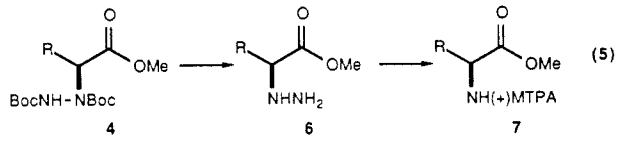
5f (R = CMe_3) were also subjected to the same reaction sequence with equal success[11] in yields ranging from 83% to 94%. Since the diastereomeric purity of the derived MTPA amides **7c** (R = CH_2Ph), **7e** (R = $CHMe_2$), and **7f** (R = CMe_3) was 200:1, racemization, which could have presented a problem during either transesterification or hydrazine reduction, proved to be inconsequential (eq 5).



(5)

In summary, the electrophilic "amination" of chiral enolates with DBAD provides an expedient approach to the synthesis of both α-hydrazino[12] and α-amino acids. This methodology nicely complements the chiral glycinate alternatives reported by others.[2a,2b]

Acknowledgment. Support has been provided by the National Science Foundation (CHE-8501707) and the National Institutes of Health (GM-33328). The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is also acknowledged for providing NMR facilities.

Supplementary Material Available: Detailed general procedures for enolate amination, transesterification, and hydrolysis and full spectral data (13 pages). Ordering information given on any current masthead page.

(11) Benzyl esters **5c**, **5e**, and **5f** were converted to the derived methyl esters **4** via successive hydrogenolysis (5% Pd–C, H_2, EtOAc) and diazomethane treatment.

(12) α-Hydrazino acids have been prepared from *N*-benzyl α-amino acids via a multistep procedure: Achiwa, K.; Yansada, S. *Tetrahedron Lett.* **1975**, 2700–2704.

Amination of Chiral Enolates by Dialkyl Azodiformates. Synthesis of α-Hydrazino Acids and α-Amino Acids†

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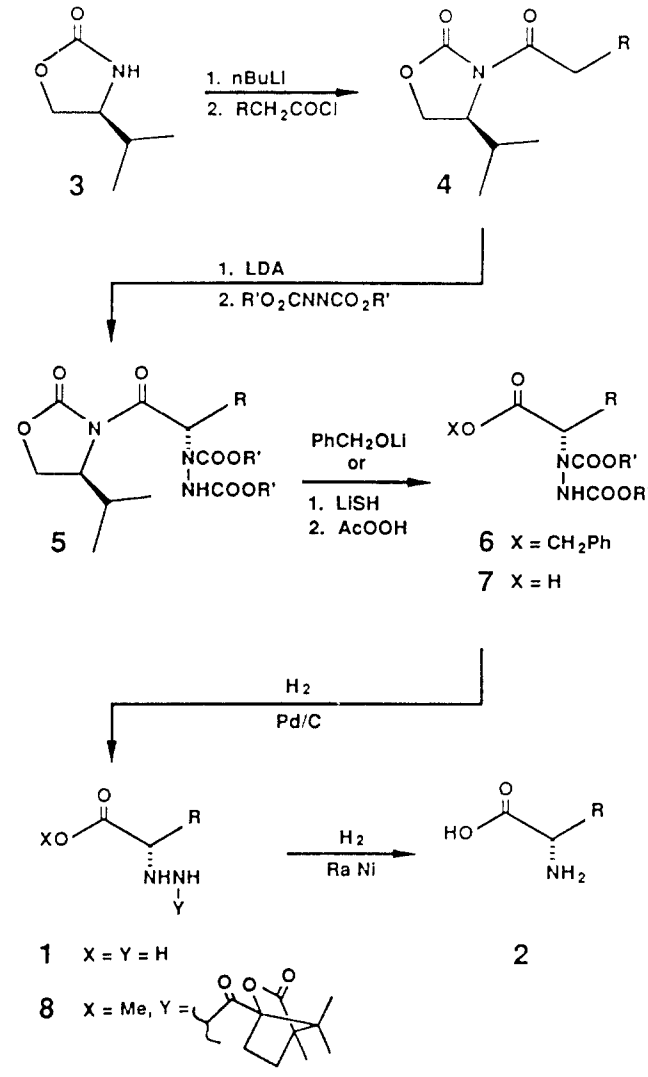
The natural occurrence of about 700 nonprotein amino acids as well as the importance of the approximately 20 amino acids common in proteins has stimulated recent work on asymmetric synthesis of such compounds.[1-3] Their structural analogues, α-hydrazino acids (**1**), are effective inhibitors of certain amino acid metabolizing enzymes, especially ammonia lyases[4] and pyridoxal phosphate dependent proteins.[5] As a result, some α-hydrazino acids (**1**) possess antibiotic activity[5d,6] or produce interesting physiological effects.[7] These attributes and the known conversion of **1** to the parent α-amino acids (**2**) by nitrosation[8] make an efficient stereospecific synthesis of these analogues highly desirable. Most previous syntheses of **1** have involved reduction of α-diazo esters,[9] nitrosation and reduction of α-amino acids,[10] Hofmann rearrangement of α-ureido acids,[8,11] or treatment of α-halo carboxylic acids with hydrazine.[12] Frequently these procedures suffer from loss of optical purity or low yields. We

Scheme I



† Presented in part at the International Symposium on the Chemistry of Natural Products, June 23–26, 1985, Edmonton, Alberta, Canada.

(1) See: Evans, D. A., et al., preceding paper in this issue. Professor Evans has independently developed similar methodology. We are deeply indebted to him for generously sharing his unpublished results with us after we learned of each other's work in July 1985.

(2) *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985.

(3) For some recent examples, see references in: (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104. (b) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833–1843. (c) Schöllkopf, U.; Neubauer, H. J.; Hauptreif, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1066–1067. (d) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131–1132. (e) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105–7109. (f) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417–419.

(4) (a) Munier, R. L.; Bompeix, G. *C. R. Acad. Sci., Ser. 3* **1985**, *300*, 203–206. (b) Brand, L. M.; Harper, A. E. *Biochemistry* **1976**, *15*, 1814–1821.

(5) For leading references, see the following. (a) Histidine decarboxylase (PLP type): Tanase, S.; Guirard, B. M.; Snell, E. E. *J. Biol. Chem.* **1985**, *260*, 6738–6746. (b) Aspartate aminotransferase: Yamada, R. H.; Wakabayashi, Y.; Iwashima, A.; Hasegawa, T. *Biochim. Biophys. Acta* **1985**, *831*, 82–88. (c) Ornithine decarboxylase: Takano, T.; Takigawa, M.; Suzuki, F. *J. Biochem. (Tokyo)* **1983**, *93*, 591–598. (d) Diaminopimelate decarboxylase: Kelland, J. G.; Arnold, L. D.; Palcic, M. M.; Pickard, M. A.; Vederas, J. C. *J. Biol. Chem.*, in press.

(6) (a) Morley, J. S.; Payne, J. W.; Hennessey, T. D. *J. Gen. Microbiol.* **1983**, *129*, 3701–3708. (b) Morley, J. S.; Hennessey, T. D.; Payne, J. W. *Biochem. Soc. Trans.* **1983**, *11*, 798–800. (c) Parsons, J. L.; Klosterman, H. J.; Ninnemann, J. L. *Antimicrob. Agents Chemother.* **1967**, 415–421.

(7) (a) Markle, R. A.; Hollis, T. M.; Cosgarea, A. J. *Exp. Mol. Pathol.* **1986**, *44*, 21–28. (b) Amrhein, N.; Wenker, D. *Plant Cell. Physiol.* **1979**, *20*, 1635–1642. (c) Kusunoki, S.; Yasumasu, I. *Dev. Biol.* **1978**, *67*, 336–345. (d) Brand, L. M.; Harper, A. E. *Biochim. Biophys. Acta* **1976**, *444*, 294–306.

(8) LiBassi, G.; Ventura, P. Monguzzi, R.; Pifferi, G. *Gazz. Chim. Ital.* **1977**, *107*, 253–255.

(9) Takamura, N.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 800–803.

(10) Achiwa, K.; Yamada, S. *Tetrahedron Lett.* **1975**, 2701–2704.

(11) Gustafsson, H. *Acta Chem. Scand., Ser. B* **1975**, *B29*, 93–98.

(12) (a) Sawayama, T.; Kinugasa, H.; Nishimura, H. *Chem. Pharm. Bull.* **1976**, *24*, 326–329. (b) Niedrich, H.; Koller, G. *J. Prakt. Chem.* **1974**, *316*, 729–740. (c) Sletzinger, M.; Firestone, R. A.; Reinhold, D. F.; Rooney, C. S.; Nicholson, W. H. *J. Med. Chem.* **1968**, *11*, 261–263.

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Table I. Amination of Enolates of **4** with $R'O_2CNNCO_2R'$

entry	R	R′	% yield of **5**[a]	diastereomeric ratio of **5**[b]	yield of **6** or **7**[a]	yield of **1**[a]	enantiomeric ratio of **1**[c]
a	Me	CH_2Ph	91	90:10[d]	82[e]	98	88:12
					93[f]	92	72:28[g]
b	CH_2Ph	Me	83	69:31			
c	CH_2Ph	Et	88	75:25			
d	CH_2Ph	CH_2Ph	90	94:6	85[e]	82	94:6
					87[f]	92	88:12
e	CH_2Ph	$C(CH_3)_3$	88	93:7	97[f]	81[h]	83:17[g]
f	$CH(CH_3)_2$	CH_2Ph	85	97:3	86[f]	98	97:3
g	Me	$C(CH_3)_3$	92		74[f]	83[h]	86:14[g]

[a] See supplementary material for experimental procedures. Yield of isolated compounds. [b] Diastereomeric ratio determined by HPLC (±2%). [c] Diastereomeric ratio determined by GC of **8** (±0.5%). [d] Structure of major diastereomer is shown. [e] Cleavage with LiSH to produce **7**. [f] Cleavage with $PhCH_2OLi$ to produce **6**. [g] Enantiomeric ratio determined by optical rotation. [h] Deprotected by hydrogenolysis followed by treatment with trifluoroacetic acid.

now report[1] that α-hydrazino acids (**1**) are easily accessible in good yield and optical purity through amination of chiral enolates by dialkyl azodiformates, and that the corresponding α-amino acids (**2**) are readily obtained by Raney nickel hydrogenolysis of **1**.

Previous studies by Evans and co-workers had shown that enolates of chiral carboximides **4** attack a variety of electrophiles with high diastereoselectivity.[13] This suggested that a source of electrophilic nitrogen[14-17] could provide a short sequence for stereospecific introduction of this element at the α-position of a carboxylic acid. When preliminary experiments indicated that most of these electrophilic nitrogen reagents[14,15] are unsuitable, attention shifted to dialkyl azodiformates. Stolle, Carpino, and others had demonstrated that some carbon nucleophiles (e.g., Grignard reagents[16]) can add to azodiformates or related *N*-acyl azo compounds in the desired fashion.[16,17] Thus, the chiral carboximides **4** (Scheme I), obtained by N-acylation of oxazolidinone (**3**), were converted to their respective *Z* lithium enolates[13] (1.1 equiv of LDA, THF, −78 °C) and a solution of the dialkyl azodiformate[18] (1.1 equiv, 0.8 M in THF, −78 °C) was added. The reactions were then immediately quenched by addition of NH_4Cl (5% in H_2O) to give the aminated carboximides **5** in good yield (Table I). The diastereomeric ratios, as determined by HPLC,[19] indicate that the substitution of both the dialkyl azodiformate and the acyl side chain of **4** influence the selectivity. As the size of the R′ group on the aminating reagent increases the ratio improves (Me < Et < CH_2Ph ≈ *t*-Bu). Similarly, greater bulk of the acyl side chain also increases the diastereoselectivity (Me < CH_2Ph < *i*-Pr). The reaction is extremely rapid even at −110 °C, and such lower temperatures do not alter the diastereomeric ratios significantly.[20] Since the diastereomers of **5** are generally difficult to separate by conventional column chromatography, the use of more hindered dibenzyl or di-*tert*-butyl azodiformates is synthetically advantageous.

Methods for removal of the chiral oxazolidinone moiety were also examined. The transesterification method ($PhCH_2OLi$, 2 equiv, THF, 0 °C, 15 min) reported for other carboximides[13b] often caused some epimerization at the newly aminated center in our cases. Thus **5f** was transformed to **6f** with no loss of stereochemistry, but under similar conditions **5d** gave **6d** with 11% racemization.[21] To avoid this, cleavage with hydrosulfide anion (HS^-) was investigated because of its increased nucleophilicity and decreased basicity.[23] Since loss of stereochemistry with alkoxide ($PhCH_2OLi$) probably occurs after departure of the oxazolidinone moiety,[13c] reaction of **5** with anhydrous LiSH (10 equiv, THF, 20 °C, 10 min) has the additional advantage of generating the anion of the thiol acid, which is less prone to deprotonation at the α-position than an ester. Treatment of the resulting reaction mixture with 1:1 THF/peracetic acid (40% in H_2O) gives the carboxylic acids **7** in 76–85% yield after medium-pressure reverse-phase chromatography (RP-8, 3:1 MeOH/H_2O). Compounds **6** and **7** were hydrogenolyzed to the free α-hydrazino acids (**1**), which were converted to **8** for stereochemical analysis.[21] In the cases studied (Table I), the amount of racemization (if any) is less than 1%, using the hydrosulfide cleavage.

Since Raney nickel[24] was known to hydrogenolyze the nitrogen–nitrogen bond of hydrazine derivatives,[25] this approach was used to convert the α-hydrazino acids (**1**) to the parent α-amino acids (**2**). In a typical example, hydrogenation of **1d** (R = CH_2Ph) with Raney nickel (500 psi, 10% aqueous HOAc) produced L-phenylalanine in 97% yield without detectable racemization.[26]

(13) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739. (c) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156. (d) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348. (e) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830–1835.

(14) For a review of aminating reagents, see: Tamura, Y.; Minawikawa, M. I. *Synthesis* **1977**, 1–17.

(15) For some examples, see references in: (a) Nomura, Y.; Anzae, H.; Tarao, R.; Shiome, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 967–969. (b) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 167–172. (c) Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 3795–3798. (d) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 1054–1056. (e) Beak, P.; Basha, A.; Kokko, B. J. *J. Am. Chem. Soc.* **1984**, *106*, 1511–1512. (f) Sakakura, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1309–1310.

(16) (a) Stolle, R.; Reichert, W. *J. Prakt. Chem.* **1929**, *122*, 344–349. (b) Carpino, L. A.; Terry, P. H.; Crowley, P. J. *J. Org. Chem.* **1961**, *26*, 4336–4340.

(17) (a) For a review of electrophilic additions of azodicarboxylates, see: Fahr, E.; Lind, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 372–384. (b) Wilson, R. M.; Hengge, A. *Tetrahedron Lett.* **1985**, *26*, 3673–3676.

(18) The dialkyl azodiformates (R = CH_3, CH_2CH_3, CH_2Ph) are commercially available. Di-*tert*-butyl azodiformate was prepared by literature procedures: (a) Paleveda, W. J.; Holly, F. W.; Veber, D. F. *Org. Syn.* **1984**, *63*, 171–174. (b) Carpino, L. A.; Crowley, P. J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 160–162.

(19) Suitable HPLC conditions for these difficult separations were suggested by Professor David Evans (see ref 1). The separations were done on Whatman Partisil M9 10/25 columns using either CH_2Cl_2/hexane/MeCN (46:46:8) or EtOAc/hexane (78:22) solvent systems. The individual isomers were separately characterized by mass spectrometry and in some cases also by NMR and IR. All spectral, chromatographic, and microanalytical data were in accord with the proposed structures (see supplementary material).

(20) In several cases the diastereomeric ratios of **5** could be determined by ^1H NMR spectroscopy. Although standard conditions ($CDCl_3$, 298 K) produce spectra with broad peaks due to restricted rotation, spectra with sharp signals could be obtained at elevated temperatures (toluene-d_8, 374 K).

(21) Enantiomeric ratios of **6** or **7** were determined by hydrogenolysis (H_2, 5% Pd/C, THF/HCl (6 N) 10:1) to the free α-hydrazino acid salt (**1**), which was then converted to the diastereomeric camphanamide methyl esters (**8**) by using (−)-camphanoyl chloride followed by diazomethane.[22] The mixture was analyzed by gas chromatography (DB-17, 15 m × 0.53 mm bonded FSOT column, 170 °C for 2 min, 2 °C/min to 250 °C, 250 °C for 5 min, 9.5 psi).

(22) Amarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2229–2237.

(23) For a review of the chemistry of hydrosulfide and thiol acids, see: Janssen, M. J. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; Interscience: London, 1969; pp 705–764.

(24) Mozingo, R. *Organic Syntheses*; Wiley: New York, 1951; Collect. Vol. III, pp 181–183.

(25) (a) Robinson, F. P.; Brown, R. K. *Can. J. Chem.* **1961**, *39*, 1171–1173. (b) For a discussion of reductions of hydrazines, see: Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927–2931. (c) An α-hydrazino acid has been hydrogenated to an α-amino acid with Pd catalyst: Karady, S.; Ly, M. G.; Pines, S. M.; Sletzinger, M. *J. Org. Chem.* **1971**, *36*, 1949–1951.

(26) Analysis for stereochemical purity was done by conversion of **2** to the corresponding camphanamide methyl esters[22] and gas chromatographic analysis by a procedure analogous to that described for **1** in ref 21. Authentic standards were prepared from pure D- and L-amino acids.

Hence the amination of enolates derived from **4** with dibenzyl or di-*tert*-butyl azodiformates provides an efficient route for conversion of carboxylic acid derivatives to both chiral α-hydrazino acids (**1**) and α-amino acids (**2**).

Acknowledgment. We thank Professor David A. Evans (Harvard University) for valuable discussions and suggestions.[1] Financial support from the National Institutes of Health (GM 29826), the Alberta Heritage Foundation for Medical Research, and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Supplementary Material Available: Experimental descriptions, analytical procedures, and spectral data for new compounds (12 pages). Ordering information is given on any current masthead page.

Photoinduced Reversible Conformational Transition of Polypeptide Solid Membranes

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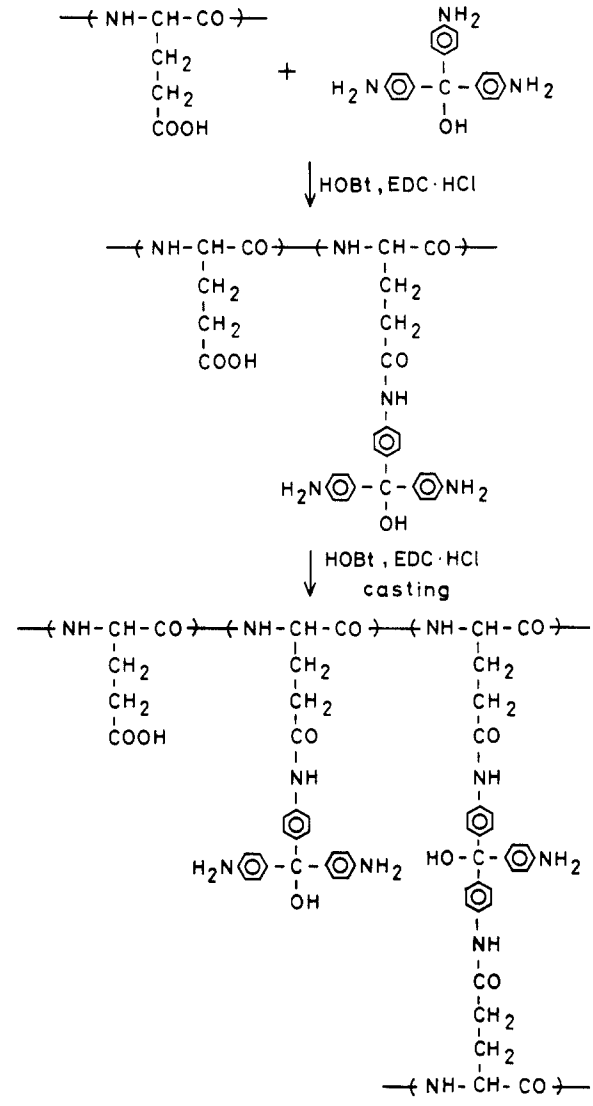
The photocontrol of physical and chemical properties of polymer gels and membranes with photochromic residues has been the subject of numerous recent investigations.[1-4] Photoinduced conformational changes of polypeptides in solution have been observed for poly(L-aspartates)[5-9] and poly(L-glutamates),[10-14] with azobenzene derivatives in their side chains. No report has appeared, however, on photoinduced α-helix to coil transition of polypeptide solid membrane. We report here on the photocontrol of the secondary structure of polypeptide solid membranes composed of poly(L-glutamic acid) (PGA) containing pararosaniline (rose) groups in the polymer side chains based on a cooperative effect between photodissociation of the pararosaniline moiety and the induced acid dissociation of the L-glutamic acid group in the membrane.

PGA polymers with incorporated pararosaniline groups (rose-PGA) were synthesized by the condensation reaction of PGA with pararosaniline in the presence of *N*-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide

Scheme I



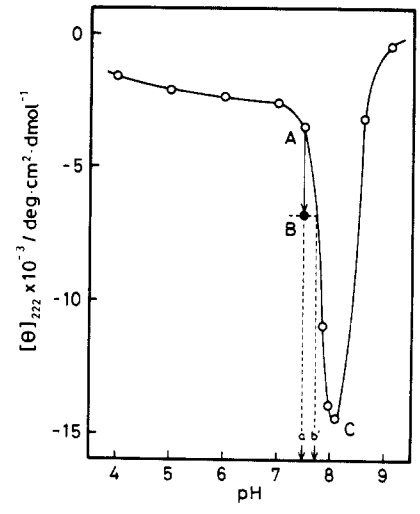


Figure 1. pH dependence of minimum ellipticity, $[\theta]_{222}$, of a dark-adapted membrane of poly(L-glutamic acid) containing 10.5 mol % pararosaniline groups in aqueous solution at 25 °C.

(1) Photocontrol of potentials across polymer membranes: (a) Kato, S.; Aizawa, M.; Suzuki, S. *J. Membr. Sci.* **1976**, *1*, 289-300. (b) Kato, S.; Aizawa, M.; Suzuki, S. *J. Membr. Sci.* **1977**, *2*, 39-47. (c) Aizawa, M.; Tomono, S.; Suzuki, S. *J. Membr. Sci.* **1977**, *2*, 289-301. (d) Irie, M.; Menju, A.; Hayashi, K. *Nippon Kagaku Kaishi* **1984**, 222-232. (e) Takizawa, A.; Sato, M.; Kinoshita, T.; Tsujita, Y. *Chem. Lett.* **1984**, 1963-1966.

(2) Photocontrol of permeabilities through polymer membranes: (a) Ishihara, K.; Hamada, N.; Kato, S.; Shinohara, I. *J. Polym. Sci., Polym. Chem. Ed.* **1984**, *22*, 881-884. (b) Ishihara, K.; Shinohara, I. *J. Polym. Sci., Polym. Lett. Ed.* **1984**, *22*, 515-518. (c) Kinoshita, T.; Sato, M.; Takizawa, A.; Tsujita, Y. *Macromolecules* **1986**, *19*, 51-55.

(3) Photocontrol of binding abilities of polymer matrices: (a) Ishihara, K.; Negishi, N.; Shinohara, I. *J. Appl. Polym. Sci.* **1982**, *27*, 1879-1902. (b) Ishihara, K.; Kim, M.; Shinohara, I. *J. Appl. Polym. Sci.* **1983**, *28*, 1321-1329. (c) Ishihara, K.; Hamada, N.; Kato, S.; Shinohara, I. *J. Polym. Sci., Polym. Chem. Ed.* **1983**, *21*, 1551-1555.

(4) Photocontrol of swelling of polymer gels and membranes; for a review, see: Smets, G. *Adv. Polym. Sci.* **1983**, *50*, 17-44.

(5) Ueno, A.; Anzai, J.; Osa, T.; Kadoma, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2995-2999.

(6) Ueno, A.; Anzai, J.; Osa, T.; Kadoma, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 549-554.

(7) Ueno, A.; Takahashi, K.; Anzai, J.; Osa, T. *Macromolecules* **1980**, *13*, 459-460.

(8) Ueno, A.; Takahashi, K.; Anzai, J.; Osa, T. *Makromol. Chem.* **1981**, *182*, 693-695.

(9) Ueno, A.; Takahashi, K.; Anzai, J.; Osa, T. *J. Am. Chem. Soc.* **1981**, *103*, 6410-6415.

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

(11) Pieroni, O.; Houben, J. L.; Fissi, A.; Constantino, P.; Ciardelli, F. *J. Am. Chem. Soc.* **1980**, *102*, 5913-5915.

(12) Houben, J. L.; Fissi, A.; Bacciola, D.; Rosano, N.; Pieroni, O.; Ciardelli, F. *Int. J. Biol. Macromol.* **1983**, *5*, 94-100.

(13) Ciardelli, F.; Pieroni, O.; Fissi, A.; Houben, J. L. *Biopolymers* **1984**, *23*, 1423-1437.

(14) Pieroni, O.; Fissi, A.; Houben, J. L.; Ciardelli, F. *J. Am. Chem. Soc.* **1985**, *107*, 2990-2991.

0002-7863/86/1508-6399$01.50/0