



**CONFORMATIONAL ANALYSIS WITH AM1 METHOD
OF THE
(3S,5S,6S)-6-ACETYLAMIDOPENICILLANIC ACID.
ELECTRONIC PROPERTIES.**

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SUMMARY

A conformational analysis with the semiempirical AM1 method was performed for (3S,5S,6S)-6-acetylamidopenicillanic acid. 13 distinct conformers were found within 6.66 kcal/mol. Dependence of some electronic properties of these conformers (HOMO and LUMO energies, dipole moment, ν_{\min} minimum vibration energy, maximum vibration energy ν_{\max} , zero point vibration energy (ZPVE) and charge densities on atoms S1, N4, N14, O8, O12, O13 and O17) with respect to some geometric characteristics : pseudochirality of the N14 atom, the *syn-anti* arrangement of the O17 and H28 atoms of the amidic group and the three puckering classes of the thiazolidinic cycle noted with a, b, c.

Keywords: conformational analysis; (3S,5S,6S)-6-acetylamidopenicillanic acid; AM1; electronic properties.

INTRODUCTION

The (3S,5S,6S)-6-acetylamidopenicillanic acid is one of the simplest antibacterial compounds of the penicillin class. Its molecular structure contains two fused rings (a four-membered β -lactamic ring and a five-membered thiazolidinic ring) and three chiral centers is presented in Figure 1[1].

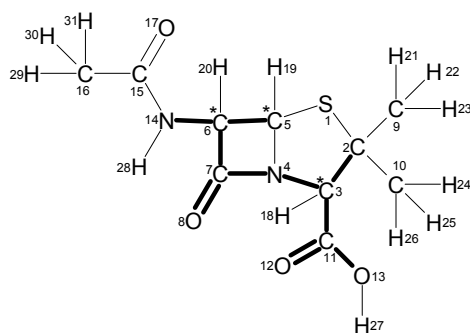


Fig.1 Atom numbering in (3S,5S,6S)-6-acetylamidopenicillanic acid (* denotes the chirality).

In this paper we present an analysis of the dependence of the electronic properties of the (3S,5S,6S)-6-acetylamido-penicillanic acid with respect to the geometrical characteristics of the conformers. The pyramidalization degree of the nitrogen N14 atom resulted from the AM1 method is measured by the “conicity” of the improper angle C6-C15-H28-N14. The electronic properties are analysed with respect to the *anti* or *syn* orientation of atoms O17 and H28 of the exocyclic amidic group and the three puckering classes of the thiazolidinic cycle [1].

MATERIALS AND METHODS

Gas phase equilibrium geometry of conformers was obtained by semiempirical AM1 calculations with an SCF convergence of 10^{-5} , and a RMS gradient of 10^{-2} kcal/Å·mol [2,3]. Conformational search was performed by varying the C2-C3-C11-C12, C5-C6-N14-C15 and C6-N14-C15-C16 dihedrals in the range $0 \pm 180^\circ$ with steps of 15° . Energy criterion was set to 30 kcal/mol above the minimum energy conformer. Calculations have been performed with Conformational Search module [4], from HyperChem7.52 package [5].

RESULTS AND DISCUSSION

The semiempirical AM1 method gives 13 conformers [1,7]. In Table I these conformers are ordered and numbered in ascending order of formation enthalpies. The obtained results for some structural properties (IP_1 , EA_1 , μ) are presented also in Table I.

Table I. Numbering of the conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid arranged in the ascending order of the formation enthalpies computed with AM1 some of their energetic, structural and electronic characteristics

Energetic order	ΔH_{form} (kcal/mol)	HOMO (eV)	LUMO (eV)	μ (Debye)	Chirality N(14)	Position 17, 28	Vibrations (cm^{-1})		ZPVE (kcal/mol)
							ν_{min}	ν_{MAX}	
1am1	-120.82	- 9.335	- 0.035	4.493	S	anti	20.01	3453.51	154.29
2am1	-120.37	- 9.147	0.090	4.919	R	anti	29.50	3445.98	154.45
3am1	-120.35	- 9.231	0.054	4.827	S	anti	13.45	3465.02	154.38
4am1	-120.30	- 9.297	- 0.011	4.871	S	anti	11.44	3457.54	154.31
5am1	-119.62	- 9.384	- 0.052	3.759	S	anti	19.80	3438.07	154.23
6am1	-119.59	- 9.395	- 0.116	2.442	R	syn	15.61	3414.22	154.39
7am1	-118.95	- 9.385	- 0.109	4.139	R	syn	10.81	3416.60	154.36
8am1	-118.32	- 9.417	- 0.110	3.502	S	syn	21.72	3410.26	154.36
9am1	-115.16	- 8.999	0.274	5.139	R	anti	36.38	3476.68	154.38
10am1	-114.92	- 9.268	- 0.072	2.224	R	syn	3.90	3419.40	154.67
11am1	-114.88	- 9.208	- 0.036	4.461	R	syn	19.22	3422.72	154.76
12am1	-114.70	- 9.238	- 0.060	3.151	R	syn	33.54	3430.09	154.64
13am1	-114.16	- 8.964	0.298	4.648	R	anti	27.69	3479.26	154.36

To be sure that the obtained conformers are minimum on the potential energy surface and not saddle points, for each conformer a normal vibration calculation was performed. For all conformers, all vibrations are positive, including $\nu_{\text{min}} > 0$. As structural elements the wavelength number of the maximum vibration, ν_{MAX} and zero point vibrational energy, ZPVE are given in Table I. A gap of 6,66 kcal/mol resulted between the lowest energy (01am1) conformer and the highest energy (13am1) one [1].

The charge densities for some atoms important for biological activity – S(1), N(4),

N(14), O(8), O(12), O(13), O(17)) – of the conformers resulted from AM1 calculations, are presented in Table II.

Table II. Charge densities on some atoms of the conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid arranged by the ascending variation of the formation enthalpies computed with AM1.

Energetic order	Net charge on atom						
	S1	N4	N14	O8	O12	O13	O17
1am1	0.051	-0.268	-0.366	-0.225	-0.304	-0.341	-0.351
2am1	0.081	-0.251	-0.366	-0.227	-0.299	-0.364	-0.360
3am1	0.063	-0.262	-0.366	-0.225	-0.305	-0.346	-0.356
4am1	0.053	-0.263	-0.366	-0.218	-0.306	-0.332	-0.352
5am1	0.035	-0.240	-0.367	-0.232	-0.283	-0.355	-0.350
6am1	0.073	-0.256	-0.377	-0.228	-0.301	-0.341	-0.348
7am1	0.074	-0.257	-0.378	-0.220	-0.308	-0.325	-0.347
8am1	0.058	-0.239	-0.379	-0.234	-0.284	-0.353	-0.346
9am1	0.050	-0.262	-0.363	-0.215	-0.275	-0.359	-0.343
10am1	0.086	-0.257	-0.369	-0.235	-0.312	-0.336	-0.356
11am1	0.087	-0.264	-0.369	-0.228	-0.304	-0.341	-0.355
12am1	0.078	-0.270	-0.371	-0.240	-0.312	-0.338	-0.355
13am1	0.050	-0.265	-0.364	-0.204	-0.323	-0.305	-0.341

After an analysis of the HOMO and LUMO energies (Table I) we cannot find a clusterization of the conformers with respect to the following geometric properties: pseudo-chirality of the N14 atom, *syn-anti* arrangement of the O17 and H28 atoms of the amidic group or after the puckering class of the thiazolidinic ring (a, b, c) [1]. For comparison of electronic properties their average values were calculated.

The HOMO and LUMO energy average values with respect to the (R, S) pseudo-chirality of the N14 atom are:

$$\text{HOMO(R)} = -9.201 \pm 0.159 \text{ eV}, \quad \text{LUMO(R)} = 0.034 \pm 0.159 \text{ eV},$$

$$\text{HOMO(S)} = -9.333 \pm 0.073 \text{ eV}, \quad \text{LUMO(S)} = -0.031 \pm 0.060 \text{ eV},$$

They are not statistically distinct. However, comparing the average values for the R conformers with the average values of the S conformers it results that the HOMO energies are lower for the (S) conformers, while the LUMO energies are higher for the (S)

conformers, and the data dispersion (SD) is narrower. Overall, one can conclude that through the pyramidalization of the N(14) atom the HOMO and LUMO energies are not significantly influenced in the AM1 method.

The HOMO and LUMO energy average values calculated with respect to the *syn-anti* criterion are:

$$\text{HOMO}(\textit{syn}) = -9.319 \pm 0.091 \text{ eV}, \quad \text{LUMO}(\textit{syn}) = -0.084 \pm 0.033 \text{ eV},$$

$$\text{HOMO}(\textit{anti}) = -9.194 \pm 0.164 \text{ eV}, \quad \text{LUMO}(\textit{anti}) = 0.088 \pm 0.144 \text{ eV},$$

Compared to *anti*, the *syn* conformers have the HOMO energy average values lower and the LUMO energy values higher. Even if they are influenced by the *syn-anti* arrangement, the differences of the HOMO and LUMO energies, respectively, are not significant. In conclusion, the *syn-anti* arrangement of the O17 and H28 atoms has a weak influence on the HOMO and LUMO energy in the AM1 method.

The HOMO and LUMO energy average values calculated with respect to the puckering criteria of the thiazolidinic cycle (a, b, c) are:

$$\text{HOMO}(\text{a}) = -9.205 \pm 0.051 \text{ eV}, \quad \text{LUMO}(\text{a}) = 0.028 \pm 0.078 \text{ eV},$$

$$\text{HOMO}(\text{b}) = -9.179 \pm 0.159 \text{ eV}, \quad \text{LUMO}(\text{b}) = 0.07 \pm 0.169 \text{ eV},$$

$$\text{HOMO}(\text{c}) = -9.395 \pm 0.015 \text{ eV}, \quad \text{LUMO}(\text{c}) = -0.097 \pm 0.030 \text{ eV},$$

There is a small difference between the average values of the three puckering classes. Due to the large dispersion for the HOMO in (b) puckering class, we cannot conclude that these average values are statistically distinct. However, we can make some remarks: the (b) puckering class has the lowest HOMO energy average values and the highest LUMO energy values.

To see the measure in which the HOMO and LUMO average values of the (a,b,c) puckering classes are influenced by the pyramidalization at N(14) or by the *syn-anti* arrangement, the average values function of these criteria were calculated.

The HOMO and LUMO average values for the (a,b,c) puckering classes calculated function of the R-S pseudo-chirality are:

$$\text{HOMO}(\text{R,a}) = -9.193 \pm 0.064 \text{ eV}, \quad \text{LUMO}(\text{R,a}) = 0.015 \pm 0.106 \text{ eV},$$

$$\text{HOMO}(\text{S,a}) = -9.238, \quad \text{LUMO}(\text{S,a}) = -0.06,$$

$$\text{HOMO}(\text{R,b}) = -9.110 \pm 0.151 \text{ eV}, \quad \text{LUMO}(\text{R,b}) = 0.116 \pm 0.197 \text{ eV},$$

$$\text{HOMO}(\text{S,b}) = -9.316 \pm 0.269 \text{ eV}, \quad \text{LUMO}(\text{S,b}) = -0.023 \pm 0.017 \text{ eV},$$

$$\text{HOMO}(\text{R,c}) = -9.390 \pm 0.007 \text{ eV}, \quad \text{LUMO}(\text{R,c}) = -0.113 \pm 0.005 \text{ eV},$$

$$\text{HOMO}(\text{S,c}) = -9.401 \pm 0.023 \text{ eV}, \quad \text{LUMO}(\text{S,c}) = -0.081 \pm 0.041 \text{ eV}.$$

The statistical analysis of the data suggests that both for the average values of the HOMO and LUMO energies with respect to the (a), (b) and (c) puckering classes and the R-S N14 pyramidalization, there are no statistically distinct values.

In Figure 2 is given the orbital distribution in HOMO and LUMO levels for three conformers: 01am1 (with the lowest energy) and 13am1 (with the worst concordance with experimental geometry)[1].

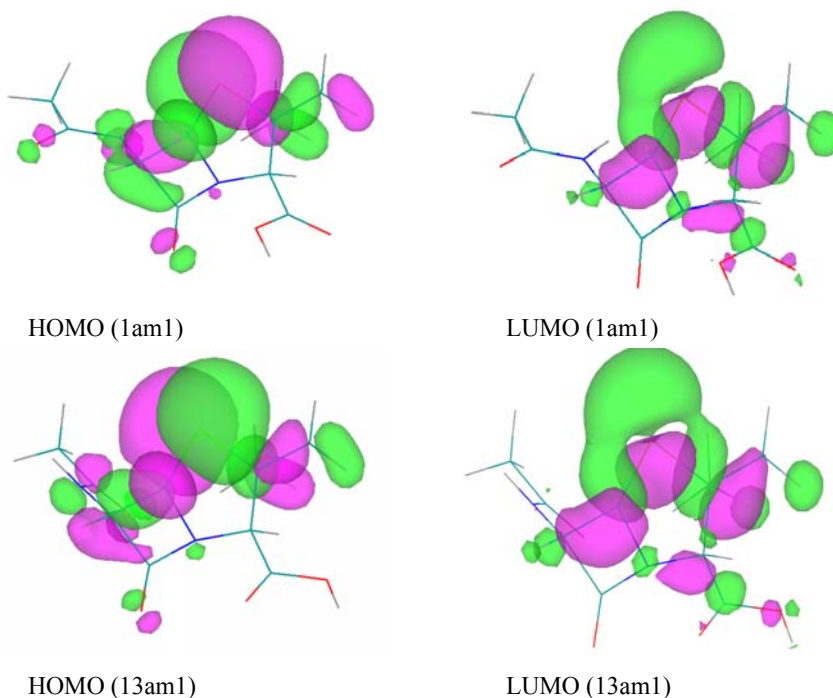


Fig. 2. The weight of the Sulphur (S1) atom in HOMO and LUMO of conformers 01am1 (with the lowest energy) and 13 am1 (with the worst concordance with experimental geometry) computed with AM1.

For all the conformers the contribution of the sulphur atom, S1 to the HOMO or LUMO level is the most important. For the HOMO level are of importance also the contributions of the σ bonds between C2-C9, C2-C10, C5-C6 and C5-H19 and of lower importance the local contributions of the N4, O8, N14 and O17 atoms. For the LUMO level are of importance the contributions of the C2 and C5 atoms and in lower measure those of the N3, C6, C7 and O8 atoms.

Analyzing the data in Table I can observe that there is no influence of the pyramidalization of the N14 atom on the dipole moment, as it results from the average values calculated with the R-S criterion: $\mu(R) = 3.890 \pm 1.134$ Debye, $\mu(S) = 4.290 \pm 0.627$. Even if these average values seem different, due to their high standard deviation they are not statistically distinct.

The influence of the *syn-anti* arrangement on the dipole moment is more obvious. The *syn* structures have lower values of the dipole moment in the interval 2.224 - 4.461 Debye for conformers 10am1 and 11am1, respectively. Comparatively, the *anti* structures have higher values in the interval 3.759 - 5.139 Debye for conformers 5am1 and 9am1, respectively (Table I). The average values are $\mu(\textit{syn}) = 3.320 \pm 0.895$ Debye, and $\mu(\textit{anti}) = 4.665 \pm 0.449$ Debye. Statistically these average values are distinct.

The influence of the puckering on the dipole moment is proven by the average values for the three puckering classes (a,b,c):

$$\mu(\textit{a}) = 4.299 \pm 0.995 \text{ Debye}$$

$$\mu(\textit{b}) = 4.306 \pm 1.051 \text{ Debye}$$

$$\mu(\textit{c}) = 3.461 \pm 0.728 \text{ Debye}$$

Even if these average values are different, due to the high dispersion they are not statistically distinct.

The influence of the *syn-anti* arrangement on the average values of the dipole moment calculated with respect to the (a,b,c) puckering classes are:

$$\mu(\textit{syn,a}) = 3.151 \text{ Debye}$$

$$\mu(\textit{anti,a}) = 4.873 \pm 0.065 \text{ Debye}$$

$$\mu(\textit{syn,b}) = 3.343 \pm 1.582 \text{ Debye}$$

$$\mu(\textit{anti,b}) = 4.787 \pm 0.28 \text{ Debye}$$

$$\mu(\textit{syn,c}) = 3.759 \text{ Debye}$$

$$\mu(\textit{anti,c}) = 4.873 \pm 0.065 \text{ Debye}$$

From these data, for each puckering class there is an evident differentiation of the dipole moments function of the *syn-anti* arrangement.

As expected, these average values prove that for all conformers the dipole moment is strongly influenced by the *syn-anti* spatial arrangement of the O17 and H28 atoms of the exocyclic amidic group.

Comparing these average values one observes that the ν_{min} backbone vibration depends on the puckering classes, but is not influenced by pseudochirality and the *syn-anti* arrangement. At the same time the ν_{MAX} vibration is not influenced neither by the pseudochirality, the *syn-anti* arrangement, nor by the puckering classes. We can generalize that independent of the conformer the vibrations of the functional groups are not influenced by the three factors: pseudochirality, *syn-anti* arrangement and puckering classes, while the vibrations implicating the backbone depend on the puckering classes and do not depend on pseudochirality and *syn-anti* arrangement.

$$\nu_{\text{min}}(\textit{S}) = 17.284 \pm 4.536 \text{ cm}^{-1} \quad \nu_{\text{MAX}}(\textit{S}) = 3444.880 \pm 21.710 \text{ cm}^{-1}$$

$$\nu_{\text{min}}(\textit{R}) = 22.081 \pm 11.526 \text{ cm}^{-1} \quad \nu_{\text{MAX}}(\textit{R}) = 3438.119 \pm 26.532 \text{ cm}^{-1}$$

$$\begin{array}{ll}
v_{\min.}(syn) = 17.467 \pm 10.113 \text{ cm}^{-1} & v_{\max.}(syn) = 3418.882 \pm 6.956 \text{ cm}^{-1} \\
v_{\min.}(anti) = 22.610 \pm 9.002 \text{ cm}^{-1} & v_{\max.}(anti) = 3459.437 \pm 15.263 \text{ cm}^{-1} \\
v_{\min.}(a) = 25.497 \pm 10.626 \text{ cm}^{-1} & v_{\max.}(a) = 3447.03 \pm 17.489 \text{ cm}^{-1} \\
v_{\min.}(b) = 19.773 \pm 11.491 \text{ cm}^{-1} & v_{\max.}(b) = 3451.518 \pm 25.705 \text{ cm}^{-1} \\
v_{\min.}(c) = 16.985 \pm 4.843 \text{ cm}^{-1} & v_{\max.}(c) = 3419.788 \pm 12.466 \text{ cm}^{-1}
\end{array}$$

Comparing these data it results that both pseudochirality and *syn* – *anti* arrangement do not influence the v_{\min} and v_{\max} vibration energies.

Based on the above results we can conclude that both the backbone vibrations as well as the vibrations of the functional groups do not depend on the *syn-anti* arrangement or the pseudochirality of the N14 atom. But they depend significantly on the puckering class. For all the 13 conformers optimized with the AM1 method, the nature of these two types of vibrations does not change.

The equilibrium energy (ZPVE) is relatively constant around the average value of 154.429 ± 0.159 kcal/mol. It is contained in the interval 154.23 kcal/mol and 154.76 kcal/mol. The average calculated values for ZPVE using the *syn-anti* arrangement, R-S pseudochirality and puckering classes criteria lead to the conclusion that this energy does not change. ZPVE is a measure who does not depend significantly on the conformer's nature.

The net charge on the S1 atom (in Table II) varies in relatively small limits, between 0.035 and 0.087 . The average value for all conformers is $q_{S1} = 0.0645 \pm 0.016$. The standard deviation is higher than the average value. To evidence some influences on the S1 charge a statistical analysis was performed applying the three criteria: the influence of the R-S pseudochirality, the influence of the *syn-anti* arrangement and the influence of the three puckering classes. The obtained average values are all almost zero and do not allow evidencing any dependence of the S1 atom charge on the three criteria:

$$\begin{array}{ll}
q_{S1}(S) = 0.052 \pm 0.011 & q_{S1}(R) = 0.37 \pm 0.006 \\
q_{S1}(anti) = 0.052 \pm 0.014 & q_{S1}(syn) = 0.076 \pm 0.011 \\
q_{S1}(a) = 0.074 \pm 0.010 & q_{S1}(b) = 0.003 \pm 0.018 \quad q_{S1}(c) = 0.06 \pm 0.018
\end{array}$$

The net charges on the atoms: q_{N4} , q_{N14} , q_{O8} , q_{O12} , q_{O13} , q_{O17} are all negative for all conformers (Table II.). Even if the two nitrogen atoms (N4, N14) are of the same type (amidic nitrogen), the N4 atom is strongly pyramidalized due to its steric vicinities in the two cycles. The N4 atom has a real pyramidalization, while N14 has a pyramidalization generated by the quato-chemical computation method. The N4 atom has a negative net charge significantly higher than the exocyclic N14 nitrogen atom. The average value of the charge is $q_{N4} = -0.258 \pm 0.010$, while $q_{N14} = -0.369 \pm 0.005$. The net charge on N4 varies in quite small limits, between -0.364 and -0.377 , , it can be considered almost constant and independent of the conformation, while the net charge on N14 varies in large limits between -0.240 and -0.270 and depends on the conformation. For these two atoms (N4, N14) the

average charges for the conformers with R and S pseudochirality are:

$$q_{N4}(R) = -0.260 \pm 0.006; \quad q_{N14}(R) = -0.370 \pm 0.006;$$

$$q_{N4}(S) = -0.254 \pm 0.138; \quad q_{N14}(S) = -0.369 \pm 0.006;$$

For the conformers with *syn-anti* arrangement they are:

$$q_{N4}(syn) = -0.257 \pm 0.014; \quad q_{N14}(syn) = -0.374 \pm 0.005;$$

$$q_{N4}(anti) = -0.259 \pm 0.010; \quad q_{N14}(anti) = -0.365 \pm 0.002;$$

and for the three puckering classes the average charges for N4 and N14 are:

$$q_{N4}(a) = -0.261 \pm 0.010; \quad q_{N14}(a) = -0.368 \pm 0.003;$$

$$q_{N4}(b) = -0.263 \pm 0.004 \quad q_{N14}(b) = -0.366 \pm 0.002;$$

$$q_{N4}(c) = -0.248 \pm 0.010; \quad q_{N14}(c) = -0.375 \pm 0.006;$$

These average charges show that the net charges for the two amidic nitrogen atoms do not differ significantly from the average values of all conformers. From this data one can draw the conclusion that the net charges on the N4 and N14 atom are relatively constant and independent of the conformation.

The average value of the net charge on the O8 β -lactamic atom: $q_{O8} = -0.225 \pm 0.010$ is lower than the average values of the net charges for the other oxygen atoms: $q_{O12} = -0.301 \pm 0.013$, $q_{O13} = -0.341 \pm 0.015$, $q_{O17} = -0.351 \pm 0.006$. The q_{O8} net charge is relatively constant, independent of the conformation and varies between -0.204 and -0.240. On the atoms O12, O13 and O17 the net charge varies between -0.275 and -0.323, -0.305 and -0.364, and respectively -0.341 and -0.360. For these oxygen atoms the average values of the net charge taking the R and S pseudochirality into account, are:

$$q_{O8}(R) = -0.225 \pm 0.011 \quad q_{O8}(S) = -0.227 \pm 0.006$$

$$q_{O12}(R) = -0.304 \pm 0.014 \quad q_{O12}(S) = -0.296 \pm 0.01$$

$$q_{O13}(R) = -0.339 \pm 0.018 \quad q_{O13}(S) = -0.345 \pm 0.009$$

$$q_{O17}(R) = -0.351 \pm 0.007 \quad q_{O17}(S) = -0.351 \pm 0.004$$

Taking into account the *syn-anti* arrangement, the average charges are:

$$q_{O8}(syn) = -0.231 \pm 0.007 \quad q_{O8}(anti) = -0.221 \pm 0.010$$

$$q_{O12}(syn) = -0.304 \pm 0.011 \quad q_{O12}(anti) = -0.299 \pm 0.016$$

$$q_{O13}(syn) = -0.339 \pm 0.009 \quad q_{O13}(anti) = -0.343 \pm 0.020$$

$$q_{O17}(syn) = -0.351 \pm 0.005 \quad q_{O17}(anti) = -0.350 \pm 0.007,$$

and taking the three puckering classes into account the following average values are obtained:

$$q_{O8}(a) = -0.231 \pm 0.008 \quad q_{O8}(b) = -0.221 \pm 0.011 \quad q_{O8}(c) = -0.229 \pm 0.006$$

$$q_{O12}(a) = -0.305 \pm 0.007 \quad q_{O12}(b) = -0.304 \pm 0.015 \quad q_{O12}(c) = -0.294 \pm 0.012$$

$$q_{O13}(a) = -0.349 \pm 0.013 \quad q_{O13}(b) = -0.336 \pm 0.017 \quad q_{O13}(c) = -0.344 \pm 0.014$$

$$q_{O17}(a) = -0.357 \pm 0.003 \quad q_{O17}(b) = -0.35 \pm 0.006 \quad q_{O17}(c) = -0.348 \pm 0.005,$$

Statistically, it results that the oxygen net charges do not differ significantly from the average values for all conformers. If the puckering classes and the *syn-anti* or R-S criteria are taken into account, there is also no regular pattern.

Based on these results we can affirm that the net charges do not fluctuate following certain regular patterns. The only exception is the N14 atom whose net charge depends on the conformation. This means that the conformational changes generated by the rotation of the free groups and by the different puckering classes do not influence significantly the charges, except for the N14 atom.

The effect of this relatively constant distribution on the net charges determines an isosurface of the electrostatic potential relatively similar for all conformers. This is illustrated by the isosurface of the electrostatic potential presented in Fig. 3 for the conformer of the minimum energy (01pm3), maximum energy (13pm3). The iso-surfaces of the electrostatic potential depend in a small degree on the spatial arrangement mode of the exocyclic groups attached to the N14 amidic atom.

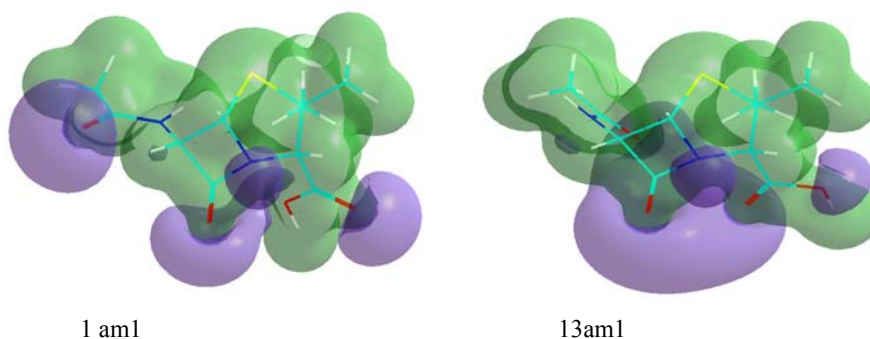


Fig. 3. Iso-surface of the electrostatic potential computed with PM3 for the contour value of 0.04, for conformers 01pm3, and 13pm3.

For the case when the O8 and O17 atoms are closer, an extended negative potential occurs (the case of conformer 13pm3). Function of distance between the O12 or O13 atoms and the N4 atom, the isosurface of the negative electrostatic potential changes its shape (the case of conformer 01pm3).

CONCLUSION

From the conformational analysis with the AM1 method it results that for all conformers the pseudochirality of the N14 atom does not influence significantly the HOMO and LUMO energies. On the contrary, the energy of these levels is influenced by the *syn-*

anti arrangement of the exocyclic amidic group as well as by the puckering of the thiazolidinic ring.

From the analysis of the orbital contribution to the HOMO and LUMO levels, one can conclude that in these levels the S1 atom has the dominant contribution, while the geometry factors - pseudochirality of the N14 atom, the *syn-anti* arrangement and the puckering of the thiazolidinic cycle do not influence significantly this contribution.

The dipole moment is influenced strongly by the *syn-anti* arrangement. The puckering slightly influences the dipole moment, while the pseudochirality does not influence it at all.

From the vibration analysis one can draw the conclusion that both the backbone vibrations as well as the vibrations of the functional groups do not depend by the *syn-anti* arrangement or by the pseudochirality at the N14 atom, but depend significantly on the puckering. ZPVE does not depend significantly on the geometry of the conformer.

Analysing the average values of the net atomic charges one can conclude that the charge densities on the N4 atom are not dependent on conformation, they being almost constant. For the N14 atom the net density is dependent on the conformation and this is proven by the high dispersion of the values. There is a certain pattern with the respect of the puckering, but such pattern was not observed for pseudochirality or the *syn-anti* arrangement. The constant charge distribution leads to an isosurface of the electrostatic potential relatively similar for all conformers.

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