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Conformational Behaviour of 11-*O*-Methylazithromycin in the Solid and Solution State

Nada Košutić-Hulita,[a] *Dijana Matak-Vinković,*[a] *Mladen Vinković,*[b,*] *Predrag Novak,*[b] *Gabrijela Kobrehel,*[c] *and Gorjana Lazarevski*[c]

[a] *Laboratory of General and Inorganic Chemistry, Faculty of Science, University of Zagreb, Ulica kralja Zvonimira 8, 10000 Zagreb, Croatia*

[b] *Analytical Centre, PLIVA-Research&Development, Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia*

[c] *Antiinfectives, PLIVA-Research&Development, Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia*

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Conformational behaviour of azithromycin 11-OMe derivative **2** (Scheme 1) has been studied in the solid and solution state. In the $CDCl_3$ and DMSO solution, **2** mainly adopts the »folded-in« conformation. 11-OMe group is oriented toward the centre of aglycone ring. The crystal structure of DMSO solvate of **2** has been solved by the molecular replacement method using the solution state conformation as the search model. Conformation of **2** in the solid and solution state is very similar. Molecules of **2** are held together in the crystal by van der Waals interactions, forming a solvent channel along the *b* axis. The DMSO molecule is found to be disordered and bound to cladinose moiety of **2** by H-bond O4"-H...O1s.

Key words: azithromycin, crystal structure, molecular replacement, NMR.

INTRODUCTION

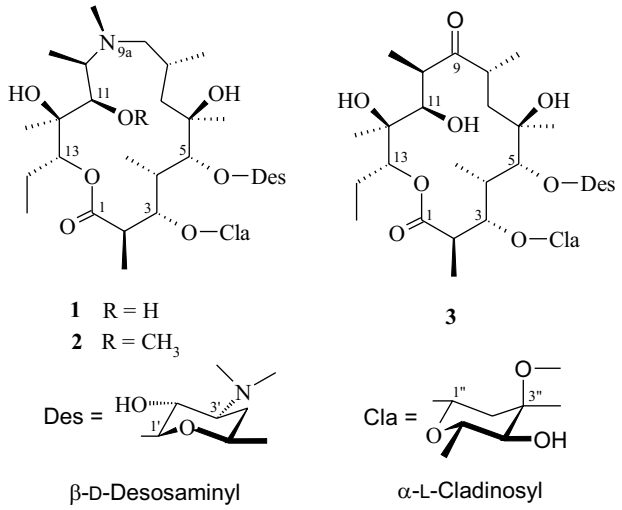
Azithromycin **1** (Scheme 1) is the first and medically most important member of azalide antibiotics.[1–3] It differs structurally from the parent erythro-

* Author to whom correspondence should be addressed. (E-mail: mladen@chem.pmf.hr)

mycin A macrolide **3** by insertion of a methyl substituted nitrogen at position 9a in the lactone ring to create a 15-membered macrocycle. In view of their medical importance, the solid and solution state conformations of various azithromycin derivatives and their aglycones have been studied by X-ray diffraction[4–6] and NMR spectroscopy combined with the molecular modelling techniques.[7–8]

Erythromycin A derivatives are known to exist in two main conformational families. The so called »folded-out« conformation is based on the crystal structure of erythromycin A hydroiodide[9] while the »folded-in« one is based on the crystal structure of dirithromycin.[10] The main difference between them is in region C3-C5 with the C4-methyl group folded into the space between sugar moieties (folded-in) or out of molecule (folded-out), adopting a more axial position. The consequence of these changes is a different spatial arrangement of sugar moieties. Desosamine and cladinose are oriented closer to each other in the »folded-out« conformation than in the »folded-in« conformation.[7] The conformation of macrolide antibiotics bound to ribosome (target) is studied by NMR. It is reported that **1** adopts the »folded-out« conformation while weakly bound to 50 S ribosome particle.[11]

As reported in our previous paper,[12] a series of *O*-methylazithromycin derivatives has been synthesised and their antibacterial activity has been compared with that of **1**. Among them, 11-*O*-methylazithromycin **2** has improved antibacterial activity in comparison to **1**. We have recently described the X-ray structure of 11,12,4''-tri-*O*-methylazithromycin monohydrate.[13] This



Scheme 1

compound adopts the »folded-in« conformation, which is also found in the solution state conformation of **1**.[7]

In this paper, we report the structure of **2** in solution and in solid state and its comparison with the conformational behaviour of other azalides.

EXPERIMENTAL

NMR Measurements

Preliminary solution state structure of **2** was published previously.[14] The structure lacked information on the orientation of 11-OMe group. Therefore, additional ROESY[15,16] experiments in $CDCl_3$ and DMSO were performed and analysed.

^1H NMR spectra in $CDCl_3$ and DMSO-d_6 were recorded at 293 K with a Varian Unity Inova 600 spectrometer operating at 14.1 T. Deuterium resonance from the solvent was used as the lock signal and TMS as the internal standard. Sample concentration was 10 mg mL^{-1}. The typical spectra conditions were as follows. Spectral width was 5631 Hz, acquisition time 3.4 s and 8–16 scans per spectrum. Spectra were zero filled to 64 K to give a digital resolution of 0.15 Hz per point after Fourier transformations. Resolution enhancement functions were used where necessary.

Two-dimensional ROESY spectra in $CDCl_3$ and DMSO-d_6 were recorded in phase sensitive mode using the TPPI method. Each experiment was obtained with 4 scans, the spectral width of 5361 Hz and relaxation delay of 2 s. Mixing time was 400 ms and the number of increments was 256. Spectra were recorded with 4096 data points in F2 and 1024 data points in F1 dimension, respectively. For processing 2D spectra, sine bell and sine bell shifted window functions were used. Cross peaks appeared as in phase multiplets with an opposite sign to the diagonal. The digital resolution was 2.6 Hz in F2 and 5.2 Hz per point in F1 dimension, respectively.

»Folded-in« model of **2**[14] was edited in such a way that 11-OMe group was oriented toward the centre of the molecule (11-OMe in) or out of the molecule (11-OMe out). Geometry of both models was optimised using the MM2 force field[17] and compared with the ROESY data (Table IV).

Crystallography

Crystals of 11-*O*-methylazithromycin **2** suitable for X-ray analysis were obtained by slow evaporation of the dimethyl sulfoxide (DMSO) – ethanol solution (1:1, *V/V*). Elongated plate-shaped single crystals of 1.5 mm length grew for about 1 week at room temperature and a crystal for diffraction experiment was cut out to the dimensions of $0.6 \times 0.5 \times 0.2$ mm^3. Crystal and experimental data are given in Table I. The X-ray diffraction data were collected in Θ range 2–25° (up to 0.84 Å) using a Philips PW1100 four circle diffractometer with graphite monochromatised Mo-Kα radiation. Intensity for the three standard reflections decayed by 12% during data collection. The data were corrected for Lorentz, polarisation and intensity decay effects using the XRED program.[18] However, the crystal had a low diffraction power and the first observed reflections ($I > 3\sigma(I)$) appeared at 1.0 Å resolution, while only 32% of reflections had $I > 3\sigma(I)$ in the resolution shell 1.32–1.52 Å. A total of 2832 independent

TABLE I

Experimental details

Chemical formula	$C_{39}H_{74}N_2O_{12} \times C_2H_6OS$
Chemical formula weight	841.13
Cell setting	monoclinic
Space group	$P2_1$
a/Å	12.163(6)
b/Å	8.879(7)
c/Å	23.168(15)
β/°	91.79(9)
V/Å^3	2501(3)
Z	2
D_x/Mg m^{-3}	1.109
Radiation type	Mo-Kα
Wavelength/Å	0.71073
Crystal size/mm	0.6 × 0.5 × 0.2
Crystal color	colourless
Diffractometer	Philips PW1100
No. of measured reflections	3193
θ_{max}/°	20.81
Range of h, k, l	$-12 \rightarrow h \rightarrow 12$ $0 \rightarrow k \rightarrow 8$ $0 \rightarrow l \rightarrow 23$
Refinement on	F^2
R_F	0.0636
$wR_F{}^2$	0.1668
S	1.002
No. of reflections used in refinement	1260
No. of parameters	508
$(\Delta\rho)_{min,\ max}$ /e Å^{-3}	–0.21, 0.27

reflections in the resolution range 10.0–1.0 Å had an overall R_{int} of 0.0629 and R_σ of 0.1456.

Attempts to solve the structure by direct methods implemented in SIR97 (Ref. 19) and SHELXS97 (Ref.20) program packages failed and we turned our attention to the molecular replacement program AMoRe[21] from the CCP4 package.[22] Search models

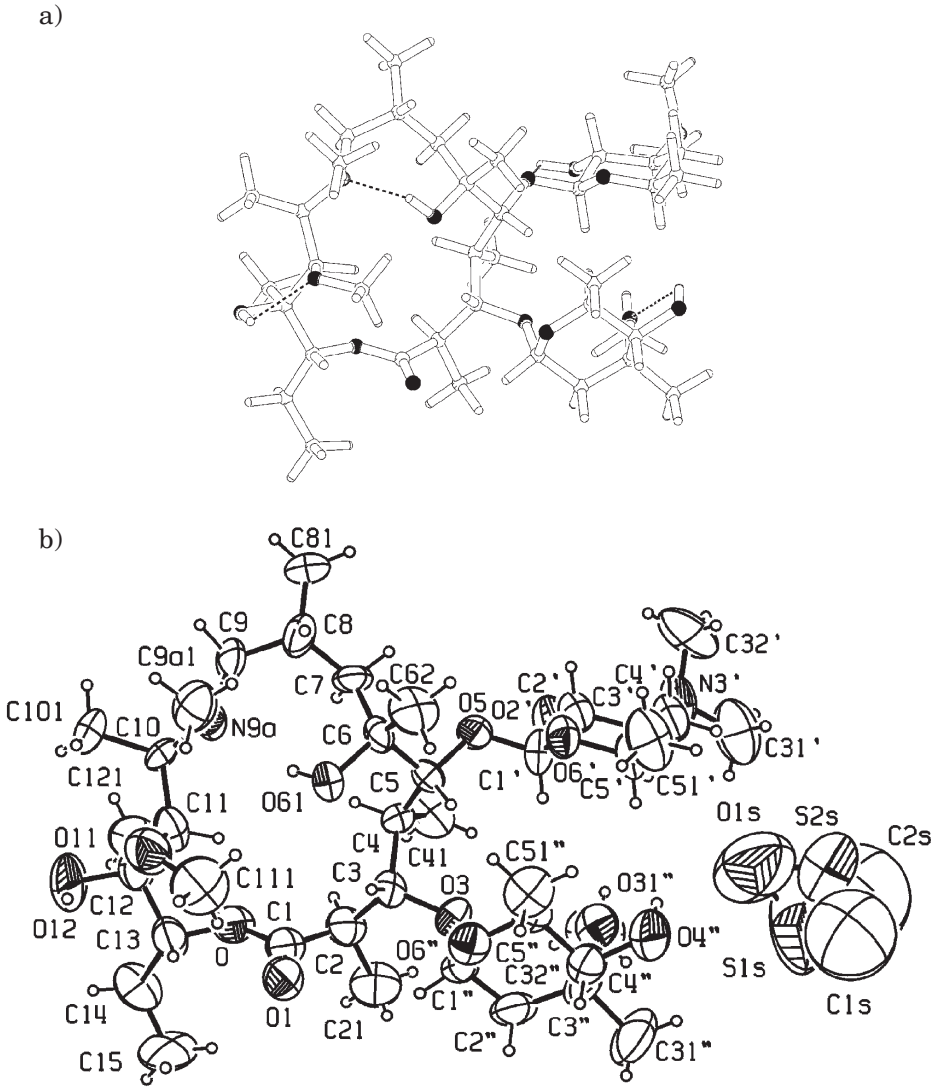


Figure 1. Conformation of **2** in solution (a) and solid (b) state. Thermal ellipsoids are drawn at the 50% probability level.

were »folded-in« and »folded-out« solution state conformations of **2** (Figure 1a), modified by removing the methyl group from 11-*O*-methyl moiety, as well as all hydrogen atoms. Initial orientation of both search models was identical.

The rotation/translation search was limited to a 9.0–1.5 Å resolution shell. Sphere radius was chosen to be 5.0 Å, *i.e.* 70% of the maximal distance from the centre of

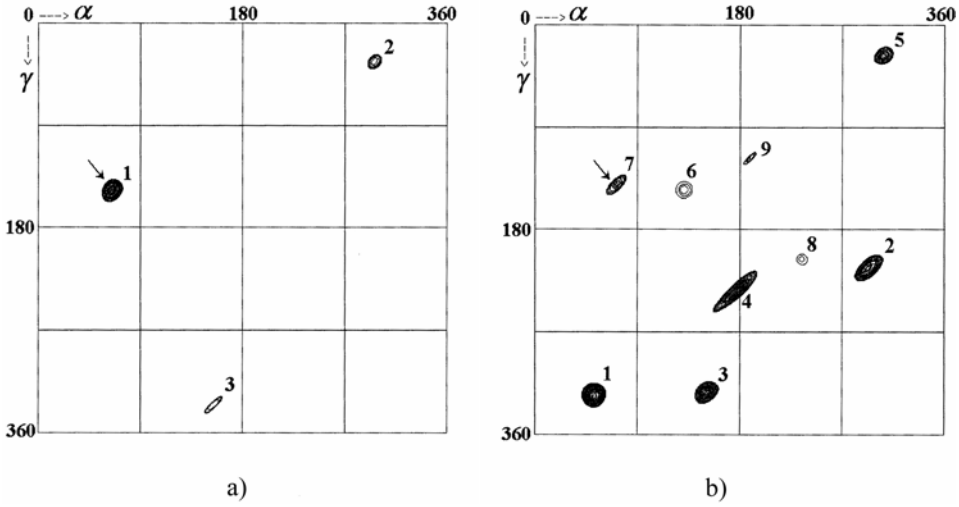


Figure 2: Map of the cross rotation function calculated within AMoRe using the »folded-in« (a) and »folded-out« (b) solution state conformations of **2** as the search model. Maps are drawn as the sum over all β angle sections within 8σ of the highest peak. Peaks are numbered according to their relative height and the correct solution is highlighted by an arrow.

mass to the edge of the model. The highest solution from the rotation function yielded a peak 5.8 σ above the second highest peak for the »folded-in« and 2.3 σ for the »folded-out« model. The peak at Eulerian angles of α = 64.32, β = 73.11, γ = 146.72°, corresponding to the maximum correlation can be seen in Figure 2a. Therefore, the »folded-in« model was further processed by translation function, with the same range of data, giving a correct solution with the correlation coefficient of 69.2%. Rigid-body refinement was applied after the translation-function search and the unique solution had a correlation coefficient of 82.4% and R_F-factor of 57.2%.

Fractional atomic coordinates were obtained by applying transformation operations from the rigid-body refinement to the original model. The structure was subject to several subsequent rounds of refinement on F^2, using SHELXL97 program[23] and data up to 1.0 Å, and analysis of electron-density maps on the graphic display using the »O« program.[24] Positions of H atoms were calculated on geometrical grounds and those of OH groups with additional aid of circular difference Fourier maps.

DMSO molecule was located by inspection of Fourier maps and it was found to be disordered. It was refined as a rigid body which was constructed on idealised geometry of two DMSO molecules with overlapping oxygen and carbon atoms (Figure 3). All non-H atoms were refined anisotropically, except for the carbons of the disordered solvent molecule (Figure 1b). The structure was refined to final wR_{F^2} = 0.1668 and R_F = 0.0636. Atomic coordinates and equivalent isotropic displacement parameters are listed in Table II.

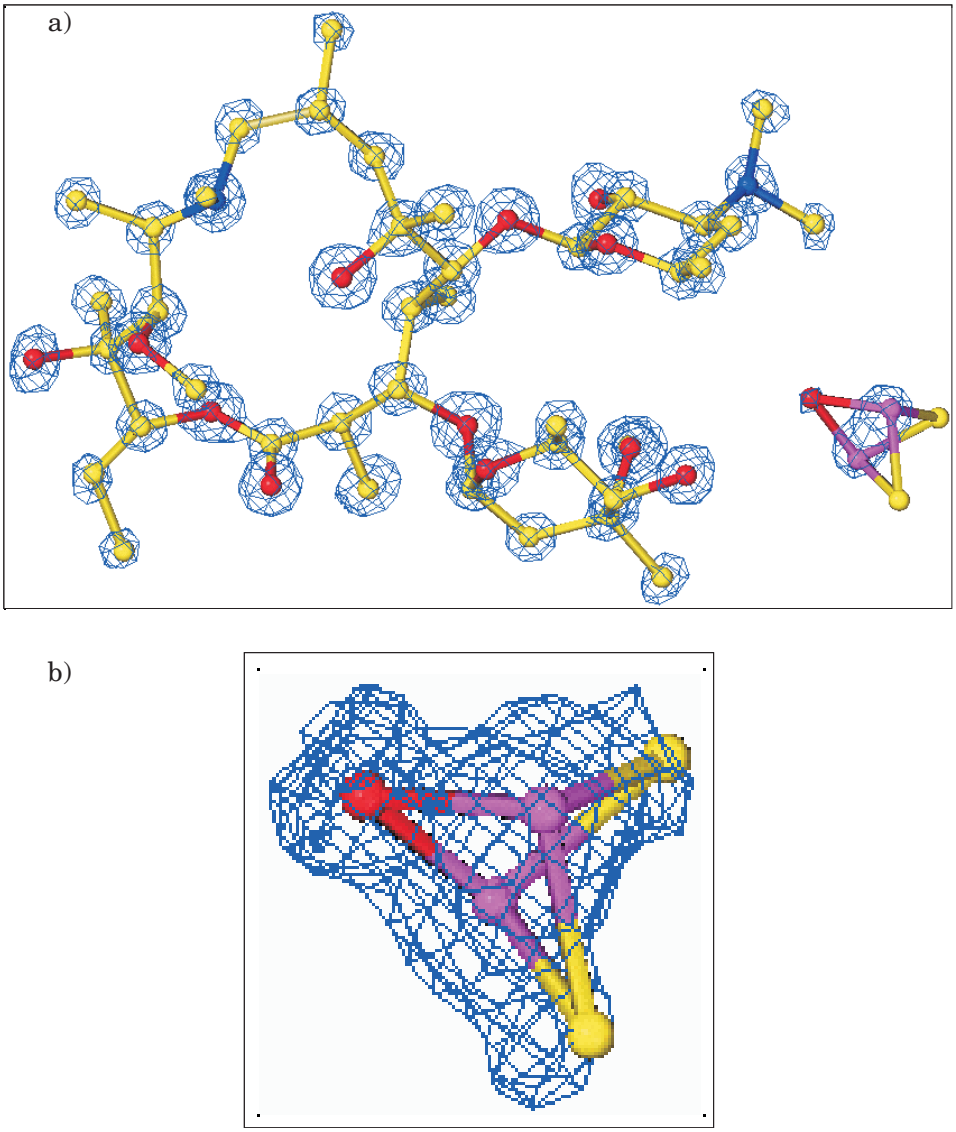


Figure 3. 2 F_o-F_c Electron density map of **2** drawn at 3 e Å^{-3} (a) and at 1 e Å^{-3} (b), only DMSO molecule. Hydrogen atoms are omitted for clarity. The DMSO molecule is disordered and each of the two sulphur atoms is modelled with 50% occupation.

Crystallographic information on macrolide compounds was retrieved from the Cambridge Structural Database.[25] Searches and geometrical calculations were performed using the QUEST3D program.[26] Statistical analyses and data visualisations were carried out using VISTA.[27]

TABLE II

Fractional atomic coordinates and equivalent isotropic displacement parameters/Å^2 for **2**

	x	y	z	U_{eq}
O	0.3008(7)	–0.1599(10)	0.4235(4)	0.079(3)
C1	0.4083(12)	–0.1478(17)	0.4114(6)	0.069(4)
O1	0.4744(7)	–0.0811(13)	0.4420(4)	0.089(3)
C2	0.4345(10)	–0.2260(16)	0.3549(5)	0.069(4)
C21	0.5035(11)	–0.3687(16)	0.3683(6)	0.107(5)
C3	0.4874(9)	–0.1105(13)	0.3139(5)	0.051(3)
O3	0.5919(6)	–0.1638(8)	0.2940(3)	0.055(2)
C4	0.4118(8)	–0.0828(15)	0.2590(4)	0.052(3)
C41	0.3973(11)	–0.2244(14)	0.2213(5)	0.085(4)
C5	0.4500(9)	0.0599(13)	0.2266(4)	0.044(3)
O5	0.4451(6)	0.0378(9)	0.1647(3)	0.055(2)
C6	0.3837(11)	0.2037(15)	0.2391(5)	0.055(4)
O61	0.3823(5)	0.2111(10)	0.3025(3)	0.061(2)
C62	0.4529(11)	0.3404(14)	0.2196(6)	0.085(5)
C7	0.2702(9)	0.2016(14)	0.2108(4)	0.058(4)
C8	0.1908(9)	0.3292(16)	0.2223(5)	0.070(4)
C81	0.1141(11)	0.346(2)	0.1688(6)	0.131(7)
C9	0.1193(8)	0.3056(15)	0.2743(4)	0.068(4)
N9A	0.1802(7)	0.3087(12)	0.3313(4)	0.058(3)
C9A1	0.2091(11)	0.4661(16)	0.3470(6)	0.089(5)
C10	0.1219(9)	0.2211(17)	0.3742(5)	0.074(4)
C101	0.0327(9)	0.3139(18)	0.4061(5)	0.110(6)
C11	0.2061(10)	0.1405(17)	0.4155(5)	0.069(4)
O11	0.2530(8)	0.2516(13)	0.4546(4)	0.098(3)
C111	0.3763(11)	0.270(2)	0.4528(6)	0.127(6)
C12	0.1586(11)	0.0071(19)	0.4533(5)	0.083(5)
O12	0.1094(8)	0.0706(16)	0.5051(4)	0.138(4)
C121	0.0704(10)	–0.0850(19)	0.4223(6)	0.108(6)
C13	0.2607(11)	–0.0894(19)	0.4755(5)	0.079(4)
C14	0.2336(13)	–0.215(2)	0.5192(6)	0.140(8)
C15	0.3360(13)	–0.292(2)	0.5430(7)	0.194(11)
C1'	0.5442(10)	–0.0033(17)	0.1400(5)	0.070(4)
C2'	0.5175(11)	–0.0657(16)	0.0797(5)	0.067(4)
O2'	0.4554(9)	–0.1990(13)	0.0839(4)	0.106(4)
C3'	0.6261(9)	–0.1009(17)	0.0513(5)	0.061(4)
N3'	0.6003(10)	–0.1858(15)	–0.0028(5)	0.096(4)

TABLE II (cont.)

	x	*y*	*z*	U_{eq}
C31'	0.6961(14)	–0.266(2)	–0.0214(6)	0.142(7)
C32'	0.5556(13)	–0.088(2)	–0.0489(5)	0.135(7)
C4'	0.6942(11)	0.0427(19)	0.0484(5)	0.083(4)
C5'	0.7142(10)	0.1107(17)	0.1090(5)	0.070(4)
C51'	0.7708(11)	0.2611(18)	0.1079(5)	0.105(5)
O6'	0.6076(7)	0.1344(11)	0.1337(3)	0.064(2)
C1"	0.6805(10)	–0.1271(17)	0.3322(5)	0.059(4)
C2"	0.7724(10)	–0.2292(18)	0.3230(5)	0.084(5)
C3"	0.8410(11)	–0.2054(18)	0.2693(7)	0.076(4)
C31"	0.9431(11)	–0.3084(18)	0.2694(7)	0.136(7)
O31"	0.7787(7)	–0.2198(11)	0.2157(4)	0.080(3)
C32"	0.7368(13)	–0.364(2)	0.2039(6)	0.124(6)
C4"	0.8727(11)	–0.0396(17)	0.2704(6)	0.076(4)
O4"	0.9329(7)	0.0045(14)	0.2206(4)	0.105(3)
C5"	0.7707(10)	0.0594(17)	0.2741(5)	0.059(4)
C51"	0.7963(10)	0.2255(18)	0.2786(6)	0.093(5)
O6"	0.7155(6)	0.0246(11)	0.3253(4)	0.070(3)
O1S	0.9477(9)	–0.112(2)	0.0992(6)	0.288(12)
S1S	1.0469(14)	–0.2109(18)	0.1077(6)	0.295(12)
S2S	1.0421(11)	–0.117(2)	0.0591(5)	0.238(9)
C1S	1.1628(10)	–0.091(4)	0.1026(12)	0.347(18)
C2S	1.062(2)	–0.309(3)	0.0419(13)	0.55(4)

RESULTS AND DISCUSSION

Solution State Conformation

The principal NMR determinants of the conformation of a molecule are vicinal coupling constants (^3J), which mainly depend on dihedral angles, and the nuclear Overhauser effect (NOE), which depends on proton-proton distances. Because of the sinusoidal nature of the Karplus equation, there are four solutions for a given coupling, but due to the cyclic nature of macrolactone and sugar moieties, only one is conformationaly reasonable or favoured for any particular case. A comparison of the $^3J_{HH}$ values in $CDCl_3$ and the corresponding dihedral angles for vicinal proton pairs, obtained by the modified Karplus equation,[28] is given in Table III.

The small $^3J_{2,3}$ value (3.5 Hz) indicates that **2** exists mainly in the »folded-in« conformation in $CDCl_3$. However, the observed value is 0.6 Hz higher

TABLE III

Coupling constants for vicinal proton pairs and the corresponding dihedral angles for **2**

Vicinal proton pair		$^3J^a_{exp}$/Hz	$\phi^b_{calc.}$/°	$\phi_{x\text{-}ray}$/°	$^3J^c_{x\text{-}ray}$/Hz	ϕ^d_{MM2}/°	$^3J^e_{MM2}$/Hz
H-2,	H-3	3.5	115	121.5(12)	4.6	111.2	2.9
H-3,	H-4	2.2	–56	–69.0(12)	0.9	–71.5	0.8
H-4,	H-5	7.2	136	135.6(10)	7.2	141.0	8.2
H-7_{eq},	H-8	~0	–84	–89.6(13)	1.0	–84.0	1.0
H-7_{ax},	H-8	ov	–	155.6(11)	10.4	163.3	11.4
H-8,	H-9_{eq}	~0	88	67.7(14)	2.6	72.3	2.1
H-8,	H-9_{ax}	11.3	–170	–175.7(11)	11.7	–174.4	11.6
H-10,	H-11	1.8	61	72.6(14)	0.9	70	1.1
H-13,	H-14_{eq}	2.7	56	71.2(18)	1.2	69.1	1.3
H-13,	H-14_{ax}	9.8	–162	–171.0(14)	10.9	–172.0	11.0
H-1',	H-2'	7.2	169	178.9(12)	6.5	175.4	7.6
H-2',	H-3'	10.2	–176	175.8(11)	10.5	179.3	10.4
H-3',	H-$4'_{eq}$	3.8	59	63.3(15)	3.2	61.3	3.5
H-3',	H-$4'_{ax}$	12.4	–176	–178.5(12)	11.8	179.9	11.8
H-$4'_{eq}$,	H-5'	1.9	–63	–57.7(16)	2.4	–60.4	2.1
H-$4'_{ax}$,	H-5'	10.5	–153	–175.9(12)	11.6	–177.1	11.6
H-1"	H-$2"_{eq}$	nr	–	71.1(15)	1.8	65.1	2.3
H-1"	H-$2"_{ax}$	4.4	–47	–44.2(16)	4.8	–49.3	4.1
H-4"	H-5"	9.5	–170	–178.4(12)	9.4	175.7	9.3

[a]Experimental values for **2** in $CDCl_3$ at 293 K.
[b]Dihedral angles were calculated from $^3J_{exp}$ using a modified Karplus equation.[26]
[c]Coupling constants calculated for X-ray geometry.[26]
[d]Dihedral angles of the solution state conformation based on MM2 calculation.
[e]Coupling constants calculated for MM2 solution state geometry.[26]

than $^3J_{2,3}$ calculated on the basis of the »folded-in« model of **2** (Table III), suggesting the presence of ≈10% of the »folded-out« conformation (calculated $^3J_{2,3}$ = 9.7 Hz) in $CDCl_3$ at room temperature. Increase of $^3J_{2,3}$ in DMSO (4.2 Hz) is a consequence of the increased presence of a more polar »folded-out« conformer. Calculation of the Connolly surface of »folded-out« and »folded-in« conformers using an in house programme showed 10.8% and 10.1% of the polar (heteroatoms and OH hydrogens) convex surface, respectively. Therefore, the aglycone moiety of **2** behaves in the solution state similarly to those of **1** ($^3J_{2,3}$ = 3.6 Hz in $CDCl_3$ and 4.7 Hz in DMSO).

There are two possible orientations of the 11-OMe group: toward the centre of the molecule (11-OMe in) or in the opposite direction, out of the molecule (11-OMe out). Molecular mechanics energy calculations[17] preferred the »11-OMe in« orientation. The observed strong ROE signals 11-OMe–9a-NMe, 11-OMe–11-H and 11-OMe–13-H, as well as weak ROE signals 11-OMe–3-H, 11-OMe–10-Me and 11-OMe–6-Me are in agreement with the related short H...H contacts for the »11-OMe in« orientation (Table IV). Therefore, the related torsion angle C(10)-C(11)-O(11)-C(111) in our solution state model of **2** has a value of –112.9° (Figure 1a).

TABLE IV

Selected H...H distances/Å involving 11-OMe hydrogens in the solution state conformation of **2** for the »11-OMe out« and »11-OMe in« model. Signals observed by ROE experiments are marked as strong or weak according to integrated peak volumes.

11-OCH_3	»11-OMe out«	»11-OMe in«	ROE signal
3-H	> 5.5	3.3	weak
9a-NCH_3	3.0	2.3	strong
10-CH_3	2.1	4.2	weak
11-H	3.7	2.4	strong
6-CH_3	> 5.5	4.0	weak[a]
12-OH	2.9	3.5	weak[b]
13-H	2.3	2.3	strong
14-H_{eq}	3.4	4.8	no signal

[a]Observed only in DMSO solution.
[b]Observed only in $CDCl_3$ solution.

The observed $^3J_{HH}$ values prove that α-L-cladinose and β-D-desosamine adopt the chair conformation with the maximum number of substituents in the more stable equatorial positions. These are the same chair conformations as observed in the crystal structures of all other erythromycin A derivatives,[29] as well as in the solution state of azithromycin[7] and bicyclic azalides.[8]

The only variability in the conformation of sugars appears to be the rotation of desosamine *N*-dimethylamino group around the C3'-N3' bond. Out of the two rotamers found in CSD,[26] we chose the one that gave lower MM2 energy. This rotamer is characterised by torsion angles C2'-C3'-N3'-C31' of –70° and C2'-C3'-N3'-C32' of 50°. Therefore, the electron lone pair of N3' is directed out of the molecule and possibly interacts with solvent molecules.

Crystal Structure

The title compound crystallises in the monoclinic $P2_1$ space group as solvate with one molecule of DMSO. The overall molecule conformation in the crystal is very similar to that in $CDCl_3$. This fact contributed to the success of molecular replacement, because the search model was the solution state conformation of **2** (Figure 2a). However, the 7th highest solution from rotation search with the »folded-out« model was also correct (Figure 2b), demonstrating the robustness of the method. Single crystals of azalides and other macrolides frequently have a low diffraction power challenging direct methods with a low resolution of data. Structural data from CSDB, NMR studies and computational chemistry software are a rich source of models for molecular replacement methods. Such an approach seems to be an alternative to data recollection with more intensive X-ray sources and/or time-consuming scanning of crystallisation conditions, especially in cases where the sample amount is limited, rapid structural analysis is expected and no accurate molecular geometry is demanded.

Aglycone moiety of **2** adopts the »folded-in« conformation in the crystal, similarly to that of 11,12,4''-tri-*O*-methylazithromycin.[13] In contrast, **1** adopts the »folded-out« conformation in the crystal structure of its dihydrate.[2]

Orientation of the 4-Me group, which is a measure of the folded-in or -out character, is described with angle C41-C4...C11. This angle has a value of 135° in the crystal structure of **2**, typical of the »folded-in« conformation of 15-membered azalides, but ≈15° less than for the »folded-in« conformation of 14-membered macrolides (Figure 4). We have found that out of all torsion angles of aglycone ring only C1-C2-C3-C4 correlates with the C41-C4...C11 angle (Figure 4). This is in agreement with ^{1}H NMR experiments where the $^3J_{2,3}$ value is an indicator of conformational changes.

Orientation of the 11-OMe group with respect to the aglycone ring is toward the centre of the molecule (»11-OMe in«, C10-C11-O11-C111 is –120.4(11)°), similar to that in $CDCl_3$ solution (»11-OMe in«, C10-C11-O11-C111 is –112.9°) and to that in the crystal structure of 11,12,4''-tri-*O*-methylazithromycin (»11-OMe in«, C10-C11-O11-C111 is –115.3(8)°).

The sugars adopt a chair conformation and their orientation with respect to each other and to the aglycone ring are similar to those found in related structures.

All hydroxy hydrogen atoms participate in hydrogen bonding (Figure 1a). The O4'' hydroxy group forms an intramolecular hydrogen bond with O31'' oxygen atom (O4''-H41''…O31'' of 2.74(1) Å) and with DMSO oxygen atom (O4''-H4''…O1s of 3.01(2) Å), thus being three-centered or bifurcated. Intramolecular hydrogen bonds O61-H61 … N9a, O12-H12 … O11, O2'-H2' … N3' of 2.71(1), 2.67(2), and 2.72(2) Å are also found.

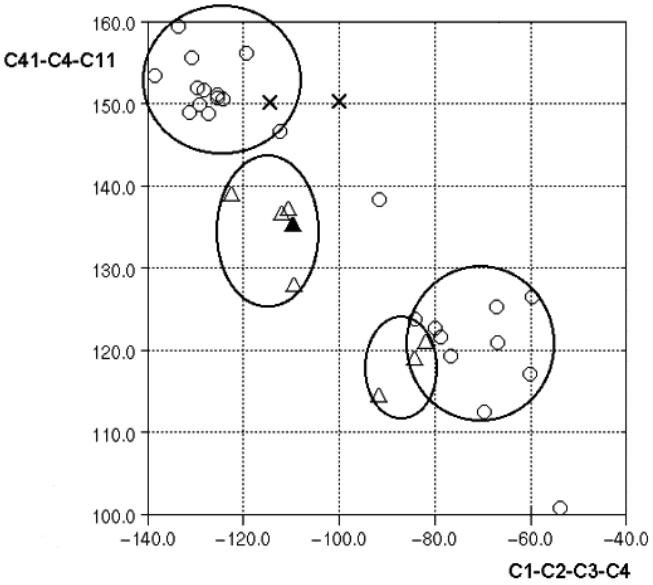


Figure 4. Correlation between the C41-C4...C11 angle and the torsion angle C1-C2-C3-C4 for 14- and 15-membered macrolides containing desosamine moiety. Labels: (O) 14-membered macrolides, (X) ketolides, (Δ) azalides.

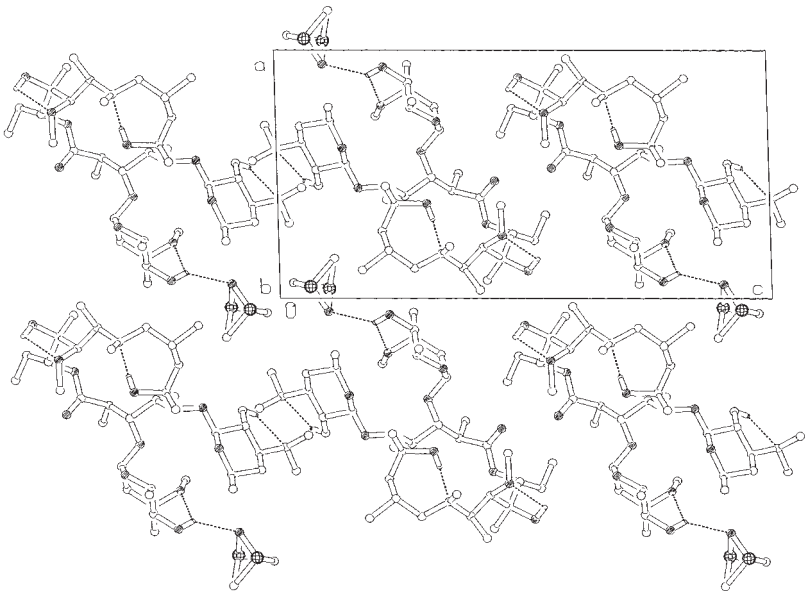


Figure 5. Crystal packing diagram with hydrogen-bonding for **2**. Only hydrogens belonging to OH groups are shown.

The crystal packing diagram of **2** is shown in Figure 5. Azalide molecules are packed together by van der Waals forces forming a solvent channel along the *b* axis. The sulphur atom of DMSO molecule was found to be disordered between two positions with an occupancy factor of 0.5.

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SAŽETAK

Konformacijsko ponašanje 11-*O*-metilaziltromicina u čvrstom stanju i otopini

Nada Košutić-Hulita, Dijana Matak-Vinković, Mladen Vinković, Predrag Novak, Gabrijela Kobrehel i Gorjana Lazarevski

Istraživano je konformacijsko ponašanje 11-OMe derivata azitromicina **2** (Shema 1) u čvrstom i tekućem stanju. U otopini $CDCl_3$ i DMSO **2** zauzima uglavnom konformaciju »folded in«. Skupina 11-OMe orijentirana je prema centru aglikonskog prstena. Kristalna struktura solvata **2** sa DMSO određena je metodom molekulske zamjene pri čemu je kao traženi model korištena konformacija spoja **2** u otopini. Konformacija spoja **2** u čvrstom stanju i u otopini je vrlo slična. U kristalnoj strukturi molekule **2** su povezane van der Waals-ovim interakcijama, tvoreći kanale popunjene otapalom duž osi *b*. Molekula DMSO je u neuređenom položaju i ujedno povezana vodikovom vezom O4"-H...O1s s kladinoze molekule **2**.