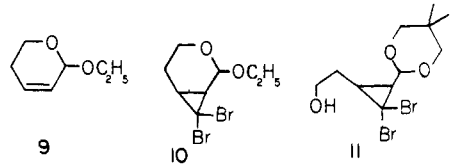
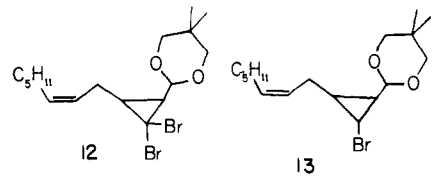
bromocarbene.[21,22] Reaction of **10** with dimethylpropanediol and



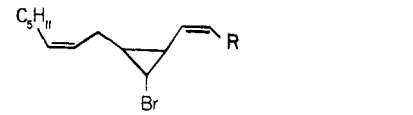
9 10 11

a trace of toluenesulfonic acid gave the acetal **11** (55%) that was oxidized to the corresponding aldehyde (75%) with pyridinium chlorochromate for 10 h.[22] The aldehyde was reacted with the ylide $PPh_3CHC_5H_{11}$ in THF at 0 °C for 2 h, giving the acetal **12** in 71% isolated yield. Reaction of **12** with methyllithium in



12 13

ether at −78 °C followed by workup by addition of water gave the bromocyclopropane **13** (80%). Only one bromine was removed in the methyllithium exchange, and published work[23] suggests that the acetal directs the methyllithium to remove the *cis*-bromine. Hydrolysis of the acetal with 88% formic acid for 31 h at 0 °C led to the corresponding aldehyde (88%) and reaction of this aldehyde with the ylide $PPh_3CH(CH_2)_6COOCH_3$ or $PPh_3CHCH_2CH{=}CH(CH_2)_3COOCH_3$ gave the target cyclopropyl bromides **14a** or **14b** in 85% isolated yield. The synthesis

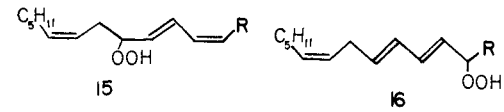


14 a, R = $-(CH_2)_6COOCH_3$

b, R = $-CH_2CH{=}CH(CH_2)_3COOCH_3$

of **14** is economical in terms of time and starting materials. Further, a judicious choice of Wittig reagents should make a variety of appropriately substituted cyclopropyl bromide precursors available for study.

Ring opening of **14a** was affected with excess silver trifluoroacetate and hydrogen peroxide present. In a typical reaction, 40 mg of **14a** and 950 μL of hydrogen peroxide in 6.6 mL of ether at 0 °C was treated with 758 mg of silver trifluoroacetate for 5 min. Chromatography of the product mixture after workup (bicarbonate and aqueous wash) on 10-μm silica showed two peroxide products (total yield 70–80%) formed in a 60:40 product ratio (**15**/**16**). The hydroperoxide **15a** was chromatographically



15 16

a, R = $-(CH_2)_6-COOCH_3$

b, R = $-CH_2CH{=}CH{-}(CH_2)_3COOCH_3$

identical with authentic material prepared by singlet oxygen oxidation of eicosatrienoic acid methyl ester. Reduction of **15a** and **16a** gave the corresponding alcohols which were characterized by IR, UV, and ^1H and ^{13}C NMR.[6,22] Hydrogenation, silylation and GC/MS analysis requires that **15a** is 12-substituted and **16a** has oxygen functionality at carbon 8. The infrared spectra confirm that **15a** has trans–cis-conjugated diene stereochemistry while **16a** has the trans,trans-substituted diene[24] structure.

The reaction of **14b** with silver trifluoroacetate and hydrogen peroxide provides the hydroperoxides **15b** and **16b**. In addition to IR, UV, GC/MS, and NMR characterization of the corresponding alcohols, decoupling experiments on the hydroperoxides, themselves, establish the stereochemistry as shown. Thus, the vinyl region of **15b** consists of signals at δ 6.57 [dd, H_{10}, $J_{10,11}$ = 15 Hz (trans 10,11)] and δ 5.95 [dd, H_9, $J_{8,9}$ = 11.3 Hz (cis 8,9)] while that of **16b** has signals at δ 6.27 [dd, H_9, $J_{9,10}$ = 15 Hz (trans 9,10)], δ 6.06 (dd H_{10}), and δ 5.72 [dt, H_{12}, $J_{11,12}$ = 15 Hz (trans 11,12)].

The ring-opening reaction of vinylcyclopropyl bromides thus affords lipid diene hydroperoxides with stereochemical control. The products formed in the ring opening of cyclopropyl bromide **14** are consistent with a mechanism involving formation of an intermediate pentadienyl cation. The preference for the thermodynamically less stable[25] trans,cis product **15** over the trans,trans isomer **16** is puzzling, however. Experiments designed to exploit the synthetic potential of this approach[26] and to provide mechanistic details of the ring-opening reaction are currently in progress.

Acknowledgments. This work was supported by NIH Grant HL-17921. N.A.P. gratefully acknowledges an RCDA 1977–1982.

Supplementary Material Available: Experimental details for the synthesis of compounds **9–16** are available upon request (8 pages). Ordering information is given on any current masthead page.

(21) Makosza, M.; Fedorynski, M. *Rocz. Chem.* **1976**, *50*, 2223.

(22) All new compounds were characterized by NMR (^1H and ^{13}C) and gave satisfactory C,H analyses. Details of the synthetic procedures may be obtained in the Supplementary Material to this communication.

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(24) Chan, H. W. S.; Levett, G. *Lipids* **1977**, *12*, 99.

(25) Chan, H. W. S.; Levett, G.; Matthew, J. A. *Chem. Phys. Lipids* **1979**, *24*, 245.

(26) Methods for hydrolysis of lipid hydroperoxide methyl esters have recently been reported. Thus, not only the methyl esters but also the free acids are available by this approach. See ref 8 and 9. While the base hydrolysis methods reported do lead to fatty acid hydroperoxides, we have found that hog pancreas lipase (ref 10 and 11) is a far superior reagent for hydrolysis.

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Reversible Conformational Changes Induced by Light in Poly(L-glutamic acid) with Photochromic Side Chains

Sir:

Polypeptides containing photoisomerizable azo aromatic chromophores were first investigated by Goodman and associated in 1966–1967 with ORD techniques.[1] In connection with more recent CD studies[2,3] in different laboratories, we report here some preliminary data indicating the possibility of producing, by irradiation, reversible $\beta \rightleftharpoons$ coil transition in water-soluble poly(L-glutamates) containing azobenzene groups in the side chains. In particular, it is shown that the pK value for the order–disorder conformational transition depends, in these polymers, on the dark and light conditions.

The photochromic polymers (Scheme I) were prepared from high molecular weight poly(L-glutamic acid) ($\bar{M}_v$ 200 000), fractionated by gel-filtration chromatography on Sephadex G50, by reaction with *p*-aminoazobenzene in the presence of dicyclohexylcarbodiimide and *N*-hydroxybenzotriazole[4] in dimethylformamide. Samples containing 13–56 mol % of azo groups were

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(2) Houben, J. L.; Pieroni, O.; Fissi, A.; Ciardelli, F. *Biopolymers* **1978**, *17*, 799–804.

(3) (a) Ueno, A.; Anzai, J.; Osa, T.; Kadoma, Y. *J. Polym. Sci., Polym. Lett. Ed.* **1977**, *15*, 407–410; (b) *Bull. Chem. Soc. Jpn* **1979**, *52*, 549–554.

(4) König, W.; Geiger, R. *Chem. Ber.* **1973**, *106*, 3626–3635.

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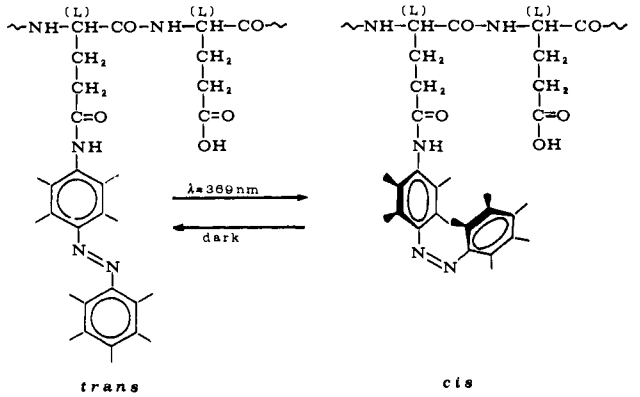
Scheme I



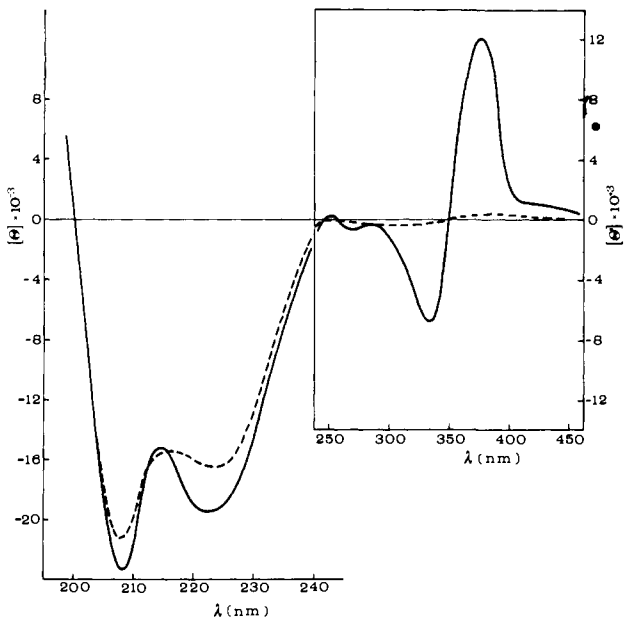


Figure 1. CD spectra in TMP solution of poly(L-glutamic acid) containing 36 mol % of azo groups before (—) and after (---) irradiation at 369 nm.

obtained by increasing temperature, duration, and molar excess of *p*-aminoazobenzene. All samples were soluble in trimethyl phosphate (TMP), and up to 36 mol % of azo groups were soluble in water, in contrast to previous samples prepared in the absence of *N*-hydroxybenzotriazole.[2]

At room temperature in the dark, the azo groups are in the trans configuration. Light produces isomerization to the cis isomer (Scheme I), the relative composition at the photostationary state depending on the incident wavelength.[2] Irradiation at 369 nm produces a 90% trans to cis photoconversion in TMP whereas only a ~30% conversion to the cis form can be reached in water. In both solvents, the photochemical reaction is entirely reversible.

The CD spectra in TMP solution of the polypeptide containing 36 mol % of azo groups are reported in Figure 1. In the peptide absorption region, the spectrum of the dark-adapted (trans) sample is characteristic of the α helix, the ellipticity at 222 nm, $[\Theta]_{222}$, being, however, lower than the standard value.[5] As the spectrum in this region is not affected by the irradiation (trans → cis isomerization), it is likely that the lower $[\Theta]_{222}$ value is due to a noncomplete α-helical conformation rather than to azo group contributions in this region. In the π–π^* absorption region of the azobenzene chromophore (350 nm), the trans polymer shows a couplet of bands, the first positive at 370 nm and the second negative at 330 nm, which disappear by trans to cis photoisomerization. The above couplet is thus probably associated with

(5) Greenfield, N.; Fasman, G. D. *Biochemistry* **1969**, *8*, 4108–4116.

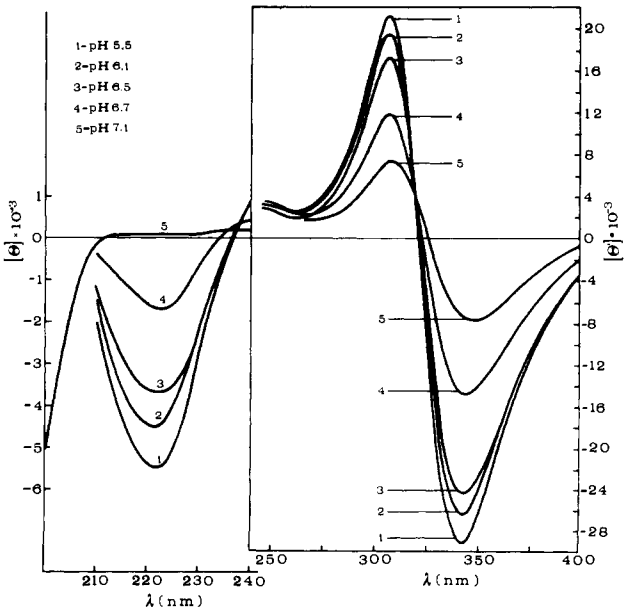


Figure 2. CD spectra of dark-adapted poly(L-glutamic acid) containing 36 mol % of azo groups in aqueous solution at different pH values.

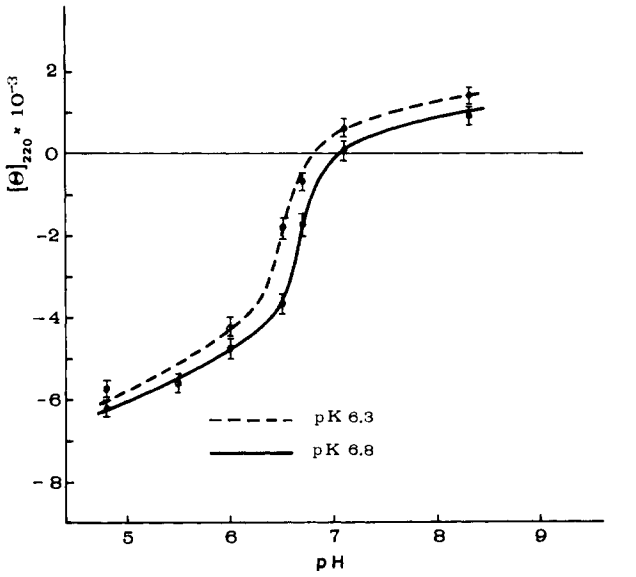


Figure 3. Order–disorder conformational transition in dark-adapted (—) and irradiated (---) samples of poly(L-glutamic acid) containing 36 mol % of azo groups.

dipole–dipole interactions of *trans*-azobenzene groups disposed along the right-handed α helix.

In water solution, the CD spectrum of the trans polymer is markedly affected by pH in both peptide and azo regions (Figure 2). In the former region at alkaline pH, the typical curve of the random-coil conformation is observed, changing to that of a β-type ordered structure when pH decreases to 5.5.[6] In the latter region, a negative couplet is present, the amplitude of which increases with increasing ordered structure content. This clearly demonstrates that the presence of the couplet is associated with the regular conformation of the polypeptide chain, the opposite sign being observed in the α helix with respect to the β structure probably due to the different relative geometries of the azo groups in the two cases. For the irradiated sample, the couplet is only partially reduced (about 50%) at any pH because of the low (~30%) photoconversion in water.

(6) The different conformations in TMP and in water are in agreement with the general observation that water favors β structure formation. Cf.: Woody, R. W. *Macromol. Rev.* **1977**, *12*, 181–321.

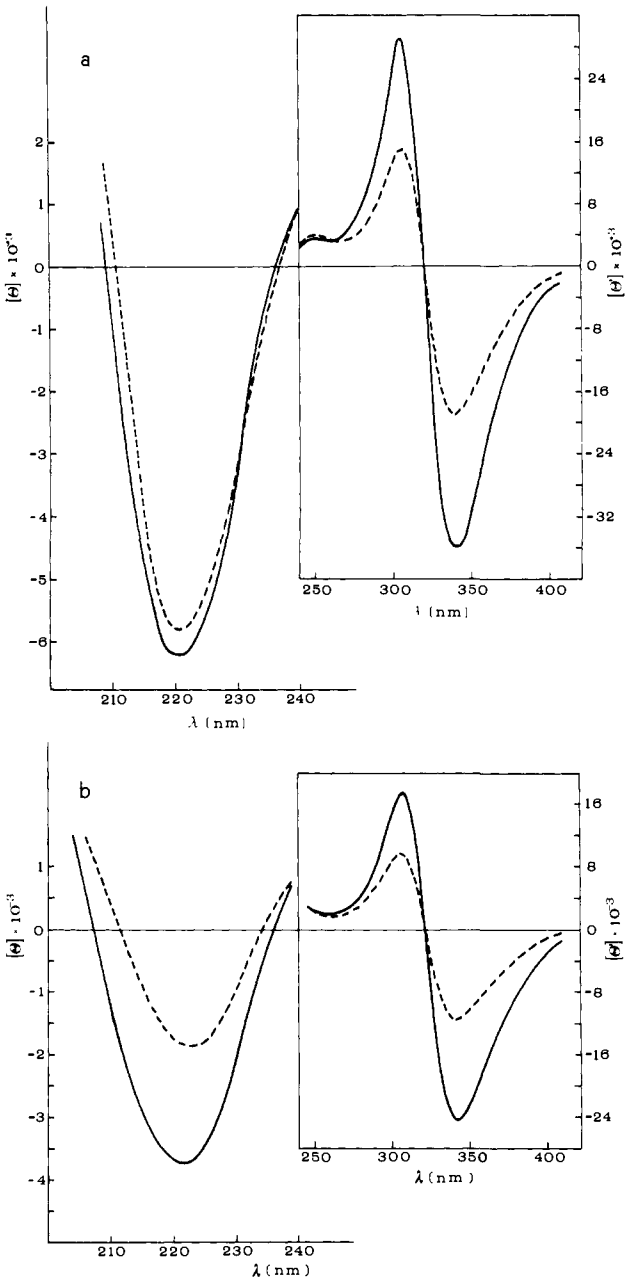


Figure 4. (a) CD spectra of poly(L-glutamic acid) containing 36 mol % of azo groups before (—) and after (---) irradiation, in aqueous solution at pH 4.8. (b) The same spectra as in (a) recorded at pH 6.5.

However, the plotting of $[\Theta]_{220}$ vs. pH indicates (Figure 3) that the order–disorder conformational transition occurs with different pK values for the dark-adapted sample (pK = 6.8) and the irradiated one (pK 6.3).[7] This means that the β structure has different stability when the 36 mol % of azo groups are either all trans or 70% trans and 30% cis. Accordingly, irradiation in the critical range of pH between the two pK values should produce a conformational change of the polypeptide chain.

The occurrence of this change is shown by the CD spectra, before and after irradiation at 369 nm, recorded at pHs 4.8 and 6.5, respectively (Figure 4a,b). At pH 4.8, where the β structure is very stable and not affected by azo side-chain photoisomerizations, the 30% trans → cis photoconversion produces a strong decrease in the ellipticity of the dichroic bands in the azo π–π^* absorption range (350 nm), but no effect is observed in the peptide region (Figure 4a). When the irradiation is carried out at pH 6.5, intermediate between the two above pK values, an analogous variation of the CD spectrum is observed in the azobenzene main absorption region. Moreover, a contemporary remarkable decrease of the ellipticity of the 220-nm band, associated with the β structure, can be observed (Figure 4b). The lack of variation in this region by irradiating at pH 4.8 excludes possible contributions of the azobenzene groups.

The conformational change induced by light is completely reversible, exposition of the polypeptide alternately to light and dark conditions reproducing exactly the two expected CD spectra, as observed in photoregulated biological processes.[8]

Systematic investigation in due course about the effect of solvent, irradiation wavelength, and azobenzene content and distribution should permit us to obtain larger conformational modifications.

(7) The same pK values were also found by plotting the amplitude of the couplet at ~350 nm vs. pH. This use of the azo chromophore as conformational probe is consistent with the direct relationship between side chains CD bands and main chain conformation.

(8) Erlanger, D. F. *Annu. Rev. Biochem.* **1976**, *45*, 267–283.

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Chiral Recognition by Small Biological Molecules. Resolution of Helicenes on Silica Gel Coated with Riboflavin

Sir:

Recent work has demonstrated that a wide range of optically active compounds shows significant differences in their distribution between two phases, one of which is chiral and can therefore be readily resolved, e.g., by gas[1] or liquid chromatography.[2] Such chromatographic experiments, when carried out with biological substances as either the resolving or the resolved species, have particular interest, as they might have relevance for the understanding of chiral discrimination in biological systems.

Optically active natural polymers can be used more or less successfully for the separation of enantiomers. It will suffice here to mention the classical resolution of Troeger's base on lactose[3] and the more recent separations achieved on starch columns[4] and on modified (triacetylated) cellulose.[5]

For small molecules, protein amino acids are examples of compounds which, derivatized as, e.g., *N*-acyl dipeptide esters,[6] *N*-acyl amino acid amides,[7] or metal complexes,[8] show chiral recognition as stationary (or mobile) phases in either gas or liquid

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(2) (a) I. S. Kroll, *Adv. Chromatogr. (N.Y.)*, **16**, 175 (1977); (b) E. B. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. S. Cram, *J. Am. Chem. Soc.*, **95**, 2692 (1973), and subsequent papers; (c) J. N. LePage, W. Lindner, G. Davies, D. E. Seitz, and B. L. Karger, *Anal. Chem.*, **51**, 433 (1979); (d) W. H. Pirkle and D. W. House, *J. Org. Chem.*, **44**, 1957 (1979).
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(7) B. Feibush, *J. Chem. Soc. D.*, 544 (1971); R. Charles, U. Beitler, B. Feibush, and E. Gil-Av, *J. Chromatogr.*, **112**, 121 (1975), and subsequent papers.
(8) P. E. Hare and E. Gil-Av, *Science (Washington, D.C.)*, **204**, 1266 (1979); S. Rhogozin and V. Davankov, *J. Chem. Soc. D.*, 490 (1971), and subsequent papers.

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