negative Cotton effect near 230 nm present in *N*-acetyl-L-proline in cyclohexane arises primarily from an intramolecular interaction of the polar hydrogen of the COOH group with the carbonyl amide group,[37,38] we cannot exclude the occurrence of OH···OC (urethane) intramolecularly hydrogen-bonded forms in the conformational equilibrium mixture of *t*-BOC-Gly-L-Pro-OH in solvents of low polarity.

The main conclusion of the present work concerns the demonstration by x-ray diffraction analysis of the absence of the type II′ 4 → 1 intramolecularly hydrogen-bonded nonhelical peptide conformation for *t*-BOC-Gly-L-Pro-OH in the solid state, in contrast to the suggestion put forward on the basis of its infrared absorption properties.[3a] Still there remains to explain the pattern of infrared band shifting for some other peptides, particularly those with the Pro-Gly (rather than the Gly-Pro) sequence.[3a] It is possible that each molecule presents an individual case. There may even be some dependence on the crystallization solvent, with less polar solvents promoting crystallization into more folded structures. Perhaps the pattern of infrared shifted bands[3a] correlates with crystal packing phenomena and may be rather independent of the stability of potential oxy analogues to the 4 → 1 intramolecularly hydrogen-bonded peptide conformations. Crystallographic data on some other peptides of these types are required, after which one may draw some more permanent conclusions on this problem. These studies are now in progress in our laboratories.

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On the Oxy Analogues to the 3 → 1 Intramolecularly Hydrogen-Bonded Peptide Conformations[1]

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ABSTRACT: The possible occurrence of the oxy analogues to the 3 → 1 intramolecularly hydrogen-bonded peptide conformations (main feature of the γ turn), recently proposed in solution by several authors, has been investigated in a number of *N*-*tert*-butyloxycarbonyl-α-amino acids by x-ray diffraction, infrared absorption, proton magnetic resonance, and circular dichroism techniques. These folded conformations are absent in the solid state in all cases so far examined; however, they seem to be present in solution, the extent of the population of these forms in the conformational equilibrium mixtures being solvent, temperature, and structure dependent. In the solid state *N*-*tert*-butyloxycarbonyl-D-valine has the urethane –CONH– group in the cis configuration; this is the first time such a configuration has been found in the solid state for a secondary amide group in a linear compound.

The seven-membered ring 3 → 1 intramolecularly hydrogen-bonded peptide conformations have been recognized as an important feature of polypeptide secondary structure.[3] They characterize the γ turn, postulated by Némethy and Printz in 1972 on the basis of conformational energy calculations,[4] and recently proposed by several authors as occurring in the solid state and in solution.[5-10]

In this paper we describe a conformational analysis in the solid state and in solution, using infrared absorption, x-ray diffraction, proton magnetic resonance, and circular dichroism techniques, of a series of *N*-*tert*-butyloxycarbonyl(*t*-BOC)-α-amino acids (and α-amino methyl esters) to shed light on the possible existence of the oxy analogues to the 3 → 1 intramolecularly hydrogen-bonded peptide conformations. In these

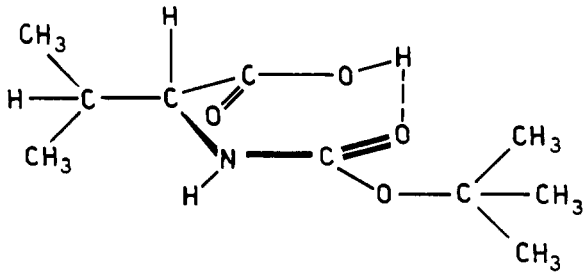

Figure 1. The equatorial oxy analogue to the 3 → 1 intramolecularly hydrogen-bonded peptide conformation for *t*-BOC-D-Val-OH.

folded structures the C-terminal OH proton and the carbonyl group nearest the C terminal are involved in a seven-membered ring containing a somewhat bent hydrogen bond. Molecular models indicate such a hydrogen bond is possible only in the trans amide isomer. When R in –NH–CHR–CO– is not a hydrogen atom, two different conformers (equatorial and axial) can exist. Figure 1 shows the equatorial conformer for *t*-BOC-D-Val-OH. These conformations, which could represent an essential feature of polypeptide chains near their C-terminal end, have been recently proposed for N-protected amino acids and free peptides in solution.[11–16]

Experimental Section

Samples. The *t*-BOC-α-amino acids were prepared according to the procedure described by Schnabel.[17] All compounds have melting points and optical rotation values in good agreement with those reported in the literature.[17]

The *t*-BOC-α-amino acid methyl esters were synthesized from the corresponding α-amino acid methyl ester hydrochlorides using *tert*-butyloxycarbonyl azide.[18]

t-BOC-L-Pro-OMe: oil; $[\alpha]^{21}D$ −48.3° (MeOH, *c* 1.0 g/dl). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.64; H, 8.33; N, 6.11. Found: C, 57.48; H, 8.25; N, 6.07.

t-BOC-L-Ala-OMe:[19–22] oil; $[\alpha]^{21}D$ −36.8° (MeOH, *c* 1.02 g/dl). Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.57; H, 8.28; N, 6.77.

t-BOC-L-Val-OMe: oil; $[\alpha]^{21}D$ −19.4° (MeOH, *c* 0.81 g/dl). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.05. Found: C, 56.51; H, 8.94; N, 6.10.

Infrared Absorption. Infrared absorption spectra were recorded using a Beckman Model IR 9 spectrophotometer. For the solid state measurements the KBr disk technique was employed. For the solution measurements demontable cells with path lengths ranging from 10 to 0.005 cm and calcium fluoride windows were used. Deuteriochloroform (99.8% *d*) was purchased from Merck, Darmstadt, purified according to Shields et al.,[23] and stored under nitrogen in the dark. The band positions are accurate to ±1 cm^{-1}.

Circular Dichroism. Circular dichroic spectra were recorded using a Cary Model 61 circular dichroic spectrophotometer. The spectra were obtained using cylindrical fused quartz cells of 0.5, 1, and 10 mm pathlengths. Dry prepurified nitrogen was employed to keep the instrument oxygen free during the experiments. A complete baseline was recorded for every measurement using the same cell in which the sample solution had been replaced with pure solvent. Solutions of 10^{-2} to 10^{-3} M concentrations were prepared by placing the weighed sample in a volumetric flask and adding the appropriate solvent. The circular dichroic data represent average values from at least four recordings. The calibration was based upon $[\theta]_{290}$ = 7.840 deg cm^2 $dmol^{-1}$ for a purified sample of camphorsulfonic-*10-d* acid (Fluka, Bucks) in 0.1% aqueous solution.[24] The Lorentz refractive index correction was not applied.[24] The solvents used were spectrograde cyclohexane (Merck, Darmstadt) and trimethyl phosphate (Schuchardt, Munchen).

Proton Magnetic Resonance. The proton magnetic resonance spectra were measured with a Bruker Model HF × 10 spectrometer at 90 MHz using tetramethylsilane as the internal standard. Deuteriochloroform (99.8% *d*) (Merck, Darmstadt) was employed as the solvent.

X-Ray Diffraction. Crystals of *t*-BOC-D-Val-OH in the form of colorless prisms were grown from a chloroform/*n*-hexane 3:1 mixture.

Table I
Crystallographic Data for *t*-BOC-D-Val-OH

Molecular formula	$C_{10}H_{19}NO_4$
Molecular weight	217.25
Crystal system	Tetragonal
Space group	$P4_12_12$
Z, molecules/unit cell	8
Cell dimensions, Å	*a* = 10.807
	b = 10.807
	c = 22.556
Density, experimental by flotation ($CHCl_3$-*n*-hexane)	1.09 g cm^{-3}
Density, calcd	1.09 g cm^{-3}
Radiation	Cu Kα, λ 1.5418 Å; Ni filtered
No. of independent reflections	1326
Temp, °C	23, ambient

A summary of crystal data is given in Table I. Intensity data were measured on a Datex-automated General Electric XRD-5 diffractometer, using Ni-filtered Cu Kα radiation (λ 1.5418 Å) by scintillation counter in the range 2–130° of 2θ and the θ/2θ scan techniques. The structure was solved by direct methods with the application of MULTAN.[25] Full matrix refinement with anisotropic thermal parameters for all heavy atoms and isotropic thermal parameters for all hydrogen atoms brought the conventional *R* factor to a final value of 0.048 for the 1326 reflections observed. More details of the molecular structure of *t*-BOC-D-Val-OH will be given in a forthcoming paper.[26]

Results and Discussion

The solid state infrared absorption spectra of the *t*-BOC derivatives of *N*-alkyl-α-amino acids, which contain a tertiary urethane chromophore, are all very similar, exhibiting in particular an intense band at 1640–1650 cm^{-1} (Table II and Figure 2). This vibration shifts to 1685–1710 cm^{-1} in the α-amino methyl esters (Table II), indicating that in the former compounds the urethane carbonyl group is hydrogen bonded (obviously with the OH group). The crystal structure of *t*-BOC-L-Pro-OH, recently determined by x-ray diffraction analysis by one of us (E.B.),[28] revealed the occurrence of hydrogen bonding between the urethane C=O and the OH moiety. However, an oxy analogue to the 3 → 1 intramolecularly hydrogen-bonded peptide conformation was not formed by this compound, the hydrogen bonding holding together in the crystals pair of molecules. The same type of intermolecular hydrogen bond has been recently found in the lower homologue *t*-BOC-L-Aze-OH.[29]

In contrast, the infrared absorption spectra in the solid state of the *t*-BOC derivatives of the various natural aliphatic α-amino acids differ consistently one from the other. The two extrema are represented by *t*-BOC-L-Ala-OH and *t*-BOC-L-Val-OH. In the former all vibrations are typical of free or weakly hydrogen-bonded groups, while in the latter the location of all bands suggests the occurrence of strong hydrogen bonding. In particular, the urethane C=O band is found at 1649 cm^{-1} in *t*-BOC-L-Val-OH and at 1692 cm^{-1} in *t*-BOC-L-Ala-OH (Table II and Figure 2).

The position of the urethane C=O band in the case of *t*-BOC-L-Ala-OMe and *t*-BOC-L-Val-OMe confirms that the urethane carbonyl is strongly hydrogen bonded in *t*-BOC-L-Val-OH, while weakly hydrogen bonded in *t*-BOC-L-Ala-OH, and indicates that, most probably, the hydrogen bonding donor is the OH group of the COOH moiety.

To ascertain whether the urethane C=O group of the *t*-BOC derivative of valine is involved in an intramolecular hydrogen bond (giving rise to an oxy analogue to the 3 → 1 hydrogen-bonded peptide conformation) or in an intermolecular hydrogen bond, we carried out an x-ray diffraction analysis of *t*-BOC-D-Val-OH. Its molecular structure is il-

Table II
Infrared Absorption Data (cm^{-1}) of *N-tert*-Butyloxycarbonyl-α-amino Acids and α-Amino Methyl Esters in the Solid State in the Urethane Carbonyl Region [a]

t-BOC-L-Pro-OH	1642	*t*-BOC-L-Pro-OMe	1708
t-BOC-Sar-OH	1650	*t*-BOC-L-MeVal-OMe	1690[c]
t-BOC-L-MeAla-OH	1650[c]	*t*-BOC-L-MeIle-OMe	1685[c]
t-BOC-L-Ala-OH	1692	*t*-BOC-L-Ala-OMe	1722
t-BOC-L-Val-OH	1649	*t*-BOC-L-Val-OMe	1723
t-BOC-Gly-OH	1677 (s),[b] 1664		
t-BOC-L-Leu-OH	1689, 1674 (s)		
t-BOC-L-Ile-OH	1675		
t-BOC-L-Phe-OH	1712, 1695, 1683		

[a] In KBr pellets. [b] s = shoulder. [c] Data taken from ref 27 (films).

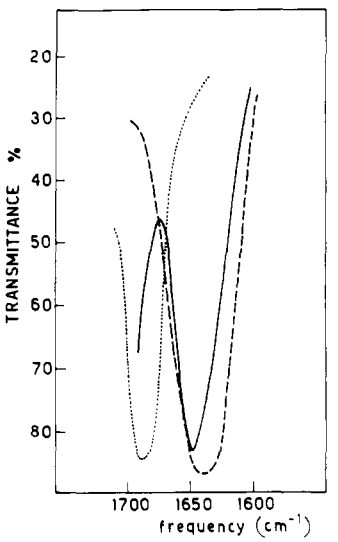

Figure 2. Infrared absorption spectra of *t*-BOC-L-Val-OH (solid line), *t*-BOC-L-Ala-OH (dotted line), and *t*-BOC-L-Pro-OH (dashed line) in KBr pellets in the 1700–1600-cm^{-1} region.

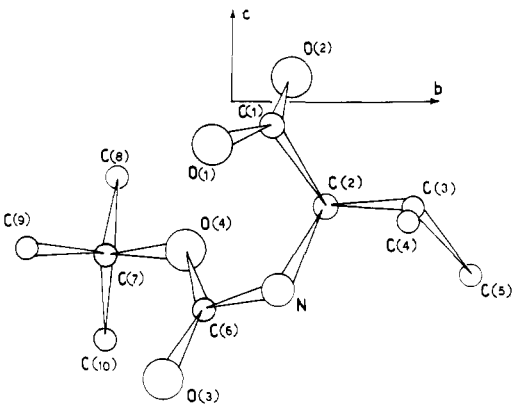

Figure 3. Molecular structure of *t*-BOC-D-Val-OH.

lustrated in Figure 3; bond distances, bond angles, and internal rotation angles are listed in Tables III–V.

The conformation of the *t*-BOC-D-Val-OH molecule is such that two methyl groups of the *tert*-butyl moiety and the two methyl groups of the isopropyl moiety are staggered with respect to the O(3) atom and the N atom, respectively. The conformation of the carboxyl group is neither anticlinal nor antiplanar, since the O(2)–C(1)–C(2)–N torsion angle is 159°. No intramolecular hydrogen bond is present. Two intermolecular hydrogen bonds link the molecules around the fourfold screw axis (along the *c* direction), their lengths being 2.92 Å for the N–H···O(2) bond and 2.63 Å for the O(1)H···O(3) bond. The rows of hydrogen-bonded molecules along the *c* axis can be described as cylinders with an hydrophilic inner surface of oxygen and nitrogen atoms and an hydrophobic outer surface of methyl groups. The hydrogen atoms of the methyl groups are engaged in van der Waals interactions among themselves, thus providing strong stabilizing forces.

The urethane –CONH– group of *t*-BOC-D-Val-OH is in the cis configuration (with only a slight deviation from planarity, the ω angle being −7°); the same holds for the urethane –CON< group of *t*-BOC-L-Pro-OH[28] and *t*-BOC-L-Aze-OH.[29] To our knowledge, this is the first time such a configuration has been found in the solid state for a secondary amide in a linear compound. Also, we were able to demonstrate that the structure assumed by *t*-BOC-D-Val-OH in the solid state does not depend upon the polarity of the solvent mixture from which the crystals were grown. This finding indicates that the molecular structure of this compound, and in particular the cis configuration at the urethane –CONH– linkage, besides being dictated by side-chain requirements (see also below), is definitely fixed by crystal packing forces, which in turn are governed by intermolecular hydrogen bonds and the unique type of van der Waals contacts present in it.

Thus, from the present x-ray diffraction results and those previously reported by Benedetti et al.[28] and Cesari et al.[29] it may be concluded that the prerequisite for the formation of the oxy analogues to the 3 → 1 intramolecularly hydrogen-bonded peptide conformations, i.e., trans –CONH– or –CON< configuration, is not met by the three *t*-BOC-α-amino acids so far examined. A preliminary x-ray diffraction investigation indicated the absence of such folded forms also in the case of *N*-benzyloxycarbonylglycine.[30]

By means of ^1H and ^{13}C nuclear magnetic resonance and infrared absorption spectroscopies the cis–trans isomerism at the urethane amide linkage of *t*-BOC-α-amino acids in solution has been recently investigated by a number of groups.[16,31–33] The special stabilization of the trans conformation was in part explained by the formation of the seven-membered ring due to intramolecular hydrogen bonding.[16] In particular, the extent of the population of the oxy analogues to the 3 → 1 intramolecularly hydrogen-bonded peptide forms in the conformational equilibrium mixtures in deuteriochloroform increases with decreasing the temperature.[16]

We have reexamined the phenomenon of the cis–trans isomerism at the urethane –CONH– bond of the *t*-BOC derivatives of L-valine, L-alanine, and L-phenylalanine in deuteriochloroform, using proton magnetic resonance and infrared absorption techniques as a function of temperature. Our findings are in excellent agreement with those recently reported by Branik and Kessler.[16] In particular, we have confirmed that the L-Ala and L-Phe derivatives show a markedly higher content of trans form than the L-Val derivative. In the case of *t*-BOC-L-Phe-OH this result has been explained on the basis of the occurrence of the stable axial oxy analogue to the 3 → 1 intramolecularly hydrogen-bonded

Table III
Bond Distances (Å) for *t*-BOC-D-Val-OH

O(1)–C(1)	1.306	N–C(6)	1.332
O(2)–C(1)	1.208	C(6)–O(3)	1.244
C(1)–C(2)	1.517	C(6)–O(4)	1.324
C(2)–C(3)	1.524	O(4)–C(7)	1.471
C(2)–N	1.458	C(7)–C(8)	1.512
C(3)–C(4)	1.482	C(7)–C(9)	1.504
C(3)–C(5)	1.535	C(7)–C(10)	1.510

Table IV
Bond Angles (deg) for *t*-BOC-D-Val-OH

O(1)–C(1)–O(2)	124.5	N–C(6)–O(3)	123.0
O(1)–C(1)–C(2)	115.0	N–C(6)–O(4)	112.8
O(2)–C(1)–C(2)	120.4	O(3)–C(6)–O(4)	124.2
C(1)–C(2)–C(3)	109.9	C(6)–O(4)–C(7)	123.4
C(1)–C(2)–N	113.4	O(4)–C(7)–C(8)	101.9
N–C(2)–C(3)	112.8	O(4)–C(7)–C(9)	109.2
C(2)–C(3)–C(4)	113.4	O(4)–C(7)–C(10)	110.1
C(2)–C(3)–C(5)	110.7	C(8)–C(7)–C(9)	112.0
C(4)–C(3)–C(5)	112.1	C(8)–C(7)–C(10)	110.4
C(2)–N–C(6)	124.3	C(9)–C(7)–C(10)	112.7

Table V
Internal Rotation Angles (deg) for *t*-BOC-D-Val-OH

O(1)–C(1)–C(2)–C(3)	104	C(3)–C(2)–N–C(6)	169
O(1)–C(1)–C(2)–N	−23	C(2)–N–C(6)–O(3)	175
O(2)–C(1)–C(2)–C(3)	−74	C(2)–N–C(6)–O(4)	−7
O(2)–C(1)–C(2)–N	159	N–C(6)–O(4)–C(7)	178
C(1)–C(2)–N–C(6)	−65	O(3)–C(6)–O(4)–C(7)	−3
C(4)–C(3)–C(2)–N	63	C(6)–O(4)–C(7)–C(8)	176
C(4)–C(3)–C(2)–C(1)	−64	C(6)–O(4)–C(7)–C(9)	−65
C(5)–C(3)–C(2)–N	168	C(6)–O(4)–C(7)–C(10)	59
C(5)–C(3)–C(2)–C(1)	−64		

peptide conformation (Figure 4),[16] in analogy with the structures adopted by Gly-X diketopiperazines in which X is an aromatic amino acid residue.[34-36] In this flagpole folded form the aromatic ring is positioned over the seven-membered ring, presumably as a result of attractive intramolecular π–π interaction between the phenyl and the carbonyl groups.

By circular dichroism we have been able to demonstrate that in cyclohexane solution an intense negative Cotton effect near 230 nm, associated primarily with an intramolecular interaction of the polar hydrogen of the carboxylic acid moiety with the carbonyl amide (urethane) group,[11,12] appears in the spectrum of *t*-BOC-L-Pro-OH (Figure 5). This band is absent in the spectra of *t*-BOC-L-Ala-OH and *t*-BOC-L-Val-OH. The origin of this Cotton effect is confirmed by the dramatic decrease in intensity: (i) of the corresponding band of *t*-BOC-L-Pro-OMe, and (ii) upon addition of a low percent of the more polar solvent trimethyl phosphate to a solution of *t*-BOC-L-Pro-OH in cyclohexane. This latter finding has been related to the disruption of the intrinsically stable oxy analogues to the 3 → 1 intramolecularly hydrogen-bonded peptide conformations by the favorable interactions of trimethyl phosphate with the COOH group.[11]

In summary, although the proton magnetic resonance and circular dichroic properties of the valine derivative in solution seem to be indicative of its behavior in the solid state, the same is not straightforward for the other *t*-BOC-α-amino acid derivatives (see, for instance, the case of *t*-BOC-L-Pro-OH). At the present state of our investigation we are not able to predict whether intermolecular or intramolecular forces will prevail in the crystalline compounds; in fact, it is quite possible that each molecule presents an individual case. Also, x-ray diffraction remains the technique of choice for substantiation of intramolecularly hydrogen-bonded forms in the solid state, postulated on the basis of infrared absorption spectroscopy. This conclusion, put forward in the preceding paper for the ten-membered ring oxy analogues to the 4 → 1 intramolecularly hydrogen-bonded peptide conformations,[1] was found here to hold also in the case of the lower homologous seven-membered ring structures.

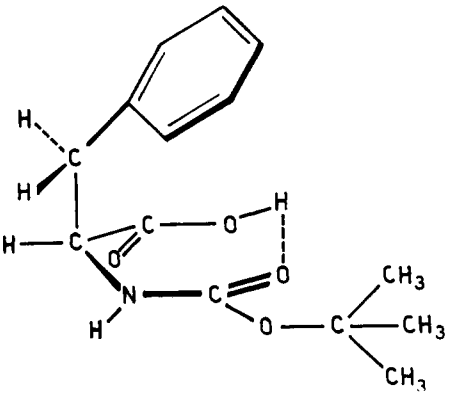

Figure 4. The axial oxy analogue to the 3 → 1 intramolecularly hydrogen-bonded peptide conformation for *t*-BOC-L-Phe-OH.

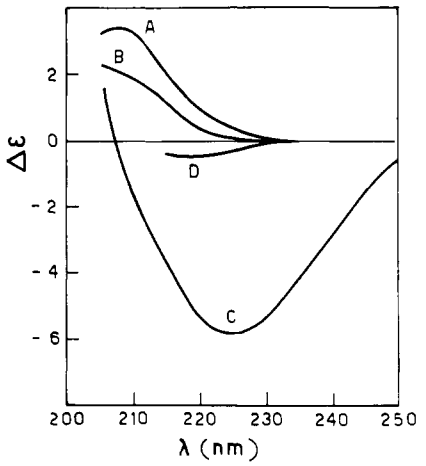

Figure 5. Circular dichroism spectra of *t*-BOC-L-Val-OH (A), *t*-BOC-L-Ala-OH (B), *t*-BOC-L-Pro-OH (C), and *t*-BOC-L-Pro-OMe (D) in cyclohexane.

To investigate more extensively the possible occurrence of the oxy analogues to the 3 → 1 intramolecularly hydrogen-bonded peptide conformations in the solid state, we are currently analyzing by x-ray crystallography the *t*-BOC derivatives of L-alanine and L-phenylalanine, and a series of *N*-acetyl-L-α-amino acids. Incidentally, *N*-acetyl-L-α-amino acids are model compounds of C-terminal regions of polypeptide chains much closer than *N-tert*-butyloxycarbonyl-L-α-amino acids. In principle, the higher basicity of the amide carbonyl with respect to that of the urethane carbonyl and the weaker van der Waals interactions of *N*-acetyl derivatives if compared to those of *N-tert*-butyloxycarbonyl derivatives could lead to different types of structures. In this context, it is encouraging that *N*-acetyl-L-norvaline, although not forming a seven-membered ring oxy analogue to the 3 → 1 intramolecularly hydrogen-bonded peptide conformation in the solid state, has the –CONH– group in the trans configuration, and the amide C=O and the C–O bond of the carboxylic acid group on the same side of the plane passing through the two carbonyl carbon atoms.[37] However, it should be admitted that *N*-acetylglycine, although having the amide

group in the trans configuration, does not adopt such a conformation.[38-40] Both *N*-acetyl amino acids possess two types of intermolecular hydrogen bonds. The former links the OH to the amide C=O, while the latter the NH to the C=O of the carboxylic acid group. A hydrogen bond between the hydroxyl group and the amide carbonyl has been recently described in the solid state also in the case of *N*-acetyl-L-leucine.[41]

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Mesomorphic Structure at Elevated Temperature in Meta and Para Forms of Poly[bis(chlorophenoxy)phosphazene]

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ABSTRACT: Two polymers, the meta (I) and para (II) isomers of poly[bis(chlorophenoxy)phosphazene], have been studied in their high-temperature mesomorphic state by x-ray diffraction. Previous studies revealed two first-order thermal transitions: a lower transition at T(l) involving a large enthalpy change, and an upper transition at T(m) involving very little enthalpy change. In the intervening temperatures, a span of 300 °C for I and 200 °C for II, a mesomorphic phase is known to be stable. Stretched films of I and II heated to 180 °C (between T(l) and T(m) for both) retain molecular orientation but transform from orthorhombic to pseudohexagonal structure. The observed sharp equatorial lines have been indexed (100), (110), and (210) for I, (100) and (110) for II. In both I and II the same spacing of 14.2 Å is observed between chain axes in the two-dimensional lattice. The question of order or disorder with respect to chain directionality is discussed. The T(l) transition involves a 30% expansion in the *ab* plane which is much larger than the previously estimated volume change suggesting a longitudinal contraction of the chains. Analogies are drawn with liquid crystal and plastic crystal structures of small molecules.

A variety of polyphosphazene polymers can be synthesized with a phosphorus–nitrogen backbone and various organic side groups. Allen, Lewis, and Todd[1] and later Singler and co-workers[2-4] reported unusual thermal transition behavior observed by calorimetry and other techniques in several polyphosphazenes. A common feature of many polymers of this class is the existence of two first-order transitions, the lower one denoted T(l) and the upper T(m). The T(l) transition appears to be a transformation between two ordered phases, while the T(m) transition, which occurs just below the decomposition temperature T(d), is the true melting temperature. Spherulitic morphology and birefringence present at room temperature persist above T(l), disappearing only when T(m) is reached, although a change in the magnitude of the birefringence is observed at T(l). On the other hand, the polymer shows fluid properties between T(l) and T(m) and can be molded in this temperature range, which can extend for 150 to 300 °C (see Table I).