Crystal Structure and Molecular Conformation of the Cyclic Hexapeptide *cyclo*-(Gly-L-Pro-Gly)$_2$

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Abstract: The structure of *cyclo*-(Gly-L-Pro-Gly)$_2$ has been determined by X-ray diffraction methods on a single crystal of symmetry $P2_1$. There are two formula weights of $C_{18}H_{26}N_6O_6 \cdot 4H_2O$ in a unit cell having parameters a = 7.6194 (6), b = 21.0709 (19), c = 7.7018 (6) Å and β = 108.904 (9)°. An orientation-translation search utilizing a model derived from the known geometry of *cyclo*-(Gly-L-Pro-D-Ala)$_2$ yielded the structure, which refined to $R = \Sigma||F_o| - |F_c||/\Sigma F_o = 0.060$ for 2040 reflections. This cyclic hexapeptide deviates from internal twofold symmetry by forming one 4-1 transannular hydrogen bond in a type II β turn, and in the other half of the molecule a type I β turn without an internal hydrogen bond. In contrast, two earlier NMR studies have shown that this molecule has C_2 symmetry on the NMR time scale. We also describe here the hydrogen bonds to water of crystallization.

The role of glycine in reverse turns, and of proline in limiting conformations of protein structures, is very well modeled in small cyclic peptides, perhaps especially in (Gly-L-Pro-Gly)$_2$ which we study here by X-ray diffraction methods. Comparison of NMR results in solution with X-ray diffraction results in single crystals[2-7] is beginning to show evidence for conformational differences associated with averaging on the NMR time scale[8,9] or solid state constraints. Although *cyclo*-(D-Ala-L-Pro-D-Phe)$_2$[4] and *cyclo*-(Gly-L-Pro-D-Phe)$_2$[5] have the same structure in solution and in the crystal,[4] *cyclo*-(Gly-L-Pro-D-Ala)$_2$[7] and, as we shall show, *cyclo*-(Gly-L-Pro-Gly)$_2$ both lose their C_2 symmetry on the NMR time scale, as they crystallize to yield molecules having but one transannular hydrogen bond. Also, the proline has a trans peptide bond in all of these cyclic structures.

Experimental Section

Crystals of *cyclo*-(Gly-L-Pro-Gly)$_2 \cdot 4H_2O$, grown by slow evaporation from aqueous solution, have monoclinic symmetry in the space group $P2_1$. There are two formula weights per unit cell, which has parameters a = 7.6194 (6), b = 21.0709 (19), c = 7.7018 (6) Å and β = 108.904 (9)°. The experimental density of 1.39 ± 0.01 g/cm^3 is consistent with the presence in the unit cell of eight water molecules as well as the two hexapeptide molecules, leading to a calculated density of 1.40 g/cm^3.

Two data sets were measured on a Syntex $P2_1$ diffractometer with the use of graphite-monochromated Cu Kα radiation. The first data set consisted of 1393 reflections ($3° \le 2\theta \le 105°$) from which we were unable to solve the structure by the usual direct methods. Structure solution was achieved by an orientation-translation search with a rigid 24-atom model derived from the known[6] crystal structure of *cyclo*-(Gly-L-Pro-D-Ala)$_2$. The 32 nonhydrogen atoms of this molecule were related to a Cartesian coordinate system such that the origin was at the centroid and the maximal axis of inertia was along z; i.e., the x-y plane was the least-squares best plane. This operation is conveniently performed by the 506 instruction of ORTEP-II.[10] The 12 pairs of atoms whose positions were within 0.35 Å of the corresponding atom related by a 180° rotation about z were selected and averaged pairwise to yield a search group containing a true dyad. The pairs 10-40, $2C_\gamma$-$5C_\gamma$, 30-60, and, of course, $3C_\beta$-$6C_\beta$, which is not present in *cyclo*-(Gly-L-Pro-Gly)$_2$, were not included.

The orientation of this molecular fragment was sought by using the 160 unique reflections having $|E_o|_h \ge 1.5$ as data in program ORTRAN.[11] The best orientation, whose figure of merit $S = \Sigma_h[|E_o|_h^2 - |E_c|_h^2]$ was 2.5% better than any other, was then submitted to a two-dimensional translation search (origin choice in the **b** direction is arbitrary in space group $P2_1$) by using program ORSCAN.[12] As a precaution, the three other orientations with high merit-figures were also submitted. The best solution emerged from the orientation with the highest merit-figure and was 3.6% better than the next best solution.

Two rounds of $2|F_o| - |F_c|$ syntheses developed a plausible model for the molecule and for the four water molecules in the asymmetric unit, and full-matrix least-squares refinement was initiated but was discontinued when the 2C-2O, 2C-3N, 3N-3CA, and 3CA-3C distances reached unreasonable values (0.85, 0.66, 1.91, and 1.82 Å, respectively). Accordingly an $|F_o|$ synthesis was made by using phases from a model excluding 2C, 2O, 3N, and 3CA. In the $|F_o|$ map, these atoms appeared in the "turned-over" configuration described below.

Least-squares refinement was then resumed, eventually including anisotropic nonhydrogen and isotropic hydrogen atoms. At R = 0.14 the refinement became unstable and was terminated. Since an $|F_o| - |F_c|$ map computed at this stage had no peak above 0.6 e/Å^3 and pointed to no obvious defect in the model, we concluded that the data were inaccurate and therefore collected a second data set. Here we used a crystal 0.4 × 0.3 × 0.3 mm. Measurements were carried out in the θ-2θ mode in the range $3.0° \le 2\theta \le 135°$ at scan speeds of 2.93-29.30°/min depending on the intensity of the reflection. Lorentz and polarization factors were applied, but no absorption correction was made (μ = 8.77 cm^{-1} for Cu Kα radiation). Data reduction then yielded 2040 independent reflections for which $I \ge 2\sigma(I)$, all of which were used in the refinement which then converged with judicious use of fractional shifts. Of the 26 H atoms in the cyclic peptide, all were observed at reasonable electron density in the difference map, although two were displaced from their ideal positions by 0.2-0.3 Å. Inclusion of all H atoms with isotropic temperature factors (B = 6.0 Å^2) and all other atoms with anisotropic temperature factors converged to the final value of R = 0.06 in block least-squares refinements. In the final cycle, the largest ratio of shift to estimated standard deviations was

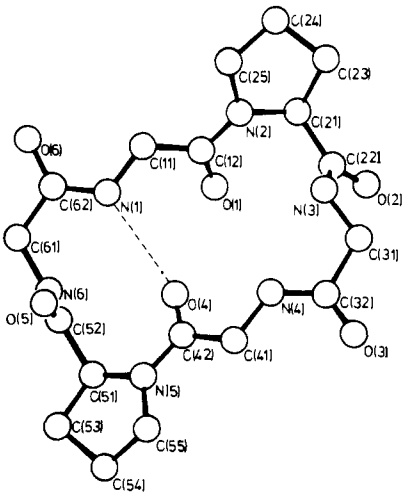

Figure 1. Atom labeling in *cyclo*-(Gly-L-Pro-Gly)$_2$.

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Table I. Fractional Atomic Coordinates × 10^4

atom	*x*	*y*	*z*
N(1)	2891(6)	−811(2)	1653(6)
C(11)	1593(7)	−306(3)	1614(8)
C(12)	2081(7)	287(3)	791(7)
O(1)	3333(5)	311(2)	59(6)
N(2)	1109(6)	807(2)	862(6)
C(21)	1441(7)	1399(3)	−3(7)
C(22)	3378(7)	1681(3)	906(7)
C(23)	−67(9)	1854(3)	184(11)
C(24)	−1605(9)	1400(4)	267(12)
C(25)	−554(8)	844(3)	1416(9)
O(2)	4172(5)	1964(2)	−21(6)
N(3)	4080(6)	1620(2)	2716(6)
C(31)	5813(8)	1925(3)	3801(8)
C(32)	7417(7)	1477(3)	4757(7)
O(3)	8904(6)	1709(2)	5601(8)
N(4)	7058(6)	871(2)	4690(7)
C(41)	8401(7)	390(3)	5598(8)
C(42)	7930(7)	−217(3)	4507(7)
O(4)	6566(5)	−253(2)	3107(6)
N(5)	9052(6)	−715(2)	5091(6)
C(51)	8694(7)	−1322(3)	4093(8)
C(52)	6711(7)	−1558(2)	3796(7)
C(53)	10159(8)	−1767(3)	5358(9)
C(54)	11764(8)	−1308(3)	6276(9)
C(55)	10761(8)	−732(3)	6711(8)
O(5)	6081(5)	−1615(2)	5060(5)
N(6)	5739(6)	−1688(2)	2033(6)
C(61)	3831(7)	−1925(3)	1550(8)
C(62)	2367(7)	−1412(3)	1328(7)
O(6)	716(5)	−1584(2)	837(6)
O)7)	3363(7)	475(3)	5419(8)
O(8)	5970(7)	−121(3)	−1518(8)
O(9)	7026(6)	−1418(3)	−1166(6)
O(10)	2782(7)	1768(3)	6148(7)

Table II. Hydrogen Coordinates × 10^3

atom	*x*	*y*	*z*
H(1)	412	−62	213
H(111)	172	−27	307
H(112)	36	−41	108
H(211)	135	135	−127
H(231)	−23	217	−86
H(232)	42	214	145
H(241)	−245	123	−109
H(242)	−246	165	110
H(251)	−137	40	112
H(252)	−16	95	264
H(3)	268	154	347
H(311)	552	221	486
H(312)	626	223	286
H(4)	597	66	433
H(411)	849	31	695
H(412)	986	62	604
H(511)	910	−127	281
H(531)	1029	−215	493
H(532)	959	−202	657
H(541)	1235	−110	520
H(542)	1252	−162	760
H(551)	1133	−40	697
H(552)	1063	−71	786
H(6)	627	−161	91
H(611)	362	−228	270
H(612)	362	−212	10
H(71)	432	28	644
H(72)	311	90	549
H(81)	653	−46	947
H(82)	554	−5	949
H(91)	671	−149	754
H)92)	826	−147	950
H(101)	232	150	524
H(102)	306	190	740

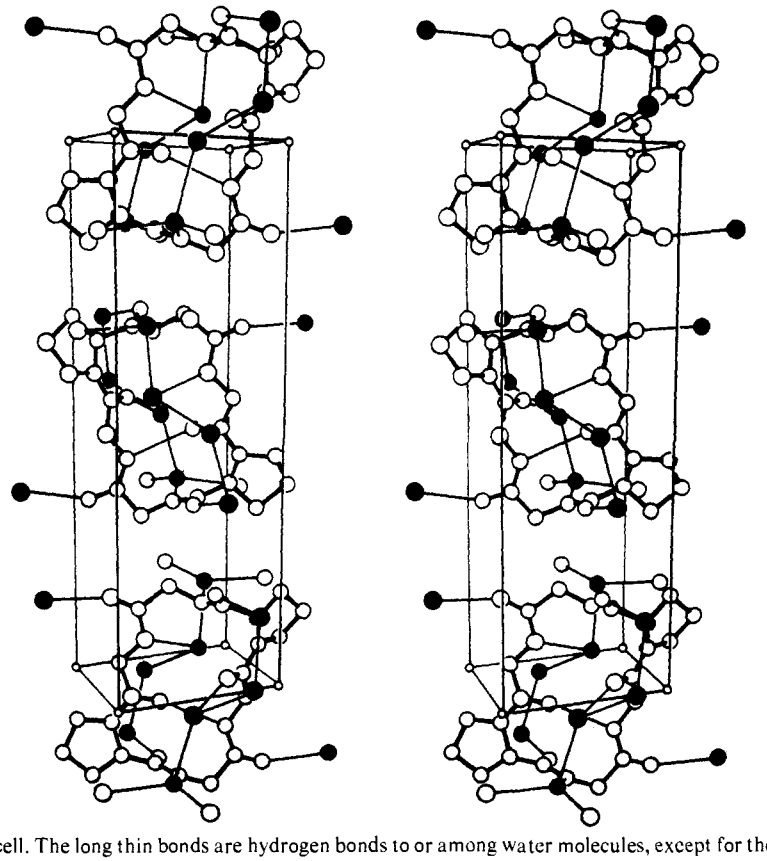

Figure 2. Stereoview of the unit cell. The long thin bonds are hydrogen bonds to or among water molecules, except for the one intramolecular hydrogen bond. Black dots are water molecules.

Table III. Bond Lengths (Å) and Angles (deg)

N(1)-C(11)	1.447(8)	C(11)-C(12)	1.501(9)
N(2)-C(21)	1.473(8)	C(21)-C(22)	1.535(7)
N(3)-C(31)	1.463(7)	C(31)-C(32)	1.531(8)
N(4)-C(41)	1.449(7)	C(41)-C(42)	1.508(9)
N(5)-C(51)	1.473(8)	C(51)-C(52)	1.536(8)
N(6)-C(61)	1.467(7)	C(61)-C(62)	1.523(8)
av for GPG	1.462	av for GPG	1.522
av[9] for polypeptides	1.455	av for polypeptides	1.51
C(12)-O(1)	1.256(8)	C(12)-N(2)	1.334 (8)
C(22)-O(2)	1.228(8)	C(22)-N(3)	1.328(7)
C(32)-O(3)	1.212(6)	C(32)-N(4)	1.304(8)
C(42)-O(4)	1.234(6)	C(42)-N(5)	1.335(7)
C(52)-O(5)	1.222(7)	C(52)-N(6)	1.347(6)
C(62)-O(6)	1.245(6)	C(62)-N(1)	1.326(7)
av for GPG	1.232	av for GPG	1.329
av for polypeptides	1.24	av for polypeptides	1.325
N(2)-C(25)	1.464(9)	C(23)-C(24)	1.529(11)
N(5)-(55)	1.484(6)	C(53)-C(54)	1.539(8)
C(21)-C(23)	1.538(9)	C(24)-C(25)	1.529(10)
C(51)-C(53)	1.539(8)	C(54)-C(55)	1.528(9)
C(62)-N(1)-C(11)	122.4(5)	N(1)-C(11)-C(12)	111.1(5)
C(12)-N(2)-C(21)	119.9(5)	N(2)-C(21)-C(22)	113.7(5)
C(22)-N(3)-C(31)	122.6(5)	N(3)-C(31)-C(32)	115.8(5)
C(32)-N(4)-C(41)	124.1(5)	N(4)-C(41)-C(42)	108.8(5)
C(42)-N(5)-C(51)	121.1(5)	N(5)-C(51)-C(52)	111.5(5)
C(52)-N(6)-C(61)	120.1(4)	N(6)-C(61)-C(62)	114.6(5)
av for GPG	121.7	av for GPG	112.6
av for polypeptides	122	av for polypeptides	111
C(11)-C(12)-O(1)	123.4(5)	C(11)-C(12)-N(2)	116.7(5)
C(21)-C(22)-O(2)	120.3(5)	C(21)-C(22)-N(3)	116.2(5)
C(31)-C(32)-O(3)	118.1(5)	C(31)-C(32)-N(4)	117.4(5)
C(41)-C(42)-O(4)	121.3(5)	C(41)-C(42)-N(5)	117.9(5)
C(51)-C(52)-O(5)	122.3(5)	C(51)-C(52)-N(6)	114.1(4)
C(61)-C(62)-O(6)	117.3(5)	C(61)-C(62)-N(1)	119.4(5)
av for GPG	120.5	av for GPG	117.0
av for polypeptides	120.5	av for polypeptides	116
O(1)-C(12)-N(2)	119.9(5)	C(12)-N(2)-C(25)	126.9(5)
O(2)-C(22)-N(3)	123.4(5)	C(42)-N(5)-C(55)	126.5(5)
O(3)-C(32)-N(4)	124.3(6)	C(21)-N(2)-C(25)	112.2(4)
O(4)-C(42)-N(5)	120.9(5)	C(51)-N(5)-C(55)	112.4(5)
O(5)-C(52)-N(6)	123.6(5)	N(2)-C(21)-C(23)	104.0(5)
O(6)-C(62)-N(1)	123.3(5)	N(5)-C(51)-C(53)	103.0(5)
av for GPG	122.6	C(23)-C(21)-C(22)	110.6(5)
av for polypeptides	123.5	C(53)-C(51)-C(52)	111.9(5)
		C(21)-C(23)-C(24)	102.7(6)
		C(51)-C(53)-C(54)	102.4(5)
		C(23)-C(24)-C(25)	103.8(6)
		C(53)-C(54)-C(55)	102.7(5)
		N(2)-C(25)-C(24)	102.3(5)
		N(5)-C(55)-C(54)	101.6(5)

less than 0.03. The final difference synthesis displayed no peaks greater than 0.22 e/Å^3.

Results

The molecule and labeling scheme (Figure 1[10]) refer to the positional parameters (Tables I and II), and bond lengths and angles which compare well with standard values for polypeptides[13] (Table III). A list of hydrogen bonds in the crystal structure (Figure 2) is shown in Table IV, and a stereoview of the molecule is shown in Figure 3.

The peptide bonds of *cyclo*-(Gly-L-Pro-Gly)$_2$ deviate very little (average 3.3°, maximum 7.1°) from the ideal trans conformation. Of the two β turns, one is type I while the other is type II.[14] In Table V we compare these conformational angles[15] with values for idealized type I and type II β turns, with those of the NMR studies,[15,16] and with angles in *cyclo*-(Gly-L-Pro-D-Ala)$_2$.

The 4 → 1 transannular hydrogen bond, N(1)-O(4), in *cyclo*-(Gly-L-Pro-Gly)$_2$ is 2.906 Å in length within the type II β turn, while the N(4)-O(1) distance of the type I turn is so much longer (at 3.95 Å) that a hydrogen bond must be absent. This asymmetry of the molecule leaves the O(1) ··· O(4) distance of 3.040 Å at a reasonable value. Also, each hexapeptide molecule participates in 4 N-H···O hydrogen bonds and in 5 O···HO hydrogen bonds to water molecules. The re-

Table IV. Hydrogen Bonds (Å)

N(1)-H(1)-O(4)	2.906
N(3)-H(3)-O(10)	3.123
N(4)-H(4)-O(7)	3.156
N(6)-H(6)-O(9)	2.986
O(7)-H(71)-O(8)	2.839
O(7)-H(72)-O(10)	2.844
O(8)-H(81)-O(9)	2.836
O(8)-H(82)-O(1)	2.815
O(9)-H(91)-O(5)	2.790
O(9)-H(92)-O(6)	2.756
O(10)-H(102)-O(2)	2.824
O(10)-H(101)-O(3)	2.849

Table V. Conformational Angles (deg)

angle	$(GPG)_2$	type II β turn	type I β turn	ref 17	ref 16	$(GPA)_2$[a]
ϕ_1	−142			−165	180	−173
ψ_1	−173			150	180	−163
ϕ_2	−66		−60	−70	−60	−70
ψ_2	−36		−30	120	120	116
ϕ_3	−115		−90	100	90	79
ψ_3	−7		0	0	0	19
ϕ_4	−150			−165	180	−179
ψ_4	178			−150	180	170
ϕ_5	−53	−60		−70	−60	−54
ψ_5	126	120		120	120	125
ϕ_6	83	80		100	90	94
ψ_6	−3	0		0	0	−5

[a] The $(GPA)_2$ structure has been renumbered so that its type II β turn corresponds to that in the $(GPG)_2$ structure. Note the reversed configuration of the 2-3 peptide between these two; this peptide is labeled as 5-6 in references 6. The angles ω_1-ω_6 are −177°, −173°, −177°, 180°, 179°, and −175°. In the NMR studies,[16,17] these angles were assumed to be 180°. In all other parts of this paper, the relationship of the numbering system used here to that (in parentheses) in reference 6 is N1 (1N), C11, ($1C_\alpha$), C12 (1C), O1 (1O), C23 ($2C_\beta$), C24 ($2C_\gamma$), C25 ($2C_\delta$), etc.

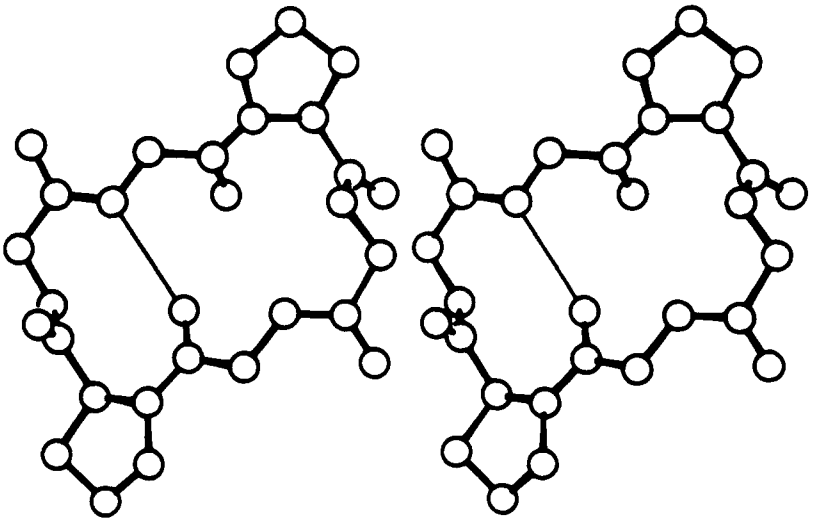

Figure 3. Stereoview of the molecule.

maining 3 hydrogen atoms form hydrogen bonds between these water molecules. Thus, neighboring peptide molecules are connected by water molecules along the **a** and **c** directions of the crystal, and all carbonyl oxygens of the peptide participate in hydrogen bonds.

Other aspects include the expected nonplanarity of the five-membered rings of proline, and the rather wide range of CH bonds (0.81-1.17 Å), NH bonds (0.98-1.38 Å), and OH bonds (0.87-1.03 Å).

Discussion

Although the four proline-containing cyclic hexapeptides now studied by X-ray diffraction methods all have trans peptide bonds, they show striking differences in their conformations.

In *cyclo*-(L-Ala-L-Pro-D-Phe)$_2$, transannular internal NH···O bonds are not formed, or are unusually weak.[4] The N···O distance is rather long, at 3.20 Å. Nevertheless, the molecule shows C_2 symmetry in the crystal as well as in its NMR spectrum in solution.[9] Here, there are two type II β turns. If both hydrogen bonds are shortened to 3.0 Å, an abnormally short intramolecular O···O distance of 2.5 Å would occur, if the C_2 symmetry is maintained.[4] The same situation occurs in *cyclo*-(Gly-L-Pro-D-Phe)$_2$.[7]

In *cyclo*-(Gly-L-Pro-D-Ala)$_2$, abbreviated as $(GPA)_2$ below, the apparent C_2 symmetry of the NMR spectrum in solution is lost in the crystal as one transannular hydrogen is broken when a type II β turn converts to type I. If some allowance is made for this lowever symmetry, one can still see general agreement between the gross conformations of $(GPA)_2$ in the crystal and in solution (NMR time scale).

These new results on *cyclo*-(Gly-L-Pro-Gly)$_2$, abbreviated as $(GPG)_2$, are surprising: the symmetry is lowered from C_2 to C_1, as only one transannular hydrogen bond remains, but, in addition, the plane of the peptide within the hydrogen bonded half has become reoriented by about 180° (ψ_2, ϕ_3 in Table V). Two NMR studies[16,17] have indicated C_2 symmetry in solution. While this equivalence of the two halves of the molecule may be actual or statistical in solution on the NMR time scale, we think it unlikely that this equivalence would have been observed if the 2-3 and 5-6 peptide bonds were differently oriented as they are in the crystalline state. Excluding the ψ and ϕ angles of the peptide bond (ψ_2, ϕ_3) the conformations in the crystal and in solution show deviations of observed ψ and ϕ angles of 11° (reference 16) or 16° (reference 17) in $(GPG)_2$, and of 13° in $(GPA)_2$. Possibly $(GPG)_2$ is more subject to the effects of intermolecular forces than is $(GPA)_2$. Certainly there are many more intermolecular hydrogen bonds to $(GPG)_2$ in its crystal than there are to $(GPA)_2$ in its anhydrous crystalline

form. It would be interesting to study the NMR spectrum as a function of temperature.

A referee has called our attention to the structures of two cyclic hexapeptides, *cyclo*-(D-Phe-Pro-Val)$_2$[18] and *cyclo*-(Gly-D-Leu-L-Leu)$_2$,[19] neither of which contains a transannular hydrogen bond. He also has pointed out a recent compilation[20] of bond lengths and angles in peptide units.

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Supplementary Material Available: Temperature factors (2 pages). Ordering information is given on any current masthead page.

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Selenium-77 Relaxation Time Studies on Compounds of Biological Importance: Dialkyl Selenides, Dialkyl Diselenides, Selenols, Selenonium Compounds, and Seleno Oxyacids

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Abstract: Spin-lattice relaxation times have been determined for several classes of selenium compounds that are biologically important. The classes of compounds include dialkyl selenides, dialkyl and diaryl diselenides, selenols, selenonium compounds, and seleno oxyacids and their salts. The relaxation times were measured under a variety of conditions, including aqueous and nonaqueous solutions, variable temperature, variable concentration, and variable pH. For the molecules studied, the spin-rotation and chemical-shift anisotropy mechanisms were found to be the most important means of spin-lattice relaxation for the ^{77}Se nucleus. The dipole-dipole mechanism was totally absent in all compounds studied. For selenium-containing biopolymers, the spin-rotation mechanism is not likely to contribute to spin-lattice relaxation. However, it has been shown that chemical-shift anisotropy and dipole-dipole mechanisms will most likely be effective mechanisms in larger molecules and that ^{77}Se Fourier transform (FT) NMR of these large molecules will not be encumbered by exceptionally long recycle times.

Introduction

While Fourier transform nuclear magnetic resonance (FT NMR) spectroscopy has been used to great advantage to study the chemistry of many elements of the periodic table, those of group 6A have received little attention. For oxygen and sulfur, the two lightest and most chemically prolific members of this group, the only NMR active isotopes (^{17}O and ^{33}S) are quadrupolar nuclei that suffer from very low natural abundance and relatively low sensitivity. Selenium and tellurium, on the other hand, both have spin-$^1/_2$ isotopes (^{77}Se, ^{123}Te, ^{125}Te) with sufficient sensitivity to make their study readily accessible by Fourier transform (FT) NMR. For the purposes of this investigation, our interest in selenium stems from the active role it plays in many biological systems, not to mention its increasing involvement in organic synthesis and an extensive inorganic chemistry.[1] Selenium-77 NMR has great potential as a means of exploring the chemistry of this interesting element and, as part of our continuing interest in the applications of multinuclear NMR to biological systems,[2] we have initiated a program aimed in this direction.

Early continuous wave (CW) NMR studied by Birchall et al.[3] followed by the INDOR studies of McFarlane and Wood[4] demonstrated the large chemical-shift range of ^{77}Se and the stereospecificity of its coupling constants. To date there have been only a few reports concerned with the direct observation of ^{77}Se by FT NMR.[2c,5-9] The nuclear spin-lattice relaxation time, T_1, is a critical parameter in determining the recycle time of FT NMR experiments. More importantly, it can often be used as a powerful, diagnostic tool for the determination of molecular structure, conformation, and composition.[10] It can also be employed as a probe to investigate molecular motions and interactions. Dawson and Odom,[2c] Pan and Fackler,[6] Gansow et al.,[7] and Koch et al.[8] have briefly examined spin-lattice relaxation times for ^{77}Se in a variety of chemical envi-

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