Crystal and Molecular Structure of a Derivative of the Free Acid of the Antibiotic X-537A

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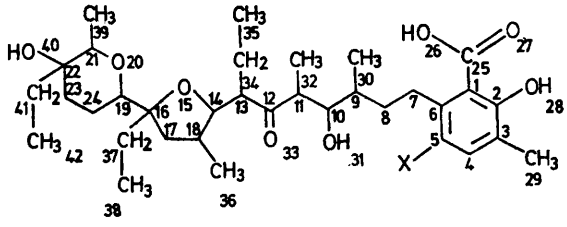
Summary The structure of the metal-free acid of the antibiotic X-537A has been determined using a bromo-derivative and reveals a dimer enclosing a water molecule.

THE antibiotic, X-537A(I),[1]† is one of a series of oxygen-containing organic acids[2,3] that can inhibit metal ion transport in membranes by forming metal complexes. In contrast to the other reported members of the series, X-537A forms *dimeric* complexes with both bivalent and monovalent metal ions, $M^{2+}X_2^-$ and $(M^+X^-)_2$, where X^- represents the X-537A anion. The crystal structures of the barium salt and of the silver salt of X-537A have been reported.[4,5] In these salts, the four crystallographically-independent antibiotic anions adopt almost identical conformations, dictated largely by intramolecular hydrogen bonding. We now report the results of an *X*-ray study on the 5-bromo derivative (II) of the metal-free antibiotic to assess the differences in molecular conformation that take place upon metal complex formation.



(I); X = H

(II); X = Br

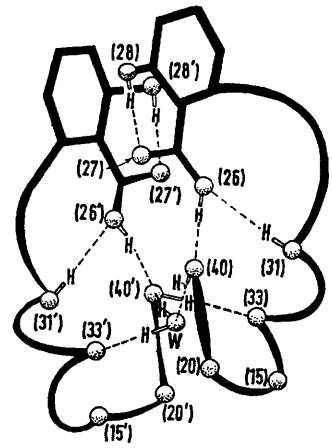


FIGURE 2. *Schematic view of the dimer of the 5-bromo derivative of* X-537A. *Only the oxygen atoms are shown while the carbon atom chain is represented by solid lines. The hydrogen bonds are shown by discontinuous lines.*

The colourless crystals of the 5-bromo derivative of X-537A were found to deteriorate quite rapidly upon exposure to *X*-rays. *Crystal data:* $(C_{34}H_{53}O_8Br)_2 \cdot H_2O$, $M = 1537{\cdot}4$, monoclinic, $a = 14{\cdot}622(7)$, $b = 17{\cdot}096(9)$, $c = 14{\cdot}693(8)$ Å, $\beta = 95{\cdot}73(5)°$, $U = 3655$ Å^3, D_m (flotation in aqueous zinc chloride) = 1·23 g cm^{-3}, $Z = 2$, $D_c = 1{\cdot}233$ g cm^{-3}, $F(000) = 1444$. Space group $P2_1$. Two crystals were used to accumulate intensity data on a Picker FACS-1 diffractometer (Cu-K_α radiation) out to $2\theta = 100°$, beyond which limit no significant diffraction maxima could be detected. After correction for crystal deterioration, absorption, and scaling between the crystals, a total of 2669 reflections was considered above zero at the 2σ level. The structure was solved by the heavy atom method and has

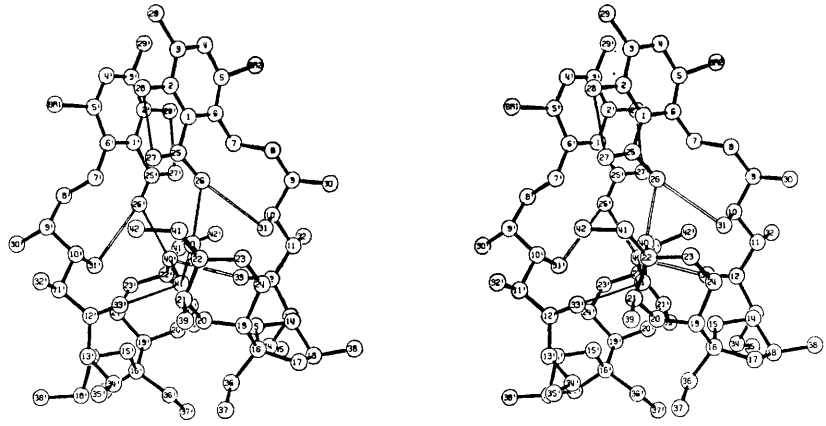


FIGURE 1. *Stereoscopic view of the dimer of the 5-bromo derivative of* X-537A. *The* C *and* O *labels on the atoms have been omitted for clarity in viewing. Hydrogen bonds are shown by the unshaded lines.*

† The numbering system used in (I) and Figures 1 and 2 is that used in earlier *X*-ray papers,[4,5] but differs from that used in papers on the biosynthesis of X-537A (ref 7).

been refined to an R-factor of 0·091 incorporating anisotropic thermal parameters for the two bromine atoms and the oxygen atom of the water molecule and isotropic thermal parameters for all the other non-hydrogen atoms. A stereoscopic view of the molecular structure is shown in Figure 1.

The structure is dimeric, with the two antibiotic acid molecules enclosing a water molecule in the region usually occupied by metal ions. Unfortunately, as we were unable to locate many of the hydrogen atoms with a high degree of certainty, some details of the hydrogen bonding scheme must be regarded as rather speculative. In the case of the Ba^{2+} and Ag^{+} salts of X-537A,[4,5] there was no intracomplex, intermolecular hydrogen bonding. The most reasonable hydrogen bonding scheme for Br–X-537A is shown in Figure 2 and, in that case, there is a $O_{40'}$-H $\cdots$ O_{38} intermolecular hydrogen bond. The additional proton on the free acid, rather than the hydroxyl O_{40} proton as in the case in the metal complexes, is used to form the "head-to-tail" hydrogen bond which constrains the molecule to a circular shape. The O_{40} proton is thus free (in one molecule) to form a hydrogen bond to the water molecule, and (in the other) to stabilize the complex by intermolecular hydrogen bonding. The manner in which the dimer is formed from the two monomers is different in this free acid from that in the previously examined salts, although the general features of a hydrophobic exterior and the placement of the oxygen atoms near the centre of the complex are preserved. If one imagines the benzoic acid group as the "head" and the oxacyclohexane ring as the "tail" of the antibiotic molecule, then in the metal complexes the two antibiotic ions associate in a head-to-tail fashion, whereas in the free acid dimer it is a head-to-head association. Thus while metal complex formation with X-537A does not greatly alter the conformation of an individual antibiotic molecule, it not only causes some changes in hydrogen bonding, as was also noted in the case of a structure determination of the free acid of monensin,[6] but also affects the mode of assembly of the dimer.

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[1] J. Berger, A. I. Rachlin, W. E. Scott, L. H. Sternbach, and M. W. Goldberg, *J. Amer. Chem. Soc.*, 1951, **73**, 5295; J. W. Westley, R. H. Evans, jun., T. Williams, and A. Stempel, *Chem. Comm.*, 1970, 71.
[2] M. Pinkerton and L. K. Steinrauf, *J. Mol. Biol.*, 1970, **49**, 533.
[3] L. K. Steinrauf, M. Pinkerton, and J. W. Chamberlin, *Biochem. Biophys. Res. Comm.*, 1968, **33**, 29; M. Shiro and H. Koyama, *J. Chem. Soc.* (*B*), 1970, 243.
[4] S. M. Johnson, J. Herrin, S. J. Liu, and I. C. Paul, *J. Amer. Chem. Soc.*, 1970, **92**, 4428.
[5] C. A. Maier and I. C. Paul, *Chem. Comm.*, 1971, 181.
[6] W. K. Lutz, F. K. Winkler, and J. D. Dunitz, *Helv. Chim. Acta*, 1971, **54**, 1103.
[7] J. W. Westley, R. H. Evans, jun., D. L. Pruess, and A. Stempel, *Chem. Comm.*, 1970, 1467; J. W. Westley, D. L. Pruess, and R. G. Pitcher, *ibid.*, 1972, 161.

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