Collection des données: *CAD*-4 *Software* (Enraf–Nonius, 1989). Affinement des paramètres de la maille: *CAD*-4 *Software*. Réduction des données: *MolEN* (Fair, 1990). Programme(s) pour la solution de la structure: *SHELXS*86 (Sheldrick, 1985). Programme(s) pour l'affinement de la structure: *SHELXL*93 (Sheldrick, 1993).

Les listes des facteurs de structure, des facteurs d'agitation thermique anisotrope, des coordonnées des atomes d'hydrogèn et des distances et angles des atomes d'hydrogène ont été déposées au dépôt d'archives de l'UICr (Référence: DU1108). On peut en obtenir des copies en s'adressant à: The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, Angleterre.

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2,3-Benzo-11-(2-cyanoethyl)-1,4-dioxa-7,11,15-triazacycloheptadec-2-ene-6,16-dione–Water (1/1)

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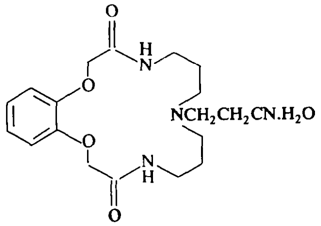
Abstract

The structure of the title compound, $C_{19}H_{26}N_4O_4.H_2O$, with a water molecule in the cavity of the macrocycle, is an example of a solvent(water)–lariat macrocycle complex where the macrocycle binds the solvent strongly. The cyanoethyl side chain does not interact with the water molecule, showing that solvent–macrocycle interactions can also affect the thermodynamic properties of the side chain of the macrocyclic ring.

Comment

The selective receptor properties of ionophores are greatly affected by the number and nature of heteroatoms, their placement in the structural periphery of the ionophore, their spatial disposition, the flexibility of various functional units and the molecular skeleton (Lehn, 1973; Bajaj & Poonia, 1988; Fenton, 1987). In ionophores containing O atoms as ligating sites, the oxygen may be present as ether, ester, carbonyl and amide. The amide unit has a special role, mainly as a result of its ability to bind the metal ion through N or O atoms, delocalizing the lone-electron pair of nitrogen with the C=O unit. This makes the oxygen more negative than other types of O atoms encountered in the ionophores. Delocalization enables the ionophore to acquire a more rigid spatial disposition as compared with other oxygen-based ionophores. The role of cooperative binding of the side arm to the guest cation in enhancing the selectivity and transport abilities in lariat ethers is well documented (Gokel, 1992; Tsukube, Adachi & Morosawa, 1989, 1991; Dishong, Diamond, Cinaman & Gokel, 1983; Arnold, Echegoyen & Gokel, 1987). In a few C-pivoted lariat ethers (Dishong *et al*., 1983), some lowering of cation-complexation ability, but not transport efficiency, has been attributed to strong solvation (hydrogen bonding), with the assistance of the side arm resulting in partial blocking of the cavity. It has been found that placement on the macrocyclic ring of an arm incapable of donation to a ring-bound cation generally reduces the binding. However, as the lipophilicity of the side chain increases, irrespective of the availability of donor groups on the ring, the extraction constants rise. In order to investigate the mode of solvation and the role of any appendage on solvation, the crystal structure of the title compound (2*c*) has been solved (Fig. 1).



(2*c*)

All bond distances and angles are as expected (Table 2). The compound is comparable to a substituted coronand having a cavity with five potential donors, *i.e.* O1, O2, N1, N2 and N3, deviating significantly from a planar arrangement. Torsion angles (Table 2) show that

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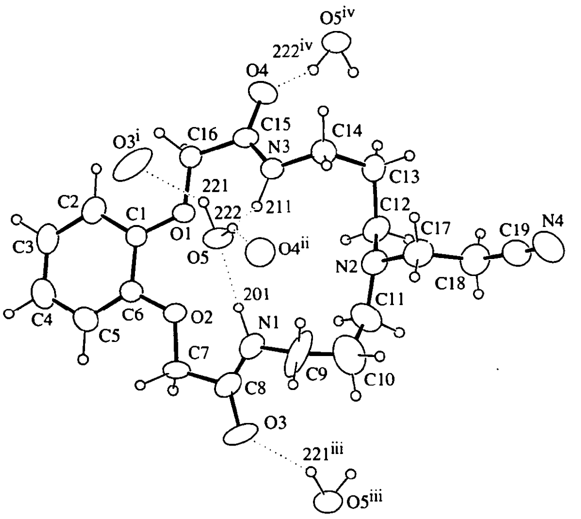


Fig. 1. *ORTEP* (Johnson, 1965) drawing of the final X-ray model showing the atomic labelling and the hydrogen-bonding scheme. Displacement ellipsoids are drawn at the 30% probability level. For symmetry operators see Table 3.

the group O1—C1—C6—O2 is in a *syn* conformation. Both amide groups deviate significantly from planarity.

The most important feature of the structure is the presence of a water molecule in the cavity of the macrocycle. This water is involved in strong inter- and intramolecular hydrogen bonding (Table 3), the former between atoms of the water molecule and amide O atoms of symmetry-related molecules, the latter between O atoms of water and amide H atoms.

Macrocycle (2*a*) extracts and transports alkali, alkaline earth and Ag^I, Pb^{II} and Tl^I cations (Kumar, Singh & Singh, 1992) with significantly high efficiency which is retained in the case of compound (2*b*) where NH has been replaced by NCH_3. However, the presence of the cyanoethylene arm on the amine N atom remarkably lowers both the extraction and transport characteristics (Table 4). Compounds (2*a*) and (2*b*) crystallize from 95% ethanol to give analytically pure samples but (2*c*) is obtained as a 1:1 complex with water, showing a signal due to H_2O in the ^1H NMR spectrum. On application of a vacuum, the latter loses water to give analytically pure (2*c*). As extraction and transport experiments are carried out in the presence of water, (2*c*) preferentially binds with water resulting in a lack of binding with cations. The orientation of the cyanoethylene side arm is such that it cannot interact with the macrocycle and cannot thereby block the macrocycle. The lowering of the transport/extraction characteristics of the macrocycle are not a result of the side arm, but are due to the interactions of water with the macro ring. The structure also reveals that apart from the previously proposed factors (Dishong *et al.*, 1983) affecting the transport/extraction characteristics in lariat macrocycles, the role of solvent in the macro ring is also important.

Experimental

Crystal data

$C_{19}H_{26}N_4O_4.H_2O$
$M_r = 392.46$
Monoclinic
$C2/c$
$a = 21.395$ (3) Å
$b = 13.517$ (1) Å
$c = 14.905$ (2) Å
$\beta = 107.75$ (1)°
$V = 4105.6$ (9) Å^3
$Z = 8$
$D_x = 1.27$ Mg m^{-3}
$D_m = 1.25$ Mg m^{-3}
D_m measured by flotation

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 43 reflections
$\theta = 2$–40°
$\mu = 0.730$ mm^{-1}
$T = 298$ K
Prism
0.3 × 0.1 × 0.1 mm
Colourless

Data collection

Seifert XRD3000S diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3125 measured reflections
3049 independent reflections
1428 observed reflections [$I > 2\sigma(I)$]

$R_{\rm int} = 0.02$
$\theta_{\rm max} = 60°$
$h = -23 \rightarrow 23$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 16$
3 standard reflections monitored every 100 reflections
intensity decay: none

Refinement

Refinement on F
$R = 0.049$
$wR = 0.058$
$S = 0.54$
1428 reflections
253 parameters
H-atom parameters not refined
$w = k/[a + b|F_o|]^2$

$(\Delta/\sigma)_{\rm max} = 0.12$
$\Delta\rho_{\rm max} = 0.20$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.05$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

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

	x	y	z	$U_{\rm eq}$
C1	0.5494 (3)	0.1974 (5)	0.5842 (4)	0.048 (2)
C2	0.5026 (4)	0.2481 (5)	0.6144 (5)	0.067 (2)
C3	0.4367 (4)	0.2444 (6)	0.5616 (6)	0.071 (2)
C4	0.4166 (4)	0.1909 (6)	0.4781 (6)	0.071 (2)
C5	0.4630 (4)	0.1400 (5)	0.4476 (5)	0.062 (2)
C6	0.5285 (4)	0.1424 (5)	0.5000 (4)	0.050 (2)
C7	0.5620 (4)	0.0488 (5)	0.3862 (4)	0.064 (2)
C8	0.6243 (5)	−0.0006 (6)	0.3762 (6)	0.074 (3)
C9	0.7330 (6)	−0.0673 (6)	0.4576 (8)	0.123 (4)
C10	0.7829 (5)	−0.0171 (9)	0.4400 (10)	0.151 (5)
C11	0.8007 (4)	0.0842 (7)	0.4742 (7)	0.094 (3)
C12	0.8313 (4)	0.2039 (5)	0.5992 (5)	0.066 (2)
C13	0.8523 (4)	0.2221 (5)	0.7044 (5)	0.068 (2)
C14	0.8125 (4)	0.1624 (5)	0.7541 (5)	0.065 (2)
C15	0.7114 (4)	0.2525 (5)	0.7482 (4)	0.054 (2)
C16	0.6381 (3)	0.2566 (5)	0.7108 (5)	0.057 (2)
C17	0.8978 (4)	0.0525 (6)	0.6075 (5)	0.080 (3)
C18	0.9508 (4)	0.1024 (6)	0.5782 (6)	0.092 (3)
C19	1.0135 (5)	0.0436 (7)	0.6118 (6)	0.087 (3)
O1	0.6153 (2)	0.1985 (3)	0.6279 (3)	0.055 (1)
O2	0.5778 (2)	0.0950 (3)	0.4762 (3)	0.057 (1)
O3	0.6213 (3)	−0.0242 (4)	0.2945 (4)	0.116 (2)
O4	0.7403 (3)	0.3125 (4)	0.8094 (3)	0.077 (2)

O5	0.6842 (2)	−0.0149 (3)	0.6562 (3)	0.065 (1)
N1	0.6723 (3)	−0.0135 (5)	0.4521 (5)	0.072 (2)
N2	0.8337 (3)	0.0993 (4)	0.5732 (4)	0.064 (2)
N3	0.7419 (3)	0.1806 (4)	0.7169 (3)	0.053 (2)
N4	1.0611 (4)	0.0027 (6)	0.6380 (6)	0.107 (3)

Table 2. *Selected geometric parameters* (Å, °)

C1—C2	1.396 (11)	C10—C11	1.470 (15)
C1—C6	1.409 (8)	C11—N2	1.443 (11)
C1—O1	1.361 (7)	C12—C13	1.514 (10)
C2—C3	1.390 (11)	C12—N2	1.471 (9)
C3—C4	1.390 (12)	C13—C14	1.520 (12)
C4—C5	1.393 (13)	C14—N3	1.463 (10)
C5—C6	1.381 (10)	C15—C16	1.497 (10)
C6—O2	1.370 (10)	C15—O4	1.236 (8)
C7—C8	1.538 (14)	C15—N3	1.332 (10)
C7—O2	1.424 (7)	C16—O1	1.419 (8)
C8—O3	1.242 (11)	C17—C18	1.494 (13)
C8—N1	1.287 (10)	C17—N2	1.454 (10)
C9—C10	1.356 (18)	C18—C19	1.507 (13)
C9—N1	1.469 (14)	C19—N4	1.119 (13)
C2—C1—C6	118.8 (6)	C13—C12—N2	114.0 (6)
C2—C1—O1	125.5 (6)	C12—C13—C14	112.7 (6)
C6—C1—O1	115.7 (6)	C13—C14—N3	113.2 (6)
C1—C2—C3	120.2 (7)	C16—C15—O4	118.8 (6)
C2—C3—C4	120.6 (8)	C16—C15—N3	117.8 (6)
C3—C4—C5	119.5 (8)	O4—C15—N3	123.3 (7)
C4—C5—C6	120.3 (7)	C15—C16—O1	110.3 (6)
C1—C6—C5	120.5 (7)	C18—C17—N2	114.8 (7)
C1—C6—O2	114.7 (6)	C17—C18—C19	110.0 (7)
C5—C6—O2	124.8 (6)	C1—O1—C16	117.0 (5)
C8—C7—O2	108.5 (6)	C6—O2—C7	118.0 (5)
C7—C8—O3	114.8 (8)	C8—N1—C9	124.8 (8)
C7—C8—N1	117.2 (8)	C11—N2—C12	111.1 (6)
O3—C8—N1	128.0 (9)	C11—N2—C17	114.4 (6)
C10—C9—N1	118.4 (10)	C12—N2—C17	115.5 (6)
C9—C10—C11	122.3 (11)	C14—N3—C15	123.3 (6)
C10—C11—N2	118.7 (8)		

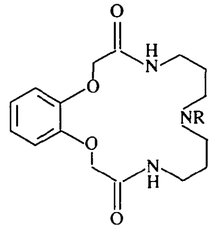
C1—C2—C3—C4	−0.4 (12)
C1—C6—C5—C4	−0.9 (11)
C1—C6—O2—C7	−171.9 (6)
C1—O1—C16—C15	−178.2 (5)
C2—C1—C6—C5	1.0 (10)
C2—C1—C6—O2	−179.8 (6)
C2—C1—O1—C16	−0.4 (9)
C2—C3—C4—C5	0.5 (13)
C3—C2—C1—C6	−0.3 (11)
C3—C2—C1—O1	177.4 (7)
C3—C4—C5—C6	0.2 (12)
C4—C5—C6—O2	180.0 (7)
C5—C6—C1—O1	−177.0 (6)
C5—C6—O2—C7	7.3 (10)
C6—C1—O1—C16	177.5 (6)
C6—O2—C7—C8	−179.0 (6)
C7—C8—N1—C9	174.1 (8)
C8—N1—C9—C10	86.4 (13)
C9—C10—C11—N2	73.1 (14)
C9—N1—C8—O3	−5.0 (15)
C10—C11—N2—C12	−164.2 (8)
C10—C11—N2—C17	62.8 (11)
C11—C10—C9—N1	40.5 (16)
C11—N2—C12—C13	168.1 (7)
C11—N2—C17—C18	73.9 (9)
C12—C13—C14—N3	−56.9 (8)
C12—N2—C17—C18	−57.0 (9)
C13—C12—N2—C17	−59.5 (8)
C13—C14—N3—C15	−88.1 (8)
C14—C13—C12—N2	−56.3 (8)
C14—N3—C15—C16	−174.0 (6)
C14—N3—C15—O4	2.5 (11)
C19—C18—C17—N2	−176.0 (7)
O1—C1—C6—O2	2.2 (9)
O1—C16—C15—O4	166.8 (6)
O1—C16—C15—N3	−16.5 (9)
O2—C7—C8—O3	−164.7 (7)
O2—C7—C8—N1	16.1 (10)

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H201···O5	1.02	2.07	2.97 (1)	145
N3—H211···O5	1.02	2.13	2.94 (1)	133
O5—H221···O3^{i}	0.97	1.98	2.83 (1)	146
O5—H222···O4^{ii}	0.96	1.94	2.79 (1)	146

Symmetry codes: (i) $x, -y, \frac{1}{2}+z$; (ii) $\frac{3}{2}-x, y-\frac{1}{2}, \frac{3}{2}-z$. (iii) $x, -y, z-\frac{1}{2}$; (iv) $\frac{3}{2}-x, y+\frac{1}{2}, \frac{3}{2}-z$.

Table 4. *Cation transport and extraction rates of macrocycles*



(2*a*) R = H
(2*b*) R = CH_3
(2*c*) R = CH_2CH_2CN

	Li^+	Na^+	K^+	Tl^+	Mg^+	Ca^{2+}	Sr^{2+}	Ba^{2+}	Pb^{2+}	Ag^+
Transport data										
(2*a*)	550	665	510	600	493	530	–	400	–	615
(2*b*)	478	628	410	459	193	484	–	214	–	440
(2*c*)	5.1	21.9	27.2	75.9	24.9	17.7	–	14.9	–	33.7
Extraction data										
(2*a*)	4.3	37.0	37.0	40.0	11.7	23.7	21.4	–	254.0	34.5
(2*b*)	35.8	33.0	31.7	27.6	24.8	22.2	58.5	–	133.2	98.8
(2*c*)	9.9	13.0	13.1	10.3	11.1	6.1	16.2	–	12.3	18.7

In the weighting scheme, $0 \leq F_o \leq 7.5$, $a = 1.5$, $b = 0.2$; $7.5 \leq F_o \leq 32.0$, $a = 4.7$, $b = -0.2$; $32.0 \leq F_o$, $a = 1.5$, $b = 0.0$.

The structure was solved with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). The initial *E* map revealed 80% of the non-H atoms, the remainder being found in successive Fourier syntheses. The H atoms were fixed geometrically except for the two belonging to the water molecule which were located in a difference Fourier synthesis. All calculations were performed with the *XRAY*80 package (Stewart, 1978) and *PESOS* (Martínez-Ripoll & Cano, 1975). Molecular graphics were obtained using *ORTEP* (Johnson, 1965).

GH is thankful to the Ministry of Science and Education in Spain for the award of a postdoctoral fellowship in Spain.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HR1051). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1995). **C51**, 1462–1464

2′,3′-Dideoxy-3′-*C*,2′-*N*-[(3*R*,5*R*)-5-ethoxycarbonyl-2-methyl-1,2-isoxazolidine]-ribothymidine†

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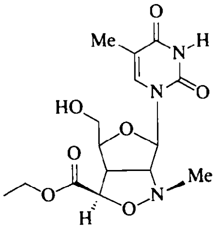
Abstract

The title compound, $C_{15}H_{21}N_3O_7$, is a thymidine derivative with a tetrahydroisoxazole (THI) ring fused to the sugar ring at the 2′- and 3′-C atoms. The thymine base is in an *anti* conformation [$\chi = -122.5\,(3)^\circ$] while the ribose moiety has a C2′-*exo*,C3′-*endo* ($^3T_2$) conformation with a highly flattened sugar ring [$P = -5.8$, $\tau_m = 13.1^\circ$]. The molecule contains a pseudo-twofold axis on the C2′—C3′ bond with the ethyl ester group acting as the base and the *N*-methyl group acting as the 5′-hydroxyl group in a nucleoside. The THI ring fused to the furanose has a C3′-*endo*,C4′-*exo* ($^3T_4$) conformation [$P = 41.8$, $\tau_m = 19.3^\circ$]. The ethyl ester moiety is disordered with respect to two conformations, the population of the major form being 87.4 (8)% and that of the minor form 12.6 (8)%.

Comment

Nucleoside analogues combat viruses by blocking replication and/or transcription. They function as chain terminators because they lack the O3′ hydroxyl groups required for chain elongation. Two notable examples of these compounds, zidovudine (AZT) and didanosine (ddI), are in current use as anti-HIV drugs. In our search for new nucleoside analogues for therapeutic use against HIV, the title compound (I) was synthesized and its structure determined. The 2′,3′-α-fused isoxazolidine nucleoside was prepared by a ring-closure dipolar cycloaddition reaction in which the stereochemistries of four prochiral centers were fixed in one step (Papchikhin & Chattopadhyaya, 1994) in a yield of >90%. The one-dimensional NOE difference (^{1}H at 500 MHz) studies (Papchikhin & Chattopadhyaya, 1994) of this isoxazolidine nucleoside have already shown C2′(*R*), C3′(*S*), C3″(*R*) and N2″(*R*) configurations which are consistent with the results of the present X-ray study.



(I)

The title compound is a thymidine derivative which is bonded to the five-membered disubstituted tetrahydroisoxazole (THI) ring at the sugar 2′- and 3′-positions. The molecule contains an approximate local dyad (r.m.s. deviation for the two five-membered rings and the immediate substituent atoms is 0.252 Å) normal to the C2′—C3′ bond in the best plane of the fused rings. In this orientation, the *N*-methyl group of the THI ring acts as the ribose 5′-hydroxyl group and the ethyl ester group of THI acts as the nucleosidic base. An *ORTEP*II (Johnson, 1976) drawing with the atom-labeling scheme is shown in Fig. 1. Conformational parameters are given in Table 2.

The crystal structure confirms the structure predicted by the synthesis. The bond lengths and angles for the molecule are normal within e.s.d. limits. The sugar pucker of the disubstituted ribose has a C2′-*exo*,C3′-*endo* conformation [$P = -5.8^\circ$] (Altona & Sundar-

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† Alternative name: ethyl 4-(2-hydroxymethyl)-1-methyl-6-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-1,3,3a,6a-tetrahydro-4*H*,-6*H*-furano[3,4-*c*][1,2]isoxazole-3-carboxylate.

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