of only $\bar{1}$ symmetry. H_2TTP does not sit at, nor is it structurally near, a site of $\bar{4}$ symmetry, as found for tetragonal H_2TPP where amino hydrogen disorder is crystallographically imposed and there is consequently a symmetric double-minimum potential. Significant perturbations from various 4-fold symmetries include slightly different orientations of the two independent phenyl groups (see Figure 1) and a pattern of atomic displacements from the least-squares plane of the 24-atom porphyrin skeleton (maximum deviation 0.044 Å, mean absolute deviation 0.021 Å) that lacks any 4-fold symmetry. The most important deviations from 4-fold symmetry are the trans annular and adjacent N···N separations given above. The structure of H_2TTP is, therefore, *less symmetrical* than that of triclinic H_2TPP. Thus the symmetric double-minimum potential apparently present for monoclinic H_2TTP, if it is symmetric, is only accidentally so.

We have examined the structures of the symmetrically substituted porphyrins, tetragonal ($\bar{4}$) H_2TPP,[18] triclinic ($\bar{1}$) H_2TPP[17] and H_2OEP,[22] monoclinic ($\bar{1}$) H_2TTP and H_2TPrP,[23] and monoclinic (no symmetry imposed) H_2P,[19c] for clues to proton order and disorder and as to the nature of the reaction coordinate in the proton migration. The adjacent protons in H_4TPP^{2+}[24] lead to a highly domed structure. There is not room in the crystal lattice for this type of distortion and no abnormal thermal motion parameters are shown perpendicular to the plane of the porphyrin in any of the above structures. This precludes a stepwise migration via path B of Scheme I (predicted by high-temperature CNDO calculations[13b]). The molecular packing coefficients[20b] of the above materials do not show any trends: both modifications of H_2TPP have a packing coefficient of 0.75. For H_2TTP the value is 0.71, for H_2OEP 0.70, and for H_2TPrP 0.77, while for H_2P[19c] the value is 0.80. Neither nearly planar nor substantially buckled porphyrin skeletons are associated with the presence of proton order or disorder.

We do find two clues as to the nature of the reaction coordinate. First, in contrast to the symmetrical placement of the amino hydrogen atoms in triclinic H_2TPP and the equivalence in separations between these nitrogen atoms, no such symmetry is apparent for H_2TTP. The two pairs of H–N–C_a bond angles are both 124 (2)° and 128 (2)°. When combined with the asymmetrical N···N separations, N1···H2 separations of 2.33 (3) and 2.44 (3) Å and N2···H1 separations of 2.40 (3) and 2.40 (3) Å result. A similar bending was observed for H_2P.[19c] Thus one conformation of lowest energy in the solid state lies partway along a plausible proton-transfer reaction coordinate that involves the asymmetric N–H bending mode.

The second clue, of greater statistical significance, is the cis-annular N···N separations. The triclinic form of H_2TPP entombs the equilibrium geometry of one of the two degenerate tautomers of the solution state where the nitrogen atoms form a rhombus, analogous to an ordered Jahn–Teller system. Tetragonal H_2TPP represents the disordered Jahn–Teller-type system in the crystalline state. In monoclinic H_2TTP the molecule, with its lower symmetry than both of the above, appears to be held in a nonequilibrium conformation of the solution state that, as previously noted, may lie on the reaction coordinate to the transition state between one tautomer and the other in solution. In those porphyrin structures examined to date ordered protons are found where crystal packing is accompanied by a symmetrical rhombic (but not square) arrangement of nitrogen atoms.

The trans-annular separation of the nitrogen atoms provides a clue as to the origin of the degree of proton disorder in triclinic H_2TPP (K = 0.149, 302 K[15]) and monoclinic H_2TTP (K = 1). The amino nitrogen separations are 4.20 and 4.154 Å; the imino nitrogen separations 4.06 and 4.079 Å, respectively. This expansion of some 0.02 Å on the short axis, coupled with slightly asymmetric proton placement, provides sufficient space on the short axis for two trans protons to fit without significant unfavorable van der Waals interaction.

It appears that the crystal packing forces in free-base porphyrins can entomb any of a variety of closely related molecular conformations. Subtle differences in these structures will control the characteristics of the N–H tautomerism in the solid state and a clear understanding of these structures is required for an interpretation of any kinetic solid-state effect observed. We are pursuing low-temperature X-ray diffraction and neutron diffraction studies on these free-base porphyrins in order to obtain structures of the required detail and accuracy.

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Supplementary Material Available: Tables of final atomic positions, isotropic temperature factors, anisotropic thermal parameters for non-hydrogen atoms and structure factor amplitudes for H_2TTP (12 pages). Ordering information is given on any current masthead page.

(22) Lauher, J. W.; Ibers, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 5148–5152.
(23) Codding, P. W.; Tulinsky, A. *J. Am. Chem. Soc.* **1972**, *94*, 4151–4157.
(24) Stone, A.; Fleischer, E. B. *J. Am. Chem. Soc.* **1968**, *90*, 2735–2748.

Iron/Copper Promoted Fragmentation Reactions of α-Alkoxy Hydroperoxides. The Conversion of Octalins into 14-Membered Ring Macrolides

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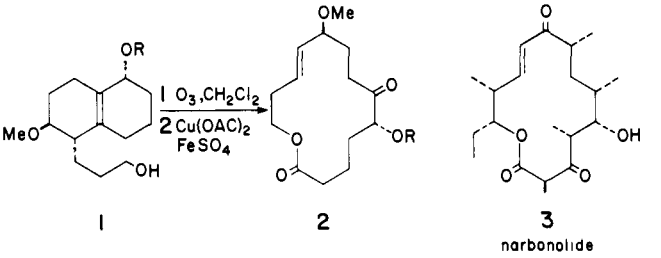
There has been considerable interest in recent years in the field of macrolide synthesis. The attractive features of the macrolides include their unusual structure as well as their ability to inhibit bacterial protein synthesis.[1] Macrocyclization techniques represent the most common method of forming the lactone ring, and these have been employed in the synthesis of many members of this class.[2,3] Nevertheless, the success of these cyclization procedures would appear to be strongly correlated to the substitution pattern of the acyclic precursor.[4] Convincing evidence for this was provided by the investigations of Woodward et al.[5b] which culminated in the synthesis of erythromycin A.[5]



(1)

(1) Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. "The Molecular Basis of Antibiotic Action", 2nd ed.; Wiley Interscience: New York, 1981; Chapter 6.
(2) For reviews, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (c) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (d) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23.
(3) For syntheses of macrolides and their aglycones see ref 4[3a] in the report of a new methymycin synthesis: (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303. (b) Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312.
(4) (a) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Reference 2b, p 591.
(5) (a) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (b) Woodward, R. B.; et al. *Ibid.* **1981**, *103*, 3213. (c) Woodward, R. B.; et al. *Ibid.* **1981**, *103*, 3215.

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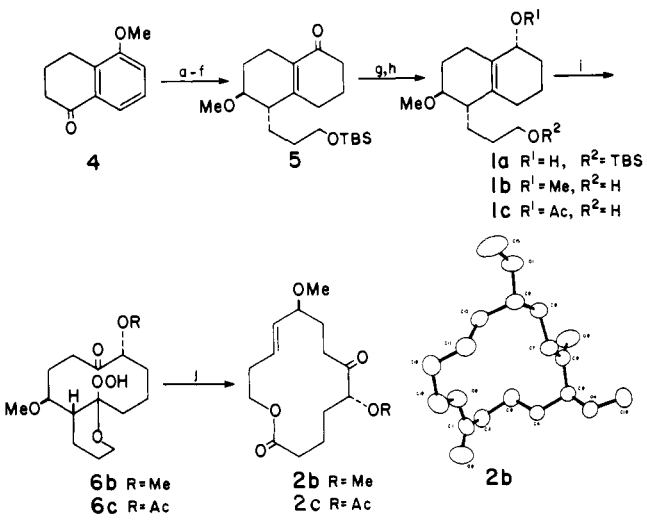
Scheme I[a]

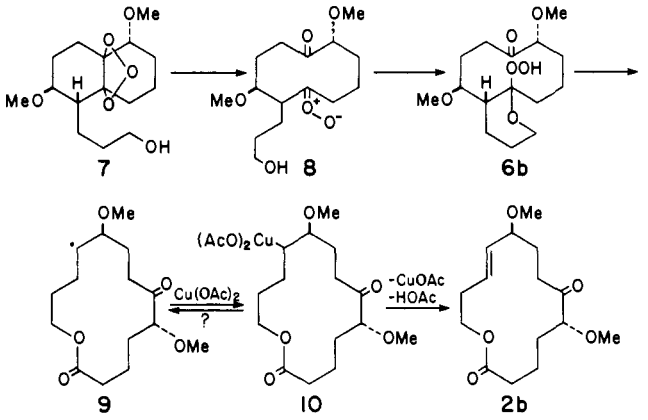


[a] (a) $Br(CH_2)_3OTHP$, Li, sonication, THF, 25 °C, 88%. (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 72%. (c) $BH_3 \cdot Me_2S$, THF, 25 °C; H_2O_2, NaOH, 0 °C, 82%. (d) NaH, MeI, DME, 85 °C, 96%. (e) Li, NH_3/THF/EtOH (40:1:10); 10% HCl/THF (1:1) 3 h, 25 °C, 58%. (f) *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2, room temperature, 91%. (g) $LiAlH_4$, THF, −78 °C (1a), 78%. (h) 1b: (d); *n*-Bu_4NF, THF, 61%. 1c: Ac_2O, Et_3N, CH_2Cl_2; *n*-Bu_4NF, THF, 98%. (i) O_3, CH_2Cl_2, −78 °C; 6b, 89%, 6c, 83%. (j) $Cu(OAc)_2$, $FeSO_4$, MeOH, 25 °C; 2b, 83%; 2c, 78%.

Fragmentation and/or ring expansion routes to macrolides from polycyclic systems exist that can be employed in the preparation of macrolides of varied ring sizes.[2,6,7] One such method, which employs the metal ion promoted fragmentation reactions of α-alkoxy hydroperoxides,[8] serves as the subject of this report. For application to the synthesis of complex members of this class, the polycyclic precursor must be easily obtained by a route that allows for stereocontrolled introduction of substituents. Herein we report on the preparation of a $\Delta^{9,10}$-octalin and a peroxide-mediated fragmentation/ring expansion reaction sequence to the trans-$\Delta^{10,11}$-14-membered macrolide ring system common to several macrolide antibiotics.

The $\Delta^{9,10}$-octalins employed in this study were prepared from 5-methoxy tetralone as outlined in Scheme I. Reduction of enone **5**, prepared in seven steps from tetralone **4**, with lithium aluminum hydride in THF at −78 °C afforded a 4:1 mixture of **1a** and the diastereomeric β-alcohol. The major alcohol could be separated from its epimer by flash chromatography[9] and was employed as the test substrate in subsequent transformations. Ozonolysis in methylene chloride of the methyl ether **1b** or acetate **1c** provided

Scheme II



the α-hydroperoxytetrahydropyrans **6b** (mp 123–125 °C) and **6c** (mp 142–143 °C) in 89% and 83% yields, respectively.[10] The 10-membered ring peroxides could be purified by silica gel chromatography for characterization purposes. Subsequent fragmentation with cupric acetate and ferrous sulfate in methanol was most conveniently performed directly following ozonolysis (without chromatography) and provided the *trans*-$\Delta^{10,11}$ macrolides **2b** (mp 75.5–76 °C) and **2c** (mp 75–76 °C) in 75–80% yields from **1b** and **1c** and with ≥20:1 regio- and stereocontrol.[11] The structure and stereochemistry of macrolide **2b** was secured through crystallographic analysis (see ORTEP in Scheme I).[12] The location of the olefin in the macrolide product indicates the reaction process could be employed in the synthesis of narbonolide **3**[13] and related congeners as indicated in eq 1.

The design of the macrolide-forming reaction was based upon several previously reported observations from these laboratories. Allylic acetates had been shown to direct the breakdown (retro 2 + 3) of primary ozonides analogous to **7** produced in the ozonolysis reaction.[8c,14] A parallel study of an octalin that lacks this group (**1c'**, AcO is replaced by H) indicates that an allylic electron-withdrawing substituent (acetoxy or methoxy) is required as a regiocontrol device, since this substrate gives rise to several products when subjected to the ozonolysis protocol. In the case of ozonide **7**, the carbonyl oxide **8** was anticipated on consideration of the electron-withdrawing properties of the allylic methoxy group. Intramolecular alcohol trapping of the carbonyl oxide via a 1,3-addition results in the formation of the carbon–oxygen ring bond and can be considered as an equivalent to the lactonization step in macrocyclization strategies.[15]

In an earlier study that resulted in a synthesis of the 12-membered macrolide recifeiolide, we employed the reagent combination of cupric acetate and ferrous sulfate as a means of affecting peroxide fragmentation with regio- and stereocontrolled olefin formation.[8b] Treatment of **6b** in methanol saturated with cupric acetate with a methanolic solution of ferrous sulfate was expected to afford the 14-membered carbon radical **9** by way of the alkoxy radical. Selectivty in the olefin formation could arise from a hydrogen atom abstraction by the d^9 radicaloid copper acetate reagent or by prior σ-bond formation to provide the organocopper(III) intermediate **10** with subsequent syn β-hydrogen elimination to produce **2b** (Scheme II).[8b,16] The coordination of copper in **10** with the β-methoxy substituent at C_9 would result

(6) For recent examples, see: (a) Corey, E. J.; Brunelle, D. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1977**, *99*, 7359. (b) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075. (c) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. (d) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860. (e) Sternbach, D.; Shibuya, M.; Jaisli, F.; Bonetti, M.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 634 636. (f) Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008. (g) Kostova, K.; Lorenzi-Riatsch, A.; Nakashita, Y. Hesse, M. *Helv. Chim. Acta* **1982**, *65*, 249. (h) Cookson, R. C.; Ray, P. S. *Tetrahedron Lett.* **1982**, *23*, 3521. (i) Kostova, K.; Hesse, M. *Helv. Chim. Acta* **1983**, *66*, 741. (j) Aono, T.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 1448. (k) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.

(7) For examples of peroxide mediated fragmentation routes to macrolides, see: (a) Borowitz, I. J.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G. J. *J. Org. Chem.* **1966**, *31*, 3032. (b) Borowitz, I. J.; Williams, G. J.; Gross, L.; Rapp, R. *J. Org. Chem.* **1968**, *33*, 2013. (c) Borowitz, I. J.; Williams, G. J.; Gross, L.; Beller, H.; Kurland, D.; Sucia, N.; Bandurco, V.; Rigby, R. D. G. *J. Org. Chem.* **1972**, *37*, 581. (d) Borowitz, I. J.; Bandurco, V.; Heyman, M.; Rigby, R. D. G.; Ueng, S.-N. *J. Org. Chem.* **1973**, *38*, 1234. (e) Story, P. R.; Busch, P. *Adv. Org. Chem.* **1972**, *8*, 67.

(8) The first example of macrolide synthesis through the fragmentation of an α-alkoxy hydroperoxide (Na_2SO_3/$NaHSO_3$) was achieved by Ohloff and v. Becker and resulted in an industrial synthesis of exaltolide: (a) v. Becker, J.; Oholff, G. *Helv. Chim. Acta* **1971**, *54*, 2889. See also: (b) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163. (c) Schreiber, S. L.; Liew, W.-F. *Tetrahedron Lett.* **1983**, *24*, 2363.

(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(10) Compounds **6b** and **6c** exist as diastereomeric mixtures of two anomers. Melting points refer to the major anomer in each case.

(11) Based on high-field NMR analysis.

(12) See supplementary material for the fractional coordinates, temperature factors, bond distances, and bond angles for compound **2b**.

(13) The synthesis of narbonolide has been recorded: Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

(14) (a) Schreiber, S. L., Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 4889.

(15) Carman, R. M.; Cowley, D. E. *Tetrahedron Lett.* **1968**, 2723.

(16) (a) Kochi, J. K. "Free Radicals"; Wiley-Interscience: New York, 1973; Vol. 1, Chapter 11, Vol. 2, Chapter 23. (b) Kochi, J. K.; Bemis, A.; Jenkins, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 4038, 4616. (c) Walling, C.; El-Taliawi, G. M.; Amarnath, K. *J. Am. Chem. Soc.* **1984**, *106*, 7573.

in a chelated complex with a hydrogen at C_{11} properly aligned for syn elimination (to provide the trans allylic ether). Elimination toward the methoxyl would be disfavored since the carbon–hydrogen bond at C_9 cannot achieve syn-coplanarity with the C_{10}–copper bond in the chelated complex. Indeed, the fragmentation of the hydroperoxide that lacks this methoxyl substituent (**6c'**, MeO is replaced by H) resulted in the formation of all four possible olefin-containing macrolides.[17]

The conversion of octalin **1** into the 14-membered macrolide **2** provides an indication of the regio- and stereocontrolling elements required for the implementation of this new strategy for macrolide synthesis. To reach the intended goal of complex macrolide synthesis, we are in need of methods for the stereocontrolled synthesis of $\Delta^{9,10}$-octalin systems. Studies that pertain to this issue are currently under way and will be reported in due course.

Acknowledgment. This investigation was supported by the Institute for General Medical Sciences of the National Institutes of Health (GM-30378) to whom we are grateful. We thank the Chicago Community Trust/Searle Scholars Program and the Camille and Henry Dreyfus Foundation, Inc. (Dreyfus Teacher-Scholar Grant) for additional support. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by the NSF Chemistry Division Grant CHE 7916210. The x-ray crystallographic analysis was performed by Dr. Brigitte E. Segmuller.

Supplementary Material Available: Experimental procedures and spectroscopic data for all new compounds, as well as crystallographic data for compound **2b**[12] (22 pages). Ordering information is given on any current masthead page.

(17) Four macrolides are produced in a 12:2:1:1 ratio. On hydrogenation (H_2, Pd/C, EtOAc) a single saturated macrolide was obtained, indicating the fragmentation products are olefin isomers.

Synchrotron Light Source Applied to Measuring the Vacuum Ultraviolet Circular Dichroism of Heparin

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Heparin[2] is a glycosaminoglycan widely used therapeutically as an anticoagulant and antilipemic agent. It is a linear alternating copolymer of a hexosamine and uronic acid, with a predominant repeating disaccharide unit (Figure 1) of 2-sulfamino-2-deoxy-α-D-glucopyranosyl-6-sulfate and α-L-idopyranosyluronic acid 2-sulfate with both linkages being (1→4). Substantial microheterogeneity exists, the major features of which include the occurrence of β-D-glucopyranosyluronic acid as a minor uronic acid component, the occurrence of 2-acetamido-2-deoxy-α-D-glucopyranose as a minor hexosamine component, incomplete sulfation, with the number of sulfate groups per disaccharide ranging from approximately 2.0 to 2.5, and molecular weight polydispersity, with mean molecular weights in the range of 8000 to 15000.

Circular dichroism (CD), applied to saccharides, has been shown to be sensitive to anomeric configuration, linkage type, and orientation of substituents on the sugar ring.[3] Extension of CD measurements to the vacuum ultraviolet region allows ring transitions to be observed directly. The vacuum ultraviolet circular dichroism (VUCD) of chondroitin and chondroitin-6-sulfate[4] has previously been measured and is of particular relevance to the present study. This report represents the first measurement of saccharide CD using synchrotron radiation[5] as a light source and the first observation of a 175-nm CD band in glycosaminoglycans.

The heparin sample (pig mucosa, Na salt, Sigma) contained 17.1% water (carbon analysis) and 2.28 sulfate groups per disaccharide (sulfur analysis) (disaccharide mol wt 578). Spectra were obtained on two instruments. One[5-7] uses radiation from

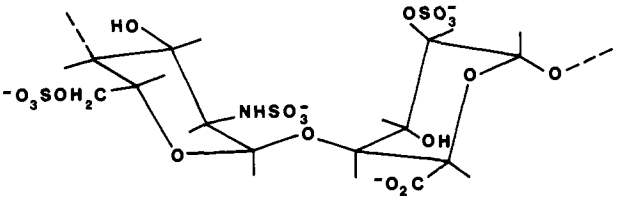

Figure 1. Dominant repeating disaccharide unit in heparin.

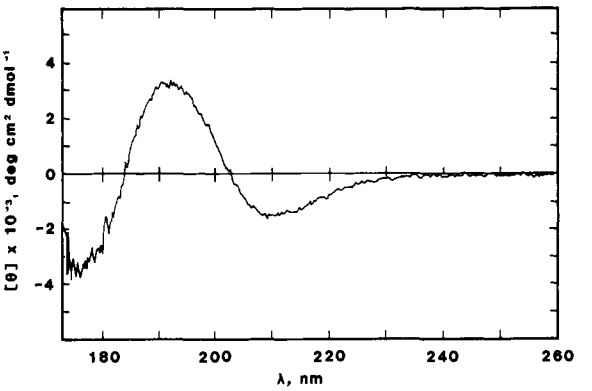

Figure 2. Circular dichroism of heparin (D_2O, 25.5 mg/mL, 0.050-mm pathlength). Molar ellipticity, [θ], is given per disaccharide.

Table I. CD Summary of Heparin and Chondroitinsulfate

compound	[θ],[a] 10^3 deg cm^2 dmol^{-1} n–π*	π–π*	175 nm	ref
heparin	−1.58	+3.37	−3.47	present work
	−1.9	+2.8		9[b]
	−2.74	+3.48		10[c]
	−1.45	+2.8		10[c]
	−1.28	+2.58		13[d]
	−1.8	+3.28		13[d]
chondroitin	−6.5	−2.5	−8.0	4
	−6.8			10
	−6.7			14, 15[e]
chondroitin-6-sulfate	−6.8	−2.5	−4.6	4
	−5.9			10
	−6.78			16[f]
	−11.2	−7.1		13

[a] Molar ellipticity, per disaccharide. [b] Boyd and Williamson[9] report molar ellipticities per tetrasaccharide; their values are reduced by $^1/_2$ for proper comparison. [c] Park and Chakrabarti[10] measured two heparins from different sources. See also ref 11 and 12. [d] Stone[13] measured two heparins differing in source. [e] Values reported in ref 14 are corrected in ref 15. [f] Eyring and Yang[16] report molar ellipticities per monomer molecular weight; their values are doubled for proper comparison.

(1) (a) State University of New York. (b) National Institute of Medical Research. (c) Brookhaven National Laboratory.
(2) Casu, B. *Adv. Carbohydr. Chem. Biochem.*, in press.
(3) Morris, E. R.; Frangou, S. A. In "Techniques in Carbohydrate Metabolism"; Elsevier: London, 1981; B308, 109–160.
(4) Stipanovic, A. J.; Stevens, E. S. *Biopolymers* **1981**, *20*, 1565–1573.
(5) Sutherland, J. C.; Desmond, E. J.; Takacs, P. Z. *Nucl. Instrum. Methods* **1980**, *172*, 195–199.
(6) Sutherland, J. C.; Griffin, K. P.; Keck, P. C.; Takacs, P. Z. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4801–4804.
(7) Sutherland, J. C.; Griffin, K. P. *Biopolymers* **1983**, *22*, 1445–1448.

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