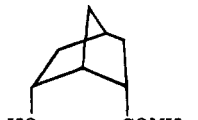
tion of amido and hydroxyl groups in model compounds so that the positions of these groups in the ground state more closely resemble their positions in the transition state for lactonization.



5

Perhaps the hydroxyamide **5** will be more susceptible than **1a** to imidazole-catalyzed lactonization. The parent acid of **5** has been reported to lactonize $\sim 3 \times 10^4$ times faster than hydroxymethylbenzoic acid.[19]

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Polyene Macrolide Antibiotic Amphotericin B.[1] Crystal Structure of the *N*-Iodoacetyl Derivative

Paolo Ganis,*[2,3] Gustavo Avitabile,[2,4] Witold Mechlinski,*[5] and Carl P. Schaffner[5]

Contribution from the Polymer Research Institute, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201, and the Institute of Microbiology, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08903.
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Abstract: The *N*-iodoacetyl derivative of the important antifungal polyene macrolide antibiotic amphotericin B was found to be biologically active and was used as a heavy atom derivative of the antibiotic for X-ray single-crystal analysis. Monoclinic crystals of the *N*-iodoacetylamphotericin B tritetrahydrofuran monohydrate, $C_{49}H_{74}O_{18}NI \cdot 3C_4H_8O \cdot H_2O$, were grown from tetrahydrofuran solution. The unit cell parameters are: $a = 21.28$, $b = 8.78$, $c = 18.69$ Å, $\beta = 103° 58'$, $V = 3387$ Å^3, $Z = 2$, $D_m = 1.33$, $D_c = 1.30$, space group $P2_1$. Data were collected for 3702 reflections including 2658 nonzero ones with a Picker automated diffractometer. The structure was solved by the Patterson method to the reliability R factor of 0.137. The following features of the molecule of the antibiotic were indicated for the first time: the presence of a ketalic six-membered ring included in the macrolactone ring, the locations of all the hydroxylic groups, and the position of the β-glycosidically bound mycosamine moiety in the form of a pyranoside. The crystal structure is described in terms of intermolecular hydrogen bondings. The function of the solvent molecules in the crystal is also explained.

N-Iodoacetylamphotericin B is a biologically active heavy atom derivative of one of the most important polyene macrolide antibiotics, amphotericin B (review by Oroshnik and Mebane[6]). Antibiotics of this group of natural products have in common a very pronounced activity against yeast and fungi. They found medical use in the treatment of systemic mycotic infections caused by *Candida albicans*, *Cryptococcus neoformans*, and other pathogenic fungi. Very recently, Gordon and Schaffner[7,8] discovered the effect of these antibiotics on prostatic hypertrophy and hypercholesterolemia in animals.

Because of the difficulties in purification, the very unstable chemical character, and large molecular weight (*ca.* 700–1300) the chemical investigation of the polyenic macrolide antibiotics is a complicated task, and only a few partial structures have been described out of the *ca.* 80 antibiotics reported in the literature. No total structure as yet has been described. The polyenic macrolide antibiotics feature a large number of asymmetric centers in the molecule and also may undergo a cis–trans transformation of the chromophore. The elucidation of the full chemical and stereochemical structure of these molecules is very important for a better understanding of the relationship between similar members of this antibiotic family and their behavior in chemical and biological studies. It is very likely that some polyenic antibiotics have identical chemical structures but are stereochemical isomers.

Amphotericin B, described in 1956 by Vandeputte, Wachtel, and Stiller,[9] is produced by *Streptomyces nodosus*. The chemical structure of this antibiotic was investigated since 1957.[10–15] The results can be summarized by the partial chemical structure of

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(3) On sabbatical leave from Universita' di Napoli, Istituto Chimico, Napoli, Italy.
(4) Postdoctoral Fellow on leave from Universita' di Napoli, Istituto Chimico.
(5) Institute of Microbiology.
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amphotericin B proposed by Cope, Axen, Burrows, and Weinlich[16] in Figure 1.

In this paper we present a new approach to the structural elucidation of the polyenic macrolide antibiotics by employing the technique of X-ray single-crystal analysis. Amphotericin B was chosen as an example because of its importance in medicine, its availability in a high degree of purity, and the general interest for chemists.

The parent antibiotic amphotericin B could not be readily crystallized. Hence, chemical studies were carried out in order to produce suitable single crystals of a heavy atom derivative. From the number of derivatives of amphotericin B synthesized, only those showing antifungal activity were considered. The *N*-iodoacetylamphotericin B turned out to be the one of choice. The crystals were grown from tetrahydrofuran solution in the form of thick yellow needles elongated in the direction of the *b* axis. They are very fragile and break rapidly when removed from the mother liquor. The measurements of the intensities were therefore performed together with the solvent in Lindemann sealed capillaries. Weissenberg and precession photographs indicated that the crystals are monoclinic with space group $P2_1$. A single crystal with dimensions 0.2 × 1.0 × 0.2 mm was mounted on a Picker automated diffractometer with the *b* axis parallel to the spindle axis. The unit cell constants were determined from a least-squares fit of the angular position of 12 independent reflections. Data were taken to a 2θ value of 40° with Zr-filtered Mo Kα radiation. Intensities were collected for 3702 reflections of which 2658 were observable. Two standard reflections were measured every 50 reflections. The decrease in standard intensities after a period of 8 days was about 30%.

Crystal Data. *N*-Iodoacetylamphotericin B monohydrate tritetrahydrofuran, $C_{49}H_{74}O_{18}NI \cdot H_2O \cdot 3C_4H_8O$ showed the following: mol wt 1323.9; monoclinic, $a = 21.28 \pm 0.02$, $b = 8.78 \pm 0.01$, and $c = 18.69 \pm 0.02$ Å; $\beta = 103° 58' \pm 5'$; $V = 3387$ Å^3; $Z = 2$; $D_o = 1.33 \pm 0.01$ g cm^{-3}; $D_c = 1.30$ g cm^{-3}; space group $P2_1$. The formula of the asymmetric unit has been established through the crystal analysis. The intensities were corrected for the decreasing reflecting power as measured by standards and for Lorentz polarization effects; no absorption corrections were made ($\mu = 1.4$ cm^{-1}).

Solution of Structure. The structure was solved by three-dimensional Patterson and Fourier methods. The first Fourier synthesis using the phases given by iodine showed only 30% of the lighter nonhydrogen atoms. It clearly indicated the position of the "full extended" sequence of the double bonds and the linear saturated moiety on the opposite side of the lactone ring. The pseudosymmetry $P2_1/m$ introduced by the iodine atom alone was removed in successive Fourier syntheses with the aid of chemical and stereochemical considerations. The model in its absolute structure has been chosen assuming the known *D* configuration for the sugar moiety.[17,18] The positions of three

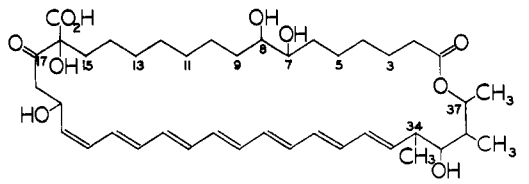

Figure 1. Partial chemical structure of amphotericin B proposed by Cope, *et al.*,[16] in 1966.

molecules of tetrahydrofuran and one molecule of water in the asymmetric unit were found after all of the nonhydrogen atoms were located in the *N*-iodoacetylamphotericin B molecule.

The structure was refined by the block-diagonal least-squares method[19] with an anisotropic thermal factor for iodine and with isotropic thermal factors for the remaining 84 nonhydrogen atoms. The positions of the hydrogen atoms were assumed geometrically with the exception of those in the hydroxylic and carboxylic groups, the water molecule, and in the two clathrated molecules of tetrahydrofuran. The hydrogen atoms were included in the structure factor calculations with a temperature factor $B = 4.0$ Å^2, but not refined. The reliability *R* factor at the end of the refinement was 0.137. A difference Fourier analysis at this stage showed the standard deviations of the electron density less than ± 0.5 e/Å^3. Because of the relatively small number of experimental data the refinement with anisotropic thermal factors for all of the atoms has not been attempted. In Table I are listed the coordinates and the thermal parameters. In the calculations the atomic scattering factors of Moore[20] and the unit weight for all of the reflections have been used. A table of observed and calculated structure factors has been deposited with the ASIS National Publications Service.[21]

Description of the Molecular Structure. The chemical structure of *N*-iodoacetylamphotericin B and the absolute configuration of all 14 asymmetric centers of the macrolide lactone ring are represented in Figure 2.[1] The molecular structure of this compound is shown in Figure 3. In the chemical structure the most interesting feature is the six-membered ketal ring formed from a ketone group at C-13 and the hydroxyl group at C-17. The locations of the hydroxyl groups at C-3, C-5, C-11, C-15, and of the amino sugar moiety mycosamine, bound β glycosidically as a pyranoside to the hydroxyl at C-19, are proposed for the first time. Comparing the amphotericin B structure solved by X-ray analysis with the most advanced partial structure proposed by Cope, *et al.*,[16] in 1966 (Figure 1) we found an important difference in the location of the *vic*-glycol system. Cope, *et al.*,[16] proposed the position of the *vic*-glycol at C-8 and C-7. In the present structure it was found to be at C-8 and C-9. To confirm this last important result, difference Fourier syntheses have been performed after removing the hydroxylic

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(21) To procure a copy of this table, order NAPS Document No. 01373 from ASIS National Auxiliary Publications Service, c/o CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022, remitting $1.00 for microfilm or $3.00 for photocopies. Advance payment is required. Make checks or money orders payable to: ASIS-NAPS.

Table I. Positional and Thermal Parameters of the Asymmetric Unit of *N*-Iodoacetylamphotericin B Tritetrahydrofuran Monohydrate and Their Standard Deviations in Parentheses[a]

Atom	*x*	*y*	*z*	*B*	Atom	*x*	*y*	*z*	*B*
O-1, -37	0.3927 (8)	0.1620 (22)	0.7828 (9)	4.5 (4)	C-36	0.2837 (9)	0.2192 (27)	0.7742 (10)	2.1 (4)
C-1	0.4308 (13)	0.0841 (37)	0.7489 (15)	4.8 (6)	C-37	0.3286 (10)	0.0920 (27)	0.7845 (11)	2.3 (4)
O-1	0.4173 (10)	−0.0385 (28)	0.7212 (11)	6.3 (5)	C-38	0.3367 (12)	0.0079 (33)	0.8535 (14)	4.1 (6)
C-2	0.4900 (11)	0.1785 (32)	0.7441 (13)	3.7 (5)	C-39	0.2967 (13)	0.3175 (36)	0.8497 (15)	4.9 (6)
C-3	0.5199 (14)	0.1095 (40)	0.6854 (16)	5.4 (7)	C-40	0.1228 (12)	0.1068 (34)	0.6415 (14)	3.8 (5)
O-3	0.5427 (12)	−0.0351 (35)	0.7098 (14)	8.9 (7)	C-41	0.0570 (12)	0.2949 (35)	0.1892 (14)	4.5 (6)
C-4	0.5870 (11)	0.1895 (30)	0.6824 (12)	3.2 (5)	O-41	0.0650 (8)	0.1608 (22)	0.1748 (9)	4.4 (4)
C-5	0.6165 (12)	0.1301 (33)	0.6197 (14)	3.7 (5)	O-41′	0.0700 (9)	0.4070 (25)	0.1580 (10)	5.2 (4)
O-5	0.6294 (11)	−0.0243 (30)	0.6282 (12)	7.0 (6)	O-19, -42	0.8963 (6)	−0.0237 (18)	0.1881 (8)	2.4 (3)
C-6	0.6786 (12)	0.2234 (36)	0.6250 (13)	4.4 (6)	C-42	0.8991 (11)	−0.0731 (30)	0.1188 (12)	3.1 (5)
C-7	0.7119 (12)	0.1539 (32)	0.5628 (13)	3.7 (5)	O-42, -46	0.8439 (7)	−0.1758 (20)	0.0910 (8)	3.7 (4)
C-8	0.7801 (10)	0.2225 (30)	0.5752 (11)	2.7 (4)	C-43	0.9639 (10)	−0.1650 (27)	0.1277 (11)	2.3 (4)
O-8	0.8204 (7)	0.1934 (19)	0.6441 (8)	2.9 (3)	O-43	0.9662 (7)	−0.2844 (21)	0.1822 (8)	3.8 (3)
G-9	0.8086 (10)	0.1596 (28)	0.5095 (12)	2.9 (5)	C-44	0.9648 (11)	−0.2434 (36)	0.0534 (13)	3.9 (5)
O-9	0.8063 (7)	−0.0029 (19)	0.5093 (8)	3.1 (3)	C-45	0.9097 (10)	−0.3380 (27)	0.0289 (11)	2.3 (4)
C-10	0.8795 (10)	0.2180 (29)	0.5209 (11)	2.7 (4)	O-45	0.9051 (8)	−0.3944 (23)	−0.0456 (9)	4.2 (4)
C-11	0.8992 (10)	0.1857 (26)	0.4473 (11)	2.2 (4)	C-46	0.8451 (13)	−0.2558 (43)	0.0194 (15)	5.3 (6)
O-11	0.9047 (7)	0.0308 (19)	0.4415 (8)	2.9 (3)	C-47	0.7827 (11)	−0.3358 (31)	0.0028 (13)	3.5 (5)
C-12	0.9708 (10)	0.2346 (30)	0.4589 (11)	2.6 (4)	N	0.0278 (8)	−0.3273 (21)	0.0707 (9)	2.0 (3)
C-13	0.0018 (9)	0.1943 (24)	0.3945 (10)	1.7 (4)	C-48	0.0774 (12)	−0.2929 (35)	0.0438 (14)	4.3 (6)
O-13	0.0146 (7)	0.0400 (19)	0.3957 (8)	2.9 (3)	O-48	0.0734 (10)	−0.1836 (26)	−0.0027 (11)	6.1 (5)
O-13, -17	0.9571 (5)	0.2443 (17)	0.3317 (6)	1.5 (2)	C-49	0.1399 (13)	−0.3579 (35)	0.0714 (14)	4.4 (6)
C-14	0.0660 (9)	0.2832 (27)	0.4018 (11)	2.3 (4)	I	0.1842 (2)	−0.2500[b]	0.1730 (2)	
C-15	0.0923 (8)	0.2715 (25)	0.3309 (10)	1.5 (4)					
O-15	0.1442 (8)	0.3733 (21)	0.3373 (9)	4.0 (4)			H_2O		
C-16	0.0363 (9)	0.3160 (24)	0.2655 (10)	1.4 (4)	O	0.9487 (9)	0.3256 (24)	0.7014 (10)	5.3 (4)
C-17	0.9783 (8)	0.2140 (24)	0.2655 (9)	1.3 (4)					
C-17	0.9783 (8)	0.2140 (24)	0.2655 (9)	1.3 (4)			Tetrahydrofuran A		
C-18	0.9203 (10)	0.2588 (31)	0.1983 (11)	2.8 (4)	O	0.2267 (11)	0.2412 (37)	0.2712 (12)	8.2 (6)
C-19	0.8690 (14)	0.1308 (38)	0.1902 (15)	5.1 (7)	C	0.3029 (14)	0.2048 (40)	0.2091 (15)	5.6 (7)
C-20	0.8340 (12)	0.1118 (33)	0.2552 (14)	3.9 (6)	C	0.2493 (16)	0.2945 (45)	0.2068 (18)	6.9 (8)
C-21	0.7739 (12)	0.1631 (31)	0.2538 (13)	3.6 (5)	C	0.3167 (15)	0.0958 (42)	0.2667 (17)	6.0 (7)
C-22	0.7420 (9)	0.1104 (26)	0.3084 (10)	1.8 (4)	C	0.2607 (19)	0.1218 (55)	0.3036 (21)	8.7 (10)
C-23	0.6831 (11)	0.1422 (29)	0.3110 (12)	2.8 (5)					
C-24	0.6448 (13)	0.0818 (36)	0.3623 (15)	4.5 (6)			Tetrahydrofuran B		
C-25	0.5852 (16)	0.1261 (46)	0.3608 (18)	6.9 (8)	C	0.6276 (25)	0.2014 (79)	0.9174 (28)	14.2 (17)
C-26	0.5500 (11)	0.0583 (30)	0.4123 (12)	3.1 (5)	C	0.6568 (32)	0.0653 (97)	0.9199 (36)	18.3 (24)
C-27	0.4918 (11)	0.1063 (31)	0.4156 (13)	3.2 (5)	C	0.7022 (24)	0.0581 (72)	0.9776 (28)	12.6 (15)
C-28	0.4569 (11)	0.0522 (32)	0.4698 (13)	3.4 (5)	C	0.7267 (20)	0.1883 (56)	0.0156 (22)	9.8 (11)
C-29	0.4025 (12)	0.1239 (33)	0.4778 (13)	3.6 (5)	C	0.6636 (26)	0.2874 (84)	0.9828 (30)	15.3 (18)
C-30	0.3595 (10)	0.0582 (28)	0.5257 (12)	2.5 (4)					
C-31	0.3124 (12)	0.1379 (34)	0.5413 (14)	4.2 (6)			Tetrahydrofuran C		
C-32	0.2762 (10)	0.0794 (29)	0.5928 (12)	2.8 (5)	C	0.5238 (30)	0.0466 (90)	0.0943 (34)	17.3 (21)
C-33	0.2302 (10)	0.1585 (28)	0.6171 (12)	2.7 (5)	C	0.4773 (29)	0.0851 (88)	0.0368 (33)	16.8 (21)
C-34	0.1965 (11)	0.0931 (31)	0.6751 (12)	3.2 (5)	C	0.4432 (25)	0.1902 (74)	0.0724 (28)	14.0 (17)
C-35	0.2133 (9)	0.1922 (25)	0.7465 (10)	1.8 (4)	C	0.4668 (25)	0.2136 (83)	0.1371 (28)	14.3 (17)
O-35	0.1880 (8)	0.1148 (21)	0.8002 (9)	3.8 (4)	C	0.5208 (34)	0.1424 (103)	0.1480 (39)	21.4 (27)

[a] The oxygen atoms and the carbon atoms of the methyl groups are labeled with numbers of the corresponding carbon atoms to which they are bonded. [b] This coordinate was kept fixed during the refinement, in order to fix the origin. The anisotropic thermal factors of the iodine atom, in the form $\exp[-1/4(h^2a^{*2}B_{11} + k^2b^{*2}B_{22} + l^2c^{*2}B_{33} + 2hka^*b^*B_{12} + 2hla^*c^*B_{13} + 2klb^*c^*B_{23})]$, are: B_{11} = 10.9 ± 0.2; B_{22} = 14.0 ± 0.3; B_{33} = 7.4 ± 0.1; B_{12} = 1.3 ± 0.2; B_{13} = 0.8 ± 0.1; B_{23} = −2.3 ± 0.2.

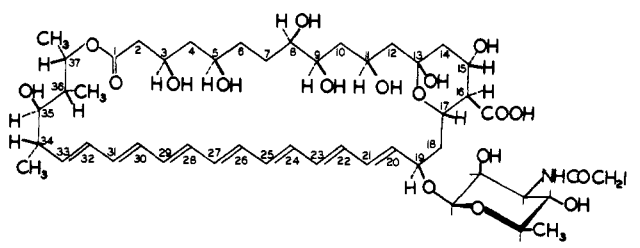

Figure 2. Chemical structure of *N*-iodoacetylamphotericin B[1] with indicated absolute configuration. Dotted lines indicate bonds directed below the plane of the page.

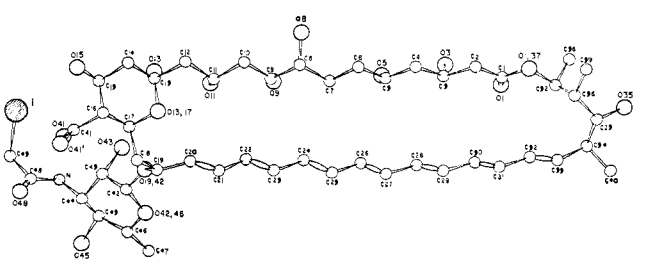

Figure 3. Molecular structure of *N*-iodoacetylamphotericin B. The atoms are labeled according to Table I.

group bonded to C-9 and also after changing its position to C-7. These syntheses agreed with the structure reported here. The arrangement of side groups at C-16 and C-17 proposed by Cope, *et al.*,[16] could not be confirmed although the position of the carboxyl group at C-16 as well as the locations of the double bonds and methyl groups were found the same. Several considerations for the molecular conformation are possible in spite of the large standard deviations of the geometrical parameters. The heptaene chromophore lo-

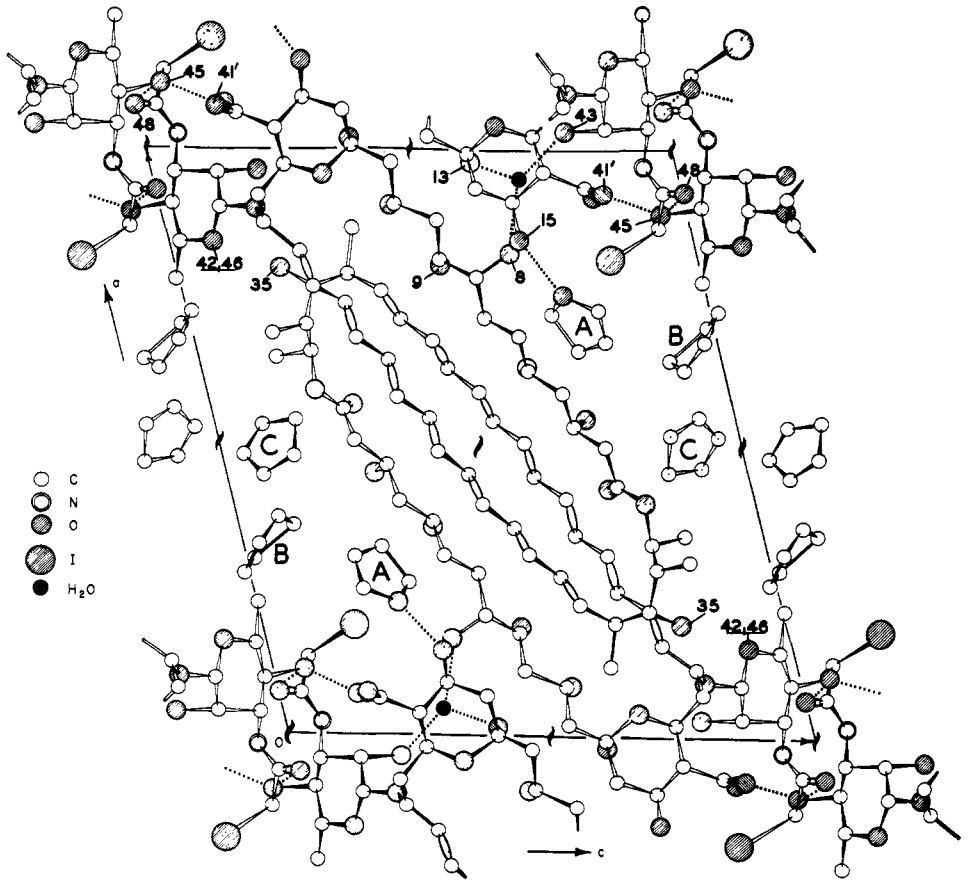

Figure 4. Crystal structure of *N*-iodoacetylamphotericin B tritetrahydrofuran monohydrate on 010 plane. Some hydrogen bridges are indicated with dotted lines. The water molecules form hydrogen bonds between molecules laying almost on the planes 101.

cated from C-19 to C-34 is characterized by seven conjugated double bonds in the trans configuration. Within the standard deviations the conformation is planar, "full extended."

The single and double bonds are clearly recognizable: (C=C) 1.33 ± 0.05 Å, (C—C) 1.50 ± 0.05 Å. The saturated chain from C-1 to C-13 on the opposite side of the chromophore in the macrolidic ring is almost in a trans "full-extended" conformation. The torsion angles about the bonds C(1)–C(2) through C(11)–C(12) are 180 ± 6°. The six-membered ketal ring build of C-13 to C-17 and O-13 and O-17 as well as the mycosamine pyranosidic ring both have chair conformations. The lengths of bonds and torsion angles are quite normal. The largest deviations from the usual values can be found on the less rigid parts of the molecule, that is, at the opposite side to the ketal ring, and at the mycosamine moiety. This fact can be explained in terms of thermal vibrations. The difference in rigidity of this large molecule can be explained on grounds of stereochemical and packing considerations and also by the high concentration of hydrogen bonds only in some regions of the crystal. The C–OH bond lengths of the hydroxyl groups of the macrolidic lactone ring are all about 1.41 ± 0.05 Å. This fact makes it possible to recognize the hydroxylic groups. Within the standard deviations all the single bonds have "staggered" conformations and those at the two ends of the conjugated heptaene chain have the expected "skew" conformation.[22] Out of the three molecules of tetrahydrofuran included in the asymmetric unit and indicated as A, B, and C in Figure 4, only molecule A is hydrogen bonded from $O_A \cdots$O-15 (2.69 Å); the other two are clathrated in the crystal. The geometry of these three rings is very distorted and the thermal parameters are also very high. This fact is clearly related to the high disorder of the molecules of solvent. Therefore, no particular meaning can be attributed to the conformational parameters of the tetrahydrofuran rings.

Crystal Structure. The projection of the structure on the *a*–*c* plane is shown in Figure 4. The molecules of *N*-iodoacetylamphotericin B are arranged in stackwise fashion and displaced pairwise by 0.5 (from the twofold screw axes) with the macrolactone rings nearly parallel to each other at distances of about 4.3 Å. It is remarkable that the long sequences of conjugated double bonds are packed closely together and form a narrow (*ca.* 1.6 × 16 Å) hydrophobic channel parallel to the *b* axes. This hydrophobic channel is surrounded quite equally by the hydrophilic groups of the lactone rings. The most hydrophilic parts of the *N*-iodoacetylamphotericin B molecules—the amino sugar moieties and the carboxyl groups—are packed along the *b* axes and form a strong hydrophilic channel. In this channel an amino sugar moiety of one molecule is linked to a carboxyl group and an amide group related by the twofold screw axes neighbor molecule through hydrogen bridges between atoms from O-45$\cdots$O-41′ (2.68 Å) and O-45$\cdots$O-48 (2.70 Å). The amino sugar moiety is also joined intramolecularly to the lactone ring by hydrogen bonds with water

(22) C. W. Bunn, *Proc. Roy. Soc., Ser. A*, 180, 67 (1942).

molecules through atoms $H_2O\cdots O$-43 (2.62 Å) and $H_2O\cdots O$-13 (2.85 Å). Inspection of the intermolecular distances below 3.0 Å revealed a number of possible hydrogen bonds. Molecules in which the lactone rings partially overlap each other and form the discussed hydrophobic channel (Figure 4) are joined by weak hydrogen bonds from atoms O-35$\cdots$O-42, -46 (2.94 Å). A list of true and possible hydrogen bonds is presented in Table II. The empty space between molecular planes in the crystal structure is filled with molecules of tetrahydrofuran. It is interesting that the clathrated molecules of tetrahydrofuran (B and C) are packed parallel to the *a–b* plane and the hydrogen-bonded water molecules are packed parallel to the *b–c* plane.

Table II. Intermolecular O$\cdots$O Distances in the Crystal Structure of *N*-Iodoacetylamphotericin B Tritetrahydrofuran Monohydrate Corresponding to Hydrogen and Possible Hydrogen Bonds

a. Hydrogen bonds	b. Possible hydrogen bonds
$H_2O\cdots$O-43 (2.62 Å)	O-8$\cdots$O-15 (2.91 Å)
$H_2O\cdots$O-13 (2.85 Å)	$H_2O\cdots$O-8 (2.92 Å)
O-45$\cdots$O-41 (2.68 Å)	O-42, -46$\cdots$O-35 (2.94 Å)
O-45$\cdots$O-48 (2.70 Å)	
O_A[a]$\cdots$O-15 (2.69 Å)	

[a] Oxygen atom of the tetrahydrofuran molecule A.

Conclusions

The total structure of *N*-iodoacetylamphotericin B was fully elucidated by X-ray single-crystal analysis. Apart from the interesting chemical findings, the structure reveals a significant stereochemical feature of the polar groups of the macrolactone ring. Most hydroxyl groups are "axial" in respect to the mean plane of the lactone ring and disposed on the same side of the plane, together with the pyranosidal mycosamine moiety which is β glycosidically bound through the "axial" oxygen atoms O-19 and -42. A similar phenomenon can be observed when one compares the two "full extended" fragments of the lactone ring, that is the chromophore moiety from C-18 to C-34 and the part opposite to it from C-15 to C-37. The chromophore part is thoroughly hydrophobic while the other one is hydrophilic. As expected, the hydrophobic regions of molecules pack together, and the hydrophilic regions hydrogen bond the rest of the structure together. It is worthy to note also that of all the "axial" hydroxyl groups of the lactone ring only the one at C-13 takes part in hydrogen bondings in the crystal structure (Figure 4) while in case of the "equatorial" groups—at C-8, C-15, C-35, and the carboxyl group at C-16—all are so involved. The specific polarization of the hydrophilic and hydrophobic properties between different regions of the very elongated molecule and the observed difference between "axial" and "equatorial" hydroxyl groups toward forming hydrogen bridges undoubtedly bears an important role in the mode of action of amphotericin B and similar antibiotics. Also the conformation established for the studied compound in the crystal state could be useful in this regard. Perun and Egan[23] found that in the case of erythromycin—a macrolide antibiotic—the conformation of the macrolactone ring in solution did not change when compared with the crystal state.[24]

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