STUDIA UBB CHEMIA, LVI, 3, 2011 (p. 111 - 127)

PM3 CONFORMATIONAL ANALYSIS OF THE (3S,5S,6S)-6 ACETYLAMIDOPENICILLANIC ACID. ELECTRONIC PROPERTIES.

DANIELA IVAN[a], MIRCEA MRACEC[b]

ABSTRACT. A conformational analysis with the semiempirical PM3 method was performed for (3S,5S,6S)-6-acetylamidopenicillanic acid. 105 distinct conformers were found within 25.53 kcal/mol. Dependence of some electronic properties of these conformers (HOMO and LUMO energies, dipole moment, ν_{min} minimum vibration energy, maximum vibration energy $\nu_{MAX.}$, 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 thyazolidinic cycle noted with a, b, c, is demonstrated.

Keywords: *conformational analysis, (3S,5S,6S)-6-acetylamidopenicilanic acid, PM3 method, 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, as shown in Figure 1 [1].

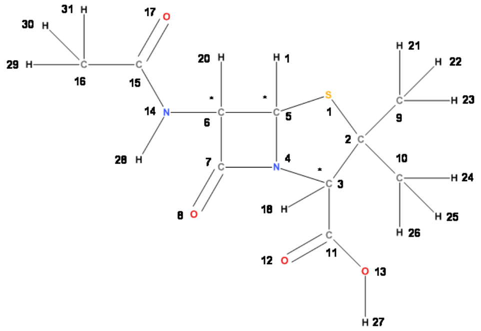


Figure 1. Atom numbering in (3S,5S,6S)-6-acetylamidopenicillanic acid (* denotes the chirality).

---

[a] *Institute of Chemistry of Romanian Academy, 24 Mihai Viteazul Bvd., RO-300223, Timisoara, Romania, dana_ivan@ acad-icht.tm.edu.ro*

[b] *Institute of Chemistry of Romanian Academy, 24 Mihai Viteazul Bvd., RO-300223, Timisoara, Romania, mracec@acad-icht.tm.edu.ro*

In this paper we present an analysis of the dependence of the electronic properties of the (3S,5S,6S)-6-acetylamido-penicillanic acid by the geometric characteristics of the conformers. The pyramidalization degree of the nitrogen N14 atom, as resulted from the PM3 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 *sy*n orientation of atoms O17 and H28 of the exocyclic amidic group and the three puckering classes of the thyazolidinic cycle [1].

RESULTS

The semiempirical PM3 methods give 105 conformers [1,7]. Table 1 gives the list of ordered conformers, numbered in ascending order of formation enthalpies. Some related structural properties are also included in Table 1.

To be sure that the obtained conformers are minima on the potential energy surface (PES) and not saddle points, for each conformer a normal vibration calculation was performed. All vibrations were positive for all conformes. The wavelength number of the maximum vibration, **v_{MAX}** and zero point vibration energy, **ZPVE** are given in Table 1, too. A gap of 25.53 kcal/mol resulted between the lowest energy (01pm3) conformer and the highest energy (105pm3) one [1].

Table 1. Conformers of the (3S,5S,6S)-6-acetilamidopenicillanic acid in ascending order of the formation enthalpies, at PM3 level of theory and some of their energetic, structural and electronic characteristics.

Ascending Energy Order	HOMO (eV)	LUMO (eV)	Pseudo chir. N14	Position 17,28.	μ (Debye)	Vibrations (cm^{-1})		ZPVE (kcal/mol)
						$v_{min.}$	$v_{MAX.}$	
01	-9.802	-0.482	S	anti	4.116	25.32	3484.89	149.602
02	-9.795	-0.465	S	anti	4.114	27.79	3849.57	149.921
03	-9.776	-0.485	S	syn	3.546	26.06	3849.84	150.131
04	-9.753	-0.453	S	syn	3.248	27.97	3849.77	150.424
05	-9.827	-0.507	S	anti	3.980	28.32	3849.53	149.614
06	-9.773	-0.439	S	anti	3.331	37.04	3847.56	150.007
07	-9.800	-0.510	S	syn	1.605	27.34	3849.25	150.160
08	-9.826	-0.491	S	anti	3.939	31.86	3849.35	149.886
09	-9.780	-0.477	S	syn	1.590	29.66	3848.95	150.403
10	-9.667	-0.391	R	syn	3.425	13.27	3849.61	150.356
11	-9.693	-0.396	S	anti	4.315	20.51	3848.73	149.675
12	-9.681	-0.443	R	syn	3.789	26.88	3849.51	149.989
13	-9.780	-0.462	S	anti	3.229	28.24	3847.74	149.525
14	-9.760	-0.465	S	syn	3.445	27.89	3849.30	150.120
15	-9.730	-0.436	S	syn	3.479	31.84	3847.74	150.493
16	-9.658	-0.398	R	anti	3.946	25.43	3849.91	149.510
17	-9.817	-0.490	S	anti	4.337	36.38	3842.31	150.238
18	-9.753	-0.472	S	syn	3.697	29.12	3847.75	150.086
19	-9.707	-0.472	R	syn	3.819	26.51	3849.78	149.680

Ascending Energy Order	HOMO (eV)	LUMO (eV)	Pseudo chir. N14	Position 17,28.	μ (Debye)	Vibrations (cm^{-1})		ZPVE (kcal/mol)
						$\nu_{min.}$	$\nu_{MAX.}$	
20	-9.703	-0.465	R	syn	1.839	28.96	3849.19	150.007
21	-9.693	-0.416	R	syn	1.773	18.27	3849.10	150.333
22	-9.573	-0.313	R	anti	4.323	23.72	3847.99	149.646
23	-9.775	-0.485	S	syn	1.304	31.02	3842.38	150.744
24	-9.787	-0.488	S	syn	1.729	29.33	3848.84	150.098
25	-9.655	-0.386	R	syn	3.649	29.16	3847.32	150.383
26	-9.648	-0.356	R	anti	3.293	33.47	3847.59	149.890
27	-9.736	-0.447	S	syn	3.642	28.56	3847.67	150.129
28	-9.686	-0.426	R	anti	3.899	27.33	3849.45	149.499
29	-9.822	-0.511	S	anti	4.428	24.91	3842.04	149.732
30	-9.735	-0.500	R	syn	1.829	27.97	3849.01	149.703
31	-9.686	-0.398	R	anti	3.924	28.85	3849.04	149.795
32	-9.795	-0.518	S	syn	1.405	28.08	3842.23	150.362
33	-9.712	-0.436	R	syn	1.732	27.30	3848.61	150.057
34	-9.601	-0.371	R	syn	4.504	17.68	3848.11	150.122
35	-9.699	-0.436	R	syn	1.506	28.19	3842.35	150.641
36	-9.671	-0.437	R	syn	3.912	31.60	3847.35	149.863
37	-9.652	-0.389	R	anti	3.087	29.83	3847.46	149.406
38	-9.673	-0.405	R	syn	3.666	30.59	3847.28	150.102
39	-9.779	-0.494	S	syn	1.497	27.68	3842.09	150.381
40	-9.693	-0.410	R	anti	4.332	32.46	3842.26	150.114
41	-9.630	-0.406	R	syn	4.539	14.45	3848.28	149.808
42	-9.638	-0.368	R	anti	3.714	18.63	3846.82	149.576
43	-9.698	-0.467	R	syn	3.934	29.97	3847.61	149.605
44	-9.717	-0.455	R	syn	1.496	29.83	3841.94	150.369
45	-9.691	-0.435	R	anti	4.336	10.87	3842.18	149.561
46	-9.738	-0.511	R	syn	1.673	29.79	3841.60	149.868
47	-9.690	-0.498	R	syn	4.024	31.66	3848.19	150.231
48	-9.811	-0.569	R	anti	4.907	27.23	3848.79	150.179
49	-9.854	-0.600	R	anti	4.151	30.51	3848.64	150.170
50	-9.730	-0.533	R	syn	1.734	33.04	3848.21	150.194
51	-9.818	-0.557	R	anti	4.156	36.26	3847.04	150.203
52	-9.582	-0.344	S	syn	3.610	24.52	3849.30	150.181
53	-9.580	-0.408	S	syn	4.684	31.16	3848.24	149.888
54	-9.574	-0.393	S	syn	4.524	23.10	3848.69	149.775
55	-9.587	-0.281	R	anti	4.385	38.71	3851.67	149.961
56	-9.682	-0.341	R	anti	4.272	31.07	3851.14	149.662
57	-9.562	-0.255	R	anti	4.055	26.45	3852.10	149.921
58	-9.860	-0.608	R	anti	4.529	38.25	3841.93	150.402
59	-9.603	-0.318	R	anti	4.237	25.06	3851.52	149.582
60	-9.613	-0.381	S	syn	1.493	25.17	3848.50	150.135
61	-9.588	-0.286	R	anti	4.073	28.97	3849.97	149.826
62	-9.625	-0.452	S	syn	2.477	35.65	3848.09	149.874

Ascending Energy Order	HOMO (eV)	LUMO (eV)	Pseudo chir. N14	Position 17,28.	μ (Debye)	Vibrations (cm^{-1})		ZPVE (kcal/mol)
						$\nu_{min.}$	$\nu_{MAX.}$	
63	-9.616	-0.430	S	syn	2.237	22.78	3848.44	149.737
64	-9.635	-0.351	R	anti	4.088	22.67	3849.91	149.491
65	-9.693	-0.500	R	syn	3.669	27.05	3846.97	150.181
66	-9.544	-0.254	R	anti	3.887	37.21	3849.50	149.703
67	-9.642	-0.465	R	syn	4.160	22.64	3845.02	150.206
68	-9.708	-0.510	R	syn	1.730	42.18	3844.90	150.315
69	-9.569	-0.328	S	syn	3.075	30.66	3847.90	150.028
70	-9.556	-0.403	S	syn	5.002	53.11	3845.33	150.327
71	-9.300	-0.035	S	anti	3.289	28.98	3852.59	149.620
72	-9.329	-0.065	S	anti	4.490	38.41	3851.36	149.641
73	-9.617	-0.335	R	anti	3.862	31.32	3848.22	149.541
74	-9.333	-0.095	S	anti	4.239	31.16	3851.65	149.348
75	-9.737	-0.547	R	syn	1.725	35.72	3841.73	150.423
76	-9.300	-0.065	S	anti	3.332	27.16	3852.53	149.276
77	-9.585	-0.301	R	anti	4.348	34.66	3842.85	150.196
78	-9.326	-0.066	S	anti	4.185	28.60	3850.44	149.502
79	-9.541	-0.203	R	syn	2.200	24.14	3850.53	149.845
80	-9.612	-0.446	S	syn	2.822	55.13	3841.29	150.334
81	-9.613	-0.375	S	syn	1.829	33.70	3841.73	150.450
82	-9.700	-0.515	R	syn	2.283	39.59	3843.72	150.378
83	-9.342	-0.103	S	anti	4.103	23.65	3850.51	149.172
84	-9.664	-0.386	R	anti	4.314	29.70	3843.84	149.854
85	-9.575	-0.236	R	syn	2.891	34.42	3848.58	149.828
86	-9.617	-0.453	S	syn	4.445	29.36	3849.38	150.047
87	-9.327	-0.088	S	anti	4.189	35.07	3843.10	149.856
88	-9.311	-0.079	S	anti	3.809	33.59	3849.50	149.174
89	-9.352	-0.126	S	anti	4.129	30.53	3844.08	149.561
90	-9.571	-0.374	S	syn	2.946	9.40	3849.19	149.752
91	-9.556	-0.359	S	syn	2.945	20.21	3849.32	149.164
92	-9.550	-0.341	S	syn	3.325	16.07	3850.22	149.809
93	-9.561	-0.326	S	syn	2.817	26.89	3849.93	149.755
94	-9.611	-0.487	S	syn	3.216	11.09	3848.28	149.871
95	-9.549	-0.382	S	anti	2.892	32.05	3843.13	149.658
96	-9.527	-0.242	R	anti	3.424	33.76	3852.73	149.991
97	-8.565	-0.132	S	anti	0.567	30.72	3850.40	150.083
98	-8.560	0.005	R	anti	2.328	30.73	3851.68	150.023
99	-8.650	-0.194	S	anti	2.909	31.22	3848.41	150.035
100	-8.640	-0.064	R	anti	4.431	30.73	3849.80	150.032
101	-8.507	-0.246	S	anti	2.057	15.41	3849.52	149.681
102	-8.450	-0.045	R	anti	3.064	26.99	3849.67	149.636

Ascending Energy Order	HOMO (eV)	LUMO (eV)	Pseudo chir. N14	Position 17,28.	μ (Debye)	Vibrations (cm^{-1})		ZPVE (kcal/mol)
						$\nu_{min.}$	$\nu_{MAX.}$	
103	-8.505	-0.255	S	anti	2.861	33.32	3843.62	149.986
104	-8.483	-0.092	R	anti	3.806	35.55	3843.70	149.994
105	-8.516	-0.236	S	anti	2.084	25.86	3842.61	149.892

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 PM3 calculations, are listed in Table 2.

Table 2. Charge densities on some atoms of the conformers of (3S,5S,6S)-6-acetilamidopenicillanic acid, arranged in ascending variation of the formation enthalpies, computed at PM3 level of theory.

Ascending Energy Order	Net Charge on atom (e)						
	S(1)	N(4)	N(14)	O(8)	O(12)	O(13)	O(17)
1	-0.022	-0.124	-0.030	-0.229	-0.363	-0.298	-0.353
2	-0.012	-0.122	-0.037	-0.226	-0.366	-0.297	-0.352
3	-0.004	-0.122	-0.039	-0.228	-0.360	-0.300	-0.348
4	0.001	-0.120	-0.039	-0.224	-0.362	-0.298	-0.349
5	-0.021	-0.122	-0.031	-0.237	-0.376	-0.290	-0.351
6	-0.019	-0.114	-0.039	-0.242	-0.377	-0.282	-0.352
7	-0.003	-0.120	-0.040	-0.238	-0.376	-0.289	-0.348
8	-0.010	-0.120	-0.038	-0.234	-0.374	-0.294	-0.350
9	0.003	-0.117	-0.041	-0.233	-0.374	-0.292	-0.349
10	0.009	-0.117	-0.035	-0.229	-0.363	-0.298	-0.354
11	-0.014	-0.137	-0.023	-0.240	-0.377	-0.294	-0.358
12	0.001	-0.118	-0.031	-0.234	-0.361	-0.299	-0.354
13	-0.029	-0.114	-0.033	-0.246	-0.378	-0.282	-0.352
14	0.000	-0.119	-0.037	-0.223	-0.362	-0.298	-0.347
15	-0.005	-0.112	-0.042	-0.240	-0.373	-0.285	-0.347
16	-0.008	-0.122	-0.024	-0.234	-0.366	-0.297	-0.352
17	-0.017	-0.116	-0.039	-0.242	-0.362	-0.296	-0.351
18	-0.011	-0.112	-0.041	-0.246	-0.375	-0.284	-0.346
19	0.002	-0.118	-0.041	-0.234	-0.360	-0.299	-0.351
20	0.002	-0.116	-0.030	-0.243	-0.375	-0.291	-0.355
21	0.011	-0.114	-0.035	-0.239	-0.374	-0.294	-0.355
22	0.002	-0.136	-0.025	-0.244	-0.386	-0.292	-0.356
23	-0.003	-0.114	-0.043	-0.240	-0.364	-0.293	-0.347
24	0.002	-0116	-0.039	-0.232	-0.374	-0.292	-0.347
25	0.002	-0.109	-0.037	-0.247	-0.373	-0.285	-0.353
26	-0.005	-0.113	-0.034	-0.248	-0.379	-0.282	-0.352

Ascending Energy Order	Net Charge on atom (e)						
	S(1)	N(4)	N(14)	O(8)	O(12)	O(13)	O(17)
27	-0.006	-0.111	-0.040	-0.239	-0.373	-0.284	-0.345
28	-0.008	-0.120	-0.024	-0.242	-0.375	-0.293	-0.352
29	-0.026	-0.118	-0.033	-0.244	-0.364	-0.293	-0.351
30	0.003	-0.116	-0.041	-0.244	-0.375	-0.290	-0.352
31	0.003	-0.118	-0.032	-0.240	-0.373	-0.296	-0.351
32	-0.008	-0.116	-0.041	-0.244	-0.365	-0.291	-0.347
33	0.012	-0.114	-0.040	-0.240	-0.373	-0.296	-0.351
34	0.009	-0.131	-0.029	-0.245	-0.372	-0.295	-0.351
35	0.004	-0.110	-0.037	-0.247	-0.363	-0.294	-0.354
36	-0.006	-0.109	-0.033	-0.252	-0.374	-0.284	-0.353
37	-0.016	-0.113	-0.027	-0.252	-0.379	-0.283	-0.353
38	0.003	-0.109	-0.043	-0.247	-0.373	-0.285	-0.349
39	-0.004	-0.113	-0.040	-0.240	-0.363	-0.293	-0.346
40	-0.004	-0.114	-0.033	-0.248	-0.362	-0.297	-0.351
41	0.009	-0.131	-0.038	-0.245	-0.371	-0.295	-0.348
42	-0.005	-0.131	-0.026	-0.251	-0.368	-0.307	-0.353
43	-0.005	-0.109	-0.043	-0.252	-0.374	-0.285	-0.350
44	0.005	-0.111	-0.043	-0.247	-0.363	-0.294	-0.350
45	-0.013	-0.115	-0.027	-0.250	-0.364	-0.295	-0.352
46	-0.003	-0.112	-0.042	-0.251	-0.364	-0.291	-0.351
47	0.000	-0.124	-0.032	-0.238	-0.371	-0.296	-0.352
48	-0.001	-0.125	-0.080	-0.219	-0.368	-0.295	-0.305
49	0.000	-0.123	-0.078	-0.225	-0.370	-0.298	-0.306
50	-0.002	-0.120	-0.030	-0.248	-0.371	-0.299	-0.350
51	-0.010	-0.115	-0.080	-0.234	-0.378	-0.281	-0.307
52	0.010	-0.117	-0.051	-0.243	-0.370	-0.297	-0.348
53	0.006	-0.126	-0.025	-0.245	-0.373	-0.296	-0.361
54	0.007	-0.124	-0.025	-0.245	-0.373	-0.296	-0.362
55	-0.033	-0.118	-0.013	-0.230	-0.389	-0.272	-0.354
56	-0.032	-0.125	-0.022	-0.227	-0.386	-0.274	-0.348
57	-0.034	-0.122	-0.014	-0.218	-0.346	-0.310	-0.350
58	-0.009	-0.118	-0.078	-0.233	-0.360	-0.297	-0.307
59	-0.033	-0.128	-0.023	-0.216	-0.347	-0.307	-0.342
60	0.009	-0.113	-0.045	-0.253	-0.373	-0.297	-0.349
61	-0.042	-0.108	-0.015	-0.232	-0.386	-0.283	-0.357
62	0.003	-0.121	-0.022	-0.255	-0.370	-0.301	-0.359
63	0.005	-0.119	-0.023	-0.255	-0.371	-0.300	-0.361
64	-0.041	-0.114	-0.024	-0.228	-0.382	-0.285	-0.350
65	-0.008	-0.110	-0.035	-0.256	-0.376	-0.284	-0.349
66	-0.041	-0.111	-0.016	-0.236	-0.375	-0.286	-0.352
67	0.011	-0.131	-0.041	-0.239	-0.382	-0.287	-0.353

Ascending Energy Order	Net Charge on atom (e)						
	S(1)	N(4)	N(14)	O(8)	O(12)	O(13)	O(17)
68	0.006	-0.123	-0.031	-0.247	-0.361	-0.309	-0.350
69	0.002	-0.107	-0.059	-0.261	-0.377	-0.285	-0.340
70	0.011	-0.132	-0.031	-0.242	-0.380	-0.289	-0.358
71	-0.014	-0.117	-0.005	-0.231	-0.349	-0.310	-0.352
72	-0.013	-0.114	-0.004	-0.244	-0.391	-0.273	-0.356
73	-0.039	-0.117	-0.026	-0.228	-0.376	-0.284	-0.347
74	-0.012	-0.120	-0.011	-0.243	-0.389	-0.274	-0.350
75	-0.006	-0.113	-0.033	-0.254	-0.362	-0.296	-0.349
76	-0.012	-0.123	-0.012	-0.232	-0.348	-0.309	-0.344
77	-0.039	-0.116	-0.014	-0.235	-0.374	-0.281	-0.352
78	-0.024	-0.104	-0.005	-0.245	-0.385	-0.286	-0.359
79	0.001	-0.116	-0.098	-0.242	-0.367	-0.299	-0.327
80	0.007	-0.125	-0.025	-0.253	-0.363	-0.307	-0.356
81	0.004	-0.108	-0.059	-0.260	-0.363	-0.295	-0.340
82	0.000	-0.128	-0.023	-0.247	-0.363	-0.307	-0.361
83	-0.021	-0.110	-0.012	-0.242	-0.382	-0.287	-0.353
84	-0.036	-0.123	-0.025	-0.226	-0.371	-0.282	-0.345
85	0.001	-0.114	-0.101	-0.249	-0.379	-0.292	-0.325
86	-0.006	-0.121	-0.023	-0.236	-0.360	-0.302	-0.358
87	-0.020	-0.112	-0.005	-0.248	-0.376	-0.279	-0.354
88	-0.020	-0.113	-0.013	-0.242	-0.375	-0.287	-0.351
89	-0.018	-0.119	-0.013	-0.241	-0.375	-0.279	-0.350
90	-0.017	-0.113	-0.076	-0.241	-0.380	-0.286	-0.308
91	-0.026	-0.114	-0.081	-0.240	-0.380	-0.286	-0.314
92	-0.013	-0.126	-0.077	-0.224	-0.359	-0.300	-0.305
93	-0.011	-0.124	-0.077	-0.229	-0.381	-0.284	-0.311
94	-0.020	-0.111	-0.052	-0.252	-0.383	-0.283	-0.329
95	-0.019	-0.123	-0.081	-0.239	-0.368	-0.287	-0.312
96	-0.019	-0.134	-0.038	-0.233	-0.322	-0.300	-0.299
97	0.135	-0.121	-0.009	-0.257	-0.388	-0.297	-0.292
98	0.136	-0.122	0.010	-0.257	-0.377	-0.302	-0.302
99	0.130	-0.116	-0.008	-0.266	-0.378	-0.304	-0.289
100	0.132	-0.118	0.005	-0.264	-0.384	-0.296	-0.298
101	0.105	-0.099	-0.013	-0.265	-0.387	-0.289	-0.282
102	0.108	-0.108	-0.005	-0.262	-0.397	-0.291	-0.290
103	0.109	-0.109	-0.014	-0.262	-0.375	-0.289	-0.282
104	0.110	-0.113	-0.004	-0.260	-0.378	-0.287	-0.290
105	0.107	-0.100	-0.012	-0.259	-0.367	-0.299	-0.283

Analysis of some energetic properties

Analysis of the HOMO and LUMO energies (Table 1) did not alow a clustering of the conformers with respect to the following geometric properties: pseudochirality of the N14 atom, *syn-anti* arrangement of the O17 and H28 atoms of the amidic group or the puckering class of the thiazolidinic ring (a, b, c) [1]. Average values of the above properties were calculated.

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

HOMO(R) = -9.585±0.312eV LUMO(R) = -0.384±0.136eV
HOMO(S) = -9.519±0.360 eV LUMO(S) = -0.355 ±0.152 eV

They are not statistically distinct. However, comparing the average values for the R conformers with the average values of the S conformers it seems 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 described by the PM3 method.

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

HOMO(*syn*) = -9.686±0.068eV LUMO(*syn*) = -0.451 ±0.050eV
HOMO(*anti*) = -9.434±0.419eV LUMO(*anti*) = -0.306 ±0.160eV

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 PM3 merthod.

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

HOMO(a) = -9.343±0.464 eV LUMO(a) = -0.314 ±0.154eV
HOMO(b) = -9.510 ±0.350 eV LUMO(b) = -0.345 ±0.157eV
HOMO(c) = -9.720 ±0.081 eV LUMO(c) = -0.441 ±0.074 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 extent 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 pseudochirality are:

HOMO(R,a) = -9.106 ±0.540 eV LUMO(R,a) = - 0. 213±0.144eV
HOMO(S,a) = -9.326 ±0.493 eV LUMO(S,a) = - 0.347 ±0.129 eV
HOMO(R,b) = -9.580±0.321eV LUMO(R,b) = -0.389±0.130eV
HOMO(S,b) = -9.443±0.369eV LUMO(S,b) = -0.303±0.170eV
HOMO(R,c) = -9.700±0.076eV LUMO(R,c) = -0.431 ±0.091 eV
HOMO(S,c) = -9.741 ±0.082eV LUMO(S,c) = -0.452 ±0.052 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.

The HOMO and LUMO average values for the (a,b,c) puckering classes calculated with respect to the *syn-anti* criterion are:
HOMO(*syn*,a) = -9.615±0.046eV LUMO(*syn*,a) = -0.429 ±0.047eV
HOMO(*anti*,a) = -9.359 ±0.471 eV LUMO(*anti*,a) = -0.284 ±0.176eV
HOMO(*syn*,b) = -9.667±0.073eV LUMO(*syn*,b) = -0.451 ±0.063eV
HOMO(*anti*,b) = -9.396 ±0.423 eV LUMO(*anti*,b) = -0.269 ±0.160eV
HOMO(*syn*,c) = -9.698±0.077eV LUMO(*syn*,c) = -0.425 ±0.068eV
HOMO(*anti*,c) = -9.765 ±0.072 eV LUMO(*anti*,c) = -0.474 ±0.078 eV

Even admitting a superimposition of the confidence intervals, we can appreciate that the average values are distinct only for the (c) puckering class. For (a) puckering class, the average values for the HOMO *syn* and *anti* energies are not distinct, while the LUMO energies are distinct and respect the rule of statistical differentiation: the LUMO(*syn*,a) energy is lower than the LUMO(*anti*,a) energy. For the (b) puckering class, the average values of HOMO as well as for LUMO energies are not statistically distinct: the (*anti*,b) average values are lower than the (*syn*,b) average values. For (c) puckering class, the average values of both HOMO and LUMO energies are statistically distinct, and the (*syn*,c) average values are lower than the *(anti*,c) average values. In conclusion, only in the (c) puckering class the *syn-anti* orientation influences significantly both the values of the HOMO and the LUMO energies.

These results prove that for all *syn-anti* conformers the HOMO and LUMO energies are influenced more by the spatial arrangement of the exocyclic amidic group, while the N14 atom pseudochirality does not influence significantly these values.

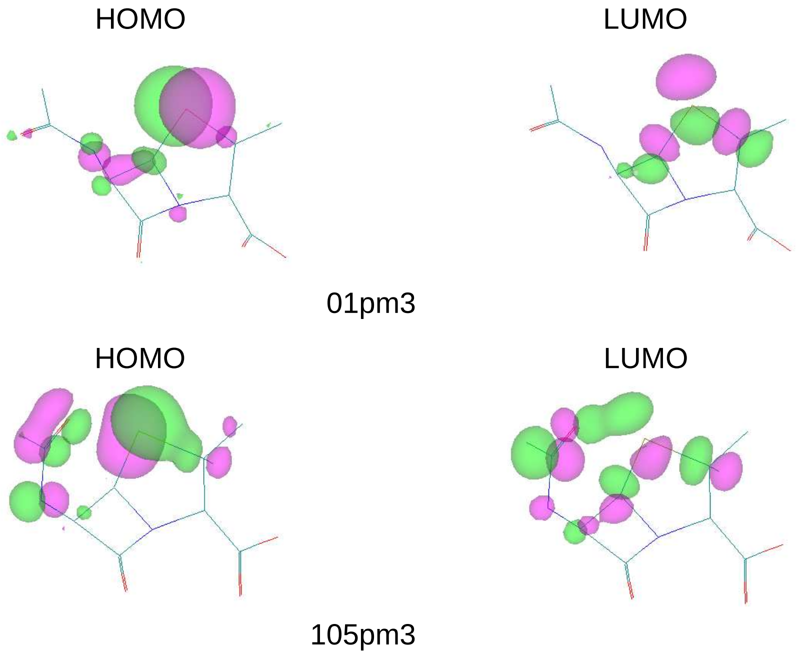


Figure 2. The weight of the Sulphur (S1) atom in HOMO and LUMO of conformers 01pm3 (with the lowest energy) and 105 pm3 (with the worst concordance with experimental geometry) computed with PM3

Orbital distribution at HOMO and LUMO levels for the conformers: 01pm3 (with the lowest energy) and 105 pm3 (with the worst concordance with experimental geometry) are given in Figure 2 [1].

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

Analyzing the data in Table 1 one 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: μ(R) = 3.447 ±1.010 Debye, μ(S) = 3.203 ±1.055. 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 1.304 - 5.002 Debye for conformers 23pm3 and 70pm3, respectively. Comparatively, the *anti* structures have higher values in the interval 0.567 - 4.907 Debye for conformers 97pm3 and 48pm3, respectively (Table 1).

The average values are $\mu(\textit{syn}) = 2.889 \pm 1.076$ Debye, and $\mu(\textit{anti}) = 3.771 \pm 0.777$ 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):

$$\mu(a) = 3.488 \pm 1.234 \text{ Debye}$$
$$\mu(b) = 3.483 \pm 0.886 \text{Debye}$$
$$\mu(c) = 2.982 \pm 1.124 \text{ Debye}$$

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:

$$\mu(\textit{syn},a) = 3.759 \pm 1.174 \text{Debye}$$
$$\mu(\textit{anti},a) = 3.693 \pm 0.944 \text{ Debye}$$
$$\mu(\textit{syn},b) = 3.068 \pm 1.018 \text{ Debye}$$
$$\mu(\textit{anti},b) = 3.784 \pm 0.636 \text{ Debye}$$
$$\mu(\textit{syn},c) = 2.418 \pm 0.905 \text{ Debye}$$
$$\mu(\textit{anti},c) = 4.109 \pm 0.480 \text{ Debye}$$

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.

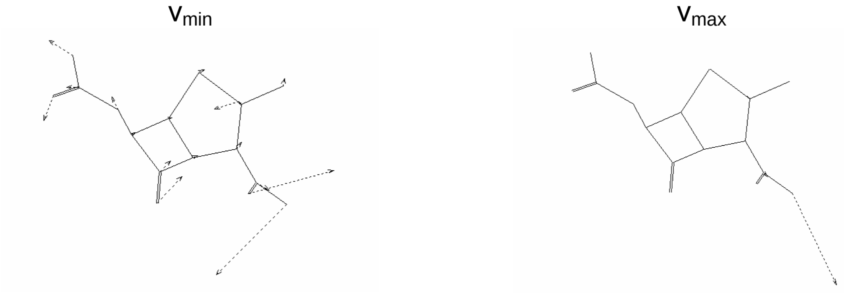
The minimum vibration energy, v_{min}, is a backbone vibration and all atoms are implicated in it through their out-of-the-plane vibration (Fig. 3). The v_{min} average value is of 27.733 ±10.605 cm^{-1}, with a large dispersion, which proves the dependence of this vibration on the conformation. The maximum vibration energy, v_{MAX}, is an elongation vibration implicated only in the bond between the O13 and H27 atoms and it takes place in the bond plane. Its average value is of 3844.159 ±35.529 cm^{-1} while disperion is large, which proves the non-dependence on the conformation. If the dependence of these vibrations on the N14 pyramidalization (R-S pseudochirality), on the *syn*-*anti* arrangement and on the puckering classes are taken into account, the following average values are obtained:

$$v_{min.}(R) = 28.82 \pm 6.47 \text{ cm}^{-1} \qquad v_{MAX.}(R) = 3847.58 \pm 3.04 \text{cm}^{-1}$$
$$v_{min.}(S) = 26.63 \pm 13.57 \text{ cm}^{-1} \qquad v_{MAX.}(S) = 3840.67 \pm 50.40 \text{ cm}^{-1}$$
$$v_{min.}(\textit{syn}) = 26.03 \pm 13.69 \text{cm}^{-1} \qquad v_{MAX.}(\textit{syn}) = 3847.25 \pm 2.76 \text{ cm}^{-1}$$
$$v_{min.}(\textit{anti}) = 29.47 \pm 5.66 \text{cm}^{-1} \qquad v_{MAX.}(\textit{anti}) = 3841.01 \pm 50.46 \text{ cm}^{-1}$$

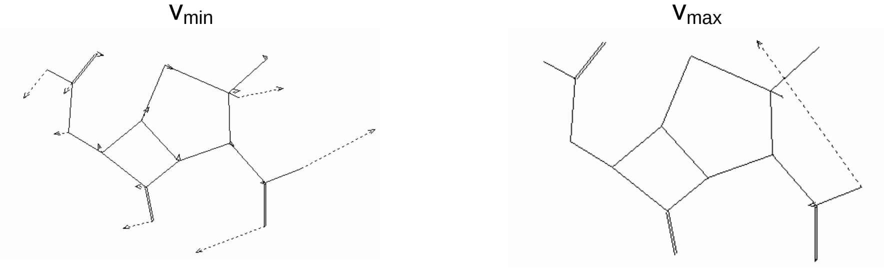
$\nu_{min.}(a) = 31.12\pm11.78\ cm^{-1}$ $\nu_{MAX.}(a) = 3847.98\pm2.90\ cm^{-1}$
$\nu_{min.}(b) = 26.39\pm11.94\ cm^{-1}$ $\nu_{MAX.}(b) = 3841.84\pm48.21\ cm^{-1}$
$\nu_{min.}(c) = 28.52\pm6.78 cm^{-1}$ $\nu_{MAX.}(c) = 3846.43\pm3.22\ cm^{-1}$

Comparing these average values one observes that the $\nu_{min.}$ backbone vibration depends on the puckering classes, but is not influenced by pseudochirality and the *syn-anti* arrangement. At the same time the $\nu_{MAX.}$ vibration is not influenced neither by thepseudochirality, 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 involving the backbone depend on the puckering classes and do not depend on pseudochirality and *syn-anti* arrangement.

The average values of the puckering classes calculated for the backbone vibration energies ν_{min}, and $\nu_{MAX.}$ with respect to the R-S pseudochirality or the *syn-anti* arrangement are:



01pm3



105pm3

Figure 3. Movement vectors proportional with force constants for vibration ν_{min} and ν_{MAX} of conformers 01pm3, 105pm3, computed b PM3.

$\nu_{min.}(a,R) = 27.50\pm5.68 cm^{-1}$ $\nu_{MAX.}(a,R) = 3849.57\pm1.97\ cm^{-1}$
$\nu_{min.}(a,S) = 36.77\pm12.71 cm^{-1}$ $\nu_{MAX.}(a,S) = 3847.21\pm3.01 cm^{-1}$
$\nu_{min.}(b,R) = 30.20\pm4.70 cm^{-1}$ $\nu_{MAX.}(b,R) = 3848.11\pm2.73\ cm^{-1}$

$v_{min.}(b,S) = 22.70 \pm 15.34 cm^{-1}$ $v_{MAX.}(b,S) = 3835.78 \pm 67.\ 55 cm^{-1}$
$v_{min.}(c,R) = 27.79 \pm 7.50 cm^{-1}$ $v_{MAX.}(c,R) = 3846.22 \pm 3.30\ cm^{-1}$
$v_{min.}(c,S) = 29.30 \pm 6.08 cm^{-1}$ $v_{MAX.}(c,S) = 3846.66 \pm 3.22 cm^{-1}$
$v_{min.}(a,\mathit{syn}) = 35.25 \pm 15.77 cm^{-1}$ $v_{MAX.}(a,\mathit{syn}) = 3846.15 \pm 2.79\ cm^{-1}$
$v_{min.}(a,\mathit{anti}) = 26.16 \pm 8.87 cm^{-1}$ $v_{MAX.}(a,\mathit{anti}) = 3848.64 \pm 2.82\ cm^{-1}$
$v_{min.}(b,\mathit{syn}) = 22.17 \pm 16.79 cm^{-1}$ $v_{MAX.}(b,\mathit{syn}) = 3848.18 \pm 1.94 cm^{-1}$
$v_{min.}(b,\mathit{anti}) = 29.46 \pm 4.89\ cm^{-1}$ $v_{MAX.}(b,\mathit{anti}) = 3837.22 \pm 63.34\ cm^{-1}$
$v_{min.}(c,\mathit{syn}) = 27.31 \pm 6.12 cm^{-1}$ $v_{MAX.}(c,\mathit{syn}) = 3846.\ 58 \pm 3.67 cm^{-1}$
$v_{min.}(c,\mathit{anti}) = 30.95 \pm 7.67 cm^{-1}$ $v_{MAX.}(c,\mathit{anti}) = 3846.15 \pm 3.25 cm^{-1}$

Comparing these data it seems 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. However, they depend significantly on the puckering class. For all the 105 conformers optimized with the PM3 method, the nature of these two types of vibrations do not change.

The equilibrium energy (ZPVE) is relatively constant around the average value of 149.935 ±0.331 kcal/mol. It is contained in the interval 149.164 kcal/mol and 150.744 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 which does not depend significantly on the conformer's nature.

The net charge on the S1 atom varies in relatively small limits, between 0.136 and -0.042. The average value for all conformers is $q_{S1} = -0.002 \pm 0.038$. 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:

$q_{S1}(S) = 0.0024 \pm 0.038$ $q_{S1}(R) = 0.0015 \pm 0.038$
$q_{S1}(\mathit{anti}) = 0.005 \pm 0.054$ $q_{S1}(\mathit{syn}) = -0.0001 \pm 0.008$
$q_{S1}(a) = 0.036 \pm 0.061$ $q_{S1}(b) = -0.003 \pm 0.038$ $q_{S1}(c) = -0.002 \pm 0.008$

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 2*). 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 vicinity in the two cycles. The N4 atom has a real pyramidalization, while N14 has a pyramidalization generated by the quanto-chemical computation method. The N4 atom has a negative net charge significantly higher than the exocyclic N14 notrogen atom. The average value of the charge is $q_{N4} = -0.118 \pm 0.007$, while $q_{N14} = -0.034 \pm 0.021$. The net charge on N4 varies in quite small limits, between -0.137 and -0.099; it can be considered almost constant and independent of the conformation, while the net charge on N14 varies in large limits between -0.101 and 0.01 and depends on the conformation. For these two atoms (N4, N14) the average charges for the conformers with R and S pseudochirality are:

$q_{N4}(R) = -0.118 \pm 0.007$ $q_{N14}(R) = -0.034 \pm 0.022$
$q_{N4}(S) = -0.117 \pm 0.007$ $q_{N14}(S) = -0.033 \pm 0.020$

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

$q_{N4}(syn) = -0.117 \pm 0.006$ $q_{N14}(syn) = -0.042 \pm 0.017$
$q_{N4}(anti) = -0.118 \pm 0.007$ $q_{N14}(anti) = -0.025 \pm 0.021$

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

$q_{N4}(a) = -0.127 \pm 0.006$ $q_{N14}(a) = -0.020 \pm 0.014$
$q_{N4}(b) = -0.116 \pm 0.006$ $q_{N14}(b) = -0.029 \pm 0.019$
$q_{N4}(c) = -0.114 \pm 0.004$ $q_{N14}(c) = -0.048 \pm 0.019$

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. Even if for the N14 atom the values are different between R and S and *syn* and *anti*, because of the high standard deviations their charges are not statistically distinct. For N14 there is a certain dependence on the puckering classes. On N14 the lowest charge is for class c, followed by class a, and the most negative charge is obtained for the puckering class b. Taking the puckering classes into account together with *syn-anti* or R-S criterion one does not observe any supplementary regularity. From these data one can draw the conclusion that the net charges on the N4 atom are relatively constant and independent of the conformation. For the N14 atom the net charge depends obviously on the conformation. This fact is demonstrated by the high dispersion of the values. There is a certain regularity, but only function of the puckering class.

The average value of the net charge on the O8 β-lactamic atom: $q_{O8} = -0.242 \pm 0.011$ is lower than the average values of the net charges for the other oxygen atoms: $q_{O12} = -0.371 \pm 0.011$, $q_{O13} = -0.292 \pm 0.008$, $q_{O17} = -0.341 \pm 0.021$. The q_{O8} net charge is relatively constant, independent of the conformation and varies between -0.266 and -0.216. On the atoms O12, O13 and O17 the net charge varies between -0.397 and -0.322, -0.31 and -0.272and respectively -0.362 and -0.282. For these oxygen atoms the average values of the net charge taking the R and S pseudochirality into account, are:

$q_{O8}(R) = -0.241 \pm 0.011$ $q_{O8}(S) = -0.242 \pm 0.011$
$q_{O12}(R) = -0.371 \pm 0.011$ $q_{O12}(S) = -0.372 \pm 0.009$
$q_{O13}(R) = -0.292 \pm 0.008$ $q_{O13}(S) = -0.291 \pm 0.008$
$q_{O17}(R) = -0.341 \pm 0.021$ $q_{O17}(S) = -0.340 \pm 0.022$

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

q_{O8}(syn) = -0.243±0.008 q_{O8}(anti) = -0.241±0.012
q_{O12}(syn) = -0.370±0.006 q_{O12}(anti) = -0.372±0.013
q_{O13}(syn) = -0.293±0.006 q_{O13}(anti) = -0.291±0.010
q_{O17}(syn) = -0.346±0.013 q_{O17}(anti) = -0.335±0.026

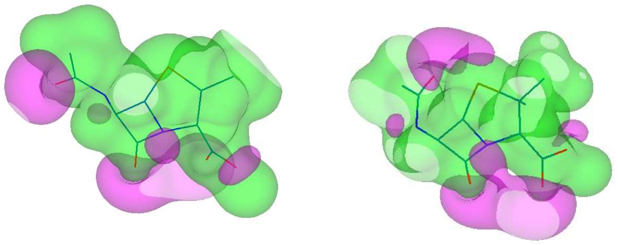
and taking the three puckering classes into account the following average values are obtained:

q_{O8}(a) = -0.249±0.009; q_{O8}(b) = -0.240±0.011 q_{O8}(c) = -0.240±0.009
q_{O12}(a) = -0.371±0.015 q_{O12}(b) = -0.372±0.011 q_{O12}(c) = -0.369±0.006
q_{O13}(a) = -0.298±0.005 q_{O13}(b) = -0.290±0.011 q_{O13}(c) = -0.291±0.005
q_{O17}(a) = -0.336±0.029 q_{O17}(b) = -0.341±0.021 q_{O17}(c) = -0.342±0.015

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. 4 for the conformers of the minimum energy (01pm3) and maximum energy (105pm3), respectively. 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.



01pm3 105pm3

Figure 4. Iso-surface of the electrostatic potential computed with PM3 for the contour value of 0.04, for conformers 01pm3,and 105pm3.

In case the atoms O8 and O17 are closer, an extended negative potential occurs (the case of conformer 105pm3). 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).

CONCLUSIONS

A conformational analysis performed by the PM3 method on the 105 conformational isomers of (3S,5S,6S)-6-acetylamidopenicillanic acid led to the conclusions:

- for all the conformers, the pseudochirality of the atom N14 does not influence significantly the HOMO and LUMO energies. On the contrarily, 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.

- the analysis of orbital contribution to the HOMO and LUMO levels, suggested 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 was proved by the high dispersion of the values. There is a certain pattern with 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.

METHODS

Gas phase equilibrium geometry of conformers was obtained by semiempirical PM3 calculations with an SCF convergence of 10^{-5}, and an 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 ±180° 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].

ACKNOWLEDGMENTS

The authors thank the National Councilor for Research and High Education (CNCSIS) for financial support - CNCSIS grant nr.776/2005/Agrement 27658/2005/GR177/2006/1973/2006.

REFERENCES

1. D. Ivan, M. Mracec, *Annals of West Univerity of Timisoara,* **2010**,*19(4)*,83.
2. C. D. Nenițescu, ”Chimie organică” Vol. 2, Editura Didactică and Pedagogică, Bucureşti, **1968**, Ed. 6-a, 629.
3. I. N. Levine, ”Quantum Chemistry”, 5th Edition, Prentice Hall, Inc., Upper Saddle River, New Jersey 07458, **2000,** Chap. 15, Chap. 17.
4. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *Journal of The American Chemical Society*, **1985**, *107*, 3902.
5. *** ChemPlus 1.6TM, ”Extension for HyperChem®, Molecular Modeling for WindowsTM”, Hypercube, Inc., Gainesville, Florida, US, 1994, Chap. 8.
6. *** HyperChemTM, Release 7.52 for Windows, Copyright 2003, Hypercube, Inc, 1115 NW 4th Street, Gainesville, FL 32601, US.
7. M. Mracec, M. Schulz, E. Şişu, N. Dincă, and M. Mracec, *Science and Technology Bulletin of University ”A. Vlaicu” Arad,* **2007,** *12,* 1.
8. I. Csoregh, and T.-B. Palm*, Acta Crystallogr., Sect.B: Struct. Crystallogr. Cryst.Chem.,***1977**,*33*,2169.
   http://www.middlebury.edu/~ch0337/atteridge/penicillin/fig1.gif