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Dedicated to Professor Eugen Segal
on the occasion of his 80th anniversary

FORMATION ENTHALPY FOR CONFORMERS OF (3S,5S,6S)-6-ACETYLAMIDOPENICILLANIC ACID CALCULATED BY THE PM6 AND PM7 SEMIEMPIRICAL MO METHODS**

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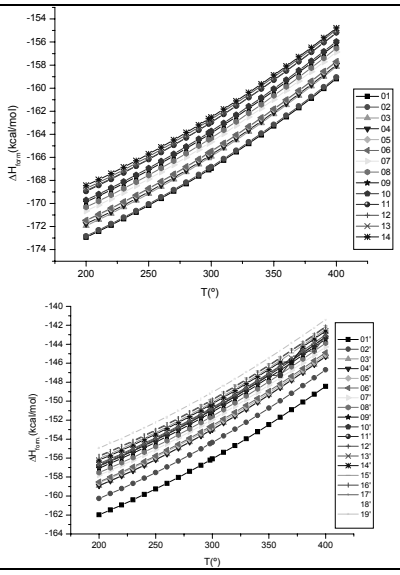
28 distinct conformers of the (3S,5S,6S)-6-acetylamidopenicillanic acid previously optimized at HF/STO-3G *ab initio* level were energetically minimized with the PM6 and PM7 semiempirical MO methods included in the MOPAC12 software. After energy minimization 14, respectively 19 distinct conformers were obtained. The difference ($\Delta H_{form}(298)$) between the lowest and the highest standard formation enthalpy of conformers is 4.42 kcal/mol, and 7.03 kcal/mol for PM6, and PM7 semiempirical MO methods, respectively. For the conformers obtained by the PM6 and PM7 semiempirical MO methods quadratic interpolation relations of functional dependence of formation enthalpy on temperature ($\Delta H_{form} = a_0 + a_1T + a_2T^2$) were established. The a_1 and a_2 values are neither dependent on the method of calculation, nor the conformer geometry. The a_0 free term is the only one which depends on the conformer geometry. It increases with the decreasing of the thermodynamic stability of conformers. These interpolation relations allow the calculation of molar fraction of each conformer in the mixture at a certain temperature in the interpolation range of 200-400K.



INTRODUCTION

The interest for the thermal behavior of drugs is given by the necessity to know which is their thermal stability, especially for the establishment of storage and transport conditions.[1-9]

Even if chemical synthesis of drugs had a similar evolution as chemical thermodynamics,[10-12] only few information on drug thermodynamic properties are reported. Generally thermodynamic properties are seldom reffered to in the introduction sections of organic chemistry books

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** Supplementary material on http: //web.icf.ro/rrch/ or http: //revroum.getion.ro/

and the content of this information is rarely used.[13-14] Most of the time it is considered that thermodynamic properties have only technological interest.[10-12] Drugs and biological products are obtained by certain technological processes in which the main product (drug) is in a mixture with a series of secondary products. For example, the synthesis of antibacterial products – antibiotics,[15-20] especially penicillins and cephalosporins is described in literature as a stereospecific one. From this reaction different conformers, very unstable intermediates, intermediates being in equilibrium or in transition states result. For such a complex system a series of thermodinamic data should be taken into account. The thermal analysis solves partially some of the thermodynamic problems related to the thermal stability, phase transitions, thermal oxidative or inert gas decompositions and kinetics of thermal decompositions.[1-9] Under these circumstances the data obtained by termal analysis are only partially useful. If from synthesis result many conformers, an important problem is to know the thermodynamic properties and the procent of each conformer in the mixture, especially in the case when a single conformer is active. There are many ways to calculate such thermodynamic properties. One is the conformational analysis followed by the use of a quantitative structure-property/activity relationships (QSPR/QSAR) method. QSPR/QSAR methods are known also as free energy relationships, because they are based on Gibbs free energy (ΔG), a thermodynamic property.[21-40]

The conformational analysis of molecules of biological interest is performed using thermodynamic properties, too.[41-53] This implies the knowledge of geometry and energy of distinct conformers. M. J. S. Dewar *et al.* developed semiempirical quantum mechanical methods, which can simulate chemical reactions.[54-58] These approaches allow a good estimation of molecular chemical (thermodynamic) stability and an acceptable assessment of molecular geometry. The standard enthalpy of formation ($\Delta H_{form}(298)$) was considered to be the basic experimental property for the optimization of quantum chemical parameters. J. J. P. Stewart,[56] Dewar's co-worker, developed the MOPAC software and continued to improve the optimization of AM1 and PM3 hamiltonians.[59,60] In the last 10 years J. J. P. Stewart built up the MOPAC package, with versions MOPAC07, MOPAC09 and MOPAC12, by improving the AM1 to RM1 parametrization, the PM3 parametrization and by developing a hamiltonian in the NDDO approximation – PM6 and PM7.[61-69] In the PM3 parametrization (in HyperChem, MOPAC, SPARTAN softwares)[70,71] the estimation of standard enthalpy of formation ($\Delta H_{form}(298)$), ionization energies and electron affinities are satisfactory calculated, relative to the experimental data. Starting with MOPAC07 fundamental thermodynamic properties, like: ($\Delta H(T)$) (enthalpy at the T temperature), ($\Delta H_{form}(298)$), ($\Delta H_{form}(T)$), $C_p(T)$ (heat capacity), $\Delta S(T)$ (entropy) and implicitely $\Delta G(T)$ (Gibbs free energy; $\Delta G(T) = \Delta H(T) + T\,\Delta S(T)$), outside the phase transformations can be satisfactoryly estimated.[72] This way the quantum mechanics offers a tool for the evaluation of certain thermodynamic properties, for which experimental thermodynamic data do not exist.

In this study the geometries of conformers of the (3S,5S,6S)-6-acetylamidopenicillanic acid previously obtained by the HF/STO-G *ab initio* approach[73] were reoptimized by the PM6 and PM7 hamiltonians, respectively. The enthalpies of formation ($\Delta H_{form}(T)$) obtained by these semiempirical MO methods were calculated.

METHOD

Quantum chemical calculations were carried out by the PM6 and PM7 hamiltonians included in the MOPAC12 Version 13.004W program.[69] The conformer geometries of the (3S,5S,6S)-6-acetylamidopenicillanic acid,[70,73] obtained by using the *ab initio* HF/STO-3G approach (calculated with the Hyperchem software) were converted into MOPAC type files by the AVOGADRO software[74] by using the "MOPAC" and "Geometry Optimization" keywords. For geometry reoptimization using MOPAC12 software in the first step the same keywords were employed: PM6 (or PM7), SCFCRT=1.D-10, GEO-OK, PRECISE, GNORM=0.01, CYCLES=5000, T=345600, LET. The resulted optimized geometries thus derived by MOPAC12 were transformed into input MOPAC files by the AVOGADRO software[74] by using the "MOPAC" and "Frequencies" keywords. In the second step, last created MOPAC files with the following keywords: AUX, LARGE, CHARGE=0, SINGLET, FORCE, THERMO, PM6 (or PM7), LET were used for the calculation of $\Delta H_{form}(T)$ with MOPAC12.

Same atom numbering used in the previous studies[40,47,48,50,51] of the (3S,5S,6S)-6-acetylamidopenicillanic acid (see Fig. 1) was employed. The total energy (E_{tot} – in case of HF/STO-3G calculations) and standard formation enthalpy

($\Delta H_{form}(298)$ – in case of PM6 and PM7 calcualtions) were considered for the ordering of conformers. In addition, the E_{HOMO} and E_{LUMO} energies, the vibration energy for the equilibrium state R_0 (E_{ZVP}) and the total dipole moment (μ_{TOT}) were collected in Table 1 (Supplementary material) and in Tables 1 and 2 in this paper. The wave number of the minimum vibration ν_0 was considered to demonstrate that the molecular geometry obtained by optimization is a thermodynamicaly stable conformation and not a transition state. The calculated formation enthalpy includes all conformer vibrations being thus accurately calculated.[72]

The dihedral angles $<_{d}(^{o})$: 5-1-2-3 and 5-4-3-2 were measured in order to appreciate the puckering of the thiazolidinic ring and the dihedral angle $<_{d=28\text{-}14\text{-}15\text{-}17}$ for the *anti*/*syn* conformation of the exocyclic amidic group. A value of ±180º, respectively ±0º of $<_{d=28\text{-}14\text{-}15\text{-}17}$ indicates an *anti*, respectively *syn* conformation of the amido group. Thermodynamically the most stable is the *anti* conformer. In agreement with the partition function $f_i = \exp(-E_i/kT) / \sum_{i=1}^{n} \exp(-E_i/kT)$, at a given T temperature, all conformers are possible because this function takes into account the molecular conformation, not the molecular energy state.[10]

In addition two other improper dihedral angles $<_{id}(^{o})$ were considered. The $<_{id=4\text{-}5\text{-}6\text{-}7}(^{o})$ angle was taken into account in order to estimate the non-planarity of the *β*-lactamic ring and $<_{id=6\text{-}15\text{-}28\text{-}14}$ angle for the pseudochirality at the N14 atom belonging the exocyclic amidic group. Pseudochirality is estimated also by the value of the improper dihedral $<_{id=6\text{-}15\text{-}28\text{-}14}$. This pseudochirality was experimentally proved, being generated by the electron pair of the amidic nitrogen atom.[75] In the title structure *S*, respectively *R* pseudochirality at the N14 atom can be present if the $<_{id=6\text{-}15\text{-}28\text{-}14}$ angle has a positive, respectively negative value.

RESULTS

In a previous paper[73] 28 conformers of the (3S,5S,6S)-6-acetylamidopenicillanic acid diastereoisomer were found by HF/STO-3G *ab initio* calculations. A summary of energy and structural conformer features are presented in Table 1 from Supplementary material. The conformers were noted in increasing order of their total energy. The energy difference between the most stable (Pn-01) and unstable (Pn-28) conformer was of 8.93 kcal/mol. From Table 1 (Supplementary material) it can be seen that 12 conformers have negative value of the $<_{id=6\text{-}15\text{-}28\text{-}14}$ at N14 atom and *R* pseudochirality and 16 conformers have positive value of $<_{id=6\text{-}15\text{-}28\text{-}14}$ and *S* pseudochirality. The range of the positive (*S*) values is between 23.4º and 28.9º and the range of negative (*R*) ones: -30.5º and -24.7º (Table 1, Supplementary imaterial). Among all 28 conformers 16 have *anti* and 12 *syn* amido conformation (Table 1, Supplementary material). The minimum energy conformer has *anti* amido conformation and *R* pseudochirality at the N14 atom. All conformers have ν_0 positive values, confirming that the conformer geometries were accurately optimized and they are not pseudostationary states.

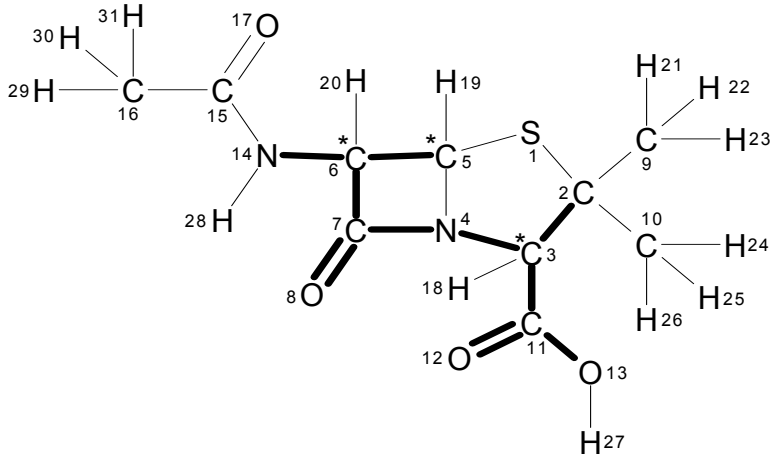


Fig. 1 – The (3S,5S,6S)-6-acetylamidopenicillanic acid structure and the atom numbering (*marks the three chiral atoms: C3, C5 and C6).

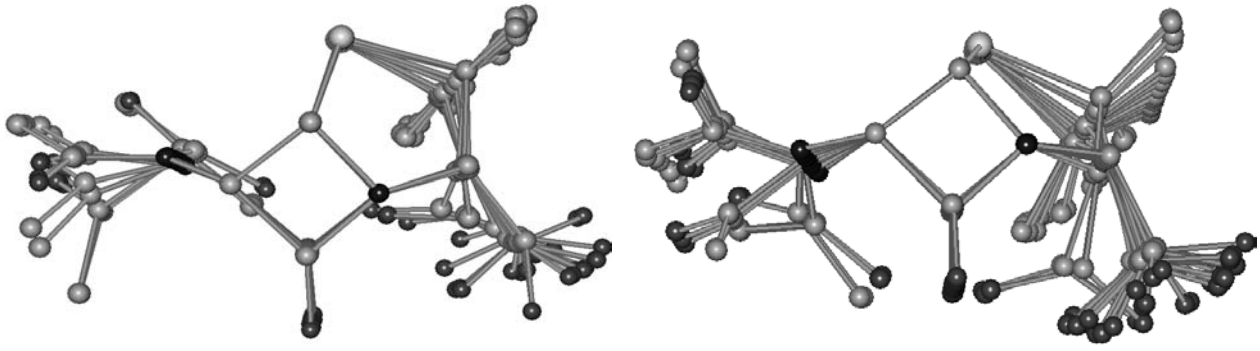
By optimizing all 28 HF/STO-3G conformers of the (3S,5S,6S)-6-acetylamidopenicillanic acid by the PM6 hamiltonian 14 distinct conformers resulted. Energy and structural features of these conformers are included in Table 1, in which conformers were numbered in increasing order of their standard enthalpy of formation ($\Delta H_{form}(298)$). During the optimization process a smaller number of conformers was obtained. The difference ($\Delta\Delta H_{form}(298)$) between the standard enthalpy of formation of the conformers having the lowest and highest standard enthalpy of formation was of only 4.42 kcal/mol. The same PM6 conformer was obtained from several HF/STO-3G conformers: Pn-01 and Pn-05 generate the 01 PM6 conformer; Pn-02, Pn-07, Pn08 and Pn-11 produced the 02 PM6 conformer; Pn10 and Pn-14 yielded 03 PM6 conformer; Pn-03 and Pn-04 generate 04 PM6 conformer; Pn-06 and Pn-09 generate 05 PM6 conformer; Pn-13, Pn-17, Pn-18 and Pn-20 generate 06 PM6 conformer; Pn-21 and Pn-24 generate 07 PM6 conformer; Pn-16 and Pn-19 generate 08 PM6 conformer; and Pn-22, Pn-23 and Pn-25 generate 11 PM6 conformer. Each of the Pn-15, Pn-12, Pn-28, Pn-26 and Pn-27 conformers generated only a single different conformer: 09, 10, 12, 13 and 14, respectively.

Three puckering classes were observed by the superposition of the 14 PM6 conformers, in which N4, C5 and C6 atoms were considered in the superposition procedure (Fig. 2 a).

Seven out of the 14 PM6 conformers have *anti* amido conformation (01 – 05, 11 and 13); the other seven conformers (06 – 10, 12 and 14) have *syn* amido conformation. There are some few *anti* conformers which do not have the most low energies. The *syn* conformers have tendency to form intramolecular hydrogen bonds. A result of the PM6 geometry optimization is that all conformers keep their *anti* or *syn* conformation of the amido group with respect to the starting HF/STO-3G geometries. The first five PM6 conformers have *S* pseudochirality at the N14 atom; the other nine conformers have *R* pseudochirality. Several HF/STO-3G conformers (Pn-01, Pn-03, Pn-08, Pn-09, Pn-11, Pn-14, Pn-17, Pn-19, Pn-20, Pn-22, Pn-23, Pn-24, Pn-25, Pn-26, Pn-27, Pn-28) change their pseudochirality by the PM6 optimization. These facts suggest that the N14 atom chirality can be changed, but the *anti-syn* conformation of the amido group remains unchanged by geometry optimization with the PM6 hamiltonian. Thus the interconversion between the *anti*/*syn* conformations of the amido group implies a higher energy barrier than does a pseudochirality change at the N14 atom.

19 geometrical distinct conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid were obtained by the optimization of the 28 HF/STO-3G conformers by the PM7 hamiltonian. Energy and structural features of these conformers are displayed in Table 2. The PM7 conformers were numbered in the increasing order of their values of the standard enthalpy of formation ($\Delta H_{form}(298)$). The energy difference ($\Delta\Delta H_{form}(298)$) between the conformer with the lowest standard enthalpy of formation and the one having the highest standard enthalpy of formation was of 7.03 kcal/mol.

Three folding classes and the amido group conformations resulted from the superposition of the 19 PM7 conformers. The same three atoms (N4, C5 and C6) were used in the superposition procedure (Fig. 2 b). Among the distinct conformers, nine (01'–04', 06' and 08', 14', 17') have *anti* amido conformation; the other ten conformers: (05', 07', 09'–13', 16', 18' and 19') have *syn* amido conformation.



a b

Fig. 2 – Superposition of the 14 and 19 distinct conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid obtained by the PM6 (a), and PM7 (b) methods, respectively.

Table 1

PM6 conformer ID, PM6 $\Delta H_{form}(298)$ values, E_{HOMO}, E_{LUMO}, μ_{TOT}, ν_0, E_{ZVP},
dihedral angles $<_d$=5-1-2-3; 5-4-3-2, and 28-14-15-17; and improper diedral angles $<_{id}$=4-5-6-7, and 6-15-28-14

ID	$\Delta H_{form}(298)$	E_{HOMO}	E_{LUMO}	μ_{TOT}	$<_d$(°)			$<_{id}$(°)		N14	17, 28	ν_0	E_{ZVP}
	kcal/mol	eV	eV	D	5-1-2-3	5-4-3-2	28-14-15-17	4-5-6-7	6-15-28-14	Chir.	Conf.	cm^{-1}	kcal/mol
01	-167.0804	-9.515	-0.439	5.940	34.647	20.328	176.704	2.120	2.833	S	*anti*	25.80	138.64
02	-166.9628	-9.650	-0.508	4.999	-17.952	-37.791	-170.385	-7.007	8.779	S	*anti*	20.45	138.655
03	-166.0569	-9.647	-0.522	5.397	-12.974	-33.064	-170.341	-5.789	8.984	S	*anti*	29.74	138.644
04	-165.9029	-9.582	-0.487	5.210	30.908	9.345	-173.217	-1.564	6.452	S	*anti*	15.89	138.607
05	165.6499	-9.661	-0.484	6.424	-17.576	-40.270	-170.834	-9.186	8.334	S	*anti*	27.81	138.710
06	-165.6025	-9.710	-0.618	4.473	-21.149	-36.970	-6.330	-5.653	-4.602	R	*syn*	19.31	138.726
07	-164.7811	-9.709	-0.634	2.406	-17.308	-32.412	-6.712	-4.333	-5.724	R	*syn*	30.12	138.684
08	-164.4531	-9.714	-0.594	3.846	-20.858	-39.059	-6.700	-7.508	-5.370	R	*syn*	28.00	138.740
09	-164.0307	-9.556	-0.478	5.599	31.526	9.754	-7.232	-1.386	-6.019	R	*syn*	12.24	138.763
10	-163.8586	-9.595	-0.526	4.477	30.310	9.630	-8.624	-1.532	-9.038	R	*syn*	9.41	138.725
11	-163.0953	-9.311	-0.232	5.303	-2.718	-31.410	171.404	-7.161	-15.050	R	*anti*	20.88	138.804
12	-163.0855	-9.599	-0.550	5.787	25.160	-7.393	-3.486	-6.162	-14.194	R	*syn*	26.78	139.118
13	-162.8430	-9.325	-0.242	5.490	-2.415	-30.115	172.257	-7.125	-14.826	R	*anti*	33.11	138.810
14	-162.6560	-9.625	-0.556	3.053	7.470	-20.670	-4.374	-6.321	-15.284	R	*syn*	41.11	139.169
Mean		**-9.586**	**-0.491**	**4.886**				**-4.901**				**24.33**	**138.771**
SD		0.128	0.121	1.132				3.151				8.54	0.169

Table 2

PM7 conformer ID, PM7 $\Delta H_{form}(298)$ values, E_{HOMO}, E_{LUMO}, μ_{TOT}, ν_0, E_{ZVP},
dihedral angles $<_d$=5-1-2-3, and 5-4-3-2; 28-14-15-17; and improper diedral angles $<_{id}$=4-5-6-7, and 6-15-28-14

ID	ΔH_{form}	E_{HOMO}	E_{LUMO}	μ_{TOT}	$<_d$ (°)			$<_{id}$ (°)		N14	17, 28	ν_0	E_{ZVP}
	kcal/mol	eV	eV	D	5-1-2-3	5-4-3-2	28-14-15-17	4-5-6-7	6-15-28-14	Chir.	Conf.	cm^{-1}	kcal/mol
01’	-156.2205	-9.194	-0.701	5.657	30.531	20.606	173.761	1.535	6.513	S	*anti*	25.45	140.626
02’	-154.4911	-9.258	-0.763	4.342	28.362	13.787	-171.823	-0.649	8.526	S	*anti*	43.17	140.630
03’	-153.1251	-9.294	-0.793	5.001	-9.435	-25.648	-172.120	-3.209	8.045	S	*anti*	16.48	140.706
04’	-153.1081	-9.300	-0.793	5.019	-14.562	-30.181	-172.035	-4.632	7.820	S	*anti*	28.16	140.621
05’	-152.8652	-9.234	-0.750	5.189	29.522	19.219	7.609	1.257	9.105	S	*syn*	31.28	141.247
06’	-152.7016	-9.350	-0.828	3.800	-19.678	-36.429	-172.542	-7.828	6.950	S	*anti*	37.69	140.710
07’	-152.0553	-9.269	-0.781	4.226	27.597	13.496	7.612	-0.355	8.756	S	*syn*	28.46	140.980
08’	-151.7131	-9.334	-0.807	5.780	-16.483	-36.841	-172.376	-8.686	7.161	S	*anti*	23.08	140.512
09’	-151.2758	-9.461	-0.968	2.255	-18.343	-30.066	-6.033	-3.154	-6.000	R	*syn*	30.91	140.762
10’	-151.0534	-9.449	-0.956	4.376	-19.527	-31.543	-6.188	-4.360	-5.240	R	*syn*	30.80	140.622
11’	-151.0181	-9.301	-0.812	2.625	-12.047	-26.038	8.005	-2.490	9.525	S	*syn*	22.16	140.870
12’	-150.8836	-9.467	-0.961	3.788	-21.934	-35.716	-5.462	-6.972	-4.631	R	*syn*	36.06	140.607
13’	-150.8015	-9.300	-0.803	4.420	-15.434	-29.586	7.571	-3.895	9.324	S	*syn*	25.16	140.782
14’	-150.4238	-9.068	-0.579	5.307	-6.351	-29.864	172.313	-6.169	-11.066	R	*anti*	33.67	140.791
15’	-150.2553	-9.040	-0.544	4.643	-8.616	-32.129	172.321	-7.139	-10.854	R	*anti*	34.50	140.792
16’	-150.0141	-9.452	-0.949	4.040	-20.128	-36.147	-5.612	-7.594	-4.876	R	*syn*	30.71	140.567
17’	-149.9575	-9.032	-0.542	4.817	-6.237	-30.219	172.461	-6.778	-10.718	R	*anti*	28.09	140.657
18’	-149.5041	-9.278	-0.785	5.145	9.582	-16.530	-2.019	-6.051	-11.951	R	*syn*	27.31	140.999
19’	-149.1936	-9.304	-0.810	2.873	5.088	-21.690	-2.460	-6.342	-11.649	R	*syn*	29.27	141.012
Mean		**-9.283**	**-0.786**	**4.384**				**-4.395**				**29.60**	**140.763**
SD		0.131	0.128	0.984				3.112				6.042	0.187

It should be emphasized that there are conformers with *anti* amido conformation which do not have values among the lowest standard heat of formation. While most of the *anti* amido conformers are energetically favored to form hydrogen bonds in proteins, the *syn* conformers predominantly generate intramolecular hydrogen bonds leading to beta turns.

All conformers derived by PM7 optimization kept their *anti/syn* amido conformation compared to the one of the HF/STO-3G conformers. The first eight PM7 conformers have *S* pseudochirality at the N14 atom, the other nine conformers have *R* pseudochirality at the N14 atom.Two conformers (11' and 13') with *S* pseudochirality at the N14 atom are intercalated between the set of conformers with *R* pseudochirality at the N14 atom. Among HF/STO-3G conformers several (Pn-01, Pn-03, Pn-08, Pn-09, Pn-11, Pn-12, Pn-14, Pn-15, Pn-17, Pn-19, Pn-22, Pn-23, Pn-24, Pn-25, Pn-26, Pn-27, Pn-28) changed their pseudochirality at the N14 atom by PM7 optimization. These facts demonstrate that by the PM7 optimization of geometry the N14 atom pseudochirality can be changed from *S* to *R*, but the *anti/syn* conformation of the amido group cannot be interconverted. The *anti/syn* conformation implies a rotation barrier much higher in comparison to the modification of the pseudochirality of the N14 atom.

Statistical analysis was used to compare structural data.[73,76] While in case of HF/STO-3G calculations the obtained HOMO energy levels are negative, respectively the LUMO ones are positive, in case of PM6 and PM7 calculations negative values are obtained for both mentioned energy levels. Because there is no photoelectron spectra for penicillins to appreciate the correctness of the values for HOMO levels and polarographic data to estimate the correctness of the values of LUMO levels, we cannot appreciate the relation between the experimental and calculated data and compare the values given by the three methods. The HF/STO-3G E_{LUMO}-E_{HOMO} energy difference is of 14.681 eV, while for PM6 and PM7 this difference is of 9.095 eV, and 8.497 eV, respectively.

The mean values of the calculated total dipole moment: μ_{TOT}(HF/STO-3G) = 3.003±0.627 D, μ_{TOT}(PM6) = 4.886±1.132 D, respectively μ_{TOT}(PM7) = 4.384±0.984 D are different, but from the statistical point of view they do not differ significantly because of their high dispersion values. The mean puckering of the β-lactamic ring estimated by the HF/STO-3G approach (-9.201°±3.947) is significantly different from that estimated by PM6(-4.901°±3.151), respectively PM7 (-4.395°±3.112) methods. While HF/STO-3G predicts a relatively high deviation from planarity for the four atom ring, PM6 and PM6 predict a smaller deviation, with a high dispersion, but their values of the total dipoe moment are comparable to the average experimental value (of 5.935 D).[73] The average values of ν_0 vibration (cm^{-1}) are: ν_0 (HF/STO-3G) = 27.59±8.12; ν_0(PM6) = 24.33±8.54; respectively ν_0(PM7) = 29.601±6.042. They have different values, but because of their high dispersion they do not differ statistically. One can remark that the PM7 average values are closer to the HF/STO-3G ones. The calculated average values of the equilibrium vibration energy $E_{ZVP}(R_0)$ (kcal/mol) are: E_{ZVP}(HF/STO-3G) = 179.261±0.200, E_{ZVP}(PM6) = 138.771±0.169, respectively E_{ZVP}(PM7) = 140.763±0.187. They have small dispersion and therefore the obtained values are different with respect to the used methods. One can observe that the calculated PM6 values are comparable to the PM7 ones.

In order to compare the HF/STO-3G (black marked) calculated geometries with the PM6, respectively PM7 ones minimum energy conformers 01, respectively 01' were superposed (Fig. 3). The geometry of the 01(PM6) conformer does not significantly differ from the 01'(PM7) one. A small difference can be noticed compared to the starting PN-01 HF/STO-3G geometry.

For each geometry optimized by PM6 or PM7 hamiltonians functional dependence of the formation enthalpy ΔH_{form} were calculated as quadratic functions of temperature: $a_0 + a_1T + a_2T^2$.[77] The chosen temperature range was of 200-400K, with a step of 10°; in this range it is considered that the (3S,5S,6S)-6-acetylamidopenicillanic acid is not affected by any phase transformation. The elementary data obtained for each conformer are included in Supplementary material.

The terms of the interpolation functions (a_0, a_1 and a^2) and the statistical indices (r^2, SD and F) are presented in Table 3 for PM6 and Table 4 for PM7.

The a_0 values from Tables 3 and 4 have the same order of magnitude as the ΔH_{form}(298) ones. They differ only with respect to the employed approach: PM6 or PM7. a_1, a_2, r^2, SD and F values do not depend on the calculation method, but on the conformer geometry. We can not find any regularity of these values. From these two Tables on can see that the a_0 values increase with the increase of enthalpies of formation, respectively with decrasing of thermodynamic stability.

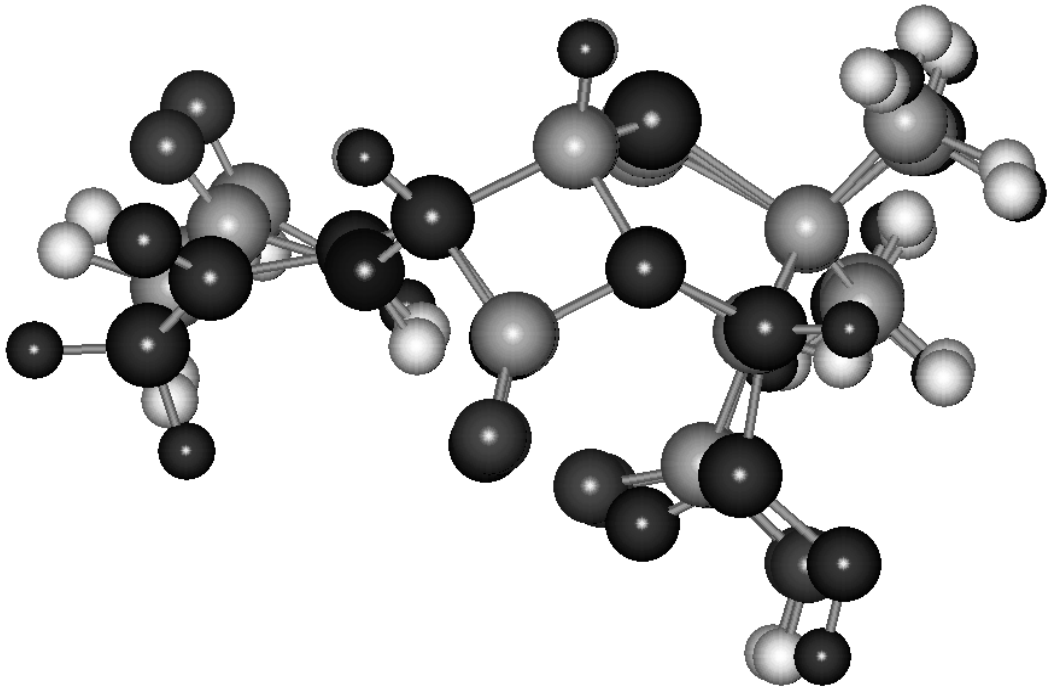


Fig. 3 – Superposition of the HF/STO-3G (black marked) minimum energy conformer of (3S,5S,6S)-6-acetilamidopenicillanic acid over the PM6, respectively PM7 one.

Table 3

Polinomial interpolation relations ($y = a_0 + a_1T + a_2T^2$) of the functional dependence of $\Delta H_{form}(T)$ for the 14 distinct conformers with geometry optimized by the PM6 hamiltonian[77]

Conformer	a_0	a_1	$a_2 \cdot 10^5$	r^2	SD	$F \cdot 10^{-7}$
01	-179.5520	0.0153	8.9165	1.0000	0.0030	1.979
02	-179.5047	0.0156	8.8813	1.0000	0.0032	1.842
03	-178.6321	0.0157	8.8707	1.0000	0.0032	1.854
04	-178.4189	0.0155	8.9010	1.0000	0.0032	1.766
05	-178.1660	0.0154	8.9134	1.0000	0.0034	1.579
06	-178.0967	0.0154	8.9208	1.0000	0.0034	1.618
07	-177.3318	0.0156	8.8871	1.0000	0.0032	1.771
08	-176.9475	0.0153	8.9301	1.0000	0.0037	1.383
09	-176.4821	0.0152	8.9261	1.0000	0.0033	1.655
10	-176.3115	0.0152	8.9299	1.0000	0.0034	1.624
11	-175.5745	0.0153	8.9311	1.0000	0.0033	1.701
12	-175.3229	0.0141	9.0474	1.0000	0.0038	1.254
13	-175.3340	0.0153	8.9270	1.0000	0.0033	1.657
14	-174.8374	0.0138	9.0796	1.0000	0.0042	1.043

Table 4

Polinomial interpolation relations ($y = a_0 + a_1T + a_2T^2$) of the functional dependence of $\Delta H_{form}(T)$ for the 19 distinct conformers with geometry optimized by the PM7 hamiltonian[77]

Conformer	a_0	a_1	$a_2 \cdot 10^5$	r^2	SD	$F \cdot 10^{-7}$
01	-168.5003	0.0150	8.7966	1.000	0.0031	1.803
02	-166.7771	0.0150	8.8138	1.000	0.0034	1.537
03	-165.5385	0.0156	8.7608	1.000	0.0034	1.540
04	-165.5479	0.0157	8.7415	1.000	0.0034	1.585
05	-165.0900	0.0147	8.8094	1.000	0.0034	1.470
06	-165.1694	0.0158	8.7352	1.000	0.0034	1.591
07	-164.2576	0.0146	8.8521	1.000	0.0037	1.290
08	-164.2055	0.0159	8.7363	1.000	0.0033	1.628
09	-163.6532	0.0154	8.7844	1.000	0.0036	1.354

Table 4 (continued)

10	-163.4856	0.0156	8.7506	1.000	0.0034	1.564
11	-163.3327	0.0151	8.8085	1.000	0.0037	1.292
12	-163.3189	0.0156	8.7571	1.000	0.0037	1.328
13	-163.1509	0.0153	8.7860	1.000	0.0034	1.551
14	-162.8302	0.0155	8.7800	1.000	0.0037	1.310
15	-162.6331	0.0153	8.8037	1.000	0.0038	1.244
16	-162.4632	0.0157	8.7604	1.000	0.0035	1.460
17	-162.4103	0.0157	8.7630	1.000	0.0035	1.486
18	-161.6780	0.0144	8.8873	1.000	0.0039	1.143
19	-161.4001	0.0145	8.8727	1.000	0.0040	1.107

In Figs. 1 and 2 from Supplementary material are displayed the curves representing the functional dependence of $\Delta H_{form}(T)$ in the temperature range: 200-400K for the 14 and 19 conformers obtained from the PM6, and PM7 optimization of their geometry.

From Figs. 1 and 2 from Supplementary material and from Tables 1 and 2 one can see that the first two PM6 conformers have very close values of their $\Delta H_{form}(298)$, $\Delta H_{form}(T)$, while the first two PM7 conformers have a difference of around 2 kcal/mol. This result suggests that PM7 semiempirical MO method gives a smaller number of conformers in a range of 3 kcal/mol than the PM6 does.

CONCLUSIONS

Through optimization of the 28 distinct HF/STO-3G conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid by the PM6, respectively PM7 hamiltonians included in the MOPAC12 software 14, respectively 19 distinct conformers were obtained. For the 14 distinct conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid obtained by the PM6 hamiltonian, respectivaly for 19 distinct conformers derived by PM7 hamiltonian quadratic interpolations relations of the functional dependence of formation enthalpy as function of temperature ($\Delta H_{form} = a_0 + a_1T + a_2T^2$) were obtained. The a_1 and a_2 values do not depend on the method of calculation and on conformer geometry. The free term a_0 is the only one which depends on the geometry and which increases with the decreasing of the thermodynamic stability of conformers. These interpolations relations allow the calculation of molar fraction of the conformers of the title compound in the interpolation range (200-400K).

Such a relation affords to estimate the temperature at which a 1H-NMR signal could appear for one conformer, if the ΔH_{form} dependence on temperature is known.

The energy difference ($\Delta\Delta H_{form}(298)$) between the conformers with the lowest and highest standard enthalpy of formation was of 4.4244kcal/mol for PM6, respectively 7.0269kcal/mol for PM7.

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