Registry No. I, 57-83-0; II, 1424-09-5; 21-hydroxyprogesterone, 64-85-7; cortisone, 53-06-5; cortisol, 50-23-7; 9α-fluorocortisol, 127-31-1; 9α-chlorocortisol, 10119-05-8; 9α-bromocortisol, 50732-00-8; 9α-fluorocortisone, 79-60-7; 17α-progesterone acetate, 302-23-8; 6α-methyl-9α-fluoroprednisolone, 382-52-5; 6α-hydroxyprogesterone, 604-20-6; 16β-methylpregnane-3,20-dione, 81737-73-7.

Chirality and Structures of Bacteriochlorophylls *d*

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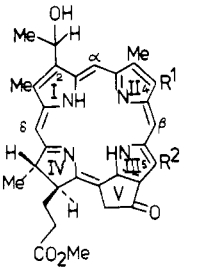
Bacteriochlorophylls (BChl) *c* and *d* comprise two homologous series of chlorophylls found in the antenna and reaction centers of green sulfur bacteria[2] (*Chlorobiacae*). Despite the continuing controversy concerning the structures of the six BChl *c* pigments,[3] assignments of the BChl *d*, which lack the δ methine methyl substituent found in BChl *c*, have been generally accepted. Smith et al.[4] recently deduced that the difference between pairs of BChl *c* lay in the absolute stereochemistry of the chiral 2-(1-hydroxyethyl) substituent; i.e., the bacteriopheophorbide bearing a 4-isobutyl and 5-ethyl was shown to have an *S* absolute stereochemistry,[4] contrary to assignments of *R* for the complete mixture of pigments.[5,6] Here, we show that the 4-isobutyl-5-ethyl- and 4-isobutyl-5-methylbacteriopheophorbides *d* also possess the 2-(*S*)-(1-hydroxyethyl) absolute configuration but that the other bacteriopheophorbides *d* (and presumably BChl *d*) exhibit the expected[5,6] *R* stereochemistry (Table I).

BChl *d* were isolated from *Chlorobium vibrioforme* forma *thiosulfatophilum* (NCIB No. 8327); treatment of the crude chlorophyll extract with methanol and sulfuric acid gave the pheophorbides **1–6** as an intimate mixture, the gross structures of which had been determined earlier by degradative[7] and synthetic work.[8] The stereochemistry of the 2-substituent had subsequently been established through Horeau analysis and degradation as *R*.[5,6] High-pressure liquid chromatography (HPLC)[9] of the intact mixture of methylbacteriopheophorbides *d* (**1–6**) gave the trace shown in Figure 1A, a separation that is superior to that in previous reports.[10,11] Prior separation of the mixture into 5-ethyl (**1**, **3**, **5**) and 5-methyl (**2**, **4**, **6**) series[10] gave the traces shown in Figure 1, parts B and C, respectively. Lengthy HPLC work resulted in accumulation of preparative quantities of all six methylbacteriopheophorbides *d*.

The previous observation that the naturally occurring band 1 of the methyl bacteriopheophorbides *c* (4-isobutyl-5-ethyl) had the unexpected 2*S* configuration[4] suggested that some of the BChl *d* might also have the *S* chirality.[12] The purified individual bands **1–6** were therefore treated with 80% trifluoroacetic acid in water and racemized at the 2-position to give an equal mixture of the

Table I



compd.	R^1	R^2	confign. at 2-position
1	*i*-Bu	Et	*S*
2	*i*-Bu	Me	*S*
3	*n*-Pr	Et	*R*
4	*n*-Pr	Me	*R*
5	Et	Et	*R*
6	Et	Me	*R*

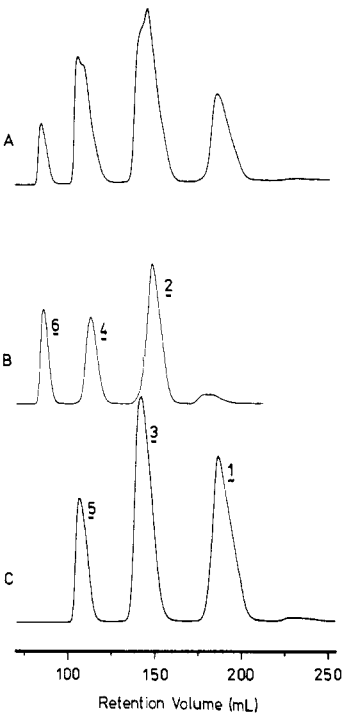


Figure 1. HPLC traces[9] of the methylbacteriopheophorbides *d*: (A) complete mixture; (B) the 5-methyl series, after preliminary separation by chromatography on silica; (C) the 5-ethyl series, after preliminary separation by chromatography on silica. The ratio of the 5-ethyl to the 5-methyl series is 3:1 in our preparation, compared with 10:1 reported by Kemmer et al.[10]

(1) Address inquiries regarding the chemistry to K.M.S. and the crystallography to K.M.B.

(2) Holt, A. S. In "The Chemistry and Biochemistry of Plant Pigments"; Goodwin, T. W., Ed.; Academic Press: New York, 1965; pp 3–28.

(3) For example: Kenner, G. W.; Rimmer, J.; Smith, K. M.; Unsworth, J. F. *Philos. Trans. R. Soc. London, Ser. B* **1976**, *273*, 255–276.

(4) Smith, K. M.; Kehres, L. A.; Tabba, H. D. *J. Am. Chem. Soc.* **1980**, *102*, 7149–7151.

(5) Brockmann, H., Jr.; Tacke-Karimdadian, R. *Liebigs Ann. Chem.* **1979**, 419–430. Risch, N.; Brockmann, H., Jr. *Ibid.* **1976**, 578–583. Tacke, R. Dissertation, T. U. Braunschweig, Germany, 1975.

(6) However, the Horeau method is not quantitative and would not have detected small amounts of the *S* compound. A back calculation from the slightly low rotation obtained[5] for the methyl benzoyllactate degradation product could, with hindsight, be interpreted to indicate contamination with *S* material.

(7) Purdie, J. W.; Holt, A. S. *Can. J. Chem.* **1965**, *43*, 3347–3353.

(8) Archibald, J. L.; Walker, D. M.; Shaw, K. B.; Markovac, A.; MacDonald, S. F. *Can. J. Chem.* **1966**, *44*, 345–362.

(9) A Waters Associates instrument consisting of a RCM-100 radial compression module, a Model 6000A solvent delivery system, and C-18 μBondapak reverse phase columns were used. The detector was a Perkin-Elmer LC 55B variable-wavelength detector set at 660 nm, and solvents were 10–15% water in methanol, run at 2.5 mL/min, generating a back pressure of 2000 psi.

(10) Kemmer, T.; Brockmann, H., Jr.; Risch, N. *Z. Naturforsch., B* **1979**, *34B*, 633–637.

(11) Reductive C-alkylation has shown the earlier partition separations on Celite to be inefficient: Chapman, R. A.; Roomi, M. W.; Norton, J. C.; Krajcarski, D. T.; MacDonald, S. F. *Can. J. Chem.* **1971**, *49*, 3544–3564.

(12) This suggestion resulted from the fact that the methyl benzoyllactates from degradation of both the bacteriopheophorbides *c* and *d* had the same (slightly low) rotation.[5]

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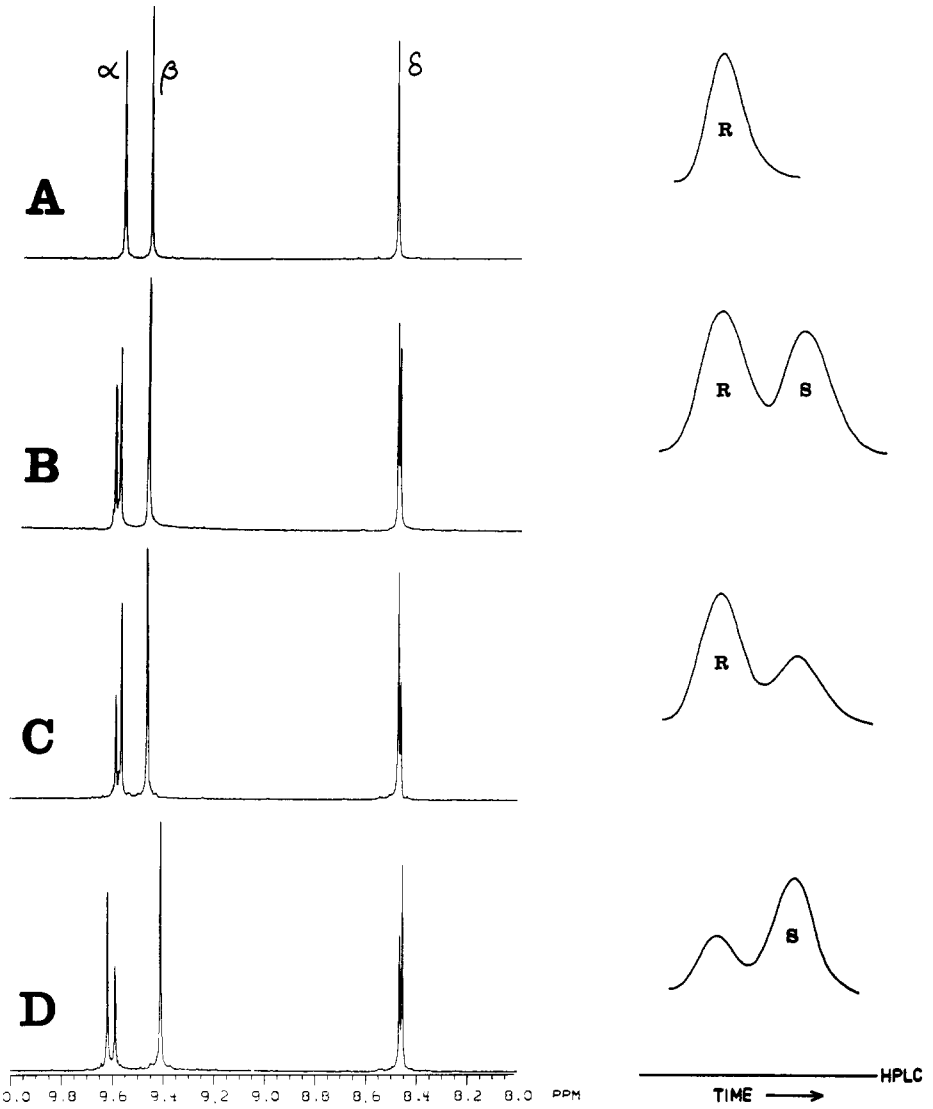

Figure 2. 360-MHz NMR spectra (Nicolet NT-360 spectrometer, solutions in $CDCl_3$) (left) and HPLC traces[9] (right) for the following: (A) pure 4-ethyl-5-ethylbacteriopheophorbide *d* methyl ester (**5**); (B) **5** after racemization at the 2-position; (C) **5** after racemization and spiking with pure natural **5**; (D) 4-isobutyl-5-ethylbacteriopheophorbide *d* methyl ester (**1**) after racemization and spiking with pure natural **1**.

2*R* and 2*S* compounds in each case. Figure 2A illustrates the methine proton region in the 360-MHz NMR spectrum for compound **5**, and on the right, its HPLC trace. Figure 2B shows the NMR spectrum and HPLC trace after racemization; the α and δ methine protons of the 2*S* compound are clearly shown to be to lower and higher field, respectively, of those for the natural 2*R* compound. Furthermore, as shown previously,[13] the 2*R* compound has a smaller HPLC retention volume than the *S* diastereomer. In Figure 2C, the conclusions from Figure 2B are confirmed by spiking of the 2*R*/2*S* mixture with the natural 2*R* diastereomer. A similar experiment with the racemized 4-isobutyl-5-ethylpheophorbide (**1**), however, shows (Figure 2D) that this compound and the chlorophyll from which it is derived possess the 2*S* configuration. In conclusion, the racemization work showed that compounds **3**–**6** have the expected[5] 2*R* absolute stereochemistry, whereas **1** and **2** have the unexpected 2*S* orientation.

The conclusions arrived at above depend upon consistent trends within the group of BChl homologues; for example, we have assumed that the diastereomer with the smallest HPLC retention volume is always that with a 2*R* orientation and that, likewise, the 2*R* diastereomer for a given pigment has the highest field α and lowest field δ methine proton in the NMR spectrum.[14] To verify these assumptions, we subjected crystallized samples of the methylbacteriopheophorbides **5**[15] and **1**[16] to X-ray analysis.

Figures 3 and 4 depict the molecular structures[17] and atomic nomenclature for **1** and **5**, respectively. Because the crystallo-

(13) Smith, K. M.; Bisset, G. M. F.; Bushell, M. J. *J. Org. Chem.* **1980**, *45*, 2218–2224.
(14) Risch, N.; Reich, H. *Tetrahedron Lett.* **1979**, 4257–4260.

(15) **5**: mp 215–216 °C. Anal. Calcd for $C_{35}H_{40}N_4O_4$: C, 72.39; H, 6.94; N, 9.65. Found: C, 72.13; H, 7.02; N, 9.51.
(16) **1**: mp 155–157 °C. Anal. Calcd for $C_{37}H_{44}N_4O_4$: C, 73.00; H, 7.28; N, 9.20. Found: C, 73.07; H, 7.26; N, 9.16.
(17) Compound **5** crystallizes from dichloromethane/hexane with $Z = 2$ in the triclinic space group $P\bar{1}$ in a cell of dimensions $a = 12.960$ (1) Å, $b = 15.162$ (1) Å, $c = 8.313$ (1) Å, $\alpha = 92.38$ (1)°, $\beta = 93.19$ (1)°, $\gamma = 68.07$ (1)°, $V = 1513$ Å^3. A sphere of data was collected on an Enraf-Nonius CAD 4 diffractometer with graphite monochromated Cu Kα radiation in the scan range $0 \le 2\theta \le 154°$. Of the 15 291 reflections measured, symmetry equivalents were averaged to give 6350 unique and 5930 with $F_o > 2\sigma(F_o)$. An anisotropic model was refined by least squares to $R_F = 0.048$ and $R_{wF} = 0.057$. Because of the large program size required to accommodate 166 atoms and the associated large number of variable parameters, five matrix blocks were used. Within each block, the positional and thermal parameters for atoms in molecule 1 and their counterparts in molecule 2 (labeled with primes) were varied. Hydrogens were idealized 0.95 Å from their respective carbons, except for HN1, HN3, H17, H18, H29, H22, HO2, and their primed counterparts, which were located from difference Fourier maps. Compound **1** also crystallizes from dichloromethane/hexane with $Z = 2$ in the triclinic space group $P\bar{1}$ in a cell of dimensions $a = 15.021$ (1) Å, $b = 15.675$ (2) Å, $c = 7.934$ (1) Å, $\alpha = 93.02$ (1)°, $\beta = 100.58$ (1)°, $\gamma = 62.30$ (1)°, $V = 1625$ Å^3. A sphere of 15 574 data was collected as before to give 6781 unique and 5786 with $F_o > 2\sigma(F_o)$. An anisotropic model was refined by least squares to $R_F = 0.056$ and $R_{wF} = 0.067$, again in five matrix blocks. Details of the structures will be presented elsewhere.

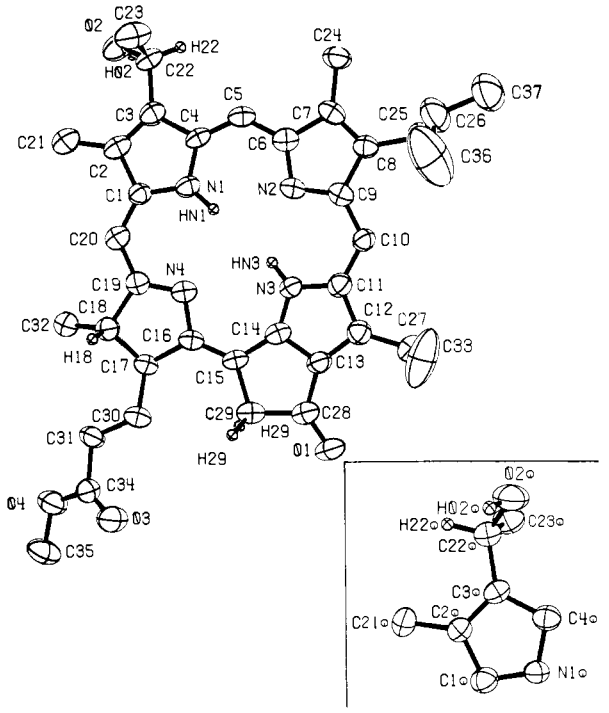

Figure 3. Molecular structure of one independent molecule of **1** and associated nomenclature. The insert shows ring I and the relative orientation of the 2-(1-hydroxyethyl) substituent for the second crystallographically independent molecule. Ellipsoids are drawn to enclose 50% probability except for those of the hydrogens, which are not to scale. Hydrogens on side chains other than the 2-(1-hydroxyethyl) have been eliminated for clarity.

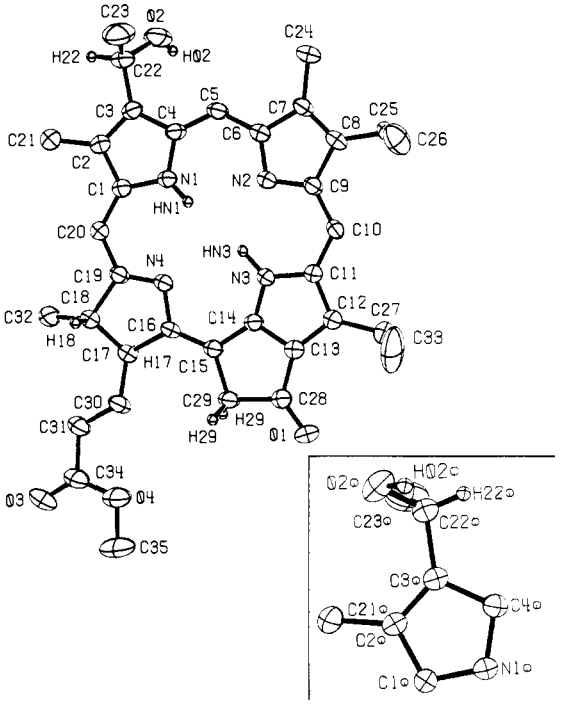

Figure 4. Molecular structure of one independent molecule of **5** and associated nomenclature. The insert shows ring I and the relative orientation of the 2-(1-hydroxyethyl) substituent for the second crystallographically independent molecule. Ellipsoids are drawn to enclose 50% probability except for those of the hydrogens, which are not to scale. Hydrogens on side chains other than the 2-(1-hydroxyethyl) have been eliminated for clarity.

graphic asymmetric unit in both structures consists of two independent molecules, the insert in each figure shows ring I and the geometry of the 2-(1-hydroxyethyl) group of the second molecule. Within a pair, the difference in orientation of the 2-(1-hydroxyethyl) substituents is conformational in nature. Their rotation enables the formation of dimers that are held together by two intermolecular hydrogen bonds between the hydroxyl group of ring I and the keto group of ring V (O2 and O1′, and O2′ and O1). However, neither 2-(1-hydroxyethyl) substituent in **1** is superimposable on the analogous group in **5**.[18] Thus, **1** and **5**, being *S* and *R*,[18] respectively, at position 2, are configurationally distinct, in agreement with the NMR and HPLC results.

Acknowledgment. This research was supported by grants from the National Science Foundation and Research Corporation (HPLC equipment) at the University of California and by the Division of Chemical Sciences, U.S. Department of Energy, Washington, D.C., under Contract No. DE-AC02-76CH00016 at Brookhaven National Laboratory. We are grateful to Professor Norbert Pfennig (Konstanz) for providing us with the *Chlorobium vibrioforme* strain and the Chemistry Department at Brookhaven for use of the diffractometer.

Registry No. (2*S*)-**1**, 81873-38-3; (2*R*)-**1**, 59924-08-2; (2*S*)-**2**, 81873-39-4; (2*R*)-**2**, 59924-05-9; (2*R*)-**3**, 59924-07-1; (2*S*)-**3**, 81873-40-7; (2*R*)-**4**, 59954-19-7; (2*S*)-**4**, 81938-66-1; (2*R*)-**5**, 59924-06-0; (2*S*)-**5**, 81873-41-8; (2*R*)-**6**, 59954-18-6; (2*S*)-**6**, 61665-26-7.

Supplementary Material Available: Final positional and anisotropic thermal parameters for the non-hydrogen atoms of **1** and **5** (5 pages). Ordering information is given on any current masthead page.

(18) The enantiomorph was chosen such that the orientation of substituents in ring IV was consistent with the chemical studies and the previously defined absolute stereochemistry in that ring.[19] The absolute configuration of the chiral centers was not determined by the present crystallographic analyses.

(19) Brockmann, H., Jr. *Philos. Trans. R. Soc. London, Ser. B* **1976**, *273*, 277–285.

Spectroscopic Evidence for Directed Electronic Influences within Norbornyl Frameworks[1]

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Revealing early studies by Jensen[2] and Traylor,[3] which gave indication of preferential electron supply to an *exo*-2-norbornyl substituent, have not been accorded proper importance because their key conclusions were couched in terms of a less than satisfactory[4] hyperconjugative model. Brown challenged "if there is a hunger for a directed electron contribution in the *exo*-norbornyl system, one can only hope that someone will demonstrate unambiguously the existence of such a directed electronic effect."[5] In the intervening years, several additional relevant experiments have been reported.[6-11] Also, norbornenes and 2-methylenenorbornanes

(1) Electronic Control of Stereoselectivity. 12. For part 11, see: Paquette, L. A.; Klinger, F. *J. Org. Chem.* **1982**, *47*, 272.

(2) Jensen, F. R.; Smart, B. E. *J. Am. Chem. Soc.* **1969**, *91*, 5686, 5688.

(3) Traylor, T. G.; Hanstein, W.; Berwin, H. J.; Clinton, N. A.; Brown, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 5715.

(4) Brown, H. C. "The Nonclassical Ion Problem"; Plenum Press: New York, 1977; Chapter 14.

(5) Brown, H. C.; Guedin, B. G.; Takeuchi, K.; Peters, E. N. *J. Am. Chem. Soc.* **1975**, *97*, 610.

(6) Nugent, W. A.; Wu, M. M.-H.; Fehlner, T. P.; Kochi, J. K. *J. Chem. Soc., Chem. Commun.* **1976**, 456.

(7) (a) Huisgen, R.; Ooms, P. H. J.; Mingin, M.; Allinger, N. L. *J. Am. Chem. Soc.* **1980**, *102*, 3951. (b) Huisgen, R. *Pure Appl. Chem.* **1981**, *53*, 171.

(8) (a) Paquette, L. A.; Carr, R. V. C.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186. (b) Böhm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *Ibid.* **1980**, *102*, 7218. (c) Paquette, L. A.; Carr, R. V. C.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 4907. (d) Paquette, L. A.; Bellamy, F.; Böhm, M. C.; Gleiter, R. *Ibid.* **1980**, *45*, 4913. (e) Paquette, L. A.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *Ibid.* **1980**, *45*, 4922.

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