

On the Structure of the Peptide Linkage. The Structures of Formamide and Acetamide at -165°C and an *ab initio* Study of Formamide, Acetamide, and *N*-Methylformamide

TOR OTTERSEN

Department of Pharmacy, University of Oslo, Oslo 3, Norway

The crystal and molecular structures of formamide and rhombohedral acetamide have been refined using X-ray data sets collected at -165°C . The principal bond lengths found are, formamide: CO, 1.243(2) Å, CN, 1.319(2) Å; acetamide: CO, 1.243(4) Å, CN, 1.336(4) Å, CC, 1.510(3) Å. The influence of hydrogen bonding on the conjugated N—C=O fragment is evident. A series of *ab initio* calculations has been performed on acetamide and *N*-methylformamide. The results are compared with those obtained earlier for formamide.

In a recent series of theoretical investigations utilizing *ab initio* methods (see Ref. 1 and references therein) the effect of hydrogen bonding has been studied for the conjugated peptide linkage, using formamide as a model compound. The results obtained (*i.e.* an increased conjugation over the N—C=O fragment expressed as a shortening of the N—C bond and a lengthening of the C—O bond) are in good agreement with those found in a series of structure investigations of 3,6-pyridazinediones and related compounds (see Ref. 2 and references therein).

The crystal structure of formamide has been determined earlier by film methods.³ However, the accuracy of this investigation is relatively poor, and a new structure determination was, therefore, carried out in order to study the effect of hydrogen bonding on the structural parameters. A series of structure investigations in the gaseous state of formamide and related molecules has recently been published.⁴⁻⁷ In these investigations significant differences were found between the C—N and C—O bond lengths obtained for formamide⁸ and acet-

amide,⁵ and between *N*-methylformamide⁷ and *N*-methylacetamide.⁴ Similar differences (*i.e.* a lengthening of both bonds upon substitution at C) were found between the results obtained in the crystal structure determinations of *N,N'*-diformylhydrazine⁹ and succinic hydrazide.² It was, therefore, decided to carry out a structure investigation of acetamide within the same experimental framework as for formamide (for earlier crystal structure determinations of acetamide see Refs. 9—11).

In order to study changes in electron populations of the N—C=O fragment induced by substitution, a series of *ab initio* calculations was performed on acetamide and *N*-methylformamide to complement earlier calculations on formamide.^{1,12} It was further decided to optimize the C—C, C—N and C—O bonds in order to see if the changes found experimentally upon substitution are reflected by the *ab initio* method.

EXPERIMENTAL AND CALCULATIONS

A. X-Ray diffraction

A computer-controlled Syntex P1 four circle diffractometer (at the Dept. of Chemistry) with graphite monochromatized MoK α radiation and equipped with an Enraf-Nonius liquid nitrogen cooling device (modified by H. Hope), was utilized in the determination of unit cell parameters and the collection of intensity data. For both data sets the temperature at the crystal site was -165°C . All computer programs utilized are part of a local assembly of computer

Table 1. Crystal data at -165°C .

Parameter	Formamide CH_3NO	Acetamide $\text{C}_2\text{H}_5\text{NO}$
Space group	$P2_1/c$	$R3c$
a (Å)	3.613(3)	11.516(2)
b (Å)	9.053(6)	
c (Å)	8.419(4)	13.091(2)
β ($^{\circ}$)	125.39(4)	
V (Å ³)	224.5	1503.4
Z	4	18
M (amu)	45.04	59.07
D_{calc} (g/cm ³)	1.332	1.174
$F(000)$	96	576

programs which is described in Ref. 13. Atomic scattering factors used were those of Doyle and Turner¹⁴ for oxygen, nitrogen and carbon, and of Stewart *et al.*¹⁵ for hydrogen.

I. Formamide. A crystal of dimensions $0.6 \times 0.6 \times 0.2$ mm, grown by slow evaporation of an ethyl alcohol solution at -30°C (the air was kept free from water by use of CaCl_2), was used for all experiments. Cell constants and their standard deviations were determined by a least-squares treatment of the angular coordinates of fifteen symmetry-independent reflections with 2θ -values between 39 and 55° . Three-dimensional intensity data were recorded using the ω scanning mode with scan speed variable from 2 to 8°min^{-1} , depending on the peak intensity of the reflection. Background counting time was $0.6 \times$ scan time. The varia-

tions in the intensities of three standard reflections which were remeasured after every sixty reflections were random and less than three times their standard deviations. Accordingly no corrections were applied for these variations.

The estimated standard deviations were taken as the square root of the total counts with a 2% addition for experimental uncertainties. Of the 822 symmetry-independent reflections measured ($2\theta_{\text{max}} = 60^{\circ}$) 721 had intensities larger than 2.5 times their standard deviations. These were regarded as "observed" reflections, and the remaining were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects. Crystal data are given in Table 1.

Least-squares refinements, utilizing the positional parameters found by Ladell and Post³ as starting values, of all positional parameters, anisotropic thermal parameters for nonhydrogen atoms, and isotropic thermal parameters for hydrogen atoms, using all observed data, converged to a weighted R_w of 0.088 and a conventional R of 0.070. In order to reduce the influence of valence electrons on the refined parameters, all reflections with $\sin \theta/\lambda < 0.5$ were excluded from the refinement, leaving 494 F_o 's. Least-squares refinement of all parameters involving nonhydrogen atoms resulted in a weighted R_w of 0.071, a conventional R of 0.061 and an R for the total data set of 0.084. Parameters obtained in this refinement for nonhydro-

Table 2. Fractional atomic coordinates and thermal parameters with estimated standard deviations for nonhydrogen atoms. The temperature factor is given by $\exp\{-2\pi^2[U_{11}(a^*h)^2 + U_{22}(b^*k)^2 + U_{33}(c^*l)^2 + U_{12}(a^*b^*)hk + U_{13}(a^*c^*)hl + U_{23}(b^*c^*)kl]\}$

Atom x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}	
Formamide									
O	.7173(4)	-.0688(1)	.2484(1)	.0367(6)	.0163(5)	.0365(6)	.0032(3)	.0217(4)	.0053(3)
N	.4208(4)	.1570(1)	.1190(1)	.0342(7)	.0150(5)	.0361(7)	.0030(3)	.0209(5)	.0010(3)
C	.5929(4)	.0568(1)	.2583(1)	.0265(6)	.0176(6)	.0311(6)	-.0013(3)	.0158(5)	-.0008(3)
Acetamide									
O	.2403(2)	-.0024(1)	-.0014(1)	.0230(9)	.0207(8)	.0322(8)	.0097(6)	-.0037(6)	.0032(5)
N	.3328(2)	-.1009(2)	.0915(1)	.0212(9)	.0223(9)	.0262(8)	.0086(6)	-.0015(6)	.0036(6)
C	.4758(2)	.1281(2)	.0350(2)	.0207(9)	.0223(9)	.0269(10)	.0037(6)	-.0010(7)	.0008(7)
Cl	.3401(2)	.0024(1)	.0395(2)	.0194(10)	.0189(9)	.0196(7)	.0078(5)	.0008(7)	-.0010(7)

Table 3. Fractional atomic coordinates and isotropic thermal parameters with estimated standard deviations for hydrogen atoms. Results from the refinements using all observed data.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
Formamide				
H1	.398(7)	.140(3)	.007(3)	2.9(4)
H2	.341(7)	.293(3)	.154(3)	3.5(5)
H3	.611(7)	.087(2)	.362(3)	2.4(4)
Acetamide				
H1	.254(4)	-.173(3)	.100(3)	2.8(6)
H2	.402(3)	-.097(2)	.120(2)	.6(4)
H4	.481(4)	.193(4)	.095(3)	4.1(8)
H5	.544(4)	.108(5)	.047(3)	4.0(8)
H6	.484(4)	.187(4)	-.019(3)	3.5(7)

gen atoms are given in Table 2, and parameters for hydrogen atoms, from the refinement using all observed data, are listed in Table 3. The molecular parameters obtained (Fig. 2) are in agreement with the earlier results.³

II. Acetamide. A crystal of dimensions $0.3 \times 0.3 \times 0.4$ mm, grown from the melt, was used for all experiments. The analysis of the angular coordinates of fifteen reflections (the computer program used is part of the diffractometer program library) with 2θ -values between 7 and 25° indicated the rhombohedral space group $R\bar{3}c$ ($R3c$). This is rather surprising since metastable orthorhombic crystals (space group $Pccn$) are usually formed by cooling of the melt.¹¹ Later, several crystals grown from melts of acetamide were examined, and in all cases the rhombohedral system was found. Cell constants and their standard deviations were determined by a least-squares treatment of fifteen symmetry-independent reflections with 2θ -values between 19 and 38° . Three-dimensional intensity data were recorded using the ω - 2θ scanning mode with scan speed variable from 2 to 8° min^{-1} , depending on the peak intensity of the reflections. All reflections which had integrated counts of less than 15 cps, determined in a 2 s scan over the peak, were not measured. The intensities of three standard reflections, which were remeasured after every fifty reflections, showed a small regular decrease (to about 0.97 of their initial

value). Accordingly the intensities were corrected for this decrease.

The estimated standard deviations were taken as the square root of the total counts with a 2 % addition for experimental uncertainties. Of the 465 symmetry-independent reflections measured ($2\theta_{\text{max}} = 60^\circ$), all had intensities larger than twice their standard deviations and were used in the refinements. The intensities were corrected for Lorentz and polarization effects. Crystal data are given in Table 1.

Least-squares refinements, utilizing the positional parameters found by Denne and Small¹⁰ as starting values, of all positional parameters, anisotropic thermal parameters for nonhydrogen atoms, and isotropic thermal parameters for hydrogen atoms, converged to a weighted R_w of 0.054 and a conventional R of 0.043. In order to reduce the influence of valence electrons on the refined parameters, all reflections with $\sin \theta/\lambda < 0.5$ were excluded from the refinement, leaving 282 F_o 's. Least-squares refinement of all parameters involving nonhydrogen atoms resulted in a weighted R_w of 0.044, a conventional R of 0.038 and an R for the total data set of 0.045. Parameters obtained in this refinement for nonhydrogen atoms are given in Table 2, and parameters for the hydrogen atoms, from the refinement using all observed data, are listed in Table 3. The molecular parameters obtained (Fig. 2) are in good agreement with those found earlier.¹⁰ Listings of observed and calculated structure factors for both structure determinations are available upon request from the author or the Department of Chemistry, University of Oslo, Oslo 3, Norway. Standard deviations in molecular parameters were calculated from the correlation matrix ignoring standard deviations in cell parameters.

B. Theoretical calculations

The calculations were carried out using the program MOLECULE¹⁶ which solves the Roothan-Hall equations for a Gaussian type basis. A $(7s3p/4s)$ basis set¹⁷ contracted to $(4s2p/2s)$ was applied. In all cases a scale factor of 1.2 was applied¹⁸ for the exponents of the hydrogen s functions. This basis set has been used previously for studies like the present one and has turned out to be adequate.^{1,12,17} A further discussion of this basis set compared

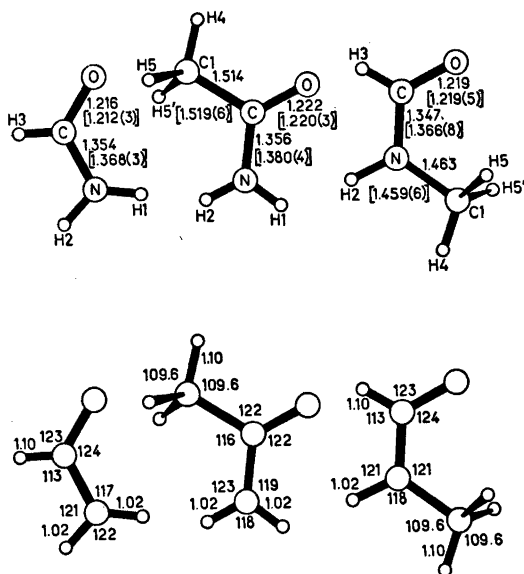


Fig. 1. Optimized (top) and assumed molecular parameters from the *ab initio* calculations. The numbers in brackets are those found in the gaseous state by electron diffraction (see Refs. 5–7) with estimated limits or error.

with larger ones may be found in Ref. 12.

The molecules were assumed to have a plane of symmetry according to Fig. 1, where also the labelling of the atoms is indicated, and assumed structural parameters are given. All results from theoretical calculations for formamide are taken from Ref. 12.

The CO (R_{CO}), CN (R_{CN}) and CC (R_{CC}) bonds were optimized simultaneously for acetamide and *N*-methylformamide. The optimized bond lengths are given in Fig. 1, and the optimized total energies obtained are listed in Table 4.

Only small differences are found in the R_{CO} and R_{CN} values of formamide and acetamide. A

Table 4. Total energies (a.u.) for the optimized molecules.

Molecule	Total energy (a.u.)
Formamide	–168.68145
Acetamide	–207.67915
<i>N</i> -Methylformamide	–207.66671

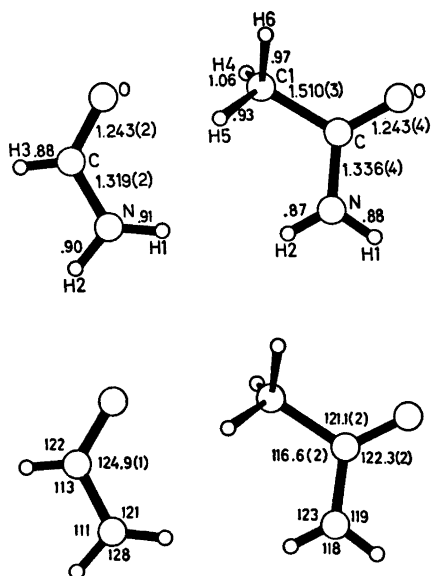


Fig. 2. Bond lengths (Å) and bond angles (°) with estimated standard deviations. Positional parameters used for non-hydrogen atoms are those from the refinement using only high-angle data. Standard deviations in dimensions involving hydrogen atoms (positional parameters used for hydrogen atoms are those from the refinement using all observed reflections) are about 0.03 Å and 2°.

small lengthening of the CO bond upon introduction of a methyl group at C is indicated, in agreement with the results obtained by electron diffraction studies.^{4–7} (see also Fig. 1, where some of these results are given). However, the significant lengthening of the CN bond upon substitution found in a series of structure investigations,^{4–9} (see also the present results for formamide and acetamide, which are given in Fig. 2), is not reflected by the *ab initio* calculations. Also, the shortening obtained by the optimization procedure, of the CN bond in *N*-methylformamide compared with that of formamide, is not found in the experimental results.^{4–7}

Stretching force constants and some of the interdependencies in the force fields are given in Table 5. Only small differences are found between the three molecules. However, it is interesting to note that for both acetamide and *N*-methylformamide F_{CO} has increased and F_{CN} decreased compared to formamide.

Table 5. Stretching force constants in mdyn/Å, and regression coefficients.^a

	Form- amide	Acet- amide	M-ethyl-N form- amide
F_{CO}	13.0	13.8	13.6
F_{CN}	8.0	7.7	7.6
F_{CC1}		4.4	
F_{NC1}			5.7
$\Delta R_{CO}^{\circ}/\Delta R_{CN}$	-0.100	-0.090	-0.100
$\Delta R_{CO}^{\circ}/\Delta R_{CC1}$		-0.040	
$\Delta R_{CO}^{\circ}/\Delta R_{CN1}$			0
$\Delta R_{CN}^{\circ}/\Delta R_{CO}$	-0.160	-0.170	-0.170
$\Delta R_{CN}^{\circ}/\Delta R_{CC1}$		-0.040	
$\Delta R_{CN}^{\circ}/\Delta R_{NC1}$			-0.010
$\Delta R_{CC1}^{\circ}/\Delta R_{CO}$		-0.125	
$\Delta R_{CC1}^{\circ}/\Delta R_{CN}$		-0.075	
$\Delta R_{NC1}^{\circ}/\Delta R_{CO}$			0
$\Delta R_{NC1}^{\circ}/\Delta R_{CN}$			-0.020

^a The regression coefficients, $c = \Delta R_A^{\circ}/\Delta R_B$, are given such that a forced change ΔR_B in (each of) the bond length(s) induces a shift $\Delta R_A^{\circ} = c\Delta R_B$ in the equilibrium value of R_A .

DISCUSSION

Bond lengths and bond angles obtained in the X-ray structure analyses are listed in Fig. 2, where the labelling of the atoms is indicated. The molecules are planar (see Table 6, where deviations from least-squares planes are given). When the bond lengths are compared with those obtained in the gaseous state^{5,6} (see also Fig. 1, where these bond lengths are listed), the effect of hydrogen bonding on the N=C=O fragment is evident. Both the formamide and acetamide molecules participate in four hydrogen bonds. (Parameters for these bonds are given in Table 7). The C-N bond is shortened by 0.04–0.05 Å and the C-O bond is length-

Table 6. Deviations from least squares planes through the nonhydrogen atoms.

Atom	Deviation (Å × 10 ³)	
	Formamide	Acetamide
O	0	-3
N	0	-3
C	0	9
C1		-3
H1	47	-57
H2	-40	9
H3	-8	

ened by 0.02–0.03 Å upon formation of the hydrogen bonds. This increased conjugation caused by hydrogen bonding from nitrogen to oxygen is generally found for these N=C=O systems.^{2,8} The C-N length obtained for formamide in the present work [1.319(2) Å] is very close to those found for pyridazine hydrochloride¹⁹ [1.314(5) Å], and is far shorter than those obtained for 3,6-pyridazinediones (Ref. 2 and references therein). *Ab initio* calculations on formamide^{12,20} indicate a significant transfer of electron density from the C-O bond to the C-N bond upon dimerization *via* hydrogen bonding.

However, the $\angle NCO$ is unaffected by this increased conjugation. The values found for this parameter in formamide and acetamide in the present work are the same as those obtained in the gaseous state.^{5,6} The anomalous $\angle CNH2$ in formamide (111°) is probably caused by the hydrogen bond formation.

The lengthening of the C-N bond in acetamide compared to formamide must be caused by the introduction of a methyl group at C, and has been noted earlier.^{4-7,2,8} Mulliken type population analyses (see Table 8) indicate that this substitution results in a decreased population at C and increased overlap populations in both the C-O and C-N bonds. The C-C1 bond is about 0.01 Å shorter in the crystal than in the gas⁵ probably because of the increased conjugation over the N=C=O fragment caused by the hydrogen bonding. A similar C-C bond is found in cyclic succinhydrazide² [1.509(1) Å].

Results from Mulliken type population analyses for formamide, acetamide and *N*-methylformamide are listed in Table 8. It is interesting to note how the overlap population of the C-N bond varies with the optimized bond lengths. For *N*-methylformamide, and also diformylhydrazine¹² (C-N length: 1.341 Å, overlap population 0.165), a decreasing overlap population, as compared with that found for formamide, results in a shortened bond distance, while for acetamide, where a small increase in the C-N bond length is indicated, a larger overlap population is found. However, in the case of the hydrogen bonded formamide structures^{1,12,20} which have been studied by *ab initio* calculations, a different situation is found. In these complexes a shortening of the C-N bond, caused by the formation of hydrogen

Table 7. Hydrogen bond parameters. The coordinates of the acceptor atom are related to those given in Table 2 by the symmetry operation given.

Donor	Acceptor	Symmetry operation	N...O (Å)	H...O (Å)	N-H...O (°)	C-O...N (°)
Formamide						
N-H1	O	$1-x, \frac{1}{2}+y, -z$	2.944(2)	2.04	170	118.1(1)
N-H2	O	$1-x, -y, -z$	2.881(2)	1.99	169	127.7(1)
Acetamide						
N-H1	O	$1/3-x, -1/3+y, 1/6+z$	2.913(3)	2.06	162	123.8(2)
N-H2	O	$1/3+x, -1/3+x-y, 1/6+z$	2.883(3)	2.02	172	128.9(2)

bonds, leads to an increased overlap population. In all structures studied the gross atomic population of O has increased with increasing C-O length, and, except in acetamide, the overlap population of the C-O bond has decreased with increasing C-O length. Also, the gross atomic population of C obtained for acetamide is much smaller (by 0.12-0.15) than those found for the other molecular systems

Table 8. Gross atomic populations, overlap populations and dipole moments (D) of the optimized molecules. The geometries may be found in Fig. 1.

Atom	Formamide	Acetamide	N-Methylformamide
Gross atomic populations			
O	8.551	8.560	8.561
C	5.456	5.306	5.436
N	7.863	7.865	7.870
C1		6.643	6.273
H1	.646	.648	
H2	.655	.659	.653
H3	.829		.825
H4		.755	.810
H5		.782	.786
Overlap populations			
C-O	1.163	1.252	1.145
C-N	.257	.279	.206
C-C1		.475	
N-C1			.245
N-H1	.602	.619	
N-H2	.621	.632	.633
C-H3	.795		.809
C1-H4		.722	.772
C1-H5		.723	.779
Dipole moments (D)			
	4.136	4.196	4.221

containing the N-C=O linkage which have been studied (Ref. 1 and references therein).

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