Molecular Structure of Proline

Wesley D. Allen,*[a] Eszter Czinki,[b] and Attila G. Császár*[b]

Abstract: The molecular structures of the two lowest-energy conformers of proline, Pro-**I** and Pro-**II**, have been characterized by ab initio electronic structure computations. An extensive MP2/6-31G* quartic force field for Pro-**I**, containing 62835 unique elements in the internal coordinate space, was computed to account for anharmonic vibrational effects, including total zero-point contributions to isotopomeric rotational constants. New r_e and improved r_0 least-squares structural refinements were performed to determine the heavy-atom framework of Pro-**I**, based on experimentally measured (A. Lesarri, S. Mata, E. J. Cocinero, S. Blanco, J. C. Lopez, J. L. Alonso, *Angew. Chem.* **2002**, *114*, 4867; *Angew. Chem. Int. Ed.* **2002**, *41*, 4673) rotational constant sets of nine isotopomers and our ab initio data for structural constraints and zero-point vibrational (ZPV) shifts. Without the ab initio constraints, even the extensive set of empirical rotational constants cannot satisfactorily fix the molecular structure of the most stable conformer of proline, a 17-atom molecule with no symmetry. After imposing the ab initio constraints, excellent agreement between theory and experiment is found for the heavy-atom geometric framework, the root-mean-square (rms) residual of the empirical rotational constant fit being cut in half by adding ZPV corrections. The most significant disparity, about 0.07 Å, between the empirical and the best ab initio structures, concerns the $r(\mathrm{N}\cdots\mathrm{H})$ distance of the intramolecular hydrogen bond. Some of the experimental quartic centrifugal distortion constants assigned to Pro-**II** have been corrected based on data obtained from a theoretical force field.

Keywords: ab initio calculations · conformation analysis · quartic force field · spectroscopic constants · structural refinement

Introduction

Proline (Pro) is unique among the natural amino acids in that its amino group is fixed within a pyrrolidine ring (Figure 1). Structural studies on Pro-containing peptides frequently find Pro in β- and γ-turns, and Pro residues relatively often exhibit a *cis* peptide bond.[1] Furthermore, L-Pro is a favorite organocatalytic agent for assembling stereochemically complex molecules from achiral building blocks.[2,3] These observations have prompted investigations into the relationship between *cis–trans* isomerism and ring puckering. Experimental[4–10] and theoretical[11–17] structural studies on neutral proline have helped to establish those structural features of Pro that may change during peptide or protein formation and catalytic processes.

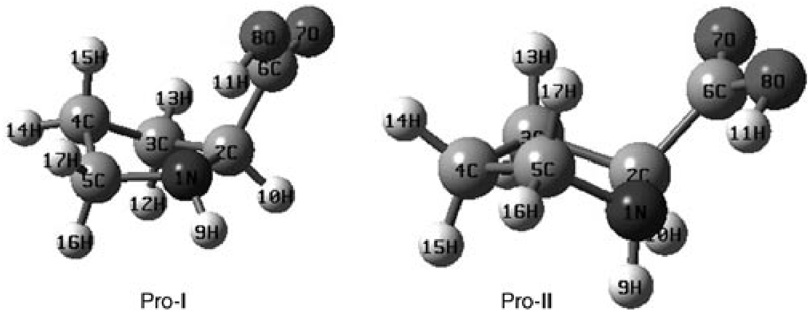

Figure 1. Structure of and atomic numbering in the two lowest-energy conformers of neutral proline.

In the last three years three relevant studies[10,16,17] have been published on the structural and energetic features of neutral proline. First, Stepanian et al.[16] reported the results of computations with an aug-cc-pVDZ basis set[18,19] at vari-

---

[a] Dr. W. D. Allen
Center for Computational Chemistry, University of Georgia
Athens, Georgia 30602-0525 (USA)
Fax: (+1) 706-542-0406
E-mail: wdallen@ccqc.uga.edu

[b] E. Czinki, Prof. Dr. A. G. Császár
Department of Theoretical Chemistry, Eötvös University
1518 Budapest 112, P. O. Box 32 (Hungary)
Fax: (+361) 209-0602
E-mail: csaszar@chem.elte.hu

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

DOI: 10.1002/chem.200400112

ous levels of theory. A study[17] by two of us improved upon these results by performing focal-point analyses[20,21] with basis sets as large as cc-pV5Z[18,22] and correlation treatments as extensive as CCSD(T),[23] together with small corrections for auxiliary physical effects, including relativistic contributions,[24] to arrive at definitive relative energy predictions. When the results of our detailed ab initio structural investigation,[17] which contained rotational constants and quartic centrifugal distortion constants for 18 conformers of Pro, was sent for publication, no experimental results were available for comparison. In fact, it was noted in reference [17] that “the theoretical estimates given for the as yet unobserved conformers should be most valuable in searching for these conformers by MW and MMW spectroscopy.” Since then Lesarri et al.,[10] by using laser-ablation molecular-beam Fourier-transform microwave (MW) spectroscopy, have reported sets of spectroscopic constants for the two lowest-energy conformers Pro-**I** and Pro-**II**, as well as r_0 structural parameters for Pro-**I**. The observation of Pro-**I** and Pro-**II** has been aided by their very substantial dipole moments.[17] The experimental study of Lesarri et al.[10] prompted us to further extend our ab initio treatment of Pro, and the results are reported herein.

From our earlier high-level focal-point extrapolations,[17] which included core correlation and even relativistic corrections in establishing the energy (enthalpy) ordering of the conformers of proline, we predicted that only four conformers have relative energies less than 10 kJ mol^{-1} and only two lie below 6.5 kJ mol^{-1}. These two conformers, Pro-**I** and Pro-**II** shown in Figure 1, have relative energies of 0.0 and 2.2 kJ mol^{-1}, respectively, and basically share the same structural features, differing only in the puckering angle of the pyrrolidine ring. Both Pro-**I** and Pro-**II** were deemed to be present in the carefully executed and novel MW experiments of Lesarri and co-workers.[10] We restricted the ab initio structural study reported herein to these two observed conformers to maximize the rigor of our treatment.

Computational Methods

In the calculations reported in reference [17], all the geometry optimizations were performed at the DFT(B3LYP)/6-311++G**[25] level, which has proved to be dependable for this class of molecule.[14,26–29] Nevertheless, it is preferable to optimize geometries by using purely ab initio techniques. Therefore, the equilibrium structures of Pro-**I** and -**II** have been reoptimized in this study at the frozen-core (FC) and all-electron (AE) MP2[30] level by using the 6-31G*[31] and cc-pVTZ[18,22] basis sets. To account for zero-point vibrational effects in the detailed MW rotational constants, force-field expansions of the vibrational potentials were computed. In addition to MP2(AE)/cc-pVTZ quadratic force fields for both conformers, an extensive anharmonic force field in curvilinear internal coordinates was computed for Pro-**I** by using finite differences of tightly converged MP2(FC)/6-31G* second derivatives.[32] This anharmonic force field included all the force constants of type F_{ij}, F_{ijk}, and F_{ijkk} for all 45 internal degrees of freedom, totalling 62 835 unique elements, which is virtually unprecedented for correlated ab initio methods. All force fields were computed for the respective equilibrium structures in order to avoid the nonzero force dilemma.[33] The electronic structure computations were performed with the TURBOMOLE[34] and Gaussian 98[35] program packages.

After the determination of the quartic force field for Pro-**I** in the internal coordinate representation, an analytic nonlinear transformation to Cartesian space was performed with the INTDER2000 program,[33,36,37] which implements **B** tensor formulae[37,38] through fourth order for all common internal variables. Upon subsequent linear transformation of the force field to the reduced normal coordinate space, vibrational anharmonic constants (χ_{ij}), vibration-rotation interaction constants (α_i^B), and quartic and sextic centrifugal distortion constants were determined for each isotopomer using the formulae of vibrational second-order perturbation theory (VPT2) as applied to the standard vibration-rotation Hamiltonian for semi-rigid asymmetric top molecules.[39–42] This procedure has been investigated extensively in systematic ab initio studies of vibrational anharmonicity in our laboratories.[43–48] The computation of spectroscopic constants from input force fields was performed by employing both the ANHARM[49,50] and ASYM40[51] programs. In determining the *total* vibrational contributions to ground-state rotational constants, Coriolis resonances need not be considered because all resonance denominators cancel in the summation over normal modes. An INTDER2000 input file specifying the internal coordinate set for Pro-**I** and containing all elements of the quartic force field is available as Supporting Information.[52]

Results and Discussion

As the data in Table 1 show, the directly computed ab initio equilibrium rotational constants may deviate substantially from the experimentally measured vibrationally averaged ones both for Pro-**I** and Pro-**II**. Generally the MP2(FC)/cc-pVTZ equilibrium constants give superior comparisons, displaying differences of 20–31 MHz with the empirical rotational constants for the better characterized Pro-**I** conformer. Note that in the Pro-**I** case the corrections for vibrational averaging computed from the MP2(FC)/6-31G* anharmonic force field, amounting to 0.6–1.0% of the rotational constants, significantly reduce the differences with experiment to 7–12 MHz, in accord with the high accuracy of theoretical vibration–rotation interaction (α_i) constants that is usually observed.[43–47] The theoretical differences between the vibrationally averaged rotational constants of the parent isotopomer and those of the substituted ones of Pro-**I**, as reported in Table 2, reproduce the experimentally measured values remarkably well. The shift in the A_0 constant for the

Table 1. Rotational constants [MHz] for the parent isotopomers of conformers Pro-**I** and Pro-**II**.

Level	Pro-**I**			Pro-**II**		
	$A_e(A_0)$	$B_e(B_0)$	$C_e(C_0)$	$A_e(A_0)$	$B_e(B_0)$	$C_e(C_0)$
RHF/6-31+G*	3847.7	1628.6	1373.4	4196.4	1531.1	1251.3
B3LYP/6-311++G**	3730.2	1641.5	1369.5	4030.2	1551.4	1246.9
MP2(FC)/cc-pVTZ[a]	3704.3	1708.7	1428.2	3816.1	1673.9	1322.9
	(3666.1)	(1698.1)	(1419.1)			
Expt.[b]	(3673.9)	(1688.4)	(1407.4)	(3923.6)	(1605.9)	(1279.8)

[a] Zero-point vibrational contributions to the rotational constants were determined from MP2(FC)/6-31G* vibration–rotation interaction constants. [b] Ref. [10].

Table 2. Isotopic shifts of rotational and quartic centrifugal distortion constants for Pro-**I**.[a]

	Parent	$^{13}C_2$	$^{13}C_3$	$^{13}C_4$	$^{13}C_5$	$^{13}C_6$	^{15}N	ND	OD	ε[b]
A_0	3666.06	−17.30	−49.94	−30.76	−8.82	0.14	−35.54	−110.71	**−72.48**	0.29
	(3673.90)	(−16.97)	(−49.80)	(−30.27)	(−9.37)	(0.16)	(−35.83)	(−110.91)	(−75.33)	
B_0	1698.14	−3.37	−3.19	−18.84	−24.04	−10.32	−6.06	−18.19	−2.79	0.25
	(1688.42)	(−3.25)	(−3.24)	(−19.02)	(−23.79)	(−10.25)	(−5.87)	(−17.65)	(−3.40)	
C_0	1419.11	−0.02	−9.46	−12.11	−18.03	−7.19	−6.70	−13.26	−12.13	0.18
	(1407.38)	(0.00)	(−9.29)	(−12.30)	(−17.82)	(−7.11)	(−6.62)	(−13.08)	(−12.67)	
Δ_J	0.5611	−0.0070	−0.0103	0.0015	−0.0122	−0.0053	−0.0105	−0.0365	−0.0061	
	(0.6341)	(0)	(0)	(0)	(0)	(0)	(−0.014)	(−0.0401)	(−0.033)	
Δ_{JK}	−1.9548	0.0066	0.0600	−0.0118	−0.0139	0.0098	0.0300	0.2409	**0.1023**	
	(−2.402)	(0)	(0)	(0)	(0)	(0)	(0.060)	(0.162)	(4.45)	
Δ_K	4.3182	0.0047	**−0.1603**	−0.0127	0.0615	−0.0051	−0.0770	**−0.6074**	−0.2273	
	(5.118)	(0)	(0)	(0)	(0)	(0)	(0.022)	(0)	(0)	
δ_J	0.0984	−0.0035	−0.0003	−0.0013	−0.0025	−0.0012	0.0015	−0.0113	0.0034	
	(0.1210)	(0)	(0)	(0)	(0)	(0)	(−0.008)	(0)	(0)	
δ_K	0.5956	−0.0176	−0.0383	0.0150	−0.0043	−0.0016	0.0048	0.0097	−0.0228	
	(0.581)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	

[a] Shifts are given for the isotopically substituted species relative to the absolute values listed for the parent molecule. MP2(FC)/cc-pVTZ values are listed first with measured quantities from reference [10] in parentheses. All theoretical rotational constants include MP2(FC)/6-31G* zero-point vibrational corrections. See Figure 1 for numbering of the atoms. The units assumed for the vibrationally averaged rotational constants and the A-reduced quartic centrifugal distortion constants are MHz and kHz, respectively. Points of significant disparity are printed in boldface. [b] Mean absolute difference between theoretical and experimental isotopic shifts. The statistics for A_0 exclude the outlying datum for the OD isotopomer.

OD isotopomer is clearly an outlying datum in this comparison, as the theoretical result differs by 2.85 MHz from the experimental value, whereas the corresponding mean absolute deviation for the other isotopomers is only 0.29 MHz.

For Pro-**I**, changes in the isotopically substituted quartic centrifugal distortion constants mostly support the constraints introduced by Lesarri et al.[10] due to the lack of sufficient experimental line information, although there are a few striking disparities, such as Δ_{JK}(OD) and Δ_K(ND). More importantly, data presented in Table 1 and Table 3 suggest that the experimental quartic centrifugal distortion (QCD) constants, Δ_K and δ_K, of Pro-**II** are not valid.[53,54] By using the method of predicate observations, Demaison[54] observed that 1) setting δ_K to zero was a somewhat unfortunate choice of Lesarri et al.[10] as its value is relatively large, as predicted correctly by ab initio calculations; 2) the spectroscopic constants Δ_K and δ_K are highly correlated, so that refitting these constants results in different but much improved values, $\Delta_K = 8.2(25)$ kHz and $\delta_K = 0.91(14)$ kHz; 3) the originally reported value for Δ_K was given in MHz and not in kHz; and 4) Δ_J, Δ_{JK}, and δ_J are well determined.

Based on their vibrationally averaged rotational constants for nine isotopomers, Lesarri et al.[10] published selected structural parameters of Pro-**I**, including bond lengths, bond angles, and torsion angles of mostly heavy atoms of the pyrrolidine ring. With the aid of our fully optimized MP2(FC)/cc-pVTZ geometry, we undertook a new least-squares refinement (LSR) to determine empirical structural parameters for Pro-**I**. To achieve this goal a new computer program, MolStruct, written in *Mathematica*,[55] has been developed. Performance of the code was checked by application to synthetic rotational constant data for the nine isotopomers of concern, generated from the optimized MP2(FC)/cc-pVTZ structures. Upon constraining diverse sets of internal coordinates to their MP2(FC)/cc-pVTZ values and then performing LSR on the rest, we were always able to achieve facile convergence to an exact fit of the synthetic rotational constants, even from rather poor initial guesses of the structural variables. The preliminary studies on the synthetic rotational constant data provided important information on how well determined the structural parameters are under various choices of constraints.

Table 3. Computed and experimental rotational and quartic centrifugal distortion constants for the two experimentally observed (parent and ^{15}N) isotopomers of Pro-**II**.[a]

	Rotational constants [MHz]			QCD constants [kHz]				
	A	B	C	Δ_J	Δ_{JK}	Δ_K	δ_J	δ_K
Parent								
B3LYP/6-311++G**	4030.19	1551.36	1246.91	0.37	−1.36	5.56	0.11	0.95
MP2(AE)/cc-pVTZ	3837.02	1693.76	1339.05	0.88	−3.32	8.95	0.14	0.65
Expt.	3923.56	1605.88	1279.80	1.02	−4.65	−0.01	0.25	[0.00]
^{15}N								
B3LYP/6-311++G**	3988.01	1547.60	1241.97	0.37	−1.38	5.51	0.11	0.91
MP2(AE)/cc-pVTZ	3796.19	1689.06	1333.28	0.87	−3.35	8.87	0.13	0.58
Expt.	3880.40	1602.38	1274.92	1.01	−4.62	[−0.01]	0.26	[0.00]

[a] The calculations refer to equilibrium rotational and QCD constants, while experiment (Expt.) refers to vibrationally averaged experimental constants from reference [10]. Note that according to a refitting performed by Demaison,[54] based on predicate observations, the experimental QCD constants [kHz] of the parent isotopomer change to $\Delta_J = 1.025(6)$, $\Delta_{JK} = -4.59(4)$, $\Delta_K = 8.2(25)$, $\delta_J = 0.247(3)$, and $\Delta_K = 0.91(14)$.

Although the isotopomeric rotational constant data for proline are extensive, they are insufficient to define a geometric structure without the imposition of numerous constraints. To wit, there are 45 geometric degrees of freedom for proline, but only 27 empirical rotational constants in the data set. It is stated in reference [10] that the "only" constraints imposed on the original structural refinement were the planarity of the carboxy group and the local C_{2v} symmetry of the three methylene units. However, these specifications technically only reduce the problem to 31 variables, so there must have been other assumptions that were not stated. The number of separate geometric parameters reported in reference [10] for proline is 14.

We are in a position to impose more realistic and reliable constraints on the structural refinement of proline, based on our MP2(FC)/cc-pVTZ optimum geometric parameters. For example, the MP2(FC)/cc-pVTZ wagging, twisting, and rocking angles of the methylene groups range from −6.3 to 5.7°, as opposed to zero when local C_{2v} symmetry is assumed. Likewise, the C−C bond lengths display a variability of 0.01 Å instead of a common value. After extensive testing, we found that the 33 MP2(FC)/cc-pVTZ geometric constraints shown in Table 4 could be imposed without significant reduction in the goodness of the structural fit. These constraints 1) fully determine all the hydrogen positions with respect to the heavy-atom framework, 2) specify the internal structure of the -COOH moiety, and 3) fix the *differences* in the C−C, C−N, and C−O bond lengths. With 12 geometric parameters remaining after enforcing the constraints, the empirical rotational constants can be fitted quite well: the weighted rms error is only 0.0645 MHz, no residual is over 1 MHz, and no correlation coefficient exceeds 0.91. The results are listed under r_0(Fit 1) in Table 5. There is general but not precise agreement with the structure in reference [10], the most notable disparities, 3–4°, occurring for $\tau(C_5\text{-}N\text{-}C_2\text{-}C_6)$ and $\tau(N\text{-}C_2\text{-}C_6\text{-}O)$, the tilting and internal rotation angles of the -COOH group, respectively. The r_0(Fit 1) mean bond distances differ by 0.010–0.018 Å from their

Table 4. Geometric constraints of Pro-**I** structural fits.[a]

1. $r(3,4)-r(2,3)=-0.0046$
2. $r(4,5)-r(2,3)=-0.0087$
3. $r(2,6)-r(2,3)=0.0021$
4. $r(1,5)-r(1,2)=-0.0000$
5. $r(6,7)-r(6,8)=-0.1291$
6. $r(8,11)=0.9905$
7. $r(1,9)=1.0104$
8. $r(2,10)=1.0890$
9. $r(3,12)=1.0903$
10. $r(3,13)=1.0864$
11. $r(4,14)=1.0871$
12. $r(4,15)=1.0907$
13. $r(5,16)=1.0932$
14. $r(5,17)=1.0880$
15. $\theta(7,6,8)=124.00°$
16. $\theta(6,8,11)=102.16°$
17. $\theta(1,2,10)=112.13°$
18. $\theta(3,2,10)=112.07°$
19. $\theta(2,1,9)=111.56°$
20. $\theta(5,1,9)=111.72°$
21. $\theta(14,4,15)=108.47°$
22. $\theta(3,4,14)+\theta(5,4,14)-\theta(3,4,15)-\theta(5,4,15)=5.71°$
23. $\theta(3,4,14)-\theta(5,4,14)-\theta(3,4,15)+\theta(5,4,15)=0.81°$
24. $\theta(3,4,14)-\theta(5,4,14)+\theta(3,4,15)-\theta(5,4,15)=1.14°$
25. $\theta(12,3,13)=108.78°$
26. $\theta(2,3,12)+\theta(4,3,12)-\theta(2,3,13)-\theta(4,3,13)=-6.26°$
27. $\theta(2,3,12)-\theta(4,3,12)-\theta(2,3,13)+\theta(4,3,13)=3.24°$
28. $\theta(2,3,12)-\theta(4,3,12)+\theta(2,3,13)-\theta(4,3,13)=-3.04°$
29. $\theta(16,5,17)=108.46°$
30. $\theta(1,5,16)+\theta(4,5,16)-\theta(1,5,17)-\theta(4,5,17)=-2.36°$
31. $\theta(1,5,16)-\theta(4,5,16)-\theta(1,5,17)+\theta(4,5,17)=4.54°$
32. $\theta(1,5,16)-\theta(4,5,16)+\theta(1,5,17)-\theta(4,5,17)=-1.28°$
33. $\tau(7,6,8,11)=179.39°$
34. $\gamma(2,6,8,7)=0.41°$

[a] Based on the MP2(FC)/cc-pVTZ optimum structure. Units are Å for distances (r), and degrees for bond (θ), torsion (τ), and out-of-plane (γ) angles. See Figure 1 for labeling of the atoms.

Table 5. Structural parameters of Pro-**I**.[a,b]

	Expt. Ref. [10]	MP2(FC)/ cc-pVTZ	r_0(Fit 1)	r_0(Fit 2) (−5,−15)	r_0(Fit 3) (−6,−16)	r_0(Fit 4) (−3,−4)	r_e(Fit 1)
$r_{av}(C-N)$	1.451(6)	1.479	1.465(8)	1.467(12)	1.469(9)	1.456(9)	1.473(4)
$r_{av}(C-C)$	1.544(16)	1.529	1.547(4)	1.548(6)	1.545(5)	1.550(8)	1.530(2)
$r(C_6-O)$	1.340(10)	1.337	1.327	1.305(124)	1.331	1.330	1.328
$r(C_6=O)$	1.210(10)	1.208	1.198	1.218(97)	1.202	1.201	1.198
$\theta(O=C_6-O)$	124.9(9)	124.0	124.0	124.1(30)	124.0	124.0	124.0
$\theta(C_2-C_6-O)$	116.2(8)	113.4	116.1(8)	117.0(59)	115.3(9)	115.3(13)	115.3(3)
$\theta(N-C_2-C_6)$	111.0(9)	109.8	110.5(7)	109.8(47)	110.3(8)	111.1(13)	110.4(3)
$\theta(C_5-N-C_2)$	108.3(9)	108.6	109.5(6)	109.6(8)	109.3(6)	109.3(8)	109.1(3)
$\theta(N-C_2-C_3)$		105.7	106.5(10)	106.3(11)	106.4(12)	107.6(15)	105.7(4)
$\theta(C_4-C_5-N)$	103.7(1)	103.3	103.6	103.5	103.6	103.5	103.6
$\theta(C_3-C_4-C_5)$	101.9(9)	101.9	101.9	101.9	101.9	101.9	101.9
$\tau(C_5-N-C_2-C_6)$	121(1)	116.5	117.5(14)	117.3(24)	117.5(16)	117.5(22)	117.1(6)
$\tau(N-C_2-C_6-O)$	0(2)	2.3	3.9(22)	4.1(35)	3.7(23)	3.7(36)	3.3(9)
$\tau(C_3-C_2-N-C_5)$	2(2)	−2.5	−0.7(10)	−1.0(12)	−0.6(11)	−0.8(13)	−2.7(4)
$\tau(C_2-C_3-C_5-C_4)$	138(2)	137.3	139.4(5)	139.4(6)	139.4(6)	139.5(6)	138.4(2)
$r(N\cdots H)$	1.915(6)	1.809	1.922	1.922	1.925	1.922	1.881
$r(O-H)$		0.991	0.991	0.991	0.968(16)	0.991	0.991
$\theta(C-O-H)$		102.2	102.2	102.2	103.4(11)	102.2	102.2
$r(N-C_2)-r(N-C_5)$		0.000	0.000	0.000	0.000	−0.030(26)	0.000
$r(C_6-C_2)-r(C_3-C_2)$		0.002	0.002	0.002	0.002	0.012(46)	0.002
Rms resid. [MHz]			0.0645	0.0636	0.0629	0.0664	0.0342

[a] See footnote [a] to Table 4. Standard errors of fit are given in parentheses. [b] Fit 1 imposes all constraints 1–34 listed in Table 4; Fits 2–4 release constraints (5,15), (6,16), and (3,4), respectively, from Fit 1. The weights in the fits to the experimental rotational constants are set to the reciprocal uncertainties.

Table 6. Zero-point vibrational corrections [MHz] to rotational constants of Pro-**I** isotopomers.[a]

	Parent	$^{13}C_2$	$^{13}C_3$	$^{13}C_4$	$^{13}C_5$	$^{13}C_6$	^{15}N	ND	OD
A_e–A_0	38.2754	38.1881	37.9842	37.5943	37.9435	38.0869	37.6450	37.2504	36.7852
B_e–B_0	10.5853	10.4239	10.4109	10.4818	10.4832	10.4506	10.5628	10.0590	10.8617
C_e–C_0	9.0674	8.9457	8.9461	8.9751	8.9648	8.9527	8.9728	9.2756	9.1590

[a] Computed from the MP2(FC)/6-31G* cubic force field. See Figure 1 for labeling of the atoms.

MP2(FC)/cc-pVTZ r_e counterparts, whereas the agreement for bond and torsion angles is within 1.0° and 2.1°, respectively, except for the angle $\theta(C_2\text{-}C_6\text{-}O)$. This exception reveals one striking difference between the r_0(Fit 1) and MP2(FC)/cc-pVTZ structures; namely, in the empirical structure the -COOH group is rocked outward by almost 3°, which increases the hydrogen-bonded r(N···H) distance from 1.81 to 1.92 Å. Because the experimental r(N···H) distance is dependent on the changes in the rotational constants upon deuterium substitution in the hydrogen bond, the disagreement between theory and experiment seen above for the shift in the A_0 constant for the OD isotopomer is significant. We return to this issue below after accounting for zero-point vibrational effects.

The degree of accuracy of the empirical determination of the proline structure can be gauged by performing additional fits with various relaxations of constraints. As detailed in Table 5, r_0(Fit 2) shows that the internal structure of the carboxy group is not well defined by the empirical data, which is not surprising since no oxygen substitutions were included. In r_0(Fit 3) the release of constraints on the hydroxy hydrogen causes the O–H bond to contract by 0.023 Å, and increases θ(C-O-H) by 1.2°, but barely has an effect on the hydrogen-bonded distance r(N···H). Finally, r_0(Fit 4) reveals that the differences in the C–C and C–N bond lengths are poorly determined and spuriously exaggerated if the MP2(FC)/cc-pVTZ constraints are removed. Nonetheless, it is clear from the various fits that two key parameters, the ring puckering angle $\tau(C_2\text{-}C_3\text{-}C_5\text{-}C_4)$ and the hydrogen-bonded distance r(N···H), are well determined by the data set of empirical rotational constants.

Theoretical results for the total zero-point vibrational (ZPV) contributions to the rotational constants of the nine isotopomers of Pro-**I** appear in Table 6. These quantities were computed as one-half of the sum of the MP2(FC)/6-31G* vibration–rotation interaction constants (α_i). In order to obtain empirically based r_e parameters for Pro-**I**, our vibrational corrections were added to the (A_0, B_0, C_0) constants of reference [10], and another least-squares structural refinement was executed with the (Fit 1) constraints of Table 4. This accounting of vibrational effects satisfyingly reduced the weighted rms residual in the fit by almost a factor of 2, to 0.0342 MHz. The resulting r_e parameters, listed in the last column of Table 5, also show substantial improvements in relation to their MP2(FC)/cc-pVTZ counterparts. For example, the r_0(Fit 1)→r_e(Fit 1) effect decreases the average C–C distance by 0.017 Å, the twist angle $\tau(C_3\text{-}C_2\text{-}N\text{-}C_5)$ by 2.0°, and the flap angle $\tau(C_2\text{-}C_3\text{-}C_5\text{-}C_4)$ by 1.0°, bringing them to within 0.001 Å, 0.2°, and 1.1°, respectively, of the corresponding MP2(FC)/cc-pVTZ values. Also significant is the $^1/_3$ reduction of the disparity seen above for the hydrogen-bonded N···H distance: r_0(Fit 1) = 1.922 Å and r_e(Fit 1) = 1.881 Å versus r_e(MP2(FC)/cc-pVTZ) = 1.809 Å. An equivalent trend is seen in the carboxylic rocking angle $\theta(C_2\text{-}C_6\text{-}O)$. Thus, ZPV effects on r(N···H) are large, but insufficient to bring theory and experiment into full accord for this parameter, which is important to the accurate characterization of the intramolecular hydrogen bond in gaseous proline. For all other geometric variables there is excellent agreement between the empirically based r_e(Fit 1) values and the best (MP2(FC)/cc-pVTZ) theoretical predictions. Resolution of the r(N···H) issue will require electronic structure computations on an even larger scale to determine fully converged ab initio limits for this sensitive parameter. Moreover, further experimental work is needed to investigate the isotopic-shift anomalies in the reported spectroscopic constants of the OD isotopomer and to obtain rotational constants for new isotopomers to fully define the empirical structure of the carboxy group.

Acknowledgements

Work performed in the USA and in Hungary was supported by the U.S. National Science Foundation (NSF-CHE01–36186) and by the Hungarian Scientific Research Fund, OTKA T033074, respectively. Collaboration between the two research groups was supported by an NSF-MTA-OTKA collaboration grant (INT-0312355). The authors are particularly grateful to Professor Jean Demaison for refitting the spectroscopic constants of the parent isotopomer of Pro-**II**.

---

[1] G. Nemethy, M. P. Printz, *Macromolecules* **1972**, *5*, 755.
[2] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.
[3] C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2891; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785.
[4] R. L. Kayushina, B. K. Vainstein, *Sov. Phys. Crystallogr. (Engl. Transl.)* **1966**, *10*, 698.
[5] R. Balasubramanian, A. V. Lakshminarayanan, M. N. Sabesan, G. Tegoni, K. Venkatesan, G. N. Ramachandran, *Int. J. Pept. Protein Res.* **1971**, *3*, 25.
[6] D. F. DeTar, N. P. Luthra, *J. Am. Chem. Soc.* **1977**, *99*, 1232.
[7] C. A. G. Haasnoot, F. A. A. M. De Leeuw, H. P. M. De Leeuw, C. Altona, *Biopolymers* **1981**, *20*, 1211.
[8] I. D. Reva, S. G. Stepanian, A. M. Plokhotnichenko, E. D. Radchenko, G. G. Sheina, Yu. P. Blagoi, *J. Mol. Struct.* **1994**, *318*, 1.
[9] A. W. Herlinger, T. V. Long II, *J. Am. Chem. Soc.* **1970**, *92*, 6481.
[10] A. Lesarri, S. Mata, E. J. Cocinero, S. Blanco, J. C. Lopez, J. L. Alonso, *Angew. Chem.* **2002**, *114*, 4867; *Angew. Chem. Int. Ed.* **2002**, *41*, 4673.
[11] M. Ramek, A.-M. Kelterer, S. Nikolic, *Int. J. Quantum Chem.* **1997**, *65*, 1033.
[12] D. Cabrol, H. Brock, D. Vasilescu, *Int. J. Quantum Chem.* **1979**, *6*, 365.
[13] A.-M. Sapse, L. Mallah-Levy, S. B. Daniels, B. W. Erickson, *J. Am. Chem. Soc.* **1987**, *109*, 3526.
[14] A. G. Császár, A. Perczel, *Prog. Biophys. Mol. Biol.* **1999**, *71*, 243.
[15] P. Tarakeshwar, S. Manogaran, *J. Mol. Struct.* **1996**, *365*, 167.

[16] S. G. Stepanian, I. D. Reva, E. D. Radchenko, L. Adamowicz, *J. Phys. Chem. A* **2001**, *105*, 10664.
[17] E. Czinki, A. G. Császár, *Chem. Eur. J.* **2003**, *9*, 1008.
[18] T. H. Dunning, Jr., *J. Chem. Phys.* **1989**, *90*, 1007.
[19] R. A. Kendall, T. H. Dunning, Jr., R. J. Harrison, *J. Chem. Phys.* **1992**, *96*, 6769.
[20] W. D. Allen, A. L. L. East, A. G. Császár, *Structures and Conformations of Non-Rigid Molecules* (Eds.: J. Laane, M. Dakkouri, B. van der Veken, H. Oberhammer), Kluwer, Dordrecht, **1993**, p. 343.
[21] A. G. Császár, W. D. Allen, H. F. Schaefer III, *J. Chem. Phys.* **1998**, *108*, 9751.
[22] Basis sets were obtained from the Extensible Computational Chemistry Environment Basis Set Database, as developed and distributed by the Molecular Science Computing Facility, Environmental and Molecular Sciences Laboratory, which is part of the Pacific Northwest Laboratory, P. O. Box 999, Richland, Washington 99352 (USA), and funded by the U.S. Department of Energy. The Pacific Northwest Laboratory is a multi-program laboratory operated by the Battelle Memorial Institute for the U.S. Department of Energy under contract DE-AC06–76RLO 1830. Contact David Feller or Karen Schuchardt for further information.
[23] K. Raghavachari, G. W. Trucks, J. A. Pople, M. Head-Gordon, *Chem. Phys. Lett.* **1989**, *157*, 479.
[24] G. Tarczay, A. G. Császár, W. Klopper, H. M. Quiney, *Mol. Phys.* **2001**, *99*, 1769.
[25] a) A. D. Becke, *Phys. Rev. B* **1988**, *38*, 3098; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; d) S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200.
[26] A. G. Császár, *J. Am. Chem. Soc.* **1992**, *114*, 9569.
[27] C.-H. Hu, M. Shen, H. F. Schaefer III, *J. Am. Chem. Soc.* **1993**, *115*, 2923.
[28] A. G. Császár, *J. Mol. Struct.* **1995**, *346*, 141.
[29] A. G. Császár, *J. Phys. Chem.* **1996**, *100*, 3541.
[30] a) C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618; b) R. Krishnan, M. J. Frisch, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 4244.
[31] P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213.
[32] M. Head-Gordon, T. Head-Gordon, *Chem. Phys. Lett.* **1994**, *220*, 122.
[33] W. D. Allen, A. G. Császár, *J. Chem. Phys.* **1993**, *98*, 2983.
[34] R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165.
[35] Gaussian 98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
[36] INTDER2000 is a general program developed by W. D. Allen and co-workers which performs various vibrational analyses and higher-order nonlinear transformations among force field representations.
[37] W. D. Allen, A. G. Császár, V. Szalay, I. M. Mills, *Mol. Phys.* **1996**, *89*, 1213.
[38] A. R. Hoy, I. M. Mills, G. Strey, *Mol. Phys.* **1972**, *24*, 1265.
[39] H. H. Nielsen, *Rev. Mod. Phys.* **1951**, *23*, 90.
[40] I. M. Mills in *Molecular Spectroscopy: Modern Research*, *Vol. 1* (Eds.: K. N. Rao, C. W. Mathews), Academic Press, New York, **1972**, p. 115.
[41] D. Papousek, M. R. Aliev, *Molecular Vibrational-Rotational Spectra*, Elsevier, Amsterdam, **1982**.
[42] J. K. G. Watson in *Vibrational Spectra and Structure* (Ed.: J. R. Durig), Elsevier, Amsterdam, **1977**, Vol. *6, p. 1*.
[43] A. L. L. East, W. D. Allen, S. J. Klippenstein, *J. Chem. Phys.* **1995**, *102*, 8506.
[44] D. A. Clabo, Jr., W. D. Allen, R. B. Remington, Y. Yamaguchi, H. F. Schaefer III, *Chem. Phys.* **1998**, *123*, 187.
[45] W. D. Allen, Y. Yamaguchi, A. G. Császár, D. A. Clabo, Jr., R. B. Remington, H. F. Schaefer III, *Chem. Phys.* **1990**, *145*, 427.
[46] A. L. L. East, C. S. Johnson, W. D. Allen, *J. Chem. Phys.* **1993**, *98*, 1299.
[47] W. Thiel, G. Scuseria, H. F. Schaefer III, W. D. Allen, *J. Chem. Phys.* **1988**, *89*, 4965.
[48] K. Aarset, A. G. Császár, E. L. Sibert III, W. D. Allen, H. F. Schaefer III, W. Klopper, J. Noga, *J. Chem. Phys.* **2000**, *112*, 4053.
[49] ANHARM is a FORTRAN program written for VPT2 analyses, Y. Yamaguchi and H. F. Schaefer III, Center for Computational Chemistry, University of Georgia, Athens, GA 30602 (USA).
[50] See program descriptions in K. Sarka, J. Demaison in *Computational Molecular Spectroscopy* (Eds.: P. Jensen, P. R. Bunker), Wiley, Chichester, **2000**, pp. 255 – 303.
[51] L. Hedberg, I. M. Mills, *J. Mol. Spectrosc.* **2000**, *203*, 82.
[52] Supporting Information for this article is available on the WWW under http://www.chemeurj.org/. The file can also be retrieved at http://theop11.chem.elte.hu.
[53] A. G. Császár, G. Fogarasi, *J. Chem. Phys.* **1988**, *89*, 7646.
[54] J. Demaison, **2004**, personal communication.
[55] S. Wolfram, *The Mathematica Book*, 5th ed., Wolfram Media, **2003**.

Received: February 4, 2004