

The Structure of *N*-Acetylprolinamide in the Solid State and in the Gasphase. A Remarkable Lattice Effect as the Result of a Competition Between Inter- and Intramolecular Hydrogen Bonds of Different Strengths

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In the solid state, the conformation of *N*-acetylprolinamide is stabilized by two intermolecular O...H bridges and one intramolecular N...H hydrogen bond. According to quantum chemical *ab initio* calculations with the 6-31+G* basis set at the one-determinant level, the intramolecular N...H bond is not strong enough to maintain the solid-state molecular conformation in the gas phase. The conformational changes predominantly consist in a rotation of the amide group about its C-C bond to the proline ring, resulting in a *cis*-like conformation which is stabilized by a presumably stronger intramolecular O...H bond between one hydrogen atom of the NH₂ group and the carbonyl oxygen of the acetyl substituent bonded to the nitrogen atom of the five-membered ring.

These conformational changes cause a reduction of the molecular dipole moment by about 50%, indicating that the conformation in solution might be strongly solvent dependent.

While both the MINDO/3 and the MNDO method in their standard parametrizations fail to reproduce the *ab initio* results, the lattice effect is reproduced at least qualitatively with the PM3 as well as with the AM1 method.

1. Introduction

It has become a common practice to explain the physical properties and the reactivity of molecules by their structure in the solid state determined by means of single-crystal X-ray crystallography. While this approach is legitimate for relatively rigid molecules, it might yield completely misleading results even in the case of molecules with only a few rotational degrees of freedom like, for example, *N*-acetylprolinamide. The structure of this molecule in the solid state was determined by Benedetti et al. [1] and Drück et al. [2]. Its crystal lattice is crosslinked by two strong intermolecular hydrogen bonds between both hydrogens of the NH₂ group and the oxygen atoms of the acetyl and amide substituents of neighbouring molecules. The molecular conformation in the solid state is further stabilized by an additional intramolec-

ular hydrogen bridge between H²³ and N¹ (**1** in Fig. 1, $r(\text{H}^{23}\cdots\text{N}^1) = 2.367 \text{ \AA}$, $\angle \text{N}^7\text{-H}^{23}\cdots\text{N}^1$: 104.9°). Computational results, however, indicate that the conformation of the free molecule might be significantly different. In a series of papers Madison and Schellman [3–5] reported the results of conformational energy calculations on several proline derivatives. For free *N*-acetylprolinamide and *N*-acetylproline-*N'*-methanamide they predicted structures containing intramolecular hydrogen bonds like **2** in Figure 1. Tsuboi et al. [6] recorded the IR spectrum of *N*-acetylproline-*N'*-methanamide in carbon tetrachloride solution. According to their results, the internally hydrogen-bonded species prevails under these conditions.

Drück et al. [2] characterized the conformation of the molecule by the interplanar angle between the least-squares planes of the proline ring and the amide group. In this paper we used the N¹-C²-C⁶-O⁸ and N¹-C²-C⁶-N⁷ dihedral angles to describe the different conformers of the title compound.

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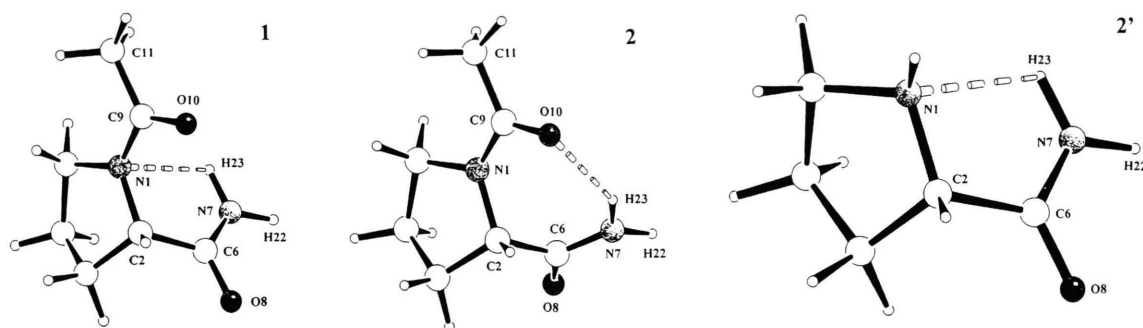


Fig. 1. Structure of the *N*-acetylprolinamide molecule in the solid state (**1**, left) and the free molecule (**2**, right) according to an HF/6-31+G* calculation. **2'** is the HF/6-31+G*-optimized structure of prolinamide.

2. Computational Methods

All *ab initio* calculations were performed employing the GAUSSIAN94 suite of quantum chemical routines [7] running on a cluster of workstations at the computing center of the RWTH Aachen. Since the species under consideration are highly polar, we used the 6-31+G* basis set [8-12] in all calculations. The correlation energy was calculated at HF-optimized geometries with the MP2 method. The semiempirical calculations were carried out on a local WS/2100 VAX workstation employing the MOPAC6 program package [13].

3. Results and Discussion

A quantum chemical *ab initio* calculation at the one-determinant (HF, *Hartree Fock*) level employing the 6-31+G* basis set and the experimentally determined molecular solid-state structure [2] (**1**, cf. Fig. 1) ($E_{\text{tot}}(\mathbf{1}) = -530.706938$ a. u.) yields a high dipole moment of 7.630 D. Since the positions of the hydrogen atoms can usually not be determined precisely by means of X-ray diffraction, another HF calculation with the same basis set was performed in which only the positional parameters of the hydrogen atoms were optimized. Due to the uncertainty of the experimentally determined hydrogen density, no structural information is lost in this way. This relaxation of the hydrogen atoms lowers the total energy by more than 18 kcal/mol, and at this level the dipole moment of the resulting structure (**3**) is 7.363 D ($E_{\text{tot}}(\mathbf{3}) = -530.735879$ a. u.). Optimization of all structural parameters except the dihedral angles resulted in structure **4** ($E_{\text{tot}}(\mathbf{4}) = -530.736113$ a. u.), which is only

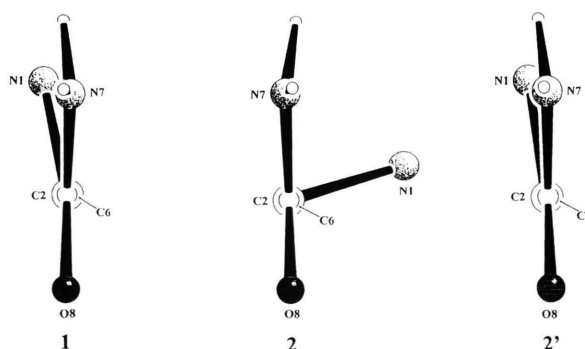


Fig. 2. The $\text{N}^1\text{-C}^2\text{-C}^6\text{-N}^7$ and $\text{N}^1\text{-C}^2\text{-C}^6\text{-O}^8$ dihedral angle in the solid state structure (**1**), and the free molecule (**2**) of *N*-acetylprolinamide, and the free molecule of prolinamide (**2'**).

0.2 kcal/mol lower in energy than **3**. At this level, the molecular dipole moment is 7.053 D and the geometry of the $\text{N}^7\text{-H}^{23}\cdots\text{N}^1$ segment is $r(\text{H}^{23}\cdots\text{N}^1) = 2.435$ Å, $r(\text{H}^{23}\text{-N}^7) = 0.992$ Å, $\angle \text{N}^7\text{-H}^{23}\cdots\text{N}^1$: 102.1° .

Remarkable changes of the molecular conformation occur when the geometry of the structure is optimized completely ($E_{\text{tot}}(\mathbf{2}) = -530.745589$ a. u.). These changes mainly concern the $\text{N}^1\text{-C}^2\text{-C}^6\text{-N}^7$ and $\text{N}^1\text{-C}^2\text{-C}^6\text{-O}^8$ dihedral angles (cf. Figure 2).

While the $\text{N}^1\text{-C}^2\text{-C}^6\text{-N}^7$ angle is -14.2° in the solid state structure (**1**), it amounts to 74.5° after optimization (**2**). This rotation of the amide group about the $\text{C}^2\text{-C}^6$ bond upon optimization of the geometry is accompanied by a significant reduction of the molecular dipole moment, yielding a final value of 3.846 D. The value of the $\text{N}^1\text{-C}^2\text{-C}^6\text{-O}^8$ dihedral angle is 167.1° in the solid state. It changes to -106.6° when the geometry of the molecule is optimized, corresponding to a more *cis*-like structure (cf. Fig. 1) similar to those

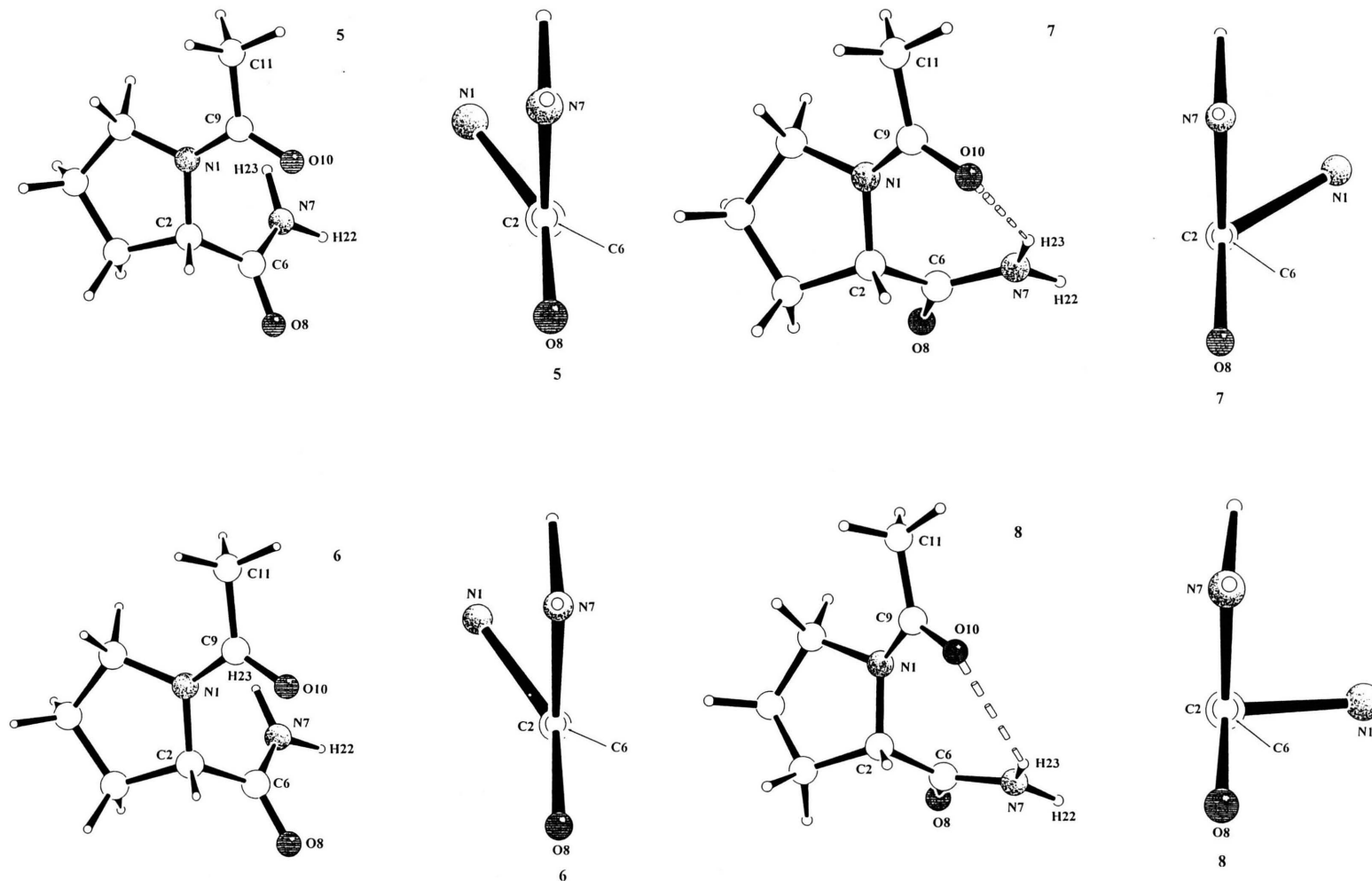


Fig. 3. The MINDO/3- (5), MNDO- (6), AM1- (7), and PM3-optimized (8) structures of *N*-acetylprolinamide obtained starting from the molecule's solid state structure.

predicted by Madison and Schellman [4, 5]. In contrast, the $O^{10}\text{-C}^9\text{-N}^1\text{-C}^2$ dihedral angle is essentially the same in the crystal (7.4°) and the free molecule (7.7° , cf. Figure 1). According to the spectrum of its normal vibrations, this stationary point for the free molecule is a minimum, with the lowest vibrational frequency occurring at 47.2 cm^{-1} (zero point energy: $\varepsilon_0 = 0.209910\text{ a. u.}$).

Obviously, the molecular conformation in the solid state is energetically unfavorable in the gas phase. Drück *et al.* [2] argued that the relative orientation of the amide group and the proline ring is halfway between *cis* and *trans* and thus energetically unfavourable.

In contrast to its conformation in the solid state, the optimized structure of the free molecule is stabilized by an intramolecular hydrogen bridge between O^{10} and H^{23} ($O^{10}\cdots H^{23}$: 2.104 Å , $H^{23}\text{-N}^7$: 0.998 Å , $O^{10}\cdots N^7$: 2.931 Å , $\angle O^{10}\cdots H^{23}\text{-N}^7$: 138.95°). Thus we conclude that if stabilizing interactions of the molecule with neighbouring species are not possible, the strength of the presumably relatively weak intramolecular $H^{23}\cdots N^1$ bridge ($N^1\cdots H^{23}$: 2.367 Å , $N^1\cdots N^7$: 2.796 Å , $\angle N^1\cdots H^{23}\text{-N}^7$: 104.9°) does not suffice to maintain the unusual structure of the molecule in the solid state. As a result, the $N^1\text{-C}^2\text{-C}^6\text{-N}^7$ dihedral angle changes to a value that allows intramolecular stabilization by formation of the presumably stronger $O^{10}\cdots H^{23}$ hydrogen bond. The $N^1\cdots H^{23}$ hydrogen bridge is most likely weaker than an ordinary $N\cdots H\text{-N}$ bridge between, for example, primary or secondary amines. The reason is that in both **1** and **2** the nitrogen lone pair interacts conjugatively with the neighbouring carbonyl group. This interaction is reflected by the planar environment of N^1 in **1** and **2**; the sums of bond angles at N^1 are 359.4 and 358.7° , respectively. Thus it is the competition between the $O^{10}\cdots H^{23}$ and the $H^{23}\cdots N^1$ bond that causes the conformational changes. The energy difference between the completely optimized structure **2** and the one where all structural parameters except the dihedral angles were optimized amounts to 5.9 kcal/mol . Thus, the $O^{10}\cdots H^{23}$ hydrogen bond might be by as much as 6 kcal/mol stronger than the $H^{23}\cdots N^1$ bridge. If the acetyl group is replaced by a hydrogen atom, no $O^{10}\cdots H^{23}$ bond can be formed and, consequently, no rotation of the amide group about the $C^2\text{-C}^6$ bond occurs. Optimization of the prolinamide structure at the HF/6-31+G* level, starting from the geometry of the prolinamide segment in the

Table 1. Results of semiempirical calculations on *N*-acetylprolinamide in comparison with the corresponding *ab initio* data.

	MINDO/3	MNDO	AM1	PM3	HF/6-31+G* ^{a)}	
ΔE_1	-8.3	-6.3	-8.5	-5.6	-5.9	(-6.2)
ΔE_2	-11.1	-14.3	-11.9	-12.4	-6.1	(-2.3)
ΔE_3	-34.5	-36.5	-29.9	-25.6	-24.3	(-17.2)
$\Delta\mu_1$	+0.47	+0.47	-2.18	-2.70	-3.21	
$\Delta\mu_2$	-0.10	± 0.00	-2.47	-3.29	-3.52	
$\Delta\mu_3$	-0.35	-0.09	-2.46	-3.22	-3.79	
$\Delta\Theta$	-23.4	-22.9	+75.4	+99.9	+88.7	

a) The numbers in parentheses were calculated at the MP2/6-31+G**/HF/6-31+G* level.

solid state structure of *N*-acetylprolinamide, results in a conformation ($E_{\text{tot}}(\mathbf{2}') = -378.947001\text{ a. u.}$) with an only slightly changed $N^1\text{-C}^2\text{-C}^6\text{-N}^7$ dihedral angle of -8.34° , an intramolecular $H^{23}\cdots N^1$ bond distance of 2.273 Å , and an $N^1\cdots H^{23}\text{-N}^7$ bond angle of 105.7° (cf. Figs. 1 and 2). Calculation of the normal frequencies showed that this structure corresponds to a minimum ($\varepsilon_0 = 0.169031\text{ a. u.}$). Retention of the conformation in this case might also in part be due to a stronger $N^1\cdots H^{23}$ bridge caused by the absence of delocalization of the nitrogen lone pair. In contrast to **1** and **2**, where the environment of N^1 is essentially planar, the sum of bond angles at N^1 is 335.3° in **2'**.

Detection of lattice effects like the one described above, and especially elucidation of their origin, is of high interest, since molecular structures determined in the solid state are frequently used to explain the chemical reactivity and many physical properties of the corresponding compound in the gas phase and in solution. In most cases, however, the molecules of interest are too large to be dealt with at a sufficiently high level of *ab initio* theory. Thus, semiempirical quantum chemical methods have to be employed to test the stability of molecular solid-state structures in the absence of the surrounding crystal lattice. In this regard it is important to know which of the most frequently used semiempirical methods are able to reproduce structural changes like the one observed for *N*-acetylprolinamide in reasonable agreement with *ab initio* data or, if available, with the results of structure determinations in the gas phase. We therefore repeated the calculations employing the semiempirical MINDO/3 [14], MNDO [15], AM1 [16], and PM3 [17] methods. The semiempirical and *ab initio* results are compiled in Table 1.

Here $\Delta E_1 = E_{\text{tot}}(\mathbf{2}) - E_{\text{tot}}(\mathbf{4})$ is the difference between the total energy of the completely optimized

molecule in the gas phase (E_{tot} (**2**)) and the one obtained if all bond lengths and angles are optimized but the dihedral angles are constrained to the values determined in the solid state (E_{tot} (**4**)). $\Delta E_2 = E_{\text{tot}}$ (**2**) – E_{tot} (**3**) is the difference between the total energy of the completely optimized geometry and the one obtained if only the positional parameters of the hydrogen atoms are optimized (E_{tot} (**3**)). Finally, $\Delta E_3 = E_{\text{tot}}$ (**2**) – E_{tot} (**1**) is the energy difference between the total energy of the completely optimized molecular structure and the total energy of the molecule as it occurs in the solid state (E_{tot} (**1**)). $\Delta\mu_1$, $\Delta\mu_2$, and $\Delta\mu_3$ are the corresponding changes of the dipole moments, and $\Delta\theta$ is the change of the N¹-C²-C⁶-N⁷ dihedral angle upon complete optimization starting from the molecular solid state structure.

The results in Table 1 show that both MINDO/3 and MNDO completely fail to reproduce the *ab initio* results. It is well known that both methods in their standard parametrization overestimate the repulsion between hydrogen-bonded molecules and, therefore, yield intermolecular distances that are too large and hydrogen-bond energies that are much too low [18–25]. Several attempts have been made to overcome these deficiencies by introducing new parametric expressions, as in MINDO/3H [18], MNDOH [21, 24], MNDO/M [26, 27], and I-MNDO [28]. In a more fundamental approach, explicit inclusion of valence shell orthogonalization, penetration integrals, and effective core potentials in the one-center part of the core Hamiltonian combined with a re-evaluation of the two center *Coulomb* interactions turned out to lead to a much better description of hydrogen bonds [25]. The resulting methods, however, still have to be tested for our purpose and only the standard methods were checked for the particular case under consideration. Thus it is not surprising that geometry optimizations with both methods result in structures which are more *trans*-like than **1**, and which are not stabilized by intramolecular hydrogen bridges (**5**, **6**, *cf.* Figure 3).

The use of both the MINDO/3- and the MNDO-optimized coordinates as starting geometries in HF/6-31+G* optimizations results in structures with N¹-C²-C⁶-N⁷ dihedral angles of 74.9° and O¹⁰...H²³ distances of 2.105 Å which are essentially identical and thus isoenergetic with **2**. Visually the PM3 and AM1 structures closely resemble **2** (**7**, **8**, *cf.* Fig. 3) and the results which are closest to the *ab initio* data are those obtained with the AM1 method (O¹⁰...H²³: 2.104 Å). In this regard, it is interesting to note that at the AM1

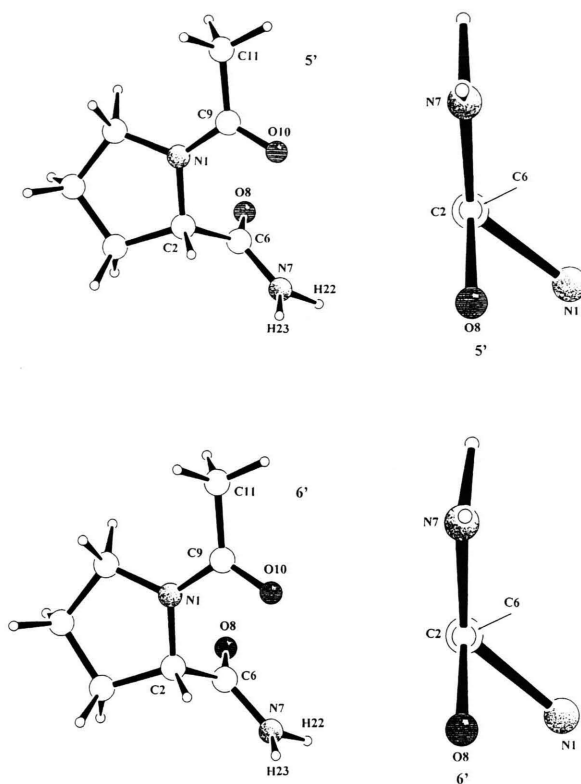


Fig. 4. The MINDO/3- (**5'**) and MNDO- (**6'**) optimized structures of *N*-acetylprolinamide obtained from the corresponding AM1 and PM3 minima.

level, formation of the hydrogen bridged complexes $\text{H}_3\text{C-CO-NH}_2\cdots\text{O}_2\text{H}$ and $\text{H}_3\text{C-CO-NH}_2\cdots\text{O=CH}_2$ is exothermic by –5.88 and –2.53 kcal/mol, respectively.

Using the AM1 and PM3 minima as starting points in MINDO/3 and MNDO geometry optimizations resulted in another set of *cis*-like structures (**5'** and **6'**) which are also minima on the corresponding hypersurfaces (*cf.* Figure 4). Although significantly different from **5** and **6**, they are almost isoenergetic with these conformers. When **5'** was used as starting point in AM1 and PM3 calculations, the final minima are identical with **7** and **8**, respectively.

At the AM1 and the PM3 level, ΔE_2 takes almost twice the value obtained at the HF/6-31+G* level. To see whether this difference is due to correlation effects partly included in the semiempirical parameters, we recalculated ΔE_2 at the MP2/6-31+G**/HF/6-31+G* level (*cf.* Table 1). However, inclusion of correlation effects further reduces ΔE_2 by more than 50%, indicating that in spite of similar structures the semiempirical energy differences are not very reliable.

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