benzene derivatives in α-CD complexes.

It is clear from Figures 6-8 that for a given carbon, a large change is induced in the ^{13}C displacement only when the borderline crosses over it. This result is important, since it suggests that the dielectric environmental effects are restricted on ^{13}C shifts of carbon atoms situated within a quite narrow region. In other words, ^{13}C shifts may serve as a sensitive probe of electrical environment change around a given carbon atom in heterogeneous systems such as those investigated here. The method presented here may be applicable to investigations of a variety of complex systems, for examples, the determination of the relative orientation of constituents in a enzyme–substrate complex and the estimation of dielectric nature around a substrate included in a cleft or cavity of the enzyme.

Experimental Section

BA, PHBA, PNP, and all solvents used were commercially available reagent-grade materials. Prior to use, almost all solvents were dried and distilled.

^{13}C NMR spectra of BA, PHBA, and PNP in a series of solvents were recorded at 30 °C on a JEOL JNM PS-100 NMR spectrometer equipped with a PFT-100 Fourier transform system at 25.1 MHz, with instrumental setting conditions of 20° pulse tip angle, 6250-Hz spectral width, 4-s pulse repetition time, 4096 data points, and more than 5000 accumulations of interferograms, using a 8-mm sample tube. The concentration of NMR samples was 0.4 M.

Molecular orbital calculations were carried out on a HITAC-M280 computer at the Information Processing Center of Tokyo Institute of Technology. The calculations of CNDO/2 containing the effects of solvaton and ^{13}C shifts were made by using the program originally written by Prof. Ando and modified by Hoshi to include the effect of the double-layer environment.

Acknowledgment. We thank Prof. I. Ando of the Tokyo Institute of Technology for the use of the MO program.

Registry No. α-CD, benzoic acid 1:1 inclusion complex, 15162-62-6; α-CD, *p*-hydroxybenzoic acid 1:1 inclusion complex, 15155-16-5; α-CD, *p*-nitrophenol 1:1 inclusion complex, 61955-25-7.

Conformational Dependencies of Vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ and $^{13}C(O)-N-C_\alpha-^{1}H$ Coupling Constants in Compounds Which Model the Peptide Backbone

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Abstract: To determine the angular dependencies of vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ and $^{13}C(O)-N-C_\alpha-^{1}H$ coupling constants on the dihedral angle about the $N-C_\alpha$ bond, a series of ^{13}C-labeled lactams and amides were synthesized and their NMR parameters were measured. The compounds were chosen to serve as model compounds for peptides while providing structural rigidity and covering the entire range of dihedral angles. Both the vicinal $^{13}C-^{13}C$ and $^{13}C-^{1}H$ coupling constants are larger in magnitude than the calculated INDO-FPT molecular orbital results over the whole range of dihedral angles. However, the $^{13}C(O)-N-C-^{1}H$ coupling constants are only about one-half of those previously obtained in systems which are less appropriate model compounds for peptide systems. Geminal $^{13}C(O)-N-^{13}C$ coupling constants are quite sensitive to cis/trans orientations of the amide bond and also offer a potential parameter for structural studies in peptides.

Nuclear spin–spin coupling constants have been used extensively[1-5] for studies of peptide conformations in solution. Alternatives to the $^{1}H-N-C_\alpha-^{1}H$ coupling constants, which can help in providing a unique specification of φ angles in the peptide backbone **1**,[6-11] include vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ and $^{13}C(O)-N-C_\alpha-^{1}H$ coupling constants. Recent studies from these laboratories have emphasized the conformational and substituent dependencies of geminal,[12,13] vicinal,[14-16] and long-range[17] $^{13}C-^{13}C$ and $^{13}C-^{1}H$ coupling constants in cases in which there are only carbon atoms in the coupling path. These studies clearly indicate the complexity of intercarbon coupling constants and emphasize the necessity for experimental measurements in appropriate model systems. The absence of systematic studies of vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ coupling would have made it inappropriate, heretofore, to use such data for conformational conclusions in peptide systems.

Several experimental and theoretical studies have treated the angular dependence of vicinal $^{13}C(O)-N-C_\alpha-^{1}H$ coupling constants. However, the plot of these, which is based on uridine and

(1) Bystrov, V. F. *Prog. NMR Spectrosc.* **1976**, *10*, 41.
(2) Deslauriers, R.; Smith, I. C. P. In "Topics in Carbon-13 NMR Spectroscopy"; Levy, G., Ed.; Wiley: New York, 1975; Vol. 2.
(3) Thomas, W. A. In "Annual Reports on NMR Spectroscopy"; Mooney, E. F., Ed.; Academic Press: New York, 1976; Vol. 6B.
(4) Urry, D. W.; Onishi, M. In "Spectroscopic Approaches to Biomolecular Conformation"; Urry, D. W., Ed., American Medical Association: Chicago, 1970; pp 260, 270.
(5) Hruby, V. J. In "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins"; Weinstein, B., Ed., Marcel Dekker: New York, 1974; Vol. 3.
(6) Barfield, M.; Karplus, M. *J. Am. Chem. Soc.* **1969**, *91*, 1.
(7) Bystrov, V. F.; Portnova, S. L.; Tsetlin, V. I.; Ivanov, V. T.; Ovchinnikov, Yu. A. *Tetrahedron* **1969**, *25*, 493.
(8) Ramachandran, G. N.; Chandrasekaren, R.; Kopple, K. D. *Biopolymers* **1971**, *10*, 2113.
(9) Barfield, M.; Gearheart, H. L. *J. Am. Chem. Soc.* **1973**, *95*, 641.
(10) Bystrov, V. F.; Ivanov, V. T.; Portnova, S. L.; Balashova, T. A.; Ovchinnikov, Yu. A. *Tetrahedron* **1973**, *29*, 873.
(11) De Marco, A.; Llinás, M.; Wüthrich, K. *Biopolymers* **1978**, *17*, 637.
(12) Barfield, M.; Walter, S. R. *J. Am. Chem. Soc.* **1983**, *105*, 4191.
(13) Barfield, M.; Della, E. W.; Pigou, P. E. *J. Am. Chem. Soc.* **1984**, *106*, 5051.
(14) Barfield, M. *J. Am. Chem. Soc.* **1980**, *102*, 1.
(15) Barfield, M.; Marshall, J. L.; Canada, E. D., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7.
(16) Barfield, M.; Canada, Jr., E. D.; McDaniel, C. R., Jr.; Marshall, J. L.; Walter, S. R. *J. Am. Chem. Soc.* **1983**, *105*, 3411.
(17) Walter, S. R.; Marshall, J. L.; McDaniel, C. R., Jr.; Canada, E. D., Jr.; Barfield, M. *J. Am. Chem. Soc.* **1983**, *105*, 4185.

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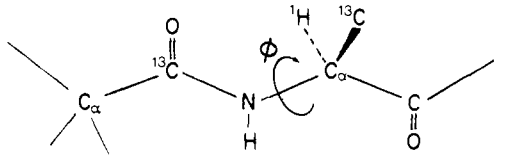

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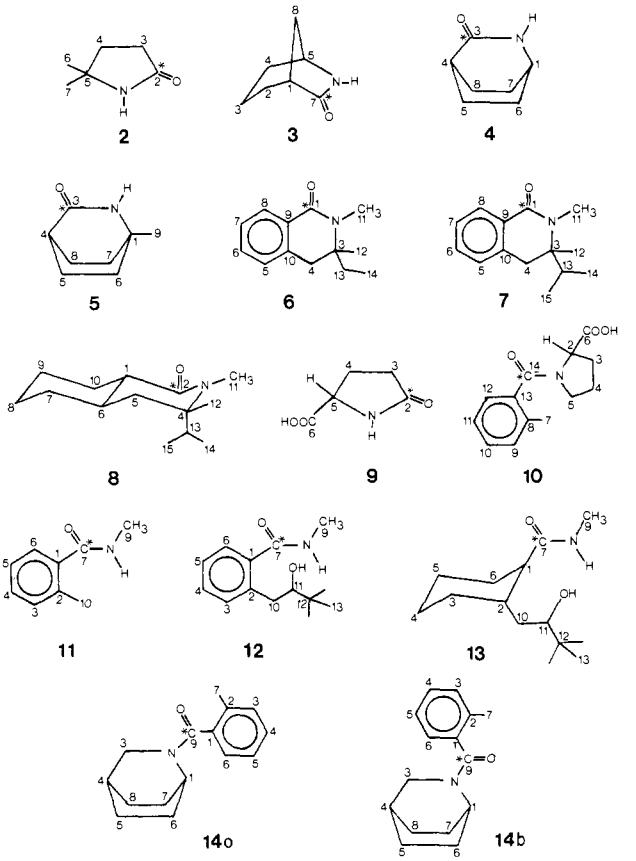
related compounds,[18] may not be applicable to peptide systems. Moreover, the angular dependence of $^{13}C-^{1}H$ coupling constants which was inferred[1,19,20] from the experimental data for *N*-methylacetamide,[21] *N*-acetyl-L-tryptophan bound to δ-chymotrypsin,[22] and *N*-acetyl-L-alanyl-*N*-methylacetamide[23] give maxima which are almost twice those obtained in the INDO-FPT MO[19,24] and Dirac vector model[25] calculations for model compounds.

In this study, a series of 14 ^{13}C-labeled lactams and amides **2–14** were synthesized and their NMR spectra were used to obtain vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ and $^{13}C(O)-N-C_\alpha-^{1}H$ coupling constants over a range of dihedral angles in molecules of defined geometry. Since all the observed $^{3}J_{CC'}$ and most of the $^{3}J_{CH'}$ occur for situations in which the amide bond has a cis arrangement, it was of interest to use the INDO-FPT MO method to compare these coupling constants in the cis and trans amides.

1. Experimental Angular Dependence of $^{3}J[^{13}C(O)-N-C_\alpha-^{13}C]$ in Lactams and Amides

Entered in the third column of Table I are the observed values of $^{13}C-^{13}C$ coupling constants in the series of lactams and amides (see the Experimental Section) **2–14**. These experimental values (between carbon atoms designated in the second column of Table I) involve a vicinal coupling contribution $^{3}J_{CC'}$ along a $^{13}C(O)-N-C-^{13}C$ path and at least one additional coupling contribution $^{n}J_{CC'}$ along an *n*-bond path $^{13}C(O)-(C)_{n-1}-^{13}C$ where $n = 2-5$. Estimates of the latter, which are given in the fourth column of Table I, are based on experimental criteria in related systems (vide infra). Estimated values of the vicinal $^{13}C(O)-N-C-^{13}C$ coupling constants in Table I are obtained by subtracting the $^{n}J_{CC'}$ from the observed values. Approximate values of the dihedral angles θ, which are measured about the $N-C_\alpha$ bond, are entered in the last column of Table I. Dihedral angles for **2** and **3** were based on lanthanide shift reagent studies and were optimized via MINDO/3 calculations.[26] The geometries for **4** and **5** were taken from the X-ray diffraction results,[27] while those for **6** and **7** were based on vicinal and long-range H–H coupling constants (see Experimental Section). The dihedral angles for **8** and **11–14** were estimated from Dreiding stereomodels, the one for **9** was assumed by analogy to **2**, and the geometry for **10** was based on X-ray data and molecular mechanics calculations.[28]

The assumption of additivity of coupling constants along various paths[29] is implicit in the approach used here to ascertain the



2 3 4 5 6 7 8 9 10 11 12 13 14o 14b

angular dependence of the $^{13}C(O)-N-C-^{13}C$ coupling constants. All but six of the observed values in Table I involve a second path in which the coupled carbons are separated by four or five bonds. In a recent study of the conformational dependence of $^{4}J_{CC'}$, which included a series of carboxylic acids,[17] it was concluded that $^{13}C-^{13}C$ coupling constants over single four- or five-bond paths were quite small (≤0.2 Hz).[17] As a consequence, coupling contributions $^{4}J_{CC'}$ and $^{5}J_{CC'}$ were set equal to zero in Table I.

Six of the entries in Table I involve either a second geminal $[^{13}C(O)-C-^{13}C]$ or vicinal $[^{13}C(O)-C-C-^{13}C]$ path. Geminal $^{13}C(O)-C-^{13}C$ coupling constants have been shown to be dependent on hydridization and substituent effects at the intervening atom C2, the C1–C2–C3 angle, the substitutent orientations, and the hybridization of the C1 and C3 carbon atoms.[30] Geminal $^{13}C-^{13}C$ coupling constants in the HO–C1C2–C3 moiety follow an angular dependence of the form

$$^{2}J_{CC'}(\theta') = A\cos^2\theta' + B\cos\theta' + C \qquad (1)$$

where θ′ is the dihedral angle measured about the C1–C2 bond.[12] Geminal $^{13}C-^{13}C$ coupling constants involving a terminal carboxylic acid group are negative in sign[22,30] and range from −1.0 to −1.5 Hz.[31,32] However, these coupling constants are average values since the carboxylic acid group undergoes rotation about the C–C single bond. The geminal $^{13}C(O)-C-^{13}C$ coupling constants for lactams **3–5** and **8**, which are given in Table II, range in magnitude from 1.6 to 2.0 Hz and, by analogy to the carboxylic acids, are assumed to be negative in sign. Similarly, in the bicyclic ketones **15** and **16**, the magnitudes range from 1.5 to 2.0 Hz.[31,33]

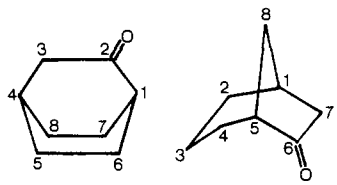
The calculated INDO-FPT MO results for $^{2}J[^{13}C(O)-C-^{13}C]$ in model compounds containing the N1–C2(O)–C3–C4 moiety depend on the substitution patterns at C3 and C4 and also follow

(18) Lemieux, R. U.; Nagabhushan, T. L.; Paul, B. *Can. J. Chem.* **1972**, *50*, 773. Lemieux, R. U. *Ann. N. Y. Acad. Sci.* **1973**, *222*, 915.
(19) Solkan, V. N.; Bystrov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, 1308. Bystrov, V. F.; Gavrilov, Yu. D.; Solkan, V. N. *J. Magn. Reson.* **1975**, *19*, 123. Bystrov, V. N.; Arseniev, A. S.; Gavrilov, Yu. D. *J. Magn. Reson.* **1978**, *30*, 351.
(20) Hansen, P. E. *Prog. NMR Spectrosc.* **1981**, *14*, 175.
(21) Dorman, D. E.; Bovey, F. A. *J. Org. Chem.* **1973**, *38*, 2379.
(22) Rodgers, P.; Roberts, G. C. K. *FEBS Lett.* **1973**, *36*, 330.
(23) Gavrilov, Yu. D.; Solkan, V. N.; Bystrov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, *11*, 2482.
(24) Barfield, M.; Gearhart, H. L. "Abstracts of Papers", 165th National Meeting of the American Chemical Society, Dallas, TX, April 9–13, 1973; American Chemical Society: Washington, DC, 1973; No. 172.
(25) Mohanakrishnan, P.; Easwaran, K. R. K. *Biopolymers* **1979**, *18*, 1769.
(26) Babaqi, A. S. Ph.D. Thesis, University of Arizona, Tucson, 1982.
(27) Aubry, A.; Protas, J.; Thong, C. M.; Marraud, M.; Néel, J. *Acta Crystallogr., Ser. B* **1973**, *B29*, 2576.
(28) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1977**, *99*, 1232.
(29) Marshall, J. L.; Faehl, L. G.; Kattner, R. *Org. Magn. Reson.* **1979**, *12*, 163.
(30) Hansen, P. E. *Org. Magn. Reson.* **1978**, *11*, 215.
(31) Wray, V. *Prog. NMR Spectrosc.* **1979**, *13*, 177.
(32) Walter, S. R. Ph.D. Thesis, University of Arizona, Tucson, 1982.
(33) Wray, V.; Hansen, P. E. *Annu. Rept. NMR Spectrosc.* **1981**, *11a*, 99.

Table I. Estimated Vicinal $^{13}C(O)$-N-C-^{13}C Coupling Constants and Dihedral Angles for a Series of Lactams and Amides

compd	coupled nuclei C,C′	obsd[a] $^3J_{CC'} + {}^nJ_{CC'}$, Hz	estd[b] $^nJ_{CC'}$, Hz	estd[c] $^3J[^{13}C(O)-N-C_\alpha-^{13}C]$, Hz	dihedral angle θ, deg
2	2,6	1.2 (2)	0.0 (^4J)	1.2 (2)	120
	2,4	1.0 (2)	−1.5 (^2J)	2.5 (4)	5
3	4,7	<0.4	0.0 (^4J)	<0.4 (2)	90
	7,8	2.0 (2)	(^2J)[d]	*d*	15
5	3,9	2.6 (2)	0.0 (^5J)	2.6 (2)	180
6	1,12	1.2 (2)	0.0 (^5J)	1.2 (2)	120
	1,13	1.2 (2)	0.0 (^5J)	1.2 (2)	120
	1,4	3.2 (2)	1.3 (^3J)	1.9 (4)	5
7	1,12	0.9 (2)	0.0 (^5J)	0.9 (2)	100
	1,13	1.6 (2)	0.0 (^5J)	1.6 (2)	140
	1,4	3.1 (2)	1.3 (^3J)	1.8 (4)	20
8	2,12	0.7 (2)	0.0 (^5J)	0.7 (2)	100
	2,13	1.9 (2)	0.0 (^5J)	1.9 (2)	140
	2,5	2.0 (2)	0.9 (^3J)	1.1 (4)	45
9	2,4	0.8 (2)	−1.5 (^2J)	2.3 (4)	5
10	4,14	2.5 (2)	0.0 (^4J)	2.5 (2)	175
14a	6,9	0.83 (10)	0.0 (^5J)	0.83 (10)	60
14b	4,9	2.39 (10)	0.0 (^5J)	2.39 (10)	180

[a] These are experimental values from Table IV. These are sums of the three-bond $^3J[^{13}C(O)-N-C_\alpha-^{13}C]$ coupling constant and coupling over a second path $^nJ_{CC'}$. Values in parentheses are errors in the last figure quoted. [b] Estimates of coupling constants over two, three, four, or five bonds as described in the text. [c] These values are differences between the observed multiple path values in column 3 and the estimated second path coupling in column 4. [d] No satisfactory criterion for estimating $^2J_{CC'}$ was found for this situation.



15 **16**

an angular dependence on θ' which is of the form of eq 1.[34] Moreover, MO results are consistent with the observed variation of about 0.5 Hz over the range of dihedral angles in the lactams **3–5**, **8**, and the cyclic ketones **15** and **16**. Note that the $^2J_{2,4}$ = −1.5 Hz in **15** corresponds to θ' close to 0°. Since this is close to the dihedral angles in **2**, **3**, and **9**, we may suppose that the contribution along the geminal $^{13}C(O)-C-^{13}C$ paths is ca. −1.5 Hz for all three coupling situations. However, for the strained bicyclic compound **3**, this would lead to the unphysical result in which the vicinal coupling constant for 15° was greater than that for 180°. It seems likely that the reason for the disparity can be seen in analogy to a recent study[12] of geminal $^{13}C-^{13}C$ coupling in bicycloalkane-1-carboxylic acids, wherein geminal coupling between the carboxyl and the ring carbons decrease (become more positive) as the size of the ring decreases.

Three of the entries in Table I involve coupling over dual vicinal paths. In order to estimate the coupling along the $^{13}C(O)-N-C-^{13}C$ paths for these dihedral angles, it is necessary to subtract the contribution arising from the vicinal $^{13}C(O)-C-C-^{13}C$ paths. In compounds **6** and **7** one of the bonds is part of the aromatic ring. Coupling constants along the aromatic path are estimated to be 1.4 Hz from the precursors **11** and **12** in which the amide bond does not occur. The remaining dual vicinal path entry (J_{25} in **8**) in Table I corresponds to a dihedral angle of about 45°. Since the vicinal $^{13}C(O)-C-C-^{13}C$ coupling constants of 1.1 and 0.8 Hz in **3** and **13**, respectively, also correspond to dihedral angles of about 45°, the average (0.9 Hz) is used as the estimate for coupling along this second path in **8**.

Vicinal $^{13}C(O)-N-C-^{13}C$ coupling constants to the C12 and C13 carbons in the series **6–8** provide an indication of increasing nonplanarity of the lactam rings. In **6** the two coupling constants are the same ($^3J_{1,12} = {}^3J_{1,13}$ = 1.2 Hz) but the preference of the bulkier isopropyl group for the equatorial position in **7** tends to force the methyl group to a more axial position, thereby decreasing the coupling. For compound **8** in Table I, the neighboring cyclohexane ring permits greater flexibility and leads to a smaller value of $^3J_{2,12}$ (0.7 Hz) and a greater $^3J_{2,13}$ (1.9 Hz) as the isopropyl and methyl groups more nearly assume the equatorial and axial positions, respectively.

The estimated values of $^3J[^{13}C(O)-N-C-^{13}C]$ from Table I are plotted in Figure 1 as a function of the dihedral angle θ. A three-term linear regression analysis of the experimental single-path vicinal $^{13}C-^{13}C$ coupling constants led to the equation

$$^3J_{CC'}(\theta) = 1.84 \cos^2 \theta - 0.23 \cos \theta + 0.51 \quad (2)$$

where the standard deviations in the constants are 0.16, 0.08, and 0.11 Hz, respectively. Equation 2 is plotted (solid line) in Figure

Table II. Experimental Values of Geminal $^{13}C(O)-N-^{13}C_\alpha$ Coupling Constants in the Lactams and Amides

compd	CC′	^2J[C(O)-C-C′], Hz	θ', deg	C,C′	^2J[C(O)-N-C′]
3	2,7	(−) 2.0	90		
4	3,5	(−) 2.0	60	3,1	≤0.3
5	3,5	(−) 1.9	60	3,1	≤0.3
6				1,3	2.2
				1,11	4.4
7				1,3	2.3
				1,11	4.5
8	2,6	(−) 2.0	60	2,4	2.4
	2,10	(−) 1.6	150	2,11	4.8
10				2,14	≤0.3
				5,14	2.6
11				7,9	0.5
12				7,9	0.8
13	2,7	(−) 1.3		7,9	0.9
	6,7	(−) 1.1			
14a				1,9	2.10
				3,9	≤0.3
14b				1,9	≤0.3
				3,9	2.08
15	2,4	(−) 1.5	0		
	2,6	(−) 1.7	60		
16	4,6	(−) 2.0	75		
17[a]				1,2	2.6
18[a]				1,2	3.1
				1,3	~0.5
19[a]				1,2	+2.96

[a] Reference 33.

(34) Kao, L.-F. Ph.D. Thesis, University of Arizona, Tucson, 1983.

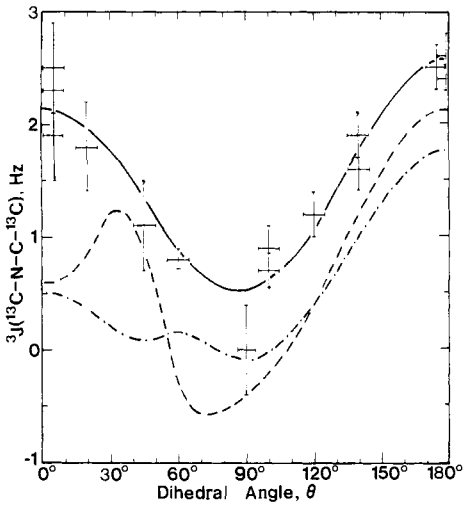


Figure 1. Experimental values of $^3J[^{13}C(O)-N-C_\alpha-^{13}C]$ coupling constants in lactams and amides plotted as a function of the dihedral angle θ, which is measured about the N–C_α bond. The solid curve is based on a three-term linear regression analysis (eq 2). The dashed curve and dot–dash curves are plots of the INDO-FPT MO results for this type of coupling in *cis*- and *trans*-*N*-ethylacetamide **20a** and **20b**, respectively.

1 as a function of the dihedral angle θ. In addition to the uncertainties implicit in the estimation of coupling constants assuming additivity relationships, there is also the possibility that certain data, i.e., magnitudes less than 1 Hz, could be negative rather than positive in Figure 1. Partial justification for the assumption of positive values is that negative values would produce a very distorted curve in the 60°–100° range of dihedral angles.

The only experimental value for this type of coupling that we could find in the literature was one of 1.95 Hz, which was reported in the cyclic dipeptide *c*-(Asp-Pro).[35] Since the authors inferred a dihedral angle of 150° by analogy to *c*-(Leu-Pro), their result is completely consistent with the values reported here.

The maximum value of 2.6 Hz for the trans (θ = 180°) orientation in Figure 1 is quite small compared to other vicinal $^{13}C-^{13}C$ coupling constants. For example, $^{13}C-^{13}C$ coupling constants in the trans (θ = 180°) arrangement of the $^{13}C(O)-C-C-^{13}C$ moiety of bicyclic ketones[33] and carboxylic acids[36] are about twice the magnitude of the $^{13}C(O)-N-C-^{13}C$ coupling constant. However, near the cis (θ = 0°) arrangements of carboxylic acids, the coupling constants are also close to 2 Hz.[36,37] All the data reported so far apply to the cis amide arrangement. There are no experimental criteria for vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ coupling in the trans amide arrangements which are most common in actual peptides. The calculated MO results in a subsequent section *suggest* that the magnitudes will be similar for a given dihedral angle.

2. Use of $^2J[^{13}C(O)-N-^{13}C_\alpha]$ To Assign Cis/Trans Stereochemistry

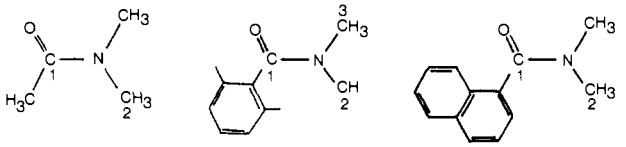
Entered in Table II are the experimental geminal coupling constants of the lactams **2–9** and the amides **10–14** and **17–19**. In the lactams the geminal coupling constants are small, and a methyl substituent at the C_α carbon of the $^{13}C(O)-N-C_\alpha$ moiety has little effect on the magnitude (both $^2J_{1,3}$ in **4** and **5** are ≤0.3 Hz). However, the effect of an *N*-methyl is appreciable as the coupling constants range from 2.2 to 2.4 Hz in **6–8**. Geminal $^{13}C-^{13}C$ coupling constants between the carbonyl carbon and the

(35) Piriou, F.; Toma, F.; Savrda, J.; Fermandjian, S. *Tetrahedron* **1979**, *35*, 441.
(36) Marshall, J. L.; Miiller, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 8305.
(37) Barfield, M.; Burfitt, I.; Doddrell, D. *J. Am. Chem. Soc.* **1975**, *97*, 2631.

Table III. Experimental Data for Vicinal $^{13}C(O)-N-C-H$ Coupling in Representative Lactams and Amides, Along with Estimated Dihedral Angles θ

compd	coupled nuclei[a] C,C_α	$^3J[^{13}C(O)-N-C-^1H]$, Hz	θ, deg
3	7,5	6.1	150[b]
4	3,1	5.8	180[b]
6	1,11	7.1	*c,d*
7	1,11	7.1	*c,d*
9	2,5	3.12	120[b]
10	14,2	1.20	60[c]
	14,5	<0.3	70[b]
	14,5	1.0	50[b]
11	7,9	3.5	*c,d*
14a	9,1	3.2	0[b]
14b	9,1	1.1	0[c]
21b	1,3	3.7[e]	*c,d*

[a] C_α is the number of the carbon atom to which the hydrogen is bonded. [b] Cisoid arrangement about the amide bond. [c] Transoid arrangement about amide bond. [d] Average value in methyl group. [e] Reference 21.



17 18 19

N-methyl carbon in the amides **11–13** are only 0.5–0.9 Hz, whereas in the lactams **6**, **7**, and **8** the magnitudes are increased to 4.4–4.7 Hz. Thus, a methyl group on the intervening nitrogen tends to increase both the cis and trans geminal coupling constants $^2J[C(O)-N-C]$.

It can be seen from the data in Table II that the geminal coupling constants range from 0.5 to 0.9 Hz in the trans arrangement of amides **11–13**, while the magnitudes decrease to less than about 0.3 Hz with the substituent at the intervening nitrogen atom (e.g., $^2J_{2,14}$ in **10** and $^2J_{1,3}$ in **19**). The geminal $^{13}C(O)-N-^{13}C_\alpha$ coupling constants in the cis arrangements are in the range 2–3 Hz ($^2J_{5,14}$ in **10** and $^2J_{1,2}$ in **17–19**). The utility of these results in conformational studies can be seen, for example, for compound **14** which includes isomers **14a** and **14b**. The measured coupling constants $J_{1,9}$ = 2.10 Hz and $J_{3,9} \leq$ 0.5 Hz in **14a** indicate that C1 and C3 are, respectively, cis and trans to the aromatic ring. This is the predominate form of the two isomers. The second isomer **14b** has $J_{3,9}$ = 2.08 Hz and $J_{1,9} \leq$ 0.5 Hz, which further confirms the assignments of the isomers.

3. Angular Dependence of Vicinal $^{13}C(O)-N-C_\alpha-^1H$ Coupling in Lactams and Amides

Experimental values of vicinal $^{13}C(O)-N-C_\alpha-^1H$ coupling constants for many of the compounds of this study are entered in Table III. Also included in the table is the 3.7 Hz value for coupling to the *N*-methyl group of *trans*-*N*-methylacetamide. This value is typical for this type of coupling in the trans amide arrangement.[20,21] Dihedral angles θ, which are measured about the N–C_α bond, are given in the last column of Table III; these were based on the geometrical criteria used in the previous sections.

The vicinal $^{13}C-^1H$ coupling constants for coupling situations of essentially fixed geometry are plotted in Figure 2 as a function of the dihedral angles θ. Of the two data points for the trans amide arrangement, the value of 1.1 Hz for θ = 0° appears to be inconsistent with the other data. A three-term linear regression analysis with the remaining seven data points in Figure 2 gives the equation

$$^3J_{CH}(\theta) = 3.96 \cos^2 \theta - 1.83 \cos \theta + 0.81 \quad (3)$$

where the standard deviations in the three constants are 0.80, 0.37,

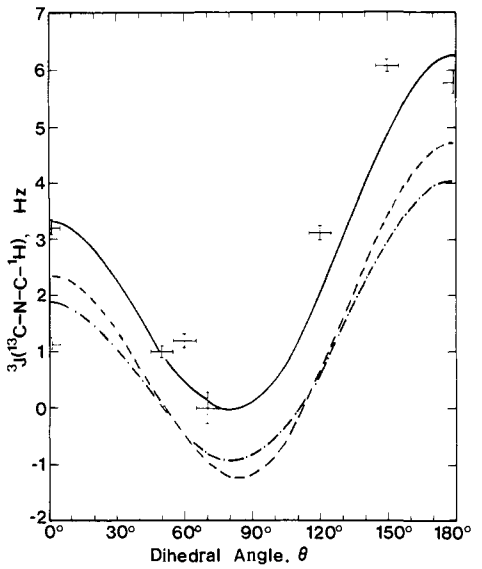


Figure 2. Experimental values of $^3J[^{13}C(O)-N-C_\alpha-^1H]$ coupling constants in lactams and amides plotted as a function of the dihedral angle θ, which is measured about the N–C_α bond. The solid curve is based on a three-term linear regression analysis (eq 3). The dashed curve and the dot–dashed curves are plots of the INDO-FPT MO results for *cis*- and *trans*-*N*-methylacetamide **21a** and **21b**, respectively.

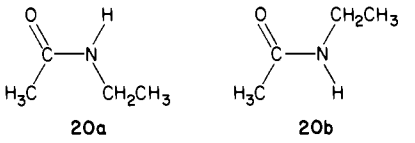
and 0.51 Hz, respectively. These data are plotted (solid curve) in Figure 2.

For the case of an *N*-methyl group, the simple average of eq 3 over θ leads to a value of 2.8 Hz. This is in very good agreement with the vicinal $^{13}C-^1H$ coupling constant of +2.72 Hz in the cis amide arrangement for *N*,*N*-dimethylformamide.[38] The somewhat larger values of 3–4 Hz for **21b** and other amides having the trans arrangement[20,21] suggest a conformational dependence in which the maximum value is greater than 6 Hz. For example, the value of 8 Hz for $\theta = 180°$ in uridine and related compounds[18] appears to be consistent with the data for coupling to an *N*-methyl group in the trans amide arrangement. The experimental values of 7 Hz for coupling between the carbonyl and the trans *N*-methyl hydrogens of **6** and **7** are unexpectedly large and cannot be explained on the basis of the empirical data presented here.

4. Calculated Angular Dependencies for Vicinal Coupling over the N–C_α Bond

Molecular orbital (MO) results for Fermi contact contributions to nuclear spin–spin coupling constants were based on the finite perturbation theory (FPT) formulation[39,40] in the semiempirical INDO (intermediate neglect of differential overlap) approximation of self-consistent-field MO theory. Molecular geometries about the C–C(O)–N moiety are based on the Corey–Pauling model,[41] and a standard geometrical model[42] was used for aliphatic groups. All calculations were performed on a Control Data Corp. CYBER 175 computer.

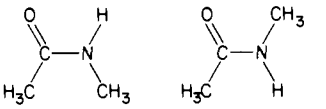
Calculated MO results for vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ coupling constants in *cis*- and *trans*-*N*-ethylacetamide **20a** and **20b**, which were obtained at 30° intervals of the dihedral angle θ,[43] are plotted (dashed and dot–dash lines, respectively) in Figure 1. The



20a **20b**

calculated results for both the cis and trans amides are consistently below the estimated values for cis amide. For dihedral angles greater than 90°, the calculated values for cis and trans amides differ by less than 0.5 Hz. For dihedral angles less than 90°, the calculated values oscillate as nonbonded interactions between the two methyl groups in **20a** and between the methyl and C=O in **20b** become important.

The MO results for $^3J[^{13}C(O)-N-C_\alpha-^1H]$ in *cis*- and *trans*-*N*-methylacetamide **21a** and **21b** are plotted (dashed and dot–dash curves, respectively) in Figure 2 as a function of the dihedral angle θ.[24] The calculated values for the cis amide are about 1 Hz



21a **21b**

smaller in magnitude than the experimental ones over the whole range of dihedral angles in Figure 2. The calculated results indicate that the values of the $^{13}C-^1H$ coupling constants in the trans amide should be slightly less than the cis amide for most dihedral angles. Of course, this is inconsistent with the rather weak argument, based on coupling to the methyl groups, which indicates that the maximum for trans coupling ($\theta = 180°$) in the trans amide should be about 2 Hz greater than that for the cis amide. Although negative values occur in the calculated results in Figure 2, the evidence for negative values in this situation is not convincing.

5. Conclusion

Multicyclic lactams provide suitable model compounds for studies of coupling constants over a range of dihedral angles. The major disadvantage is that most of the data are applicable to cis amide bonds which are less common than trans amide bonds in actual peptides. The angular dependencies of vicinal $^{13}C(O)-N-C_\alpha-^{13}C$ and $^{13}C(O)-N-C_\alpha-^1H$ coupling constants of the cis amide arrangement were investigated. The magnitudes of the former are substantially less than $^{13}C(O)-C-C-^{13}C$ coupling constants, which emphasizes the importance of using appropriate model compounds to estimate dihedral angles. The vicinal $^{13}C(O)-N-C_\alpha-^1H$ coupling constants are larger in magnitude and should be more useful in actual peptides because they can be measured without isotopic enrichment. It is also noted that the magnitude of geminal $^{13}C(O)-N-^{13}C$ coupling constants are quite dependent on cis/trans stereochemistry about the amide bond.

6. Experimental Section

A. Spectra. The carbon-13 NMR spectra were recorded on Bruker Instruments WH-90 and WM-250 Fourier transform NMR spectrometers operating at frequencies of 22.63 and 62.89 MHz, respectively. Spectra were recorded in solutions of chloroform-*d* (**5** was also recorded in benzene-d_6 and **9** was recorded in D_2O), which served as the internal ^2H lock. Chemical shifts were measured in parts per million (ppm) downfield from internal tetramethylsilane (TMS). Carbon–carbon coupling constants were measured directly from the splitting of the resonance signals by using the techniques of resolution enhancement. Unless noted otherwise, the ^{13}C NMR spectra were obtained with a 600-Hz spectral width collected into 8K/4K data points (digital resolution 0.15 Hz) on the WH-90 or 12000-Hz spectral width collected into 128K data points (digital resolution 0.18 Hz) by using Bruker Instruments Disk Interactive Software on the WM-250.[44]

(38) Jakobsen, H. J.; Lund, T.; Hansen, R. S.; Daugaard, P. *J. Magn. Reson.* **1978**, *32*, 459.
(39) Pople, J. A.; McIver, J. W., Jr.; Ostlund, N. S. *J. Chem. Phys.* **1969**, *49*, 2960, 2965.
(40) Dobosh, P. A. Quantum Chemistry Program Exchange, Program 142, modified for FPT calculations by M. Barfield, 1971.
(41) Pauling, L.; Corey, R. B. *Proc. R. Soc. London, Ser. B* **1953**, *141*, 21. Ramachandran, G. N.; Venkatachalam, C. M. *Biopolymers* **1968**, *6*, 1255. Scheraga, H. A. *Adv. Phys. Org. Chem.* **1968**, *6*, 103.
(42) Sutton, L. E. *Spec. Publ. Chem. Soc.* **1965**, *No. 18* S1-S23.
(43) The dihedral angle θ is defined such that it is 0° and 180° when the carboxyl carbon and the methyl groups are cis and trans, respectively.

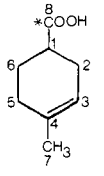
Table IV. Carbon-13 Chemical Shifts and $^{13}C-^{13}C$ Coupling Constants for Compounds **2–14** and **22–24**[a]

compd		C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15
2	δ	*b*	177.5	30.9	35.4	56.8	29.1	29.1								
	J	*b*	*c*	45.5	1.0	6.9	1.2	1.2								
3	δ	40.6	25.9	18.4	28.2	51.9	*b*	180.9	39.1							
	J	46.0	2.0	1.1	≤0.4	4.7	*b*	*c*	2.0							
4	δ	47.4	*b*	178.8	37.7	24.0	27.6	27.6	24.0							
	J	≤0.3	*b*	*c*	46.9	2.0	1.6	1.6	2.0							
5	δ	52.9	*b*	178.5	37.7	24.7	34.3	34.3	24.7	24.7						
	J	≤0.3	*b*	*c*	47.0	1.9	1.4	1.4	1.9	2.6						
6	δ	154.0	*b*	79.1	38.4	128.0	130.3	126.8	127.0	128.4	134.6	33.4	24.3	33.1	8.0	
	J	*c*	*b*	2.2	3.2	3.8	≤0.5	4.2	1.6	70.9	1.1	4.4	1.2	1.2	≤0.5	
7	δ	153.8	*b*	81.5	36.7	128.1	130.3	126.7	126.9	128.5	134.5	33.5	20.0	36.3	17.5[d]	16.7[d]
	J	*c*	*b*	2.3	3.1	3.8	≤0.5	4.2	1.4	70.8	1.2	4.5	0.9	1.6	≤0.5	≤0.5
8[e]	δ	45.2	161.1	*b*	83.2	39.4	35.4	34.1	25.7	26.2	27.8	33.4	21.9	39.2	17.0[d]	16.8[d]
	J	55.8	*c*	*b*	2.5	2.0	2.0	3.6	≤0.5	4.0	1.6	4.9	0.7	1.9	≤0.5	≤0.5
9[f]	δ	*b*	176.2	29.2	24.4	55.9	181.8									
	J	*b*	*c*	46.0	0.8	7.5	≤0.5									
10[g]	δ	*b*	58.8	29.1	24.7	49.2	174.9	18.8	134.4	130.5	129.3	125.8	125.7	136.2	171.4	
	J	*b*	<0.5	2.0	2.5	2.6	≤0.6	1.4	2.2	3.7	≤0.5	4.2	2.2	64.7	*c*	
11	δ	136.6	136.1	131.0	129.8	125.7	126.7	170.8	*b*	26.7	19.6					
	J	64.4	2.4	4.0	≤0.5	4.7	2.4	*c*	*b*	0.5	1.4					
12[h]	δ	136.8	138.8	130.4	130.1	126.0	127.6	171.1	*b*	26.6	34.7	81.6	35.4	25.7		
	J	63.7	2.5	3.9	≤0.5	4.0	2.2	*c*	*b*	0.8	1.4	≤0.5	≤0.5	≤0.5		
13	δ	45.3	35.1	31.4	23.3	23.9	26.3	175.7	*b*	26.0	33.2	78.4	35.0	25.7		
	J	50.1	1.3	2.2	≤0.5	2.4	1.1	*c*	*b*	0.9	0.8	≤0.5	≤0.5	≤0.5		
14a[h,i]	δ	47.3	*b*	48.6	25.7	24.3	26.1	26.1	24.3	170.2	19.1					
	J	2.10	*b*	≤0.3	1.57	≤0.5	0.83	0.83	≤0.5	*c*	1.86					
14b[h,j]	δ	41.4	*b*	51.8	26.0	24.3	27.1[k]	27.1[k]	24.3	170.5	18.7					
	J	≤0.3	*b*	2.08	2.39	≤0.5	*i*	*i*	≤0.5	*c*	1.53					
22	δ	39.1	25.2	119.1	133.8	29.2	27.4	23.4	182.5							
	J	46.0	1.4	3.9	≤0.5	4.0	1.2	≤0.5	*c*							
23a[l]	δ	41.0	24.7	27.2	49.0	27.2	24.7	183.5								
	J	45.6	1.0	1.6	≤0.5	1.6	1.0	*c*								
23b[l]	δ	44.6	27.5	29.5	49.8	29.5	27.5	184.3								
	J	45.6	≤0.5	4.7	≤0.5	4.7	≤0.5	*c*								
24[m]	δ	42.9	33.9	51.9	31.3	24.3	28.9	180.5								
	J	56.2	0.8	5.8	≤0.5	5.0	1.6	*c*								

[a] Chemical shifts δ in parts per million downfield from tetramethylsilane; chloroform-*d* used as solvent and lock material unless noted otherwise; coupling constants in hertz; digital resolution 0.2 Hz unless noted otherwise. [b] Nitrogen. [c] Carbonyl carbon. [d] The assignment may be reversed. [e] It was assumed that the trans fused ring was the isomer present in highest concentration. [f] Measured in D_2O solvent. [g] Resonances from the major isomer. [h] Digital resolution: 0.1 Hz. [i] For aromatic carbons C1′–C6′, the chemical shifts in parts per million (coupling constants in hertz) are 137.2 (65.1), 134.4 (1.9), 130.4 (3.8), 128.5 (<0.5), 125.8 (4.1), and 125.4 (1.9). [j] For aromatic carbons C1′–C6′, the chemical shifts in parts per million (coupling constants in hertz) are 137.1 (64.7), 133.5 (1.9), 130.3 (3.6), 128.6 (<0.5), 126.0 (4.0), 125.6 (2.0). [k] Broad lines. [l] Solvent: D_2O. Internal reference: dioxane. [m] Solvent: 50/50 D_2O/trifluoroacetic-*d* acid. Reference: TMS.

Entered in Table IV for compounds **2–14** and the precursors **22–24** are the ^{13}C chemical shifts (δ) in parts per million to low field of internal tetramethylsilane and $^{13}C-^{13}C$ coupling constants (*J*) in hertz.

Carbon-13 chemical shift assignments were based on relative intensities, single-frequency off-resonance decoupling, additivity relationships,[31,45] lanthanide shift reagents,[26,46–48] and the attached proton test.[49,50]



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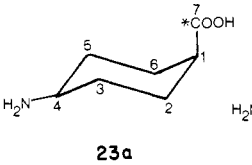
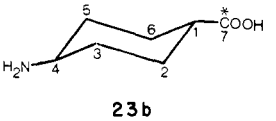
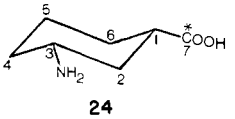


23a



23b



24

When the latter procedure and spectral addition or subtraction were used, subspectra contained only resonances from methine and methyl or quaternary and methylene carbons.

Proton NMR spectra of compounds **3**, **4**, 6, **7**, **10**, **11**, **14a**, and **14b** were recorded at 250.1 MHz on a WM-250 NMR spectrometer with chloroform-*d* as the solvent and internal lock (compound **9** was measured in Me_2SO-d_6). All samples were degassed by the freeze–thaw method and sealed off under vacuum in 5-mm sample tubes. Spectra were obtained in 1000-Hz spectral widths collected into 16K data points (digital resolution 0.1 Hz per point) or 3000-Hz spectral widths collected into 64K data points (digital resolution 0.09 Hz per point). To further remove ambiguities in the proton chemical shift assignments, two-dimensional heteronuclear shift-correlated spectra[51–55] were obtained. The 250-MHz proton NMR spectra of **7** and **9** which were treated as six-spin systems were carefully analyzed[43] by using Bruker Instruments PANIC.81 computer program.[44]

Coupling constants $^3J[^{13}C(O)-N-C_\alpha-^1H]$ for compounds **6**, **7**, and **11** were determined directly from the splittings of the *N*-methyl ^1H reso-

(44) Bruker Instruments, Inc., Manning Park, Billerica, MA 01821.
(45) Clerc, J. T.; Pretsch, E.; Sternhell, S. "Carbon-13 Kernresonanzspektroskopie"; Akad. Verlag: Frankfurt, 1973.
(46) Tori, K.; Yoshimura, Y.; Kaniosho, M.; Ajisaka, K. *Tetrahedron Lett.* **1973**, 3127.
(47) Inagaki, F.; Miyazawa, T. *Prog. NMR Spectrosc.* **1981**, *14*, 67.
(48) Chadwick, D. J.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1202.
(49) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.
(50) Brown, D. W.; Nakashima, T. T.; Rabenstein, D. L. *J. Magn. Reson.* **1981**, *45*, 302.
(51) Bodenhausen, G.; Freeman, R.; Morris, G. A.; Turner, D. L. *J. Magn. Reson.* **1977**, *28*, 17.
(52) Maudsley, A. A.; Müller, L.; Ernst, R. R. *J. Magn. Reson.* **1977**, *28*, 463.
(53) Müller, L. *J. Magn. Reson.* **1979**, *36*, 301.
(54) Bax, A. "Two-Dimensional Nuclear Magnetic Resonance in Liquids"; D. Reidel: London, 1982.
(55) Bendall, M. R.; Pegg, D. T.; Doddrell, D. M.; Thomas, D. M. *J. Magn. Reson.* **1982**, *46*, 43.

nances, and the data are entered in Table III. The entries in the table for compounds **3**, **4**, **10**, **14a**, and **14b** were based on homonuclear double-resonance experiments. The vicinal ^{13}C–^{1}H coupling constants ^{13}C-(O)-N-Cl-H and H-N-Cl-H in **4** were found to be 5.83 and 5.77 Hz, respectively, by decoupling the eight methylene protons which are 491.5 Hz upfield of the Cl bridgehead proton. Since a value of 5.8 Hz was previously reported[56] for the H-N-Cl-H coupling in this compound, it seems unlikely that the ^{13}C–^{1}H coupling is perturbed by the decoupling field.

B. Synthesis. Labeled carbon dioxide-^{13}C (≥90%) was purchased from Monsanto Research Corp. All of the ^{13}C-labeled compounds of this study were based on the reaction of the labeled carbon dioxide with the appropriate Grignard reagents by using the usual vacuum line techniques.[36] Intermediates were monitored by NMR and IR techniques. Melting points were determined in a sealed capillary tube or on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were taken on Perkin-Elmer 337 or 983 spectrophotometers between potassium bromide plates or in a solution cell. Mass spectral data were collected on a Varian MAT 311A mass spectrometer, and elemental analyses were performed by Mic Anal Inc., Tucson, AZ. Unless indicated otherwise, proton NMR spectra were recorded at 60 MHz on Varian Assoc. T-60 or EM-360 NMR spectrometers.

5,5-Dimethyl-2-pyrrolidone-*2*-^{13}C (2). Acrylic-*carboxyl*-^{13}C acid was converted to acryloyl-*carboxyl*-^{13}C chloride by using the procedure of Brown,[57] followed by conversion to methyl acrylate-*carboxyl*-^{13}C,[58] which was used to obtain methyl γ-methyl γ-nitrovalerate-*carboxyl*-^{13}C by a Michael addition of 2-nitropropane. Hydrogenation and distillation[59] gave 5,5-dimethyl-2-pyrrolidone-*2*-^{13}C (**2**).

6-Azabicyclo[3.2.1]octan-7-one-*7*-^{13}C (3) and 2-Azabicyclo[2.2.2]octan-3-one-*3*-^{13}C (4) were prepared by heating 3-aminocyclohexanecarboxylic-*carboxyl*-^{13}C acid (**24**) and 4-aminocyclohexanecarboxylic-*carboxyl*-^{13}C acid (**23**), respectively, according to the literature procedures.[60-62] The NMR spectra of **23** indicated the presence of cis (**23a**) and trans (**23b**) isomers. Compounds **23** and **24** were obtained by hydrogenation of *m*- and *p*-nitrobenzoic-*carboxyl*-^{13}C acids,[63] respectively. The latter was obtained by nitration of benzyl acetate followed by oxidation.[64]

4-Methyl-3-cyclohexenecarboxylic-*carboxyl*-^{13}C Acid (22).[65] Isoprene (2.8 g, 0.04 mol) and 2.9 g (0.04 mol) of acrylic-*carboxyl*-^{13}C acid (vide supra) were heated in a sealed glass tube at 115 °C for 24 h. The product was distilled to give 2.5 g (45%) of 4-methyl-3-cyclohexanecarboxylic-*carboxyl*-^{13}C acid (**22**): bp 120–125 °C/5 torr; mp 94–96 °C; ^{13}C NMR ($CDCl_3$) Table IV; ^{1}H NMR ($CDCl_3$) δ 5.4 (br, 1 H), 2.8–1.9 (br, 7 H), 1.65 (s, 3 H).

1-Methyl-2-azabicyclo[2.2.2]octan-3-one-*3*-^{13}C (5). 4-Methyl-3-cyclohexenecarboxylic-*carboxyl*-^{13}C acid (1.6 g, 0.011 mol), 3.4 g of ammonium chloride, and 40 mL of 14% ammonium hydroxide were heated in an autoclave at 290 °C for 8 h. After cooling, the mixture was extracted with three 100-mL portions of chloroform. The product was distilled at reduced pressure and purified by recrystallization from cyclohexane to give 0.9 g (60%) of 1-methyl-2-azabicyclo[2.2.2]octan-3-one-*3*-^{13}C (**5**): bp 128–130 °C/5 torr, mp 112 °C; ^{13}C NMR ($CDCl_3$ or C_6D_6) Table IV; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.45 (br, 1 H), 2.51 (m, 1 H), 2.0–1.5 (m, 8 H), 1.27 (s, 1 H); IR (KBr) 3200, 1000 cm^{-1}; mass spectrum, *m/e* (%) 138 (p, 68.7), 124 (*p*-CH_3, 8.1), 110 (54.7), 95 (36.1), 83 (100). Anal. Calcd for $C_8H_{13}NO$: C, 69.02; H, 9.42; N, 10.07. Found: C, 68.85; H, 9.22; N, 10.18.

Compounds **6** and **7** were prepared by condensation of 2-butanone and trimethylacetaldehyde, respectively, with *N*-methyl-*o*-toluamide-*carboxyl*-^{13}C (**11**) by means of *n*-butyllithium; the product were cyclodehydrated with sulfuric acid to form **6** and **7**, as was described in the similar procedures of Mao et al.[66,67] and Vaulx et al.[68] The structure of **7**, which was confirmed by a series of double-resonance experiments, involved carbonium ion rearrangement from the precursor *N*-methyl-2-(2-hydroxy-3,3-dimethylbutyl)benzamide-*carboxyl*-^{13}C in acidic solution. This is consistent with the reported mechanism.[66,67]

***N*-Methyl-o-toluamide-*carboxyl*-^{13}C (11).** A solution of 5.0 g (0.037 mol) of *o*-toluic-*carboxyl*-^{13}C acid and 20 mL of thionyl chloride was heated under reflux in a 200-mL round-bottomed flask for 2 h. After removal of excess thionyl chloride, the *o*-toluoyl-*carboxyl*-^{13}C chloride was added dropwise to 100 mL of saturated aqueous methylamine, which was cooled in an ice bath. The solid product was removed by filtration and recrystallized from aqueous ethanol to give 4.2 g (0.028 mol) of *N*-methyl-*o*-toluamide-*carboxyl*-^{13}C (76% yield): mp 77–79 °C; ^{13}C NMR ($CDCl_3$) Table IV; ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 4 H), 2.9 (q, 3 H), 2.4 (s, 3 H).

***N*-Methyl-2-(2-methyl-2-hydroxybutyl)benzamide-*carboxyl*-^{13}C.** A 500-mL three-necked round-bottomed flask was equipped with a condenser and a nitrogen inlet. To a stirred solution of 3.0 g (0.02 mol) of *N*-methyl-*o*-toluamide-*carboxyl*-^{13}C in 80 mL of dry tetrahydrofuran (THF), which was cooled in an ice bath, was added by syringe 0.04 mol of *n*-butyllithium in hexane. The solution turned deep red at the end of the addition of *n*-butyllithium and was assumed to contain 0.02 mol of *N*-methyl-*N*,γ-dilithiotoluamide-*carboxyl*-^{13}C. After the solution was stirred for 30 min, the reaction vessel was cooled in a dry ice–acetone bath, and 3 mL (0.03 mol) of 2-butanone was added via syringe to the reaction vessel. The light-yellow solution was stirred for another hour and was poured onto 250 mL of stirred ice–water. The organic layer was separated and combined with the two ethereal extracts of the aqueous layer. The solvent was removed, and solid product was recrystallized from acetonitrile to give 3.5 g (80%) of *N*-methyl-3-(2-methyl-2-hydroxybutyl)benzamide-*carboxyl*-^{13}C:[66,67] mp 126–128 °C; ^{1}H NMR ($CDCl_3$) δ 7.5–7.1 (m, 4 H), 5.2–5.0 (br, 1 H), 3.0–2.6 (m, 5 H), 1.5 (m, 2 H), 1.2 (s, 3 H), 1.0 (t, 3 H).

***N*-Methyl-3-methyl-3-ethyl-3,4-dihydroisoquinol-1-one-*1*-^{13}C (6).** To a 20-mL solution of concentrated sulfuric acid, cooled in an ice bath, was added 3.0 g (0.013 mol) of *N*-methyl-2-(2-methyl-2-hydroxybutyl)-benzamide-*carboxyl*-^{13}C over a period of 30 min. The solution was stirred for another 2 h and then was poured into 50 mL of water containing 100 g of ice. The mixture was made alkaline by adding 6 N sodium hydroxide solution and then extracted twice with 100-mL portions of ether. The ethereal solution was dried with magnesium sulfate and concentrated by rotary evaporation. The product was distilled to give 1.82 g (69%) of *N*-methyl-2-methyl-3-ethyl-3,4-dihydroisoquinol-1-one-*1*-^{13}C (**6**): bp 150–153 °C/5 torr; ^{13}C NMR ($CDCl_3$) see Table IV; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (m, 1 H), 7.28 (m, 2 H), 7.12 (m, 1 H), 3.12 (d, $^{3}J_{C,H}$ = 7.1 Hz, 3 H), 2.98 (m, 1 H), 2.84 (m, 1 H), 1.69 (m, 2 H), 1.28 (s, 3 H), 1.00 (t, 3 H); IR (neat) 2969, 2938, 1652 cm^{-1}.

***N*-Methyl-2-(2-hydroxy-3,3-dimethylbutyl)benzamide-*carboxyl*-^{13}C (12).** Three grams of *N*-methyl-*o*-toluamide-*carboxyl*-^{13}C (**11**), 0.04 mol of *n*-butyllithium in hexane, and 3.2 mL (0.03 mol) of trimethylacetaldehyde were reacted by the same procedure as described (vide supra) to give, after recrystallization from acetonitrile, 3.8 g (81% yield) of *N*-methyl-2-(2-hydroxyl-3,3-dimethylbutyl)benzamide-*carboxyl*-^{13}C: mp 128–130 °C; ^{13}C NMR ($CDCl_3$) see Table IV; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 4 H), 4.7 (d, 1 H), 3.2–2.8 (m, 5 H), 1.1 (s, 9 H); IR (neat) 3210, 1640 cm^{-1}.

***N*-Methyl-3-methyl-3-isopropyl-3,4-dihydroisoquinol-1-one-*1*-^{13}C (7).** Three grams (0.012 mol) of *N*-methyl-2-(2-hydroxy-3,3-dimethylbutyl)benzamide-*carboxyl*-^{13}C (**12**) was dissolved in 20 mL of cooled concentrated sulfuric acid, and the procedure used to prepare **6** gave 1.5 g (57.6%) of *N*-methyl-3-methyl-3-isopropyl-3,4-dihydroisoquinol-1-one-*1*-^{13}C (**7**): bp 147–150 °C/5 torr; ^{13}C NMR ($CDCl_3$) Table IV; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (H8), 7.26 (H7), 7.34 (H6), 7.11 (H5), 3.02 (H4a), 2.79 (H4b), 3.14 (H11), 1.18 (H12), 2.00 (H13), 0.95 (H14), 0.98 (H15), *J* = −15.97 Hz, H4a, H4b), 7.59 (H5, H6), 7.41 (H6, H7), 7.86 (H7, H8), 6.89 (H13, H14 and H13, H15), −0.79 (H4a, H5), −0.84 (H4b, H5), 0.50 (H4a, H12), 1.28 (H5, H7), 1.38 (H6, H8), 0.69 (H5, H8), 0.23 (H4a, H8), 0.20 (H4b, H8), 0.02 (H4a, H6), 0.01 (H4b, H6), −0.61 (H4a, H7 and H4b, H7); IR (neat) 2966, 2911, 1652, cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.42; H, 8.75; N, 6.45. Found: C, 76.88, H, 8.99; N, 6.36.

***N*-Methyl-2-(2-hydroxyl-3,3-dimethylbutyl)cyclohexanecarboxamide-*carboxyl*-^{13}C (13).** To a solution of 4.0 g (0.012 mol) of *N*-methyl-2-(2-hydroxyl-3,3-dimethylbutyl)benzamide-*carboxyl*-^{13}C and 100 mL of water in a pressure bottle was added 5 g of 5% ruthenium on carbon. The reaction bottle was hydrogenated at 45 psi for 48 h in a Parr apparatus.

(56) Aubry, A.; Giessner-Prettre, C.; Cung, M. T.; Marraud, M.; Neel, J. *Biopolymers* **1974**, *13*, 523.
(57) Brown, H. C. *J. Am. Chem. Soc.* **1938**, *60*, 1325.
(58) Hauser, C. R.; Hudson, B. E.; Abramovitch, B.; Shivers, J. C. "Organic Syntheses"; 1955; Wiley: New York, Collect. Vol. 3, p 142.
(59) Moffett, R. B. "Organic Syntheses"; 1963; Wiley: New York, Collect. Vol. 4, pp 652, 357.
(60) Pearlman, W. M. "Organic Syntheses"; 1973; Wiley: New York Collect. Vol. 5, p 620.
(61) Schneider, W.; Dillman, R. *Chem. Ber.* **1963**, *26*, 2377.
(62) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 1209.
(63) The *m*-nitrobenzoic-*carboxyl*-^{13}C acid was kindly supplied by Prof. James, L. Marshall of North Texas State University.
(64) Schaeffer, J. R.; Snoddy, A. O "Organic Syntheses"; 1963; Wiley: New York, Collect. Vol. 4, p 19. Kleinfelter, D. C.; Schleyer, P. R. *Ibid.* 1973; vol. 5, p 852.
(65) Kuehne, M. E.; Horne, D. A. *J. Org. Chem.* **1975**, *40*, 1287.
(66) Mao, C.-L.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 3704.
(67) Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 83.
(68) Vaulx, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514.

The mixture was filtered several times and the residue, which remained on the filter paper, was washed with several portions of acetone. The combined filtrates were concentrated on a rotary evaporator and solid material began to form while the concentrated residue was cooling. The product was recrystallized from acetonitrile at 3 °C to give 1.6 g (55%) of *N*-methyl-2-(2-hydroxy-3,3-dimethylbutyl)cyclohexanecarboxamide-*carboxyl*-^{13}C: ^{13}C NMR ($CDCl_3$) Table IV; ^1H NMR ($CDCl_3$) δ 3.3-2.7 (m, 5 H), 2.4-1.3 (br), 0.9 (s, 9 H).

***cis*- and *trans*-3,4-Dimethyl-4-isopropyl-3-azabicyclo[4.4.0]decan-2-one-*2*-^{13}C (8).** One gram (0.004 mol) of *N*-methyl-2-(2-hydroxy-3,3-dimethylbutyl)cyclohexanecarboxamide-*carboxyl*-^{13}C and 20 mL of concentrated sulfuric acid were reacted following the procedure used in the preparation of **6** to give a 0.7 g (80%) mixture of *cis*- and *trans*-3,4-dimethyl-4-isopropyl-3-azabicyclo[4.4.0]decan-2-one-*2*-^{13}C isomers (bp 130-132 °C/5 torr). The mixture of cis and trans isomers was used without further separations: ^{13}C NMR ($CDCl_3$). Table IV; ^1H NMR ($CDCl_3$) δ 2.9 (d, 3 H), 2.5-1.3 (br), 1.2 (s, 3 H), 1.1-0.8 (m, 6 H).

2-Pyrrolidone-5-carboxylic-*2*-^{13}C Acid (9). DL-Glutamic-*5*-^{13}C acid was prepared by the reaction of acrylic-*carboxyl*-^{13}C acid with diethyl acetamidomalonate;[69] DL-glutamic-^{13}C acid monohydrate 2.0 g (0.12 mol) in 15 mL of water was sealed in a glass tube, and the solution was heated at 140 °C for 8 h.[70] After cooling, the solution was eluted with water on a column of Dowex 50H-X8H$^+$ ion-exchange resin (30 × 1 cm), and the product was obtained by evaporating the water to give 1.3 g (85%) of 2-pyrrolidone-5-carboxylic-*2*-^{13}C acid (**9**); ^{13}C NMR (D_2O) Table IV; ^1H NMR (250 MHz, Me_2SO-d_6) δ 7.93 (H1), 4.07 (H5), 2.32 (H4a, 2.14 (H3b), 2.12 (H3a), 1.97 (H4b) (J = -13.03 Hz, H4a, H4b), -17.57 (H3a, H3b), 5.46 (H3a, H4b), 9.55 (H3b, H4b), 4.39 (H4b, H5), 9.94 (H3a, H4a), 7.47 (H3b, H4a), 9.16 (H5, H4a), 1.20 (H1, H5), -0.04 (H1, H4b), -0.17 (H3a, H5), -0.58 (H1, H3a), -0.08 (H3b, H5), 0.63 (H1, H3b), 0.11 (H1, H4a).

***N*-(2-Methylbenzoyl-^{13}C)proline (10)** was obtained by means of a Schotten-Baumann-type reaction wherein 2-methylbenzoyl chloride was the acylating agent. The procedure is similar to that described by Davies[71] and Greenstein.[72] The crude product was recrystallized from aqueous ethanol to give 3.6 g (76.5%) of **10**: mp 152-154 °C NMR ($CDCl_3$) Table IV; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25 (m, 4 H), 4.73 (m, 1 H), 3.77 (m, 1 H), 3.25 (m, 2 H), 2.35 (s, 3 H), 2.25 (m, 2 H), 1.97 (m, 2 H); IR (KBr) 2950-2450, 1737, 1608, 1589 cm^{-1}.

***N*-(2-Methylbenzoyl)-2-azabicyclo[2.2.2]octane-*carboxyl*-^{13}C (14a and 14b).** 2-Azabicyclo[2.2.2]octane was prepared by a procedure similar to that of Wilson et al.[73] wherein 2-azabicyclo[2.2.2]octan-2-one was reduced with lithium aluminum hydride. One gram of 2-azabicyclo-[2.2.2]octane was dissolved in a mixture of 30 mL of benzene and 20 mL of pyridine. To this mixture was added dropwise a solution of 1.4 g (0.009 mol) of *o*-toluoyl-*carboxyl*-^{13}C chloride in 5 mL of benzene. The solution was stirred for 10 h, and the solvent was evaporated under reduced pressure. The residue was dissolved in 100 mL of benzene and was washed with two 30-mL portions of saturated sodium bicarbonate solution, followed by washing with water. After evaporating the benzene, the compound was recrystallized from methanol/water to give 1.4 g (68%) of *N*-(2-methylbenzoyl)-2-azabicyclo[2.2.2]octane-*carboxyl*-^{13}C (**14a** and **14b**); mp 87-88 °C; ^{13}C NMR ($CDCl_3$) Table IV; ^1H NMR (250 MHz, $CDCl_3$) δ 7.05-7.28 (m, 4 H), 4.65 (m, 2 H, minor isomer, 3.63 (m, 2 H, major isomer), 3.33 (m, 1 H, major isomer), 3.07 (m, 1 H, minor isomer), 2.31 (s, 3 H), 2.05 (m, 1 H), 1.56-1.87 (m, 8 H); IR (KBr) 2946, 2872, 1632, 1605 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.60; H, 8.30; N, 6.11. Found: C, 78.70; H, 8.46; N, 6.12.

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(69) Snyder, H. R.; Shekleton, J. F.; Lewis, C. D. *J. Am. Chem. Soc.* **1945**, *67*, 310.
(70) Moav, B.; Harris, T. N. *Biochem. Biophys. Res. Commun.* **1967**, *29*, 773.
(71) Davies, J. S.; Thomas, W. A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1157.
(72) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961.
(73) Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 3887.

Ultrashort Nonbonded H···H Distance in a Half-Cage Pentacyclododecane

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Abstract: A nonbonded H···H distance of only 1.617 (3) Å has been measured by low-temperature neutron diffraction in the pentacyclic half-cage compound **8**, by far the shortest such contact hitherto observed. NMR estimates based on nuclear Overhauser measurements are in satisfactory agreement with the neutron result while empirical force-field calculations with the MM2 potential overestimate the short H···H distance by 0.19 Å. The strong H···H repulsion in **8** leads to an enhanced C-H stretching frequency of 3119 cm^{-1}.

The strain of numerous sterically overcrowded molecular structures originates from short nonbonded H···H contacts. Such structures may correspond to potential energy minima or conformational transition states and frequently the latter involve particularly severe H···H repulsions leading to substantial interconversion barriers. The often unusual and therefore interesting properties of many congested molecules thus depend critically on the nature of nonbonded H···H interactions at short distances. The development of theoretical tools for the computational treatment of overcrowded molecules, in particular empirical force field methods, requires reliable experimental reference data of compounds with short H···H distances on which the calculational models can be tested and calibrated. Obviously, a key property of overcrowded molecules concerns the short nonbonded contacts

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