References

Allen, F. H., Kennard, O. & Taylor, R. (1983). *Acc. Chem. Res.* **16**, 146–153.

Desiraju, G. R. (1991). *Acc. Chem. Res.* **24**, 290–296.

Engels, M., Bashford, D. & Ghadiri, M. R. (1995). *J. Am. Chem. Soc.* **117**, 9151–9158.

Panneerselvam, K., Soriano-García, M., Reyes-Arellano, A., Tamariz-Mascarúa, J. & Mendoza-Sánchez, R. I. (1996). *Anal. Sci.* In the press.

Reyes-Arellano, A., Boese, R., Steller, I. & Sustmann, R. (1995). *Struct. Chem.* **6**, 391–395.

Sheldrick, G. M. (1985). *SHELXS86. Program for the Solution of Crystal Structures.* University of Göttingen, Germany.

Sheldrick, G. M. (1990). *SHELXTL-Plus.* Release 4.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Siemens (1992). *XSCANS Users Manual.* Version 2.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Thalladi, V. R., Panneerselvam, K., Carrell, C. J., Carrell, H. J. & Desiraju, G. R. (1995). *J. Chem. Soc. Chem. Commun.* pp. 341–342.

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6-Ammonio-(1*H*$^+$)-1,4,8,11-tetraazacyclotridecane-5,7-dione Dichloride Methanol Solvate: an Amino-Pendant Tetraazacyclotridecane Derivative

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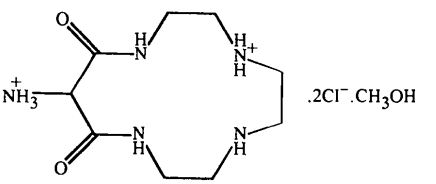
Abstract

The structure of a new aminotetraazacycloalkane derivative, 6-amino-1,4,8,11-tetraazacyclotridecane-5,7-dione, has been determined in its diprotonated form. Charge balance is supplied by two chloride anions and the lattice also contains a methanol solvate to give the formula $C_9H_{21}N_5O_2^{2+}.2Cl^-.CH_3OH$.

Comment

The attachment of metal ions to proteins such as monoclonal antibodies can create new tools for use in biology (Meares & Wensel, 1984) and medicine (Sundberg, Meares, Goodwin & Diamanti, 1974). The reagents used for such attachment are normally referred to as bifunctional chelating agents because they incorporate a strong metal-chelating group and a chemically reactive group. Such agents are most often used to endow biological molecules with the nuclear (Sundberg, Meares, Goodwin & Diamanti, 1974), physical (Leung & Meares, 1977) or chemical (Dreyer & Dervan, 1985) properties of the chelated metal ions. In the last few years, substantial progress has been made in the application of such reagents to problems such as cancer therapy and diagnosis (Scheinberg, Strand & Gansow, 1982; Hnatowich, Layne, Childs, Lanteigne, Davis & Griffin, 1983), clinical immunoassays (Siitari, Hemmila, Sioni, Lorgen & Koisteinen, 1983) and DNA fingerprinting (Van Dyke & Dervan, 1983).

The properties of the chelated metal ions play a major role in the application of the bifunctional chelates. Radioisotopes of copper such as ^{67}Cu have been shown to be potentially useful in radioimmunotherapy (DeNardo, Jungerman, DeNardo, Lagunas-Solar, Cole & Meares, 1985). We have undertaken the development of new bifunctional chelates containing ^{67}Cu which, when conjugated to antitumour monoclonal antibodies, will serve as tumour-imaging and tumour-therapeutic agents. For this application, it is essential that the radioactive copper ion remains attached to the antibody for several days in a living system. Cu^{II} is a very labile metal ion and to counteract this, we have prepared the title compound (I), a ligand specially designed to form a kinetically inert complex with Cu^{II} and to provide a side chain for attachment to a protein.



(I)

Our single-crystal X-ray study of (I) represents a complete structural determination for a tetraazacycloalkanedione compound. Previous IR, NMR and mass spectroscopic studies (Kimura, Koike, Machida, Nagai & Kodama, 1984; Kimura, Haruta *et al.*, 1993) of the analogous amino-pendant dioxocyclam were consistent with the existence of a dioxotetraazacycloalkane molecule. However, no structural conclusions regarding the packing of the dioxocyclam molecules or related species could be drawn from the NMR data recorded in solution. It was only possible to establish that the amino-dioxocyclam existed in a protonated form. Our structure determination confirms the protonation of the amino[13]ane-N_4-dione to give the [amino[13]ane-N_4-dione]$^{2+}.2Cl^-$, (I), shown in Fig. 1. The facile location and stable refinement of all the H atoms in the structure leave no doubt as to the identity of the protonated sites at N1 and N6. This is confirmed by the C6—

N6 distance of 1.474 (1) Å and the C2—N1 and C13—N1 distances of 1.491 (1) and 1.492 (2) Å, respectively, in good agreement with literature values (Allen *et al.*, 1987). Note that the amide groups impose two regions of planarity in the ring, as indicated by the valence angles and the torsion angles.

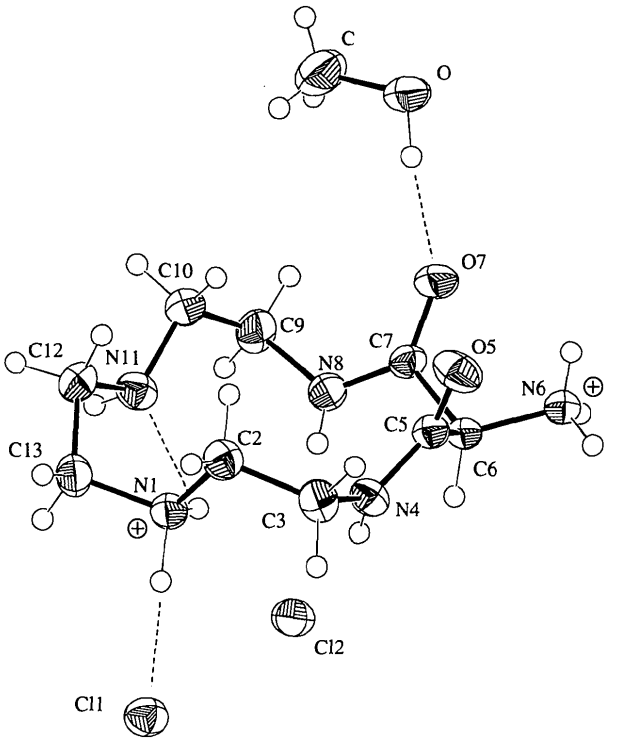


Fig. 1. *ORTEP* view of (I) showing 50% probability displacement ellipsoids. The H atoms are shown as spheres of arbitrary radius.

The cations are organized in layers, alternatively separated by Cl^- ions and methanol solvent molecules. The three-dimensional arrangement is strengthened by electrostatic interactions between the Cl^- ions and the protonated amine groups [Cl1···N 3.080 (1) Å] on the one hand, and hydrogen bonds between the methanol molecules and the O atoms of the amide groups on the other. Of the two amide groups of the cation, only one forms a hydrogen bond [O7···H 1.84 (3) Å] which elongates the C=O double bond of this amide group [C7=O7 1.232 (2) Å] in comparison to the other [C5=O5 1.219 (1) Å].

Experimental

The macrocyclic ligand (I) was prepared as reported by Kimura, Haruta *et al.* (1993) with little modification. X-ray quality crystals were obtained by slow crystallization from methanol at 277 K.

Crystal data

$C_9H_{21}N_5O_2^{2+}.2Cl^-.CH_4O$
M_r = 334.2
Triclinic
$P\bar{1}$
a = 9.0659 (9) Å
b = 10.0897 (10) Å
c = 10.4858 (10) Å
α = 109.350 (11)°
β = 108.260 (11)°
γ = 97.640 (10)°
V = 828.86 (14) Å^3
Z = 2
D_x = 1.339 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 20–30°
μ = 0.41 mm^{-1}
T = 293 K
Parallelepiped
0.31 × 0.16 × 0.11 mm
Colourless

Data collection

Enraf–Nonius CAD-4*F* diffractometer
ω scans
Absorption correction: analytical
T_{min} = 0.84, T_{max} = 0.93
10654 measured reflections
10248 independent reflections
5943 observed reflections [$F > 4\sigma(F)$]
R_{int} = 0.021
θ_{max} = 39.99°
$h = -16 \rightarrow 16$
$k = -18 \rightarrow 18$
$l = 0 \rightarrow 19$
3 standard reflections
frequency: 60 min
intensity decay: 25%

Refinement

Refinement on F
R = 0.040
wR = 0.052
S = 1.753
5730 reflections
271 parameters
H atoms: refined freely with isotropic displacement parameters
$w = 1/[\sigma^2(F_o^2) + (0.019F_o^2)]$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.45 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}
Extinction correction: Zachariasen (1968)
Extinction coefficient: 0.047 (2)
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)*

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

	x	y	z	U_{eq}
Cl1	0.37629 (4)	0.95661 (3)	0.80163 (3)	0.0378 (1)
Cl2	0.21977 (4)	0.10872 (3)	0.28780 (3)	0.0380 (1)
C	1.3300 (3)	0.5392 (2)	0.6629 (2)	0.0674 (8)
O	1.41822 (14)	0.54316 (12)	0.80097 (12)	0.0529 (4)
N1	0.61336 (13)	0.17969 (11)	0.76915 (11)	0.0309 (3)
C2	0.70156 (16)	0.30826 (14)	0.91024 (14)	0.0354 (4)
C3	0.79856 (15)	0.26252 (15)	1.02743 (14)	0.0351 (4)
N4	0.91592 (12)	0.19147 (12)	0.98616 (11)	0.0315 (3)
C5	1.07078 (14)	0.25987 (12)	1.03243 (12)	0.0288 (3)
O5	1.13640 (12)	0.38437 (10)	1.12219 (12)	0.0451 (4)
C6	1.16509 (13)	0.16959 (11)	0.95534 (12)	0.0266 (3)
N6	1.33019 (12)	0.19943 (12)	1.06036 (12)	0.0311 (3)
C7	1.17177 (14)	0.21870 (12)	0.83322 (13)	0.0298 (4)
O7	1.28597 (12)	0.31814 (11)	0.85925 (11)	0.0449 (4)
N8	1.04464 (13)	0.15316 (12)	0.70933 (11)	0.0340 (4)
C9	1.01320 (17)	0.20065 (17)	0.58825 (15)	0.0394 (5)
C10	0.89755 (16)	0.29567 (15)	0.59110 (15)	0.0383 (4)
N11	0.74129 (13)	0.21012 (11)	0.56857 (12)	0.0345 (3)
C12	0.62561 (16)	0.29288 (15)	0.59561 (15)	0.0373 (4)
C13	0.51559 (15)	0.21317 (16)	0.64563 (15)	0.0367 (4)

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

C—O	1.402 (3)	C6—N6	1.474 (1)
N1—C2	1.491 (1)	C6—C7	1.533 (2)
N1—C13	1.492 (2)	C7—O7	1.232 (2)

C2—C3	1.518 (2)	N8—C9	1.461 (2)
C3—N4	1.456 (2)	C9—C10	1.512 (2)
N4—C5	1.333 (2)	C10—N11	1.462 (2)
C5—O5	1.219 (1)	N11—C12	1.463 (2)
C5—C6	1.538 (2)	C12—C13	1.520 (2)
C2—N1—C13	115.1 (1)	O7—C7—N8	125.9 (1)
N1—C2—C3	110.8 (1)	O7—C7—C6	119.3 (1)
N4—C3—C2	111.8 (1)	N8—C7—C6	114.6 (1)
C5—N4—C3	123.4 (1)	C7—N8—C9	123.4 (1)
O5—C5—N4	125.7 (1)	N8—C9—C10	111.4 (1)
O5—C5—C6	120.4 (1)	N11—C10—C9	109.3 (1)
N4—C5—C6	113.82 (9)	C10—N11—C12	115.8 (1)
N6—C6—C7	109.3 (1)	N11—C12—C13	108.7 (1)
N6—C6—C5	109.58 (8)	N1—C13—C12	110.1 (1)
C7—C6—C5	107.0 (1)		
C3—N4—C5—O5	6.1 (2)	C6—C7—N8—C9	169.0 (1)
C3—N4—C5—C6	−170.7 (2)	O7—C7—N8—C9	−6.7 (2)

Data collection: *CAD-4F Software* (Enraf–Nonius, 1989). Data reduction: *Xtal* (Hall, King & Stewart, 1995). Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1996). Program(s) used to refine structure: *Xtal*. Molecular graphics: *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *Xtal*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1095). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Allen, F. H., Kennard, O., Watson, D., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–19.

DeNardo, S. J., Jungerman, J. A., DeNardo, G. L., Lagunas-Solar, M. C., Cole, W. & Meares, C. F. (1985). *The Developing Role of Short-Lived Radionuclides in Nuclear Medical Practice*, edited by P. Paras & J. W. Theissen, pp. 401–414. Washington DC: US Department of Energy.

Dreyer, G. B. & Dervan, P. B. (1985). *Proc. Natl Acad. Sci. USA*, **82**, 968–972.

Enraf–Nonius (1993). *CAD-4 Software*. Version 5.0. Enraf–Nonius, Delft, The Netherlands.

Hall, S. R., King, G. S. D. & Stewart, J. M. (1995). Editors. *Xtal3.4 Users Manual*. University of Western Australia, Australia.

Hnatowich, D. J., Layne, W. W., Childs, R. L., Lanteigne, D., Davis, M. A. & Griffin, T. W. (1983). *Science*, **220**, 613–615.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Kimura, E., Haruta, M., Koike, T., Shionoya, M., Takenouchi, K. & Itika, Y. (1993). *Inorg. Chem.* **32**, 2779–2784.

Kimura, E., Koike, T., Machida, R., Nagai, R. & Kodama, M. (1984). *Inorg. Chem.* **23**, 4181–4188.

Leung, C. S.-H. & Meares, C. F. (1977). *Biochem. Biophys. Res. Commun.* **75**, 149–155.

Meares, C. F. & Wensel, T. G. (1984). *Acc. Chem. Res.* **17**, 202–209.

Scheinberg, D. A., Strand, M. & Gansow, O. A. (1982). *Science*, **215**, 1511–1513.

Sheldrick, G. M. (1996). *SHELXTL*. Siemens Analytical Instrumentation Inc., Madison, Wisconsin, USA.

Siitari, H., Hemmila, I., Sioni, E., Lorgen, T. & Koisteinen, V. (1983). *Nature (London)*, **301**, 258–260.

Sundberg, M. W., Meares, C. F., Goodwin, D. A. & Diamanti, C. I. (1974). *Nature (London)*, **250**, 587–588.

Van Dyke, M. W. & Dervan, P. B. (1983). *Biochemistry*, **22**, 2373–2377.

Zachariasen, W. H. (1968). *Acta Cryst.* A**24**, 212–216.

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A Corticosteroid Ester

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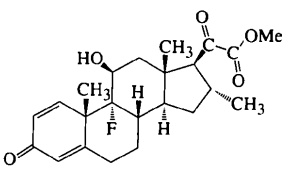
Abstract

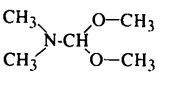
The unit cell of the title compound, 9α-fluoro-11β-hydroxy-21-methoxy-16α-methylpregna-1,4-diene-3,20,-21-trione, $C_{23}H_{29}FO_5$, contains two symmetry-related molecules and no solvent. One of the five O atoms is hydrogen-bonded to a neighbouring molecule.

Comment

The title compound, (1), belongs to a family of corticosteroid esters possessing high topical anti-inflammatory activity without any systemic effects. Their synthesis has already been described (Laurent, Gerhards & Wiechert, 1975), but a new synthetic route by reaction of *N,N*-dimethylformamide dimethyl acetal (DMF-DMA), (2), on artificial corticosteroid dexamethasone, (3), has recently been established. This latter DMF-DMA reaction represents a far simpler way of synthesizing corticosteroid esters. The structure of the major reaction product, (1), has been determined with high-resolution mass spectrometry and nuclear magnetic resonance (Negriolli, Maume, Deniaud & André, 1996). However, in order to confirm the results and analyse the packing of the molecules, an X-ray structure determination was carried out.



(1)



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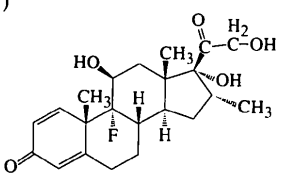

(3)

An *ORTEP* (Johnson, 1965) plot of (1) is shown in Fig. 1. This molecule is based upon the cyclo-