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Structure of 9-Deoxo-9a-*N*-[*N'*-(4-pyridyl)-carbamoyl]-9a-aza-9a-homoerythromycin A and Conformational Analysis of Analogous 9a-Aza 15-Membered Azalides in the Solid State

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Abstract

$C_{43}H_{74}N_4O_{13}.C_3H_6O$, M_r = 913, triclinic, $P1$, a = 10.3796 (5), b = 14.5809 (5), c = 17.1521 (9) Å, α = 105.225 (3), β = 96.140 (5), γ = 90.248 (3)°, V = 2489.0 (2) Å^3, Z = 2 (two independent molecules in the asymmetric unit), D_x = 1.218 g cm^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, T = 106 (3) K, $F(000)$ = 992, μ(Cu $K\alpha$) = 7.0 cm^{-1}, R = 0.057 for 8724 observed unique reflections with $I > 2\sigma(I)$. Conformational analysis is based on X-ray structure determinations of 9-deoxo-9a-*N*-[*N'*-(4-pyridyl)-carbamoyl]-9a-aza-9a-homoerythromycin A (1) and its *N*-isopropyl-carbamoyl congener (2) and data for 9a-aza 15-membered azalides retrieved from the Cambridge Structural Database (Version 5.07). The analysis reveals that the aglycone ring conformation has been influenced by the presence or absence of glyco conjugation at C3 and C5 sites in azalide derivatives. However, more drastic influence is related to the appearance of intramolecular hydrogen bonds. Compounds with 9a N atoms in sp^3 hybridization exhibit N—H···O contacts which are absent in compounds with 9a N atoms in sp^2 hybridization; they reveal O—H···O intramolecular hydrogen bonds. The 15-membered azalides studied are in 'folded-out' conformation in the solid state. The α-L-cladinose sugar moiety is in $^1C_4$ conformation, while the β-D-desosamine adopts a $^4C_1$ conformation. The absolute configurations at the aglycone chiral centres are as follows: *C2R*, *C3S*, *C4S*, *C5R*, *C6R*, *C8R*, *C10R*, *C11R*, *C12S* and *C13R*.

Introduction

9-Deoxo-9a-*N*-[*N'*-(4-pyridyl)-carbamoyl]-9a-aza-9a-homoerythromycin A (1) is a member of the novel series of 9-deoxo-9a-(*N*-substituted-carbamoyl)-9a-aza-9a-homoerythromycin A compounds (Kujundžić,

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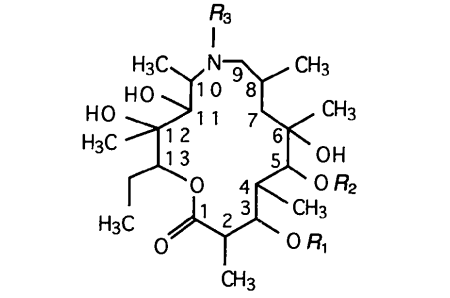
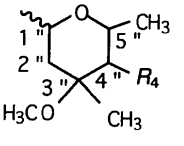
Kobrehel & Kelnerić, 1993), synthesized within the development programme of new macrolide antibiotics – azalides. Originally, azalides were a group of semi-synthetic antibiotics modified to a 15-membered ring by introducing nitrogen into the 14-membered ring of erythromycin A (Đokić, Kobrehel, Lazarevski, Lopotar, Tamburašev, Kamenar, Nagl & Vicković, 1986; Đokić, Kobrehel, Lopotar, Kamenar, Nagl & Mrvoš, 1988*a*,*b*; Bright, Nagel, Bordner, Desai, Dibrino, Nowakowska, Vincent, Watrous, Sciavolino, English, Retsema, Anderson, Brennan, Borovoy, Cimochowski, Faiella, Girard, Girard, Herbert, Manousos & Mason, 1988). The stereochemistry of 12-, 14- and 16-membered macrolides has already been described (Celmer, 1971; Nakagawa & Omura, 1984; Everett & Tyler, 1987; Keller, Neeland, Retting, Trotter & Weiler, 1988; Everett, Hatton, Hunt, Tyler & Williams, 1989). However, solid-state conformations of 15-membered azalides have not yet been reviewed. Therefore, we report on the conformational analysis of 15-membered azalides (Scheme 1) retrieved from the Cambridge Structural Database (Version 5.07; 1994) (3)–(7), and our data obtained by crystal structure determinations of (1), reported in this paper, and its analogue (2) (Kujundžić, Kobrehel, Kelnerić, Banić, Kojić-Prodić, 1995).

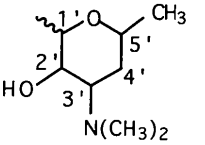
Experimental

Crystals of (1) suitable for X-ray analysis were grown from acetone/*n*-heptane solution by slow evaporation at room temperature over 2–3 d. The crystal data and a summary of the experimental details are listed in Table 1. The X-ray intensity data were collected on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromatized Cu $K\alpha$ radiation at liquid nitrogen temperature. There were no significant variations in intensity for the standard reflections. The data were corrected for Lorentz and polarization effects using the Enraf–Nonius *SDP/VAX* package (B. A. Frenz & Associates Inc., 1982). The structure was solved by the 'phase annealing' direct method (Sheldrick, 1990) using 50 000 sets of random starting phases. The solution with clearly the best figures of merit [$R(\alpha) = 0.085$, $NQUAL = -0.80$] yielded, after three cycles of *E*-Fourier recycling, all 128 atoms. Refinement was by full-matrix least-squares, minimizing $\Sigma w(|F_o| - |F_c|)^2$ with the *SHELX*76 system of programs (Sheldrick, 1976) using *F* values. Scattering factors were those included in *SHELX*76 (Sheldrick, 1976). For the structure solved in the space group $P1$, the origin was fixed with the *x*, *y*, *z* coordinates of O1*A*. Some of the H-atom coordinates were determined





α-L-Cladinosyl



β-D-Desosaminyl

Compound	Refcode	R_1	R_2	R_3	R_4
(1)		α-L-Cladinosyl	β-D-Desosaminyl	—C(=O)—NH— 	—OH
(2)		α-L-Cladinosyl	β-D-Desosaminyl	—C(=O)—NH— 	—OH
(3)	GEGJAD	α-L-Cladinosyl	β-D-Desosaminyl	$-CH_3$	—OH
(4)	SAWHAZ	α-L-Cladinosyl	β-D-Desosaminyl	$-CH_3$	$-NH_2$
(5)	CUHPUQ10	—H	—H	—H	
(6)	KEYNIL	—H	—H	$-CH_3$	
(7)	VOHCEA	—H	—H	$-CH_2CH_3$	

Scheme 1. Chemical diagrams of the compounds studied (1 and 2) and those extracted from the literature (3–7).

from successive difference Fourier syntheses and the others were calculated on stereochemical grounds and refined riding on their respective C atoms with an overall temperature factor. H atoms on O121*A*, O41″*A*, N16*B* and O21′*B* were not located. The O—H and N—H bond distances, except O111*A*—H, were normalized to the values 0.98 and 1.01 Å, respectively, obtained by neutron diffraction (Allen, Kennard & Watson, 1987). The molecular geometry was calculated by the program package *EUCLID* (Spek, 1982). Drawings were prepared by the programs *ORTEP*II (Johnson, 1976) and *PLUTON* incorporated in *EUCLID* (Spek, 1982). The final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 2.* Calculations were performed on MicroVAXII and Silicon Graphics workstation IRIS-4D25G of the X-ray Laboratory, Rudjer Bošković Institute (Zagreb, Croatia).

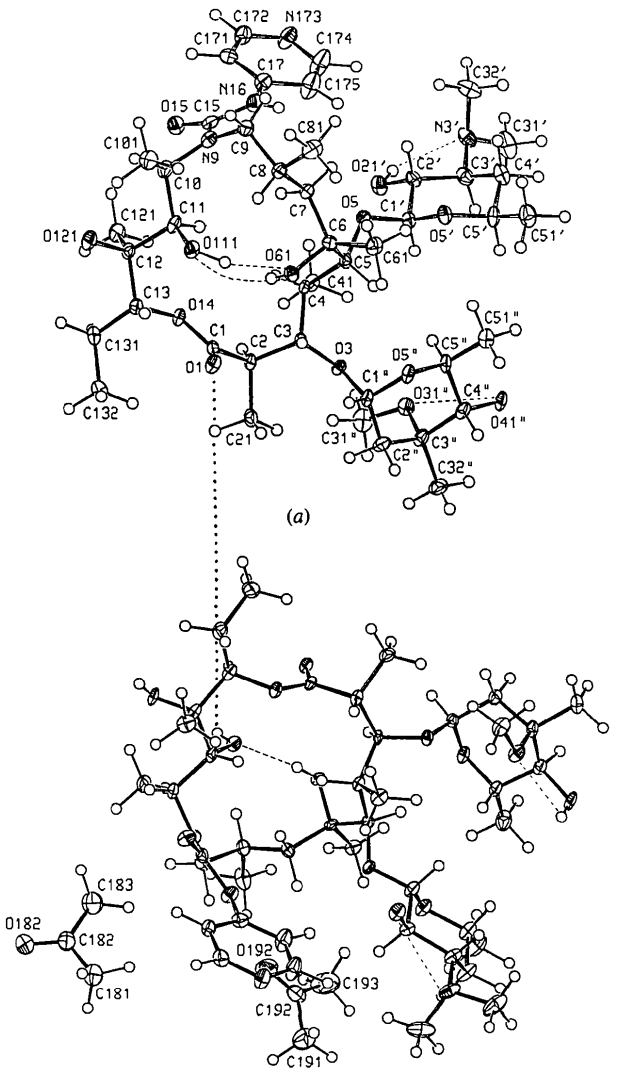


Fig. 1. Molecular structure of (1) using *ORTEP* (Johnson, 1976), with atom numbering. The thermal ellipsoids are at the 50% probability level. In order to avoid the overlap of molecules (*a*) *A* and (*b*) *B*, translation of molecule *B* from its original location was applied. Intramolecular hydrogen bonds are indicated by dashed lines. A striking difference in the hydrogen-bonding pattern of molecules *A* and *B* is shown: O61—H···O111*A*, O111*A*—H···O61*A*, O61*B*—H···O111*B* (dashed lines), O111*B*—H···O1*A* (dotted line).

Results and discussion

X-ray structure analysis

The molecular structure of (1) consists of a polyfunctional 15-membered azalactone ring and two sugar residues: α-L-cladinose – neutral sugar (double-primed atoms) and β-D-desosamine – amino sugar (primed

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SE0165). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CHI 2HU, England.

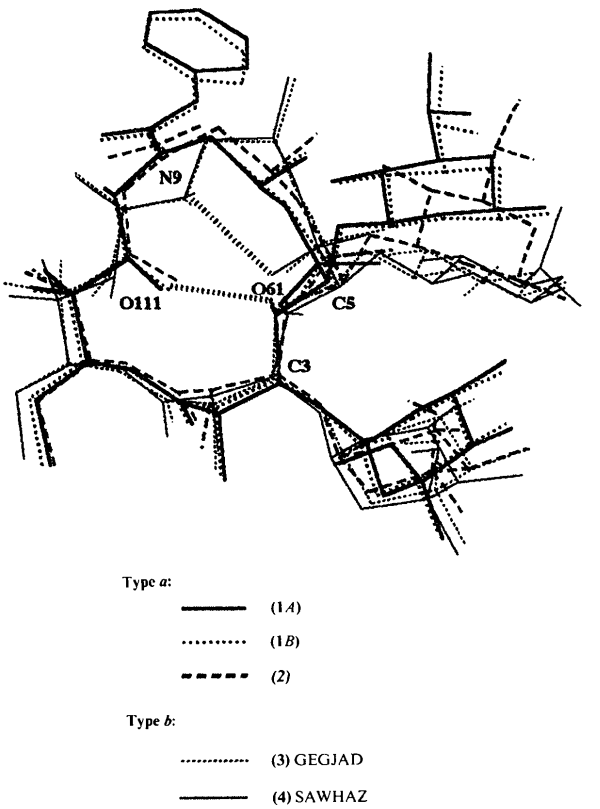


Fig. 2. The superposition diagram of aglycone moieties in azahomoerythromycins A. Two distinctive types of conformations are shown: (*a*) (1*A*), (1*B*) and (2) characterized by the intramolecular hydrogen bond O61—H···O111 and (*b*) (3) and (4) characterized by the O61···N9 interaction; intramolecular hydrogen bonds are indicated by dashed lines.

atoms), linked by a glycosidic linkage to positions 3 and 5 of the aglycone macrocycle, respectively. The molecular structure with the atom numbering is shown in Fig. 1; the *ORTEP*II plot (Johnson, 1976) is drawn with thermal ellipsoids at the 50% probability level. The compound crystallizes with two independent molecules (*A* and *B*) in the asymmetric unit and two solvent acetone molecules. Molecular geometries of (1) and (2) are compared (Tables 3, 4 and 6). The bond angles about the glycosidic bond for cladinose sugar residues are: 115.1 (5) (*A*) and 115.8 (5)° (*B*) in (1) and 114.4 (6)° in (2), and for the desosamine sugar residues: 118.5 (6) (*A*) and 116.8 (6)° (*B*) in (1) and 118.0 (5)° in (2) (Table 4). Both sugar residues are in the chair conformation: α-L-cladinose in $^1C_4$ and β-D-desosamine in $^4C_1$. The overall conformation of both independent molecules is very similar (Fig. 2, Table 6). The known absolute configurations of β-D-desosamine and α-L-cladinose have been used as internal standards to determine the absolute configuration of aglycone chiral centres. The absolute configurations are as follows: C2*R*, C3*S*, C4*S*, C5*R*, C6*R*, C8*R*, C10*R*, C11*R*, C12*S* and C13*R*.

The crystal packings of (1) and (2) (not published in Kujundžić *et al.*, 1995) are dominated by hydrogen bonds (Figs. 3 and 4, Table 5). In the crystal structure of (1) infinite chains of molecules *A*, formed by the hydrogen bond O121—H*···O41″ (* not located in a difference Fourier map, Table 5), are running along *b*. The same type of hydrogen bond connects *B* molecules. These alternating *A* and *B* chains are cross-linked in the *bc* plane *via* O41″—H···N173 hydrogen bonds in an *AB* and *BA* fashion. An infinite two-dimensional network in the *bc* plane is completed by the O111*B*—H···O1*A* hydrogen bond. In addition to these intermolecular hydrogen bonds, one intramolecular contact involving O41″—H···O31″ (in both molecules, *A* and *B*; Table 5) occurs. The pattern obtained might be assigned as a bifurcated hydrogen bond (Steiner &

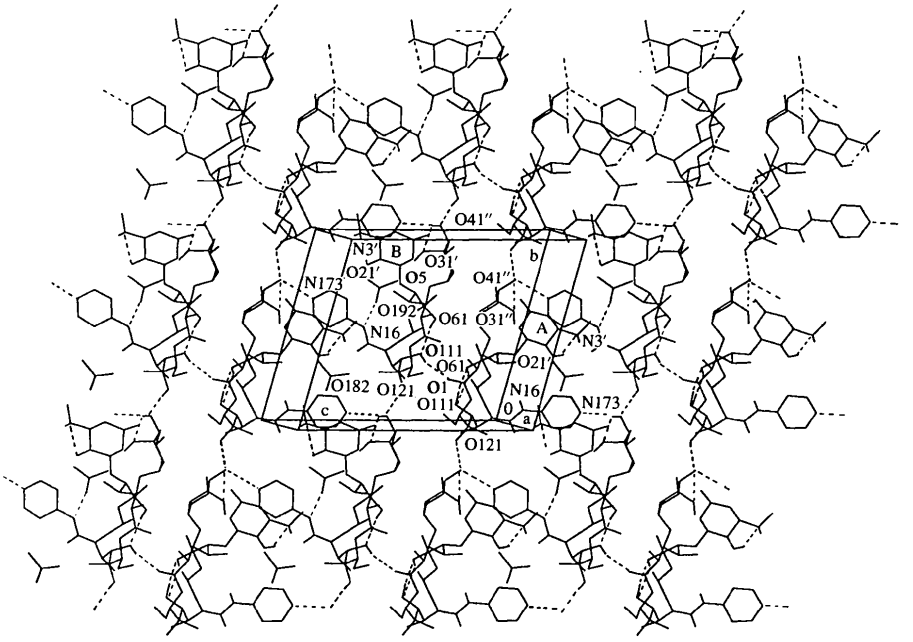


Fig. 3. Crystal structure with hydrogen-bond network for (1). The H atoms involved in hydrogen bonds are shown, whereas others are omitted for clarity. Hydrogen bonds between the carbamoyl nitrogen (N16*A*) and water molecule (O182) are not indicated on the figure.

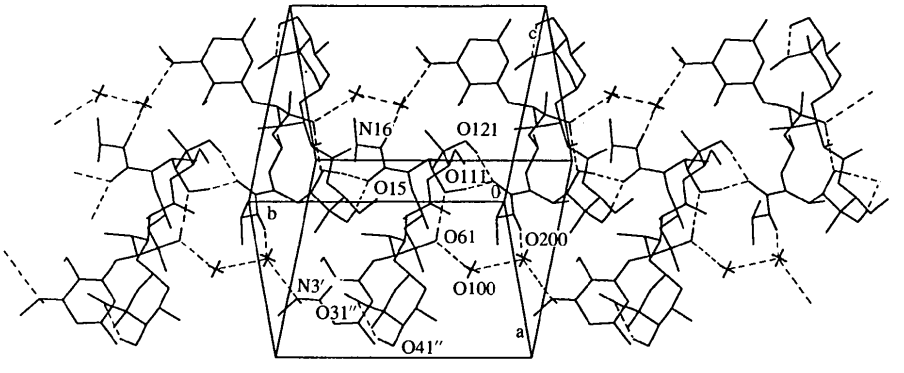


Fig. 4. Crystal structure with hydrogen-bond network for (2). The H atoms involved in hydrogen bonds are shown, whereas others are omitted for clarity.

Saenger, 1994). In molecule *A* there are three more intramolecular hydrogen bonds (Table 5) involving two hydroxyl groups of the aglycone moiety (O61—H···O111, O111—H···O61) and the O21′ hydroxyl group of the β-D-desosamine moiety, being a donor to its amino N3′ atom (Table 5). However, molecule *B* reveals a somewhat different pattern of intramolecular hydrogen bonds; there is no double intramolecular proton donation between O61 and O111 (as in molecule *A*). The hydroxyl O61*B*—H group acts as a donor to O111*B*, forming an intramolecular hydrogen bond, whereas O111*B* is a donor to O1*A*, participating in the intermolecular hydrogen bond (Fig. 1). The different pattern is due to the various local molecular environments around particular hydroxyl groups of molecules *A* and *B* (Fig. 3). The H atom of the O21′*B* hydroxyl group was not located. However, the donor···acceptor distance (Table 5) suggests an O21′*B*—H*···N3′*B* hydrogen bond; this type of interaction is detected in molecule *A* (Table 5). Each azalide molecule with a carbamoyl nitrogen is hydrogen bonded to a solvent acetone molecule.

In the crystal packing of (2) (Table 5, Fig. 4) azalide molecules related by a 2_1 operation are connected by two hydrogen bonds involving two hydroxyl groups, O111 and O121, as donors and the carbamoyl O15 atom as an acceptor (Table 5); a spiral along *b* is formed. Intramolecular hydrogen bonds between the two hydroxyl groups O61—H···O111 and O41″—H···O31″ are present again, as in (1). Water molecules complete the hydrogen-bond network.

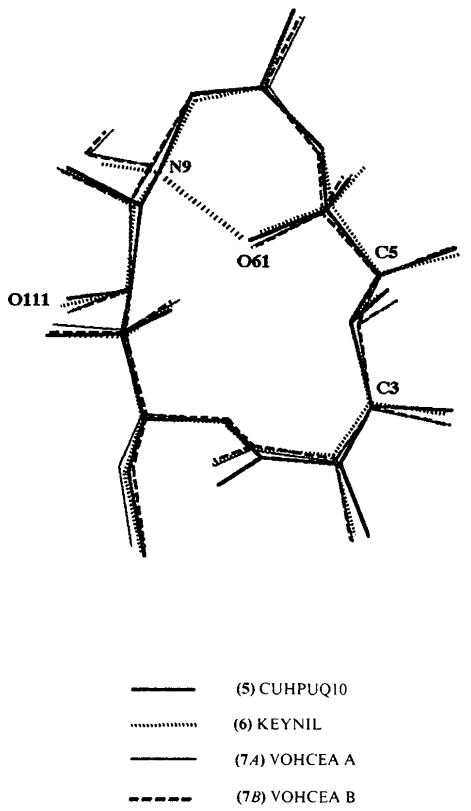


Fig. 5. The superposition diagram of aglycone in the azahomoerythronolides A (5, 6, 7*A* and *B*), illustrating the similarity of conformations defined by the intramolecular hydrogen bond O61···N9 (dashed line; type *b* in Fig. 2).

Table 1. *Crystal data and summary of experimental details for* (1)

Crystal data	
Molecular formula	$C_{43}H_{74}N_4O_{13}.C_3H_6O$
M_r	913
Crystal size (mm)	0.252 × 0.144 × 0.432
Crystal system	Triclinic
a (Å)	10.3796 (5)
b (Å)	14.5809 (5)
c (Å)	17.1521 (9)
α (°)	105.225 (3)
β (°)	96.140 (5)
γ (°)	90.248 (3)
V (Å^3)	2489.0 (2)
Space group	$P1$
Z	2
D_{calc} (g cm^{-3})	1.218
μ (cm^{-1})	7.0
F(000)(e)	992
Data collection	
Diffractometer	Enraf–Nonius CAD-4
Radiation	Cu $K\alpha$
λ (Å)	1.54184
T(K)	106 (3)
No. of reflections used for cell parameters and θ range (°)	25 21–42
θ range for intensity measurement	2.7–74.3
hkl range	−12, 12; −18, 18; −21, 0
Scan	$\omega/2\theta$
$\Delta\omega$	$1.04 + 0.27 \tan\theta$
No. of measured reflections	10485
No. of symmetry independent reflections	8724, $I > 2\sigma(I)$
Refinement	
No. of variables	1292
Quantity minimized	$\sum w(\|F_o\| - \|F_c\|)^2$; $w = 1$
R,S	0.057, 1.40
Final <shift/error>	≤ 0.05
Residual electron density $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ (e Å^{-3})	0.53, −0.35

Comparative conformational analysis

Comparative conformational analysis of 9a-aza 15-membered azalides includes seven compounds (Scheme 1): 9-deoxo-9a-*N*-[*N*′-(4-pyridyl)-carbamoyl]-9a-aza-9a-homoerythromycin A (1), *N*′-isopropyl-carbamoyl analogue (2) (Kujundžić *et al.*, 1993; Kujundžić, Kobrehel, Kelnerić, Banić & Kojić-Prodić, 1995), and Cambridge Structural Database hits (3)–(7) (Đokić *et al.*, 1988*a*,*b*): (3) GEGJAD (Bright *et al.*, 1988); (4) SAWHAZ (Đokić *et al.*, 1986); (5) CUHPUQ10 (Kamenar, Mrvoš-Sermek, Vicković & Nagl, 1990); (6) KEYNIL (Kamenar, Mrvoš-Sermek, Banić, Nagl & Kobrehel, 1991); (7) VOHCEA (Scheme 1). Erythronolide A iminoether (9-deoxo-6-dehydroxy-6,9-epoxy-9,9a-didehydro-9a-aza-9a-homoerythronolide A, refcode CUHPIE10) (Đokić *et al.*, 1986) was not included in the analysis because of chemically imposed

Table 2. *Final atomic coordinates and equivalent isotropic thermal parameters* (Å^2), *with e.s.d.'s in parentheses, for* (1)

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

Molecule *A*†	*x*	*y*	*z*	U_{eq}(Å^2)
O1‡	0.46178 (0)	0.23913 (0)	0.33133 (0)	0.0214 (11)
O3	0.5161 (5)	0.4557 (4)	0.2130 (3)	0.0155 (11)
O5	0.2071 (6)	0.3554 (4)	0.0328 (3)	0.0177 (11)
O5′	0.1010 (6)	0.4906 (4)	0.0298 (3)	0.0219 (12)
O5″	0.3777 (6)	0.5797 (4)	0.2598 (3)	0.0195 (11)
O14	0.5127 (5)	0.1366 (4)	0.2160 (3)	0.0161 (11)
O15	0.2248 (6)	−0.0514 (4)	−0.0554 (3)	0.0242 (12)
O21′	0.3064 (6)	0.3506 (4)	−0.1148 (3)	0.0238 (12)
O31″	0.6580 (6)	0.6065 (4)	0.1684 (3)	0.0216 (12)
O41″	0.5095 (6)	0.7635 (4)	0.1738 (3)	0.0224 (11)
O61	0.1980 (6)	0.2868 (4)	0.2210 (3)	0.0176 (11)
O111	0.2178 (6)	0.0942 (4)	0.2262 (3)	0.0215 (12)
O121	0.3452 (6)	−0.0891 (4)	0.2036 (3)	0.0236 (11)
N3′	0.1766 (6)	0.4549 (5)	−0.2137 (4)	0.0246 (17)
N9	0.0884 (6)	0.0192 (4)	0.0368 (4)	0.0205 (14)
N16	0.0901 (7)	0.0605 (5)	−0.0850 (4)	0.0240 (17)
N173	0.1825 (7)	0.0526 (5)	−0.3204 (4)	0.0314 (19)
C1	0.5064 (7)	0.2240 (5)	0.2670 (4)	0.0172 (17)
C1′	0.2100 (7)	0.4348 (5)	0.0032 (4)	0.0191 (17)
C1″	0.4901 (7)	0.5331 (5)	0.2787 (4)	0.0171 (16)
C2	0.5647 (7)	0.3002 (5)	0.2356 (4)	0.0154 (16)
C2′	0.1974 (7)	0.4029 (5)	−0.0891 (4)	0.0200 (17)
C2″	0.6073 (8)	0.6011 (5)	0.3049 (4)	0.0233 (17)
C3	0.4591 (7)	0.3655 (5)	0.2127 (4)	0.0153 (17)
C3′	0.1830 (7)	0.4884 (5)	−0.1246 (4)	0.0231 (17)
C3″	0.6283 (7)	0.6618 (5)	0.2471 (4)	0.0209 (17)
C4	0.3869 (7)	0.3209 (5)	0.1270 (4)	0.0150 (16)
C4′	0.0732 (7)	0.5500 (5)	−0.0900 (5)	0.0271 (17)
C4″	0.5015 (7)	0.7078 (5)	0.2299 (4)	0.0196 (17)
C5	0.2526 (7)	0.3656 (5)	0.1177 (4)	0.0161 (17)
C5′	0.0941 (7)	0.5758 (5)	0.0022 (5)	0.0243 (17)
C5″	0.3898 (7)	0.6335 (5)	0.2005 (4)	0.0181 (16)
C6	0.1435 (7)	0.3223 (5)	0.1543 (4)	0.0174 (17)
C7	0.0795 (7)	0.2350 (5)	0.0904 (4)	0.0162 (17)
C8	−0.0121 (7)	0.1690 (5)	0.1187 (4)	0.0195 (17)
C9	−0.0293 (7)	0.0713 (5)	0.0548 (4)	0.0212 (17)
C10	0.1565 (7)	−0.0265 (5)	0.0982 (4)	0.0212 (17)
C11	0.2651 (7)	0.0410 (5)	0.1531 (4)	0.0179 (16)
C12	0.3862 (7)	−0.0120 (5)	0.1743 (4)	0.0172 (16)
C13	0.4763 (7)	0.0535 (5)	0.2436 (4)	0.0190 (17)
C15	0.1400 (7)	0.0050 (5)	−0.0353 (4)	0.0196 (17)
C17	0.1254 (7)	0.0552 (5)	−0.1627 (4)	0.0218 (17)
C21	0.6691 (7)	0.3542 (5)	0.3033 (5)	0.0228 (17)
C31′	0.2147 (9)	0.5298 (6)	−0.2497 (5)	0.038 (3)
C31″	0.7646 (8)	0.5458 (6)	0.1673 (5)	0.0302 (19)
C32′	0.0499 (8)	0.4121 (6)	−0.2521 (5)	0.0344 (19)
C32″	0.7361 (8)	0.7383 (5)	0.2847 (5)	0.031 (2)
C41	0.4709 (7)	0.3285 (5)	0.0613 (4)	0.0187 (17)
C51′	−0.0156 (8)	0.6336 (5)	0.0411 (5)	0.032 (2)
C51″	0.2603 (7)	0.6794 (5)	0.1909 (5)	0.0257 (17)
C61	0.0497 (7)	0.4012 (5)	0.1857 (4)	0.0224 (17)
C81	−0.1511 (7)	0.2051 (5)	0.1286 (5)	0.0302 (19)
C101	0.0608 (7)	−0.0633 (5)	0.1460 (5)	0.0266 (17)
C121	0.4569 (7)	−0.0488 (5)	0.0979 (4)	0.0235 (17)
C131	0.6015 (7)	0.0093 (5)	0.2673 (5)	0.0258 (17)
C132	0.6765 (8)	0.0704 (5)	0.3458 (5)	0.035 (2)
C171	0.1578 (7)	−0.0289 (5)	−0.2170 (4)	0.0223 (17)
C172	0.1835 (7)	−0.0259 (5)	−0.2937 (4)	0.0248 (17)
C174	0.1533 (10)	0.1326 (6)	−0.2669 (5)	0.043 (3)
C175	0.1240 (9)	0.1378 (6)	−0.1895 (5)	0.040 (2)
Solvent molecules§				
O182	0.8706 (6)	0.2015 (4)	0.9060 (4)	0.0393 (17)
C181	0.8064 (9)	0.3572 (6)	0.9668 (5)	0.043 (3)
C182	0.8209 (7)	0.2735 (5)	0.8954 (5)	0.0305 (19)
C183	0.7697 (10)	0.2818 (6)	0.8127 (5)	0.047 (3)
O192	0.8357 (7)	0.6600 (5)	0.7942 (4)	0.0422 (17)
C191	0.9150 (11)	0.8024 (7)	0.8929 (6)	0.058 (3)
C192	0.8828 (8)	0.7398 (6)	0.8071 (5)	0.036 (2)
C193	0.9126 (11)	0.7804 (7)	0.7399 (6)	0.061 (3)
Molecule *B*†				
O1	0.2456 (5)	0.4223 (4)	0.3729 (3)	0.0184 (11)
O3	0.2066 (5)	0.7132 (4)	0.4817 (3)	0.0159 (11)
O5	0.5155 (6)	0.7408 (4)	0.6610 (3)	0.0175 (11)
O5′	0.6154 (6)	0.8783 (4)	0.6549 (3)	0.0237 (11)
O5″	0.3349 (6)	0.7954 (4)	0.4165 (3)	0.0183 (11)
O14	0.1939 (6)	0.3931 (4)	0.4892 (3)	0.0174 (11)
O15	0.4825 (6)	0.3855 (4)	0.7537 (3)	0.0221 (12)
O21′	0.4168 (6)	0.8368 (4)	0.8077 (3)	0.0256 (12)
O31″	0.0779 (6)	0.8910 (4)	0.5271 (3)	0.0209 (12)
O41″	0.2264 (6)	1.0353 (4)	0.5119 (4)	0.0235 (13)
O61	0.5361 (6)	0.5599 (4)	0.4698 (3)	0.0167 (11)
O111	0.4779 (6)	0.3732 (4)	0.4851 (3)	0.0189 (12)
O121	0.3762 (6)	0.1800 (4)	0.4921 (3)	0.0192 (11)
N3′	0.5281 (7)	1.0106 (5)	0.8930 (4)	0.0295 (17)
N9	0.6221 (6)	0.3968 (4)	0.6619 (4)	0.0184 (14)
N16	0.6120 (6)	0.5199 (4)	0.7793 (4)	0.0225 (14)
N173	0.5250 (7)	0.6645 (5)	1.0127 (4)	0.0285 (19)
C1	0.2041 (6)	0.4488 (5)	0.4387 (4)	0.0149 (16)
C1′	0.5092 (7)	0.8402 (5)	0.6841 (4)	0.0219 (17)
C1″	0.2196 (7)	0.7411 (5)	0.4093 (4)	0.0158 (16)
C2	0.1520 (7)	0.5467 (5)	0.4700 (4)	0.0167 (16)
C2′	0.5219 (7)	0.8717 (5)	0.7770 (4)	0.0202 (17)
C2″	0.1019 (7)	0.7942 (5)	0.3884 (4)	0.0201 (17)
C3	0.2626 (7)	0.6248 (4)	0.4859 (4)	0.0141 (16)
C3′	0.5262 (7)	0.9809 (5)	0.8035 (5)	0.0243 (17)
C3″	0.0924 (7)	0.8929 (5)	0.4447 (4)	0.0197 (17)
C4	0.3385 (7)	0.6382 (5)	0.5705 (4)	0.0155 (16)
C4′	0.6352 (8)	1.0214 (5)	0.7668 (5)	0.031 (2)
C4″	0.2237 (7)	0.9456 (5)	0.4538 (4)	0.0198 (17)
C5	0.4706 (7)	0.6929 (5)	0.5767 (4)	0.0155 (16)
C5′	0.6175 (8)	0.9814 (5)	0.6747 (5)	0.028 (2)
C5″	0.3378 (7)	0.8882 (5)	0.4738 (4)	0.0196 (17)
C6	0.5847 (7)	0.6295 (5)	0.5443 (4)	0.0162 (16)
C7	0.6389 (7)	0.5783 (5)	0.6077 (4)	0.0167 (17)
C8	0.7292 (7)	0.4956 (5)	0.5822 (4)	0.0179 (17)
C9	0.7416 (7)	0.4376 (5)	0.6456 (4)	0.0204 (17)
C10	0.5568 (7)	0.3123 (5)	0.6024 (4)	0.0176 (16)
C11	0.4396 (7)	0.3438 (5)	0.5525 (4)	0.0180 (16)
C12	0.3244 (7)	0.2695 (5)	0.5284 (4)	0.0174 (16)
C13	0.2275 (7)	0.2924 (5)	0.4620 (4)	0.0179 (16)
C15	0.5666 (7)	0.4300 (5)	0.7325 (4)	0.0185 (17)
C17	0.5750 (7)	0.5647 (5)	0.8563 (4)	0.0205 (17)
C21	0.0424 (7)	0.5572 (5)	0.4067 (4)	0.0210 (17)
C31′	0.4809 (9)	1.1071 (6)	0.9215 (6)	0.044 (3)
C31″	−0.0296 (8)	0.8367 (5)	0.5380 (5)	0.0279 (17)
C32′	0.6519 (8)	1.0011 (7)	0.9366 (5)	0.040 (2)
C32″	−0.0167 (7)	0.9479 (5)	0.4119 (5)	0.0291 (19)
C41	0.2567 (7)	0.6888 (5)	0.6373 (4)	0.0208 (17)
C51′	0.7287 (8)	1.0110 (5)	0.6358 (5)	0.034 (2)
C51″	0.4670 (7)	0.9347 (5)	0.4669 (5)	0.0297 (19)
C61	0.6842 (7)	0.6920 (5)	0.5218 (4)	0.0192 (17)
C81	0.8696 (7)	0.5260 (5)	0.5741 (5)	0.0287 (19)
C101	0.6511 (7)	0.2528 (5)	0.5503 (4)	0.0227 (17)
C121	0.2612 (7)	0.2677 (5)	0.6042 (5)	0.0260 (17)
C131	0.1000 (7)	0.2340 (5)	0.4451 (5)	0.0256 (19)
C132	0.0122 (7)	0.2480 (5)	0.3722 (5)	0.0307 (19)
C171	0.5532 (7)	0.5164 (5)	0.9139 (4)	0.0206 (17)
C172	0.5309 (7)	0.5695 (5)	0.9906 (4)	0.0224 (17)
C174	0.5385 (9)	0.7094 (5)	0.9547 (5)	0.035 (2)
C175	0.5643 (9)	0.6629 (5)	0.8767 (5)	0.034 (2)

† There are two independent molecules in the asymmetric unit.
‡ The origin was fixed by *x*, *y*, *z* coordinates of O1.
§ Chloroform molecules.

Table 3. *Bond lengths* (Å) *in aglycone ring for* (1) *and* (2)

	(1)		(2)
	Molecule *A*	Molecule *B*	
O1—C1	1.210 (7)	1.219 (8)	1.198 (3)
C1—C2	1.506 (1)	1.511 (10)	1.522 (9)
C2—C21	1.545 (10)	1.523 (10)	1.536 (10)
C2—C3	1.541 (10)	1.564 (10)	1.574 (10)
O3—C3	1.438 (10)	1.432 (9)	1.437 (8)
C3—C4	1.550 (9)	1.539 (10)	1.543 (9)
C4—C41	1.522 (10)	1.532 (10)	1.540 (10)
C4—C5	1.553 (10)	1.563 (10)	1.565 (8)
O5—C5	1.451 (8)	1.455 (8)	1.432 (9)
C5—C6	1.559 (10)	1.564 (10)	1.548 (9)
C6—C61	1.536 (10)	1.519 (10)	1.542 (8)
O61—C6	1.439 (9)	1.447 (9)	1.426 (9)
C6—C7	1.539 (10)	1.535 (10)	1.559 (9)
C7—C8	1.550 (10)	1.531 (10)	1.522 (9)
C8—C81	1.549 (10)	1.552 (10)	1.537 (9)
C8—C9	1.549 (10)	1.539 (10)	1.546 (9)
N9—C9	1.460 (10)	1.458 (10)	1.461 (8)
N9—C15	1.366 (9)	1.370 (9)	1.371 (9)
O15—C15	1.221 (10)	1.226 (10)	1.247 (8)
C15—N16	1.387 (10)	1.395 (10)	1.367 (8)
N16—C17	1.402 (9)	1.406 (9)	1.473 (9)
N9—C10	1.505 (10)	1.484 (10)	1.481 (9)
C10—C101	1.532 (10)	1.515 (10)	1.546 (10)
C10—C11	1.551 (10)	1.553 (10)	1.543 (9)
O111—C11	1.427 (9)	1.427 (9)	1.437 (7)
C11—C12	1.540 (10)	1.556 (10)	1.563 (9)
C12—C121	1.544 (10)	1.524 (10)	1.537 (9)
O121—C12	1.427 (9)	1.425 (9)	1.443 (9)
C12—C13	1.536 (10)	1.542 (10)	1.544 (10)
C13—C131	1.517 (10)	1.529 (10)	1.528 (8)
C131—C132	1.534 (11)	1.526 (11)	1.521 (11)
O14—C13	1.473 (9)	1.475 (9)	1.467 (9)
O14—C1	1.349 (9)	1.345 (9)	1.355 (7)

Table 4. *Bond angles* (°) *in aglycone ring for* (1) *and* (2)

	(1)		(2)
	Molecule *A*	Molecule *B*	
O1—C1—O14	123.9 (6)	123.9 (7)	125.0 (4)
O1—C1—C2	123.9 (6)	123.1 (7)	124.4 (6)
C1—O14—C13	118.4 (5)	118.6 (5)	117.2 (5)
C1—C2—C3	110.7 (6)	110.6 (6)	108.6 (5)
C1—C2—C21	106.4 (6)	106.3 (6)	108.1 (7)
C2—C3—C4	111.5 (6)	111.1 (5)	109.6 (5)
C3—C2—C21	112.8 (6)	113.3 (6)	116.0 (5)
C3—C4—C41	110.7 (6)	110.6 (6)	110.6 (5)
C3—C4—C5	110.6 (6)	110.8 (6)	111.2 (5)
O3—C3—C2	110.2 (6)	109.1 (6)	113.1 (5)
O3—C3—C4	108.2 (5)	108.7 (5)	107.0 (5)
C1″—O3—C3	115.1 (5)	115.8 (5)	114.4 (6)
C4—C5—C6	114.6 (6)	115.2 (6)	113.3 (5)
C5—C4—C41	112.9 (6)	111.4 (6)	113.6 (5)
C5—C6—C61	108.2 (6)	108.3 (6)	108.7 (5)
C5—C6—C7	109.5 (5)	109.7 (5)	107.7 (5)
O5—C5—C4	111.1 (6)	110.7 (6)	112.3 (5)
O5—C5—C6	106.7 (6)	105.3 (6)	105.1 (5)
C1′—O5—C5	118.5 (6)	116.8 (6)	118.0 (5)
C6—C7—C8	118.1 (6)	118.8 (6)	117.9 (6)
O61—C6—C5	110.3 (6)	108.8 (6)	109.4 (5)
O61—C6—C61	109.0 (5)	106.5 (5)	105.8 (5)
O61—C6—C7	105.4 (6)	109.5 (6)	111.9 (5)
C7—C6—C61	114.4 (6)	114.1 (6)	113.3 (5)
C7—C8—C81	114.9 (6)	114.5 (6)	114.6 (5)
C7—C8—C9	109.6 (5)	110.2 (6)	110.2 (5)
C9—C8—C81	105.4 (6)	106.0 (6)	106.0 (5)
C9—N9—C10	119.8 (6)	120.4 (6)	122.0 (5)
C9—N9—C15	123.9 (6)	123.3 (6)	117.4 (5)
N9—C9—C8	116.6 (6)	116.9 (6)	117.4 (5)
N9—C10—C101	111.9 (6)	111.9 (6)	110.9 (5)
N9—C10—C11	110.7 (6)	109.7 (6)	109.0 (5)
N9—C15—N16	115.0 (6)	115.0 (6)	116.6 (6)
O15—C15—N9	123.6 (7)	123.4 (7)	122.8 (5)
O15—C15—N16	121.4 (6)	121.6 (6)	120.6 (6)
C15—N16—C17	124.7 (7)	124.5 (6)	120.2 (5)
C10—N9—C15	116.2 (6)	116.2 (6)	120.6 (5)
C10—C11—C12	112.7 (6)	113.2 (6)	116.1 (5)
C11—C10—C101	113.5 (6)	113.7 (5)	113.6 (6)
C11—C12—C121	109.6 (5)	109.1 (6)	110.2 (5)
C11—C12—C13	110.3 (6)	110.3 (6)	109.5 (5)
O111—C11—C10	110.4 (6)	111.9 (6)	111.2 (5)
O111—C11—C12	109.5 (5)	113.1 (5)	110.9 (5)
C12—C13—C131	114.7 (6)	113.8 (6)	114.7 (5)
O121—C12—C11	108.1 (6)	107.0 (6)	112.3 (5)
O121—C12—C121	110.7 (6)	111.9 (6)	105.7 (5)
O121—C12—C13	107.0 (5)	106.1 (5)	106.9 (5)
C13—C12—C121	111.0 (6)	112.3 (6)	112.2 (5)
C13—C131—C132	112.6 (6)	113.3 (6)	113.5 (6)
O14—C1—C2	112.2 (6)	112.9 (6)	110.5 (4)
O14—C13—C12	107.5 (5)	108.5 (5)	107.1 (5)
O14—C13—C131	106.9 (6)	106.6 (6)	108.1 (5)

conformational rigidity due to the bicyclic structure. The conformations of azahomoerythromycins A (1)–(4) and azahomoerythronolides A (not conjugated to sugars) (5)–(7) are compared in terms of the torsion angles of the macrocyclic lactone ring (Table 6). The aglycone rings of azahomoerythronolides A (5)–(7) have not revealed significant differences in conformation (Table 6, Fig. 5); the compounds studied do not include bulky ring substituents which might affect the conformation.

The conformation is stabilized by the intramolecular hydrogen bond O61···N9 involving an sp^3-9a-aza group. The aglycone ring conformation in azahomoerythromycins A (1)–(4) is affected by glycation at C3 and C5 (Table 6, torsion angles *T*2 and *T*4). In addition to this influence, intramolecular hydrogen bonds are found to be the dominating factor in aglycone conformations (Table 6, Fig. 2). The compounds with N9 in sp^2 hybridization exhibit intramolecular hydrogen bonds between O61 and O111 (1*A*, 1*B* and 2, Fig. 2), whereas those with N9 in sp^3 show intramolecular hydrogen bonds between O61 and N9 (3 and 4, Fig. 2; 5, 6 and 7, Fig. 5). One explanation that has been offered is that in (1*A*), (1*B*) and (2) one of the electron pairs of the C=O double bond neighbouring N9 may be partially transfered to O, leaving the C atom electron deficient and thus facilitating the transfer of the lone pairs from N into the N—C bond. This accounts for the planar 120° arrangement of the bonds around nitrogen in carbamoyl derivatives (Gillespie, 1972). In addition, the delocalization of the nitrogen lone-pair decreases the electron density at N9, thus reducing nitrogen basicity, and favours the O61···O111 hydrogen bond. The deviations of N from the best least-squares planes through its next neighbours are 0.015 in (1) (both molecules) and 0.009 Å in (2), whereas in (3)–(7) with N in sp^3, departure from the plane is significant (*ca* 0.330 Å). These two distinctive conformations are represented in Fig. 6 by puckering diagrams of (1) and (3).

Thus, (3) and (4) show more similarity to azahomoerythronolides A [Fig. 6, puckering diagrams of (3) and (6)]. The conformations about the characteristic

Table 5. *Hydrogen bonds and short contacts for* (1) *and* (2)

	$D\cdots A$ (Å)	D—H (Å)	H$\cdots A$ (Å)	D—H$\cdots A$ (°)	Symmetry operations on A
(1)					
O21′*A*—H···N3′*A*	2.809 (9)	0.98 (10)	2.12 (9)	126 (7)	x, y, z
O21′*B*—H*···N3′*B*	2.750 (9)				x, y, z
O41″*A*—H*···O31″*A*	2.752 (9)				x, y, z
O41″*B*—H···O31″*B*	2.686 (9)	0.98 (10)	2.64 (10)	82 (9)	x, y, z
O61*A*—H···O111*A*	2.841 (8)	0.98 (10)	2.35 (10)	110 (7)	x, y, z
O111*A*—H···O61*A*	2.841 (8)	0.99 (9)	1.87 (9)	168 (7)	x, y, z
O61*B*—H···O111*B*	2.870 (8)	0.98 (6)	1.93 (6)	160 (5)	x, y, z
O111*B*—H···O1*A*	2.829 (5)	0.98 (7)	2.03 (7)	137 (5)	x, y, z
O41″*A*—H*···N173*B*	2.783 (8)				$x, y, z-1$
O41″*B*—H···N173*A*	2.906 (9)	0.98 (10)	2.04 (10)	146 (9)	$x, y+1, z+1$
O121*A*—H*···O41″*A*	2.726 (9)				$x, y-1, z$
O121*B*—H···O41″*B*	2.729 (9)	0.98 (7)	1.77 (7)	168 (6)	$x, y-1, z$
N16*A*—H···O182	3.094 (10)	1.01 (7)	2.22 (7)	143 (5)	$x-1, y, z-1$
N16*B*—H*···O192	3.031 (10)				x, y, z
(2)					
O61—H···O111	2.720 (6)	0.98 (3)	1.74 (3)	176 (3)	x, y, z
O41″—H···O31″	2.699 (8)	0.98 (3)	2.16 (2)	114 (2)	x, y, z
O111—H···O15	2.681 (6)	0.99 (3)	1.79 (3)	148 (2)	$1-x+1, -\frac{1}{2}+y-1, 1-z+1$
O121—H···O15	2.735 (6)	0.99 (3)	1.79 (2)	161 (2)	$1-x+1, -\frac{1}{2}+y-1, 1-z+1$
N16—H···O200	2.841 (9)	1.00 (3)	1.96 (3)	145 (2)	$1-x+1, \frac{1}{2}+y, 1-z+1$
O200—H*···N3′	2.819 (9)				$x, y-1, z$
O100—H*···O61	2.720 (6)				x, y, z
O100···O200	2.897 (10)				x, y, z

A and *B* are two crystallographically independent molecules of (1)
O182 and O192 in solvent molecules (acetone) in (1).
O100 and O200 in solvent molecules (water) in (2).
* Hydrogens not located in the difference map; donor–acceptor distances might be short contacts only.

Table 6. *Comparison of torsion angle values* (°) *of aglycone ring for 9a-aza 15-membered azalides*

	Refcode	*T*1 C1→C2	*T*2 C2→C3	*T*3 C3→C4	*T*4 C4→C5	*T*5 C5→C6	*T*6 C6→C7	*T*7 C7→C8	*T*8 C8→C9	*T*9 C9→N9	*T*10 N9→C10	*T*11 C10→C11	*T*12 C11→C12	*T*13 C12→C13	*T*14 C13→O14	*T*15 O14→C1
(1*A*)		112.29	**−81.79**	158.70	**−81.96**	−86.97	167.93	**−161.47**	58.59	**72.57**	**−93.79**	−142.37	−166.81	−59.16	133.57	171.57
(1*B*)		116.85	**−84.31**	163.66	**−85.19**	−77.97	166.07	**−164.48**	58.14	**74.75**	**−101.49**	−146.53	−165.61	−51.19	128.65	173.24
(2)		132.12	**−99.89**	160.36	**−91.32**	−71.14	171.00	**−158.13**	62.69	**73.23**	**−108.52**	−151.94	−169.65	−48.79	129.84	−178.04
(3)	GEGJAD*	122.51	**−91.53**	178.81	**−109.61**	−70.41	174.92	−109.32	67.88	−148.79	158.50	−157.11	163.13	−77.45	121.29	176.68
(4)	SAWHAZ	116.90	**−111.78**	168.23	**−96.19**	−76.42	−179.03	−92.67	64.04	−153.33	148.91	160.25	158.90	−67.05	132.11	−178.89
(5)	CUHPUQ10*	86.46	−41.87	165.56	−145.75	−67.05	169.95	−105.97	56.23	−135.81	163.03	−172.18	158.37	−72.97	137.25	178.85
(6)	KEYNIL	114.57	−58.74	172.82	−146.74	−59.46	168.27	−107.79	59.00	−141.13	157.20	−162.90	161.54	−74.97	123.01	173.19
(7*A*)	VOHCEA A	112.83	−62.06	167.65	−138.34	−62.61	−178.36	−100.40	50.29	−126.84	149.93	−165.03	168.27	−77.71	123.53	174.40
(7*B*)	VOHCEA B	113.63	−60.79	165.85	−136.64	−64.32	−178.29	−101.02	52.42	−127.74	148.54	−169.65	164.51	−70.42	121.44	169.68

The torsional angles in bold are subject to significant changes.
* The incorrect enantiomer assignments in the original references were corrected.

C7—C8, C9—N9 and N9—C10 bonds (Table 6, *T*7, *T*9 and *T*10 values), for compounds exhibiting intramolecular O61···N9 hydrogen bonds (3–7*A*, 7*B*), are (±)-anticlinal (Klyne & Prelog, 1960). However, in compounds (1*A*), (1*B*) and (2) the lack of this interaction changes the conformations to antiperiplanar about C7—C8, (+)-synclinal about C9—N9 and (−)-anticlinal about N9—C10 (Table 6, *T*7, *T*9 and *T*10 values in bold); as a consequence the intramolecular O61···O111 hydrogen bond occurs. The overall conformation of the 15-membered macrocycle is, therefore, influenced by a few factors: the size of the substituent and hybridization at N9, the presence of intramolecular hydrogen bonds and the glycation at C3 and C5 positions. The conformation about the glycosidic bond (torsion angles: C2—C3→O3—C1″, C3—O3→C1″—O5″, C4—C5→O5—C1′, C5—O5→C1′—O5′) is between (−)-anticlinal and (−)-synclinal.

In order to obtain a correlation between the conformation of the aglycone ring in solution determined by ^{1}H NMR spectroscopy and molecular modelling (Lazarevski, Vinković, Kobrehel, Đokić, Metelko & Vikić-Topić, 1993), the distances between characteristic protons were analysed. According to these authors, the conformation with a close H11···H4 contact (for numbering see Scheme 1), found in the crystalline state and more polar solutions, is defined as 'folded-out' in contrast to the typical 'folded-in' conformation in solution with a close H11···H3 contact. In the structures analysed, in spite of local conformational differences, the short proton distances C11—H11···H4—C4 were observed, which characterize the 'folded-out' conformation. However, in the structure of 4″-α-amino-4″-9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A (4), C11—H11···H3—C3 and C11—H11···H4—C4 distances are 3.37 and 3.23 Å, respectively. According

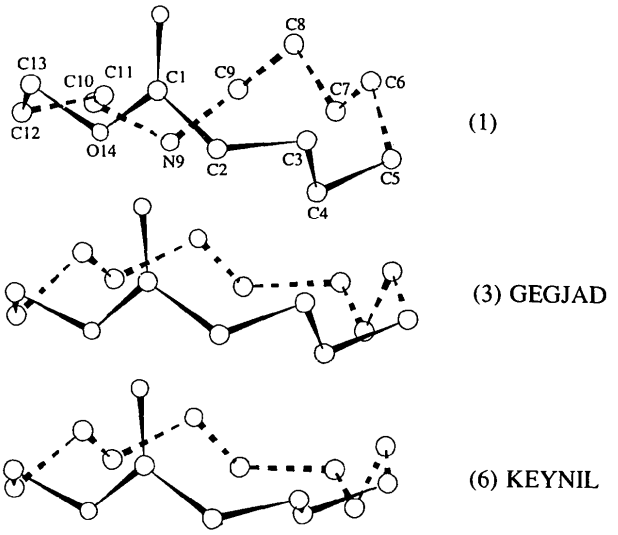


Fig. 6. Three characteristic aglycone ring puckerings observed in the 15-membered azalides studied.

to proton···proton distance criterion, this conformation can be treated as transition one between 'folded-in' and 'folded-out' conformations.

The absolute configurations of all the studied azalides are as stated previously for (1). For (3) and (5) incorrect enantiomers were published. In our comparative analysis the enantiomer conversion was applied (marked with asterisks).

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