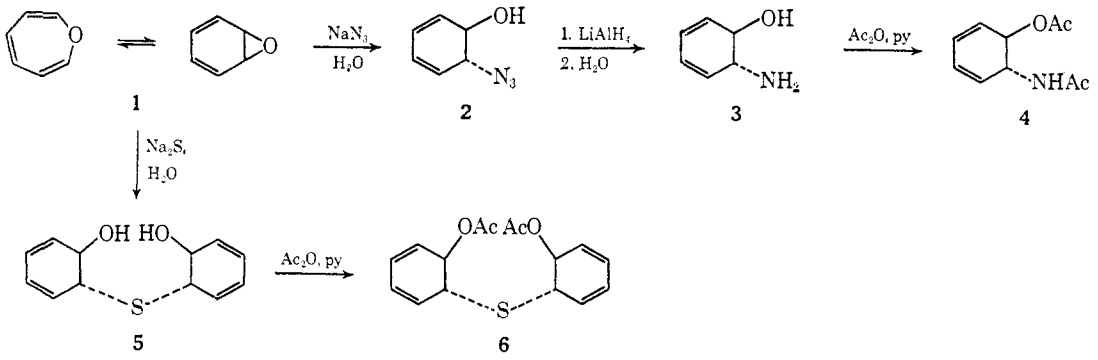

branch-point intermediate in the biosynthesis of aromatic amino acids and growth factors,[10] is the 3-enol pyruvyl ester of *trans*-3,4-dihydroxy-3,4-dihydrobenzoic acid.

Due to the importance of substituted 1,3-cyclohexadienes in nature and the suggested role of arene oxide–oxepin systems in their formation,[11] we have investigated nonenzymatic ring-opening reactions of oxepin–benzene oxide (**1**) with nucleophilic reagents.[12,13] Although no reaction was observed with **1** and $NaNH_2$ in liquid NH_3, **1** did react with NaN_3 in H_2O at room temperature for 3 hr to give *trans*-5-azido-6-hydroxy-1,3-cyclohexadiene[16] (**2**) as a pale yellow liquid in 55% yield. Reduction of **2** with $LiAlH_4$ in ether at 0° for 1 hr gave *trans*-5-amino-6-hydroxy-1,3-cyclohexadiene[16] (**3**) as white needles (60%, mp 62.0–63.5° from ether–pentane). Diacetate **4**[16] was formed in 59% yield from **3** and acetic anhydride in pyridine at 0° but could not be obtained free of acetanilide. The assignment of *trans* stereochemistry in **2** and **3** is based on the H_5–H_6 coupling in the nmr spectrum: $J_{H_5-H_6}$ in **2** = 9 Hz (CCl_4); in **3**, 12 Hz ($CDCl_3$). The values are in agreement with previous studies[17] and indicate the ring assumes the twist conformation in which the hydroxyl and azido or amino substituents are quasi-equatorial due to intramolecular hydrogen bonding.

Reaction of **1** with excess $Na_2S \cdot 9H_2O$ in H_2O at 0° for 45 min gave bis(*trans*-2-hydroxy-3,5-cyclohexadienyl) sulfide[16] (**5**) in 37% yield: mp 75–79°. This diol sulfide readily decomposed to phenol and diphenyl sulfide. Diacetate **6**[16] (mp 115.5–116.5° from ether–hexane) was prepared in 67% yield by the reaction of **5** with acetic anhydride in pyridine at 0° for 3 hr. The H_5–H_6 coupling in the nmr spectrum of **5** and **6** is 3.5 Hz (acetone-d_6) in **5** and 4.5 Hz ($CDCl_3$) in **6**. The coupling constants are in agreement with assignment of *trans* stereochemistry in which the rings assume the twist conformation with quasi-axial hydroxyl and sulfide substituents.[17]

Reaction of oxepin–benzene oxide systems with nucleophiles appears to be a useful route for the nonenzymatic synthesis of heteroatom-substituted 1,3-cyclohexadienes.[18]

(7) J. G. Young, L. M. Jackman, and F. Gibson, *Biochim. Biophys. Acta*, 148, 313 (1967).
(8) T. J. Batterham and J. G. Young, *Tetrahedron Letters*, 945 (1969).
(9) M. R. Bell, *et al.*, *J. Amer. Chem. Soc.*, 80, 1001 (1958).
(10) J. M. Edwards and L. M. Jackman, *Aust. J. Chem.*, 18, 1227 (1965), and references cited therein.
(11) D. M. Jerina, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.*, 90, 6523 (1968); D. M. Jerina, *et al.*, *ibid.*, 90, 6525 (1968); and references cited therein.
(12) Vogel[14] has reported that **1** reacts with CH_3Li to give a mixture of *cis*- and *trans*-5-hydroxy-6-methyl-1,3-cyclohexadiene and with $LiAlH_4$ to give 1,2-dihydrophenol which aromatized on attempted isolation.
(13) Jerina, *et al.*,[15] have reported enzyme-catalyzed ring opening of **1** to *trans*-5,6-dihydroxy-1,3-cyclohexadiene with rabbit liver microsomes and that incubation of **1** with rat liver supernatant and glutathione gave the premercapturic acid, S-(1,2-dihydro-2-hydroxyphenyl)-glutathione. The reaction of glutathione with **1** in the absence of enzyme occurs at one-fifth the rate of the enzyme-catalyzed reaction.[15]
(14) E. Vogel and H. Günther, *Angew. Chem.*, 79, 429 (1967).
(15) D. Jerina, *et al.*, *Arch. Biochem. Biophys.*, 128, 176 (1968).
(16) Satisfactory analytical data have been obtained for all new compounds except 4. Satisfactory spectroscopic data have been obtained for all new compounds.
(17) T. J. Batterham and J. G. Young, *Tetrahedron Letters*, 945 (1968).
(18) *cis*- and *trans*-5,6-dihydroxy-1,3-cyclohexadiene have been prepared from difficultly available starting materials.[19]
(19) M. Nakajima, I. Tomida, and S. Takei, *Chem. Ber.*, 92, 163 (1959); N. Nakajima, *et al.*, *Ber.*, 89, 2224 (1956).

Robert M. DeMarinis, Glenn A. Berchtold

Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

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A "Normal" Temperature-Induced Helix–Coil Transition of Poly-γ-N-carbobenzoxy-L-α,γ-diaminobutyric Acid in Mixed Organic Solvents[1]

Sir:

The discovery that poly-γ-benzyl-L-glutamate (PBLG) can undergo the helix–coil transition as a function of both solvent composition and temperature[2] has prompted numerous studies of such a transition for various poly-α-amino acids (for a review, see ref 3). PBLG is known to display an "inverse" transition in mixed solvents, that is, its helical form is stable at higher temperatures and its coiled form at lower ones than room temperature. This is also true for several structurally related polypeptides in mixed organic solvents. We now wish to report a "normal" reversible temperature-induced helix–coil transition of poly-γ-N-carbobenzoxy-L-α,γ-diaminobutyric acid (PCLB), as contrasted with its higher homologs, poly-δ-N-carbobenzoxy-L-ornithine (PCLO) and poly-ε-N-carbobenzoxy-L-lysine (PCLL) (Table I). In analogy to protein denaturation, PCLB becomes helical at low temperature and disordered at high temperature.

We synthesized a high molecular weight PCLB[4] having a degree of polymerization of 470, as determined from high-speed equilibrium sedimentation,[5,6] and fol-

(1) This work was supported by grants from the U. S. Public Health Service (GM-10880, HE-06285, and GM-K3-3441).
(2) P. Doty and J. T. Yang, *J. Am. Chem. Soc.*, 78, 498 (1956).
(3) G. D. Fasman in "Poly-α-Amino Acids," G. D. Fasman, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, Chapter 11.
(4) S. Kubota, J. Noguchi, and J. T. Yang, submitted for publication; lot SK-0667.
(5) D. Yphantis, *Biochemistry*, 3, 297 (1964).

Table I. Temperature-Induced Helix–Coil Transition of Several Polypeptides, $-(HNCHRCO)_n-$, in Mixed Solvents at Room Temperature

Side chain, R[a]	Solvent transition, % DCA[b] in $CHCl_3$ (v/v)	Direction of temperature transition
(1) $CbzNH(CH_2)_2$	51[c]	Normal[c]
(2) $CbzNH(CH_2)_3$[d]	35;[e] 38[f]	Inverse[c]
(3) $CbzNH(CH_2)_4$	37[g]	Inverse[h]
(4) $BzOCO(CH_2)_2$	69;[i] 80[j]	Inverse[i]

[a] Cbz = N-carbobenzoxy; Bz = benzyl; (1) poly-γ-N-carbobenzoxy-L-α,γ-diaminobutyric acid (PCLB); (2) poly-δ-N-carbobenzoxy-L-ornithine (PCLO); (3) poly-ε-N-carbobenzoxy-L-lysine (PCLL); (4) poly-γ-benzyl-L-glutamate (PBLG). [b] DCA, dichloroacetic acid. [c] This work. [d] Purchased from The Pilot Chemicals, Inc., Watertown, Mass.; lot 0-22 (mol wt 192,000). [e] M. Hatano, M. Yoneyama, I. Ito, T. Nozawa, and M. Nakai, *J. Am. Chem. Soc.*, **91**, 2165 (1969). [f] F. Gaskin and J. T. Yang, unpublished data. [g] G. D. Fasman, M. Idelson, and E. R. Blout, *J. Am. Chem. Soc.*, **83**, 709 (1961). [h] F. E. Karasz, J. M. O'Reilly, and H. E. Bair, *Biopolymers*, **3**, 241 (1965). [i] R. H. Karlson, K. S. Norland, G. D. Fasman, and E. R. Blout, *J. Am. Chem. Soc.*, **82**, 2268 (1960). [j] E. M. Bradbury, A. R. Downie, A. Elliott, and W. E. Hanby, *Proc. Roy. Soc.* (London), **A259**, 110 (1960).

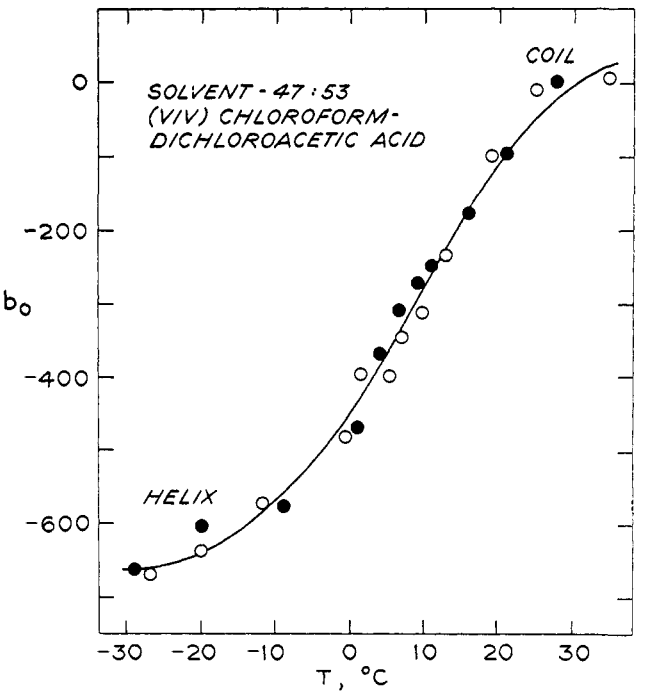

Figure 1. The temperature dependence of optical rotation for poly-γ-N-carbobenzoxy-L-α,γ-diaminobutyric acid. The symbols ○ and ● represent duplicate experiments.

lowed its conformational change in mixed solvents by optical rotation. A solution of PCLB in dichloroacetic acid (DCA) was diluted with chloroform in varying proportions up to 70% (v/v) $CHCl_3$ (the polymer was insoluble in $CHCl_3$). A sharp change in rotation occurred near 51 vol % DCA. We studied the temperature dependence of the optical rotatory dispersion (ORD) from 500 to 320 nm[7] in 53 vol % DCA. The data were analyzed with the Moffitt equation[8] using a computer program. Figure 1 shows the parameter b_0 of the Moffitt equation as a function of temperature. Since a b_0 of about -630 is currently interpreted to be characteristic of a helical structure, it is this conformation that is the stable form at lower temperatures. On the other hand, b_0 is close to zero once the secondary structure is completely disrupted upon raising the temperature of the solution above 30°. Thus, PCLB displays a normal temperature-induced transition. In contrast, we show in Table II the effect of temperature on PCLO in 63:37 (v/v) chloroform–DCA. Since $[\alpha]_{400}$ is positive for the helical form and negative for the coiled form, PCLO undergoes an "inverse" temperature-induced transition. Note also that the PCLB transition occurs over a broad temperature range of about 50° (Figure 1), as compared with about 20° in the case of PCLO (Table II).

Comparison of the first three homologs in Table I suggests that the number of methylene groups in the side chain markedly influences the direction of the temperature transition. Such a conformational change has long been recognized to involve the participation of the solvent. That the helical form is favored at lower temperatures for PCLB, but not for the other two homologs, could arise because of a smaller extent of interaction of PCLB with DCA.

Table II. Optical Rotation of PCLO in 63:37 (v/v) Chloroform–DCA

Temp, °C	$[\alpha]_{400}$, deg	Temp, °C	$[\alpha]_{400}$, deg
0.5	−54	18.3	−8
7.5	−54	20.3	+4
11.8	−52	25.0	+16
15.0	−42	30.0	+19
16.8	−25	33.3	+20

In a recent communication Hatano, *et al.* (see Table I, footnote *e*) reported a helix-coil transition of PCLB near 40 vol % DCA, using a low molecular weight sample (DP = 33). This perhaps can explain the discrepancy between their finding and ours (*cf.* Table I). On the basis of the per cent DCA needed to initiate the transition, Hatano, *et al.*, further claim that the helical structure of PCLB seems to be the most stable of the three homologs (see Table I). We wish to emphasize that such conclusions concerning relative stability of helices are valid only at a particular temperature and solvent composition. Furthermore, we find that there is no correlation between the stability of a helix in mixed organic solvents at room temperature and the direction of the temperature-induced helix-coil transition. Work is in progress to determine the thermodynamic parameters of the helix-coil transition for various polypeptides.

(6) The value 0.759 ml/g for the partial specific volume was determined by density measurements in N,N-dimethylformamide at 25° and used in the calculation of the molecular weight from sedimentation equilibrium runs (0.05–1.3% in N,N-dimethylformamide) at 20°.

(7) All ORD spectra were measured with a Cary 60 spectropolarimeter using a specially designed thermostatable cell holder and jacket. The temperature of the holder was read with a copper–constantan thermocouple and found to be constant to ±0.03°.

(8) W. Moffitt and J. T. Yang, *Proc. Natl. Acad. Sci. U. S.*, **42**, 596 (1956); $[m'] = a_0\lambda_0^2/(\lambda^2 - \lambda_0^2) + b_0\lambda_0^4/(\lambda^2 - \lambda_0^2)^2$, with λ_0 preset at 212 nm.

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Felicia Gaskin, Shigeo Kubota, Jen Tsi Yang
Cardiovascular Research Institute and Department of Biochemistry and Biophysics University of California Medical Center San Francisco, California 94122
Received August 8, 1969

The Addition of Undissociated Strong Acids to Alkenes. "Hidden Return" Revealed

Sir:

We wish to report observations which shed new light on the behavior of the ion pairs which are involved in the trifluoroacetolysis of secondary arenesulfonate esters.[1,2] Isopropyl *p*-bromobenzenesulfonate (ROBs) reacts in trifluoroacetic acid (TFA) at 25° to give, within the limits of nmr detection, a quantitative yield of isopropyl trifluoroacetate ($ROCOCF_3$). The half-life based on the rate of disappearance of the nmr signal is 182 min. Neither the product yield nor the half-life is significantly different if the reaction is carried out in the presence of excess sodium trifluoroacetate. Propene is converted to $ROCOCF_3$ relatively slowly by TFA either alone or buffered (half-life ~300 min). However, *in trifluoroacetic acid, propene (0.2 M) and p-bromobenzenesulfonic acid (HOBs, 0.1 M) react within less than 1 min to produce isopropyl p-bromobenzenesulfonate apparently quantitatively.* We interpret this to mean that propene and undissociated HOBs react directly to produce a "tight" ion-pair ($R^+\bar{O}Bs$) which covalently combines at a rate much faster than it dissociates. Dewar and Fahey[3] have argued that the *cis* addition of HBr to acenaphthylene in acetic acid involves formation and rapid combination of ion pairs. It is obvious that in these reactions ion-pair combination is faster than solvolysis.[4]

Isopropyl alcohol (ROH, 0.1 *M*) on the other hand is converted by HOBs (0.12 *M*) in TFA exclusively to $ROCOCF_3$ with a half-life of 7 min; no intermediate formation of ROBs is detected even though its solvolytic half-life is much longer. This is interpreted as indicating that HOBs reacts with ROH to form isopropyloxonium brosylate ($R^+OH_2O^-Bs$) ion pairs which are converted in the rate-determining step to isopropyl cation and brosylate ion *separated* by a molecule of water ($R^+OH_2{}^-OBs$);[6] this molecule-separated ion pair solvolyzes rapidly and does not undergo kinetically significant internal return to ROBs. Thus, we conclude that the trifluoroacetolysis of ROBs must involve rate-determining dissociation of the tight ion pair

$$ROBs \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+\bar{O}Bs \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R^+\,|\!|\,\bar{O}Bs \xrightarrow{k_3} ROCOCF_3$$

$$\uparrow \qquad\qquad \uparrow$$

propene + HOBs ROH + HOBs

The formation of ROBs from propene and HOBs shows that $k_{-1} > k_2$; the lack of formation of ROBs from ROH and HOBs indicates that the *water*-separated ion pair does not return; it seems reasonable that *solvent*-separated ion pairs would not return either so that $k_3 > k_{-2}$.[9]

Streitwieser and Dafforn[10] have reported that in trifluoroacetolysis isopropyl toluenesulfonate shows an α-deuterium rate effect (k_H/k_D) of 1.22 ± 0.02 and a β-d_6 effect of 2.12 ± 0.1. It has previously been suggested[11] that the α-*d* effect on a limiting reaction of an alkyl arenesulfonate should be about 1.22 and that the lower effects observed in other solvents indicate some nucleophilic character, probably nucleophilic attack on the tight ion pair.[12] The idea that *many reactions classified as limiting*[11-13] *involve rate-determining dissociation of tight ion pairs*[12] is thus further reinforced. It is important to note that the β-d_3 effect of 1.46 (or $\sqrt{2.12}$) reported for the limiting solvolytic formation of a simple secondary carbonium ion is significantly larger than that for a simple tertiary system,[14] *e.g.*, 1.3304 for the solvolysis of *t*-butyl-d_3 chloride in 60% aqueous ethanol.[15]

Experiments with other alkene–alcohol–alkyl ester systems in TFA and in other solvents which do not ionize the conjugate acids of the usual leaving groups are currently underway to determine the generality of the pattern of results reported here. Preliminary observations indicate a similar pattern with styrene–1-phenylethanol–1-phenylethyl chloride in trifluoroethanol and with isobutylene–*t*-butyl alcohol–*t*-butyl chloride in trifluoroethanol. These two cases show, however, a lower ratio (*ca.* 6:1 and 2:1, respectively) of rates of covalent recombination to solvolysis for the ion pairs produced

(1) For a recent discussion of the evidence relating to the importance of ion pairs in solvolysis see S. Winstein, B. Appel, R. Baker, and A. Diaz, "Organic Reaction Mechanism," Special Publication No. 19, The Chemical Society, London, 1965, p 109.

(2) For references to the use of trifluoroacetic acid as a solvolysis medium see P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Amer. Chem. Soc.*, **89**, 5902 (1967).

(3) M. J. S. Dewar and R. C. Fahey, *Angew. Chem. Intern. Ed. Engl.*, 3, 245 (1964).

(4) The reaction of diazoneopentane with carboxylic acids in ether[5] which leads to 99% rearranged products probably involves the production of tight ion pairs in which the rearrangement is faster than recombination, despite the low dielectric constant of the solvent and the fairly high nucleophilicity of the counter ion.

(5) D. Y. Curtin and S. M. Gerber, *J. Amer. Chem. Soc.*, **74**, 4052 (1952).

(6) If the $R^+OH_2{}^-OBs$ ion pairs dissociate before the C–O bond of ROH_2^+ ionizes then the free carbonium ion rather than the water-separated ion pair would be produced in the rate-determining step. We believe that the dissociation does not precede C–O bond cleavage because the low dielectric constant (8.42, 20°)[7] of the TFA solvent does not support extensive ion dissociation.[8] In any event, the results are *consistent* with return from the water-separated ion pair being slow.

(7) W. Dannhauser and R. H. Cole, *J. Amer. Chem. Soc.*, **74**, 6105 (1952).

(8) J. H. Simons and K. E. Lorentzen, *ibid.*, **74**, 4746 (1952).

(9) We do not mean to indicate that $R^+OH_2{}^-OBs$ is identically the same species as $R^+HO_2CCF_3{}^-OBs$ but both can be represented by the general notation $R^+\,|\!|\,\bar{O}Bs$ and their relative rates of dissociation and recombination in the same solvent should be similar. Also, $R^+\bar{O}Bs$ may not be *exactly* the same species (in terms of conformation and solvation especially) when formed by proton transfer from HOBs to propene as when produced by ionization of ROBs; the differences are probably slight, however, and $R^+\bar{O}Bs$ from the latter source should not be any *less* likely to recombine than that from the former.

(10) A. Streitwieser, Jr., and G. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969).

(11) V. J. Shiner, Jr., M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *J. Amer. Chem. Soc.*, **90**, 7171 (1968).

(12) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *ibid.*, **91**, 4838 (1969).

(13) V. J. Shiner, Jr., W. L. Buddenbaum, B. L. Murr, and G. Lamaty, *ibid.*, **90**, 418 (1968).

(14) T. Koenig and R. Wolf, *ibid.*, **91**, 2569 (1969).

(15) V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *ibid.*, **85**, 2413 (1963).