line broadening.[13,14] To solve this problem, the spectrum of $Al_2(CH_3)_4(c\text{-}C_3H_5)_2$, in which the cyclopropyl groups have been shown to reside in the bridging positions,[15] was investigated as a function of temperature. The spectra for the methyl region obtained between −29 and −73° are shown in Figure 2.

Preliminary calculations using these data indicate that the activation energy for the process giving rise to equivalent methyl groups is approximately 11 kcal/mol, which is considerably less than the ~15 kcal/mol observed for bridge–terminal exchange in $Al_2(CH_3)_6$.[16] The process is thought to be a rotation inversion of the cyclopropyl group which equates the four terminal methyl groups. This represents the first clear evidence for this process in an electron-deficient aluminum system and suggests that further studies should be carried out on this system, the phenyl-bridged system, and systems such as the phenylethynyl-bridged derivatives,[17] to determine if they also have distorted structures showing nonequivalent terminal groups.

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Conformation of Tetracycline Ring Systems. Structure of 5,12a-Diacetyloxytetracycline

Sir:

The numerous chemical and structural investigations[1] of tetracycline derivatives include only two single-crystal X-ray structure analyses, namely, the hydrochlorides of Aureomycin[2,3] (**1**, 7-chlorotetracycline) and Terramycin[4,5] (**2**, 5-hydroxytetracycline). These structures, which are very nearly isomorphous, helped to establish the relative configurations of the chiral centers in the molecules and provided a model conformation for the tetracycline ring system. We now report the determination of the structure of the free base, 5,12a-diacetyloxytetracycline[6] (**3**); the molecule has relative chiralities identical with those in 5-hydroxytetracycline, but it displays a strikingly different molecular conformation.

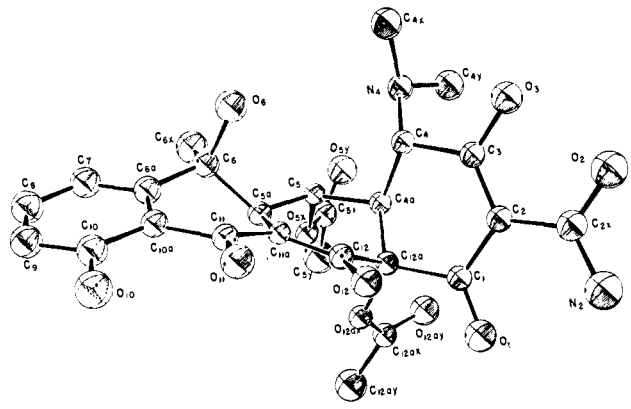
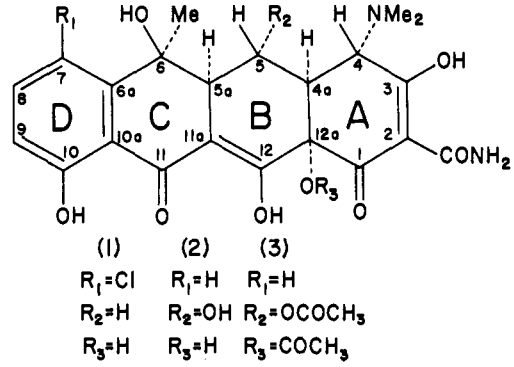


Figure 1. A perspective representation of the structure of 5,12a-diacetyloxytetracycline.



Excellent crystals which provided data of high quality were obtained by slow evaporation of a 2-propanol solution of material which was prepared and carefully purified by one of us (H. M.). The observed Laué symmetry and extinctions correspond to the orthorhombic space group $P2_12_12_1$ with $a = 18.896 \pm 0.010$, $b = 14.229 \pm 0.007$, $c = 9.406 \pm 0.006$ Å; $Z = 4$; $\rho_{calcd} = 1.430$ g/cm³; and $\rho_{obsd} = 1.44$ g/cm³. Diffraction intensities were measured in the θ–2θ scan mode with Zr-filtered Mo Kα radiation on a Picker FACS-I diffractometer; of the 3292 independent reflections investigated ($\sin\theta/\lambda \leq 0.6486$), a total of 3124 were retained as objectively observed. No corrections were applied for either absorption or extinction.

The equal-atom structure was solved by direct methods[7,8] using a computerized[9] multiple-solution procedure and tangent-formula[10] phase refinement. Full-matrix least-squares refinement of the structure (157 independent variables) with isotropic thermal parameters yielded a standard residual $R = 0.101$ for all observed data; a weighted residual $R_w = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2)^{1/2}$ of 0.104 was obtained with $w = 1/\sigma_{F^2}$. Nearly all hydrogen positions were determined with good resolution from a difference-Fourier synthesis.

The perspective view shown in Figure 1 displays the essential configurational and conformational features of the molecule. The six chiral centers are (*R*)-C_4, (*R*)-C_{4a}, (*S*)-C_5, (*R*)-C_{5a}, (*S*)-C_6, and (*R*)-C_{12a}. Since the

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absolute configuration at C_6 has been determined,[11] the molecule is shown in the correct enantiomorphic form.

The conformation of the tetracycline ring system in the present structure differs markedly from that found in the hydrochloride salt structures.[3a,5a] As can be seen from the listing of dihedral angles in Table I, the major differences appear in the A and B rings; while there are significant variations in several structural parameters of the C and D rings, the basic conformations are very similar. In the A ring, the shift between the two conformers involves a drastic twist about the sequence C_4–C_{4a}–C_{12a}–C_1. The required rotations in the ring about the bonds C_4–C_{4a}, C_{4a}–C_{12a}, and C_{12a}–C_1 are 95.6, 109.4, and 94.0°, respectively. As would be expected, the associated rotations about C_1–C_2, C_2–C_3, and C_3–C_4 are relatively small. Similarly, in the B ring, the conformers differ by rotations of 88.1, 108.4, and 103.4° about C_{12}–C_{12a}, C_{12a}–C_{4a}, and C_{4a}–C_5, respectively.

Table I. Selected Dihedral Angles[a] in the Tetracycline Ring System

	Atoms	Angle, deg: 5-Hydroxytetracycline hydrochloride[b]	Angle, deg: 5,12a-Diacetyloxytetracycline[c]
Ring A	C_{12}–C_{12a}–C_1–C_2	−174.7	−80.7
	C_{12a}–C_1–C_2–C_3	19.2	−6.7
	C_1–C_2–C_3–C_4	17.1	−3.9
	C_2–C_3–C_4–C_{4a}	−17.0	−17.6
	C_3–C_4–C_{4a}–C_5	74.0	169.6
	C_4–C_{4a}–C_{12a}–C_1	49.1	−60.3
Ring B	C_{11}–C_{11a}–C_{12}–C_{12a}	−178.5	169.5
	C_{11a}–C_{12}–C_{12a}–C_1	80.7	168.8
	C_{12}–C_{12a}–C_{4a}–C_5	48.7	−59.7
	C_4–C_{4a}–C_5–C_{5a}	170.9	−85.7
	C_{4a}–C_5–C_{5a}–C_6	162.5	133.6
	C_5–C_{5a}–C_{11a}–C_{12}	−13.2	−24.9
Ring C	C_{10}–C_{10a}–C_{11}–C_{11a}	166.5	157.0
	C_{10a}–C_{11}–C_{11a}–C_{21}	178.9	−168.3
	C_{11}–C_{11a}–C_{5a}–C_6	43.0	34.9
	C_5–C_{5a}–C_6–C_{6a}	175.8	174.9
	C_{5a}–C_6–C_{6a}–C_7	−135.1	−139.0
	C_6–C_{6a}–C_{10a}–C_{11}	1.8	6.1
Ring D	C_8–C_9–C_{10}–C_{10a}	7.7	−1.8
	C_9–C_{10}–C_{10a}–C_{11}	177.0	−175.1
	C_{10}–C_{10a}–C_{6a}–C_7	11.4	0.0
	C_6–C_{6a}–C_7–C_8	−178.1	−178.4
	C_{6a}–C_7–C_8–C_9	2.0	1.3
	C_7–C_8–C_9–C_{10}	−2.7	0.4

[a] An arbitrary but self-consistent set defined for the sequence a–b–c–d as the positive clockwise rotation from a to d in the projection of the array down the line b–c. [b] The angles reported here have been calculated from the coordinates provided in ref 5a, with an estimated error given as ~0.01 Å. [c] The estimated error fhr the coordinates from which these angles were calculated is ~0.005 Å.

Despite the inevitable uncertainties in extrapolating from a crystal structure, it is useful to speculate upon the merits of this new conformation as a model for oxytetracycline or tetracycline derivatives in solution;[12] the issue is basic to the detailed understanding of important reaction mechanisms. Of particular interest is a comparison with the interpretation[13] of the nmr spectra of oxytetracycline derivatives in a variety of nonaqueous solvents. The bonding at C_4 and C_{4a} is precisely tetrahedral, the dihedral angle is 169.6°, the hydrogen atoms are in trans positions, and both are axial to the A ring; this conformation is in accord with the apparent coupling constants of 9–13 cps reported[13] for several oxytetracycline derivatives, including the present one. Similarly, in the same molecules, the small (0–2 cps) apparent coupling constants between the C_{4a} and C_5 protons indicate[13] an approximate right-angle relationship between the two protons. Indeed, in the present structure, the actual dihedral angle is 85.7°; the proton at C_{4a} is clearly equatorial with respect to the B ring and the proton at C_5 is, at best, pseudoaxial. The dihedral angle between the protons on C_5 and C_{5a} is 133.6°; this nearly eclipsed configuration about the C_5–C_{5a} bond is consistent with the relatively small coupling constant (<4 cps) observed.[13]

Thus, the present structure fully supports the interpretation of the nmr spectra and provides an excellent detailed model for oxytetracyclines in solution. Nevertheless, in the case of tetracycline, the earlier conformation appears to be more appropriate.[13] The driving force between the two conformations is obscure, but in view of the results[5a,11] on 5-hydroxytetracycline, it cannot simply be the interaction of the –OH or –OAc at C_5 with the substituents at C_6.

Comparison with the two earlier structures reveals some significant differences in bond lengths and angles in the tetracycline ring system; these will be discussed in a detailed presentation of the structure.

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The Reactions of Nonspecific Ester Substrates with δ-Chymotrypsin

Sir:

The analysis of the pH dependence of chymotrypsin-catalyzed reactions remains a knotty problem. In the present communication we wish to report our findings with two nonspecific ester substrates, 4-nitrophenyl 3-nitrophenylacetate (I)[1] and 2-hydroxy-5-nitro-α-toluenesulfonic acid sultone (II),[2] which show that the pH dependencies of the rate parameter k_2/K_s for the acylation or sulfonylation of δ-chymotrypsin by these compounds differ markedly from that previously observed for this enzyme with specific substrates.[3] In particular, we have found that the rates of acylation or sulfonylation of δ-chymotrypsin by the nonspecific substrates I and II, as reflected by the pH dependence of the rate parameter k_2/K_s, are strongly retarded at

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