

Fig. 1.—Infrared spectra of oriented film (on silver chloride plate) of poly- α -L-glutamic acid: — electric vibration direction parallel to orientation direction; --- electric vibration direction perpendicular to orientation direction.

to those obtained with the free acid, and correspond to those obtained with " β " polypeptides⁷ or extended intermolecularly bonded configurations from random coils. The infrared spectra (Fig. 2) are characterized by perpendicular dichroism of the 3300 cm^{-1} and 1655 cm^{-1} bands. Particularly important is the appearance of a perpendicularly dichroic absorption band at 1628 cm^{-1} (C=O stretch, amide I). The 1550 cm^{-1} band is overshadowed by the 1575 cm^{-1} ionized carboxyl absorption band which is very strong.

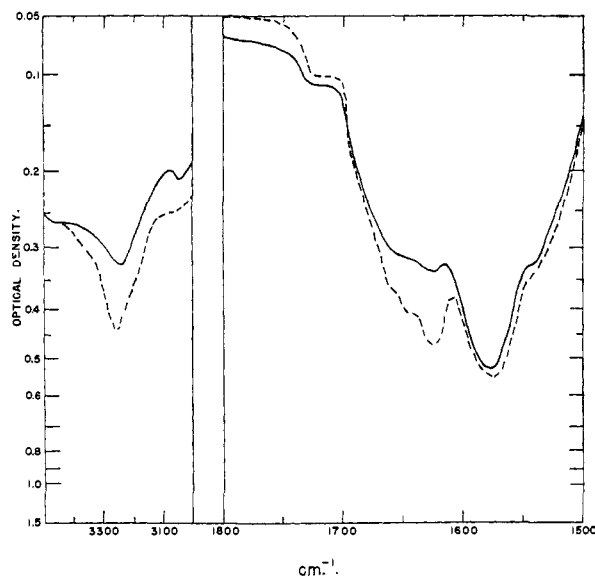


Fig. 2.—Infrared spectra of oriented film (on silver chloride plate) of sodium poly- α -L-glutamate: — electric vibration direction parallel to orientation direction; --- electric vibration direction perpendicular to orientation direction.

Solutions of the sodium salt of PGA upon acidification, dialysis, lyophilization and re-resolution

in dioxane:water give oriented films characteristic of helical configurations which correspond exactly in their infrared dichroic properties to that in Fig. 1. It is therefore concluded that *with PGA, helix* \rightarrow *non-helix* \rightarrow *helix* transformations can be obtained by altering the ionization of the γ -carboxyl groups.

It is interesting to speculate that similar transformations occur in solution. Some indication is offered by the large, reversible change in optical rotation of aqueous PGA solutions; $[\alpha]^{25D}$ (0.2 M Na_2SO_4 solution) varies from -83° at $\text{pH} > 7$ to -8° at $\text{pH} 4.5$. These changes are comparable to those which occur with changes of configuration in PBG^{9,10} and in proteins.¹¹

(9) P. Doty, A. M. Holtzer, J. H. Bradbury and E. R. Blout, *THIS JOURNAL*, **76**, 4493 (1954).

(10) P. Doty and J. T. Yang, *ibid.*, **76**, 498 (1956).

(11) C. Cohen, *Nature*, **175**, 129 (1955).

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RECEIVED DECEMBER 12, 1955

POLYPEPTIDES. VII. POLY- γ -BENZYL-L-GLUTAMATE: THE HELIX-COIL TRANSITION IN SOLUTION¹ *Sir:*

In earlier investigations² it has been shown that poly- γ -benzyl-L-glutamate exists in a randomly coiled configuration in dichloroacetic acid and in a rigid, rod-like helical configuration in a number of other organic solvents. Since the helix possesses a definite ordering of hydrogen bonds in one direction it would be anticipated that the conversion of this configuration into that of a random coil should have the characteristics of a first order transition. We have observed this transition both as a function of solvent composition and temperature and have found it to be rapidly reversible.

Solutions of equal concentration of poly- γ -benzyl-L-glutamate of high molecular weight^{3,4} in ethylene dichloride and dichloroacetic acid were mixed in varying proportions and the intrinsic viscosity, the double refraction of flow and the optical rotation were determined. Except for a small change upon the first addition of the dichloroacetic acid solution to the ethylene dichloride solution⁵ these properties remained essentially constant until a sharp change occurred in the vicinity of 76 volume per cent. dichloroacetic acid. At higher concentrations the properties were those of the pure dichloroacetic acid solution. The transition appeared to occur most sharply in terms of optical rotation, presumably because this quantity varied in direct proportion to the change

(1) This work was supported by the Office of Naval Research (N5ori-07654).

(2) (a) P. Doty, A. M. Holtzer, J. H. Bradbury and E. R. Blout, *THIS JOURNAL*, **76**, 4493 (1954); (b) P. Doty, J. H. Bradbury and A. M. Holtzer, *ibid.*, in press.

(3) E. R. Blout, R. H. Karlson, P. Doty and B. Hargitay, *ibid.*, **76**, 4492 (1954).

(4) E. R. Blout and R. H. Karlson, *ibid.*, in press.

(5) This small change at low dichloroacetic acid concentrations is thought to be associated with a change in the average orientation of the benzyl groups to the helix core.

in configuration, whereas the hydrodynamic properties undergo substantial changes at the first weakening of the helical structure.

When the solvent composition is chosen as that at the center of the transition (76 volume per cent. dichloroacetic acid) the temperature dependence of the specific rotation shows that the transition occurs in a relatively narrow temperature range⁶ for high molecular weight samples (Fig. 1). Moreover, since the +14 value is associated with the helix^{1,2} it is this configuration which is the stable form at higher temperatures. Although this is opposite to the analogous case of protein denaturation it can be understood by recognizing that the transition involves the participation of the solvent. That is, we view the change occurring as: $\text{HELIX} + x \text{DCA} = \text{COIL} \cdot (\text{DCA})_x$. The gain in configurational entropy by the polymer in the forward direction is more than offset by the loss in translational entropy by the very large number of dichloroacetic acid molecules which solvate the coiled form. The heat of the transition can be determined readily from the type of data shown in Fig. 1: it is found to be about -100 calories per

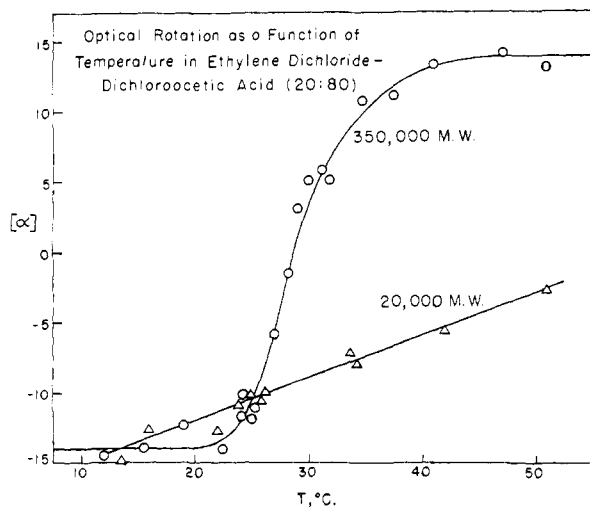


Fig. 1.—The temperature dependence of the optical rotation (Na D line) for two poly- γ -benzyl-L-glutamates in ethylene dichloride-dichloroacetic acid.

monomer unit after corrections for the effect of polydispersity of molecular weight. The sharpness of the transition would be expected to be dependent on the molecular weight⁷ and molecular weight distribution since the molar heat of transition is proportional to the molecular weight. The data for a 20,000 molecular weight polymer in Fig. 1 shows this effect. Although the transition is now spread out over a large temperature range the transition temperature is not lowered as would be predicted⁷ if the role of the solvent were neglected.

(6) The range in temperature is due principally to the polydispersity of molecular weight. In the experiments involving solvent composition 90% of the change occurred within less than 5% change in the solvent composition.

(7) J. A. Schellman, *Compt. rend. trav. Lab. Carlsberg, Serie Chimique*, **29**, No. 15 (1955).

The origin of the 25–30° greater specific rotation of the helix is a matter of some interest, particularly since this corresponds closely to the amount by which the rotation of many native proteins exceed that of their denatured forms.⁸ It would appear that this difference may arise either from an environmental difference at the asymmetric carbons in the two configurations or from a direct contribution of the helix itself to the optical rotation.⁹ With this in mind measurements of the rotatory dispersion of the two configurations have been made. The results (Fig. 2) show that the rotatory dispersion is normal for the randomly coiled configuration and not normal for the helix.¹⁰

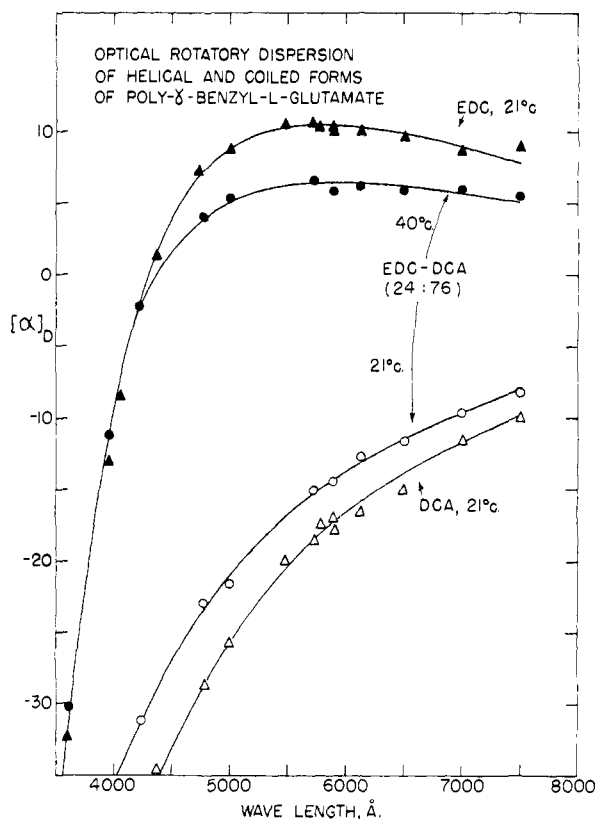


Fig. 2.—The rotatory dispersion for poly- γ -benzyl-L-glutamate (M.W. 130,000) in the helical and randomly coiled configurations. The two lower curves correspond to the randomly coiled case and normal dispersion.

This indicates that the increased rotation of the helix is not simply due to an environmental change at the asymmetric centers but rather that the helical configuration has either augmented the

(8) For comparison with proteins the value of 25–30° must be approximately doubled because the residue weight of benzyl-L-glutamate is about double that of the average naturally occurring amino acid residue. A change of 75° brought about by a change of pH in poly-L-glutamic acid solutions (E. R. Blout and M. Idelson, *THIS JOURNAL*, **78**, 497 (1956)) is indicative of the occurrence of a similar transition, since most of this cannot be associated with the ionization of the carboxyl group.

(9) C. Cohen, *Nature*, **175**, 129 (1955).

(10) The prediction of a particular type of anomalous dispersion for α -helices is contained in a forthcoming paper by Professor W. Moffitt in the *Journal of Chemical Physics* and our results are consistent with this prediction.

activity of the asymmetric centers or has conferred new activity on additional chromophoric groups.

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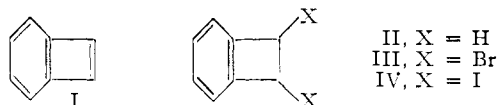
RECEIVED DECEMBER 16, 1955

BENZOCYCLOBUTENE AND BENZOCYCLOBUTADIENE DIMER¹

Sir:

Several fully aromatic hydrocarbons are known which may be considered to be dibenzo derivatives of the unknown cyclobutadiene.^{2,3,4a,b} The simpler benzocyclobutadiene (I) has not been described, although molecular orbital calculations for the system have been made.⁵ The closely related benzocyclobutene (II), the lower homolog of indane, also has not been described; doubts have been expressed concerning the stability of such a system⁶ in which the considerable strain upon the ring is not compensated by any added resonance energy. We now wish to report the synthesis of the stable benzocyclobutene (II) and the generation of the unstable benzocyclobutadiene (I), isolated only as a dimer.

Treatment of $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene with excess sodium iodide in refluxing ethanol for two days has been reported⁷ to give 1,2-dibromobenzocyclobutene (III). This reaction has been repeated and pure III isolated as colorless crystals, m.p. 52.4–52.8°. *Anal.* Calcd. for C₈H₆Br₂: C, 36.68; H, 2.31; Br, 61.02; mol. wt., 262. Found: C, 36.72; H, 2.35; Br, 60.83; mol. wt. (isothermal distillation), 258, 259. Dibromide III was unchanged by refluxing bromine after two days, and unaffected by maleic anhydride after fifteen hours at 90°. Nitric acid oxidized III to phthalic acid and bromine at 150° slowly converted III to $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene.



Refluxing a solution of III and excess sodium iodide in ethanol for eight days gave 1,2-diiodobenzocyclobutene (IV); m.p. 62.7–62.9°. *Anal.* Calcd. for C₈H₆I₂: C, 26.99; H, 1.70; I, 71.31; mol. wt., 356. Found: C, 26.84; H, 1.93; I, 71.05; mol. wt. (isothermal distillation), 350. Oxidation of IV with nitric acid gave phthalic acid. Hydrogenolysis of IV at room temperature in ethanol in the presence of palladium charcoal and sodium ethoxide gave, after distillation through a Nester spinning band column, pure II, b.p. 150.0° (748 mm.). *Anal.* Calcd. for C₈H₈: C, 92.26;

(1) A part of this material was presented before the Division of Organic Chemistry at the 128th meeting of the American Chemical Society, Minneapolis, Minnesota, September, 1955.

(2) W. C. Lothrop, *THIS JOURNAL*, **63**, 1187 (1941).

(3) R. F. Curtis and G. Viswanath, *Chem. and Ind.*, 1174 (1954).

(4) (a) M. P. Cava and J. F. Stucker, *ibid.*, 446 (1955); (b) *THIS JOURNAL*, **77**, 6022 (1955).

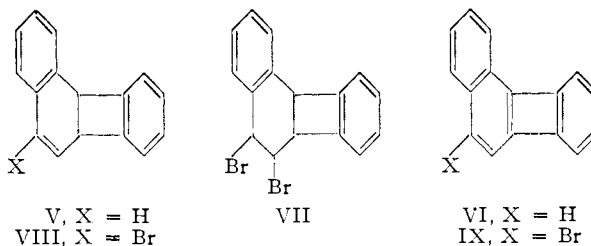
(5) J. D. Roberts, A. Streitweiser, Jr., and Clare M. Regan, *ibid.*, **74**, 4579 (1952).

(6) W. Baker, *J. Chem. Soc.*, 258 (1945).

(7) H. Finkelstein, Dissertation, Strassbourg, 1910.

H, 7.74. Found: C, 92.33, 92.47; H, 7.74, 7.72; $\lambda_{\text{max}}^{\text{EtOH}}$ 260 m μ (log ϵ = 3.09), 265.5 m μ (log ϵ = 3.28), 271.5 m μ (log ϵ = 3.27); $d_{25}^{425} = 0.957$; $n_D^{25} = 1.5409$. The mass spectrum of II exhibited a parent peak at 104 m/e.; the infrared spectrum contained a band at 10.05 μ characteristic of a cycloalkane ring.⁸

Dehalogenation of either III or IV with zinc in ethanol (containing hydroquinone) gave, in 70–80% yield, not the expected I, but a crystalline dimer (V), m.p. 74.5°. *Anal.* Calcd. for C₁₆H₁₂: C, 94.07; H, 5.92; mol. wt., 204. Found: C, 93.89; H, 5.93; mol. wt. (isothermal distillation), 200. Dimer V was aromatized by N-bromosuccinimide in benzene to 1,2-benzobiphenylene (VI), identical with an authentic sample.^{4b} Only one mole of bromine added to V to give a dibromide (VII), m.p. 111.5–112.2°. *Anal.* Calcd. for C₁₆H₁₂Br₂: C, 52.78; H, 3.32; Br, 43.90. Found: C, 52.91; H, 3.46; Br, 43.70. Reaction of VII with potassium *t*-butoxide in *t*-butyl alcohol gave the monobromide (VIII), m.p. 124.3–124.6°. *Anal.* Calcd. for C₁₆H₁₁Br: C, 67.86; H, 3.92; Br, 28.22. Found: C, 67.59; H, 4.02; Br, 28.01. Aromatization of VIII by N-bromosuccinimide in benzene gave 3-bromo-1,2-benzobiphenylene (IX), m.p. 125–



126°, identical in all respects with a sample synthesized from simple naphthalene precursors.⁹ These reactions establish the structure of V, including the position of the double bond.

The formation of dimer V appears to occur via a Diels–Alder condensation between two molecules of I, followed by spontaneous aromatization of the initially formed product to V.

(8) L. W. Marrison, *J. Chem. Soc.*, 1614 (1951).

(9) M. P. Cava and J. F. Stucker, to be published shortly.

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RECEIVED DECEMBER 20, 1955

SYNTHESIS OF POTENT ORAL ANABOLIC-ANDROGENIC STEROIDS

Sir:

In the course of studies on the synthesis of 11-oxygenated C-19 steroids¹ we have prepared a number of analogs (III, XI and XII) of this category which have been shown to possess oral anabolic and androgenic potency considerably higher than any other hitherto reported (see Table I).

The preparation of these compounds was in part accomplished by extension of the utility of 3-enamines formed selectively from polycarbonyl

(1) M. E. Herr and F. W. Heyl, *THIS JOURNAL*, **75**, 5927 (1953).