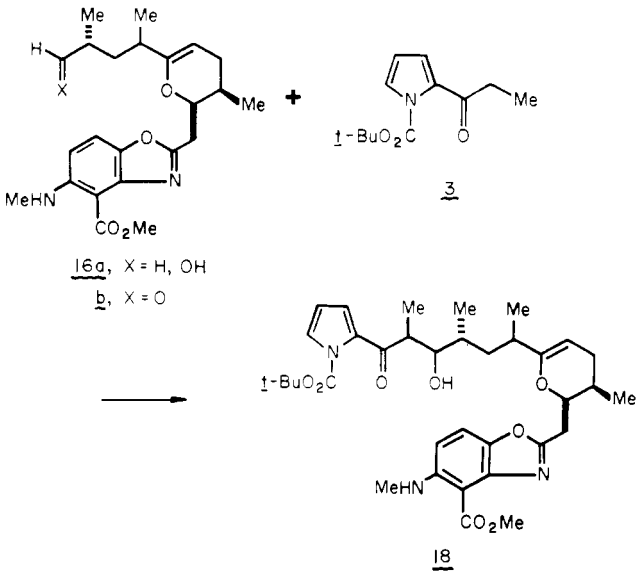

HMPA.[26] Synthetic **1a**,[11] mp 184.5–186 °C, $[\alpha]^{24}_D$ −56° (*c* 0.010, $CHCl_3$),[27] was identical in all respects (IR, UV, MS, ^1H NMR, ^{13}C NMR, $[\alpha]_D$, mixture melting point) with an authentic sample of A-23187. This study establishes the absolute configuration of A-23187 as that depicted in structure **1a.**

Further studies are in progress to enhance the aldol diastereoselection (**3** + **16** → **18**) via the use of boron enolates.[28]

Acknowledgment. Support from the National Institutes of Health and the Eli Lilly Company is greatly appreciated.

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(12) **1b:** IR 3440, 1715, 1635, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.2 (1 H, br s), 7.83 (1 H, br s), 7.61 (1 H, d, *J* = 9 Hz), 6.89 (2 H, m), 6.65 (1 H, d, *J* = 9 Hz), 6.20 (1 H, m), 3.95 (3 H, s), 2.94 (3 H, d, *J* = 3 Hz). **5b:** IR 1725, 1695, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (1 H, d, *J* = 9 Hz), 7.22 (1 H, d, *J* = 9 Hz), 3.99 (3 H, s), 3.33 and 3.49 (3 H, s), 2.70 (3 H, s). **7:** ^1H NMR (CCl_4) δ 7.2–7.9 (10 H, m), 3.50 (1 H, d of d, *J* = 9.9, 5.0 Hz), 3.46 (1 H, d of d, *J* = 9.9, 6.3 Hz), 3.27 (2 H, d, *J* = 5.5 Hz), 1.69 (1 H, m), 1.07 (9 H, s), 0.97 (3 H, d, *J* = 6.8 Hz). **8:** ^1H NMR (CCl_4) δ 7.23 (5 H, s), 4.39 (2 H, s), 3.29 (1 H, d of d, *J* = 9.2, 5.6 Hz), 3.19 (2 H, *J* = 5.6 Hz), 3.16 (1 H, d of d, *J* = 9.2, 6.3 Hz), 1.70 (1 H, m), 0.94 (3 H, d, *J* = 6.1 Hz). **11b:** ^1H NMR (CCl_4) δ 7.2–7.8 (10 H, m), 3.2–3.7 (2 H, m), 2.28 (6 H, s), 1.74 (3 H, s), 1.04 (9 H, s), 0.97, 0.94, and 0.92 (6 H, d, *J* = 6.8, 8.4, and 8.4 Hz). **12:** IR 1707 cm^{-1}; ^1H NMR (CCl_4) δ 7.0–7.9 (10 H, m), 7.22 (5 H, s), 4.39 (2 H, s), 3.41 (2 H, d, *J* = 5.4 Hz), 3.20 (2 H, d, *J* = 5.4 Hz), 1.09 (9 H, s). **13b:** IR 1723 cm^{-1}; ^1H NMR (CCl_4) δ 9.54 and 9.58 (1 H, d, *J* = 2.0 and 2.0 Hz), 7.1–7.8 (10 H, m), 2.9–3.8 (6 H, m), 1.08 (9 H, s). **14a:** IR 3340, 1729, 1701, 1567, 1562, 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1–8.0 (12 H, m), 2.8–4.6 (10 H, m), 3.94 (3 H, s), 3.33 (3 H, s), 1.09 (9 H, s).
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(21) HPLC conditions: column, Altex LiChrosorb Si 60, 5μ (10 mm × 25 cm); solvent, 35% ethyl acetate–hexane; flow rate, 5.0 mL/min; t_R(**14a**) = 19 min, t_R(**14b**) = 17.9 min.
(22) Ketone **3** (R = *t*-BOC), mp 57.5–58.5 °C, was prepared from **3** (R = H)[9] and KO-*t*-Bu (THF) and $(t\text{-}BuO_2C)_2O$ in 85% yield. The resultant zinc enolate was prepared by successive treatment of **3** (R = *t*-BOC) with LDA (−78 °C, Et_2O) followed by anhydrous $ZnCl_2$ (1 equiv) and dimethoxyethane (DME).
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Preparation and Properties of a Chlorophyllide–Apomyoglobin Complex

Sir:

The spectroscopy of large molecules like chlorophyll poses a number of problems because it is difficult to obtain a transparent host matrix for single-crystal optical and magnetic resonance investigations. In order to surmount this problem we have pursued the simple subterfuge of substituting chlorophyll derivatives in the place of heme in the protein apomyoglobin (apoMb). Myoglobin (Mb) is ideal because it is available in large quantities, is readily crystallizable, and has a very well-characterized crystal structure.[1,2] Our goals are to determine precisely the geometric relationships between the chlorophyll molecular structure and (1) the orientations of transition dipole moments for the lowest singlet excited states, (2) the principal axis systems of the **g** and hyperfine tensors in the radical ions, and (3) the principal axis system of the zero-field tensor in the lowest triplet excited state. Each of these relationships is required for an analysis of recent photoselection experiments on bacterial photosynthetic reaction centers.[3-7] A single crystal of this type is very well suited for studies of energy transport, since the chromophores should interact weakly and are regularly separated (in this respect the protein host is much superior to typical lattices, because of the large size of the unit cell and regular site substitution). Furthermore, a well-defined water-soluble chlorophyll–protein complex offers many interesting possibilities for electrochemical and photochemical studies. We report here the preparation and characterization of the complex in solution.

Zinc[8] or magnesium pyrochlorophyllides[9,10] (R_1 in Figure

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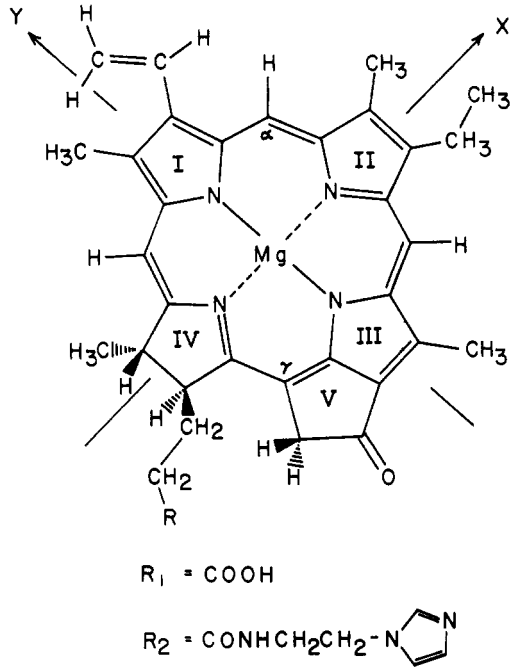

Figure 1. Structure and numbering system for pyrochlorophyll derivatives. Y and X label the commonly assumed orientations for the transition dipole moments of the first and second singlet excited states, respectively.

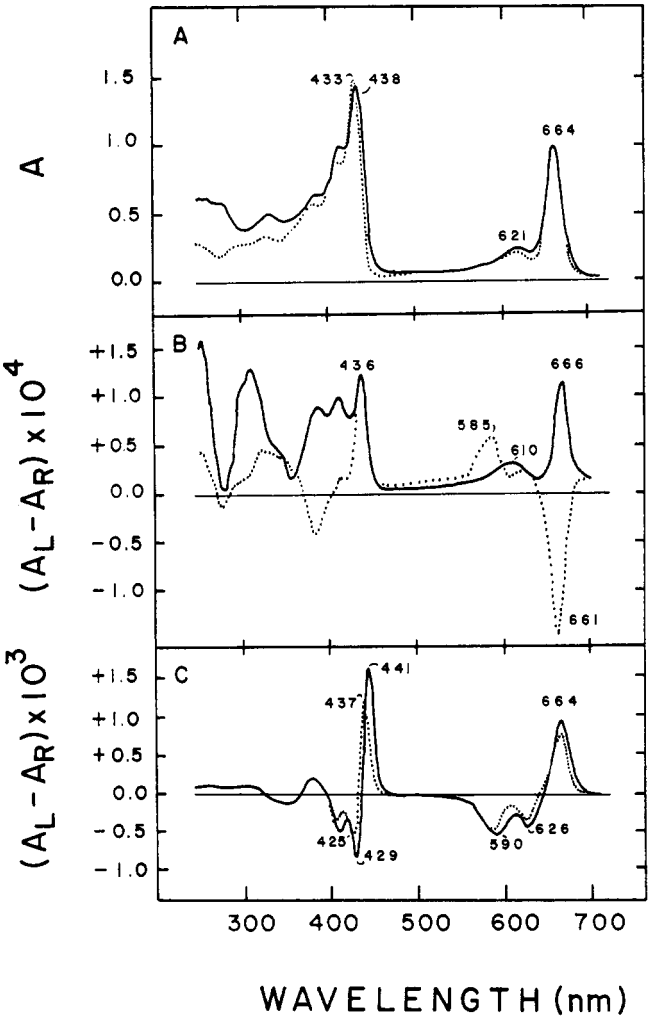

Figure 2. Comparison of (A) electronic absorption, (B) circular dichroism, and (C) magnetic circular dichroism spectra (15-Kg external magnetic field, corrected by subtracting CD), 1-cm path length at 20 °C for (—) Mg-PChl-Mb, 10^{-5} M in H_2O, and (···) Mg-Pimc, 10^{-5} M in CH_2Cl_2.

1, Zn- or Mg-PChl), the corresponding metalated protoporphyrins IX,[8,11] and apoMb[12] (horse heart or sperm whale) are prepared by well-known methods. Reconstitution follows established literature procedures.[13] The product is purified on a Sephadex G-25 column, followed by elution at pH 7.0 from a CM-52 ion-exchange column (see below). The following nomenclature is used in this paper for these green proteins: Zn- or Mg-PChl-Mb for the zinc- or magnesium-pyrochlorophyllide-apoMb complexes.[14] Appropriate model compounds for histidine ligation in the protein are Zn- or Mg-PChl coupled[15] to 3-(1-imidazolyl)propylamine[16-18] (R_2 in Figure 1, Zn- or Mg-Pimc).

In addition to the spectroscopic evidence presented below, several analytical methods have been used to prove that the PChl is bound in the heme pocket. After being exhaustively dialyzed against deionized water, lyophilized at 10^{-3} Torr, weighed, and redissolved in water, Zn-PChl-Mb exhibits an extinction coefficient at 661 nm of $5.7 \pm 0.2 \times 10^4$ cm^{-1} M^{-1}. This compares with an extinction coefficient for Zn-Pimc of $6.5 \pm 0.2 \times 10^4$ cm^{-1} M^{-1}, suggesting that a 1:1 complex has been formed. When native Mb is mixed with Zn-PChl under the conditions of reconstitution, the electronic absorption spectrum of the eluate from the Sephadex column shows that ~20% of the protein contains Zn-PChl. However, after eluting from the CM-52 column, the Zn-PChl is quantitatively removed, giving native Mb. From this we conclude that it is possible to bind additional Zn-PChl on the protein surface, but an ion-exchange column removes the loosely bound chromophore. It has been known for many years that the dye 1-anilino-8-naphthalenesulfonate (ANS) binds selectively in the heme pocket of apoMb.[19] When Zn-PChl-Mb is treated with ANS in phosphate buffer under conditions suitable for ANS insertion, the ANS is recovered quantitatively by dialysis. We conclude that no vacant binding sites are available, and, taken together, these experiments prove that the chlorophyllide is substituted for hemin in our complex.

The electronic absorption, circular dichroism, and magnetic circular dichroism spectra of Mg-PChl-Mb and Mg-Pimc are compared in Figure 2. The absorption and fluorescence (not shown) spectra are very similar, indicating that the chromophore is found in monomeric form in a nonpolar environment.[20] It is seen in Figure 2B that the CD associated with each transition is profoundly affected by the presence of the protein. In particular the rotation associated with the main red band at 664 nm is inverted and shifted when the chromophore is in the protein. This contrasts with the MCD spectra, which are virtually identical (Figure 2C).

A variety of factors can be considered to explain the CD spectra. We have shown (unpublished results) that the imidazole in Mg-Pimc coordinates specifically on the side of the macrocycle from which it emerges at the asymmetric center at position 7 (see Figure 1); this could be opposite to that in the protein. However, the CD spectra of solutions of monomeric Mg-PChl in ether[21] and pyridine, where the ligand is bound on either or both sides, are very similar to that of Mg-Pimc. Instead, it is reasonable to suggest that the observed change is a consequence of the interaction between the chiral chromophore and the chiral environment found in the protein. It is well known that the protein imparts an asymmetry to nonchiral chromophores, but we are surprised that this effect is sufficient to reverse the large intrinsic rotation of the Mg-PChl chromophore. This result is significant because CD has been used extensively as a probe for interchromophore exciton coupling in intact photosynthetic organisms, reaction centers, and antenna chlorophyll-protein complexes.[22-24] The analysis of this effect assumes that the chirality of the protein plays a

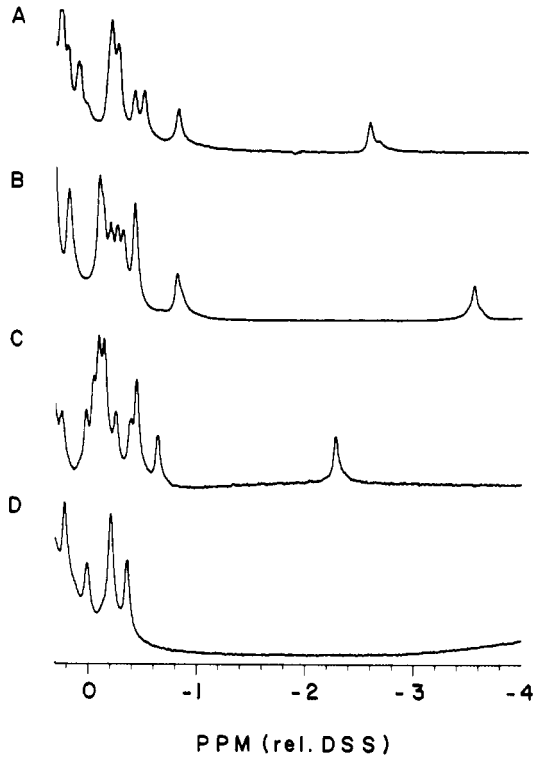

Figure 3. High-field region of the 360-MHz ^{1}H NMR spectra of (A) Mg-PChl-Mb, (B) Mg-Mb (Mg replaces Fe in reconstituted Mb), (C) CO-Fe(II)-Mb, (D) apoMb (all $\sim 10^{-3}$ M in D_2O at 20 °C).

negligible role compared with interchromophore interactions, which can be analyzed with the well-established exciton-CD formalism.[25] Although the particular effects that we observe in Mg-PChl-Mb are not transferable to photosynthetic reaction centers, the chromophores are believed to interact with proteins in vivo, and Figure 2B shows that the consequences cannot be ignored.[26] The MCD spectra arise from the asymmetry imposed by the externally applied field. The close similarity of the MCD spectra for Mg-PChl-Mb and Mg-Pimc may therefore be taken as further evidence that the protein has little effect on the properties of the ground or excited singlet electronic states of the chromophore.[27]

The high-field portion of the 360-MHz ^{1}H NMR spectra of Mg-PChl-Mb, Mg-myoglobin (reconstituted Mb where Mg replaces Fe), diamagnetic CO-Fe(II)-Mb, and apoMb are compared in Figure 3.[28] For CO-Fe(II)-Mb, transitions in this region are ascribed to the effect of the diamagnetic anisotropy of the macrocycle on nearby amino acid residues, notably the valine E-11 methyl protons on the distal side.[29-31] Similarly shifted peaks are observed for our complexes, providing a very sensitive test for the integrity of the complex. The shifts caused by the ring current of Mg-PChl are smaller than those due to Mg-protoporphyrin IX by $\sim$1 ppm (compare Figures 3A and 3B). Recently LaMar and co-workers[32] have elegantly demonstrated that the heme in reconstituted Mb is disordered in the sense that the heme may adopt two distinguishable orientations in the pocket (one strongly predominates). Similarly, Mg-PChl could assume either of two orientations differing by rotation about the α-γ axis (see Figure 1). On the assumption that the orientation of Mg-PChl is otherwise the same as for heme, this would place valine E-11 in close proximity with either ring I or II. The chlorin ring current is less symmetric than that for a porphyrin for rotation about this axis; consequently we might expect to detect two sets of shifted protons. This may be the origin of the small shoulder on the upfield side of the peak at -2.7 ppm in Figure 3A. Much more detailed NMR studies are underway to resolve this question and specify the absolute orientation of the chromophore.[33]

In conclusion, the properties of Mg-PChl in Mb are remarkably similar to those in organic solvents, with the exceptions of the CD spectrum and the triplet state ESR parameters.[27] These molecules are the first well-defined chlorophyll-protein complexes containing a single chromophore[34] and promise to be most useful for single crystal spectroscopy (suitable crystals are in hand). Parallel work with the bacteriochlorophyllides and other chlorophyll derivatives is underway and will be reported shortly.

Acknowledgment is made to Ruth Records in Professor Djerassi's laboratory for the CD and MCD spectra. We thank Professors Hodgson, LaMar, Marshall, and Stryer for very helpful discussions. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Stanford Institute for Energy Studies, and the Science and Education Administration of the U.S. Department of Agriculture under Grant No. 5901-0410-8-0147-0. The 360-MHz NMR spectra were obtained at the Stanford Magnetic Resonance Laboratory supported by National Science Foundation and National Institutes of Health Grants GR23633 and RR00711, respectively. S.G.B. is a Fellow of the Alfred P. Sloan Foundation.

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(27) The zero-field splittings of the lowest photoexcited triplet state have been measured: Mg-PChl-Mb, $|D|/hc = 0.0297 \pm 0.003$ cm^{-1}, $|E|/hc = 0.0035 \pm 0.0003$ cm^{-1}; Mg-Pimc, $|D|/hc = 0.0273 \pm 0.0003$ cm^{-1}, $|E|/hc = 0.0039 \pm 0.0003$ cm^{-1}. In addition to these differences, substantial differences in spin polarization are observed, which will be reported shortly (Boxer, S. G.; Wright, K. A., unpublished results).
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(33) Rotation about the α–γ axis exchanges the orientation commonly associated with the directions of the two principal transition dipole moments of the chlorophylls (labeled X and Y in Figure 1), which would complicate single-crystal polarized absorption studies of these proteins.
(34) A bacteriochlorophyll–protein complex containing seven bacteriochlorophyllys per protein and three identical subunits has been isolated, and the crystal structure determined to 2.8 Å resolution (Matthews, B. W.; Fenna, R. E.; Bolognesi, M. C.; Schmid, M. F.; Olson, J. M. *J. Mol. Biol.*, in press). Of the seven bacteriochlorophylls, five appear to be coordinated to histidine.

In an independent study which appeared after this work was submitted, chloro*phyllin* (the water-soluble degradation product of chlorophyllide in which ring V is lost) has been combined with apoMb (Davis, R. C.; Pearlstein, R. M. *Nature (London)* **1979,** *208,* 413). The chromophore is photochemically unstable and undergoes a series of interesting, irreversible transformations in the protein. The binding site of the 1:1 complex and the chemical identities of the transformed chromophores have not yet been established. By contrast, we note that the chlorophyll chromophore is stable in the protein.

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Book Reviews

Mathematical Foundations of Quantum Theory. Edited by A. R. MARLOW (Loyola University, New Orleans). Academic Press, New York. 1978. x + 372 pp. $22.00.

This book consists of presentations to a conference at Loyola University (June 2-4, 1977) by 19 contributors including, most notably, P. A. M. Dirac and John Archibald Wheeler. Wheeler analyzes the "delayed-choice" double-slit diffraction experiment, from which follows some fascinating speculations concerning the organization of the universe. The past, proposes Wheeler, may be determined partly by actions in the present: "present choice influences past dynamics"; "the past has no existence except as it is recorded in the present." Also implied is that we might live in a "participatory universe" in which "no phenomenon is a phenomenon until . . . it is an observed phenomenon." Most of the other contributions are of a highly technical nature, concerning quantum logics, orthomodular structures, C*-algebras, and the like.

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Quantum Chemistry. By J. P. LOWE (Pennsylvania State University). Academic Press, New York. 1978. xvi + 599 pp. $49.50.

This is a textbook on quantum chemistry for graduate students and advanced undergraduates. The Schrödinger equation and the requisite principles of quantum mechanics are developed along standard lines, but the writing is distinguished by clarity and style. The focus of the book is on ground-state molecular-orbital theories. Full chapters are devoted to the simple Hückel method, the extended Hückel method, and SCF-LCAO-MO methods. Detailed derivation is given of the basic SCF equations, partly in an appendix. The variational method and its matrix formulation, perturbation theory, and group theory are covered in individual chapters, with emphasis quite appropriately on chemical applications rather than mathematical rigor. A concluding chapter deals with qualitative molecular orbital theories, featuring Walsh diagrams and the Woodward-Hoffmann principles. Some 90 pages of appendices include mathematical supplements to the text, a listing of Hückel MO's, computer programs, and group-theoretical tables. Each of the 14 chapters contains a selection of problems and references. Readers of Lowe's book should acquire an excellent appreciation of the present status of both ab initio and semiempirical quantum chemistry. Only its rather steep price might deter the book's adoption as a course text. (Recently, however, a paperback student edition has appeared costing $19.50.)

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Affinity Chromatography. Journal of Chromatography Library. Volume 12. By J. TURKOVA (Prague). Elsevier Scientific Publishing Co., Amsterdam. 1978. ix + 405 pp. $69.75.

The uniquely specific complexes which form between many biologically important substances have in recent years provided the basis for a wide variety of analytical and preparative techniques useful for diagnostic medicine as well as fundamental research. This new monograph on affinity chromatography is an exhaustive treatment of one of the more important of these techniques. Historical perspective, theoretical background, laboratory practice, and existing applications are presented in an organized and lucid manner. The text will be very useful to both experts and newcomers to this important experimental technique. A very useful feature is the extensive tabulation of applications of affinity chromatography to the isolation of biologically active products including antibodies, antigens and haptens, cells and organelles, cofactors, enzymes, glycoproteins, proteins, and nucleic acids, etc. Some attention is also given to hydrophobic chromatography and immobilized enzymes, topics not inclusive to the title of this excellent effort.

Peter T. Kissinger, *Purdue University*

Cyclodextrin Chemistry. Reactivity and Structure Concepts in Organic Chemistry. Volume 6. By M. L. BENDER and M. KOMIYAMA (Northwestern University). Springer-Verlag, Berlin. 1978. x + 96 pp. $22.00.

Cyclodextrins are fascinating substances which make very good enzyme models. But they are much more than just that: they can make simple organic reactions quite stereospecific, they stabilize free radicals, and they even improve the efficacy of cockroach poison! In this small book these and other aspects of the chemistry of cyclodextrins are reviewed by one of the leading investigators in the field.

Myron Bender wrote another review of cyclodextrin chemistry some six years ago [*Advances in Catalysis,* **23,** 209 (1973)]. This book is a much expanded and completely rewritten version of that review; it has, for example, three times the number of references, which attests to the very rapid recent growth of interest in this subject. Although the emphasis in this book is on catalysis by cyclodextrins through inclusion of substrates into their central cavities, and what can be learned from this about catalysis by enzymes, there are sections on the properties and structure of cyclodextrins as well as a thoughtful analysis of the forces that bind substrate and catalyst together.

I enjoyed reading this book. I am sure that chemists working with cyclodextrins will find it a valuable reference work and that others who read it will discover that it contains some very interesting chemistry.

A. J. Kresge, *University of Toronto, Scarborough College*

Applications of Polymer Spectroscopy. Edited by E. G. BRAME, JR. (E.I. du Pont de Nemours & Co.). Academic Press, Inc., New York. 1978. xiv + 289 pp. $29.50.

This book is based on the papers presented at the American Chemical Society meeting in San Francisco in 1977; however, as the editor states, it contains new and updated material in addition to that presented at the meeting. The collection of 16 papers deals with three important areas of application of spectroscopy for structural studies: NMR, IR, and mass spectroscopy. The first group of seven papers contains coverage of the use of carbon-13, proton and fluorine-19 NMR for determination of polymer structure including studies of cis-trans and 1,2-1,4 isomerism, determination of copolymer composition and comonomer sequence distribution, end-group analysis, determination of the degree of branching, and studies of conformational transitions in amorphous and semicrystalline polymers, as well