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PM3 Conformational Analysis of the (3R,5R,6R)-6 Acetylamidopenicillanic Acid. I. Geometrical Properties

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Summary

A conformational analysis with PM3 semiempirical MO method was performed for the (3R,5R,6R)-6-acetylamidopenicillanic acid. Because the N atom of the exocyclic amidic group is pyramidalized by the PM3 method, a larger number of conformers (92) than the number of theoretically possible conformers have been obtained. The difference between the lowest energy and highest energy conformer is 12.14 kcal/mol. The calculated average values of various bond lengths, bond angles and dihedrals helped to observe some regularities in the conformers geometries that otherwise could not be observed. The conformers could be divided in three distinct classes of puckering of the thiazolidinic ring. Ring puckering is not influenced by the rotation of the carboxylic group.

Keywords: conformational analysis; (3R,5R,6R)-6-acetylamidopenicilanic acid; PM3.

Introduction

The (3R,5R,6R)-6-acetylamidopenicillanic acid is one of the simplest antibacterial compounds from the penicillin class. Its molecular structure, as that of all penicillins, contains two fused rings (a four-member β-lactamic ring and a five-member thiazolidinic ring) and three chiral centers, [1] marked with an asterisk in Figure 1. These chiral centers generate 2^3=8 diastereoisomers: 3S,5S,6S, 3S,5R,6R, 3R,5S,6R, 3R,5R,6S, 3S,5S,6R, 3S,5R,6S, 3R,5S,6S, 3R,5R,6R [2]. The 3S,5R,6R diastereoisomer is the natural product. Its two-fused rings represent the general structure of all antibacterials forming the penicillin class [3].

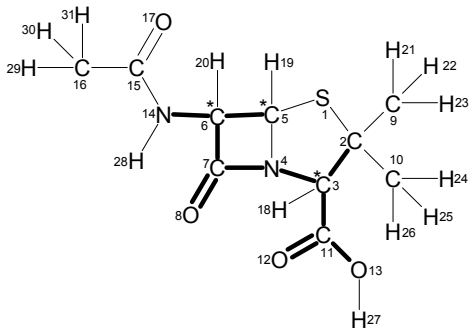


Figure 1. Atom numbering in (3R,5R,6R)-6-acetylamidopenicillanic acid (* denotes the chirality).

Only the molecular and electronic structures of the (3S,5R,6R)-natural diastereoisomer of penicillins have been studied extensively with different quantum-chemical methods [8-15], but in any of them is mentioned that the N14 nitrogen atom (Figure 1) is pyramidalized. This effect influences the results of the quantum chemical methods applied to structures with rotatable bonds [12].

This work presents a study of the influence of substituents on the geometry of the (3R,5R,6R)-6-acetylamidopenicillanic acid conformers resulted from a conformational search using the PM3 semiempirical MO method [16-18].

MATERIALS AND METHODS

The gas phase equilibrium geometry of the conformers was obtained by PM3 calculations with an SCF convergence of 10^{-5}, and a RMS gradient of 10^{-2} kcal/Å·mol [12, 16-18]. 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 ±180° with steps of 15°. The energy criterion was set to 30 kcal/mol above the lowest energy conformer. Calculations have been performed with the Conformational Search module from by HyperChem7.52 package [17, 18]. To obtain all conformers including the minimum energy conformer for structures with more than two flexible bonds the conformational search is generally performed by the grid method [12, 17, 18-20]. Unlike the AM1 method that gave 13 conformers after ~300 starting conformers, the PM3 method gave 92 distinct conformers only after around 1000 starting conformers [18, 20].

RESULTS AND DISCUSSION

As for other compounds containing amidic groups the amidic nitrogen atom in the penicillanic acid is also pyramidalyzed by the PM3 method [18, 22]. This generates a pseudochiral configuration for the N14 atom in the (3R,5R,6R)-6-acetylamidopenicillanic acid. The C6-C15-H28-N14 improper dihedral measures the "conicity" of the out-of-plane substituents at the N14 nitrogen atom. This can be considered a measure of the pyramidalyzation of the N14 atom.

Although the most stable form of the amido group is the *anti* form, the conformer with the lowest energy resulted from PM3 calculations is also an *anti*. The numbering of conformers, their ranking in increasing order of the formation enthalpies and some geometric data are presented in Table I. As it can be seen in Figure 2 and Table I the PM3 method leads to 92 distinct conformers. Between the formation enthalpy of the lowest energy conformer (02pm3) and the highest energy conformer (97pm3) is a difference of 12.14 kcal/mol. The calculated geometry data is dispersed and does not show any correlation. To find some rules the average values and their standard deviations have been calculated for the main angles and bond lengths of the rings and of the exocyclic distances between the sulphur atom and the methylic carbon atoms 9 and 10 (Figure 1), taking into account all conformers, the pseudochiral structures, the *syn* or *anti* arrangements of the O17 and H28 atoms, as well as the three observed puckering classes (Table I) [18].

Table I. Some geometric features of the conformers resulted from PM3 calculations for the (3R,5R,6R)-6-acetylamidopenicillanic acid arranged by increasing order of the calculated formation enthalpies.

Enegetic order	ΔH_{form} (kcal/mol)	Dihedral angles (°)		Improper angle (°)	Pseudo chirality N14	Position O17, H28
		5-1-2-3	5-4-3-2	6-15-28-14		
01(2pm3)	-141.387	17.483	27.659	-24.332	R	anti
02(3pm3)	-141.283	22.867	25.823	-23.888	R	anti
03(4pm3)	-141.197	18.377	27.300	-23.475	R	syn
04(5pm3)	-141.036	23.019	24.827	-22.547	R	syn
05(6pm3)	-140.885	16.082	27.229	-24.547	R	anti
06(7pm3)	-140.839	23.521	27.869	-24.158	R	anti
07(8pm3)	-140.790	16.954	26.786	-23.609	R	syn
08(9pm3)	-140.669	22.113	25.327	-24.141	R	anti
09(10pm3)	-140.559	22.296	24.192	-22.645	R	syn
10(11pm3)	-140.527	23.731	25.214	21.472	S	syn
11(12pm3)	-140.491	-20.255	-7.662	-23.340	R	anti
12(13pm3)	-140.471	17.959	27.201	20.248	S	syn

Enegetic order	ΔH_{form} (kcal/mol)	Dihedral angles (°)		Improper angle (°)	Pseudo chirality N14	Position O17, H28
		5-1-2-3	5-4-3-2	6-15-28-14		
13(14pm3)	-140.448	19.121	29.870	-24.421	R	anti
14(15pm3)	-140.424	23.153	25.109	-22.518	R	syn
15(16pm3)	-140.420	23.956	27.298	-22.806	R	syn
16(17pm3)	-140.338	17.134	27.067	21.201	S	anti
17(18pm3)	-140.162	23.838	29.122	-24.225	R	anti
18(19pm3)	-140.155	19.935	29.597	-23.590	R	syn
19(20pm3)	-140.060	18.072	27.407	21.411	S	syn
20(21pm3)	-140.066	16.845	26.867	20.466	S	syn
21(22pm3)	-140.012	23.079	24.648	21.685	S	syn
22(23pm3)	-139.998	-22.762	-11.349	19.236	S	anti
23(24pm3)	-139.959	24.220	28.440	-22.917	R	syn
24(25pm3)	-139.945	22.487	24.611	-22.595	R	syn
25(26pm3)	-139.825	24.550	27.781	21.183	S	syn
26(27pm3)	-139.776	24.271	27.963	21.404	S	anti
27(28pm3)	-139.760	23.983	27.681	-22.760	R	syn
28(29pm3)	-139.729	15.959	27.196	21.018	S	anti
29(30pm3)	-139.673	19.898	30.987	-24.486	R	anti
30(31pm3)	-139.625	16.568	26.740	21.571	S	syn
31(32pm3)	-139.555	20.443	30.712	-23.621	R	syn
32(33pm3)	-139.495	22.837	24.449	22.523	S	syn
33(35pm3)	-139.476	-18.768	-5.548	20.480	S	syn
34(36pm3)	-139.377	24.782	28.797	21.307	S	syn
35(37pm3)	-139.356	19.924	29.838	19.989	S	syn
36(38pm3)	-139.333	19.334	29.991	20.833	S	anti
37(39pm3)	-139.315	24.421	27.624	22.128	S	syn
38(40pm3)	-139.287	24.234	28.834	-22.798	R	syn
39(41pm3)	-139.056	24.606	29.368	21.289	S	anti
40(42pm3)	-139.046	-17.839	-29.244	4.379	S	syn
41(43pm3)	-139.004	-18.083	-2.130	21.268	S	anti
42(44pm3)	-138.950	19.714	29.914	21.123	S	syn
43(45pm3)	-138.882	24.594	28.608	22.262	S	syn
44(46pm3)	-138.543	20.186	30.984	20.925	S	anti
45(47pm3)	-138.379	20.271	30.734	21.321	S	syn
46(48pm3)	-136.774	6.886	20.069	21.823	S	syn
47(49pm3)	-136.750	20.767	24.783	29.406	S	anti
48(50pm3)	-136.099	19.849	24.515	29.098	S	anti
49(51pm3)	-136.077	7.370	22.466	21.824	S	syn
50(52pm3)	-135.842	18.712	24.558	-26.984	R	syn
51(53pm3)	-135.693	-2.357	13.932	-20.723	R	syn
52(55pm3)	-135.335	15.762	26.857	22.426	S	anti
53(56pm3)	-135.323	8.988	23.751	22.964	S	anti
54(57pm3)	-135.260	16.100	27.173	22.438	S	anti
55(58pm3)	-135.209	22.813	29.875	28.806	S	anti
56(59pm3)	-135.138	10.452	25.452	23.037	S	anti
57(60pm3)	-135.077	18.374	26.188	-26.621	R	syn

Enegetic order	ΔH_{form} (kcal/mol)	Dihedral angles (°)		Improper angle (°)	Pseudo chirality N14	Position O17, H28
		5-1-2-3	5-4-3-2	6-15-28-14		
58(61pm3)	-135.066	19.100	30.068	22.388	S	anti
59(63pm3)	-134.991	-1.083	16.906	-20.612	R	syn
60(64pm3)	-134.869	15.682	29.731	22.825	S	anti
61(65pm3)	-134.663	15.370	28.691	21.920	S	syn
62(66pm3)	-134.277	5.761	13.767	22.645	S	syn
63(67pm3)	-134.234	23.033	29.524	-29.010	R	syn
64(68pm3)	-134.173	16.501	26.382	-20.259	R	anti
65(69pm3)	-134.152	16.301	26.173	-21.928	R	anti
66(70pm3)	-134.070	14.233	27.023	23.101	S	anti
67(71pm3)	-134.002	9.133	23.449	-20.131	R	anti
68(72pm3)	-133.972	15.762	29.485	21.848	S	syn
69(73pm3)	-133.898	9.721	24.351	20.693	S	syn
70(74pm3)	-133.835	18.680	30.758	22.371	S	anti
71(75pm3)	-133.834	19.891	29.522	-19.367	R	anti
72(76pm3)	-133.751	26.725	23.109	28.939	S	syn
73(77pm3)	-133.543	23.282	30.593	-28.812	R	syn
74(78pm3)	-133.517	16.327	29.475	-19.653	R	anti
75(79pm3)	-133.506	15.880	28.363	23.038	S	anti
76(80pm3)	-133.119	12.457	31.577	20.406	S	syn
77(81pm3)	-132.972	15.188	33.776	21.026	S	syn
78(82pm3)	-132.951	26.559	23.927	29.652	S	anti
79(83pm3)	-132.809	11.286	29.835	-21.478	R	syn
80(84pm3)	-132.639	19.367	30.186	-19.491	R	anti
81(85pm3)	-132.625	14.670	26.828	-19.495	R	anti
82(86pm3)	-132.599	8.360	25.752	-21.757	R	syn
83(87pm3)	-132.518	14.620	33.212	-21.705	R	syn
84(88pm3)	-132.465	12.048	32.327	20.350	S	syn
85(89pm3)	-132.419	-2.286	17.311	-21.837	R	syn
86(90pm3)	-132.369	9.732	22.608	-20.298	R	anti
87(91pm3)	-132.134	16.312	28.058	-19.759	R	anti
88(92pm3)	-131.693	-16.595	-7.193	-24.021	R	anti
89(94pm3)	-130.450	18.927	30.601	-30.320	R	anti
90(95pm3)	-130.452	20.051	31.399	-31.011	R	anti
91(96pm3)	-130.377	19.25	29.787	-30.826	R	anti
92(97pm3)	-129.248	17.378	29.088	-30.608	R	anti

Following the data in Table I, one can see that 45 conformers have (R) pseudo-chirality and negative conicity at the N14 atom (improper dihedral C5-C15-H28-N14), while 47 conformers have (S) pseudo-chirality and positive conicity. The negative conicity has an average value of -23.583±3.161º. The positive conicity has an average value of 21.994 ±3.645º. Regarding the *syn-anti* arrangement of the O17 and H28 atoms, from the 92 conformers 48 are *syn* and 44 are *anti*.

The N4, C5 and C6 atoms of the β-lactamic ring were used as a base for the superposition of all distinct conformers given by PM3 method. The resulted hyperstructure is given in Figure 2.

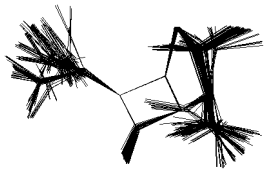


Figure 2. Superposition of the 92 conformers given by the PM3 method

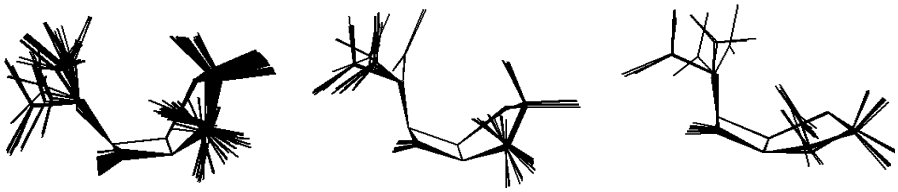
From the superposition presented in Figure 2 one can observe the existence of three puckering classes of the tiazolidinic ring. The puckering of this ring was defined by two dihedral angles: 5-1-2-3 and 5-2-3-4. The average values of these dihedral angles are:

5-1-2-3(*syn*) = 15.896±10.267; 5-2-3-4(*syn*) = 24.663±10.182;
5-1-2-3(*anti*) = 14.714±11.632; 5-2-3-4(*anti*) = 24.635±10.438;
5-1-2-3(R) = 15.931±10.076; 5-2-3-4(R) = 25.461±8.102;
5-1-2-3(S) = 14.756±11.765; 5-2-3-4(S) = 23.872±11.988;

The average and SD values demonstrate that the puckering of the tiazolidinic ring is independent of the (R or S) pseudochirality, the *syn-anti* arrangement of the O17 and H28 atoms, or the rotation of the COOH group.

The conformers belonging to the three puckering classes (Figure 3) are:

Class (a) contains 57 conformers: 26 with a (R) and 31 with a (S) pseudochiral N14 atom. In this class 31 conformers have *anti* and 26 conformers have *syn* disposal of the O17 and H28 amidic atoms. The dihedral angle 5-1-2-3 varies between 5.761º and 20.767º. The dihedral angle 5-4-3-2 varies between 13.767º and 33.776º. The geometries' dispersion can be observed in Figure 3 (a).



a b c

Fig. 3. The three puckering classes of the thiazolidinic ring with the dispersion specific to each class, for the conformers resulted from PM3 calculations.

Class (b) contains 26 conformers: 14 with (R) pseudochirality and 12 with (S) pseudochirality at the N14 atom. Of the 26 conformers 8 have *anti*, while 18 have *syn* arrangement of the O17 and H28 amidic atoms. In this class the dihedral angle 5-1-2-3 varies between 22.113º and 26.725º. The dihedral angle 5-4-3-2 varies between 23.109º and 30.593º. The geometries' dispersion can be observed in Figure 3 (b).

Class (c) contains 9 conformers: 5 with a (R) pseudochiral N14 atom and 4 with a (S) pseudochiral N14 atom. Of the 9 conformers 4 have *anti* and 5 have *syn* arrangement of the O17 and H28 amidic atoms. The 5-1-2-3 dihedral angle varies between -1.083º and -22.762º. The 5-4-3-2 dihedral angle varies between -29.244º and 17.311º. The geometries' dispersion can be observed in Figure 3 (c).

By comparing the average values of the dihedral angles for the three puckering classes of the thiazolidinic ring:

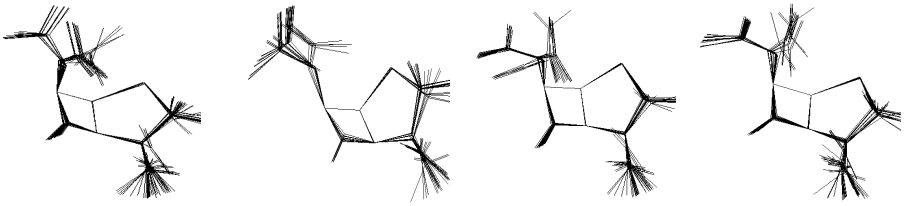
5-1-2-3(a) = 15.911±3.946; 5-4-3-2(a) = 27.757±3.370;
5-1-2-3(b) = 23.806±1.133; 5-4-3-2(b) = 26.946±2.172;
5-1-2-3(c) = -13.336±8.749; 5-4-3-2(c) = -1.664±15.347;

This classification of the conformers resulted from PM3 calculation is evident.

By dividing the conformers in four groups (R,*anti*) – (R,*syn*) and (S,*anti*) – (S,*syn*), (Figure 4) the three puckering groups are maintained.

The average values of the dihedral angles for the three puckering classes (a), (b) and (c), grouped by their *syn-anti* arrangement and by the (R-S) pseudochirality at the N14 atom, are as follows:

5-1-2-3(a,*syn*) = 15.079±4.581; 5-2-3-4(a,*syn*) = 27.566±4.345
5-1-2-3(a,*anti*) = 16.704±3.269; 5-2-3-4(a,*anti*) = 27.906 ±2.418
5-1-2-3(b, *syn*) = 23.823±1.375; 5-2-3-4(b,*syn*) = 27.321±2.079
5-1-2-3(b,*anti*) = 23.799±1.052; 5-2-3-4(b,*anti*) = 26103±2.275
5-1-2-3(c,*syn*) = -8.466±9.000; 5-2-3-4(c, *syn*) = 9.798±2.910
5-1-2-3(c,*anti*) = -19.423±2.685; 5-2-3-4(c,*anti*) = 6.521±0.991
5-1-2-3(a,R) = 16.672±3.494; 5-2-3-4(a,R) = 28.201±2.559
5-1-2-3(a,S) = 15.420±4.261; 5-2-3-4(a,S) = 27.284±3.928
5-1-2-3(b,R) = 23.285±0.701; 5-2-3-4(b,R) = 27.294±2.062
5-1-2-3(b,S) = 24.414±1.260; 5-2-3-4(b,S) = 26.540±2.316
5-1-2-3(c,R) = -8.515±9.125; 5-2-3-4(c,R) = -11.186±10.634
5-1-2-3(c,S) = -19.363±2.299; 5-2-3-4(c,S) = 10.293±11.718



(R) *anti* conformers (R) *syn* conformers (S) *anti* conformers (S) *syn* conformers

Figure 4. The four conformers groups resulted from PM3 calculations, with pseudochirality (R) and (S) at the N14 atom and with atoms' 17 and 28 arranged *anti*, or *syn*. respectively.

Analysing the average values one can observe that the dihedral angles for the *anti* arrangement are generally greater than those for the *syn* arrangement, while for (R) pseudochirality the average values are greater than for the (S) pseudochirality. However, this rule is not valid for both angles in all puckering classes. The average values of the two dihedrals suggest that the ring puckering classes are independent of the N14 atom pseudochirality. The puckering of the thiazolidinic ring is a real fact proven by experimental values. For BENPEN10 the values are 5-1-2-3 = 17.851º, 5-2-3-4 = 40.257º; for BPENCE10 they are 5-1-2-3 = 21.079º, 5-2-3-4 = 39.801º; and for PMEPEN they are 5-1-2-3 = 23.540º, 5-2-3-4 = 35.582º [16, 17, 21, 23, 24]. Comparing these experimental data with the calculated values with the semiempirical PM3 method one can observe that theoretical results obtained for puckering the thiazolidinic ring are lower than the experimental values.

In Table II are presented the average values of the bond angles of the two cycles (β-lactamic and thiazolidinic) and the conicity for the β-lactamic cycle (measured as 4-5-6-7) calculated for all conformers (92), for conformers with (R) (45), respectively (S) (47) pseudo-chirality at the N14 atom, for the conformers with *syn* (48), respectively *anti* (44) arrangement of the H28-N14 atoms and for the three puckering classes of the thiazolidinic cycle: class a (57 conformers), class b (26 conformers) and class c (9 conformers), as well as the standard deviations, compared to the experimental data for some penicilins [3, 16, 17, 21, 23-25]. The notation codes of the penicilins are according to the CSD (Cambridge Structural Database) [21] notations. The primary geometric data obtained through the PM3 semiempirical method from which average values were calculated are available as supplementary material.

To compare the calculated values with the experimental values in Table II are shown the calculated average values of the angles between the ring bonds, the calculated inclination angles between the β-lactamic ring and the thiazolidinic ring (S1-C5-C6 and C3-N4-C7) and the improper N4-C5-C6-C7 angle by which the planarity of the β-lactamic ring can be determined both for (R) and (S) pseudochirality of the N14 atom. To evaluate if the average values are statistically distinct, in Table II are also presented the standard deviations (SD).

Table II. Average values of the bond angles and of the improper angle for the β-lactamic cycle and the standard deviations (SD) for all conformers (92), for pseudochirality (45(R), 47(S)), for arrangement (48syn)(44anti) and for the three puckering classes (57a)(26b)(9c), in comparison with experimental data.

Calculation criteria	Average value of the angle (°)											Conicity (°)
	2-1-5	1-2-3	2-3-4	3-4-5	1-5-4	5-4-7	4-5-6	5-6-7	6-7-4	1-5-6	3-4-7	4-5-6-7
(92)	**94.101**	**107.881**	**110.464**	**115.058**	**109.328**	**91.938**	**88.920**	**87.365**	**91.353**	**122.282**	**122.354**	**4.086**
(SD)	0.374	0.446	0.370	0.512	0.296	0.247	0.234	0.094	0.246	1.122	1.191	1.996
(45R)	**94.112**	**107.933**	**110.540**	**115.101**	**109.395**	**91.960**	**88.887**	**87.360**	**91.337**	**122.374**	**122.443**	**4.110**
(SD)	0.369	0.472	0.355	0.578	0.317	0.310	0.267	0.048	0.208	1.349	1.230	1.836
(47S)	**94.090**	**107.831**	**110.391**	**115.017**	**109.263**	**91.918**	**88.952**	**87.369**	**91.367**	**122.193**	**122.269**	**4.064**
(SD)	0.387	0.424	0.377	0.449	0.265	0.170	0.199	0.124	0.281	0.872	1.172	2.177
(48*syn*)	**94.026**	**107.814**	**110.328**	**114.974**	**109.290**	**91.931**	**88.896**	**87.323**	**91.396**	**122.334**	**122.246**	**4.110**
(SD)	0.391	0.437	0.259	0.547	0.345	0.257	0.300	0.048	0.258	0.992	1.316	2.373
(44*anti*)	**94.179**	**107.950**	**110.605**	**115.146**	**109.367**	**91.946**	**88.946**	**87.408**	**91.308**	**122.227**	**122.467**	**4.061**
(SD)	0.347	0.455	0.419	0.469	0.235	0.241	0.139	0.111	0.229	1.264	1.062	1.562
(57a)	**94.328**	**107.960**	**110.428**	**115.154**	**109.178**	**91.999**	**88.855**	**87.374**	**91.207**	**121.962**	**122.876**	**5.346**
(SD)	0.018	0.100	0.224	0.106	0.232	0.187	0.210	0.102	0.057	1.277	0.300	0.764
(26b)	**93.646**	**107.411**	**110.158**	**114.529**	**109.523**	**91.811**	**89.114**	**87.340**	**91.645**	**122.059**	**121.022**	**1.908**
(SD)	0.174	0.163	0.129	0.171	0.204	0.084	0.046	0.044	0.104	0.846	0.136	1.069
(9c)	**94.349**	**108.420**	**110.974**	**115.654**	**109.316**	**92.013**	**88.757**	**87.384**	**91.192**	**123.186**	**123.344**	**4.964**
(SD)	0.311	0.413	0.268	0.534	0.362	0.403	0.259	0.128	0.217	0.662	1.364	1.972
Experimental data	*Angle (°)*											*Conicity (°)*
	2-1-5	*1-2-3*	*2-3-4*	*3-4-5*	*1-5-4*	*5-4-7*	*4-5-6*	*5-6-7*	*6-7-4*	*1-5-6*	*3-4-7*	*4-5-6-7*
Exp.BENPEN10[24,25]	*95.19*	*104.17*	*92.89*	*116.13*	*92.26*	*94.40*	*88.13*	*84.69*	*91.54*	*118.20*	*127.63*	*7.82*
Exp.BPENCE10[25,27]	*95.21*	*103.95*	*92.62*	*115.76*	*92.49*	*94.21*	*87.75*	*84.42*	*92.58*	*118.88*	*126.71*	*7.10*
Exp.PMEPEN[25,29]	*96.19*	*104.97*	*104.17*	*119.68*	*102.73*	*88.19*	*92.35*	*82.86*	*96.02*	*121.82*	*129.28*	*-5.54*
Exp.AMPC[30]	*90.4*	*103.1*	*106.0*	*117.9*	*103.8*	*93.7*	*88.5*	*85.7*	*91.6*	*118.9*	*126.1*	*4.3*
Exp.PenV[3]	*96.0*	*92.0*	*104.0*	*120.0*	*103.0*	*88.0*	*92.0*	*83.0*	*96.0*	*122.0*	*129.0*	*-*
Exp.6APA[5,31]	*95.6*	*92.7*	*106.0*	*118.0*	*103.7*	*93.5*	*88.1*	*84.6*	*91.7*	*120.2*	*132.5*	*-*

The average values have been calculated for the following categories: for all 92 conformers, for 45 conformers with (R) pseudochirality, respectively for 47 conformers with (S) pseudochirality, for 48 *syn* conformers, respectively for 44 *anti* conformers and for the three puckering classes: 57 conformers in class (a), 26 class (b), respectively 9 in class (c).

Comparing the calculated average values with experimental data (Table II) one can see that the calculated values for the angles 2-1-5, 3-4-5, 4-5-6, and 6-7-4 are in the range of the experimental values, while for the angles 1-2-3, 2-3-4, 1-5-4, 5-6-7 they are greater than the experimental values, and the 5-4-7 angle is lower than the experimental value. The inclination angle 1-5-6 is lower than the experimental determined value, while for 3-4-7 it is greater than the experimental values.

The values calculated by semiempirical, ab initio and DFT methods by other authors are comparable with the values obtained in this paper [8-15]. Taking the SD into account there are no statistically significant differences for the average value for the 92 conformers and the average values for the three classification criteria. The only angle depending on the three puckering classes of the thiazolidinic ring is the improper dihedral 4-5-6-7. Graphically, the influence of the puckering of the thiazolidinic ring can be observed in Figure 4. It can be best observed for the (S)-*anti* conformers (Figure 4). The calculated

values for the improper angle 4-5-6-7 show that the β-lactamic ring is not plane (Table II). In Table II there are three distinctive average values of the pliation of the β-lactamic ring: 5.35º, 1.91º, and 4.96º.

The average values of the 4-5-6-7 dihedral are situated around 4.09º±2.00. By comparing the experimental values of conicity with the calculated values one can observe that the average values are lower than the experimental values. The negative calculated values of the 4-5-6-7 conicity are not an isolated case, because for PMEPEN the experimental value of the 4-5-6-7 conicity is negative (Table II).

CONCLUSION

From the conformational analysis of the 6-acetylamidopenicillanic acid using the PM3 method have resulted 92 distinct conformers. Between the lowest energy conformer and the highest energy conformer there is an energy difference of 12.14 kcal/mol.

The existence of some regularities could be evidenced only by statistical analysis of the geometric data. There have been evidenced three distinctive classes of inclination of the thiazolidinic ring towards the β-lactamic cycle. The pseudochirality at the N14 atom, the *syn-anti* positions of the O17, H28 amidic atoms, and the rotation of the COOH group bound at C3 do not influence significantly the three puckering classes.

For the penicillins there are no major differences between the results obtained with the semiempririca PM3 method and the *ab initio* or DFT methods

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