45. On the Conformation of a Sterically Congested Amide Group in the Crystalline State and in Solution

by **Andreas Mühlebach** and **Gian Paolo Lorenzi***

Institut für Polymere, ETH-Zentrum, CH-8092 Zürich

and **Volker Gramlich**

Institut für Kristallographie und Petrographie, ETH-Zentrum, CH-8092 Zürich

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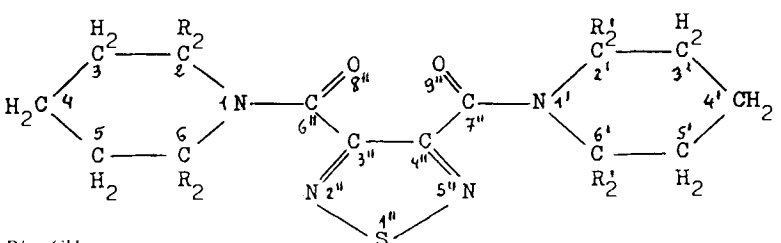
The conformation in the crystalline state and in solution of the sterically congested tetramethylpiperidine-derived amide group of the symmetric diamide **I** formed from 2,2,6,6-tetramethylpiperidine (**b**) and 1,2,5-thiadiazole-3,4-dicarbonyl dichloride (**c**), and of the mixed diamide **II** derived from **b**, **c**, and piperidine (**a**) has been investigated. In crystals, as observed with **II**, this group is strongly bent out-of-plane at both the N-atom and the carbonyl C-atom, and there is also a sizable twisting around the amide bond. Furthermore, the amide bond is abnormally long (1.37 Å). In CD_2Cl_2 (or $CDCl_3$) solution, the group is apparently planar in its ground-state conformation, but the energy barrier to rotation around the amide bond is low. This conclusion is based on low-temperature ^{1}H-NMR measurements on **I**, **II**, and on the symmetric diamide **III** derived from **a** and **c**.

Introduction. – Amide groups derived from 2,2,6,6-tetramethylpiperidine are sterically congested and – not surprisingly in view of the effects that bulky substituents have [1] [2] in facilitating rotation around the amide bond – the groups studied so far have shown [3] [4] a very low rotational barrier. Whether amide groups of this kind also have a nonplanar ground-state conformation has been considered but not substantiated [4]. We are investigating structurally isomeric [5] [6] polyamides derived from methylated piperazines and 1,2,5-thiadiazole-3,4-dicarboxylic acid [7]. In connection with these studies, we were interested in the crystal and solution conformation of the amide group derived from 2,2,6,6-tetramethylpiperidine and 1,2,5-thiadiazole-3,4-dicarboxylic acid. Here we report the results obtained by a X-ray and ^{1}H-NMR study in which we have used the low molecular weight model diamides **I**–**III**.



I R = R′ = CH_3
II R = CH_3; R′ = H
III R = R′ = H

Results and Discussion. – a) *Crystal Structures.* The crystal structure of **II** and **III** have been determined by single-crystal X-ray analyses. The following observations pertain to **II**; however, as far as the amide group derived from the unsubstituted piperidine is concerned, they apply to **III** as well, since the geometric features of this group in the two compounds are very similar. The crystal structure of **II** is made up of two independent, asymmetric molecules **A** and **B** having only slightly different conformations. The elementary cell of the centrosymmetric space group $P2_1/c$ contains two pairs of enantiomers **A**

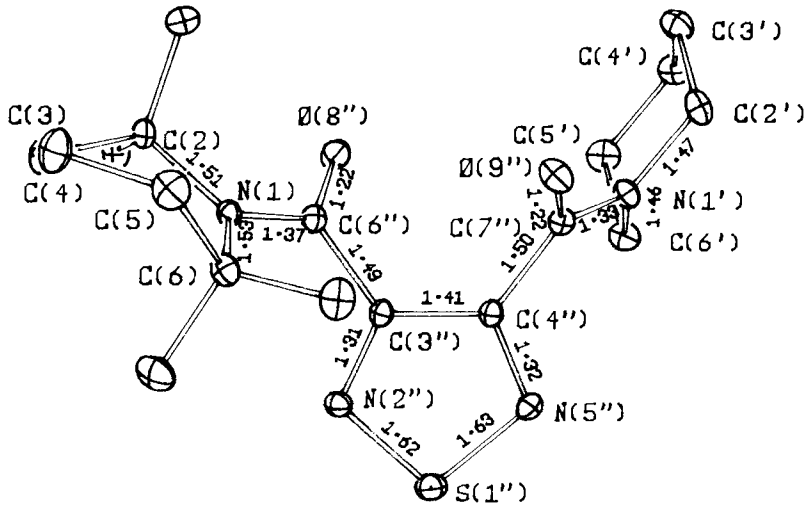


Fig. 1. *Molecular model of molecule* **IIA**. The designation of the atoms follows the arbitrary numeration used for the structural formula. Selected bond distances are indicated.

Table 1. *Torsion Angles* (°) *Observed in Crystalline* **II**

Torsion angle[a])	Molecule A	Molecule B	Torsion angle[a])	Molecule A	Molecule B
Amide group derived from tetramethylpiperidine			Thiadiazole ring		
C(3)–C(2)–N(1)–C(6")	167.5	164.7	C(6")–C(3")–C(4")–C(7")	13.9	15.4
C(5)–C(6)–N(1)–C(6")	137.9	140.2	C(6")–C(3")–C(4")–N(5")	–173.4	–171.4
C(2)–N(1)–C(6")–O(8")	14.7	19.0	N(2")–C(3")–C(4")–C(7")	–174.6	–175.4
C(2)–N(1)–C(6")–C(3")	–158.3	–154.2	N(2")–C(3")–C(4")–N(5")	–2.0	–2.6
C(6)–N(1)–C(6")–O(8")	–155.2	–152.3	S(1")–N(2")–C(3")–C(4")	1.8	1.7
C(6)–N(1)–C(6")–C(3")	31.8	34.5	S(1")–N(2")–C(3")–C(6")	173.7	171.2
N(1)–C(6")–C(3")–C(4")	–138.0	–140.0	N(5")–S(1")–N(2")–C(3")	–1.0	–0.5
N(1)–C(6")–C(3")–N(2")	51.1	51.8	N(2")–S(1")–N(5")–C(4")	–0.1	–0.9
O(8")–C(6")–C(3")–C(4")	48.3	46.3	C(3")–C(4")–N(5")–S(1")	1.1	2.0
O(8")–C(6")–C(3")–N(2")	–122.7	–121.9	C(7")–C(4")–N(5")–S(1")	174.1	175.6
Amide group derived from piperidine					
C(3')–C(2')–N(1')–C(7")	–118.7	–119.6	C(6')–N(1')–C(7")–C(4")	9.1	7.3
C(5')–C(6')–N(1')–C(7")	118.7	118.7	N(1')–C(7")–C(4")–C(3")	–125.8	–118.6
C(2')–N(1')–C(7")–O(9")	1.9	2.4	N(1')–C(7")–C(4")–N(5")	62.0	68.7
C(2')–N(1')–C(7")–C(4")	–177.1	–177.9	O(9")–C(7")–C(4")–C(3")	55.0	61.1
C(6')–N(1')–C(7")–O(9")	–171.8	–172.3	O(9")–C(7")–C(4")–N(5")	–117.1	–111.6

[a]) Estimated standard deviation 0.5°.

and two pairs of enantiomers **B**. In the following only one enantiomer is considered for each of the molecules **A** and **B**. The refined structure of **IIA** is presented in *Fig. 1*, and the torsion angles of the amide groups and of the thiadiazole ring in **IIA** and **IIB** are given in *Table 1*. The thiadiazole ring is nearly planar, but there is some pyramidalization at C(3″) and C(4″) ($|\chi|$ between 7 and 12°). Together with the torsion angles around the C(3″),C(6″) and the C(4″),C(7″) bond *(Table 1)* this contributes to bring the O-atoms of the two amide groups far from one another. A similar large distance of the carbonyl O-atoms is also present in **III**. The amide group derived from the unsubstituted piperidine in **IIA** is characterized by an amide bond of length 1.33 Å, a value close to the averages reported [8] for different classes of amides. There is some pyramidalization at the N-atom ($|\chi_N| = 6.3°$ in **IIA**; *Fig. 2*), a situation frequently encountered [8] with crystalline amides,

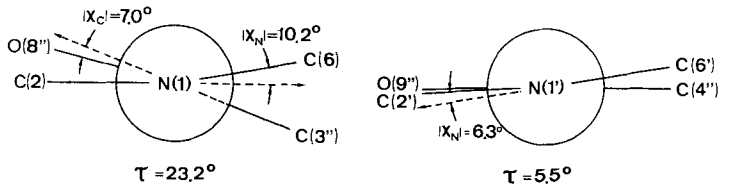


Fig. 2. *View down the N–C(O) bond of the tetramethylpiperidine-derived amide group* (left) *and of the piperidine-derived amide group* (right) *of molecule* **IIA**. The parameters, χ_N and χ_C used to express the extent of pyramidalization at the N- and C-atom, respectively, correspond to those introduced for this purpose by *Winkler* and *Dunitz* [10].

but the carbonyl C-atom is almost planar. The twist around the amide bond is relatively small (5.5° in **IIA**). The situation of the tetramethylpiperidine-derived amide group is drastically different: The amide bond is significantly longer (1.37 Å); the out-of-plane distortion affects not only the N-atom, but also the carbonyl C-atom, $|\chi_C|$ being rather large (7.0° in **IIA**; *Fig. 2*); contributing to the out-of-plane deformation of the amide group, there is also a marked twist around the amide bond, which in **IIA** corresponds to a rotation of 23.2° away from the situation of antisymmetric out-of-plane bendings [9]; and, finally, the 2,2,6,6-tetramethylpiperidine ring of **II** has a distorted conformation whereas the unsubstituted ring is in the regular chair conformation. All these anomalous features of the tetramethylpiperidine-derived amide group in both independent molecules **IIA** and **IIB** can be attributed only in part to lattice forces and manifest the magnitude of the steric constraints imposed by the CH_3 substituents. The tetramethylpiperidine-derived amide group of crystalline **I** should have a geometry very similar to that found with **II** since the frequencies of the C=O stretching of this group are virtually the same (**I**: 1620 cm^{-1}; **II**: 1618 cm^{-1}).

b) *NMR Spectra in Solution.* ^1H- and ^{13}C-NMR spectra of solutions in $CDCl_3$ (or CD_2Cl_2) indicate that the position of the conformational equilibrium of the tetramethylpiperidine-derived amide group is virtually the same in **I** and **II** and that this is the case also for the amide group derived from the unsubstituted piperidine in **II** and **III**. Spectral differences in signal positions are not observable for protons, and those found for ^{13}C-nuclei are quite small *(Table 2)*. Spectra measured at 25° *(Table 2)* exhibit separate signals for nuclei of the unsubstituted piperidine ring that are in positions 2(2′) and 6(6′) or 3(3′) and 5(5′) demonstrating that rotation around the relative amide bond is, as

Table 2. *^{1}H- and ^{13}C-NMR Chemical Shifts for* **I**–**III** *in $CDCl_3$ at 25°*

Nucleus[a])	δ[b])			
	I	**II**		**III**
		subs. ring	unsubs. ring	
CH_2–N	–	–	3.70	3.71
			3.38	3.42
CH_2–C–N	1.81	1.81	1.68[c])	1.68[c])
CH_3	1.44	1.44	–	–
$(CH_3)_2C$–N	57.71	57.83	–	–
CH_2–N	–	–	48.12	48.19
			43.40	43.44
CH_2–C–N[d])	36.72	36.45	26.16	26.17
			25.53	25.45
CH_3	29.64	29.69	–	–

[a]) The pertinent nucleus is in italics.
[b]) In ppm, ±0.01 ppm.
[c]) Broad signal with contributions from CH_2(4) and CH_2(4′).
[d]) The unsubstituted rings in **II** and **III** give an additional signal at 24.45 and 24.59 ppm, respectively. The assignment is based on that reported in [13] for *N*-thiobenzoylpiperidine.

expected, slow on the NMR time scale. For the nuclei in the corresponding positions of the tetramethylpiperidine ring, the spectra measured at 25° show instead a single signal. The spectra show a single signal also for the nuclei of the CH_3 groups. The magnetic equivalences observed for these nuclei at 25° are in keeping with the observations of other authors [3] [4] on related amides.

Lowering the solution temperature down to −95° causes the following changes in the ^{1}H-NMR spectrum of **I** *(Fig. 3)*. At *ca.* −60°, there is a splitting of the signal of CH_2(3,3′) and CH_2(5,5′). At about the same temperature, also the signal of the CH_3 protons divides giving two signals of relative intensity 3:1. The number of distinct CH_3 signals increases subsequently (between −70 and −80°) to three and finally (between −80 and −85°) to four. A similar splitting of the signal of the CH_3 protons occurs also with **II**. The successive phases of the splitting are, in this case, however, less distinct because of overlapping. As regards the unsubstituted piperidine moiety in **II** and **III**, lowering the solution temperature down to −125° causes the splitting of each of the two signals given at 25° by CH_2(2,2′) and CH_2(6,6′). This is illustrated in *Fig. 4*. In the search of an explanation for these observed splittings one may disregard inversions of pyramidal atoms and rotations around the C–C bonds of the piperidine rings, these processes being very likely still rapid at the lowest temperatures studied. A plausible explanation can be found by considering that in all cases the ground-state conformation of the central thiadiazole-dicarbonyl unit is most likely twisted as in crystalline **II** and **III** (see *Sect. a*). The minimum-energy, enantiomeric conformations of this unit should interconvert into each other through a planar transition state by concerted rotations around the C(6″)–C(3″) and C(4″)–C(7″) bonds. Then the appearance of four signals for the CH_3 protons in the NMR spectra of **I** *(Fig. 3)* and **II** can be seen as the consequence of the freezing of both this enantiomerization process and the rotation around the amide bond derived from the tetramethylpiperidine. As for the signals of the CH_2 protons, the splitting observed with **II** and **III** *(Fig. 4)* can be attributed to the freezing of the enantiomerization process only, the rotation around the amide bond derived from the

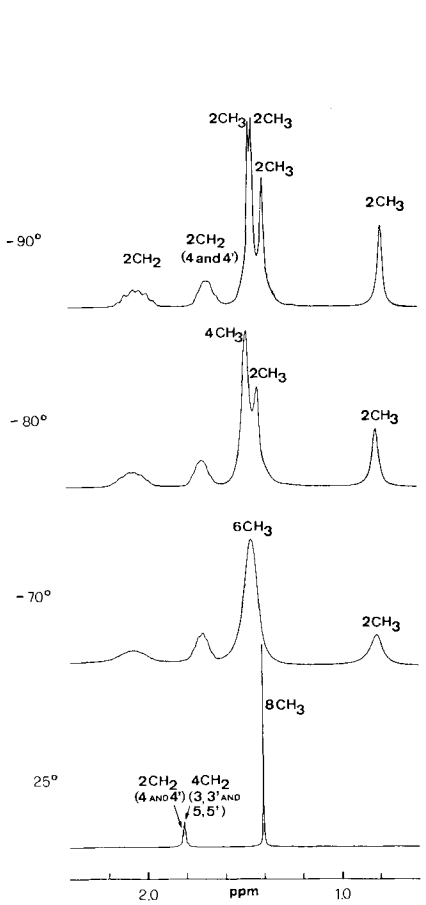


Fig. 3. *300-MHz ^{1}H-NMR spectra of* **I** *in CD_2Cl_2 at different temperatures* (c = 10 mg/ml). In the three upper spectra, one of the two signals of CH_2(3,3') and CH_2(5,5') is hidden by CH_3 signals.

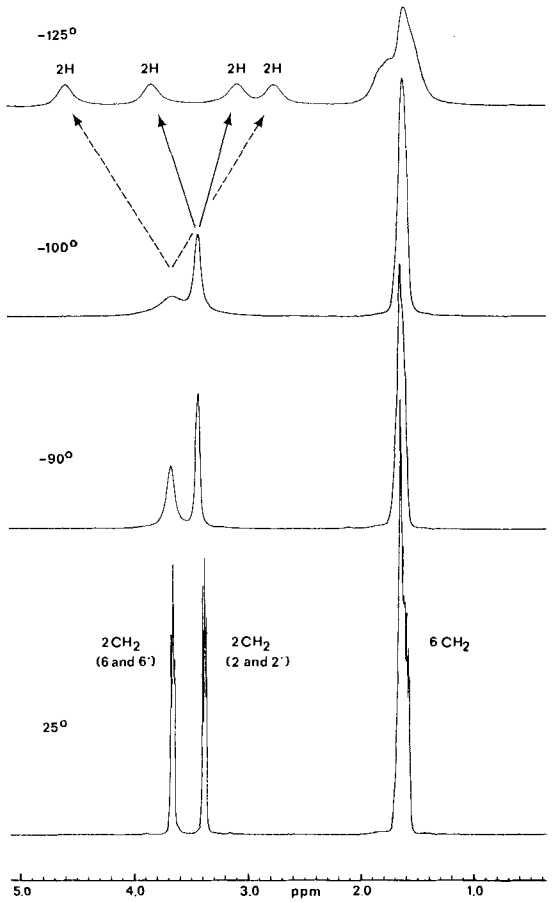


Fig. 4. *300-MHz ^{1}H-NMR spectra of* **III** *in CD_2Cl_2 at different temperatures* (c = 13 mg/ml). The assignment of the signals of CH_2(2) and CH_2(2'), and of CH_2(6) and CH_2(6') (bottom spectrum) is based on [17].

unsubstituted piperidine being already frozen at room temperature. Rotation around the amide bond derived from the substituted piperidine and enantiomerization are probably concerted. This is suggested by the spectral changes of the CH_3 signal(s), which cannot be rationalized on the basis of two consecutive processes, and also by the two values of the free energy of activation (ΔG^*) calculated in the case of **II**. These values are 32.3 ± 1.0 kJ/mol (based on the splitting of the CH_2 signals) and 34.8 ± 1.6 kJ/mol (based on the splitting of the CH_3 signal; less precise value because of overlapping), and therefore do not seem to be significantly different. Interestingly, the ΔG^* value found with **I** (42.0 ± 1.0 kJ/mol) is substantially higher. The ΔG^* value found with **III** for the enantiomerization is 30.0 ± 1.0 kJ/mol. These energy data are not consistent with the hypothesis that we have been contemplating for some time of a nonplanar ground-state conformation of the tetramethylpiperidine-derived amide group.

Supplementary Material. – The basic numerical data (unit-cell dimensions, space group, and atomic coordinates) of **II** and **III** have been deposited at the *Cambridge Crystallographic Data Centre*.

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Experimental Part

General. Piperidine (**a**) and 2,2,6,6-tetramethylpiperidine (**b**) were *Fluka* products. The 1,2,5-thiadiazole-3,4-dicarbonyl dichloride (**c**) was a gift of Dr. *G. Gianotti*. M.p.: *Mettler-DTA* (system *TA 3000*) calorimeter. IR spectra: *Perkin Elmer 177* grating spectrophotometer. ^{1}H- and ^{13}C-NMR measurements: *Bruker-WH-90-* or *AM-300* spectrometer; soln. of 6–12 mg/ml were used for the ^{1}H-NMR and of *ca.* 50 mg/ml for the ^{13}C-NMR: chemical shifts relative to internal TMS. Mass spectra: *Hitachi Perkin Elmer* model *RMU-6L* spectrometer.

N,N:N',N'-*Bis(2,6-dimethylheptane-2,6-diyl)-1,2,5-thiadiazole-3,4-dicarboxamide* (**I**). A mixture of 0.80 g (3.8 mmol) of **c**, 1.61 g (11.4 mmol) of **b**, and 2 ml of pyridine in 50 ml of benzene was refluxed under N_2 for 41 h. Then, 50 ml of $CHCl_3$ were added, and the soln. was washed twice with 50 ml of H_2O. The org. phase was dried over $MgSO_4$, and the solvents were evaporated. The crude product thus obtained was purified by recrystallization from hexane/EtOH 10:1 (*v/v*) and then from MeOH: 0.17 g (11%) of **I**; m.p. 176°. IR (KBr): 1620 (C=O). IR ($CHCl_3$): 1618 (C=O). MS: 420 (M^+). Anal. calc. for $C_{22}H_{36}N_4O_2S$: C 62.82, H 8.63, N 13.32; found: C 62.84, H 8.52, N 13.35.

N,N-*(2,6-Dimethylheptane-2,6-diyl)*-N',N'-*pentamethylene-1,2,5-thiadiazole-3,4-dicarboxamide* (**II**). A mixture of 1.00 g (4.7 mmol) of **c**, 1.34 g (9.5 mmol) of **b**, and 2 ml of pyridine in 50 ml of benzene was refluxed under N_2 for 23 h. Then, 0.40 g (4.7 mmol) of **a** were added; the mixture was refluxed for 1 h and stirred at r.t. for 3 days. Finally it was diluted with Et_2O, washed with H_2O, dried over $MgSO_4$, and evaporated. The residual oil was crystallized from MeOH/H_2O and the crystalline product purified by two recrystallizations from MeOH: 0.48 g (28%) of **II**, m.p. 108°. IR (KBr): 1618 and 1638 (C=O). IR ($CHCl_3$): 1618, 1638. MS: 364 (M^+). Anal. calc. for $C_{18}H_{28}N_4O_2S$: C 59.31, H 7.74, N 15.37; found: C 59.30, H 7.74, N 15.27.

N,N:N',N'-*Bis(pentamethylene)-1,2,5-thiadiazole-3,4-dicarboxamide* (**III**). A mixture of 1.60 g (7.58 mmol) of **c** and 1.55 g (18.2 mmol) of **a** in 50 ml of pyridine was refluxed under N_2 for 1.5 h. After cooling, 100 ml of ice-cold H_2O were added whereupon **III** crystallized. Recrystallization from hexane/EtOH 10:1 yielded 1.30 g (56%) of **III**, m.p. 137.5°. IR (KBr): 1634 (C=O). IR ($CHCl_3$): 1640. MS: 308 (M^+). Anal. calc. for $C_{14}H_{20}N_4O_2S$: C 54.52, H 6.54, N 18.17; found: C 54.45, H 6.55, N 18.15.

Crystal-Structure Determinations. Crystals suitable for the X-ray analysis were grown from an EtOH soln. Information concerning the determination of the crystal structure of **II** at r.t. is summarized in *Table 3*. A *Picker FACS-I* diffractometer with software developed by *Lenhert* [11] was used. The variances of the intensities were derived from counting statistics and the fluctuations of three periodically measured check reflections. The structure model generated by the program MULTAN [12] was refined using anisotropic temperature factors. H-Atoms with calculated positions were included in the last refinement cycles. Scattering factors for neutral atoms are from [15] and [16]. No correction for anomalous dispersion and absorption was applied.

Table 3. *Summary of Crystal Data, Intensity Measurements, Structure Solution, and Refinement for* **II**

Molecular formula	$C_{18}H_{28}N_4O_2S$	Radiation	Mo-K_α (Graphite monochromator)
Molecular weight	364.51	λ [Å]	0.71069
Crystal dimensions	0.1 × 0.1 × 0.2 mm^3	Scan method	2θ-scan
Crystal system	monoclinic	$(\sin\theta/\lambda)_{max}$	0.54
a [Å]	16.43 (1)	No. of unique refl.	2819
b [Å]	7.25 (1)	No. of refl. $< 3\sigma$	779
c [Å]	32.58 (2)	Structure analysis	X-RAY-72 [14]
β (deg)	92.82 (5)	Software used	MULTAN [12]
V [Å^3]	3876 (3)	Refinement method	Block diag. least squares
Z	4	Function minimized	$\Sigma w(\|F_o\| - \|F_c\|)^2$
$d_{calc.}$ [gcm^{-3}]	1.246	w	$1/\sigma^2$
$d_{obs.}$ [gcm^{-3}]	1.22	R	0.05
Space group	$P2_1/c$	R_w	0.04

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