naphthalenes.[40] Other such species that have been reported ("element" = C, Si[41] Ge, Sn, P[42]) are of interest because of the crowding of the "peri" substituents and the resulting distortions of their structures.

In summary, a rigid bidentate Lewis acidic receptor for small anions has been synthesized, and its complexes with hydride, fluoride, and hydroxide have been characterized by a variety of methods. The hydride complex was extraordinarily stable both kinetically and thermodynamically. The fluoride and hydroxide complexes are the first hexaorgano $R_3BXBR_3^-$ species (X = F, OH) to be isolated as pure compounds. Further work on multidentate Lewis acids is in progress.

Acknowledgment. I thank Drs. K. Raghavachari, R. W. Alder, I. B. Dicker, and D. Y. Sogah for stimulating discussions. In addition, I am grateful to A. M. Mujsce and W. D. Reents for obtaining mass spectra, J. H. Marshall for attempting the ESR experiment, and H. D. Roth and M. L. M. Schilling for running the CIDNP spectra.

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Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for $[K][C_{14}H_{19}B_2][C_4H_8O_2]_3$ (1·KH·(dioxane)$_3$) (11 pages). Ordering information is given on any current masthead page.

Influence of Pseudoallylic Strain on the Conformational Preference of 4-Methyl-4-phenylpipecolic Acid Derivatives

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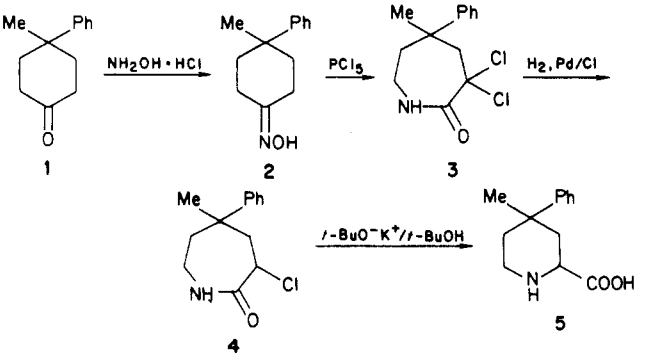
The synthesis of diastereomeric 4-methyl-4-phenylpipecolic acids and their derivatives is described. Investigation by double resonance proton spectroscopy revealed that the conformational preference of substituents attached to the piperidine ring depends upon the hybridization of the piperidine nitrogen. In the free amino acids or leucinamide dipeptides, the C-2 carboxyl group is equatorial. Introduction of a carbamyl moiety on the piperidine nitrogen induces a change in the piperidine ring conformation such that the C-2 carboxyl group is axial, despite a cis-diaxial interaction with the C-4 substituent. The inverted conformational preference of the C-2 and C-4 groups in the *tert*-butyloxycarbonyl and unprotected derivatives is attributed to a severe steric interaction between the partially sp^2 hybridized NCO moiety in the carbamate group and an equatorial C-2 carboxyl group. The X-ray crystal structures of both *cis*- and *trans*-*N*-[(*tert*-butyloxy)carbonyl]-4-methyl-4-phenylpipecolic acids corroborate the solution spectroscopic studies and the concept of pseudoallylic strain in substituted piperidine carbamates. In addition, comparison of the two crystallographically determined structures indicates that hydrogen bonding to the carbonyl of the carbamate produces delocalization into the N–C bond resulting in a shorter bond and more planar piperidyl nitrogen. The conformational preference afforded by pseudoallylic strain indicates that substituted pipecolic acids can be employed in the design of conformationally restricted peptide analogues.

The flexibility of peptide hormones precludes convenient determination of their bioactive conformation by standard spectroscopic techniques. This has necessitated the use of molecular modifications that restrict the conformational freedom of the peptide backbone or amino acid side chains.[1,2] Few convenient approaches are available for side chain restriction of individual amino acid residues. The substitution of α,β-dehydroamino acids[3] fixes the side chain torsion angle but eliminates chirality. A few cyclic amino acids have been incorporated into peptide analogues, including derivatives of aminoindane[4] and aminotetralin,[5] but no conformational information has been reported on such analogues.

A more generalized approach involving the utilization of cyclic amino acids that produce predictable restriction of side chain conformation would be quite useful. The large body of spectroscopic literature on six-membered ring systems makes pipecolic acid derivatives attractive for incuding side chain restriction as an approach to studying the relationship between the conformation of peptides and biological activity.

Scheme I



Here we report on a convenient synthesis for the preparation of C-4 disubstituted pipecolic acids and on the effect of pseudoallylic strain[6] in stabilizing a cis-diaxial

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Table I. Chemical Shift Data for Piperidine Ring Protons in *cis*- and *trans*-*N*-[(*tert*-Butyloxy)carbonyl]-4-methyl-4-phenylpipecolic Acid (6)

proton	chemical shift, ppm[a]	
	cis	*trans*
H2	4.58	4.73
$H3_{ax}$	1.94	2.13
	(J = 6.5, 14.4 Hz)	(J = 6.5, 12.5 Hz)
$H3_{eq}$	2.77	2.55
$H5_{ax}$	1.64	1.98
$H5_{eq}$	2.36	1.88
$H6_{ax}$	3.4	3.38
$H6_{eq}$	3.88	4.03

[a] 300 MHz, in chloroform-*d*.

arrangement[7] of substituents.

Synthesis. 4-Methyl-4-phenylcyclohexanone (1)[8,9] was converted to its oxime (2) which, upon treatment with phosphorus pentachloride, underwent Beckmann rearrangement and dihalogenation[10,11] to afford the dichloro lactam 3 (Scheme I). Catalytic hydrogenolysis gave a mixture of diastereomeric monochloro lactams 4 which were converted to the diastereomeric (±)-pipecolic acids 5 via a Favorskii-type rearrangement.[12,13] Conversion of 5 to the *N*-(*tert*-butyloxy)carbonyl (*N*-BOC) derivatives 6 and separation of the diastereomers by semipreparative HPLC afforded the pure (±) racemates. Condensation of each racemate 6 with L-leucinamide gave the *N*-BOC dipeptides 7 which were again separated by HPLC to afford the optically active isomers. The deprotected dipeptides 8 were obtained by acidolytic cleavage of the *N*-BOC moiety.

NMR Studies. The 300-MHz proton magnetic resonance spectra of the cis and trans isomers of the *N*-BOC amino acids 6 exhibited resonances for the individual piperidine ring protons which were well separated and could be assigned on the basis of chemical shift and selective homo decoupling experiments (Table I). Due to slow rotation of the NCO function of the carbamate group at a probe temperature of 30 °C, the resonances were broadened, and it was not possible to obtain all of the individual coupling constants.[14] In the following discussion, cis and trans refer to the relationship between the C-4 aromatic and C-2 carboxyl substituents.

The resonance for the α-proton of both isomers of the BOC-amino acid 6 suggested no strong coupling ($w_{1/2}$ = 14–16 Hz) (Table I). This is consistent with the vicinal coupling constant for H_{3ax} of both diastereomers (J = 6.5 Hz) and is the range of vicinal diequatorial coupling constants.[15] Thus the α-proton of both isomers of 6 was assigned as equatorial (conformer b).

Preliminary assignment of the relative stereochemistry was based on the chemical shift differences for the methylene protons at C-3 and C-5 which reflect the differential shielding/deshielding influences of the vicinal phenyl[16,17] and methyl[18] groups.[19] The diastereomers of the *N*-BOC amino acid 6 that exhibited the greater chemical shift difference between the geminal axial and equatorial protons at C-3 and C-5 (0.7–0.8 ppm) was assigned *cis*-phenyl:carboxyl stereochemistry. Both axial protons were shielded relative to the equatorial protons (Table I). This isomer was assigned as having axial aromatic/equatorial methyl stereochemistry at C-4. For the second isomer, the chemical shift difference between axial and equatorial protons at C-3 and C-5 was smaller, and $H5_{ax}$ was deshielded relative to $H5_{eq}$. This isomer was assigned as having an axial methyl/equatorial aromatic stereochemistry at C-4 (trans).

The previously determined geminal and vicinal relationships were confirmed by Nuclear Overhauser Enhanced Differential (NOED) spectroscopy.[20-22] These experiments also permitted assignment of H–H, CH_3–H, and H–aryl cis-diaxial relationships within the piperidine ring. While geminal and vicinal protons gave enhancements of 10–20%, the cis-diaxial enhancements were much smaller (<5%). The results of the NOED spectra obtained from selective presaturation of the $H6_{ax}$, H2, and 4-methyl resonances of the cis and trans isomers are given in Table II. For the *N*-BOC isomers (6 and 7), selective presaturation of the $H6_{ax}$ resonance resulted in an enhancement of the aryl resonance in the cis isomers and of the 4-methyl resonance in the trans isomers. This confirmed that the aromatic residue was axial in the cis isomers of carbamates 6 and 7 and that the methyl group was axial in the corresponding trans isomers. In the protected dipeptides (*cis*- and *trans*-7), presaturation of the $H6_{ax}$ resonance also resulted in an NOE for the peptide bond NH at C-2. Presaturation of the H2 resonance of either diastereomer of carbamates 6 and 7 resulted in enhancement only of the signals for the vicinal methylene protons, $H3_{ax}$ and $H3_{eq}$, confirming the assignment of this proton as equatorial.

The resonances for the piperidine ring protons in the unprotected cis and trans dipeptides 8 were not well separated, and only the H2 proton could be assigned. The vicinal coupling constant for this proton in the (+)-cis isomer was 11.4 Hz, suggesting a diaxial relationship between H2 and $H3_{ax}$. The NOED spectra confirmed a profound difference in the conformational relationship between the C-2 and C-4 substituents of the two isomers (Table II). Presaturation of the H2 resonance resulted in

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(14) At −40 °C, the geometry of the carbamate moiety of both BOC diastereomers (6) was 50% syn and 50% anti. The resonances for the piperidine ring protons of these configurational isomers were sharpened, but overlapped for all but the α proton (cis, $\delta(H2_{syn-anti})$ = 0.13 pm, J = 3, 7.2 Hz; trans, $\delta(H2_{syn-anti})$ = 0.19 ppm, J = 2.4, 7.5 Hz).
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(19) An axial phenyl group in cyclohexane is reported[16,17] to deshield both axial (+0.12 ppm) and equatorial (+0.4 ppm) vicinal hydrogens. An equatorial phenyl exerts a minimal shielding influence on vicinal equatorial protons (0–0.01 ppm) but a significant deshielding influence on the axial protons (+0.16 ppm). An equatorial methyl group induces a significant shielding effect on the resonances for both vicinal axial and equatorial protons (−0.3 to −0.5 ppm), while an axial methyl group shields the vicinal equatorial protons (−0.4 ppm) and deshields the vicinal axial protons (+0.2 ppm).[18] In the absence of other influences (i.e., the C-2 carboxyl), the resonances for the axial protons at C-3 and C-5 should be shielded relative to the equatorial protons in the axial aromatic/equatorial methyl isomer, and the reverse relationship is exected in the axial methyl/equatorial aromatic isomer.
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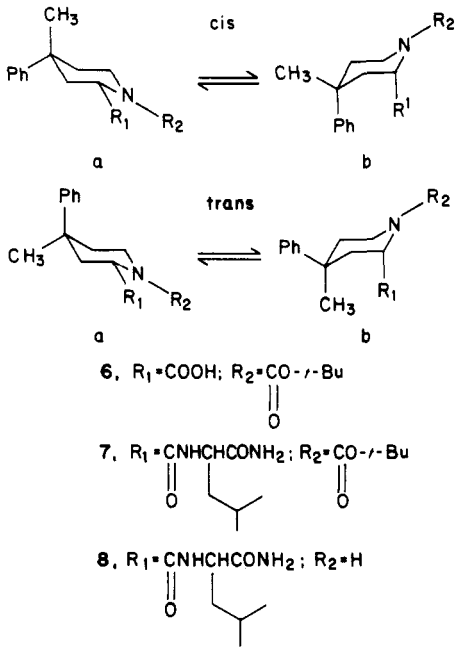

an enhancement of the signal for the methyl group in the cis isomer and an enhancement of the signal for the phenyl group in the trans isomer. When the 4-methyl group was preaturated, an enhancement of H2 was observed in *cis*-8 but not in *trans*-8. The most reasonable interpretation of these results is that the piperidine ring of carbamates **6** and **7** prefers conformation b, while the deprotected dipeptides **8** prefer the inverted conformer a.

Crystal Structure Determinations. The cis and trans isomers of *N*-[(*tert*-butyloxy)carbonyl]-4-methyl-4-phenylpipecolic acid (**6**) crystallized from the same solvent system in different monoclinic space groups and with different packing arrangements. The cis isomer formed dimers with intermolecular hydrogen bonds between the C-2 carboxylic acid substituents and only van der Waals interactions with other dimers (Figure 1a) (see paragraph at end of paper about supplemental material). The trans isomer formed an intermolecular hydrogen bond between the carbamate carbonyl and the C-2 carboxylic acid of an adjacent molecule arrangement in infinite chains parallel to the *b* axis, with only van der Waals contacts in the other directions (Figure 1b). In both isomers, the piperidine ring is in a flattened chair conformation (average torsion angles: cis, 51.9°; trans, 51.1°). In the cis isomer, the C-4 aromatic and C-2 carboxyl substituents are axial, the *N*-BOC moiety is a distorted plane (root mean square of N-1, C-7, O-7,O-8 = 0.005), and the (*tert*-butyloxy)carbonyl group is oriented anti to the C-2 carboxyl (Figure 2a). In the trans isomer, the C-4 methyl and C-2 carboxyl substituents are axial, the *N*-BOC moiety is planar, and the (*tert*-butyloxy)-carbonyl group is oriented syn to the C-2 carboxyl (Figure 2b).

Bond lengths and bond angles for *cis*- and *trans*-**2** are illustrated in Figure 3 (see paragraph at end of paper about supplementary material). All equivalent bond lengths in the two structures are equal (within 1–3 standard deviations) with the exception of the carbamate N—C and C=O bonds (cis, N—C = 1.372 Å, C=O = 1.211 Å; trans, N N—C = 1.336 Å, C=O = 1.233 Å) and the C4–C4M bond. The C4 region shows accommodation, mainly through bond angle deformation, to steric crowding in both isomers. The valence angles around the piperidine nitrogen (cis, Σ_{ang} = 354.5°; trans, Σ_{ang} = 359.6°) indicate that the piperidine nitrogen is more planar in the trans than in the cis isomer. The planarity of the carbamate moiety and the shorter

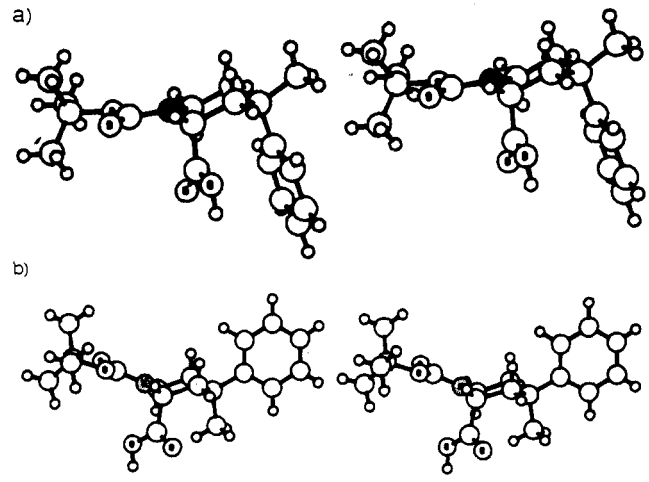

Figure 2. Stereo ORTEP views of the crystallographically determined structure of (a) cis-**6** and (b) *trans*-**6**.

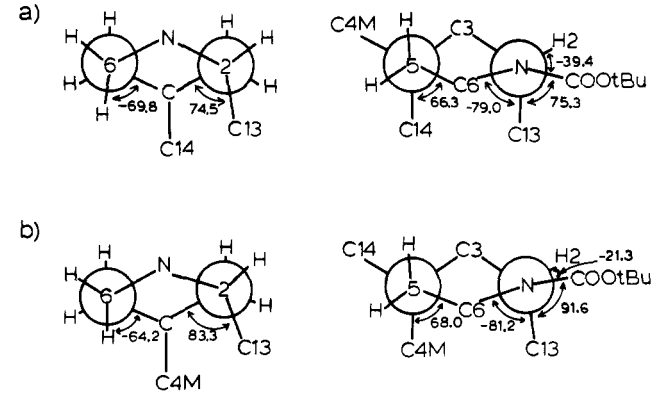

Figure 4. Newman projections of (a) *cis*-**6** and (b) *trans*-**6**. The left view is C6 → C5 and C2 → C3; the right view is C5 → C4 and N1 → C2.

C–N bond length in the trans isomer are consistent with more resonance electron delocalization. The carbamate carbonyl of the trans isomer is involved in hydrogen bonding, while that of the cis isomer is not. Torsion angles are listed in Table III (see paragraph at end of paper about supplemental material).

In the cis isomer, the C-2 carboxyl and C-4 aromatic residues are 3.07 Å apart and both are displaced slightly out from the piperidine ring. The distance between the carboxyl and the phenyl substituent and their parallel orientations indicates a π–π interaction between them. Relevant torsion angles around these substituents are illustrated in Figure 4a. In the trans isomer, the C-2 carbonyl and C-4 methyl residues are 3.26 Å apart and are displaced further from the piperidine ring (compare Figure 4a and 4b). The most dramatic difference between the two isomers is the torsion angle C7–N1–C2–C13 (trans, 91.6°; cis, 75.3°).

In their analysis of structural data (21 observations) on the C(sp^2)–N(piperidyl) bond, Gilli and Bertolasi[23] plotted *T*, the mean torsion angle of C2—N—X=Y and C6—N—X=Y (really the mean of one torsion angle and 180° minus the other torsion angle) vs. the N—C bond distance, *d*. They plotted a least-squares curve assuming a hyperbolic dependence of *T* and *d* (see Figure 5 in ref 23). The values of *T* and *d* for the cis and trans isomers reported here fall very close to this least-squares curve (see values in Table IV). They also plotted a least-squares curve

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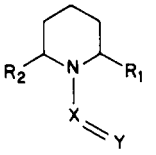
Table II. Proton NOED Spectral Data for Diastereomeric 4-Methyl-4-phenylpipecolic Acid Derivatives

	NOE detected					
proton irradiated	*cis*-6	*trans*-6[a]	(+)-*cis*-7[a]	(+)-*trans*-7[a]	(+)-*cis*-8[b]	(+)-*trans*-8[b]
4-Me	*c*	$H6_{ax}$ (5.9%)	*c*	$H6_{ax}$ (5.0%)	H2 (4.7%)	*c*
$H6_{ax}$	PhH (4%)	4-Me (2.3%)	PhH (1.6%)	4-Me (1.4%)	*d*	*d*
H2	*e*	*e*	*e*	*e*	4-Me (1.1%)	PhH (1.2%)

[a] 300 MHz, in $CHCl_3$-*d*. [b] 300 MHz, in Me_2SO-d_6. [c] Vicinal enhancements at H3 and H5 only (8–12%). [d] Resonance could not be assigned. [e] Vicinal enhancements at H3 only (5–20%).

Table IV. Geometry around the Nitrogen in Axially Substituted Piperidines



X=Y	R_1	R_2	T^a	d^b	N^c	α^d
$-N{=}NC_6H_5$[e]	CH_3	CH_3	6.2	1.338	0.092	119.5
$-C(CH_3){=}N(C_6H_5)$[f]	CH_3	CH_3	9.7	1.374	0.133	119.1
$-C(O)C_6H_5$[g]	CH_3	CH_3	7.2	1.349	0.068	119.8
$-C(O)CH_3$[h]	COOH	H	6.1	1.336	0.082	119.7
$-C(O)C_6H_5$[i]	CH_2COCH_3	CH_2COCH_3	7.7	1.355	0.077	119.7
cis-6	COOH	H	13.5	1.372	0.196	118.2
trans-6	COOH	H	3.6	1.336	0.050	119.9

[a] *T*, mean torsion angle C2-NX=Y, C6-NX=Y in degrees. [b] *d*, M–X bond length in angstroms. [c] *N*, distance of nitrogen from 2-6-X plane, in angstroms. [d] α, average of C2-N-X, C6-N-X, and C2-N-C6 bond angles in degrees. [e] Lunazzi, L.; Cerioni, G.; Foresti, E.; Macciantelli, D. *J. Chem. Soc., Perkin Trans 2* **1978**, 686. [f] Valega, T. W. *J. Org. Chem.* **1966**, *31*, 1150. [g] Arte, E.; Feneau-Dupont, J.; Declercq, J. P.; Germain, G.; Van Mewerssche, M. *Cryst. Struct. Commun.* **1977**, *6*, 773. [h] Rae, I. D.; Raston, C. L.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 215. [i] Quick, J.; Mondello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705.

assuming a parabolic dependence of α, the mean of the three valence angles around the piperidyl N, and the N–C distance, *d*. Again the values of α vs. *d* for the cis and trans isomers reported here fall on the least-squares curve (Figure 6 in ref 18). The authors proposed that the relationship of *T* and *d* results from the balance of two opposing forces, one arising from the stabilization by delocalization of electrons into the C–N bond and the other arising from steric hindrance of the substituents. Since the steric hindrance at the N–C bond should be approximately equivalent in the cis and trans isomers, our results suggest that hydrogen bonding may produce delocalization into the N–C bond resulting in a shorter bond and a more planar piperidyl nitrogen. Ab initio calculations,[24] ^1H NMR,[25] and infrared spectroscopic studies[26] have all indicated a redistribution of electron density into the N–C bond of an NC=O group when a hydrogen bond is formed to the carbonyl. These studies have concentrated on the amide bond; the results presented here would indicate that the redistribution of electron density on hydrogen bonding to the carbonyl of a carbamate group is into the N–C bond and not into the (*tert*-butyloxy)carbonyl linkage.

Summary and Conclusions. Both NMR and crystallographic studies of *cis*- and *trans*-6 indicate that the predominant conformation of these diastereomers contain an axial carboxyl group. The NMR data also suggest that a similar conformation is preferred for the corresponding isomeric dipeptide carbamates, *cis*-7 and *trans*-7.

A unique feature of these conformations is the presence of cis-diaxial groups at C-2 and C-4. Normally, such diaxial interactions would be energetically unfavorable relative to the corresponding cis-diequatorial conformation. That this is not the case for the *N*-BOC derivatives 6 and 7 can be attributed to pseudoallylic strain,[6] which in the present study is related to the NCOO coplanarity with C-2 and C-6 of the piperidine ring. Since an equatorial 2-carboxyl or 2-carboxamide group sterically interferes with the coplanarity of the carbamate moiety, the C-2 group assumes a less hindered axial orientation through ring inversion.[26]

The importance of the carbamate moiety in stabilizing the 2,4-diaxial relationship was indicated by removal of the *N*-BOC group in *cis*- and *trans*-7, as the NOED spectra of the corresponding products (*cis*- and *trans*-8) were consistent with a 2,4-diequatorial conformation.

The origin of pseudoallylic strain is related to the piperidine nitrogen which is partially sp^2 hydridized due to resonance interaction with an attached unsaturated moiety (usually a carbonyl). Since the energy barrier to rotation of this resonance-stabilized system is known to be large (15–23 kcal/mol)[27,28] relative to the standard free energy difference between an axial and equatorial carboxyl[6] (1–2 kcal/mol), steric repulsion between the N substituent and an equatorial carboxyl is minimized by ring inversion. The preference for a highly energetic diaxial arrangement between the carboxyl group and the phenyl (*cis*-6 and *cis*-7) and between the carboxyl group and the 4-methyl (*trans*-6 and *trans*-7) illustrate this point.

These conclusions are based on the reasonable assumption that the nitrogen lone pair delocalization for piperidine carbamates is similar to that of other piperidine derivatives. Indeed, the N–X bond lengths for a number of N-substituted piperidines (Table IV) agree well with the structural data obtained in the present study. All of the compounds listed in Table IV possess axial substituents, presumably as a consequence of pseudoallyic strain. Most of these compounds contain cis–diaxial groups flanking the piperidine nitrogen. The results of the present study show that a cis-2,4-diaxial conformation also can be stabilized by this mechanism. This feature endows pipecolic acids with the ability to restrict the conformation of its ring substituents when incorporated into peptides.

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The side chain conformation of amino acid residues is generally defined by the C_α–C_β torsion angle. The three predominant rotamer populations are gauche (+), θ = +60°; gauche (−), θ = −60°; and trans, θ = 180°.[29] The most highly favored rotamers are the gauche (−) and trans, since steric crowding is generally too great in the gauche (+) rotamer to allow a high population. The six-membered piperidine ring system precludes the trans rotamer. When C-4 substituted pipecolic acid derivatives are incorporated at the N-terminal position of a peptide analogue, the predominant conformer should be a spatial mimic of the parent amino acid in the gauche (−) conformation. However, when these derivatives are incorporated at an internal position, the influence of the partially sp^2 hybridized peptide amide bond should induce the same conformational preference as seen for the carbamate derivatives analyzed here. In this case, the C-4 substituted derivatives provide a model for the gauche (+) rotamer.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 281 spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. Mass spectral analyses were performed on either an AE1 MS-30 or Finnegan 4000 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter using a 1-dm cell. TLC analysis utilized precoated silica gel (GF) plates, 0.25 mm thick, obtained from Analtech, Inc., Newark, DE. HPLC separations were performed on a Beckman Model 110-A with 5-μm (Licrosorb Si 60, Altex) or 10-μm (Rsil, Alltech) semipreparative (10 mm × 250 mm) silica gel columns. HPLC grade solvents were obtained from MCB, Cincinnati, OH. HPLC grade chloroform (hydrocarbon stabilized) was passed over basic alumina to remove acidic decomposition products and used immediately.

All chemicals and solvents were reagent grade unless otherwise specified. *tert*-Butyl alcohol was distilled over calcium oxide. Tetrahydrofuran (THF) was distilled from sodium. Amino acids were obtained from Sigma Chemical Company, St. Louis, MO. All other chemicals were obtained from Aldrich Chemical Company, Milwaukee, WI. Extracts of materials in organic solvents were dried over anhydrous sodium sulfate and the solvent was evaporated under aspirator pressure with a rotary flash evaporator at a bath temperature between 25 and 45 °C.

NMR spectra were recorded on a JEOL FX-90 or Nicolet NT 300 spectrometer. Chemical shifts are reported in ppm downfield from Me_4Si. Steady-state NOE differential spectra were acquired by low power selective presaturation for 3 s. Four accumulations were acquired at each resonance frequency and the sequence was repeated until an adequate S/N ratio was achieved. A control spectrum was acquired simultaneously at a frequency at which there was no reasonance absorption.

4-Methyl-4-phenylcyclohexanone Oxime (2). A solution of 4-methyl-4-phenylcyclohexanone (1)[8,9] (10 g, 0.053 mol), hydroxylamine hydrochloride (3.6 g, 0.053 mol), and pyridine (3.45 g, 0.053 mol) in methanol (300 mL) was stirred under reflux for 1.5 h. The methanol was removed in vacuo and the oily residue was dissolved in methylene chloride (200 mL) and water (100 mL). The aqueous layer was reextracted with methylene chloride (50 mL) and the combined organic extracts were dried and evaporated in vacuo to give 10.5 g (0.051 mol, 99%) of an oily residue which crystallized on standing: mp 75 °C; MS, *m/e* 203 (M^+); IR (KBr) 3260 (OH), 1670 (C=N); NMR ($CDCl_3$) δ 8.2 (s, 1 H, NOH), 7.32 (m, 5 H, C_6H_5), 2.95–1.4 (m, 8 H, $-CH_2-$), 1.24 (s, 3 H, CH_3). Anal. Calcd $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.95; H, 8.51; N, 6.89.

3,3-Dichloro-5-methyl-5-phenyl-2-oxoperhydroazepine (3). To a stirred solution of freshly prepared phosphorus pentachloride (21.8 g, 0.16 mol) in CH_2Cl_2 (250 mL) at 10 °C was added oxime 2 (10.7 g, 0.053 mol) dissolved in CH_2Cl_2 (175 mL) and the temperature was maintained below 10 °C. After the addition, the solution was allowed to warm to room temperature and stirring was continued an additional 2–4 h. Chlorine gas was bubbled throughout at two different times to maintain a saturated solution. The reaction was stopped by careful addition of chipped ice (50 g) followed by saturated aqueous sodium bicarbonate (150 mL). After stirring overnight, the organic layer was separated and washed with additional sodium bicarbonate (100 mL) and water (100 mL) and dried, and the solvent was removed in vacuo. The oily residue was diluted with carbon tetrachloride and cooled to afford 10.9 g (76%) of crystalline product; mp 144–145 °C; MS, *m/e* (relative intensity) 275 (2.1, $M^+ + 4$), 273 (8.9, $M^+ + 2$), 271 (13.8 M^+); IR (KBr) 3330 (NH), 1680 (C=O); NMR ($CDCl_3$) v 7.36 (s, 5 H, C_6H_5), 3.54 (q, J = 15 Hz, 2 H, H6), 3.13 (q, J = 14.5 Hz, 2 H, H3), 2.7–1.58 (m, 2 H, H5), 1.42 (s, 3 H, CH_3). Anal. Calcd $C_{13}H_{15}NOCl_2$: C, 57.37; H, 5.56; N, 5.15; Cl, 26.05. Found: C, 57.53; H, 5.79; N, 4.89; Cl, 25.94.

3-Chloro-5-methyl-5-phenyl-2-oxoperhydroazepine (4). A solution of dichloro lactam 3 (0.5 g, 0.0018 mol) and 10% Pd/C (0.25 g) in glacial acetic acid (50 mL) was shaken at 40 psi of hydrogen for 2 h. The reaction mixture was filtered through Celite and the acetic acid was azeotropically removed in vacuo with carbon tetrachloride. The residue was dissolved in methylene chloride and washed twice with saturated sodium bicarbonate (50 mL) and water (50 mL). The organic layer was dried and evaporated in vacuo to give 0.39 g (91%) of the diastereomeric mixture: mp 179–180 °C; MS, *m/e* (relative intensity) 239 (7.3, $M^+ + 2$), 237 (20.1, M^+); IR (KBr) 3260 (NH), 1710 (C=O), 1650 (C=O); NMR ($CDCl_3$) δ 7.38, 7.33 (s, 5 H, C_6H_5), 4.94 (dd, J = 14.8, 7.2, 0.5 H, CHCl), 4.58 (dd, J = 14.4, 4.2, 0.5 H, CHCl), 3.62–2.92 (m, 2 H, H6), 2.82–1.68 (m, 4 H, H3 and H5), 1.52, 1.18 (s, 3 H, CH_3). Anal. Calcd for $C_{13}H_{16}NOCl$: C, 65.58; H, 6.78; N, 5.89; Cl, 14.91. Found: C, 65.88; H, 6.78; N, 5.79; Cl, 15.12.

4-Methyl-4-phenylpipecolic Acid (5). To a solution of 4 (1.56 g, 0.007 mol) in freshly distilled *tert*-butyl alcohol (50 mL) was added freshly prepared potassium *tert*-butoxide in *tert*-butyl alcohol (20 mL, 1.2 M). The solution was refluxed for 12 h and then cooled to 10 °C, 2 N hydrochloric acid (10 mL) was added, and the solution was refluxed for 1 h. After concentrating the solution in vacuo, the residue was dissolved in aqueous ethanol and passed over an ion-exchange column (Dowex 50). The residual salts were removed by elution with water (200 mL) and the amino acid was eluted with 2 N ammonium hydroxide (500 mL). Evaporation of the ammonium hydroxide gave 0.95 g (66%) of the amino acid as a 60/40 mixture of diastereomers: R_f (ethyl acetate/ethanol/5% acetic acid, 5:5:1) 0.36, 0.41; MS, *m/e* 219 (M^+); IR (KBr) 3200 (NH^+ stretch), 1640 (C=O), 1600 (COO– asymmetric stretch); NMR (CF_3COOD) δ 7.49, 7.47, 7.4 (5 H, PhH), 4.58, 4.23 (br s, 0.5 H, $W_{1/2}$ = 25 Hz, H2), 3.9, 3.7 (br s, 0.5H, $H6_{ax}$), 3.25 (m, 1 H), 2.8–1.96 (m, 3 H), 1.55 (s, 1.5 H cis CH_3), 1.41 (s, 1.5 H, trans CH_3). Anal. Calcd for $C_{13}H_{17}NO_2 \cdot {}^1/_2H_2O$: C, 68.39; H, 7.95; N, 6.14. Found: C, 68.39; H, 8.22; N, 6.35.

***cis*- and *trans*-*N*-[(*tert*-Butyloxy)carbonyl]-4-methyl-4-phenylpipecolic Acid (6).** To a diastereomeric mixture of 5 (1.97 g, 0.009 mol) in dioxane (9 mL), water (9 mL), and 2 N sodium hydroxide (9 mL) was added bis[(*tert*-butyloxy)carbonyl dicarbonate (2.15 g, 0.0099 mol). The reaction mixture was stirred at room temperature for 48 h, after which the dioxane was removed in vacuo and water (20 mL) was added. The aqueous solution was adjusted to pH 11 with 2 N sodium hydroxide prior to extraction with diethyl ether (50 mL) and dichloromethane (50 mL). The aqueous layer was acidified to pH 4 with 10% citric acid and extracted 4 times with dichloromethane (50 mL). The combined organic extracts were washed once with water (50 mL), then dried, and evaporated in vacuo to give 1.99 g (69%) of a diastereomeric mixture of 6: IR (neat) 3300 (OH), 1710 (C=O's). The diastereomeric cis and trans isomers were separated by HPLC: retention times (hexane/4% glacial acetic acid, 4 mL/min, t_0 = 2.3 min) cis, 8.3 min; trans, 11.3 min. The trans isomer, mp 128 °C, and the cis isomer, mp 142 °C, were crystallized from petroleum ether/ethyl acetate; NMR (300 MHz, $CDCl_3$) cis δ 7.31, 7.24, 7.23, 7.19 (5 H, PhH), 4.58 (br s, 1 H, $w_{1/2}$ = 16.2 Hz, H2), 3.88 (dt, 1 H, J = 14.4 Hz, $H6_{eq}$), 3.4 (br t, 1 H, J = 2.4, 9.6, 14.4 Hz, $H6_{ax}$), 2.77 (br d, 1 H, J = 14 Hz, $H3_{eq}$), 2.36 (br d, 1 H, J = 17 Hz, $H5_{eq}$), 1.94 (dd, 1 H, J = 6.5, 14 Hz, $H3_{ax}$), 1.64 (td, 1

(29) IUPAC-IUB Commission on Biochemical Nomenclature, *Biochemistry*, **1970**, *9*, 3471.

H, J = 4, 14, 16.5 Hz, $H5_{ax}$), 1.44 (s, 9 H, BOC-CH_3), 1.44 (s, 3 H, CH_3); NMR (300 MHz, $CDCl_3$) trans δ 7.31 (s, 5 H, PhH), 4.77 (br s, 1 H, $w_{1/2}$ = 16.2 Hz, H2), 4.03 (dt, 1 H, J = 16.2 Hz, $H6_{eq}$), 3.38 (m, 1 H, $H6_{ax}$), 2.55 (br d, 1 H, J = 16.2, $H3_{eq}$), 2.13 (dd, 1 H, J = 6.5, 12.5 Hz, $H3_{ax}$), 1.98 (td, 1 H, J = 4, 11.5, 14 Hz, $H5_{ax}$), 1.88 (m, 1 H, $H5_{eq}$), 1.46 (s, 9 H, BOC-CH_3), 1.26 (s, 3 H, CH_3). Anal. Calcd $C_{18}H_{25}NO_3$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.58; H, 8.22; N, 4.57.

[*N*-[(*tert*-Butyloxy)carbonyl]-4-methyl-4-phenylpipecolyl]leucinamide (7). To a solution of *trans*-**6** (0.350 g, 0.0011 mol) in freshly distilled THF (5 mL) was added *N*-methylmorpholine (0.11 g, 0.0011 mol) and the solution was cooled to −20 °C. Isobutyl chloroformate (0.149 g, 0.0011 mol) in THF (0.5 mL) was added and the solution was stirred 5 min at −20 °C, whereupon a solution of L-leucinamide hydrochloride (0.183 g, 0.0011 mol) and *N*-methylmorpholine (0.11 g, 0.0011 mol) in THF/water (1 mL, 1:1 v/v) was added and stirring was continued for 15 min. The reaction mixture was allowed to warm to 25 °C, stirred an additional hour, and then quenched with the addition of water (5 mL). The aqueous solution was extracted twice with ethyl acetate (20 mL). The organic extracts were combined, washed sequentially with portions (10 mL) of 1 N NaOH, 10% citric acid, saline, and water, dried, and evaporated in vacuo to give 0.456 g (96%) of the dipeptide trans-**7** as a foam. A small portion was separated by HPLC for spectroscopic analysis: retention times (ethyl acetate, 3 mL/min, t_0 = 4.95 min) 9.3 min, 10.1 min; NMR (+)-trans, (300 MHz, $CDCl_3$) δ 7.21, 7.37 (5 H, PhH), 6.3 (d, 1 H, J = 8 Hz, -NH-), 6.3, 5.3 (br s, 2 H, $CONH_2$), 4.51 (m, 2 H, H2 and Leu CH α), 3.93 (br s, 1 H, $H6_{eq}$), 3.26 (br t, 1 H, $H6_{ax}$), 2.46 (m, 1 H, $H3_{eq}$), 2.08 (dd, 1 H, J = 5.6, 13.7 Hz, $H3_{ax}$), 1.7 (m, 5 H, $H5_{eq}$, $H5_{ax}$, Leu β and γ CH), 1.43 (s, 9 H, BOC-CH_3), 1.24 (s, 3 H, CH_3), 0.98, 0.94 (d, 6 H, Leu CH_3).

The cis isomer **6** (60 mg, 0.00019 mol) was reacted in a similar fashion to give 60 mg (74%) of the dipeptide *cis*-**7**. The diastereomeric mixture of *cis*-**7** was separated by HPLC: retention times (0.75% methanol in $CHCl_3$, 5 mL/min, t_0 = 3.3 min) 12.9 min, $[\alpha]^{25}_D$ +2.69° (*c* 1.2, CH_3OH), 22.5 min, $[\alpha]^{25}_D$ −31.5° (*c* 1.1, CH_3OH); NMR (+)-cis (300 MHz, $CDCl_3$) δ 7.17, 7.26 (5 H, PhH), 6.08 (d, 1 H, J = 8 Hz, -NH-), 6.48, 5.53 (br s, 2 H, $CONH_2$), 4.48 (t, 1 H, J = 6.2, H2), 4.16 (m, 1 H, Leu α-), 3.92 (br d, 1 H, J = 14 Hz, $H6_{eq}$), 3.27 (br t, 1 H, J = 2.8, 10, 14 Hz, $H6_{ax}$), 2.73 (dd, 1 H, J = 13.8, 5.4, $H3_{eq}$), 2.26 (br dd, 1 H, J = 14.8, 4.4 Hz, $H5_{eq}$), 1.99 (dd, 1 H, J = 6.8, 14.2 Hz, $H3_{ax}$), 1.72 (m, 4 H, $H5_{ax}$ and Leu β and γ protons), 1.45 (s, 9 H, BOC-CH_3), 1.22 (s, 3 H, CH_3), 0.84, 0.77 (d, 6 H, J = 6.5 Hz, Leu CH_3). Anal. Calcd $C_{24}H_{37}O_4N_3 \cdot {}^1/_2H_2O$: C, 65.42; H, 8.69; N, 9.54. Found: C, 65.69; H, 8.94; N, 9.17.

[4-Methyl-4-phenylpipecolyl]leucinamide Hydrochloride (8·HCl). A solution of the diastereomeric mixture *trans*-**7** (0.456 g, .0011 mol) in 4 N hydrochloric acid in dichloromethane (20 mL) was stirred at room temperature for 1.5 h. Evaporation of solvent in vacuo and trituration of the residual oil with diethyl ether gave the dipeptide hydrochloride *trans*-**8** as a diastereomeric mixture (0.192 g, 0.0052 mol, 47%): IR (KBr) 3300 (NH^+), 2430 (NH^+), 1675 (C=O); NMR (+)-trans (300 MHz, Me_2SO-d_6) δ 8.76 (d, 1 H, J = 8 Hz, -NH-), 8.95, 8.76 (br s, 2 H, $CONH_2$), 7.52, 7.43, 7.29, 7.08 (m, 5 H, PhH), 4.26 (m, 1 H, Leu α), 3.6 (m, 1 H, H2), 3.14, 2.71, 2.43, 1.83, 1.69 (m, 1 H each) 1.62 (3 H, Leu β and γ CH), 1.17 (s, 3 H, CH_3), 0.95, 0.89 (d, 6 H, J = 6, Leu CH_3). Anal. Calcd for $C_{19}H_{29}N_3O_2HClO \cdot 5H_2O$: C, 60.54; H, 8.29; N, 11.15. Found: C, 60.09; H, 8.29; N, 10.95.

(+)-*cis*-**7** (18.5 mg 0.043 mmol) was deprotected in a similar manner to give 7.7 mg (0.021 mmol, 49%) of unprotected dipeptide, (+)-cis-**8**: $[\alpha]^{25}_D$ +17.1° (*c* 0.6, CH_3OH). (−)-*cis*-**7** (27.3 mg, 0.063 mmol) was reacted as described above to give 9.1 mg (0.025 mmol, 40%) of (−)-*cis*-**8**: $[\alpha]^{25}_D$ −40.5° (*c* 0.5, CH_3OH); NMR (+)-cis (300 MHz, Me_2SO-d_6) δ 8.64 (d, 1 H, J = 8 Hz, -NH-), 7.21, 7.4 (m, 5 H, PhH), 7.5, 7.0 (br s, 2 H, $CONH_2$), 4.29 (m, 1 H, Leu CH α), 4.05 (d, 1 H, J = 11.4, H2), 1.4 (s, 3 H, CH_3), 0.88 (dd, 3 H, J = 6 Hz, Leu CH_3). Anal. Calcd for $C_{19}H_{29}N_3O_2 \cdot NClO \cdot 5H_2O$: C, 60.54; H, 8.29; N, 11.14. Found: C, 60.52; H, 8.08; N, 11.04.

X-ray Crystallographic Studies (Tables are presented as supplementary material; see paragraph at end of paper). Crystals of both *cis*- and *trans*-**6** were grown by slow evaporation from petroleum ether/ethyl acetate solutions. The crystallographic data for both structures are given in Table V. Intensity data for each structure were measured on a computer controlled diffractometer using 0/20 scans. The structures were solved by using the direct methods program MULTAN[30] in conjunction with the NQEST figure of merit program.[31] A full-matrix least-squares procedure was used in the refinement of the atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms and isotropic thermal parameters for hydrogen atoms. Details of the intensity measurements and refinement results are included in Table V. Atomic coordinates for (±)-*trans*-**6** and (±)-*cis*-**6** are given in Tables VI and VII, respectively.

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Supplementary Material Available: Full X-ray data for *cis*-**6** and *trans*-**6** (Tables III, V, VI, and VII; Figures 1 and 3) (6 pages). Ordering information is given on any current masthead page.

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