$$(-)\text{-RSCH}_3 + \text{CH}_3\text{SCl} \longrightarrow \underset{\text{CH}_3}{\overset{+}{\text{R}}\text{SSCH}_3} + \text{Cl}^- \longrightarrow (\pm)\text{-RCl} + \text{CH}_3\text{SSCH}_3 \quad (4)$$

this reaction using (−)-IIb and find it to be very rapid at room temperature—giving *racemic* 1-phenylethyl chloride and methyl disulfide consistent with rapid formation and racemization of IV as the reactive intermediate.[14]

Reactions of I with other nucleophiles of the type RX where R is 1-phenylethyl and X is SH, SR, $SSCH_3$, OH, and OCH_3 were studied with very similar results. The products are listed in Table I and, while they may appear more complex than for IIb X = SCH_3, they can be rationalized by formation of alkylthio- and dialkylthiosulfonium salts related to IV that suffer migration of the 1-phenylethyl group along the sulfur chain prior to capture of this group by dialkyl sulfides.

These results signify that a polysulfide is an exceptionally labile leaving group in S_N reactions and that sulfides can behave as alkylating agents when the sulfur is methylthiolated. It is also possible that the rearrangement reported here is related to the allylic rearrangement described recently in the reaction of allylic thioethers with elemental sulfur[15] in which case it seems unlikely that a free carbonium ion is involved.

(14) Related reactions of methanesulfenyl chloride with optically active alcohols are reported to result in alkyl chlorides with a high degree of inversion: I. B. Douglass, R. V. Norton, P. M. Cocanour, D. A. Koop, and M-L. Kee, *J. Org. Chem.*, **35**, 2131 (1970).

(15) R. D. Baechler, J. P. Hummel, and K. Mislow, *J. Amer. Chem. Soc.*, **95**, 4442 (1973).

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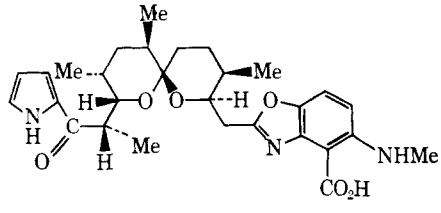
The Structure of A23187, a Divalent Cation Ionophore

Sir:

The carboxylic acid antibiotic A23187 is a divalent cation ionophore which has been shown to uncouple oxidative phosphorylation and inhibit ATPase in rat liver mitochondria.[1] The compound crystallizes from cultures of *Streptomyces chartreusensis* as the mixed magnesium–calcium salt, which can be converted to the crystalline free acid.[2] The structure of this unusual antibiotic has now been shown to be I using chemical



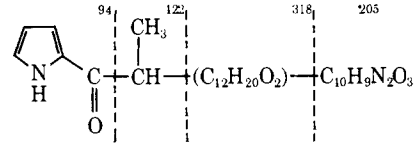
I

and physical methods. The free acid, $C_{29}H_{37}N_3O_6$, melts at 181–182°, the optical rotation is $[\alpha]^{25}D$ +362° (*c* 1, $CHCl_3$), and the pK_a' is 6.9 (90% DMSO). The infrared spectrum in chloroform shows peaks in the carbonyl region at 1640 and 1690 cm^{-1}.

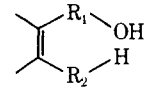
The ^1H nmr spectrum of A23187 contains five resonances in the aromatic region. Two of these occur as an isolated AB spectrum (δ_A 7.58, δ_B 6.65, J_{AB} = 9 Hz) characteristic of a 1,2,3,4-tetrasubstituted benzene derivative. The remaining three aromatic protons (δ 7.06, 6.92, 6.25) appear as multiplets with somewhat smaller coupling constants, reminiscent of five-membered heteroaromatics. From both ^1H and ^{13}C nmr spectra, using 2-formylpyrrole as a model, the presence of a pyrrole ketone moiety was inferred. The ^{13}C spectrum also suggested the presence of 13 sp^2-hybridized carbons in the molecule.

Also evident in the ^1H nmr spectrum were the resonances of five secondary methyl groups, one of which was assigned on the basis of its chemical shift (doublet at δ 2.98, J_{CH_3NH} = 4 Hz) to be an *N*-methyl group. A large nuclear Overhauser effect between this doublet and that at δ 6.65 suggested that the *N*-methyl was attached to the benzene ring. Proton resonances at δ 3.69 and 4.26 were inferred to be the carbinyl protons of secondary ether functions. Resonances at 96.0, 72.7, and 68.3 ppm (downfield from internal TMS) in the ^{13}C nmr spectrum suggested that these ethers occurred as part of a ketal structure.

The mass spectrum of A23187 had its molecular ion at *m/e* 523, with the composition $C_{29}H_{37}N_3O_6$ (found 523.2669, calcd 523.2682). Methylation yields a monomethyl derivative, $C_{30}H_{39}N_3O_6$ (found 537.2838, calcd 537.2839). Acetylation of A23187 and its methyl derivative yields acetyl and methylacetyl derivatives with molecular ions at *m/e* 565 and 579, respectively. Prominent fragments occur in the mass spectrum of A23187 at *m/e* 94 (C_5H_4NO), 123 (C_7H_9NO), 206 ($C_{10}H_{10}N_2O_3$), and 318 ($C_{19}H_{28}NO_3$ and $C_{16}H_{18}N_2O_5$). The peak at *m/e* 206 and the more oxygenated one at *m/e* 318 shift 14 mu on methylation and 56 mu on methylation, followed by acetylation. These results, in conjunction with nmr data, yielded the partial structure



where the $C_{12}H_{20}O_2$ moiety likely has an H substituent γ to the carbonyl group to account for the intense peak at *m/e* 123. Elimination of water from the peak at *m/e* 206 in the spectrum of A23187 and methanol from the peaks at *me* 220 and 262 in the spectra of the methyl and methylacetyl derivatives, respectively, indicated the presence of



in A23187, where R_2 is not oxygen.

The free acid of A23187 crystallizes from acetone as colorless needles, with the crystal parameters given in Table I. A total of 1553 independent reflections to θ = 70° were measured on a four-circle automated diffractometer using monochromated copper radiation.

(1) P. W. Reed and H. A. Lardy, *J. Biol. Chem.*, **247**, 6970 (1972); D. T. Wong, J. R. Wilkinson, R. L. Hamill, and J.-S. Horng, *Arch. Biochem. Biophys.*, **156**, 578 (1973).

(2) R. L. Hamill, M. Gorman, R. M. Gale, C. E. Higgens, and M. M. Hoehn, Abstracts, 12th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N. J., Sept 26–29, 1972, p 65.

Table I. Crystal Parameters for Antibiotic A23187

a	15.759 (4) Å
b	10.377 (4) Å
c	8.592 (3) Å
β	95.97 (2)°
Space group	$P2_1$
Molecules/cell	2
Obsd density	1.264 g cm^{-3}
Calcd density	1.244 g cm^{-3}

The structure was solved by direct methods using the program MULTAN[3] and was refined by the least-squares method. The final R factor, using anisotropic temperature factors for all heavy atoms and isotropic temperature factors for all hydrogen atoms (at assumed locations), was 0.063. The refined atomic coordinates for the heavy atoms are given in Table II.[4] The conformation of the molecule in the crystal is shown in Figure 1.

The structure consists of three basic units, α-ketopyrrole, a substituted benzoxazole, and a spiro ring system similar to those found in the polyether antibiotics—monensin,[5] nigericin,[6] grisorixin,[7] dianemycin,[8] X-206,[9] and A204A.[10] In the polyether antibiotics, the spiro ring systems consist of a five- and a six-membered ring, whereas A23187 contains two six-membered rings. Comparison of the spiro moieties in the polyethers and in A23187 shows that conformationally, they are very similar; in each case, the ring ether oxygen atoms are in axial or pseudoaxial conformations, and the points of attachment of the rest of the molecular chain are equatorial or pseudoequatorial.

Because the molecule contains no atom with strong anomalous X-ray scattering, we have been unable to determine experimentally the absolute configuration. However, in Figure 1, the chiralities of the asymmetric centers in each of the two six-membered rings of the spiro group are the same as those found in all the polyethers which contain a spiro six-membered ring.[11] It seems probable, therefore, that the absolute configuration shown is correct.

In the crystalline, free acid form of A23187, there are three internal hydrogen bonds, as shown by the dotted lines in Figure 1. The hydrogen bond between the pyrrole nitrogen atom and one of the carboxyl oxygen atoms holds the ends of the molecule in close proximity,

(3) P. Main, M. M. Woofson, and G. Germain, "MULTAN, a Computer Programme for the Automatic Solution of Crystal Structures," "University of York Printing Unit, York, England, 1971.

(4) See paragraph at end of paper regarding supplementary material.

(5) A. Agtarap, J. W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Amer. Chem. Soc.*, **89**, 5737 (1967); M. Pinkerton and L. K. Steinrauf, *J. Mol. Biol.*, **49**, 533 (1970); W. K. Lutz, F. K. Winkler, and J. D. Dunitz, *Helv. Chim. Acta*, **54**, 1103 (1971).

(6) L. K. Steinrauf, M. Pinkerton, and J. W. Chamberlin, *Biochem. Res. Commun.*, **33**, 29 (1968); T. Kubota, S. Matsutani, M. Shiro, and H. Koyama, *Chem. Commun.*, 1541 (1968); T. Kubota and S. Matsutani *J. Chem. Soc. C*, 695 (1970).

(7) P. Gachon, A. Kergomard, H. Veschambre, C. Esteve, and T. Staron, *Chem. Commun.*, 1421 (1970); M. Alleaume and D. Hickel, *ibid.*, 1422 (1970); M. Alleaume and D. Hickel, *J. Chem. Soc., Chem. Commun.*, 175 (1972).

(8) R. L. Hamill, M. M. Hoehn, G. E. Pittenger, J. Chamberlin, and M. Gorman, *J. Antibiot.*, **22**, 161 (1969); E. W. Czerwinski and L. K. Steinrauf, *Biochem. Biophys. Res. Commun.*, **45**, 1284 (1971).

(9) J. F. Blount and J. W. Westley, *Chem. Commun.*, 927 (1971).

(10) N. D. Jones, M. O. Chaney, J. W. Chamberlin, R. L. Hamill, and S. Chen, *J. Amer. Chem. Soc.*, **95**, 3399 (1973).

(11) Dianemycin (ref 8) contains two spiro ring systems. The one closest to the carboxyl end of the molecule has the same chiralities found in the polyether antibiotics mentioned above, but the other spiro moiety has several asymmetric centers with reversed chirality.

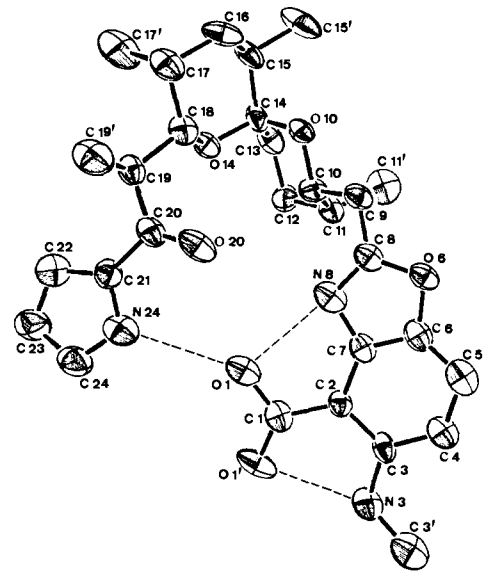


Figure 1. Conformation and proposed absolute configuration of A23187 in the crystal. The thermal ellipsoids are drawn at the 50% probability level.

a feature usually seen in the crystal structures of polyether antibiotics. Although the structure of the 2:1 antibiotic–divalent cation complex is not yet known, one can speculate that the principal ligands to the metal ion are the oxygen atoms of the carbonyl and carboxyl group, as well as one of the ether oxygen atoms from the spiro ring system.

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Supplementary Material Available. A listing of refined atomic coordinates will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1932.

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Rapid Relaxation of Spin Equilibrium in Ferric Myoglobin Hydroxide

Sir:

The hypothesis[1] that changes in the spin states of the cytochromes are intimately related to the mechanism of oxidative phosphorylation has attractive features. Electron transfer and phosphorylation could be coupled through the conformational changes induced in the

(1) D. F. Wilson, P. L. Dutton, M. Erecinska, J. G. Lindsay, and N. Sato, *Accounts Chem. Res.*, 5, 234 (1972), and references therein.