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Methyl Group Conformation-Determining Intermolecular C—H···O Hydrogen Bonds: Structure of *N*-Methyl-2-pyrrolidone

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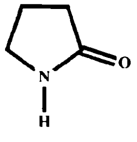
Abstract

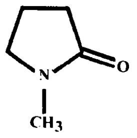
The structure of *N*-methyl-2-pyrrolidone (NMP; 1-methyl-2-pyrrolidinone) was determined at 168 K. Crystal data: m.p. 249 K, monoclinic $P2_1/c$, $a = 6.221(3)$, $b = 12.076(2)$, $c = 7.529(4)$ Å, $\beta = 111.03(2)°$, $V = 527.9(4)$ Å^3, $Z = 4$, $D_x = 1.247$ Mg m^{-3}, $\mu = 0.082$ mm^{-1}, $R = 0.058$ for 1190 unique reflections. It adopts a slightly puckered ring conformation in the solid state, which is intermediate between a twist and an envelope conformation. The *N*-methyl group takes part in two almost linear intermolecular C—H···O hydrogen bonds to neighbouring keto groups [d(H···O) = 2.57 (2)/2.65 (2) Å, d(C···O) = 3.552 (2)/3.482 (2) Å, angle (C—H···O) = 160 (1)/148 (2)°], which cause a notable deviation from its usually preferred conformation with one C—H bond being almost eclipsed to the adjacent N—C amide bond. These findings are substantiated by force-field and high-level *ab initio* calculations on isolated NMP molecules.

1. Introduction

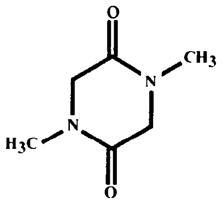
2-Pyrrolidone and *N*-methyl-2-pyrrolidone (NMP) are among the smallest cyclic amides (lactams) possible. Due to their cyclic nature, the conformation about their amide (peptide) bonds is reversed with respect to that found in open-chain amides, as *e.g.* in peptides. In the latter a *trans* conformation of the fragment C—N(H)—C(O)—C (with partial double-bond character of the central amide bond) is usually observed, while in small cyclic molecules an amide bond can only be accommodated for in a *cis* conformation. Despite their similarity to cyclic peptides of biological importance, no experimental determinations of the molecular structures of pyrrolidone or (pure) NMP seem to have been reported. Previous structure determinations of NMP have been carried out, however, but were undertaken on molecules which either had co-crystallized with or were hydrogen-bonded to other molecules (Carrell, Glusker, Job & Bruice, 1977; Peters, Ott & von Schnering, 1982*a*,*b*,*c*; Behmel & Weber, 1984; Langer, Huml & Zachová, 1984; Haller, Rheingold & Brill, 1985; Kinoshita, Shimoi & Ouchi, 1986; Mizuguchi & Rihs, 1992). Also, the structure of NMP coordinated to metal atoms has already been determined (Churchill & Rotella, 1979; Williamson, Prosser-McCartha, Mukundan Jr & Hill, 1988). Especially in the latter case the molecular structure of NMP should be severely biased by the metal coordination, while co-crystallized NMP was found to be severely disordered in some crystal structure determinations, thus preventing the extraction of reliable structural data.



2-Pyrrolidone



N-Methyl-2-pyrrolidone (NMP)



N,*N*′-Dimethyl-diketopiperazine

Computational studies on pyrrolidones indicate almost planar molecules with all dihedral angles being less than 6° (Warshel, Levitt & Lifson, 1970; Treschanke & Rademacher, 1985). One *ab initio* study of 2-pyrrolidone on the 3-21G level indicates an envelope conformation with a flap angle of 27.4°, however (Riggs, 1985). A liquid- and gas-phase IR and Raman spectroscopic study of these molecules assumed planar rings and for NMP it was stated that any deviation from strict m (C_s) symmetry would be inconsistent with its Raman spectrum (McDermott, 1986).

A second point of interest arises when the conformation of the *N*-methyl group in NMP with respect to the ring atoms and the carbonyl O atom is considered. Whereas the methyl conformation along Csp^3—CH$_3$ bonds is found to be almost invariably staggered, that

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along Csp^2—CH_3 bonds is more favorable when a C—H bond is eclipsed with respect to an adjacent double bond, as is the case in propene (Tokue, Fukujama & Kuchitsu, 1973) or acetaldehyde (Kilb, Lin & Wilson, 1957; Iijima & Kimura, 1969). In NMP the *N*-methyl group is adjacent to the amide linkage, a partial double bond, which similarly might lead to an energy minimum in an eclipsed NC—H/N═C conformation. For NMP previous studies indicate a very low barrier of rotation around the N—CH_3 single bond, however (McDermott & Strauss, 1972).

In an attempt to clarify these subtle but important conformational details (ring conformation and methyl group orientation) we determined the molecular structure of NMP in the solid state. Surprisingly, our structure determination reveals two intermolecular C—H···O hydrogen bonds between the *N*-methyl group and keto O atoms of neighbouring molecules. On the basis of all existing structural evidence and in agreement with the available energetic data, these C—H···O hydrogen bonds clearly induce the methyl group to deviate from its nearly eclipsed minimum energy conformation. Particularly important evidence for this comes from high-level *ab initio* calculations on isolated NMP molecules.

2. Experimental

2.1. *X-ray structure determination*

Crystals of NMP (m.p. 249 K) were grown directly on the diffractometer at 230 K from frozen NMP enclosed in a glass capillary with 0.2 mm diameter. With a modified zone-melting device using focussed light as a heat source (Brodalla, Mootz, Boese & Osswald, 1985), a single crystal could be grown which filled the entire diameter of the capillary and was several mm long. Thereby the quality of the single crystal was monitored with photographic X-ray exposures. For the intensity measurements the single crystal was then further cooled to 168 K. The monoclinic cell symmetry was checked for high metrical symmetry by cell reduction, as were the final atomic coordinates. Exact cell dimensions were obtained by refinement on the Bragg angles of 25 reflections carefully centred on the diffractometer. Table 1 contains a summary of the crystal data and important numbers pertinent to intensity data collection and structure refinement.

Due to the peculiar form of the single crystal an empirical absorption correction was carried out, despite the very small absorption coefficient. Thereby ψ-scans at intervals of 10° around the diffraction vectors of nine selected reflections served to evaluate the transmission. The nine reflections were selected as to give most information about the single crystal shape and orientation. The repeated measurement of three standard reflections showed only random intensity fluctuations,

Table 1. *Experimental details*

Crystal data	
Chemical formula	C_5H_9NO
Chemical formula weight	99.134
Cell setting	Monoclinic
Space group	$P2_1/c$
a (Å)	6.221 (3)
b (Å)	12.076 (2)
c (Å)	7.529 (4)
β (°)	111.03 (2)
V (Å^3)	527.9 (4)
Z	4
D_x (Mg m^{-3})	1.247
Radiation type	Mo $K\alpha$
Wavelength (Å)	0.71069
No. of reflections for cell parameters	25
θ range (°)	14.0–21.4
μ (mm^{-1})	0.082
Temperature (K)	168 (2)
Crystal form	See text
Crystal diameter (mm)	0.2
Crystal colour	Colourless
Data collection	
Diffractometer	Enraf–Nonius CAD-4 four-circle
Data collection method	$\omega/2\theta$ scans
Absorption correction	Empirical, nine ψ scans
T_{min}	0.88
T_{max}	1.00
No. of measured reflections	3721, of which 107 were rejected
No. of independent reflections	1190
No. of observed reflections	980
Criterion for observed reflections	$F^2 > 2\sigma(F^2)$
R_{int}	0.07
θ_{max} (°)	27.32
Range of h, k, l	$-8 \rightarrow h \rightarrow 3$ $-15 \rightarrow k \rightarrow 15$ $-9 \rightarrow l \rightarrow 9$
No. of standard reflections	3
Frequency of standard reflections (min)	60
Intensity decay (%)	±1.8
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0466
$wR(F^2)$	0.1236
S	1.055
No. of reflections used in refinement	1190
No. of parameters used	100
H-atom treatment	All H-atom parameters refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0684P)^2 + 0.0681P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.008
$\Delta\rho_{max}$ (e Å^{-3})	0.197
$\Delta\rho_{min}$ (e Å^{-3})	−0.328
Extinction method	None
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Computer programs	
Data collection	*CAD*-4 (Enraf–Nonius, 1989)
Cell refinement	*CAD*-4 (Enraf–Nonius, 1989)
Cell reduction and cell setting	*DELOS* (Zimmermann & Burzlaff, 1985, *LePage* (LePage, 1982), *MiSSYM* (LePage, 1987) as incorporated in *PLATON* (Spek, 1990)
Data reduction and absorption correction	*MolEN* (Fair, 1990)
Structure refinement	*SHELXL93* (Sheldrick, 1993)
Molecular graphics	*ORTEPII* (Johnson, 1976); *SCHAKAL92* (Keller, 1992)
Preparation of material for publication	*SHELXL93* (Sheldrick, 1993); *PLATON* (Spek, 1990)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N	0.2255 (2)	0.3025 (1)	0.1672 (1)	0.027 (1)
O	−0.1406 (2)	0.3629 (1)	0.1131 (1)	0.038 (1)
C1	0.0006 (2)	0.2883 (1)	0.1369 (2)	0.025 (1)
C2	−0.0453 (2)	0.1653 (1)	0.1385 (2)	0.030 (1)
C3	0.1750 (2)	0.1097 (1)	0.1424 (2)	0.033 (1)
C4	0.3575 (2)	0.2002 (1)	0.2062 (2)	0.031 (1)
C5	0.3343 (2)	0.4101 (1)	0.1872 (2)	0.034 (1)

Table 3. *Selected geometric parameters (Å, °)*

N—C1	1.345 (2)	C3—C4	1.524 (2)
N—C5	1.447 (1)	C5—O^{i}	3.552 (2)
N—C4	1.454 (1)	C5—O^{ii}	3.482 (2)
O—C1	1.225 (1)	C5—H51	1.03 (2)
C1—C2	1.514 (2)	C5—H52	1.01 (2)
C2—C3	1.517 (2)	C5—H53	0.94 (2)
C1—N—C5	123.4 (1)	N—C4—C3	104.0 (1)
C1—N—C4	113.8 (1)	N—C5—H51	113 (1)
C5—N—C4	122.2 (1)	N—C5—H52	113 (1)
O—C1—N	125.3 (1)	H51—C5—H52	103 (1)
O—C1—C2	126.5 (1)	N—C5—H53	109 (1)
N—C1—C2	108.2 (1)	H51—C5—H53	107 (2)
C1—C2—C3	105.2 (1)	H52—C5—H53	112 (2)
C2—C3—C4	104.7 (1)		
C5—N—C1—O	3.9 (2)	N—C1—C2—C3	−8.8 (1)
C4—N—C1—O	175.3 (1)	C1—C2—C3—C4	17.6 (1)
C5—N—C1—C2	−175.8 (1)	C1—N—C4—C3	15.7 (1)
C4—N—C1—C2	−4.5 (1)	C5—N—C4—C3	−172.8 (1)
O—C1—C2—C3	171.5 (1)	C2—C3—C4—N	−19.8 (1)

Symmetry codes: (i) $1 + x, y, z$; (ii) $-x, 1 - y, -z$.

which were not corrected for. The structure was solved by direct methods. All H-atom positions could be located after anisotropic refinement of the non-H atoms. They were refined freely with isotropic displacement parameters in the final refinement cycles. Table 2 contains the atomic parameters while Tables 3 and 4 summarize selected geometric parameters.*

2.2. *Calculations*

Force-field calculations were performed with the program *MOMO* (Dyrbusch, Beck & Egert, 1991), which uses the PIMM force field by Smith & Lindner (1991). It has been previously demonstrated that this force field gives particularly good results for nitrogen-containing ring compounds (Beck, 1989). *Ab initio* calculations were performed using the *GAUSSIAN94* program suite (Frisch *et al.*, 1995) on a DEC-AXP-OSF computer system. All geometries were optimized without symmetry restrictions using gradient optimization techniques and standard basis sets. Stationary points were checked to be true minima by frequency analysis at the RHF/6-31G* level. The influence of electron correlation on the geometry was evaluated by MP2 geometry optimizations, keeping the core electrons frozen. Atomic charges were calculated using the Natural Population Analysis method (Reed, Weinstock & Weinhold, 1985) included in the *GAUSSIAN94* package.

Table 4. *Hydrogen-bonding parameters (Å, °)*

D—H···A—C	D—H	H···A	D···A	D—H···A	H...A—C
C5—H51···O^{i}—C1^{i}	1.03 (2)	2.57 (2)	3.552 (2)	160 (1)	143.4 (5)
C5—H53···O^{ii}—C1^{ii}	0.94 (2)	2.65 (2)	3.482 (2)	148 (2)	130.5 (4)

Symmetry codes: (i) $1 + x, y, z$; (ii) $-x, 1 - y, z$.

3. Results and discussion

3.1. *Crystal and molecular structure*

The molecular structure of NMP is shown in Fig. 1. The amide bond in NMP [N—C1 1.345 (2) Å] is slightly longer than that in small non-cyclic amides. In formamide and acetamide, for example, C—N bond lengths of 1.319 (2) and 1.336 (4) Å were found, respectively (Ottersen, 1975). For *N*-methylacetamide d(N—C) = 1.325 (3) Å is reported (Hamzaoui & Baert, 1994).† The amide bond length in NMP agrees well with that in *N*,*N'*-dimethyl-diketopiperazine [1.348 (3) Å], however, where the amide bond likewise is part of a small-size ring system (Groth, 1969).

Of particular interest for the scope of the present study is the ring conformation (Fig. 2). As can be seen from Table 4, the torsion angles around the ring bonds deviate up to −19.8 (1)° from the standard 0° of a perfectly planar ring system. Not surprisingly, the amide bond N—C1 has the smallest torsion angle of −4.5 (1)°. Because N and C1 are perfectly planar (sum of the angles at N/C1 = 359.4/360.0°), the amide torsion originates entirely from a twist of the C_3N fragment *versus* the CC(O)N fragment. An analysis of the ring puckering according to Boeyens & Evans (1989) yields an amplitude q_2 of 0.196 and a phase φ_2 of 297.8°, equivalent to a linear combination of 46% envelope conformation [cos form, $m(C_s)$ symmetry] and 54% twist conformation [sin form, $2(C_2)$ symmetry].‡ It is immediately obvious that the amount of envelope *versus* twist conformation in NMP is predominantly determined by the torsion around the amide bond, a

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* Lists of structure factors, anisotropic displacement parameters and complete geometry have been deposited with the IUCr (Reference: SE0197). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

† Typical gas-phase amide bond lengths in small non-cyclic amides (by electron diffraction) are substantially longer and range between 1.366 (8) (*N*-methylformamide; Kitano & Kuchitsu, 1974) and 1.386 (4) Å (*N*-methylacetamide; Kitano, Fukuyama & Kuchitsu, 1973). ‡ More specifically, the pyrrolidone ring is almost halfway between the pure ^{C3}E envelope conformation with $\varphi = 288°$, where atom C3 is up, and the pure $^{C3}T_{C4}$ twist conformation with $\varphi = 306°$, where atom C3 is up and atom C4 is down (Köll, John & Kopf, 1982). See also the discussion given by Cremer & Pople (1975).

Table 5. *Intraring torsion angles (°) and ring conformation for pure crystalline NMP and NMP in ADE.2NMP and $Cu_4OCl_6(NMP)_3(NMP.H_2O)$**

Compound	C4—N—C1—C2	N—C1—C2—C3	C1—C2—C3—C4	C2—C3—C4—N	C3—C4—N—C1	Ratio envelope/twist
NMP†	−4.5	−8.8	+17.6	−19.8	+15.7	0.46/0.54
ADE.2NMP						
Molecule (1)	−2.6	−8.0	+14.8	−16.1	+12.1	0.63/0.37
Molecule (2)	−0.3	−9.9	+15.8	−15.9	+10.8	0.98/0.02
DPPT.2NMP‡	−1.5	−14.1	+23.1	−23.6	+16.1	0.91/0.09
$Cu_4OCl_6(NMP)_3.(NMP.H_2O)$						
Molecule (1)§	−0.1	−10.5	+16.4	−16.5	+10.7	0.97/0.03
Molecule (2)¶	+3.0	−6.3	+6.9	−5.1	+1.4	—
Molecule (3)¶	+2.7	−4.3	+4.2	−2.7	+0.1	—
Molecule (4)¶	+1.4	−1.1	+0.4	+0.3	−1.1	—

* As calculated from the respective coordinates contained in the Cambridge Crystallographic Database; for atom numbering see Fig. 1; in some cases all the torsion angle signs were inverted in order to have the same absolute conformation (invertomer); references: ADE.2NMP: Langer, Huml & Zachová (1984); DPPT.2NMP: Mizuguchi & Rihs (1992); $Cu_4OCl_6.(NMP)_3.NMP.H_2O$: Churchill & Rotella (1979). † This work. ‡ Only one crystallographically independent molecule NMP. § NMP only hydrogen bonded. ¶ Cu-coordinated NMP.

value approaching 0° being equivalent solely to an envelope conformation.

The ring conformation differs noticeably from previous theoretical investigations, which indicated a much smaller ring puckering (Warshel, Levitt & Lifson, 1970; Treschanke & Rademacher, 1985) or a pronounced envelope conformation (Riggs, 1985). It is also not consistent with the strict coplanarity of all non-H atoms, as assumed in the above-mentioned vibrational study (McDermott, 1986). With regard to the latter, one should not forget at this point that the barrier for a conformational inversion of the molecule into its mirror image should be well below *kT* at room temperature, *i.e.* the NMP molecules should be rapidly fluctuating in solution and in the gas phase. This is confirmed by the very small ring-puckering frequency of $162.4\,cm^{-1}$ in a RHF/6-31G* frequency analysis, a value which agrees well with the experimental one ($150\,cm^{-1}$) as assigned by McDermott (1986). Whether this fluctuation proceeds through a

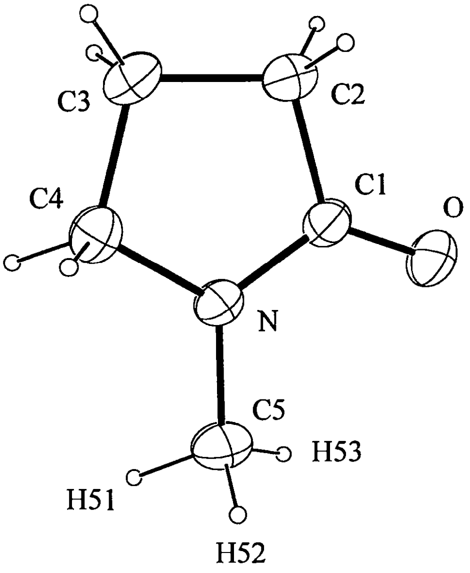


Fig. 1. Molecular structure of NMP (*ORTEPII*; Johnson, 1976). The displacement ellipsoids are at the 50% probability level and H atoms are drawn as spheres with arbitrary size.

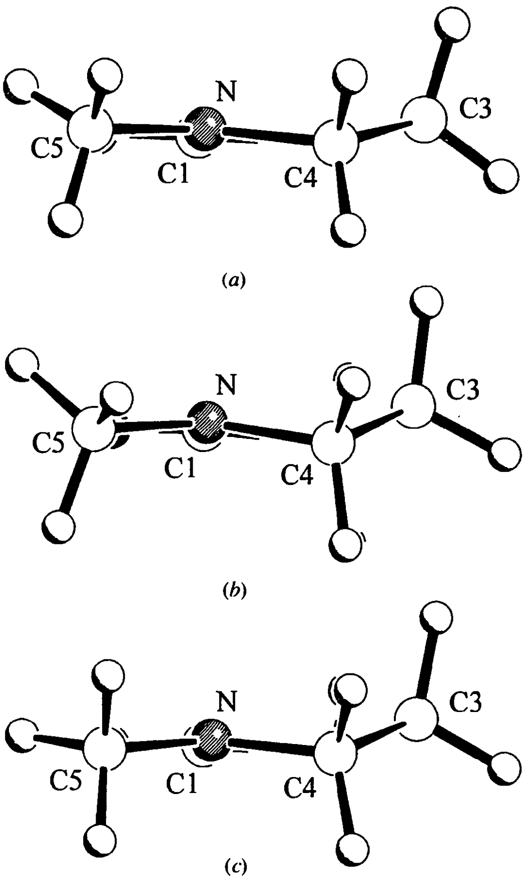
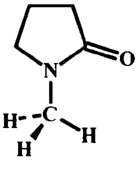


Fig. 2. Ring conformation of NMP as seen approximately down the N—C(O) axis; atoms as spheres with arbitrary size (*SCHAKAL92*; Keller, 1992). (*a*) Conformation in the solid-state; (*b*) conformation as calculated by *MOMO*; (*c*) conformation as resulting from the RHF/6-31G* *ab initio* calculations.

planar transition state is beyond the scope of the present study, however.

The question remains whether the observed solid-state NMP conformation corresponds to a true energy minimum or whether it is influenced by the packing of the molecules in the crystal. In order to assess this point on a crystallographic basis, a comparison of our results with the NMP structures in the 2:1 complexes of NMP with adenine (ADE.2NMP; Langer, Huml & Zachová, 1984) and 3,6-diphenylpyrrolo[3,4-*c*]pyrrole-1,4-dithione (DPPT.2NMP; Mizuguchi & Rihs, 1992), respectively, and in the copper complex $Cu_4OCl_6.(NMP)_3.NMP.H_2O$ (Churchill & Rotella, 1979) was found to be particularly helpful. In the first two structures the NMP molecules are only hydrogen bonded to neighbouring ADE and DTTP molecules, while the latter contains three NMP molecules coordinated to Cu *via* their carbonyl O atoms and the fourth one is only hydrogen bonded to a water molecule. In all three structures the NMP parameter is well defined in order to allow a meaningful structural comparison. Table 5 lists the intraring torsion angles of NMP in these structure determinations together with those of the present study. As can be seen, the ring conformations of the NMP molecules which are only hydrogen bonded agree well with those in pure crystalline NMP. This regards both the magnitude and the sign of the torsion angles. The Cu-coordinated NMP molecules, on the other hand, have much flatter rings, which undoubtedly must be a consequence of the metal coordination. We, therefore, conclude that the minimum energy ring conformation of NMP is basically as found in solid pure NMP, the differences in magnitude of the respective torsion angles (of non-coordinated NMP) being due to crystal packing forces. This conclusion is further substantiated by molecular mechanics (force-field) and *ab initio* calculations on free NMP, described below.

The most remarkable feature of the crystal structure of NMP is probably the occurrence of two intermolecular C—H···O hydrogen bonds between H atoms of the *N*-methyl group and carbonyl O atoms of neighbouring molecules (Fig. 3, Table 4). Both the distances [*d*(H···O) = 2.57 (2)/2.65 (2), *d*(C5···O) = 3.552 (2)/3.482 (2) Å] and the directionality [angles (C5—H···O) = 160 (1)/148 (2)°] leave no doubt that these contacts may be termed intermolecular C—H···O hydrogen bonds. These C—H···O hydrogen bonds form a network which links the individual molecules pairwise to strands which are approximately coplanar with the *ab* plane and run along the crystallographic *a* axis (Fig. 3). The C—H···O hydrogen bonds in NMP seem to be relatively weak, however, when compared with short bonds of the same type (Taylor & Kennard, 1982; Jeffrey & Saenger, 1991, and references therein; Desiraju, 1991, and references therein; Steiner & Saenger, 1992, 1993; Steiner, 1994). The relative weakness of the C—H···O hydrogen bonds may be rationalized by the sp^3 nature of the carbon (Allerhand & Schleyer, 1963), which makes the H atom much less acidic than an sp^2 or *sp* carbon would do. The strength of C—H···O hydrogen bonds is known to correlate with C—H acidity (Pedireddi & Desiraju, 1992). An adjacent N atom makes Csp^3—H more likely to participate in hydrogen bonds (Taylor & Kennard, 1982), which is the case in NMP.



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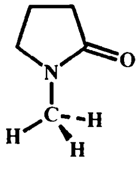

bisecting (staggered)

The orientation of the *N*-methyl group with respect to rotation around its N—CH_3 bond is characterized by the torsion angle C(1)—N—C5—H53 = −31 (1)° (Table 6). Thus, it is almost exactly half-way between a conformation in which the amide bond N—C1 is eclipsed with one C—H bond [C(O)—N—C—H = 0/120/−120°] and one in which it is bisecting [staggered; C(O)—N—C—H = 60/−60/180°]. In the latter conformation a C—H bond is obviously eclipsed with the N—C4 bond. The problem whether the observed conformation is the 'inherent' minimum energy conformation also of isolated NMP or whether the C—H···O hydrogen bonds determine the orientation of the *N*-methyl group is more difficult to tackle. Clues to the answer should come from the inherently preferred conformation of N—CH_3 groups in NMP and other amides, as revealed by structural studies in the gas phase and by calculations from the barriers of rotation around their N—CH_3 bonds and from the N—CH_3 orientation as observed in the crystalline state. Possible differences between the methyl orientation in isolated molecules (the 'inherently preferred' conformation) and in the crystalline state are a particularly important issue, because, as we will see later, the barriers to the methyl group rotation in *N*-methylated amides are, in general, very small and might well be overcome by crystal packing forces.

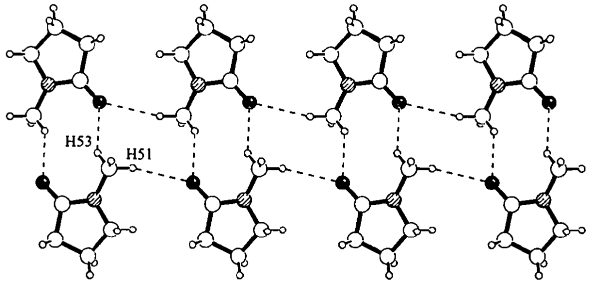

Fig. 3. Network of hydrogen bonds in the crystal structure of NMP as seen approximately down the *c* axis (*SCHAKAL92*; Keller, 1992).

Table 6. *Methyl group orientation and ring conformation for crystalline NMP and resulting from force-field and ab initio calculations*†

	X-ray	*MOMO*	RHF/ 6-31G*‡	RHF/ 6-31G*§	RHF/ 6-31G*¶	MP2/ 6-31G*‡
Torsion angle (°) C1—N—C5—H††	−31 (1)	**	−13.9	−70	−30	−13.7
ΔE (kJ mol^{-1})	—	—	0	5.02‡‡	+0.59	—
C4—N—C1—C2	−4.5	−5.4	−4.4	−4.6	− 7.1	−5.1
N—C1—C2—C3	−8.8	−15.3	−13.3	−13.4	−11.7	−14.9
C1—C2—C3—C4	+17.6	+28.8	+24.4	+24.8	+24.4	+27.8
C2—C3—C4—N	−19.8	−31.9	−26.6	−27.1	−28.1	−30.2
C3—C4—N—C1	+15.7	+23.6	+20.1	+20.5	+22.7	+22.8
Ratio envelope/twist	0.46/0.54	0.57/0.43	0.64/0.36	0.62/0.38	0.39/0.61	0.62/0.38

† Force-field calculation: *MOMO*; for the *ab inito* calculations the respective type of basis set/calculation used is given. ‡ Minimum energy conformation. § Maximum energy conformation. ¶ Conformation with the methyl group orientation as found in the solid. ** See text. †† Only the value closest to the eclipsing conformation is given, the other two values are obtained by adding or subtracting 120°; for the solid-state structure the value refers to atom H53, the other two angles are: C1—N—C5—H51 = −149 (1) and C1—N—C5—H52 = +94 (1)°; the sign of the torsion angle is important as it refers to the (chrial) ring conformation, *i.e.* to the signs of the intraring torsion angles as given below and in Table 5. ‡‡ Barrier to methyl group rotation.

In propene and acetaldehyde the eclipsed conformation of one methyl C—H bond with the adjacent double bond is energetically more favourable by 8.37 and 4.90 kJ mol^{-1}, respectively (Lowe, 1968; Kilb, Lin & Wilson, 1957; Wiberg & Martin, 1985, and references therein). The origin of this effect is seen in increased bond-pair repulsion due to H/H eclipsing occurring in the bisecting conformation, which is augmented by an unfavourable interaction of the other two C—H bonds with the C═C or C═O π-orbitals in this conformation. In addition, there might also be an attractive interaction between one C—H bond and the double bond in the eclipsing conformation.*

For *N*-methylamides a similar ground state conformation [one NC—H eclipsed to the amide N═C bond which has partial double-bond character; torsion angles C(O)—N—C—H = 0/120/−120°] has already been postulated a long time ago (Yan, Momany, Hoffman & Scheraga, 1970). In contrast to simple alkenes and keto compounds, such a conformation additionally approaches the eclipsed C—H bond not only to the amide bond, but also to the carbonyl oxygen. On purely steric grounds this interaction should be unfavourable (Hagler, Leiserowitz & Tuval, 1976), but there might also be an attractive intramolecular electrostatic C═O···H—C interaction. For open-chain (noncyclic) amides such as *N*-methylacetamide and *N*-methylformamide the experimental and computational evidence for the inherently preferred N—CH$_3$ orientation is inconclusive, however. This is clearly a consequence of a very small energy barrier to the methyl group rotation, which has been estimated by various computational methods to be between 0 and 3.35 kJ mol^{-1} (Hagler, Leiserowitz & Tuval, 1976; Radom & Riggs, 1982; Basharov, Vol'kenshtein, Golovanov, Nauchitel' & Sobolev, 1989; Mirkin & Krimm, 1991). Consequently, both the eclipsed and the bisecting conformations have been assumed as ground state by different authors (Basharov, Vol'kenshtein, Golovanov, Nauchitel' & Sobolev, 1989, and references therein). GED data on *N*-methylacetamide indicate a bisecting N—CH$_3$ conformation [torsion angles C(O)—N—C—H = 60/−60/180°; Kitano, Fukuyama & Kuchitsu, 1973], whereas those for *N*-methylformamide were found to be insensitive to the methyl orientation (Kitano & Kuchitsu, 1974). In the solid state the observed bisecting N—CH$_3$ conformation in (pure) *N*-methylacetamide might be biased by a disorder of the entire molecule, which places the methyl groups at C and N close to the same crystal site (Hamzaoui & Baert, 1994). Closely similar conformations are found in other *N*-methylformamides, however (Hagler, Leiserowitz & Tuval, 1976, and references therein). Solid *N*-methylformamide has only been structurally characterized together with other molecules in the crystal. In its crystal complex with oxalic acid an eclipsed methyl orientation has been found for two crystallographically independent molecules (Hagler, Leiserowitz & Tuval, 1976).

In NMP the situation may be even more complicated due to additional effects. In particular, an eclipsed NC—H/N═C conformation might lead to increased steric repulsion between two of the methyl H atoms with the adjacent methylene H atoms (at C4 in Fig. 1). While computational studies, which paid particular attention to the methyl orientation, do not seem to have been carried out on NMP or similar molecules, information on the solid-state structures is scarce and rather inconclusive with regard to the location of the methyl H atoms. Thus, in ADE.2NMP the H atoms were calculated in idealized positions and subsequently refined (Langer, Huml & Zachová, 1984). The published coordinates indicate a virtually eclipsed conformation. The structural information on NMP in DPPT.2NMP indicates a conformation which is 25° away from the eclipsing NC—H/N═C conformation (Mizuguchi & Rihs, 1992). In the solid state *N*,*N*′-dimethyldiketopiperazine adopts an eclipsed

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* A more detailed discussion is given by Eliel, Wilen & Mander (1994).

conformation of both (crystallographically equivalent) methyl groups with the amide bond, but this assignment is based on only one located methyl H atom in this early structure determination (Groth, 1969).

Clearly, even when all the existing evidence is combined, it hardly allows reliable conclusions to be drawn with regard to the inherently preferred methyl orientation in non-cyclic *N*-methylamides, the situation being even worse in cyclic *N*-methylamides. In the hope of finding additional evidence for the ground state methyl orientation in NMP, we resorted back to high-level *ab initio* calculations on NMP which are described below.

3.2. *Computational results*

Force-field calculations (*MOMO*) were performed on isolated NMP molecules. The most important structural parameters resulting from these calculations are given in Fig. 4. The ring conformation is characterized by the intraring torsion angles summarized in Table 6. As can be seen from these numbers, the calculated structure agrees astonishingly well with that found in the solid state. This applies not only to bond lengths and angles, but also to the torsion angles. The sequence of their signs is identical to those in the solid state, only the magnitude of the angles is generally larger. Because the *ab initio* calculations also consistently indicate a more pronounced ring puckering, we conclude that the slightly flatter ring, as observed in the solid state, is a consequence of crystal packing forces. (To a presumably lesser extent, thermal motion might also contribute to the observed ring flattening.) This agrees with the small differences in the solid-state structures of NMP in various crystalline environments, as described above. Thus, the molecular structure of NMP is well reproduced by the force field employed by *MOMO*. However, *MOMO* is not expected to reproduce correctly the methyl orientation in isolated NMP since intramolecular electronic effects are ignored, which might play a role in determining the inherently preferred methyl conformation. Therefore, although the methyl orientation resulting from the *MOMO* calculations (Fig. 2) is similar to that found in the solid state, this result should not be very reliable.

High-level *ab initio* calculations should yield much better information on the preferred methyl orientation. Again, the resulting molecular structure (Fig. 4) reproduces well the findings in the solid state, which also extends to the ring puckering (Table 6). It should be noted that the *ab initio* results also agree astonishingly well with the force-field calculations. The RHF/6-31G* minimum energy conformation of the *N*-methyl group was found to be −13.9° away from the eclipsing conformation. This amounts to a difference of 17.1° with respect to the solid-state conformation. (Table 6 summarizes the results including the ring conformation parameters. For comparison, the calculated geometry for a methyl rotation of −30°, as found in the solid state, is also given.) An additional calculation with inclusion of electron correlation at the MP2/6-31G* level basically shows a similar minimum energy structure (Table 6). Because rotation barriers are highly basis-set-independent, the RHF/6-31G* level is of sufficient quality to calculate the barrier to rotation around the N—CH_3 bond. The rotors were optimized with complete relaxation of the remaining molecule. As expected, the maximum barrier height is found to be at C(O)—N—C—H = −70°, *i.e.* ~60° away from the minimum energy conformation. The rotation barrier is 5.02 kJ mol^{-1} (Table 6).† This barrier seems to be somewhat high when compared with the 0–3.4 kJ mol^{-1} for small non-cylic amides (see above). We see the origin for the higher barrier in small, but important, geometric differences between NMP and non-cyclic amides. In particular, the peculiar methyl conformation close to eclipsed in the RHF/6-31G* minimum energy structure of NMP closely approaches the methyl hydrogen to the carbonyl oxygen. The calculated H···O distance of 2.45 Å‡ is described to be in the steep repulsive region of the non-bonded potential (Hagler, Leiserowitz & Tuval, 1976). Thus, in NMP the H···O repulsion should be comparable to that in *N*-methylacetamide and *N*-methylformamide, where non-bonded distances of 2.3–2.4 Å have been assumed for the eclipsed conformation (Hagler, Leiserowitz & Tuval, 1976). Nonetheless, the fact that NMP prefers a methyl orientation close to eclipsing undoubtedly must be due to additional attractive interactions which overcome the repulsion. We see this in the electrostatic O···H attraction between the negatively charged carbonyl oxygen and the positively polarized methyl H atom, which obviously is larger the shorter the H···O separation. Quite noticeably, the *ab initio* results seem to corroborate this. As shown in Fig. 4, the electrostatic charge on the eclipsing H atom is more positive than on the other two, suggesting an attractive dipole (C=O)-induced dipole (H—C) interaction.

In the methyl conformation corresponding to the solid state [C1—N—C5—H = −30°] the energy should be

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† Although basis set superposition errors (BSSE's) using a non-minimal basis (like 6-31G*) are supposed to be small, they can play a significant role when discussing small energy barriers as in the current rotor system (Novoa, Constans & Whangbo, 1993*a*,*b*). The barrier to rotation actually could be too high, because BSSE overestimates the intramolecular C—H···O interaction of the eclipsed minimum energy geometry. This is due to orbitals on the C—H fragment, which are used to describe the electron-rich carbonyl oxygen. Since such BSSE's are almost entirely removed when diffuse functions are added (Novoa, Tarron, Whangbo & Williams, 1991), we performed single-point SCF calculations (RHF/6-311++G**//6-31G*) on the minimum and maximum energy structures. The calculated barrier of 4.61 kJ mol^{-1} is very similar to the 6-31G* barrier, implying a small effect of BSSE in the system under investigation (estimated BSSE is ~0.42–0.84 kJ mol^{-1}).

‡ In the crystal structure the intramolecular C—H···O distance is 2.57 (2) Å.

0.59 kJ mol^{-1} higher (Table 6). This energy has to be overcome by the intermolecular C—H· · ·O hydrogen bonds if they are conformation-determining. The best estimations point to a bond strength of 2.47 kJ mol^{-1} for CH_4· · ·OH_2 hydrogen bonds (Novoa, Tarron, Whangbo & Williams, 1991). It is obvious that the two C—H· · ·O interactions observed in solid NMP are clearly energetically more than sufficient to overcome the methyl rotation barrier. Moreover, as is seen in Fig. 3, the C—H· · ·O hydrogen bonds seem to determine simultaneously the alignment of the NMP molecules in the crystal, as they lead to a two-dimensional strand-like array of the molecules. Part of an optimal alignment must be the proper methyl-group orientation. We, therefore, believe that the observed methyl conformation is not merely the coincidental result of other, less specific crystal packing forces, but clearly necessary for an optimal packing, as induced by the network of C—H· · ·O hydrogen bonds. Thus, NMP is another example where C—H· · ·O hydrogen bonds not only are evident from their structural characteristics (atom distances and directionality), but also from their effect on the molecular conformation (Berkovitch-Yellin & Leiserowitz, 1984; Seiler & Dunitz, 1989; Seiler *et al.*, 1987*a*,*b*; Smith, Haller & Shang, 1993). In contrast to the example given by Dunitz and co-workers, where a Csp^3—CH_3 rotational barrier is overcome by (three) intermolecular C—H· · ·O hydrogen bonds (Chao & Chen, 1996*a*,*b*), the amount of energy necessary to rotate the methyl group in NMP is smaller, however. Our findings that the barrier in NMP is larger than in small non-cyclic amides make further theoretical and experimental investigations on the preferred ground-state conformations of cyclic and non-cyclic amides worthwhile.

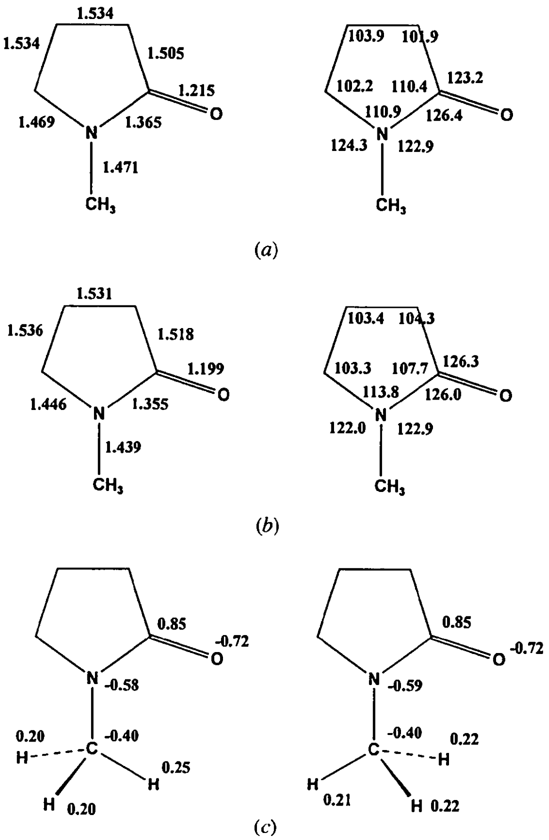

Fig. 4. Summary of computational results on NMP: (*a*) Bond lengths (left; Å) and angles (right; °) as calculated by *MOMO*; (*b*) *ab initio* (RHF/6-31G*) bond lengths and angles; (*c*) atomic NPA charges on the N(Me)—C(O) fragment of NMP as calculated on the basis of the RHF/6-31G* results (left: N—CH_3 in eclipsed conformation; right: bisecting conformation).

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