Table I. The Helical Characteristics of Poly-L-proline, Poly[(*S*)-thiazolidine-4-carboxylic acid], and Poly[(*S*)-oxazolidine-4-carboxylic acid]

	Poly-L-proline		Poly[(*S*)-thiazolidine-4-carboxylic acid]		Poly[(*S*)-oxazolidine-4-carboxylic acid]	
Peptide unit	cis[a]	trans[b]	cis	trans	cis	trans
Internal rotation angles, deg ϕ	110	105	110	110	110	120
Internal rotation angles, deg ψ	340	335	350	340	350	340
Helical sense	Right	Left	Right	Left	Right	Left
Helical axial translation per peptide unit, Å	1.69	2.42	1.52	2.29	1.83	2.38
V (energy), kcal/mol of peptide unit	1.21	−0.82	3.86	−1.15	7.38	5.05
ΔV cis–trans, kcal/mol of peptide unit	2.03		5.01		2.33	

[a] W. Traub and U. Shmueli [*Nature (London)*, **198**, 1165 (1963)] carried out X-ray diffraction analysis on a fiber of poly-L-proline (I). They found two possible structures which are similar. They prefer the structure with 10 residues per unit cell and an axial translation per peptide unit of 1.90 Å. Our calculations agree somewhat better with the other structure which has 11 residues per unit cell and an axial translation per peptide unit of 1.73 Å. [b] P. M. Cowan and S. McGavin [*Nature (London)*, **176**, 501 (1955)] reported the axial translation per peptide unit for *trans*-poly-L-proline to be 3.12 Å. The discrepancy between this and our calculated value of 2.42 Å can arise from longer range intramolecular interaction (*i.e.*, greater than in the tripeptide we employed) and from packing factors for the fiber.

synthesizing poly[(*S*)-oxazolidine-4-carboxylic acid], we include calculations on this polymer with poly-L-proline and its sulfur analog.

Our conformational calculations for a tripeptide unit include nonbonded interactions, torsional potential functions, and electrostatic interactions. Coefficients for the pairwise Lennard-Jones potential functions were taken from Scott and Scheraga.[1] For interactions involving sulfur, we calculated the coefficients following the approach used to calculate the other interactions.[4] The electrostatic contributions were computed using a partial charge approximation suggested by Poland and Scheraga.[5] We employed standard bond lengths and bond angles[6] and developed a subroutine to our program to allow bond angles to deviate from their standard values.[7] In the case of the thiazolidine ring, we utilized preliminary X-ray diffraction information on (*S*)-thiazolidine-4-carboxylic acid which shows the ring to be puckered and the C–S–C bond angle to be approximately 90°.[8] To represent internal rotation angles, the convention suggested by Edsall, *et al.*,[9] was adopted. Details of our calculation will be presented in a subsequent paper. The preliminary results are tabulated in Table I. On the basis of the differences in energy of the cis and trans forms (Table I), we predict that poly[(*S*)-thiazolidine-4-carboxylic acid] should not mutarotate from the trans to the cis form. In the following communication we present experimental evidence on poly[(*S*)-thiazolidine-4-carboxylic acid] that agrees with our calculations.

Poly[(*S*)-oxazolidine 4-carboxylic acid] shows two forms of helices with reasonable dimensions (Table I) and a cis–trans energy difference intermediate between the polyproline and its sulfur analog. The absolute values for the energy of the cis or trans tripeptide units are more positive because of the electrostatic contributions. We expect to observe mutarotation for poly[(*S*)-oxazolidine-4-carboxylic acid] under favorable conditions.

The succeeding paper presents initial experimental results which were carried out after we calculated the conformational characteristics for poly[(*S*)-thiazolidine-4-carboxylic acid]. We hope to extend these studies to the oxygen analog and other related polypeptides.

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Conformational Aspects of Polypeptide Structure. XXXII. Helical Poly[(*S*)-thiazolidine-4-carboxylic acid]. Experimental Results

Sir:

In the preceding paper we predicted that the all-trans polymer for poly[(*S*)-thiazolidine-4-carboxylic acid], a cyclic analog of poly-L-proline in which the γ-methylene has been replaced by sulfur, is more stable than the all-cis polypeptide by 5 kcal/mol of peptide unit. This compares with a difference between *trans*- and *cis*-poly-L-proline of about 2 kcal/mol of peptide unit.[1] Poly-L-proline[2–5] and its derivatives are the only poly-

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(5) L. Mandelkern in "Poly-α-Amino Acids," Vol. 1, G. D. Fasman, Ed., Marcel Dekker, New York, N. Y., 1967, p 675.

(4) (a) J. C. Slater and J. G. Kirkwood, *Phys. Rev.*, **37**, 682 (1931); (b) K. S. Pitzer, *Advan. Chem. Phys.*, **2**, 59 (1958).
(5) (a) D. Del Re, *J. Chem. Soc.*, 4031 (1958); (b) D. Poland and H. A. Scheraga, *Biochemistry*, **6**, 3791 (1967).
(6) "Tables of Interatomic Distances and Configuration in Molecules and Ions," The Chemical Society, London, 1958.
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(8) E. Benedetti and C. Pedone, private communication.
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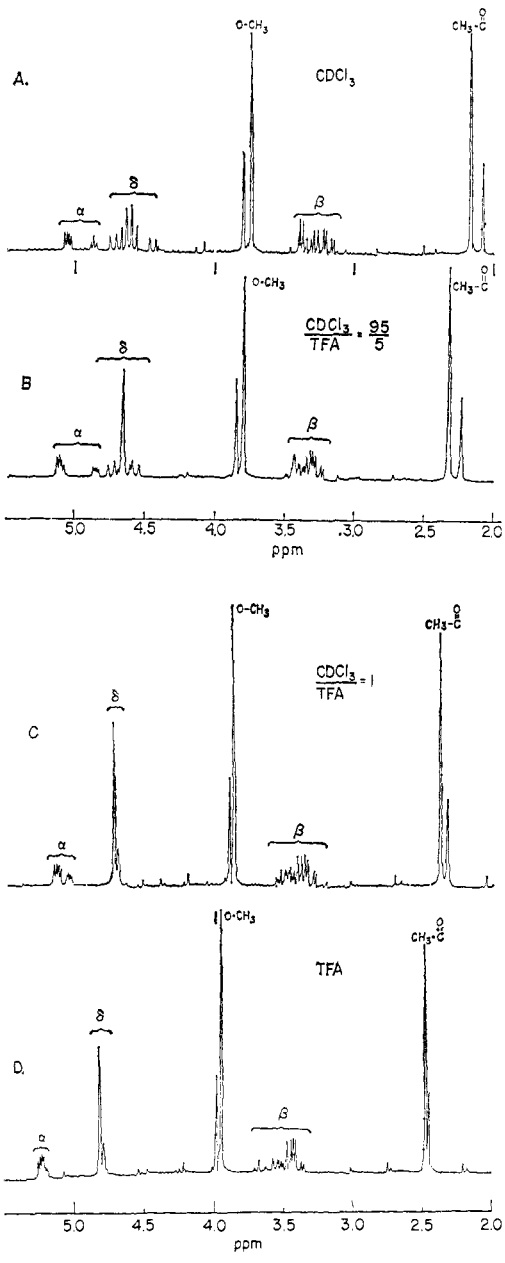


Figure 1. The high-resolution nuclear magnetic resonance spectra (220 MHz, in parts per million) of *N*-acetyl-(*S*)-thiazolidine-4-carboxylic acid methyl ester showing the profound changes of proton resonance on the α-, β-, and δ-carbons on alteration of the solvent from deuteriochloroform ($CDCl_3$) to trifluoroacetic acid (TFA) (A → D).

peptides in which mutarotation has been observed. In our work on poly-*N*-methyl-L-alanine,[6] an acyclic analog of poly-L-proline, we found no evidence of mutarotation. It is important to determine if the pyrrolidine ring is essential for mutarotation and to ascertain the role of steric and electronic effects on the mutarotation phenomenon.

We synthesized *N*-acetyl-(*S*)-thiazolidine-4-carboxylic acid methyl ester (I) as a model compound for poly[(*S*)-thiazolidine-4-carboxylic acid], and investigated its nuclear magnetic resonance (nmr) spectrum at 220 MHz. In the model compound, we find two stereoisomers. The protons on the α- and δ-carbons are

(6) M. Goodman and M. Fried, *J. Amer. Chem. Soc.*, **89**, 1264 (1967).

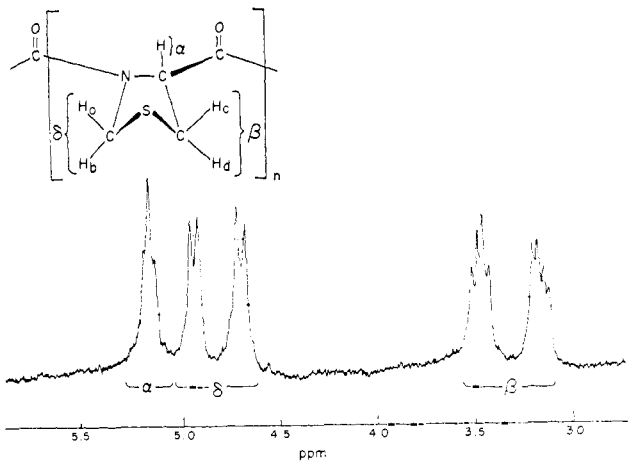
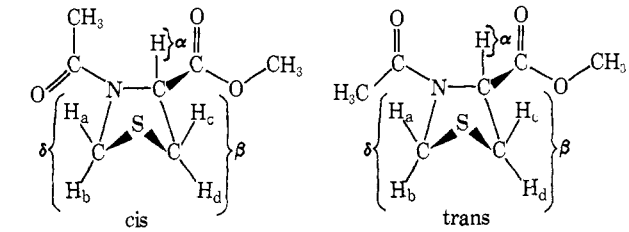


Figure 2. The high-resolution nuclear magnetic resonance spectrum (220 MHz, in parts per million) of poly[(*S*)-thiazolidine-4-carboxylic acid]. The spectrum remains unchanged on alteration of the solvent from deuteriochloroform ($CDCl_3$) to trifluoroacetic acid (TFA).

nonequivalent (I). The $-O-CH_3$ and $CH_3C{=}O$ in deuteriochloroform ($CDCl_3$) are clearly singlets from the trans and cis isomers in the ratio of 2:1. It is interesting to note the changes in the multiplets of the protons on the α-, β-, and δ-carbons and the pseudoequivalence of the protons on the δ-carbon upon the addition of trifluoroacetic acid (TFA) (Figure 1). These changes may result from protonation of the sulfur atom by the TFA, and consequent rapid flipping (on the nmr time scale) of the thiazolidine ring. For the polymer only one stereoisomer is observed with no change upon addition of TFA (Figure 2). We assign the trans structure to the major component of the model compound and to the polymer on the basis of our conformational energy calculations and proline analogs.[7] This assignment is supported by the fact that the chemical shifts for protons on the α- and δ-carbons of the polymer coincide with chemical-shift values for identical protons of the major isomer of the model compound system.



I

Circular dichroism data for the model compound (Figure 3) in hexafluoroisopropyl alcohol show troughs at 198 and 230 nm with no crossover detected above 190 nm. A red shift is observed for both troughs in the polymer, with the maxima at 209 and 245 nm, respectively. Once again no crossover is observed above 190 nm in the same solvent. We believe that the trough at 245 nm must be associated with an $n-\pi^*$ electronic transition on the sulfur atom in the thiazolidine ring. The broad trough at 209 nm is composed of the overlapping of $\pi-\pi^*$ and $n-\pi^*$ transitions for the imide

(7) C. M. Deber, F. A. Bovey, J. P. Carver, and E. R. Blout, *ibid.*, in press.

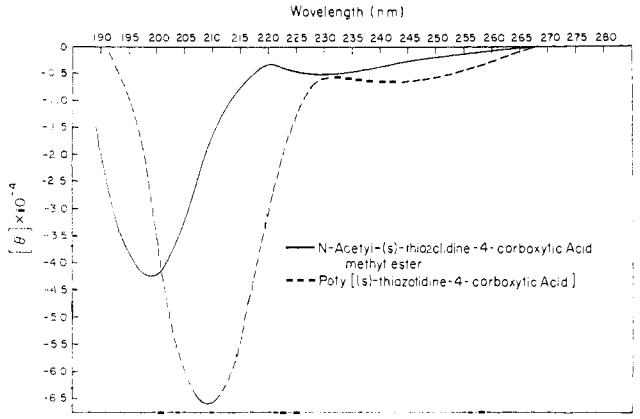


Figure 3. CD spectra of *N*-acetyl-(*S*)-thiazolidine-4-carboxylic acid methyl ester (——) and poly[(*S*)-thiazolidine-4-carboxylic acid] (- - - -) in hexafluoroisopropyl alcohol.

chromophore. These dichroic data are similar to those obtained for poly-L-proline form II.[8] We observed no mutarotations under all experimental conditions employed.

The lack of mutarotation in these systems is fully in agreement with predictions made, based on our conformational energy calculations.

We synthesized (*S*)-thiazolidine-4-carboxylic acid from cysteine hydrochloride and formaldehyde.[9] The total synthetic scheme will be reported in a subsequent paper.

We are currently in the process of preparing an oxygen analog of L-proline and (*S*)-thiazolidine-4-carboxylic acid, namely: (*S*)-oxazolidine-4-carboxylic acid. Our calculations[1] suggest that the polymer made from this compound will have properties intermediate between poly-L-proline and poly[(*S*)-thiazolidine-4-carboxylic acid]. We expect it to exhibit mutarotation.

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Carbon-13 and Oxygen-17 Nuclear Magnetic Resonance Studies of the Structure of the Nickel(II)–Ethylenediaminetetraacetate Complexes in Aqueous Solution[1]

Sir:

Despite the impressive array of physical techniques that has been applied to the study of the EDTA complexes of divalent metal ions, the structure that these complexes adopt in solution is still a matter of dispute. The crystallographic studies of metal ion–EDTA complexes by Hoard and coworkers[2-4] suggest that the complexes in solution could adopt one of the structures shown in Figure 1.

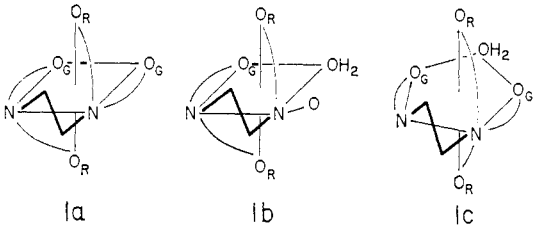

Figure 1. Probable structures for metal ion (M)–EDTA complexes in solution. N⌒O represents the $NCH_2CO_2^-$ and N⟋⟍N the NCH_2CH_2N linkages of EDTA.

It has been suggested[5] that, since the M(II)–EDTA complexes exhibit a common p*K* value of ~3 toward protonation, the complexes have structure **1b**. Structure **1b** has also been advanced on the basis of the electronic spectra of aqueous solutions of divalent transition metal ion–EDTA complexes,[6] but Bhat and Krishnamurthy[7] consider that the pH dependence of the electronic spectra of the EDTA complexes of Cu(II), Co(II), and Ni(II) can be explained by an equilibrium between **1a** and **1b** if the free CO_2 group of **1b** is protonated. An equilibrium between **1a** and **1b** with a protonated carboxyl group has also been proposed to account for the negative enthalpies and positive entropies of protonation of the M(II)–EDTA complexes.[8] Milner and Pratt[9] interpreted the pmr spectra of the aqueous Ni(II)–EDTA complexes at pH ≅11 and ≅2 in terms of an equilibrium among species having free and coordinated CO_2 groups but did not propose structures for the complex species. Wilkins and Yelin[10] argued that since Co(II)–EDTA solutions can be rapidly oxidized predominantly (≥80%) to the well-characterized octahedral, substitution-inert Co–EDTA$^-$ ion (structure **1a**), the Co–EDTA^{2-} ion must exist in solution as **1a**. However, Margerum and Rosen[11] claim that the kinetic behavior of the aqueous Ni(II)–EDTA system in temperature-jump relaxation studies indicates that the complex has structure **1b**.

We present here ^{13}C and ^{17}O nmr data which show that the Ni–EDTA complex is predominantly structure **1a** in the pH range 10–4 and that, below pH 4, there is an equilibrium between **1a** and **1b** with protonation of the "free" CO_2 group of **1b**. In this study we have taken advantage of the large chemical shifts and relatively small line broadening exhibited by the ^{13}C reso-

(1) Work performed under the auspices of the U. S. Atomic Energy Commission.

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