ABSTRACT A cyclic hexapeptide, cyclo(Pro-Gly-Pro-Gly-Pro-Gly), has been synthesized; its solution conformations were examinations by 220-MHz nuclear magnetic resonance spectroscopy. The solution structures have been deduced, and shown to vary as a function of solvent polarity. In addition, it has been found that this cyclic peptide binds alkali metal cations. While the predominant conformation of this cyclic peptide is 3-fold symmetric in the apolar solvent methane chloride, an asymmetric structure is preferred in some polar solvents (water, dimethylsulfoxide). However, addition of alkali metal salts, such as sodium thiocyanate, to dimethylsulfoxide solutions of the peptide shifts the conformational equilibrium in favor of a second type of C₃-symmetric structure, presumably the result of the formation of a stable peptide-metal ion complex. Nuclear magnetic resonance data suggest that the peptide in methane chloride solution takes up a conformation containing three cis' Pro Cα—C=O bonds and three cis Gly-Pro peptide bonds; that water and dimethylsulfoxide stabilize a conformer in which one (or two) sets of such bonds of a given Pro-Gly unit have undergone interconversion to trans'/trans forms; and that alkali metal cation complex the cyclic peptide in a C₃-symmetric all-trans'/trans structure.

The biological activity and structural simplicity of many cyclic peptides have generated considerable interest in the determination of their conformations, with the ultimate goal of ascertaining structure-function relationships. High-resolution nuclear magnetic resonance (NMR) spectroscopy, useful for the study of solution conformations of cyclic peptides, can provide information for structural determinations (1, 2).

Many naturally-occurring cyclic peptides contain proline, and it is believed that investigations of synthetic proline-containing cyclic peptides composed of repeating oligopeptide units (3-5) may clarify the structural role of the prolyl residue in biologically active cyclic peptides. An additional advantage of the investigation of proline peptides is that the number of possible conformers of the peptide backbone is limited by the restrictions to rotation about the N—Cα bond of the prolyl residues. Another consideration is the recent demonstration of the presence of cis- and trans-X-Pro peptide bonds (where X is any amino-acid residue preceding a proline residue), in both linear (6-8) and cyclic (4, 5) proline-containing peptides. Since the barrier to rotation about the peptide bond is estimated to be at least 15-20 Cal (9), different cyclic peptide conformations resulting from the presence of cis- and trans-X-Pro peptide bonds yield separate NMR spectra, thus permitting direct determination of the populations of the conformers present in solution under different conditions (e.g., various solvents or temperatures).

In NMR analyses of cyclo(Pro-Ser-Gly-Pro-Ser-Gly) [c-(Pro-Ser-Gly)₂] and its retro-isomer cyclo(Ser-Pro-Gly-Pro-Ser-Gly) [c-(Ser-Pro-Gly)₂], it was shown (4, 5) that in both compounds C₃-symmetric intramolecularly hydrogen-bonded conformations having all peptide bonds trans were in equilibrium with conformations [both asymmetric (4) and symmetric (5)] containing cis-X-Pro peptide bonds. The present report describes the synthesis of, and NMR studies on, cyclo(Pro-Gly-Pro-Gly-Pro-Gly) [designated c-(Pro-Gly)₃], in which the presence of three prolyl residues in alternating positions excludes intramolecularly hydrogen-bonded C₃-symmetric conformational similarity to those found for c-(Pro-Ser-Gly)₂ and c-(Ser-Pro-Gly)₂. In the apolar solvent [¹H]methane chloride (CD₃Cl), a 3-fold symmetric conformation is deduced for c-(Pro-Gly)₃ in which Pro Cα—C=O bonds are cis' and Gly-Pro peptide bonds are cis. In the polar solvent [¹H]dimethylsulfoxide ([(U-¹H]Me₂SO)₄, a single asymmetric conformer of c-(Pro-Gly)₃ is predominant; mixed [(U-¹H]Me₂SO-CD₃Cl solvents are used to study the equilibrium between the two conformers. The preferred conformation of c-(Pro-Gly)₃ in water is also asymmetric. Lastly, we report that alkali metal cations complex c-(Pro-Gly)₃ in [¹H]Me₂SO solution in a symmetric trans'/trans conformation.

RESULTS AND DISCUSSION

Conformation of Cyclo(Pro-Gly)₃ in Methylene Chloride. When c-(Pro-Gly)₃ (depicted schematically in Fig. 1) is dissolved in CD₃Cl, the 220-MHz NMR spectrum in Fig. 2a is obtained (NH portion not shown). The solubility of this cyclic peptide in CD₃Cl afforded an opportunity for the study of its conformation(s) unperturbed by interaction with oxygen-containing solvents. Most of the assignments indicated for various resonances are readily made by inspection (3, 4), with prolyl β- and γ-proton assignments confirmed by spin decoupling. Noteworthy in Fig. 2a is the magnetic equivalence of the three Pro-Gly units, indicating overall C₃-symmetry for the predominant conformation in CD₃Cl. In attempts to deduce the specific nature of this C₃-symmetric conformer, it is necessary to consider first the most likely isomeric structures

* Dedicated to our late colleague, Dr. Simon C. K. Wong, who was a gentleman, a scholar, and a scientist.
† This is the fourth paper in the series: “Cyclic Peptides.” The preceding paper is ref. 5.
‡ Present address: Polymer Division, National Bureau of Standards, Washington, D.C. 20234.
§ [U-¹H]Me₂SO is also called dimethylsulfoxide-d₄ by spectroscopists.
hedral angles formed by the Gly NH proton and the two Gly $C_\alpha$H's are both approximately 120°, or, in terms of peptide backbone rotational angles, the three Gly $\phi$ angles $\approx 0°$.

Second, the appearance of the Pro $C_\alpha$H as a doublet (at 5.25 $\tau$) in $\nu$-(Pro-Gly)$_3$ recalls a similar doublet (at 4.95 $\tau$ in CD$_2$Cl$_2$) in the NMR spectrum of cyclo(Pro-Pro)$_3$ (3). The conformations of the pyrrolidine rings in both cyclic peptides may, therefore, be similar, and possibly related to a common orientation of neighboring peptide bonds, i.e., cis in both instances [Pro-Pro in cyclo(Pro-Pro)$_3$, Gly-Pro in $\nu$-(Pro-Gly)$_3$].

Third, inspection of Corey–Pauling–Koltun (CPK) molecular models indicates that (a) the sequences trans’–cis and cis’–trans in a given Pro–Gly unit have unfavorably close atomic contacts, especially between neighboring carbonyl oxygen atoms; (b) both in these “mixed” Pro–Gly units and in trans'/trans Pro–Gly units, the sum of the two Gly $J_{Na}$ coupling constants is 10–12 Hz, in disagreement with the experimentally observed sum of $J_{Na}$ values (about 6.5 Hz); and (c) three peptide carbonyl oxygens (the three Pro and/or the three Gly carbonyl oxygens) in the all-trans’–all-trans structures are oriented toward each other and in close proximity, resulting in strong repulsive electrostatic interactions in the relatively nonpolar CD$_2$Cl$_2$ solvent.

The data therefore indicate that cyclo(Pro–Gly)$_3$ exists as a $C_3$-symmetric conformer in CD$_2$Cl$_2$, designated [S], that contains three cis’ Pro$C_\alpha$–C=O, and three cis Gly–Pro peptide bonds. This conformer is illustrated schematically in Fig. 1. Once these conformational features have been specified, peptide bond planarity, cyclic geometry, and steric requirements bring Gly $\phi$ angles to about 0°. The backbone conformation of [S] can thus be described approximately by three sets of Pro ($\phi$, $\psi$, $\omega$) angles $\approx (120°$, $125°$, $0°$), and three sets of Gly ($\phi$, $\psi$, $\omega$) angles $\approx (0°$, $0°$, $180°$).

**Effects of Polar Solvents on Conformation.** In our studies of cyclo(Pro–Gly)$_3$ in methylene chloride, it quickly became evident that small amounts of water strongly influenced the populations of $\nu$-(Pro–Gly)$_3$ conformations, as well as the chemical shifts of Gly NH protons. Therefore, we examined the NH region of the NMR spectrum of a dry sample of $\nu$-(Pro–Gly)$_3$ in CD$_2$Cl$_2$, the water content of which was <0.01% as determined by the absence of an H$_2$O resonance.

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*Fig. 1. Diagrammatic representation of cyclo(Pro-Gly)$_3$. Pro ($\phi_1$, $\psi_1$, $\omega_1$) and Gly ($\phi_2$, $\psi_2$, $\omega_2$) residue rotation angles are indicated.*

*Fig. 2. Portion of the 220-MHz NMR spectra of cyclo(Pro-Gly)$_3$ in (a) CD$_2$Cl$_2$, and (b) CD$_2$Cl$_2$ plus about 0.2% H$_2$O. Temperature = 23°C. Concentration: 20 mg/ml (a), 15 mg/ml (b). Chemical shifts ($\tau$ scale) given in ppm downfield from internal Me$_4$Si.*

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*While the barrier to interconversion between cis‘ and trans‘ forms of Pro $C_\alpha$–C=O bonds is not believed to be high enough at room temperature to give separate NMR spectra for each form, considerations based upon molecular geometry of $\nu$-(Pro–Gly)$_3$ and upon experimental data gathered from spectra throughout this study, suggest that in any given $\nu$-(Pro–Gly)$_3$ conformer one form only (either cis‘ or trans‘) will be significantly populated once other conformational degrees of freedom have been specified. However, the possibility cannot be rigorously excluded that the observed resonances result from rapid averaging of the conformations proposed with those containing mixed cis‘/trans‘ Pro $C_\alpha$–C=O bonds.*
In the resulting spectrum (Fig. 3a), minor NH resonances $A_1$, $A_2$, and $A_3$ were visible at 1.9, 3.3, and 3.5 $\tau$, respectively, and their area was found (with a computer of average transients) to contain 10-15% of the total NH area**. These resonances became more pronounced when approximately 0.2% water (less than 1 mol percent) was added (Fig. 3b). Note that the upfield portion of the spectrum run in this same solvent (Fig. 2b) also reveals the growth of minor resonances (visible between 5.4 and 5.8 $\tau$ but only barely evident in 2a). The presence of 0.2% water leads also to sharper resonances (compare 2b with 2a) and to a perceptible increase in the values of the Gly $J_{NH}$ (from about 2.5 and 4.0 $Hz$ in dry CD$_2$Cl$_2$ to about 3.0 and 4.5 $Hz$ in 0.2% H$_2$O).

A clear indication that the minor resonances correspond to an asymmetric conformation of cyclo(Pro--Gly)$_3$ stabilized by water is seen in Fig. 3 a-c, which shows that the single NH resonance due to the three Gly NH's of predominant symmetric conformation [S] in dry CD$_2$Cl$_2$ (3e) is replaced by a set of three NH resonances having equal area. This set of resonances is visible in both 3a and b, and is fully developed in pure water (0.5% acetic acid added to retard exchange) (Fig. 3c). Hence, in water a single asymmetric structure (having three magnetically nonequivalent Gly NH's) is the predominant conformation.

Since the polar solvent dimethyldiethyleneglycol, unlike water, is miscible with CD$_2$Cl$_2$, it was possible to monitor the conformational transitions just described over the entire range of solvent compositions. Thus, when aliquots of [U-2H]Me$_2$SO are added to a solution of c-(Pro--Gly)$_3$ in CD$_2$Cl$_2$ (Fig. 4), again three "minor" resonances of equal area are seen to grow in size ($A_1$, $A_2$, $A_3$) at the expense of S, until they are approximately each the same size S (4c), and finally predominate (4d)†. The polar solvent [U-2H]Me$_2$SO therefore stabilizes predominantly a single asymmetric conformation of c-(Pro--Gly)$_3$ in which the three Gly NH protons are nonequivalent and appear as three separate multiplets of equal area, similar to those observed in water.

A sample of c-(Pro--Gly)$_3$, dried from [U-2H]Me$_2$SO and redissolved in CD$_2$Cl$_2$, had the symmetric [S] conformation, confirming that the asymmetric conformer is in dynamic equilibrium with the symmetric conformer [S]. It is suggested from symmetry considerations and CPK model studies that these conformational transformations involve rotations of approximately 180° about both the Pro $\varphi$ angle and the Gly $\omega$ angle in one (or two) Pro-Gly units, i.e., a "flip" of the entire sequence $-C-N-CH_2-C-$ of a given Pro-Gly unit. (Note that the Pro--Gly peptide bond remains trans.)

** In one experiment, a particularly dry CD$_2$Cl$_2$ solution was obtained, as judged from (a) the upfield-shifted positions of the minor NH resonances (2.00, 3.35, and 3.55 $\tau$) and their relatively decreased population (5-10% of the total NH area), and (b) the rather poorly resolved resonances in the upfield region of the spectrum, possibly due to a tendency of c-(Pro--Gly)$_3$ to "aggregate."†

†† In pure [U-2H]Me$_2$SO (4e), [S] still gives a small resonance near 1.8 $\tau$, combined with another conformation (the symmetric trans'/trans' conformer [S']?), which gives a small resonance at about 1.9 $\tau$ (better resolved in 4d).

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**Fig. 3.** Peptide N--H region of 220 MHz spectra of cyclo(Pro--Gly)$_3$ in (a) CD$_2$Cl$_2$, (b) CD$_2$Cl$_2$ plus about 0.2% H$_2$O, and (c) H$_2$O (containing 0.5% acetic acid, V/N). The resonance due to $A_3$ is obscured by S in (b). Temperature: 23°C. Concentrations: 20 mg/ml (a); 15 mg/ml (b); 7 mg/ml (c). The signal-to-noise ratio in (c) was improved by 64 scans in a computer of average transients. Chemical shifts in (a) and (b) (c scale) given in ppm downfield from Me$_2$Si; in (c), from internal t-butyl alcohol taken at 8.77 $\tau$.

While it is certain that the predominant conformer in [U-2H]-Me$_2$SO is asymmetric, a clear choice is not possible between conformer [A] (one "unit flip"), and conformer [A'] (two "unit flips").

**Interaction of Cyclo(Pro--Gly)$_3$ with Alkaline Thiocyanate Salts.** Evidence for specific interaction between sodium thiocyanate (NaSCN) and cyclo(Pro--Gly)$_3$ is seen in Fig. 5, which shows the changes in the NH resonances resulting from addition of NaSCN to a solution of c-(Pro--Gly)$_3$ in [U-2H]Me$_2$SO. As the salt concentration increases, the population of the asymmetric conformation decreases, with the parallel increase of the population of a new symmetric conformation, signaled by the growth of the resonance designated S*. It is clear from Fig. 5e that about 90% of the c-(Pro--Gly)$_3$ molecules become symmetric when the molar ratio NaSCN/c-(Pro--Gly)$_3$ = 7. The upfield portion of spectrum 5e, appearing in Fig. 6, should be compared with Fig. 2a, where prominent differences are apparent in the chemical shifts, shapes, and coupling constants of most resonances, e.g., the Pro C$_3$H resonance is now a triplet, and the Gly $J_{NH}$ are now increased.

Because the conformation corresponding to S* resonances is C$_3$-symmetric, Gly--Pro peptide bonds must be all-cis or all-trans (see above). Since in the all-cis structure (i.e., conformation [S]), the three Pro and three Gly carbonyl groups are rigidly fixed with C=O axes approximately parallel and oxygen--oxygen distances ≈ 4-5 Å, the C=O groups are thus not well-disposed to bind a sodium cation (with radius about 1 Å). However, when the three Gly--Pro peptide bonds are trans and the Pro C$_3$--C=O bonds are trans', structures can readily be made with either the three Gly C=O's or the three Pro C=O's directed inward toward the center of the molecule in close proximity (as previously noted) and well-positioned to bind a sodium cation. The flexibility required to build these two types of trans'/trans structures is provided by the broad region of low energy about the trans' minimum in the potential well of the isolated Pro residue (10). Conformations of c-(Pro-
Fig. 4. Peptide N–H regions of 220-MHz NMR spectra of cyclo(Pro-Gly)₃. (a) in CD₃Cl₃; (b), (c), and (d) in CD₃Cl₃–[U-²H]Me₂SO mixtures; and (e) in [U-²H]Me₂SO. In (a)–(e), the mole fractions M of [U-²H]Me₂SO are 0.0, 0.1, 0.25, 0.5, and 1.0, respectively. Temperature = 23°C. Concentrations: 20 mg/ml (a); 12 mg/ml (b), (c), and (d); 15 mg/ml (e). In (b)–(e), the signal-to-noise ratio was improved by 4–16 scans in a computer. Chemical shifts (τ scale) given in ppm downfield from internal Me₂Si.

Gly)₃, having their sets of Gly or Pro carbonyl oxygens proximal and best oriented to bind Na⁺, have Pro ψ angles corresponding to the opposing limits of this broad well; when the Gly carbonyls are proximal (at Pro ψ ≈ 280°), the conformation is designated [S₀*], and when Pro carbonyls are proximal (at Pro ψ ≈ 340°), the conformation is designated [Sₚ*]. Both [S₀*] and [Sₚ*] appear favorable for complexing Na⁺, and the sodium cation may alternately (and rapidly on the NMR time scale) be bound and unbound to either the set of three Gly carbonyls [S₀*] or the set of three Pro carbonyls [Sₚ*]. The S* resonances in Fig. 5 (and Fig. 6) are taken, therefore, to represent averaged resonances corresponding to these two types of conformers. The experimental values of J₉Na obtained from Fig. 6 (5.0 and 5.5 Hz) are in good agreement with the average J₉Na predicted when Karplus-type equations (11–14) are applied to these two equally populated conformations in rapid equilibrium, i.e., when the three Gly ψ angles are alternately 300° [S₀*] and 240° [Sₚ*] as determined from the models, the calculated average J₉Na values are in the range 4.5–5.3 Hz and 6.0–6.5 Hz. Backbone rotational angles approximately describing conformation [S₀*] are: three sets each of Pro

Fig. 5. 220 MHz spectra of peptide N–H region of cyclo(Pro-Gly)₃ (a) in [U-²H]Me₂SO; (b)–(e), in [U-²H]Me₂SO with NaSCN added. In (b)–(e), the molar ratios of Na⁺ to c-(Pro-Gly)₃ are 0.5, 1, 2, and 7, respectively. Temperature = 23°C. Concentrations of c-(Pro-Gly)₃: 15 mg/ml. In (a), (b), and (c), 8 scans were accumulated in a computer to improve the signal. Chemical shifts (τ scale) given in ppm downfield from internal Me₂Si.

(φ, ψ, ω) angles ≈ (120°, 280°, 0°) and Gly (φ, ψ, ω) angles ≈ (300°, 330°, 0°). Those approximately describing [Sₚ*] are: Pro (φ, ψ, ω) ≈ (120°, 340°, 0°) and Gly (φ, ψ, ω) ≈ (240°, 30°, 0°).

An alternative conformation [Sₚ*], midway between [S₀*] and [Sₚ*] having Pro (φ, ψ, ω) ≈ (120°, 300°, 0°) and Gly (φ, ψ, ω) ≈ (270°, 0°, 0°), may be considered in which both sets of carbonyls of a given c-(Pro-Gly)₃ molecule would be simultaneously available for complexation with sodium ions on either (and/or both) faces of the cyclic peptide. Such a conformer seems less likely, since (a) sets of [Sₚ*] carbonyl oxygen atoms are significantly less proximal than the Gly's in [S₀*] or the Pro's in [Sₚ*], and (b) the experimentally observed J₉Na do not compare as well to the calculated Gly J₉Na (5.0–6.5 and 7.0–7.5) corresponding to such a structure.

The stoichiometry of the c-(Pro-Gly)₃–salt complex remains to be determined. Since three peptide carbonyls may not be sufficient to complex the cation effectively, the c-(Pro-Gly)₃–NaSCN system may be a "sandwich" complex, with the sodium ion associated on the average with two [S₀*] conformers, two [Sₚ*] conformers, or with one each, but at any moment bound to a total of six carbonyl groups.

While sodium was found to be the most effective ion, experiments with other alkali metal thiocyanates demonstrated their ability to complex c-(Pro-Gly)₃ in a symmetric con-
formation. Thus, in $[U-2H]Me_2SO$ solutions at a molar ratio of 
MNC/c-(Pro-Gly)$_3 = 8$, where $M = K^+$, $Li^+$, $Rb^+$, and 
Cs$^+$, the following fractions of symmetric c-(Pro-Gly)$_3$
conformer were observed: $K^+$, $\sim 0.75$; $Li^+ \approx Rb^+$, $\sim 0.50$; and 
Cs$^+$, $\sim 0.25$ (compared with Na$^+$ = 0.90 under similar 
conditions). The uncertainty in these measurements is estimated to 
be $\pm 10\%$.

The results reported above are of interest in relation to the 
on-ion-transport properties of naturally-occurring cyclic 
peptides. The data indicate that c-(Pro-Gly)$_3$ is a synthetic cyclic 
hexapeptide that complexes alkali metal cations; similar 
interactions of metal cations with a synthetic bicyclopeptide-
peptide have been reported (15). The preference for sodium 
shown by c-(Pro-Gly)$_3$ parallels the recent finding (16) that 
the naturally-occurring cyclic decapeptide, antamanide, also 
expresses sodium more effectively than it does potassium.

The fact that the striking conformational transitions of 
cyclo(Pro-Gly)$_3$ (as a function both of solvent polarity and 
alkali metal ion concentration) are directly observable by 
NMR illustrates the potential of this cyclic peptide as a 
model for the study of peptide-solvent interactions.

**MATERIALS AND METHODS**

*Synthesis.* t-Butyloxy carbonyl-Gly-Pro-OH was converted to 
its mixed anhydride with 2,6-dimethoxychloroforinate and 
N-methylmorpholine, and treated with Gly-Pro-benzyl ester 
hydrochloride to give the tetrapeptide, t-Boc-Gly-Pro-Gly-
Pro-OBz. After hydrogenation of this latter material in 
t-BuOH with 10% Pd-C, the acid obtained was converted to a 
similar mixed anhydride, and reacted with Gly-Pro-benzyl 
ester hydrochloride to produce the hexapeptide t-Boc-Gly-
Pro-Gly-Pro-Obz. This ester was then hydrogenated to yield the hexapeptide acid, treatment of which with 
p-nitrophenol and dicyclohexylcarbodiimide gave the active 
ester t-Boc-Gly-Pro-Gly-Pro-Obz-ONp; its t-Boc group was 
removed with HCl-ethy acetate. The resulting hydro-
chloride was cyclized in pyridine; when the acetone-insoluble 
fraction of the crude reaction product was dissolved in di-
methylformamide, a 38% yield was obtained of cyclo(Gly-
Pro-Gly-Pro-Gly-Pro-Gly) $\approx$ [cyclo(Gly-Pro-Gly-Pro-
Pro-Gly)]$\ddagger\ddagger$. As a dimethylformamide complex. Crystallization 
from methanol-ether gave the free cyclic peptide, mp 205–
210$^\circ$C, with a portion of the crystals persisting in the melt until 
its decomposition at 310–315$^\circ$C. Infrared spectra, mass spectra 
(molecular ion peak 462), and elemental analysis, in addition to 
the NMR spectra presented herein, confirmed the identity of 
this compound. Details of the synthesis and characterization 
of c-(Pro-Gly)$_3$ will be published elsewhere.

**NMR Spectra.** NMR spectra were obtained with the HR- 
220 spectrometer at Bell Laboratories. Homonuclear spin 
decoupling was accomplished by a General Radio 1107-A 
audio oscillator. In some instances, a Nicolet time averaging 
computer with 1024 channels was used in conjunction with

$\ddagger\ddagger$ The latter designation is used in the text with residues re-
versed from the order used in the synthesis for clarification in 
presentation of data.

The HR-220 instrument to improve the signal-to-noise ratio of 
the spectra. In nonaqueous solvents, tetramethyliilane 
was used as an internal reference, while in aqueous solution, 
the t-butyil resonance at 8.77 $\tau$ (relative to sodium 2,2-di-
methyl-2-silapentane-5-sulfonate) of [H$_2$]tert-butyl alcohol was 
used as internal reference.

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