known[17-21] that conformational forms found in dimer models of vinyl polymers agree with the forms occurring in the dyads of the corresponding polymers. Moreover, the most stable conformer of the dimer model usually is identical with the dyad conformation observed in the crystalline polymer. We therefore assume that also in PMMA only the dyad conformations corresponding to structures I and III of DMTG can occur, and that in crystalline isotactic and syndiotactic PMMA structure I of DMTG will be present (Figure 1).

This dyad conformation would correspond to the 3_1 helix in crystalline isotactic PMMA and to a planar zigzag chain in crystalline syndiotactic PMMA. In the helices 5_1 and 5_2 found in isotactic PMMA by X-ray diffraction,[2-5] dyad conformations differ from form I of DMTG by a shift of the angles φ_1 and φ_2 by 10–15° from the staggered values. Because the values of the angles φ_1 and φ_2 cannot be determined accurately from infrared spectra, it can be stated that the proposed structure of crystalline isotactic PMMA does not contradict the structure derived from X-ray analysis. For the same reason the chain in crystalline syndiotactic PMMA need not be strictly planar, even if the dyad structure does approximately correspond to form I of DMTG.

If only conformers analogous to the structures found in model compounds are assumed to exist in PMMA, then the ester groups should always be oriented syn with respect to the α-methyl group. This position of the ester group agrees with the structure of PMMA as proposed by Liquori[3] and Gotlib.[1] It differs from one of the structures considered by Tadokoro.[2]

Similarly as in DMTG, also in PMMA conformation-sensitive bands appear at 860 and 840 cm^{-1}. The band at 860 cm^{-1} which corresponds to the band at 868 cm^{-1} in form III of DMTG is absent in crystalline syndiotactic and isotactic PMMA, but it is weakly indicated in amorphous PMMA.[?2] The band at 840 cm^{-1}, corresponding to the band at 848 cm^{-1} in form I of DMTG, is very strong in the crystalline polymers. This indicates that in amorphous isotactic and syndiotactic PMMA, there occurs a small amount of the dyad corresponding to form III of DMTG. Infrared spectra confirm that the structure of dyads in crystalline isotactic and syndiotactic PMMA corresponds to form I of crystalline DMTG. The amount of the conformer occurring in small amounts in amorphous PMMA increases considerably in the stereo complex (iso:syndio = 1:2). Formation of the complex is probably connected with a rotation about skeletal C—C bonds, and dyads with structure III appear.

(17) S. I. Mizushima and T. Shimanouchi, *J. Amer. Chem. Soc.*, **86**, 3521 (1964).
(18) D. Doskočilová, J. Štokr, E. Votavová, B. Schneider, and D. Lím, *J. Polym. Sci., Part C*, No. 16, 2225 (1967).
(19) B. Schneider, J. Štokr, D. Doskočilová, M. Kolínský, S. Sýkora, and D. Lím, *ibid., Part C*, No. 16, 3891 (1968).
(20) L. E. Alexander, R. Engmann, and H. G. Clark, *J. Phys. Chem.*, **70**, 252 (1966).
(21) P. J. Flory and A. D. Williams, *J. Amer. Chem. Soc.*, **91**, 3118 (1969).
(22) V. N. Nikitin, N. V. Mihailova, and L. A. Volkova, *Vysokomol. Soedin.*, **7**, 1235 (1965).

Synthesis and Optical Properties of Asymmetric Polyamides Derived from Optically Active Cyclic Dicarboxylic Acids[1,2]

C. G. Overberger* and Y. Shimokawa

Department of Chemistry and the Macromolecular Research Center, The University of Michigan, Ann Arbor, Michigan 48104. *Received April 8, 1971*

ABSTRACT: Optically active dicarboxylic acids, (+)-(*S*)- and (−)-(*R*)-*trans*-1,2-cyclopropanedicarboxylic acids (1,2-C3), (−)-(*R*)-*trans*-1,2-cyclobutanedicarboxylic acid (1,2-C4), (+)- and (−)-*trans*-1,3-cyclopentanedicarboxylic acids (1,3-C5), and polyamides composed of these diacids and secondary diamines such as *trans*-2,5-dimethylpiperazine (DMPIP), piperazine (PIP), or *N,N'*-dimethylethylenediamine (DMED) have been prepared. Diamide model compounds composed of the diacids and piperidine have also been prepared. Optical properties and conformations of these polyamides and diamide model compounds in various solvents have been investigated by means of optical rotatory dispersion (ORD) and circular dichroism (CD). The results, together with previous data, suggest that the rigid DMPIP and PIP polyamides exist in some ordered conformations in 2,2,2-trifluoroethanol (TFE) and tetramethylenesulfone (TMS), allowing coupling of the amide chromophores along the polymer chains. On the contrary, the flexible open-chain DMED polyamides have an unordered conformation in solution. The DMPIP and PIP polyamides in methanesulfonic acid (MSA) exhibit quite different ORD/CD spectra than in TFE and TMS. In particular, for the case of the 1,2-C3·DMPIP and PIP polyamides, it has been suggested that some conformational transition may take place on going from TFE or TMS to MSA.

Over the past decade, the conformational behavior of synthetic polypeptides in solution has been intensively studied to help elucidate that of the more complex structure of proteins and enzymes. However, relatively little attention has been given to the optical properties and the conformations of other synthetic optically active condensation polymers.

When a polyamide is composed of conformationally rigid monomer units, portions of the polyamide chain may have an ordered conformation which can allow coupling of identical nonconjugated amide chromophores.[3] Thus, it may be expected that such a polyamide would exhibit some of the

(1) This is the 23rd in a series of papers concerned with the synthesis and properties of asymmetric polymers.
(2) For the previous paper in this series, see C. G. Overberger, A. Ohnishi, and A. S. Gomes, *J. Polym. Sci., Part A-1*, in press.
(3) For a review of exciton coupling theory, see (a) M. Kasha, *Radiat. Res.*, **20**, 55 (1963); (b) E. G. MaRae, and M. Kasha in "Physical Processes in Radiation Biology," Academic Press, New York, N. Y., 1964, p 23.

features displayed by polypeptides in the helical form,[4] such as splitting of the π–π^* transition which is usually unsymmetrical, enhancement of rotatory strength, and red shifts of the uv/ORD/CD bands with respect to an appropriate model compound. When a polyamide chain is flexible, allowing several conformational arrangements, these effects should be minimized and eventually lost.

One approach to this problem is the synthesis of a series of asymmetric polyamides, with varying degrees of rigidity imposed on the polymer chain, and the study of their optical properties and conformations in solution. These polyamides are derived from optically active cyclic 1,2-, 1,3-dicarboxylic acids and secondary diamines. We have previously reported the results for (+)-(*S*)-*trans*-1,2-cyclopentanedicarboxylic acid (1,2-C5), (+)-(*S*)-*trans*-1,2-cyclohexanedicarboxylic acid (1,2-C6), (+)-*trans*-1,3-cyclohexanedicarboxylic acid (1,3-C6), and (−)-bicyclo[2.2.2]octane-*trans*-2,3-dicarboxylic acid (2,3-BCO), and have shown that several of these polyamides probably exist in preferred conformations in solution; that is, they exhibit some secondary order.[5-9]

To strengthen this tentative conclusion, (+)-(*S*)- and (−)-(*R*)-*trans*-1,2-cyclopropanedicarboxylic acids (1,2-C3), (−)-(*R*)-*trans*-1,2-cyclobutanedicarboxylic acid (1,2-C4), (+)- and (−)-*trans*-1,3-cyclopentanedicarboxylic acids (1,3-C5), and optically active polyamides composed of these diacids and secondary diamines such as *trans*-2,5-dimethylpiperazine (DMPIP), piperazine (PIP), or *N*,*N*′-dimethylethylenediamine (DMED) have been prepared. Diamide model compounds composed of these diacids and piperidine have also been prepared. Both (+) and (−) isomers have been prepared for the comparison of enantiomers. Thus, all optically active cyclic dicarboxylic acids in the three- to six-membered ring category and their polyamides have been prepared.

Optical properties and conformations of these polyamides and diamide model compounds in various solvents have been investigated by means of optical rotatory dispersion (ORD) and circular dichroism (CD).

Experimental Section

(+)-(*S*)- and (−)-(*R*)-*trans*-1,2-Cyclopropanedicarboxylic Acids. Optically pure (+)-(*S*)- and (−)-(*R*)-*trans*-1,2-cyclopropanedicarboxylic acids were prepared by ozonolysis of (+)-(*S*)- and (−)-(*R*)-*trans*-2-phenylcyclopropanecarboxylic acids by the method of Inouye, *et al.*,[10] with modification.

Ethyl 2-phenylcyclopropanecarboxylate was prepared by the method of Burger and Yost.[11] The method of Walborsky and Plonsker with modification was utilized to isolate the trans acid.[12] Although racemic *trans*-2-phenylcyclopropanecarboxylic acid was previously resolved into the (+)-(*S*) and (−)-(*R*) isomers by Inouye, *et al.*,[10] and Walborsky and Plonsker,[12] respectively, no detailed procedures were reported. To find the best resolution procedure, various alkeloids and solvents were tested. Fractional recrystallization of the quinine salt from ethyl acetate gave the (+)-(*S*)-acid quinine (1:1) salt as a precipitate, while the (−)-(*R*)-acid brucine (2:1) salt was precipitated by fractional recrystallization of the brucine salt from acetone.

Racemic *trans*-2-phenylcyclopropanecarboxylic acid, 125.2 g (0.771 mol), and quinine, 264.2 g (0.815 mol), were dissolved in 5 l. of ethyl acetate at reflux. The solution was filtered and allowed to stand at 20–25° for a few days. The salt which precipitated was recrystallized four times from ethyl acetate (concentration ~5% w/v) until the salt showed no change in rotation in two successive recrystallizations and the solute in the mother liquor gave the same rotation as the precipitate; yield 52.1 g. The recovered salt was recrystallized in the same way to yield an additional 41.1 g of the pure (+)-(*S*)-acid salt, total 93.2 g; after drying at room temperature *in vacuo*, mp 153–154°, $[\alpha]^{20}D$ −10.9 (EtOH, *c* 1.0 g/dl).

Anal. Calcd for $C_{10}H_{10}O_2 \cdot C_{20}H_{24}N_2O_2$ (1:1 salt): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.88; H, 7.08; N, 5.69.

The (+)-(*S*)-acid salt was added to 1 *N* aqueous HCl, and the free (+)-(*S*)-acid was extracted with diethyl ether by means of a continuous extractor,[13] followed by recrystallization from petroleum ether (30–60°): mp 48.5–49.5°, $[\alpha]^{20}D$ +405° ($CHCl_3$, *c* 1.0 g/dl) (lit. mp 25–26°C, $[\alpha]^{14}D$ +381° ($CHCl_3$, *c* 0.96 g/dl)[10]).

The (−)-(*R*)-isomer-rich acid, which was recovered from the mother liquor in the first fractionation of the quinine salt, 43.2 g (0.266 mol), and brucine, 110.4 g (0.279 mol), were dissolved in 850 ml of acetone at reflux. The solution was filtered and allowed to stand at 0° for a few days. After fractional recrystallization was repeated four more times, 21.2 g of the pure (−)-(*R*)-acid salt was obtained. The recovered salt was recrystallized in the same way to yield an additional 54.9 g of the pure (−)-(*R*)-acid salt, total 76.1 g; after drying at room temperature *in vacuo*, mp 106–108°, $[\alpha]^{20}D$ −172° (EtOH, *c* 1.0 g/dl).

Anal. Calcd for $(C_{10}H_{10}O_2)_2 \cdot C_{23}H_{26}N_2O_4 \cdot H_2O$: C, 70.09; H, 6.57; N, 3.80. Found: C, 70.21; H, 6.57; N, 3.78.

Microanalysis showed that the composition of the salt was acid:brucine:H_2O = 2:1:1. On drying at 80° *in vacuo*, a part of the acid was lost to leave a mixture of the 1:1 salt and the 2:1 salt.

The (−)-(*R*)-acid was liberated quantitatively from the salt as described above, followed by recrystallization from petroleum ether: mp 48.5–49.5°, $[\alpha]^{20}D$ −410° ($CHCl_3$, *c* 1.0 g/dl) (lit. mp 51–52°, $[\alpha]^{24}D$ −368° ($CHCl_3$, *c* 0.931 g/dl)[12]).

Ozonolysis of (+)-(*S*)- and (−)-(*R*)-*trans*-2-phenylcyclopropanecarboxylic acids to the corresponding *trans*-1,2-cyclopropanedicarboxylic acids was performed according to the method of Inouye, *et al.*,[10] with a modification.

(+)-(*S*)-Diacid: mp 172–173°, $[\alpha]^{20}D$ +250° (H_2O, *c* 1.0 g/dl) (lit. mp 169.5–170.0°, $[\alpha]^{14}D$ +238° (H_2O, *c* 1.0 g/dl)[10]).

Anal. Calcd for $C_5H_6O_4$: C, 46.16; H, 4.65. Found: C, 46.24; H, 4.60.

(−)-(*R*)-Diacid: mp 172–173°, $[\alpha]^{20}D$ −247°, (H_2O, *c* 1.0 g/dl) (no available data in the literature).

Anal. Found: C, 46.20; H, 4.63.

The optical purity was estimated to be near 100% on the basis of the specific rotation estimated for the optically pure (+)-(*S*) isomer by Inouye, *et al.*[10] {$[\alpha]^{14}D$ +247° (H_2O, *c* 1.0 g/dl)}, and from the fact that both isomers which were resolved independently showed the same absolute value in the specific rotation and the same melting point within experimental error.

(−)-(*R*)-*trans*-1,2-Cyclobutanedicarboxylic Acid. Racemic *trans*-1,2-cyclobutanedicarboxylic acid (commercially available from Aldrich Chemical Co.) was resolved by a modification of Goldsworthy's method.[14,15] To improve the result, 95% ethanol, instead of water, was used as a solvent in fractional recrystallization of the diquinine salt. The pure (−)-(*R*)-diacid salt which was obtained by four successive recrystallizations was dried at room

(4) For a review, see (a) G. D. Fasman, Ed., "Poly-α-Amino Acids," Marcel Dekker, New York, N. Y., 1967; (b) J. A. Schellman and C. Schellman in "The Protein," Vol. II, H. Neurath, Ed., Academic Press, New York, N. Y., 1964, Chapter 7.

(5) C. G. Overberger, G. Montaudo, Y. Nishimura, J. Sebenda, and R. A. Veneski, *J. Polym. Sci., Part B*, 7, 219 (1969).

(6) C. G. Overberger, G. Montaudo, M. Mizutori, J. Sebenda, and R. A. Veneski, *ibid., Part B*, 7, 225 (1969).

(7) C. G. Overberger, R. A. Veneski, and G. Montaudo, *ibid., Part B*, 7, 877 (1969).

(8) C. G. Overberger and J. Sebenda, *ibid., Part A-1*, 7, 2875 (1969).

(9) C. G. Overberger, G. Montaudo, Y. Nishimura, J. Sebenda, and R. A. Veneski, presented at the IUPAC Symposium, Budapest, Hungary, 1969.

(10) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, 20, 1695 (1964).

(11) A. Burger and W. L. Yost, *J. Amer. Chem. Soc.*, 70, 2198 (1948).

(12) H. M. Walborsky and L. Plonsker, *ibid.*, 83, 2138 (1961).

(13) Y. Nishimura, Ph.D. Thesis, Polytechnic Institute of Brooklyn, Brooklyn, N. Y., 1966.

(14) L. J. Goldsworthy, *J. Chem. Soc.*, 2012 (1924).

(15) F. B. Kipping and J. J. Wren, *ibid.*, 3246 (1957).

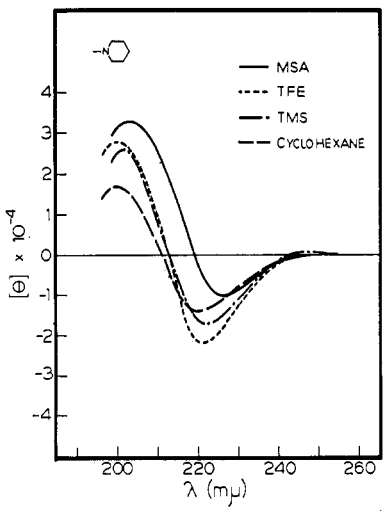

Figure 1. CD curves of (+)-(*S*)-1,2-C3 diamide in various solvents.

temperature *in vacuo:* mp ~185° dec, $[\alpha]^{20}D$ −180° (EtOH, *c* 1.0 g/dl).

Anal. Calcd for $C_6H_8O_4 \cdot (C_{20}H_{24}N_2O_2)_2 \cdot H_2O$: C, 68.12; H, 7.21; N, 6.91. Found: C, 68.24; H, 7.10; N, 6.76.

The salt was further dried at 110° *in vacuo:* mp ~185° dec, $[\alpha]^{20}D$ −187° (EtOH, *c* 1.0 g/dl).

Anal. Calcd for $C_6H_8O_4 \cdot (C_{20}H_{24}N_2O_2)_2$: C, 69.69; H, 7.12; N, 7.07. Found: C, 69.59; H, 7.10; N, 6.98.

The (−)-(*R*)-diacid was obtained from the salt as mentioned above, followed by recrystallization from benzene: mp 116–117°, $[\alpha]^{20}D$ −165° (H_2O, *c* 0.75 g/dl) (lit. mp 116–117°, $[\alpha]^{18.5}D$ −158° (H_2O, *c* 0.75 g/dl)[15]).

(+)- and (−)-*trans*-1,3-Cyclopentanedicarboxylic Acid. According to the method of Perry[16] and Temin and Baum,[17] a 50:50 mixture of *trans*- and *cis*-1,3-cyclopentanedicarboxylic acids was prepared by ozonolysis of norbornene,[16,17] followed by isomerization with 20.2% hydrochloric acid.[17] A new method of separating the trans and cis isomers was developed to eliminate the tedious procedure reported.[18]

The 50:50 mixture of the trans and cis diacids was converted to the dimethyl esters *via* the diacid chlorides. The trans isomer was successfully isolated as a lower boiling fraction by two successive fractional distillations by means of a Nester/Faust spinning-band column; approximate bp 120–121° (9–10 mm), 95–96° trans by glpc analysis (10% FFAP on 60/80 Chromosorb-W). The trans dimethyl ester was hydrolyzed with 2.5 *N* aqueous NaOH at 95°. Acidification of the resultant solution, followed by extraction with diethyl ether, gave the crude trans diacid, which was then recrystallized twice from benzene–carbon tetrachloride (1:1) to yield pure *trans*-1,3-cyclopentanedicarboxylic acid, mp 95–96° (lit. mp 95.5–96.5° [18]).

Racemic *trans*-1,3-cyclopentanedicarboxylic acid was previously resolved by Birch and Dean.[18] However, the optical purities of both (+) and (−) isomers obtained were low, and an improved method was needed. It was found that the fractional recrystallization of the monostrychnine salt of the trans diacid from 95% ethanol gave either the (+)-diacid-rich salt or the (−)-diacid-rich salt as a precipitate, depending on the conditions. In a trial run, following Birch's method,[18] the partially resolved (+)-diacid {$[\alpha]^{20}D$ +12.4° (H_2O, *c* 8.0 g/dl)} and (−)-diacid ($[\alpha]^{20}D$ − 7.7°) were obtained. Starting with these diacids, the complete resolution could be carried out *via* the monostrychnine salt.

The partially resolved (−)-diacid, 3.16 g (2.00 × 10^{-2} mol), and strychnine, 6.69 g (2.00 × 10^{-2} mol), were dissolved on heating in 40 ml of 95% ethanol. The salt which precipitated at −15° was recrystallized four times from 95% ethanol (concentration ~10% w/v) to yield 1.0 g of the pure (−)-diacid strychnine (1:1) salt; after drying at room temperature *in vacuo*, mp 213–214° (becomes colored), $[\alpha]^{20}D$ −32.5 (50% EtOH–50% H_2O v/v, *c* 2.0 g/dl).

Anal. Calcd for $C_7H_{10}O_4 \cdot C_{21}H_{22}N_2O_2$: C, 68.28; H, 6.55; N, 5.69. Found: C, 68.35; H, 6.44; N, 5.73.

Pure (−)-*trans*-1,3-cyclopentanedicarboxylic acid was obtained from the above salt, followed by recrystallization from benzene–carbon tetrachloride (1:1): mp 87.5–88.5°, $[\alpha]^{20}D$ −35.1° (H_2O, *c* 8.0 g/dl) (lit. mp 85.0–85.7°, $[\alpha]^{15}D$ −22.6° (H_2O, *c* 8.0 g/dl)[17]).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.12; H, 6.27.

Starting from the partially resolved (+)-diacid and following the exact procedure as above, interestingly the pure (+)-diacid strychnine (1:1) salt could be obtained; after drying at room temperature *in vacuo*, the product had mp 202–203° (becomes colored), $[\alpha]^{20}D$ −10.7 (50% EtOH–50% H_2O v/v, *c* 2.0 g/dl).

Anal. Found: C, 68.05; H, 6.57; N, 5.45.

Pure (+)-*trans*-1,3-cyclopentanedicarboxylic acid was obtained from the above salt, followed by recrystallization from benzene–carbon tetrachloride (1:1): mp 87.5–88.5°, $[\alpha]^{20}D$ + 35.6° (H_2O, *c* 8.0 g/dl) (lit. mp 79.5–80.5°, $[\alpha]^{15}D$ +20.09° (H_2O, C, 8.0 g/dl)[18]).

Anal. Found: C, 53.24; H, 6.38.

When a solution of the equimolar (±)-diacid and strychnine in

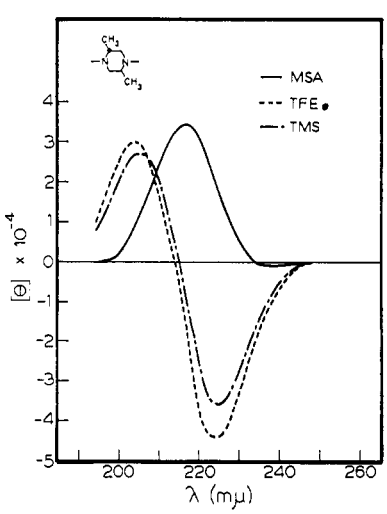

Figure 2. CD curves of (+)-(*S*)-1,2-C3·DMPIP in various solvents.

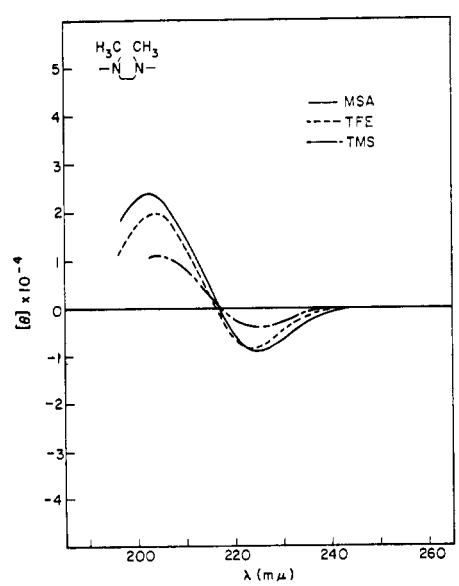

Figure 3. CD curves of (+)-(*S*)-1,2-C3·PIP in various solvents (insoluble in TMS).

(16) P. H. Perry, Jr., *J. Org. Chem.*, **24**, 829 (1959).
(17) S. C. Temin and M. E. Baum, *Can. J. Chem.*, **43**, 705 (1965).
(18) S. F. Birch and R. A. Dean, *J. Chem. Soc.*, 2477 (1953).

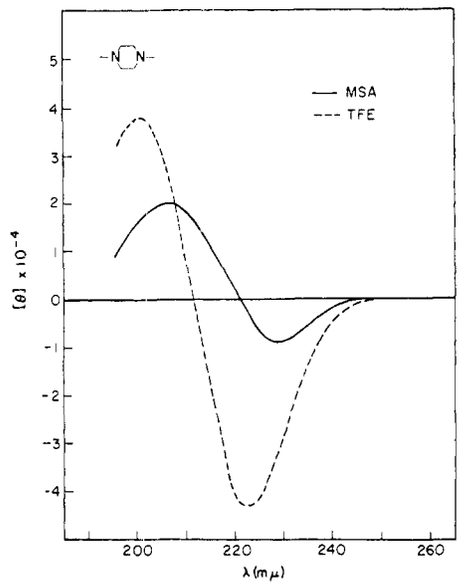

Figure 4. CD curves of (+)-(*S*)-1,2-C3·DMED in various solvents.

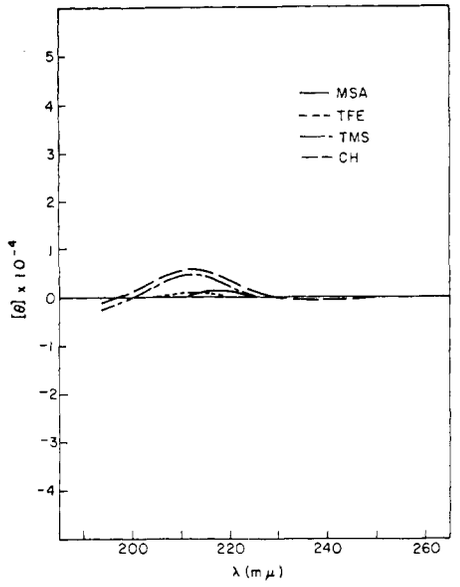

Figure 5. CD curves of (−)-(*R*)-1,2-C4 diamide in various solvents.

95% ethanol (concentration 10–30% w/v) was allowed to stand at −15°, no salt was precipitated after standing for a few days. However, on addition of either the pure (+)-diacid salt or the pure (−)-diacid salt as a seed, a corresponding isomer-rich salt was precipitated. Thus, alternately using the pure (+)-diacid salt and the pure (−)-diacid salt as a seed, while the solvent was partially evaporated so that the concentration stayed at the range of 10–15% w/v, the salts of $[\alpha]^{20}D$ −12 to −13° and the salt of $[\alpha]^{20}D$ −27 to −29° were collected. The salts were then further recrystallized from 95% ethanol to afford the pure isomers.

Polyamide and Diamide Model Synthesis. The polyamides were prepared by the interfacial polycondensation of the diacid chlorides with DMPIP, PIP, or DMED.[9,13] The synthesis of the diacid chlorides was accomplished by treating the diacids with an excess of highly purified thionyl chloride[19] in the presence of a catalytic amount of anhydrous zinc chloride under very mild conditions. After vacuum distillation, a small quantity of the acid chloride was hydrolyzed to determine if racemization had occurred. The specific rotation of the resulting diacid, which was not purified further, agreed with the original specific rotation within experimental error.

In a typical reaction, 6 g (0.046 mol) of (+)-(*S*)-*trans*-1,2-cyclopropanedicarboxylic acid and a catalytic amount of anhydrous zinc chloride were added to 24.0 g (0.202 mol) of thionyl chloride at room temperature. The mixture was heated up to 40° with stirring and was allowed to react at 40° for 3 hr. The excess of thionyl chloride was evaporated at room temperature *in vacuo* and the residue was fractionated. The purified diacid chloride was divided into small ampoules and sealed immediately after distillation: yield 6.9 g (90%), bp 40° (0.09 mm). The other diacids, *trans*-1,2-cyclobutanedicarboxylic acid and *trans*-1,3-cyclopentanedicarboxylic acid, were allowed to react at 20°; (−)-(*R*)-1,2-C4 diacid chloride, yield 85%, bp 85° (0.25 mm); (+)- and (−)-1,3-C5 diacid chloride, yield 90%, bp 69° (0.09 mm).

(+)-(*S*)-1,2-C3·DMPIP Polyamide. In a Waring semimicro blender (stainless-steel container), 0.937 g (8.20×10^{-3} mol) of *trans*-2,5-dimethylpiperazine, 3.28 ml (1.64×10^{-2} mol) of 5 *N* aqueous NaOH, 74.5 ml of methylene chloride, and 17.2 ml of water were charged and precooled to 0°. An ampoule which contained 1.240 g (7.45×10^{-3} mol) of (+)-(*S*)-*trans*-1,2-cyclopropanedicarbonyl chloride was broken in the above emulsion mixture with vigorous stirring. The mixture was allowed to react for 10 min, while being cooled with ice, and was poured into 500 ml of water through a medium sintered-glass funnel. Evaporation of methylene chloride at room temperature under reduced pressure with stirring left a suspension of the polymer in water. The polymer was washed twice by stirring with 1000 ml of warm water (~50°) for 1 hr, dried, and reprecipitated from the chloroform solution in diethyl ether; after drying over P_2O_5 at room temperature *in vacuo*, the yield was 1.26 g (86%). Microanalysis of the polymer thus obtained showed 1–4 wt % ash. The polymer was further purified by continuous extraction with hot water for 48 hr under a nitrogen atmosphere using a Soxhlet extractor, followed by reprecipitation; however, the amount of ash remained almost constant. Thus, it is probable that the ash in microanalysis was mainly due to imperfect combustion of these high molecular weight polymers. Alternatively, these types of polyamides may complex ions much more strongly than is generally realized. The data corrected for ash agreed with the calculated values, $[\eta]$ 2.44 dl/g (2,2,2-trifluoroethanol (TFE), 25°).

Anal. Calcd for $(C_5H_4O_2)(C_6H_{12}N_2)$: C, 63.4; H, 7.7; N, 13.5. Found (corr): C, 63.2; H, 8.0; N, 13.3.

(+)-(*S*)-1,2-C3·PIP Polyamide. Piperazine, 0.764 g (8.86×10^{-3} mol), 3.56 ml (1.78×10^{-2} mol) of 5 *N* aqueous NaOH, 80.5 ml

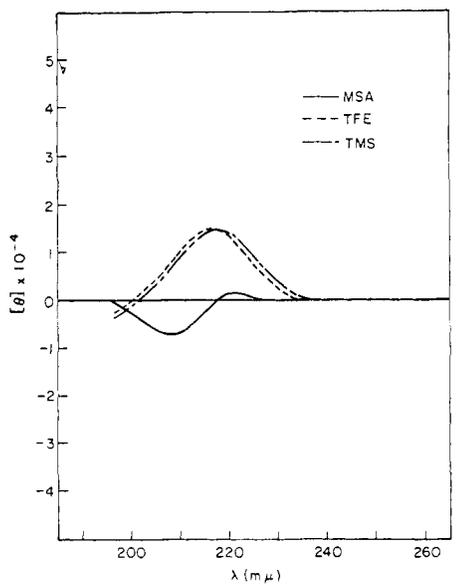

Figure 6. CD curves of (−)-(*R*)-1,2-C4·DMPIP in various solvents.

(19) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1968, p 1158.

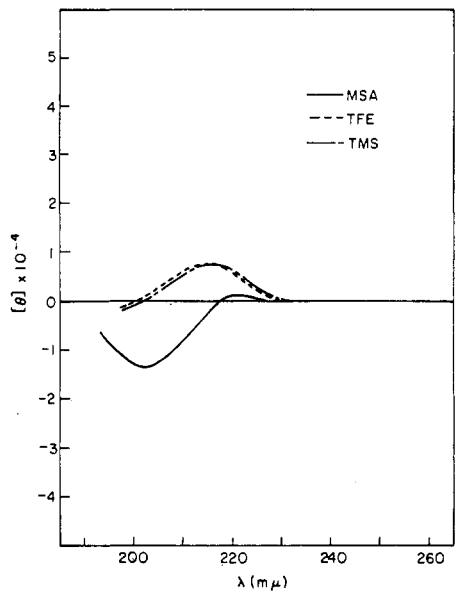

Figure 7. CD curves of (−)-(*R*)-1,2-C4·PIP in various solvents.

of methylene chloride, and 18.6 ml of water were allowed to react with 1.343 g (8.05 × 10^{-3} mol) of (+)-(*S*)-*trans*-1,2-cyclopropanedicarbonyl chloride by the same procedure as for (+)-(*S*)-1,2-C3·DMPIP polyamide. The polymer was insoluble in methylene chloride and was obtained as a suspension. The crude polymer was dissolved in 50 ml of 90% formic acid, filtered, and reprecipitated into water; 0.68 g (51%). It was then extracted with hot water using a Soxhlet extractor, and reprecipitated from the 90% formic acid solution into diethyl ether, followed by drying over P_2O_5 at room temperature *in vacuo;* [η] 2.44 g/dl (TFE, 25°).

Anal. Calcd for $(C_5H_4O_2)(C_4H_8N_2)$: C, 60.0; H, 6.7; N, 15.6. Found (corr): C, 59.8; H, 7.0; N, 15.6.

(+)-(*S*)-1,2-C3·DMED Polyamide. *N,N'*-Dimethylethylenediamine, 0.868 g (9.85 × 10^{-3} mol), 3.94 ml (1.97 × 10^{-2} mol) of 5 *N* aqueous NaOH, 89.5 ml of methylene chloride, and 20.7 ml of water were allowed to react with 1.496 g (8.95 × 10^{-3} mol) of (+)-(*S*)-*trans*-1,2-cyclopropanedicarbonyl chloride. The polymerization mixture was filtered and the methylene chloride layer was separated from the aqueous layer, which was extracted twice with 100 ml of methylene chloride. The product which was obtained by evaporation of methylene chloride to dryness was redissolved in methylene chloride, filtered, and reprecipitated twice into diethyl ether: 0.20 g (13%), [η] 0.07 dl/g (TFE, 25°), $\bar{M}_n$ 1300 (vapor pressure method, $CHCl_3$).

Anal. Calcd for $HO[(C_5H_4O_2)(C_4H_{10}N_2)]_7H$: C, 58.5; H, 7.8; N, 15.2. Found: C, 58.2; H, 7.8; N, 14.9 (little or no ash).

A cyclic dimer was isolated as a major by-product, and it is suggested that the favorable formation of the cyclic oligomers due to the flexible structure of the diamine component is responsible for the low yield and the low molecular weight of the polymer.

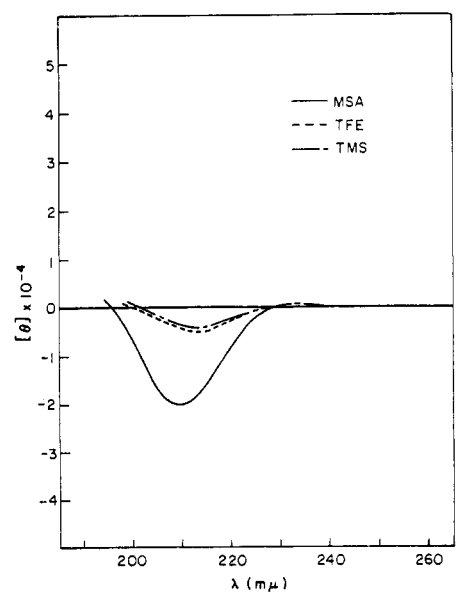

Figure 8. CD curves of (+)-1,3-C5 diamide in various solvents (CD curve in CH is similar to that in TMS).

The Other Polyamides. The 1,2-C4 and 1,3-C5 polyamides from DMPIP and PIP were prepared and purified by the same procedure as for the 1,2-C3·DMPIP polyamide. All polyamides were dried over P_2O_5 at room temperature *in vacuo*. Yields and intrinsic viscosities in TFE at 25.00 ± 0.02° are: (−)-(*R*)-1,2-C3·DMPIP yield 86%, [η] 1.3 dl/g; (−)-(*R*)-1,2-C3·PIP 50%, 2.2 dl/g; (−)-(*R*)-1,2-C3·DMED 13%; 0.10 dl/g, $\bar{M}_n$ 1400; (−)-(*R*)-1,2-C4·DMPIP 88%, 1.3 dl/g; (−)-(*R*)-1,2-C4·PIP 55%, 3.2 dl/g; (+)-1,3-C5·DMPIP 82%, 4.5 dl/g; (+)-1,3-C5·PIP 60%, 4.3 dl/g; (−)-1,3-C5·DMPIP 80%, 3.1 dl/g; (−)-1,3-C5·PIP 52%, 4.9 dl/g. Microanalysis data, corrected for ash, agreed with the calculated value.

(+)-(*S*)-1,2-C3·Piperidine Diamide. To a solution of 2.66 g (3.12 × 10^{-2} mol) of piperidine in 50 ml of anhydrous diethyl ether, 1.185 g (7.10 × 10^{-3} mol) of (+)-(*S*)-*trans*-1,2-cyclopropanedicarbonyl chloride was added dropwise with stirring at room temperature. The white precipitate, the hydrogen chloride salt of piperidine, was filtered off and the filtrate evaporated to dryness to yield the crude diamide, 1.85 g (99%), which was then recrystallized twice from *n*-hexane: mp 99–100°, $[\alpha]^{20}D$ 113° (MeOH, *c* 1.0 g/dl).

Anal. Calcd for $(C_5H_4O_2)(C_5H_{10}N_2)$: C, 68.18; H, 9.15; N, 10.60. Found: C, 68.32; H, 9.20; N, 10.66.

The Other Piperidine Diamides. Melting points follow: (−)-(*R*)-1,2-C3 mp 99–100°, (−)-(*R*)-1,2-C4 mp 104–105°, (+)- and (−)-1,3-C5 mp 78.5–79.5°. Microanalysis data of all diamides agreed with the calculated values.

Uv/ORD/CD Measurements. Measurements of uv/ORD/CD spectra were made with a Jasco-Durrum ORD/CD/UV-5 spectropolarimeter using concentrations of 10^{-2}–10^{-3} (mol of amide residue)/l., a cell length of 0.1–1.0 mm, and at a temperature of 23–25°. Measurements were carried out 15–25 hr after solvent was added to samples.

In Table I, values at extremities of curves are listed; however, values in parentheses do not represent extremities. Cyclohexane (Mallinkrodt Chemical Works, analytical reagent), *p*-dioxane (Matheson Coleman and Bell, spectroquality), methanol (Matheson Coleman and Bell, spectroquality), tetramethylene sulfone (Aldrich Chemical Co.), 2,2,2-trifluoroethanol (Matheson Coleman and Bell), and methanesulfonic acid (Eastman Kodak Co.) were used without further purification.

Results and Discussion

Optical Properties of Piperidine Diamide Model Compounds in Solution. The optical data of the diamides in 2,2,2-trifluoroethanol (TFE) are shown in Table I, together with the data for the previously prepared diamides. Each enantiomer exhibits the exact opposite ORD and CD spectra, although the data are not shown.

The uv maximum, which apparently corresponds to a π–π^* transition of amide chromophores, appears at 208 mμ for the (+)-(*S*)-1,2-C3 diamide and at 203–204 mμ for the others.[20] A weak n–π^* transition may be hidden by overlap with a stronger π–π^* transition. The uv/ORD/CD bands of the (+)-(*S*)-1,2-C3 diamide are red shifted as compared to the others because of the overlap of the amide chromophores with

(20) E. B. Nielsen and J. A. Schellman, *J. Phys. Chem.*, **71**, 2297 (1967).

TABLE I
OPTICAL DATA FOR PIPERIDINE DIAMIDE MODEL COMPOUNDS IN TFE

Compound	ORD		CD		Uv	
	λ, mμ	[m][a]	λ, mμ	[θ][b]	λ, mμ	ε[c]
(+)-(*S*)-1,2-C3	(260)	(+)				
	250	0				
	234	−4,000				
	227	0	221	−22,000		
	210	+46,000	213	0	208	15,500
	195	~0	200	+28,000		
(+)-(*S*)-1,2-C4[f]	(260)	(+1,500)[g]				
			~212[h]	−1,000		
	(200)	(+5,000)			204	12,500
(+)-(*S*)-1,2-C5[d]	(260)	(+)				
	256	0				
	225	−3,300				
	219	0	216	−18,000		
	202	+25,000			204	13,500
(+)-(*S*)-1,2-C6[d]	(260)	−600				
	216	−5,000				
	208	0	208	−20,000		
	(195)	(+18,000)			203	14,000
(+)-1,3-C5[e]	(260)	(+)				
	238	0				
	223	−1,000				
	218	0	213	−5,000		
	204	+9,000			203	15,000
	195	~0				
(+)-1,3-C6[d,e]	(260)	(+)				
	237	+450				
	232	0	226	+2,000		
	217	−6,500	220	0		
	210	0	208	−8,000		
	200	−8,000			204	15,500

[a] (deg cm²)/dmol of amide residue. [b] = 3300Δε, (deg cm²)/dmol of amide residue. [c] cm²/mmol of amide residue. [d] These samples were kindly provided by Mr. R. A. Veneski in our research group.[5,6,9] [e] The absolute configuration is unknown. [f] Taken from the data for the (−) isomer, assuming that an enantiomer gives the exact opposite ORD/CD spectra. [g] Values in parentheses do not represent maxima. [h] Very weak. Cannot be accurately located.

the cyclopropane ring orbitals,[21] and also probably because of the extreme coupling of two amide chromophores due to the rigid cyclopropane ring structure. However, contributions of these two effects cannot be separately evaluated.

The negative CD band at 221 mμ for the (+)-(*S*)-1,2-C3 diamide and at 208–216 mμ for the others may reasonably be assigned to a component of the split π–π* transition due to an exciton coupling of two amide chromophores, on the basis of the position and strength, as well as its behavior in different solvents[22–26] (Figures 1, 5, and 8). In the case of the (+)-(*S*)-1,2-C3 diamide, the other component of the split π–π* transition is clearly observable around 200 mμ. The uv maximum is located between two CD bands, which are of opposite sign and unsymmetrical, as expected for splitting of the π–π* transition. For the other diamides, a short-wavelength component of the split π–π* transition cannot be clearly observed because of the limit of measurement. In the ORD spectra, Cotton effects corresponding to CD bands are observed.

The uv/ORD/CD spectra of the (+)-1,3-C5 diamide are very similar to those of the (+)-(*S*)-1,2-C5 diamide, although the rotatory strength of the former is weaker. The uv/ORD/CD spectra of the (+)-1,3-C6 diamide are also similar to those of the (+)-(*S*)-1,2-C6 diamide but somewhat unique in exhibiting an additional CD band at 226 mμ. This band may be assigned to an n–π* transition of amide chromophores.[6,9,22–26] For the other diamides, the n–π* transition cannot be observed in TFE probably because of overlap with the stronger π–π* transition, but becomes observable in less polar solvents (Figures 1, 5, and 8).

Inouye, *et al.*,[27] studied the ORD curves of the thionamide derived from optically active *trans*-1,2-dicarboxylic acids of three-, four-, five-, and six-membered rings, and found that all of the thionamide derivatives of the (+)-(*S*)-1,2-diacids exhibited a positive Cotton effect at 345–385 mμ which were assigned to an n–π* transition.

This leads us to the prediction that the (*S*)-1,2-diamides and also the (*S*)-1,3-diamides should exhibit a positive n–π* Cotton effect (or CD band) and *vice versa*. Actually, a positive CD band assignable to the n–π* transition is found for the (+)-(*S*)-1,2,-C3 diamide and a negative CD band for (−)-(*R*)-1,2-C4 diamide in less polar solvents (Figures 1 and 5). The absolute configurations of the 1,3-C5 and 1,3-C6 diacids have not yet been established. The (+)-1,3-C6

(21) (a) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949); (b) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **89**, 3449 (1967).
(22) B. J. Litman and J. A. Schellman, *J. Phys. Chem.*, **69**, 978 (1965).
(23) (a) D. W. Urry, *ibid.*, **72**, 3035 (1968); (b) *Annu. Rev. Phys. Chem.*, **19**, 477 (1968).
(24) M. Goodman, C. Toniolo, and J. Falcetta, *J. Amer. Chem. Soc.*, **91**, 1816 (1969).
(25) N. J. Greenfield and G. D. Fasman, *Biopolymers*, **7**, 595 (1969).
(26) N. J. Greenfield and H. D. Fasman, *J. Amer. Chem. Soc.*, **92**, 177 (1970).
(27) Y. Inouye, S. Sawada, M. Ohno, and H. M. Walborsky, *Tetrahedron*, **23**, 3237 (1967).

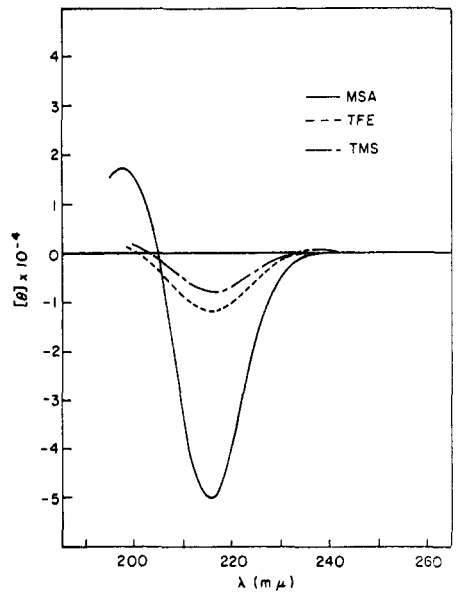

Figure 9. CD curves of (+)-1,3-C5·DMPIP in various solvents.

diamide exhibits a positive n–π^* CD band in TFE and other solvents, and the (+)-1,3-C5 diamide also shows a positive n–π^* CD band in less polar solvents (Figure 8). Thus, on the basis of the above empirical correlation, the (+)-1,3-C5 and (+)-1,3-C6 diacids may be assigned to be the *S* configuration.

The long-wavelength component of the split π–π^* transition can also be correlated with the absolute configuration: All of the (+)-(*S*)-1,2-diamides exhibit a negative Cotton effect or CD band. The (+)-1,3-C5 and (+)-1,3-C6 diamides, which may be assigned to be the *S* configuration as mentioned above, also show a negative Cotton effect or CD band at the same range.

Optical Properties of Polyamides in Solution. The CD curves of the (+)-(*S*)-1,2-C3, (−)-(*R*)-1,2-C4, and (+)-1,3-C5 series in TFE are shown in Figures 1–10. In the ORD spectra, which are not shown here, Cotton effects corresponding to CD bands are observed. Polyamides derived from an enantiomer exhibit the exact opposite ORD and CD spectra.

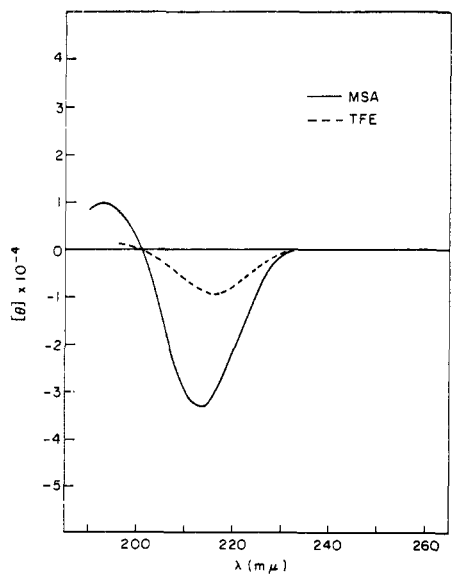

Figure 10. CD curves of (+)-1,3-C5·PIP in various solvents (insoluble in TMS).

As discussed for the diamide model compounds, in the (+)-(*S*)- and (−)-(*R*)-1,2-C3 series, two CD bands of opposite sign at 200–205 and at 220–225 mμ may be assigned as the result of the splitting of the π–π^* transition of amide chromophores. The CD band at 212–216 mμ in the (−)-(*R*)-1,2-C4 and (+)- and (−)-1,3-C5 series may be assigned to a component of the split π–π^* transition. The band for the n–π^* transition cannot be observed in TFE.

Solvent Effects on Optical Properties and Conformations. The CD curves of the polyamides and diamide model compounds in various solvents such as cyclohexane (CH), tetramethylenesulfone (TMS), 2,2,2-trifluoroethanol (TFE), and methanesulfonic acid (MSA) are shown in Figures 1–10. TMS has proven to be a good solvent for the polyamides and fairly transparent down to 200 mμ, and thus has been chosen as a non-hydrogen-bonding solvent, which is high boiling and thus suited also for temperature effect studies. MSA has been used as a strongly acidic medium.

Some amide compounds can aggregate and give different spectra, especially in nonpolar solvents. This aggregation effect can be detected by the change of uv/ORD/CD spectra on dilution.[23,24,26] For the polyamides and diamide model compounds studied, no noticeable change has been detected in concentrations of wide range, 10^{-2}–10^{-4} mol of amide residue/l. The uv/ORD/CD spectra have been taken repeatedly at the different periods, 0.5–125 hr after dissolving, and no time dependence was observed in all solvents used, indicating neither further conformational change nor decomposition.

In general, the CD bands assigned to the π–π^* transition in TFE exhibit no shift or a small blue shift in TMS and CH; the same was observed also in methanol and *p*-dioxane (DO), although the curves are not shown. In less polar solvents, an additional CD band at a longer wavelength is observable; at 248 mμ for the (+)-(*S*)-1,2-C3 diamide in TMS (Figure 1), at 239 mμ for the (−)-(*R*)-1,2-C4 diamide in CH (Figure 5), and at 232–236 mμ for the (+)-1,3-C5 diamide and polyamides in CH, DO, and TMS (Figures 8 and 9). These weak CD bands may be assigned to the n–π^* transition of amide chromophores. On going from TFE to less polar solvents, the π–π^* transition blue shifts a little and the n–π^* transition red shifts and becomes observable.[22–26] The signs of these CD bands are consistent with the prediction discussed before. The (−)-(*R*)-1,2-C4 diamide exhibits a remarkable change in both ORD and CD spectra on going from TFE to CH. Two CD bands at 212 and 239 mμ appear in CH, in contrast to only one very weak CD band around 212 mμ in TFE (Figure 5). The results suggest that in TFE the n–π^* transition is overlapped more with the π–π^* transition of opposite sign and both are considerably canceled by each other. In the case of the (+)-(*S*)-1,2-C3 and (−)-(*R*)-1,2-C4 polyamides, there is no evidence for the n–π^* transition even in TMS, probably because the π–π^* transition is located at a higher wavelength and is stronger than that of the diamide.

The (+)-(*S*)-1,2-C3·DMPIP polyamide exhibits the same pattern of CD spectra in TMS and TFE, while the CD spectrum in MSA is quite different (Figure 2). On the contrary, the (+)-(*S*)-1,2-C3 diamide or the (+)-(*S*)-1,2-C3·DMED polyamide exhibits the same pattern of CD spectra in a wide variety of solvents, from CH to MSA (Figures 1 and 4). The CD spectra of the PIP, DMED polyamides and the diamide in MSA are very similar to one another in all respects, their pattern, strength, and position. The CD spectrum of the DMPIP polyamide in MSA is somewhat different.

The results strongly suggest that the rigid (+)-(*S*)- and (−)-(*R*)-1,2-C3·DMPIP and ·PIP polyamides exist in some

ordered conformation in TFE and TMS, while some conformational transition is induced by the addition of MSA.

Acknowledgments. We wish to thank Mr. R. A. Veneski for providing certain samples. We wish to thank Dr. G. Montaudo for his suggestions. One of us (Y. S.) is grateful to Toray Industries, Inc., Japan, for giving him the opportunity to perform this work at The University of Michigan. We also thank The University of Michigan, Rackham Fund, for Chemistry fellowship support through the Macromolecular Research Center and the Department of Chemistry. The authors are grateful for financial support by the U. S. Army Research Office-Durham, under Grant No. DAHCO4-69-C-0050.

Solution Properties of Synthetic Polypeptides. Circular Dichroism Studies on Poly-L-histidine and on Random Copolymers of L-Histidine and L-Lysine in Aqueous Solution

E. Peggion, A. Cosani, M. Terbojevich, and E. Scoffone*

Institute of Organic Chemistry, University of Padova, 35100 Padua, Italy.
Received May 25, 1971

ABSTRACT: The conformational properties of poly-L-histidine (PLH) and of random copolymers of lysine and histidine in aqueous solution have been investigated by CD techniques in the spectral range 185–250 nm. It was found that PLH undergoes a cooperative conformational transition on varying the extent of protonation of the polymer side chains. CD studies on the random copolymers show that increasing amounts of histidine residues cause a linear change of the CD spectrum on going from pure protonated poly-L-lysine (PLL) to pure protonated PLH. On the basis of these data, it was concluded that completely protonated PLH exists as a random coil in aqueous solution. Similar copolymer studies have been carried out in a methanol–water solution containing 92% methanol. In this solvent mixture protonated PLL exists as a right-handed α helix, and *deprotonated* PLH is in the same conformation as in water. Increasing amounts of *deprotonated* histidine residues in the *protonated* PLL chain cause a sharp conformational transition which occurs when the histidine content is higher than 80%. From these results it was concluded that the ordered form of charge-free PLH in water *is not* that of a right-handed α helix.

At the present time the conformation of poly-L-histidine (PLH) in aqueous solution has not been safely established. Previous investigations carried out by Norland, *et al.*,[1] and by Beychok and coworkers[2] have shown that PLH undergoes a conformational transition induced by pH changes. At a pH lower than 3, the random coil was assumed to be the most probable conformation, on the basis of viscosity and CD data. At pH 5.8, Beychok and coworkers[2] assumed that PLH is in the right-handed α-helical form on the basis of the presence of a negative CD band at 223 nm. On the contrary, Norland, *et al.*,[1] on the basis of optical rotation measurements and other evidence tentatively concluded that PLH in aqueous solution at pH 5.8 exists as a left-handed α helix. None of these assignments should be considered definitive, since the interpretation of ORD and CD data in terms of conformation is complicated by the presence of imidazole side-chain groups which may contribute to the total optical activity.

In previous papers[3-6] we have studied the conformation in solution of aromatic poly(α-amino acids) by measuring the CD properties of copolymers of the aromatic amino acids with a simple amino acid whose homopolymer has a known conformation in solution. These copolymer studies allowed us to draw conclusions concerning the conformation in solution of poly-L-tryptophan,[3-4] poly-L-phenylalanine,[5] and poly(1-benzyl-L-histidine).[6]

The present paper reports CD and potentiometric studies in aqueous solution on a highly purified sample of PLH and on random copolymers of L-lysine and L-histidine of various composition in order to investigate the perturbations of the CD pattern induced by increasing amounts of histidine residues in the peptide chain. The spectroscopic studies have been extended down to 185 nm.

Experimental Section

Solvents and Materials. Reagent grade dioxane (Carlo Erba RP) was dried over potassium–anthracene complex as previously described[3] and distilled immediately before use. The water content in the distillate was less than 0.002% by weight. Petroleum ether (40–70°, Carlo Erba RP) was refluxed over sodium wire and then fractionally distilled. Spectrograde methanol (Fisher Scientific Co.) was used as received. Dichloroacetic acid (DCA) and trifluoroacetic acid (TFA), both Carlo Erba RP products, were used without any further purification. Triethylamine (Carlo Erba RP) was refluxed over KOH and then fractionally distilled from potassium metal, rejecting the first 10% of the distillate. Nitromethane (Carlo Erba RP) was dried over P_2O_5 and fractionally distilled.

1-Benzyl-L-histidine *N*-carboxyanhydride (Bz-His-NCA) was obtained from *N*-carbobenzoxy-1-benzyl-L-histidine[7] and PCl_5 follow-

(1) K. Norland, G. D. Fasman, E. Katchalski, and E. R. Blout, *Biopolymers*, **1**, 277 (1963).
(2) S. Beychok, M. N. Pflumm, and J. E. Lehmann, *J. Amer. Chem. Soc.*, **87**, 3990 (1965).
(3) A. Cosani, E. Peggion, A. S. Verdini, and M. Terbojevich, *Biopolymers*, **6**, 963 (1968).
(4) E. Peggion, A. Cosani, A. S. Verdini, A. Del Pra, and M. Mammi, *ibid.*, **6**, 1477 (1968).
(5) E. Peggion, A. Cosani, A. S. Verdini, and E. Scoffone, *Macromolecules*, **2**, 170 (1969).
(6) M. Terbojevich, M. Acampora, A. Cosani, E. Peggion, and E. Scoffone, *ibid.*, **3**, 618 (1970).
(7) B. G. Overell and V. Petrow, *J. Chem. Soc.*, 232 (1955).