

The structure and conformations of piracetam (2-oxo-1-pyrrolidineacetamide): Gas-phase electron diffraction and quantum chemical calculations

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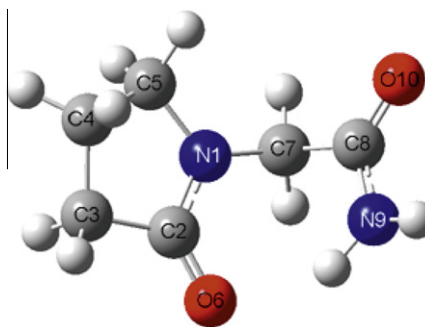
2-Oxo-1-pyrrolidineacetamide

FTIR spectroscopy

Gas electron diffraction

ABSTRACT

The geometric structure of piracetam was studied by quantum chemical calculations (DFT and *ab initio*), gas electron diffraction (GED), and FTIR spectroscopy. Two stable mirror symmetric isomers of piracetam were found. The conformation of pyrrolidine ring is an envelope in which the C4 atom deviates from the ring plane, the angle between the planes (C3–C4–C5) and (C2–C3–C5) is 154.1°. The direction of the deviation is the same as that of the side acetamide group. The piracetam molecule is stabilized in the gas phase by an intramolecular hydrogen bond between the N9H₂ group and the oxygen O6, bonded to C2. The principal structural parameters (r_e , Å and \angle_e , degrees; uncertainties are $3\sigma_{LS}$ values) were found to be: $r(C3-C4) = 1.533(1)$, $r(C4-C5) = 1.540(1)$, $r(N1-C5) = 1.456(1)$, $r(C2-C3) = 1.520(1)$, $r(N1-C7) = 1.452(1)$, $r(C7-C8) = 1.537(1)$, $r(N1-C2) = 1.365(2)$, $r(C8-N9) = 1.360(2)$, $r(C2=O6) = 1.229(1)$, $r(C8=O10) = 1.221(1)$, $\angle(C2-N1-C5) = 113.4(6)$, $\angle(N1-C2-C3) = 106.9(6)$, $\angle(N1-C7-C8) = 111.9(6)$, $\angle(C7-C8-N9) = 112.5(6)$, $\angle(N1-C2-O6) = 123.0(4)$, $\angle(C3-N1-C7) = 120.4(4)$, $\angle(C7-C8-O10) = 120.2(4)$, $\angle(C5-N1-C2-O6) = 170(6)$, $\angle(C3-C2-N1-C7) = 178(6)$, $\angle(C2-N1-C7-C8) = 84.2$, $\angle(N1-C7-C8-O10) = 111.9$.



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1. Introduction

Piracetam is a nootropic agent developed in the 1960s. Piracetam was the first drug to be labeled as nootropic, an agent that purportedly enhances the memory and the possibilities of education that is used to treat the conditions of the age-associated mental decline and the disorders of the nervous system [1]. The discovery of the nootropic properties of piracetam was the reason for the syn-

thesis of some other nootropic drugs – oxiracetam, aniracetam, pramiracetam, and nefiracetam [2].

Four polymorphs of piracetam have been identified and structurally characterized [3]. The angles φ and ψ are the C2–N1–C7–C8 and N1–C7–C8–N9 angles, respectively, according to the numbering used in the present paper (see Fig. 1). Forms II and III can be prepared by recrystallization from the various solvents (e.g. methanol, propan-2-ol) under ambient conditions, the crystal structures of both forms were described in [4]. Both forms transform above 400 K into the high-temperature phase noted as form I. Its crystal structure was determined from X-ray powder diffraction in combination with the minimization of the crystal-lattice

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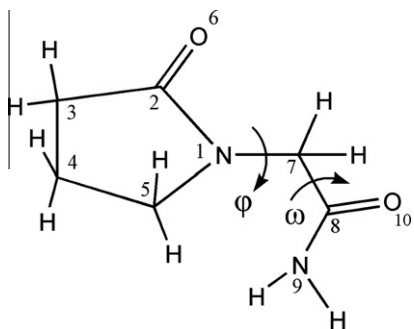
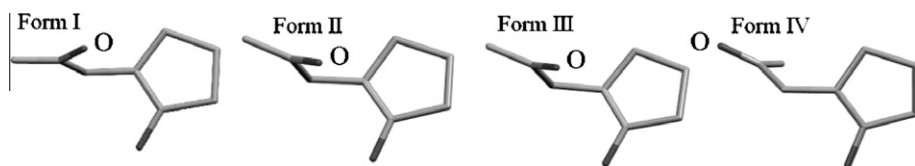


Fig. 1. Values of torsion angles φ and ω define a location of the side acetamide group.

potential energy [5]. Recrystallization from water at 0.4 GPa results in the formation of a new form (form IV) in which the molecular packing is very different from those in the known forms [3].



Approaches to crystal structure prediction involve calculations of the molecular structure by *ab initio* optimization (i.e. in the gas phase conformation) followed by modeling of the intermolecular interactions in the crystal to obtain lattice energy. Several hundreds of potential crystal structures with quite different energies were generated in this way [6]. The case of piracetam is somewhat complicated because its molecule conformation in gas phase differs from those observed in the crystalline forms. Nevertheless, form IV was successfully identified as the most favorable crystal structure with a very distinct conformation from the previously known polymorphs [7].

The conformations of the pyrrolidine ring in forms I, II, and III are similar, and the conformational analysis reveals that they should be described as twisted. Contrary, in form IV the ring adopts

an envelope conformation with the fold running from C3 to C5 and with C4 at the apex [8–10].

From the *ab initio* molecular energies of the possible conformers the preferred conformation in solution was determined [11]. The acetamide group is rotated around the N1–C7 bond in one direction ($\varphi \approx 90^\circ$) and around the C7–C8 bond in the same direction ($\angle \text{N1–C7–C8–O10} \approx 120^\circ$). The structures of two enantiomers in solution differ from that of the molecule in the crystal state.

A number of rigid and flexible piracetam-type cognition enhancers have been studied by X-ray diffraction, NMR spectroscopy, and *ab initio* and high-temperature-quenched molecular dynamics (QMD) calculations [12].

As the molecular structure and the conformational flexibility of a molecule play an important role in the drug design, to have information about these drug features is the matter of great importance. Therefore, a molecular conformation study of piracetam in the gas phase was performed in the present work.

2. Results and discussion

2.1. Quantum chemical calculations and vibration spectra

The potential energy surface (PES) as a function of two torsion angles, $\varphi = \angle \text{C2–N1–C7–C8}$ and $\omega = \angle \text{N1–C7–C8–O10}$, was determined at the B3LYP/6-31G** level. Each torsion angle was varied from 0° to 360° in steps of 30° with the simultaneous optimization of the geometrical parameters, bond lengths and bond angles (see Fig. 1). Fig. 2 represents the contour map of the calculated PES.

As it can be seen, two local minima were found on the PES, which correspond to the two stable isomers of piracetam ($\varphi_1 \approx 90^\circ$, $\omega_1 \approx 120^\circ$ and $\varphi_2 \approx 270^\circ$, $\omega_2 \approx 240^\circ$ respectively). Further

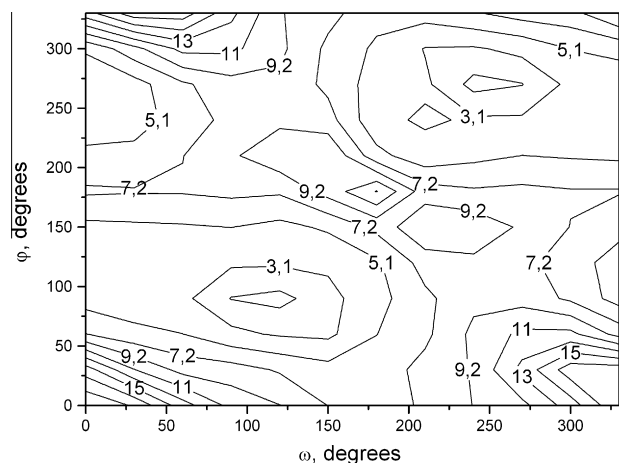


Fig. 2. Potential energy surface of piracetam obtained by a B3LYP/6-31G** level of theory. The values of relative energy on the equipotential lines are presented in kcal/mol, the reference point is the lowest energy point.

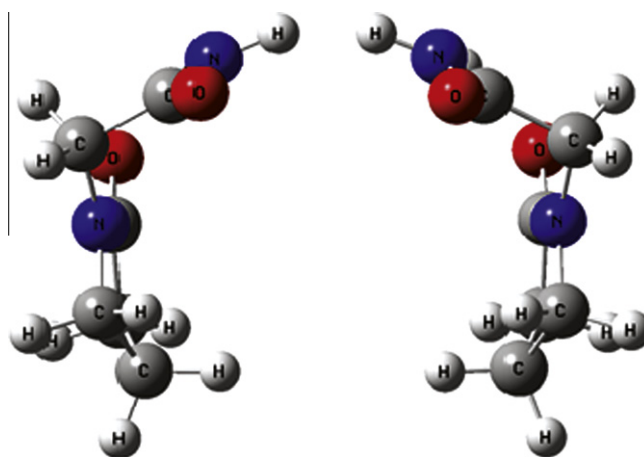


Fig. 3. Mirror symmetric isomers of piracetam (geometry calculated by MP2/cc-pVTZ level of theory; $\varphi_1 = 86.4^\circ$, $\omega_1 = 108.6^\circ$ and $\varphi_2 = -86.4^\circ$, $\omega_2 = -108.6^\circ$, respectively).

studies of its reoptimized geometry showed that they are mirror symmetric (see Fig. 3).

The geometric structure of the two lowest-energy isomers was optimized at the B3LYP/cc-pVTZ, MP2/cc-pVTZ levels of theory (with the calculation of harmonic force field) and B3LYP/6-31G** level of theory (with the calculation of anharmonic force field). As they are mirror symmetric, the bond distances and the angle values are the same for both conformers, and some torsion angle values differ by the sign. The obtained parameters (bond distances, bond and dihedral angles) are presented in Table 1. The theoretical vibrational frequencies and IR-spectrum intensities were also calculated at the levels of theory mentioned above.

The vibrational amplitudes for the interatomic distances and the correction terms for the shrinkage effect were obtained using the anharmonic force field from B3LYP/6-31G** calculations and the harmonic force fields from B3LYP/cc-pVTZ and MP2/cc-pVTZ calculations. The force constant matrices obtained in the Cartesian coordinates were transformed to the local symmetry (valence) coordinates as recommended by Pulay [13]. Frequencies and modes calculated for each method are closely related. It is worth to note that the frequencies of stretching vibrations of NH₂ and $\nu(\text{C8}=\text{O10})$, $\nu(\text{C2}=\text{O6})$ are most sensible to the level and the basis set of calculations. The higher are the level and the basis set, the lower are the calculated vibrational frequencies.

Table 1

Molecular structure of piracetam obtained by gas-phase electron diffraction and quantum chemical calculations (bond lengths in Å, bond and dihedral angles in degrees).

Parameter	B3LYP/cc-pVTZ	MP2/cc-pVTZ	B3LYP/6-31G**	GED + QC ^a
<i>Bond length</i>				
C3–C4	1.535	1.534	1.539	1.533(1) <i>p</i> ₁ ^b
C4–C5	1.541	1.529	1.545	1.540(1)
C5–N1	1.459	1.453	1.462	1.456(1)
C2–C3	1.520	1.516	1.525	1.520(1)
N1–C7	1.454	1.448	1.457	1.452(1)
C7–C8	1.538	1.526	1.542	1.537(1)
N1–C2	1.358	1.357	1.363	1.365(2) <i>p</i> ₂
C8–N9	1.354	1.356	1.359	1.360(2)
C2=O6	1.224	1.229	1.230	1.229(1) <i>p</i> ₃
C8=O10	1.217	1.222	1.223	1.221(1)
C–H	1.090	1.091	1.094	1.094 ^c
N9–H19	1.011	1.011	1.016	1.016 ^c
N9–H20	1.006	1.005	1.009	1.009 ^c
<i>Bond angle</i>				
C2–N1–C5	114.2	114.3	114.2	113.4(6) <i>p</i> ₄
N1–C2–C3	107.9	107.4	107.8	106.9(6)
N1–C7–C8	113.0	110.8	112.8	111.9(6)
C7–C8–N9	113.7	112.9	113.4	112.5(6)
N1–C2–O6	122.8	124.8	124.8	123.0(4) <i>p</i> ₅
C2–N1–C7	122.4	121.9	122.1	120.4(4)
C7–C8–O10	121.8	122.3	122.0	120.2(4)
<i>Dihedral angle</i>				
C3–C2–N1–C5	0.8	1.4	1.3	1.3 ^c
C2–C3–C5–C4	–155.1	–150.5	–154.1	–154.1 ^c
C5–N1–C2–O6	179.9	179.4	179.5	170(6) <i>p</i> ₆
C3–C2–N1–C7	173.0	173.7	172.9	177(6)
C2–N1–C7–C8	84.8	86.4	84.2	84.2 ^c
(φ)				
N1–C7–C8–N9	–67.7	–70.9	–68.7	–68.7 ^c
(ψ) ^d				
N1–C7–C8–O10	112.8	108.6	111.9	111.9 ^c
(ω)				

^a *r*_e parameters, uncertainties are 3 σ values.

^b *p*_i group; difference between parameters in group is constrained to B3LYP/6-31G** value.

^c Not refined.

^d According to the labeling for polymorphic forms.

Table 2

Observed and calculated frequencies (cm^{–1}) of piracetam molecule.

No.	Observ.	Calc. A	Calc. B	Assignment (P.E.D. %) [*]
1	3340	3674	3333	89 <i>n</i> _{as} (NH ₂) str + 11 <i>n</i> _s (NH ₂) str
2	3169	3500	3176	89 <i>n</i> _s (NH ₂) str + 11 <i>n</i> _{as} (NH ₂) str
3	2996	3132	2976	82 <i>n</i> _{as} (C ₇ H ₂) str + 18 <i>n</i> _s (C ₇ H ₂) str
4	2996	3116	2965	56 <i>n</i> _{as} (C ₃ H ₂) str + 30 <i>n</i> _{as} (C ₄ H ₂) str
5	2962	3106	2956	59 <i>n</i> _{as} (C ₄ H ₂) str + 18 <i>n</i> _{as} (C ₃ H ₂) str
6		3074	2926	54 <i>n</i> _{as} (C ₅ H ₂) str + 24 <i>n</i> _s (C ₅ H ₂) str
7	2931	3059	2911	69 <i>n</i> _s (C ₄ H ₂) str + 12 <i>n</i> _{as} (C ₅ H ₂) str
8	2877	3048	2896	43 <i>n</i> _s (C ₇ H ₂) str + 35 <i>n</i> _s (C ₃ H ₂) str
9	2877	3042	2896	39 <i>n</i> _s (C ₇ H ₂) str + 37 <i>n</i> _s (C ₃ H ₂) str
10	2813	2996	2852	68 <i>n</i> _s (C ₅ H ₂) str + 31 <i>n</i> _{as} (C ₅ H ₂) str
11	1697	1773	1697	71 <i>n</i> (C8=O10) str + 11 <i>n</i> (C8N9) str
12	1657	1739	1657	72 <i>n</i> (C2=O6) str
13	1647	1626	1597	77 δ (NH ₂) sciss
14	1494	1540	1500	89 δ (C ₅ H ₂) sciss
15	1469	1506	1473	91 δ (C ₃ H ₂) sciss
16	1456	1483	1456	80 δ (C ₇ H ₂) sciss
17	1435	1475	1439	89 δ (C ₄ H ₂) sciss
18	1412	1452	1412	29 ρ (C ₅ H ₂) wag + 19 <i>n</i> (N1C2) str
19	1369	1384	1367	46 ρ (C ₇ H ₂) wag + 16 <i>n</i> (C8N9) str
20	1330	1357	1333	43 ρ (C ₇ H ₂) wag + 16 <i>n</i> (C8N9) str
21	1309	1349	1317	32 ρ (C ₄ H ₂) wag + 14 ρ (C ₇ H ₂) twist
22	1303	1330	1292	54 ρ (C ₃ H ₂) wag
23	1290	1313	1287	27 ρ (C ₄ H ₂) wag + 21 ρ (C ₄ H ₂) twist
24		1300	1265	34 ρ (C ₅ H ₂) wag + 14 <i>n</i> (N1C7) str + 12 <i>n</i> (N1C5) str
25	1227	1247	1223	36 ρ (C ₃ H ₂) twist + 35 ρ (C ₅ H ₂) twist
26	1193	1229	1195	25 ρ (C ₄ H ₂) twist + 24 ρ (C ₃ H ₂) twist
27	1172	1200	1168	24 ρ (C ₅ H ₂) rock + 21 ρ (C ₃ H ₂) twist + 15 ρ (C ₄ H ₂) twist
28		1178	1144	27 ρ (NH ₂) rock + 14 <i>n</i> (N1C5) str
29		1136	1110	25 ρ (NH ₂) rock + 17 <i>n</i> (N1C7) str + 11 <i>n</i> (C8N9) str
30	1073	1097	1069	22 ρ (C ₃ H ₂) rock + 21 ρ (C ₅ H ₂) rock + 17 ρ (C ₄ H ₂) rock
31	1034	1063	1054	20 <i>n</i> (C2C3) str + 13 <i>n</i> (N1C7) str
32		1028	1033	25 <i>n</i> (C3C4) str + 25 <i>n</i> (C4C5) str + 20 ρ (C ₄ H ₂) wag
33	953	953	950	35 <i>n</i> (C4C5) str + 34 <i>n</i> (C3C4) str
34	924	926	925	42 ρ (C ₇ H ₂) rock + 13 <i>n</i> (N1C5) str
35	902	909	886	28 ρ (C ₅ H ₂) rock + 26 ρ (C ₃ H ₂) rock
36	862	878	863	39 <i>n</i> (C7C8) str + 15 <i>n</i> (C8N9) str + 14 δ (N1C7C8) bend + 13 ρ (C8=O10) wag
37	809	862	817	38 ρ (C ₄ H ₂) rock + 25 ring def + 12 <i>n</i> (N1C2) str + 12 ρ (C3H ₂) rock
38	774	787	774	21 (C8=O10) wag + 19 <i>n</i> (C2C3) str + 17 <i>n</i> (C7C8) str
39	719	743	713	31 τ (C8N9) + 14 <i>n</i> (N1C5) str
40	640	687	651	52 τ (C8N9) + 11 ring def
41	618	659	608	36 ρ (C2=O6) wag + 22 ring def
42	569	599	586	18 <i>n</i> (C2C3) str + 16 ring def + 13 ρ (C2=O6) rock + 10 ρ (C8=O10) rock
43	546	577	541	23 ρ (C8=O10) rock + 15 ring def + 13 δ (C5N1C7) bend
44	508	535	516	23 ρ (C2=O6) wag + 22 ρ (C8=O10) rock + 18 ring def + 11 ρ (C3H ₂) rock
45		482	473	29 ρ (C8N9) wag + 27 ρ (C2=O6) rock
46		436	431	52 ρ (C8N9) wag + 23 δ (C7C8N9) bend
47		406	396	24 δ (C7C8N9) bend + 13 δ (C5N1C7) bend + 13 ρ (C8=O10) rock + 12 ρ (C8N9) wag + 11 ring def
48		286	281	41 δ (N1C7C8) bend + 27 δ (C5N1C7) bend + 15 δ (C7C8N9) bend
49		259	254	77 δ (C2N1C7) bend + 11 ρ (C2=O6) rock
50		174	170	72 ring tors + 12 ring tors'
51		157	157	91 ring tors + 10 ring tors
52		112	111	43 τ (N1C7) + 20 ring tors + 13 ring def
53		66	64	64 τ (N1C7) + 11 ring def
54		47	46	87 τ (C7C8)

A, from an unscaled force field; B, from a scaled force field.

* Only PED values larger than 10% are listed.

To obtain the better agreement between the calculated and experimental vibrational frequencies, we made an attempt to scale the force field using the method described in Ref. [14].

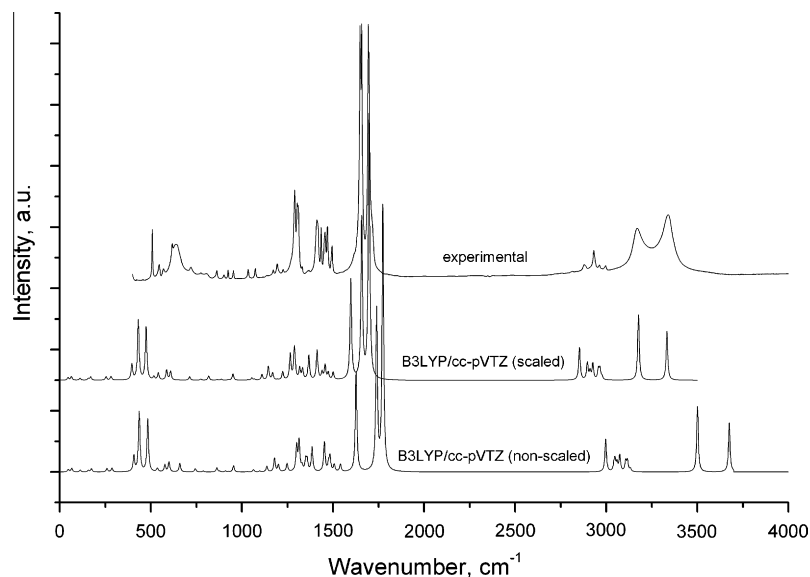


Fig. 4. Experimental and calculated IR spectra of piracetam.

Table 3
Scale factors used for piracetam molecule.

No.	Value	Coordinate ^a	No.	Value	Coordinate
1	1.04	$n(\text{C}_{\text{ring}})$	14	0.98	$\rho(\text{C}2=\text{O}6)$ rock
2	0.91	$n(\text{C}_{\text{ring}}\text{H})$	15	0.97	$\delta(\text{C}_7\text{H}_2)$, $\delta(\text{N}1\text{C}7\text{C}8)$
3	0.88	$n(\text{C}_{\text{ring}}\text{N}1)$	16	0.98	$\rho(\text{C}_7\text{H}_2)$
4	0.97	$n(\text{C}7\text{N}1)$, $n(\text{C}7\text{C}8)$	17	0.98	$\delta(\text{C}7\text{C}8\text{N}9)$
5	0.90	$n(\text{C}=\text{O})$	18	0.94	$\rho(\text{C}8=\text{O}10)$ rock
6	0.90	$n(\text{C}_7\text{H}_2)$	19	0.97	$\delta(\text{NH}_2)$
7	0.98	$n(\text{C}8\text{N}9)$	20	0.85	$\rho(\text{C}2=\text{O}6)$ wag
8	0.82	$n(\text{NH}_2)$	21	0.96	$\rho(\text{C}8=\text{O}10)$ wag
9	0.92	$\delta, \rho(\text{C}4\text{H}_2)$	22	0.99	$\rho(\text{C}8\text{N}9)$ wag
10	0.99	$\delta, \rho(\text{C}3\text{H}_2)$	23	1.01	Ring tors
11	0.95	$\delta, \rho(\text{C}5\text{H}_2)$	24	1.00	$\tau(\text{N}1-\text{C}7)$, $\tau(\text{C}7-\text{C}8)$
12	0.96	$\delta(\text{C}_{\text{ring}}\text{N}1\text{C}7)$	25	0.92	$\tau(\text{C}8-\text{N}9)$
13	0.78	Ring def			

^a ν are stretching, δ are bending, ρ are rocking, twisting and wagging vibrations; τ are torsional vibrations.

In Table 2 the calculated frequencies for the piracetam molecule (obtained from B3LYP/cc-pVTZ force field) with the non-scaled (column A) and scaled (column B) force fields are compared with those experimentally obtained. The latter were extracted from the FTIR spectrum of the crystalline piracetam (Fig. 4). The scale factors are listed in Table 3. The IR spectra calculated with non-scale and scale force fields are compared with experimental IR spectrum in Fig. 4.

As it is represented in Table 2 and Fig. 4, the calculated frequencies and its intensities are in good agreement with observed those. The interpretation of IR spectrum can be performed in consistency with the calculated modes. However, some problems appear in the assignment of frequencies in 1770–1500 cm^{-1} region.

According to the solution of the vibrational problem with the non-scaled force field, $\nu(\text{C}8=\text{O}10)$, $\nu(\text{C}2=\text{O}6)$, and $\delta(\text{NH}_2)$ vibrations are almost pure modes with potential energy distribution (PED) about 80%, and they have high intensities. The calculated frequencies and intensities of these vibrations are 1773, 1739, 1626 cm^{-1} and 433, 263, 165 KM/mol , respectively.

In the IR spectrum of crystalline piracetam the intense band at 1697 and doublet at 1657 and 1647 cm^{-1} are observed. No other bands in the 1630–1500 cm^{-1} range are available. The band at 1697 cm^{-1} is $\nu(\text{C}8=\text{O}10)$, unambiguously. We suppose that one component of the doublet at 1657 cm^{-1} is $\nu(\text{C}2=\text{O}6)$ vibration, and another one at 1647 cm^{-1} is $\delta(\text{NH}_2)$ vibration. The formation

of intermolecular hydrogen bonds in crystal state brings to the shift of the $\nu(\text{C}2=\text{O}6)$ and $\delta(\text{NH}_2)$ bands to lower and higher frequencies, respectively. The frequencies of these vibrations approach each other, and it results in Fermi resonance between them.

Scaling the harmonic force field by the method [14], we did not take into account the frequency at 1647 cm^{-1} . The frequency of $\delta(\text{NH}_2)$ vibration obtained by this way is 1597 cm^{-1} (column B in Table 2). It is in agreement with the same frequency in other amides. The $\nu(\text{C}8=\text{O}10)$, $\nu(\text{C}2=\text{O}6)$, and $\delta(\text{NH}_2)$ modes are identical to those found with the non-scaled force field.

Torsional vibrations about the C7–C8 bond are the almost pure mode, and torsion vibrations about the N1–C7 bond are mixed with ring deformation and torsional vibrations.

The vibrational amplitudes for the interatomic distances and correction terms for the shrinkage effect from scale force field led to a slight decrease (about 0.6%) of the R_f -factor in case of B3LYP/cc-pVTZ and MP2/cc-pVTZ levels of theory. However, the using of scale factors for B3LYP/6-31G** quadratic force field for scaling of the cubic force constants [15] resulted in the growing of R_f from 3.9% to 5.8%.

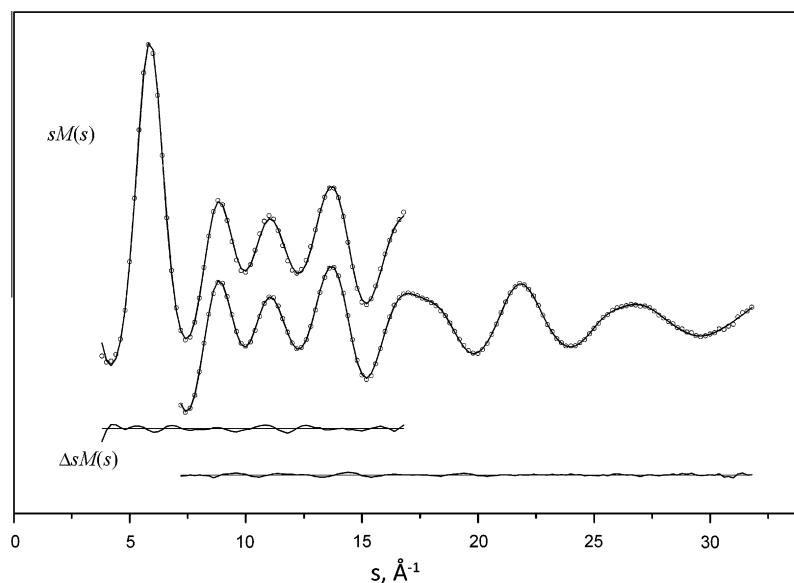
2.2. Electron diffraction analysis

The following assumptions for the geometric parameters were made: (1) all C–H bond lengths are equal, (2) all HCH angles are equal, (3) local C_{2v} symmetry for CH_2 groups is presented. The following bond lengths and angles were used as independent structural parameters: $r(\text{N}1-\text{C}2)$, $r(\text{C}3-\text{C}4)$, $r(\text{C}2=\text{O}6)$, $\angle\text{C}2-\text{N}1-\text{C}5$, $\angle\text{N}1-\text{C}2-\text{O}6$, $\angle\text{C}3-\text{C}2-\text{N}1-\text{C}5$, $\angle\text{C}2-\text{C}3-\text{C}5-\text{C}4$, $\angle\text{C}5-\text{N}1-\text{C}2-\text{O}6$, $\angle\text{C}3-\text{C}2-\text{N}1-\text{C}7$, $\angle\text{C}2-\text{N}1-\text{C}7-\text{C}8$ (φ), $\angle\text{N}1-\text{C}7-\text{C}8-\text{N}9$ (ψ), $\angle\text{N}1-\text{C}7-\text{C}8-\text{O}10$ (ω). Bond lengths, bond and dihedral angles were refined in six groups with the differences fixed at the calculated values; the C–H and N–H bond lengths were not refined and were fixed at the calculated values. Some torsion angles (see the Table 1) were not refined because of a strong increase in the R_f -factor when they have been varied. The vibrational amplitudes were collected in seven groups. The initial values of geometric parameters were taken from all three theoretical calculations. As there is no difference between mirror symmetric conformers in GED analysis because the internuclear distances are the same, the static single-conformer model was used. The vibrational amplitudes and corrections were calculated from the scaled harmonic B3LYP/cc-pVTZ, MP2/cc-pVTZ, and non-scaled anharmonic

Table 4

Theoretical (B3LYP/6-31G**) and experimental vibrational amplitudes of piracetam molecule (Å, without C...H, N...H, O...H and H...H distances; uncertainties are 3σ values).

Distance	r_e (Å)	l_{calc} (Å)	l_{exp} (Å)	Distance	r_e (Å)	l_{calc} (Å)	l_{exp} (Å)
N–H ^a	1.013	0.068	0.065(6) p_7 ^b	O6...C7	2.786(6)	0.109	0.099(17) p_{10}
C–H ^a	1.094	0.077	0.073(6)	N1...N9	2.986(7)	0.170	0.160(17)
C=O ^a	1.225(1)	0.038	0.032(3) p_8	O6...N9	2.767(25)	0.222	0.283(42) p_{11}
C8–N9	1.360(2)	0.045	0.045 ^c	C2...N9	3.165(9)	0.190	0.251(42)
N1–C2	1.365(2)	0.045	0.045 ^c	C2...C8	3.232(4)	0.124	0.186(42)
N1–C7	1.452(1)	0.050	0.050 ^c	C5...C8	3.487(11)	0.219	0.280(42)
N1–C5	1.456(1)	0.050	0.050 ^c	O6...C8	3.277(15)	0.155	0.178(17) p_{12}
C2–C3	1.520(1)	0.053	0.053 ^c	N1...O10	3.352(3)	0.220	0.242(17)
C4–C5	1.533(1)	0.053	0.053 ^c	C5...O6	3.519(3)	0.062	0.085(17)
C7–C8	1.537(1)	0.055	0.055 ^c	C4...O6	3.598(8)	0.075	0.098(17)
C3–C4	1.540(1)	0.054	0.054 ^c	C3...C7	3.712(3)	0.072	0.095(17)
N1...O6	2.280(2)	0.055	0.073(4) p_9	C4...C7	3.785(7)	0.079	0.101(17)
N9...O10	2.314(3)	0.056	0.074(4)	C5...O10	4.017(13)	0.419	0.441(17)
N1...C3	2.320(3)	0.058	0.076(4)	C5...N9	4.180(14)	0.264	0.287(17)
C2...C5	2.358(3)	0.059	0.077(4)	C2...O10	4.309(4)	0.232	0.273(31) p_{13}
N1...C4	2.377(7)	0.064	0.082(4)	O6...O10	4.476(16)	0.186	0.226(31)
C3...C5	2.388(10)	0.071	0.088(4)	C3...N9	4.478(16)	0.246	0.287(31)
C7...O10	2.396(2)	0.068	0.085(4)	C4...C8	4.490(18)	0.249	0.289(31)
C7...N9	2.411(3)	0.070	0.087(4)	C3...C8	4.498(11)	0.169	0.210(31)
C2...C4	2.434(7)	0.066	0.083(4)	C4...N9	4.810(22)	0.327	0.367(31)
C2...C7	2.444(2)	0.071	0.088(4)	C4...O10	5.136(20)	0.485	0.526(31)
N1...C8	2.477(3)	0.096	0.113(4)	C3...O10	5.433(12)	0.350	0.391(31)
C3...O6	2.487(3)	0.066	0.083(4)				
C5...C7	2.594(3)	0.077	0.095(4)				

^a Average values.^b p_i group; difference between parameters in group is constrained to B3LYP/6-31G** value.^c Not refined.**Fig. 5.** Experimental (open circles) and theoretical (solid line) molecular intensities $sM(s)$ and the difference curve for piracetam.

B3LYP/6-31G** force fields. As it may be seen from Table 4, the B3LYP/cc-pVTZ geometric parameters closely correspond to those obtained experimentally; $R_f = 5.2\%$. However, the best agreement between theory and experiment with the R_f -factor of 3.9% was obtained in case of B3LYP/6-31G** calculations with the anharmonic force field. The lowest result was obtained using the MP2/cc-pVTZ level of theory ($R_f = 5.8\%$). The Table 2 represents the final vibrational amplitudes.

The resulting intensity curves $sM(s)$ are shown in Fig. 5. The final radial distribution curve, which is in the closest agreement with the results of both GED analysis and quantum chemical calculations, is shown in Fig. 6.

3. Conclusions

All quantum calculations predicted the existence of two stable isomers of piracetam which are mirror symmetric. The structure of these conformers is stabilized by the intramolecular hydrogen bond between the $N9H_2$ group and O6 atom (see Fig. 7). The strength of this hydrogen bond is demonstrated by the short O...H distance, 1.9 Å. The N–H...O angle has a value of 143.8°. The closest agreement between quantum calculations and the experimental data was obtained using the geometric parameters and the vibrational amplitudes obtained at the B3LYP/6-31G** level of theory with the calculation of the anharmonic force field.

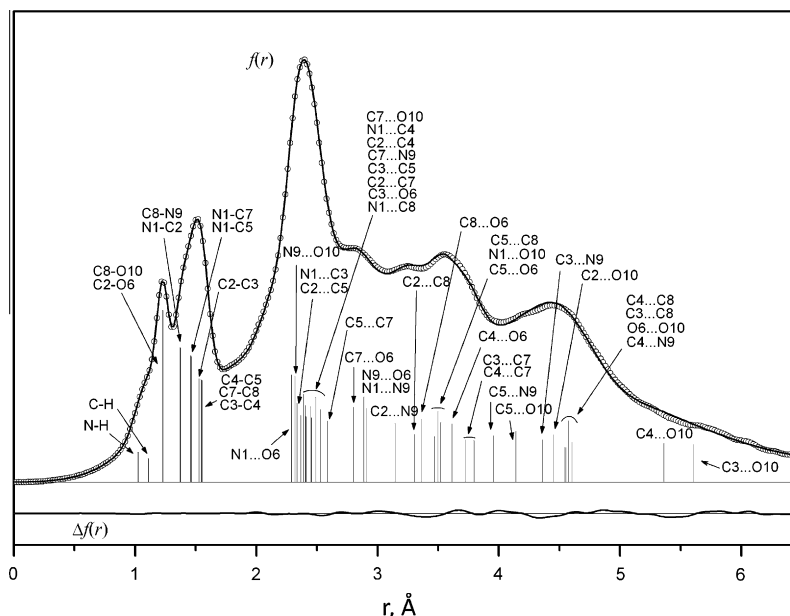


Fig. 6. Experimental (open cycles) and theoretical (solid line) radial distribution curves $f(r)$ with the difference curve of piracetam. The strong distance terms are indicated by vertical bars; weak terms of unbound C··H, N··H and O··H distances are not shown.

It is interesting to note that the configuration of N1 atom bonds is planar: the sum of the C5–N1–C7, C2–N1–C7, and C2–N1–C5 angles is 360.0(7)°. This can be explained by the conjugation of nitrogen lone electron pair with π -electrons of the double C2=O6 bond. This effect combined with the sp^2 -hybridization of C2 atom has an influence on the conformation of pyrrolidine ring. The N1, C2, C3, and C5 atoms form an almost planar conformation (\angle C3–C2–N1–C5 = 1.3°). The C4 atom deviates from the pyrrolidine ring plane, \angle C2–C3–C5–C4 = –154.1°. The direction of the deviation is the same as that of the side acetamide group (see Figs. 3 and 7). Thus, the only possible conformation of pyrrolidine ring

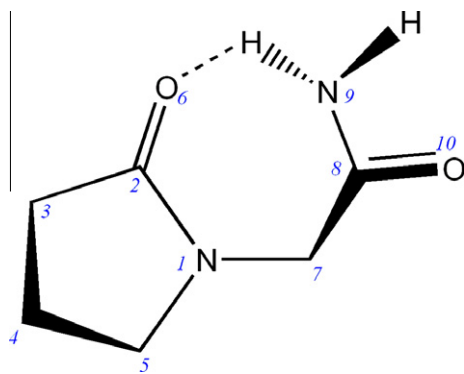


Fig. 7. The structure of piracetam is stabilized by an intramolecular hydrogen bond.

Table 5
Comparison of structural parameters of piracetam, pyrrolidine and acetamide obtained by GED.

Parameter	Piracetam	Pyrrolidine ^a	Acetamide ^b
(C(sp ³)-C) _{av} (ring)	1.537(1)	1.543(8)	–
C(sp ³)-N (ring)	1.456(1)	1.469(10)	–
C7–C8	1.537(1)	–	1.519(6)
C8=O10	1.221(2)	–	1.220(3)
C8–N9	1.360(2)	–	1.380(4)

^a Ref. [20].

^b Ref. [21].

in piracetam in gas phase is an envelope, in contrast to that in polymeric forms I–III [3].

The comparison of some structural parameters of piracetam with those in the similar substances is given in the Table 5. The values of C(sp³)-N (ring) and C8–N9 internuclear distances in piracetam are slightly shorter than those in pyrrolidine and acetamide (on 0.013 Å and 0.020 Å, respectively), and the C7–C8 distance is 0.018 Å longer in piracetam in comparison with acetamide.

4. Experimental

Quantum chemical calculations were performed using the Gaussian 03 software [16]. A commercial sample of piracetam (purity 99%) was used in the experiments. The FTIR spectrum was recorded in KBr pellets using Tensor-27 (Bruker) spectrometer with a resolution of 1 cm⁻¹. The electron diffraction patterns were recorded at the Electron Diffraction Laboratory, Moscow State University, using the apparatus reconstructed in 1998 from an ER-100 M commercial unit and equipped with an r^3 -sector [17]. The temperature of the sample, inlet system and nozzle was 277 °C. Kodak electron image films were used. The wave length of incident electrons (nominal accelerating voltage 60 kV) was determined from the diffraction photographs of CCl₄ obtained in the same experiment. The optical densities were measured using a commercial scanner Epson Perfection 4870 PHOTO and the data were processed by a program system UNEX [18]. The experiment yielded leveled intensities in the s -ranges 7.2–31.8 and 3.8–16.8 Å⁻¹, in steps of $\Delta s = 0.2$ Å⁻¹, for the short (193.9 mm) and long (362.3 mm) nozzle-to-plate distances respectively. An analysis of GED data was performed using the UNEX program [18]. The vibrational amplitudes and harmonic vibrational corrections were calculated using the SHRINK program [19].

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