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The equilibrium molecular structure of 3-cyanopyridine according to gas-phase electron diffraction and microwave data and the results of quantum-chemical calculations

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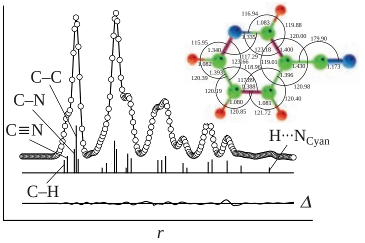
The equilibrium structure of the 3-cyanopyridine molecule was experimentally obtained for the first time. The calculations performed by the CCSD(T) method show a good agreement with the results of the electron diffraction and microwave data analysis.



3-Cyanopyridine (3-CNP), a precursor of nicotinamide (niacinamide), is widely used in pharmaceutical industry. Nevertheless, the accurate structure of this molecule in a gas phase is not known so far. Its partial structure was roughly estimated from microwave (MW) spectroscopic data,[1,2] whereas a detailed structural study was carried out only in a crystalline phase by X-ray diffraction (XRD).[3] The recently published results of the quantum-chemical (QCh) study[4] were computed only at the level of density functional theory [B3LYP/6-311++G(d,p)].

In this work, we carried out a gas electron diffraction (GED) study of the 3-CNP molecule (Figure 1).[†] The conditions of the GED experiments at the long (LD) and short (SD) nozzle-to-film distances are described in Table S1 (see Online Supplementary Materials). The total intensities of electron scattering $I^{\text{tot}}(s)$ were obtained as a result of their primary processing by the Plate program.[5] The intensity curves $I^{\text{tot}}(s)$ are presented in Table S2 and Figure S1 (see Online Supplementary Materials). For structural analysis, in addition to the GED data, the experimental values of the ground-state rotational constants $B_0^{(k)}$ for the 3-CNP molecule,[2] its vibrational spectra,[6] and the results of high-quality QCh calculations were also used. Small differences in the structural parameters refined in the same group were assumed at the values taken from the high-level coupled-cluster computations, CCSD(T).[7,8] The structure optimization at the CCSD(T) level was carried out with the cc-pwCVTZ basis set[9] taking into account all electron correlation effects (AE). Structural changes in the computed structure due to the enlargement of basis set from triple- to quadruple-ζ quality, $\Delta r_{\text{T}\to\text{Q}}$, were estimated at the MP2 level,[10] $\Delta r_{\text{T}\to\text{Q}} = r_{\text{e}}(\text{MP2\_AE/cc-pwCVQZ}) - r_{\text{e}}(\text{MP2\_AE/cc-pwCVTZ})$. Thus, the final *ab initio* structure was estimated as

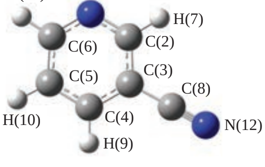


Figure 1 Atom numbering of 3-CNP.

$$r_{\text{e}}(\text{CCSD(T)\_AE/cc-pwCV(T}\to\text{Q)Z}) = r_{\text{e}}(\text{CCSD(T)\_AE/cc-pwCVTZ}) + \Delta r_{\text{T}\to\text{Q}}. \qquad (1)$$

The results are given in Table 1. The accuracy of such computations for molecules consisting of first-row elements was estimated previously to be very high (a few thousandths of angstrom unit for the bond lengths and a few tenths of degree for the bond angles).[11–14] In the course of solving the vibrational problem, the quadratic and cubic force fields calculated at the MP2(frozen core) level with the cc-pVTZ basis set[15] were used after scaling according to the Pulay technique.[16] The scaling was performed by fitting to the frequencies of the experimental vibrational spectra[6] after a reassignment. All the QCh calculations were carried out at the University of Ulm using the Molpro[17,18] and Gaussian 09[19] programs.

The joint structural analysis was carried out using the Symm/Disp/Eldiff/Large software package.[20–25] The analysis procedure implemented in this package implies a refinement of intramolecular potential function parameters (equilibrium geometry and harmonic and anharmonic force constants) which combine the data of the methods used.[26,27] Apart from harmonic shrinkages [Δr_{ij}(harm)] and centrifugal rotational corrections [Δr_{ij}(rot)], the technique allowed us to reliably take into account the contributions of kinematic

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[†] The sample with 98% purity was purchased from Sigma-Aldrich and used without further purification. The diffraction patterns were obtained on an EG-100M apparatus at the M. V. Lomonosov Moscow State University.

Table 1 Equilibrium molecular structure, r_e, of 3–CNP from the joint analysis of GED+MW data in comparison with structures from QCh computations and in the solid state (distances in Å, angles in degrees, atom numbering in Figure 1).

Bond distance, angle	MP2_AE/CVTZ[a]	MP2_AE/CVQZ[a]	CCSD(T)_AE/CVTZ[a]	CCSD(T)_AE/CV(T→Q)Z[b]	GED + MW[c]	XRD[3]
N(1)–C(2)	1.3306	1.3285	1.3343	1.3323	1.330(1)[d]	1.3348(11)
C(2)–C(3)	1.3953	1.3939	1.4004	1.3990	1.397(1)[d]	1.3919(12)
C(3)–C(4)	1.3915	1.3901	1.3948	1.3934	1.391(1)[d]	1.3856(12)
C(4)–C(5)	1.3833	1.3818	1.3850	1.3834	1.381(1)[d]	1.3755(12)
C(5)–C(6)	1.3884	1.3869	1.3925	1.3910	1.389(1)[d]	1.3844(13)
C(6)–N(1)	1.3356	1.3336	1.3396	1.3376	1.336(1)[d]	1.3370(11)
C(3)–C(8)	1.4266	1.4250	1.4350	1.4334	1.432(2)[e]	1.4303(12)
C(8)≡N(12)	1.1680	1.1663	1.1605	1.1587	1.157(2)[e]	1.1499(12)
C(2)–H(7)	1.0811	1.0805	1.0826	1.0820	1.088(17)[f]	
C(4)–H(9)	1.0792	1.0785	1.0810	1.0803	1.086(17)[f]	
C(5)–H(10)	1.0788	1.0781	1.0805	1.0797	1.086(17)[f]	
C(6)–H(11)	1.0809	1.0802	1.0824	1.0817	1.088(17)[f]	
C(6)N(1)C(2)	117.36	117.57	117.21	117.42	116.5(3)[g]	117.21(7)
N(1)C(2)C(3)	123.13	122.98	123.48	123.33	124.0(5)[h]	122.53(8)
C(2)C(3)C(4)	119.03	119.06	118.51	118.54	118.5[i]	119.49(8)
C(3)C(4)C(5)	117.90	117.91	118.32	118.34	118.2(1)[g]	118.13(8)
C(4)C(5)C(6)	118.97	118.98	118.89	118.90	118.8(1)[g]	118.76(8)
N(1)C(5)C(6)	123.61	123.50	123.59	123.48	124.1(5)[h]	123.87(8)
C(8)C(3)C(2)	120.00	119.98	120.24	120.22	120.3(1)[j]	
C(8)C(3)C(4)	121.97	120.96	121.25	121.24	121.3(1)[j]	
H(7)C(2)N(1)	116.99	117.06	116.74	116.81	115.6(23)[g]	
H(7)C(2)C(3)	119.88	119.96	119.78	119.86	120.4(23)[k]	
H(9)C(4)C(3)	120.39	120.38	120.25	120.23	120.3(1)[g]	
H(9)C(4)C(5)	121.71	121.71	121.43	121.43	121.5(1)[g]	
H(10)C(5)C(4)	120.84	120.83	120.87	120.86	120.9[i]	
H(10)C(5)C(6)	120.19	120.19	120.25	120.25	120.3(1)[g]	
H(11)C(6)C(5)	120.39	120.45	120.45	120.52	121.1(23)[k]	
H(11)C(6)N(1)	116.00	116.05	115.96	116.01	114.8(24)[g]	
C(3)C(8)N(12)[l]	180.10	180.09	180.08	180.07	180.5(1)	179.53(11)

[a] The basis sets cc–pwCVTZ and cc–pwCVQZ are abbreviated by CVTZ and CVQZ, respectively. [b] Estimated according to equation (1). [c] Uncertainties of the last significant digits are 3σ for distances and 2σ for angles. [d,e,f,h,j,k] Parameters indicated by the same subscript were fitted in one group with differences fixed at the values of the CCSD(T)_AE/cc–pwCV(T→Q)Z structure. [g] Dependent parameter. [i] Assumed at the value from CCSD(T)_AE/cc–pwCV(T→Q)Z calculation. [l] Cyano group is bend away from the N(1) atom.

(nonlinear kinematic effects) and dynamic anharmonicity [Δr_{ij}(kin) and Δr_{ij}(dyn)] when using scaled quadratic and cubic QCh force fields. The magnitude of all these corrections at the experimental temperature and the resulting values of $\Delta r = r_{g,ij} - r_{e,ij}$ are given in Table S3 (see Online Supplementary Materials) together with calculated root mean squares amplitudes, u_{ij}.

The formerly suggested straightforward technique[21] of handling MW data in terms of equilibrium molecular geometry allows one to calculate the $B_0^{(k)} - B_e^{(k)}$ corrections to the ground-state $B_0^{(k)}$ constants with a sufficient accuracy. The rotational term in the quantum mechanical Hamiltonian for a vibrating rotor[28,29] is averaged over all normal molecular vibrations. For the ground vibrational state, the calculation of the $B_0^{(k)} - B_e^{(k)}$ corrections takes into account all vibrational contributions similar to those listed above for internuclear distances, as well as the rotation–vibration interaction.

The results of our QCh calculations allowed us to perform structural analysis in a small vibration approximation (the frequencies of all fundamental vibrations were about 150 cm^{-1} or higher) with C_s symmetry assumed for the equilibrium configuration of the 3-CNP molecule. The background lines $I^b(s)$ (see Table S2 and Figure S1, Online Supplementary Materials) were initially based on the results of these calculations and corrected during the analysis. The agreement between the theoretical and experimental $sM(s)$ molecular intensities (Figure S2, Online Supplementary Materials), which was achieved as a result of structural analysis, is characterized by the *R*-factor of 3.96%. The radial distribution curves $f(r)$ are shown in Figure 2.

The weights of the MW rotational constants relative to the GED intensities were empirically adjusted to attain a balance between sufficiently accurate reproductions of the MW and GED experimental data. Errors in refined theoretical $B_0^{(k)}$ values depend on uncertainties in the $B_0^{(k)} - B_e^{(k)}$ corrections estimated as 5% of their magnitudes. As can be seen in Table 2, the calculated $B_0^{(k)}$ values are quite close to the experimental ones.

The equilibrium structure parameters determined by the joint analysis, r_e(GED + MW), are presented in Table 1 in comparison

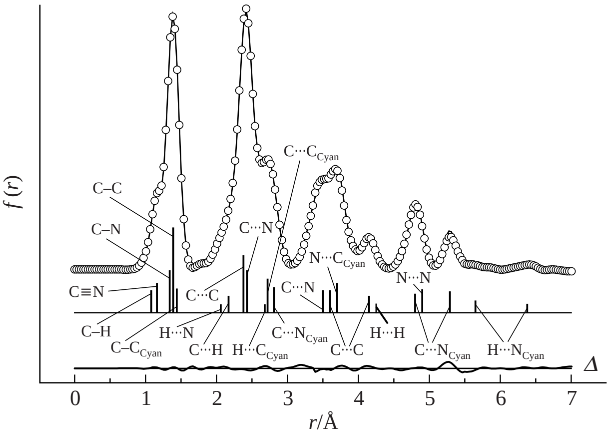

Figure 2 Experimental (open circles) and theoretical (solid line) radial distribution curves and their difference $\Delta = f^{\text{theor}}(r) - f^{\text{exp}}(r)$ for 3-CNP. Distribution of internuclear distances is indicated by vertical bars (for details, see Table S3, Online Supplementary Materials).

Table 2 Equilibrium ($B_e^{(k)}$) and ground-state ($B_0^{(k)}$) rotational constants of the parent isotopologue from the joint analysis of GED+MW data in comparison with experimental $B_0^{(k)}$(exp) rotational constants.

Rotational constant	$B_e^{(k)}$/MHz	$B_0^{(k)} - B_e^{(k)}$/MHz	$B_0^{(k)}$/MHz	$B_0^{(k)}(\text{exp})^2$/MHz
A	5874.2	–49.2(25)	5825.0	5823.01(5)
B	1577.2	–6.2(3)	1571.0	1571.34(3)
C	1243.4	–6.1(3)	1237.3	1237.17(3)

with the results of our QCh calculations and the XRD data.[3] The computed structure, CCSD(T)_AE/cc-pwCV(T→Q)Z, reproduces well both the r_e(GED + MW) values and the XRD data. The latter reflects the weak effect of intermolecular interactions in the crystalline phase of 3-CNP. The deviations of the r_e(GED + MW) bond lengths from their best QCh estimates reach 0.0020 Å for the bonds between heavy atoms and 0.0065 Å for the C–H bonds. For the bond angles, the largest discrepancies are about 1°. As usual, the distances to hydrogen atoms could not be determined precisely due to low electron scattering by light atoms, and the uncertainties in the dependent parameters are somewhat larger than those in independent ones due to error propagation.

In conclusion, the equilibrium structure of a molecule of 3-cyanopyridine widely used in pharmaceutics was first experimentally obtained. The accumulation of structural data contributes to the establishment of qualitative and quantitative structure–property relationship and opens a way to the purposeful synthesis of medicines.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.002.

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