring, the minimum of the energy of the free molecule is obtained also for $\tau_1 = -140°$, $\tau_2 = +20°$. Thus we have tried the two pairs of torsion angles for the minimization of the crystalline energy and have kept only the better for the minimization. The energy obtained is -359 kcal/mole for the serotonin creatinine sulphate complex and the molecules are only very slightly displaced.

The same conformation yields $-148{\cdot}1$ kcal/mole for the crystal of serotonin picrate monohydrate with a slight displacement of the molecules.

B_4. Perpendicular-trans conformation ($\tau_1 \simeq 90°$, $\tau_2 \simeq 180°$) ($\perp t$)

This conformation corresponds to a side chain perpendicular to the indole ring and completely extended.

The energy minimum is $-409{\cdot}5$ kcal/mole for the serotonin creatinine sulphate complex and $-168{\cdot}4$ kcal/mole for serotonin picrate monohydrate.

B_5. 'Exchange' of the conformations between the two crystals

In this part, we consider a mixed crystal serotonin creatine sulphate with the serotonin molecule having the conformation observed in the *other* mixed crystal (serotonin picrate), namely $\tau_1 \simeq 90°$, $\tau_2 = 60°$ ($\perp g$), and we obtain after minimization $-365{\cdot}1$ kcal/mole. Conversely, we consider the serotonin picrate crystal

Table 3. *Lattice energies and conformational energies (kcal/mole) for several crystals of serotonin creatinine sulphate (water) and serotonin picrate*

Symbols: exp: experimental; hyp: hypothetical; $=$: $\tau_1 \simeq 0$ or $180°$, bond C(10)–C(11) approximatively coplanar with the ring; $\perp$: $\tau_1 \simeq \pm 90°$, C(10)–C(11) approximately perpendicular to the ring; t: $\tau_2 \simeq 180°$, a *trans*, extended form; g: $\tau_2 = \pm 60°$, a *gauche*, folded form.

Mixed crystal of serotonin with	Conformation of serotonin τ_1	τ_2	Symbol	Total lattice energy	Conformational energy of serotonin with respect to PCILO	Lattice energy + conformational energy
Creatinine sulphate complex (exp)	13·3	172·6	$=t$	-451	$+7$	-444
Creatine sulphate complex (hyp)	140	-20	PCILO	-359	0	-359
Creatinine sulphate complex (hyp)	90	180	$\perp t$	$-409{\cdot}5$	$+7$	$-402{\cdot}5$
Creatinine sulphate complex (hyp)	$\simeq 90$	$\simeq 60$	$\perp g$	$-365{\cdot}1$	$+5$	$-360{\cdot}1$
Picrate monohydrate (hyp)	$\simeq 0$	$\simeq 180$	$=t$	$-140{\cdot}2$	$+7$	$-133{\cdot}2$
Picrate monohydrate (hyp)	140	-20	PCILO	$-148{\cdot}1$	0	$-148{\cdot}1$
Picrate monohydrate (hyp)	90	180	$\perp t$	$-168{\cdot}4$	$+7$	$-161{\cdot}4$
Picrate monohydrate (exp)	112·5	$-66{\cdot}6$	$\perp g$	-177	$+5$	-172

using for serotonin the conformation observed in the other crystal, namely $\tau_1 \simeq 0°$, $\tau_2 \simeq 180°$ ($=t$), and we obtain after minimization $-140{\cdot}15$ kcal/mole.

The various results obtained for the lattice intermolecular energy in (1) to (5) are collected in Table 3. To make comparison easier, we have grouped together the results concerning the serotonin creatinine sulphate crystals on the one hand and those concerning the serotonin picrate crystals on the other. It appears in both cases that the lowest energy is actually obtained for the experimental geometry of the crystal. The differences of the lattice intermolecular energies associated with various conformations are much larger than the corresponding differences of intramolecular conformational energies of serotonin: thus, the lattice energy appears as the dominant factor for the determination of the conformation adopted by the serotonin molecule in its two crystalline environments.

4. Conclusion

The present work further confirms the view expressed in our previous paper (Caillet, Claverie & Pullman, 1976) concerning the importance of the crystalline environment for determining molecular conformation. In the previous work on adrenaline, we were able to explain the occurrence in the adrenaline tartrate crystal of a conformation of adrenaline which did not correspond to any minimum on the conformational energy map of the isolated molecule. Serotonin is still more striking, since this molecule is found in two different conformations when two different cocrystallizing species are used (creatinine sulphate and picrate). Moreover, according to the theoretical study of the isolated molecule, none of these observed conformations corresponds to the lowest minimum of the conformational energy map. Nevertheless, as for adrenaline, the calculation of the intermolecular lattice energy shows that, for every mixed crystal, the observed conformation of serotonin actually leads to a markedly lower energy than to the other conformations (whether the one observed in the *other* mixed crystal or the theoretically most stable one for isolated serotonin). Thus, the experimentally observed variability of the conformations according to the crystalline environment is interpreted from the theoretical analysis as a consequence of the predominance of intermolecular lattice energy variations over those of the intramolecular conformational energy.

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