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Structure and Conformation of the Hydrate of 8,11-Dihydroxypentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-carbolactam

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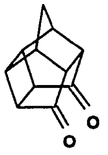
Abstract

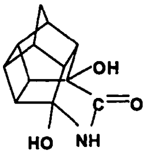
The crystalline modification of the title compound from aqueous medium depends critically on factors such as concentration and pH. Crystallographic analysis of a hydrated crystal showed that this effect related to the formation of an extended network of hydrogen bonds that requires the water molecule, as H_2O, to be hydrogen bonded three ways. The crystals are monoclinic, $C2/c$, $a = 10.030(1)$, $b = 9.840(2)$, $c = 21.625(2)$ Å, $\beta = 90.87(1)°$, $Z = 8$. The hydrogen-bond network between water of hydration and the functional groups on the cage compound has identical geometries for both chiralities and during crystallization there is hence no discrimination between enantiomers. Both forms are thus accommodated at the same sites in random distribution, causing disorder of the molecular fragment remote from the functional region. The final arrangement is similar to a hydrated solid solution of the two enantiomers with an IR spectrum sufficiently different from the anhydrous form to suggest a different molecular arrangement.

1. Introduction

As part of a programme designed to explore the synthesis and chemistry of amino acids and lactams containing polycyclic cage moieties, we have examined the influence of reaction conditions on the conversion of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (1) to lactam derivatives utilizing Strecker reagents. It was recently reported (Martins, Viljoen, Kruger & Joubert, 1993) that (1) produces the dihydroxy lactam derivative (2) upon treatment with 1 equiv. aqueous sodium cyanide. With 2 equiv. aqueous sodium cyanide the cyanohydroxy lactam derivative (3) is obtained. Treatment of (1) with an aqueous mixture of sodium cyanide, ammonium chloride and ammonia produces the aminohydroxy lactam derivative (4) (Martins, Viljoen, Kruger, Joubert & Wessels, 1994).



(1)



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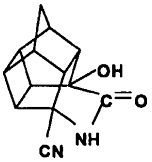

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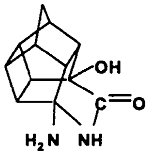

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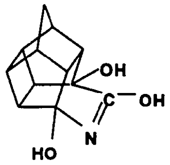

(5)

In order to isolate some of the intermediates in the conversion of (1) to (2) in aqueous sodium cyanide, the reaction was carried out with 75% less water than reported previously (Martins *et al.*, 1993) to induce precipitation. Precipitation of a product of which the IR spectrum (KBr discs) differs markedly from that of (2) occurred after 5 h. The IR spectrum exhibits no absorptions in the C—N triple bond stretching region. A broad absorption band is registered between 3550 and 2870 cm^{-1} with much less identifiable absorption peaks than in the case of (2). A strong carbanylic group absorption peak appears at 1665 cm^{-1} [compared with 1660 cm^{-1} for (2)]. In the case of (2) a strong absorption at 1410 cm^{-1} is associated with the N—H bending vibrations of the lactam group. However, a much weaker and broader absorption band is displayed at 1450 cm^{-1} for the precipitated product.

The electron impact (EI)-induced mass spectrum (MS) of the precipitated product exhibits a molecular ion at m/z 219. The MS fragmentation pattern is identical to that of (2). ^{13}C and ^{1}H NMR data are also identical to those of (2). These observations suggested possible hydrate formation, which was confirmed by azeotropic distillation of the precipitate product in benzene, whereby (5) was obtained. Depending on the solvent used to isolate the lactam (2), a lactim (5) can also be obtained (Martins *et al.*, 1993). Recrystallization of (2) or (5) from water did not produce a hydrate. However, treatment of either (2) or (5) with 25% ammonia at room temperature produced the same hydrate isolated from the conversion of (1) to (2) as described above. The structure of this hydrate was established by X-ray crystallographic analysis.

2. Experimental

2.1. *Preparation*

IR spectra (KBr discs) were recorded on a Nicolet 5DX FT spectrophotometer. EI mass spectra were obtained at 70 eV on a VG 7070-E mass spectrometer.

2.1.1. *Preparation of 8,11-dihydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-lactam (2).* A solution of (1) (1 g) in water (20 cm^3) was stirred in an ice bath for 10 min. A solution of sodium cyanide (0.4 g) in water (1 cm^3) was added dropwise over a period of 3 h and the reaction mixture stirred for a further 15 h with cooling. Precipitation with acetone, extraction of the organic compound on a Soxhlet apparatus with 1,4-dioxane as extractant and recrystallization from water produced (2) (0.8 g, m.p. 498 K). ν_{max} 3395, 3360, 3165, 2968, 1672, 1400, 1302, 1155, 1015, 990, 940, 802 and 777 cm^{-1}. EI MS, *m/z* 219 (M$^+$), 191 (M$^+$ –CO), 174 (M$^+$ –CO–OH). Calc. for $C_{12}H_{13}NO_3$: C 65.75, H 5.94, N 6.39; found: C 65.74, H 5.92, N 6.37%.

2.1.2. *Preparation of the hydrate of (2) from the dione (1).* A solution of (1) (1 g) in water (5 cm^3) was stirred in an ice bath for 10 min. A solution of sodium cyanide (0.4 g) in water (1 cm^3) was added dropwise over a period of 3 h and the reaction mixture stirred for a further 2 h with cooling. The precipitated product was filtered off and recrystallized from water (0.8 g, m.p. 473 K, decomposition). ν_{max} 3550–2870 (br), 1665, 1640, 1450, 1320, 1295, 1145 and 810 cm^{-1}. EI MS, *m/z* 219 (M$^+$ –H$_2$O). Calc. for $C_{12}H_{15}NO_4$: C 60.76, H 6.33, N 5.91; found: C 60.74, H 6.30, N 5.89%.

2.1.3. *Preparation of the hydrate of (2) from the lactam (2) [or lactim (5)].* A solution of (2) [or (5); 1g] in 25% ammonia (15 cm^3) was stirred in a sealed vessel for 24 h. The product was filtered off and proved to be identical to the hydrate obtained in §2.1.1.

2.2. *Crystallographic analysis*

To produce single crystals, a sealed glass tube with the reaction mixture was heated for 6 h at 393 K and allowed to cool down overnight in a stainless steel high-pressure vessel. A diffraction quality crystal of the hydrated lactam (2) was screened for structure analysis by standard photographic X-ray techniques. Crystal data and a summary of data collection and refinement parameters are given in Table 1. All measurements were made on an Enraf-Nonius CAD-4 single-crystal diffractometer with an incident beam graphite-crystal monochromator [λ(Mo $K\alpha$) = 0.7104 Å]. Fixed scan and aperture widths were used while the scan speed was varied. Crystal decay and orientation were monitored during data collection. Data reduction consisted of correction for background and Lp effects. No absorption corrections were applied because of the low absorption coefficient. The *SHELX* programs (Sheldrick, 1978, 1993) were used for all computations and least-squares refinements based on F^2. *SCHAKAL*92 (Keller, 1989) was used for plotting all structure diagrams. Refined atomic coordinates are given in Table 2 according to the numbering scheme of Fig. 1.*

Table 1. *Experimental details*

Crystal data	
Chemical formula	$C_{12}H_{13}NO_3.H_2O$
Chemical formula weight	237.25
Cell setting	Monoclinic
Space group	*C*2/*c*
a (Å)	10.030 (1)
b (Å)	9.840 (2)
c (Å)	21.625 (2)
β (°)	90.87 (1)
V (Å^3)	2134.0 (5)
Z	8
D_x (Mg m^{-3})	1.477
Radiation type	Mo $K\alpha$
Wavelength (Å)	0.71069
No. of reflections for cell parameters	25
θ range (°)	3–30
μ (mm^{-1})	0.111
Temperature (K)	293 (2)
Crystal form	Cubic
Crystal size (mm)	0.31 × 0.24 × 0.19
Crystal colour	Colourless
Data collection	
Diffractometer	Enraf–Nonius CAD-4
Data collection method	ω–2θ
Absorption correction	None
No. of measured reflections	3963
No. of independent reflections	2219
No. of observed reflections	1479
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.0752
θ_{max} (°)	29.97
Range of *h*, *k*, *l*	$-9 \rightarrow h \rightarrow 14$ $-9 \rightarrow k \rightarrow 13$ $-30 \rightarrow l \rightarrow 16$
No. of standard reflections	3
Frequency of standard reflections	120 min
Refinement	
Refinement on	F^2
R	0.0539
wR	0.1486
S	1.148
No. of reflections used in refinement	2219
No. of parameters used	285
H-atom treatment	All H-atom parameters refined
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1260P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.156
$\Delta\rho_{max}$ (e Å^{-3})	0.382
$\Delta\rho_{min}$ (e Å^{-3})	−0.320
Extinction method	None
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

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* Lists of anisotropic displacement parameters, H-atom coordinates and structure factors have been deposited with the IUCr (Reference: AN0518). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

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

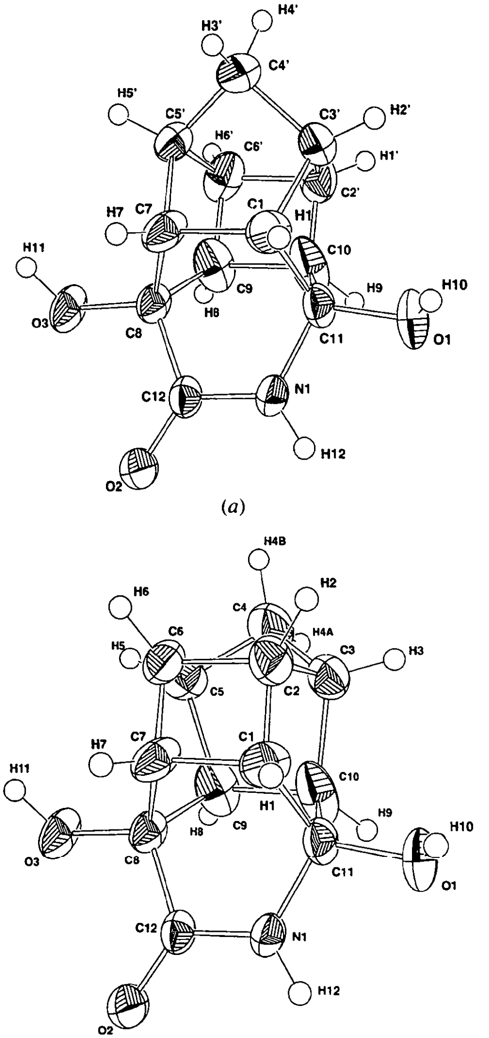
	x	y	z	U_{eq}
C1	0.6632 (2)	0.3188 (2)	0.60159 (12)	0.0468 (6)
C2	0.7368 (6)	0.3813 (4)	0.6531 (2)	0.0479 (12)
C3	0.6834 (8)	0.2999 (8)	0.7080 (4)	0.045 (2)
C4	0.8113 (5)	0.2541 (7)	0.7430 (2)	0.0627 (13)
C5	0.8726 (6)	0.1907 (5)	0.6857 (3)	0.0449 (10)
C6	0.8694 (12)	0.3064 (10)	0.6372 (4)	0.043 (2)
C7	0.7986 (2)	0.2470 (2)	0.58727 (12)	0.0459 (6)
C8	0.7821 (2)	0.0925 (2)	0.59287 (8)	0.0327 (4)
C9	0.7526 (2)	0.0801 (3)	0.66208 (10)	0.0534 (6)
C10	0.6174 (2)	0.1515 (3)	0.67647 (9)	0.0605 (7)
C11	0.5600 (2)	0.2116 (2)	0.61697 (8)	0.0352 (5)
C12	0.6659 (2)	0.0431 (2)	0.55463 (8)	0.0324 (4)
O1	0.43217 (13)	0.2627 (2)	0.62631 (7)	0.0492 (4)
O2	0.67274 (13)	−0.04755 (14)	0.51477 (7)	0.0476 (4)
O3	0.89852 (13)	0.01992 (13)	0.57746 (7)	0.0457 (4)
N1	0.55403 (15)	0.10813 (14)	0.56886 (7)	0.0341 (4)
O4	0.1047 (2)	0.1668 (2)	0.54125 (12)	0.0821 (7)
C2′	0.6739 (9)	0.2460 (8)	0.7147 (4)	0.049 (2)
C3′	0.6779 (5)	0.3748 (5)	0.6742 (3)	0.0454 (11)
C4′	0.8259 (5)	0.4155 (5)	0.6752 (3)	0.0609 (14)
C5′	0.8745 (11)	0.2753 (8)	0.6551 (4)	0.043 (2)
C6′	0.8100 (5)	0.1767 (5)	0.7019 (2)	0.0504 (14)

Once the disorder discussed below had been resolved all H atoms (including those at sites of fractional occupation) could be located by difference syntheses and refined freely with isotropic displacement parameters.

3. Discussion

Automated direct methods gave a complete structure that matched the expected connectivity, but as soon as least-squares refinement was attempted a region of disorder appeared. According to the atomic numbering scheme of Fig. 1 the disorder consists of alternative orientations for the five-membered ring C2–C6 and the way it links up with the six-membered ring, C1—C7—C8—C9—C10—C11. The two alternatives therefore correspond to a bicyclic system that carries all the functional groups and is capped by a five-membered ring (C2–C6), which assumes two different orientations with respect to the bicyclic base. The observed arrangement corresponds to the superposition of these two units with a common base. Only the capping five-membered ring therefore appears disordered. The two units shown in Fig. 1 are clearly isomers and if one is rotated through a vertical twofold axis they are seen to be mirror images and hence enantiomers. In one instance, Fig. 1(*a*), it links up to form a four-membered ring C2′—C10—C9—C6′, which in the alternative arrangement, Fig. 1(*b*), is defined as C2—C1—C7—C6. The C3′—C1 and C5′—C7 bonds of the first orientation are replaced by C3—C10 and C5—C9 for the second. The overall effect therefore is the superposition of two isomers at the same site and these are readily recognized as the enantiomers. Disorder like this could result from an incorrect space group, for instance if one of the symmetry elements with inversion is absent in the correctly assigned space group. Refinement was therefore attempted in both *C*2 and *Cc*, but in each case the same composite picture emerged again at both sites, now related by pseudo-symmetry only.

One therefore has the unusual situation of two enantiomers sharing the same site, with a substantial part of the two structures in exact register. To explain this pattern it is necessary to examine the network of hydrogen bonds (Fig. 2) between the lactam and the water of crystallization. The water molecule forms three hydrogen bonds, through its two H atoms and a lone pair, with three different lactam molecules. The lactam molecule in turn is hydrogen-bonded to two neighbours and three water molecules. The carbonyl



(*a*)

(*b*)

Fig. 1. Schematic drawings to define the atomic numbering scheme. The two frames depict the two enantiomers, sharing the same crystallographic site and with the functional region in exact register.

Table 3. *Selected geometric parameters* (Å, °)

C1—C2	1.462 (6)	C3′—C4′	1.536 (6)
C1—C11	1.518 (3)	C4′—C5′	1.528 (9)
C1—C7	1.566 (3)	C5′—C6′	1.549 (8)
C1—C3′	1.668 (5)	C5′—C7	1.667 (12)
C2—C3	1.535 (8)	C6′—C9	1.401 (6)
C2—C6	1.563 (10)	C7—C8	1.534 (2)
C3—C4	1.547 (8)	C8—O3	1.413 (2)
C3—C10	1.738 (9)	C8—C12	1.500 (3)
C4—C5	1.524 (6)	C8—C9	1.535 (3)
C5—C6	1.548 (7)	C9—C10	1.563 (3)
C5—C9	1.696 (6)	C10—C11	1.521 (3)
C6—C7	1.411 (13)	C11—O1	1.395 (2)
C2′—C10	1.362 (9)	C11—N1	1.456 (2)
C2′—C3′	1.543 (7)	C12—O2	1.243 (2)
C2′—C6′	1.554 (10)	C12—N1	1.332 (2)
C2—C1—C11	117.6 (3)	C6—C7—C8	113.8 (4)
C2—C1—C7	84.9 (2)	C6—C7—C1	95.2 (4)
C11—C1—C7	109.03 (14)	C8—C7—C1	109.66 (14)
C11—C1—C3′	94.3 (2)	C8—C7—C5′	98.3 (3)
C7—C1—C3′	105.7 (2)	C1—C7—C5′	97.8 (3)
C1—C2—C3	101.0 (5)	O3—C8—C12	110.12 (14)
C1—C2—C6	93.2 (5)	O3—C8—C7	113.09 (13)
C3—C2—C6	103.4 (5)	C12—C8—C7	111.2 (2)
C2—C3—C4	103.5 (5)	O3—C8—C9	111.21 (15)
C2—C3—C10	105.7 (5)	C12—C8—C9	110.6 (2)
C4—C3—C10	104.8 (5)	C7—C8—C9	100.3 (2)
C5—C4—C3	93.6 (4)	C6′—C9—C8	117.5 (3)
C4—C5—C6	104.2 (5)	C6′—C9—C10	85.5 (3)
C4—C5—C9	102.4 (4)	C8—C9—C10	109.8 (2)
C6—C5—C9	105.1 (7)	C8—C9—C5	95.5 (3)
C7—C6—C5	102.6 (7)	C10—C9—C5	105.4 (2)
C7—C6—C2	86.7 (7)	C2′—C10—C11	113.4 (4)
C5—C6—C2	101.9 (5)	C2′—C10—C9	94.2 (4)
C10—C2′—C3′	103.3 (6)	C11—C10—C9	109.0 (2)
C10—C2′—C6′	87.2 (5)	C11—C10—C3	98.2 (3)
C3′—C2′—C6′	103.2 (5)	C9—C10—C3	97.4 (3)
C4′—C3′—C2′	103.8 (5)	C2′—C10—C6′	50.4 (4)
C4′—C3′—C1	99.9 (4)	C11—C10—C6′	122.1 (2)
C2′—C3′—C1	105.1 (5)	C9—C10—C6′	43.9 (2)
C5′—C4′—C3′	94.2 (5)	O1—C11—N1	109.13 (15)
C4′—C5′—C6′	104.0 (5)	O1—C11—C1	114.32 (15)
C4′—C5′—C7	104.9 (6)	N1—C11—C1	110.49 (13)
C6′—C5′—C7	106.3 (7)	O1—C11—C10	110.78 (14)
C9—C6′—C5′	101.3 (5)	N1—C11—C10	110.1 (2)
C9—C6′—C2′	93.1 (5)	C1—C11—C10	101.8 (2)
C5′—C6′—C2′	102.6 (5)	O2—C12—N1	124.1 (2)
C9—C6′—C10	50.6 (2)	O2—C12—C8	124.37 (14)
C5′—C6′—C10	107.9 (5)	N1—C12—C8	111.55 (14)
C2′—C6′—C10	42.5 (4)	C12—N1—C11	118.37 (15)

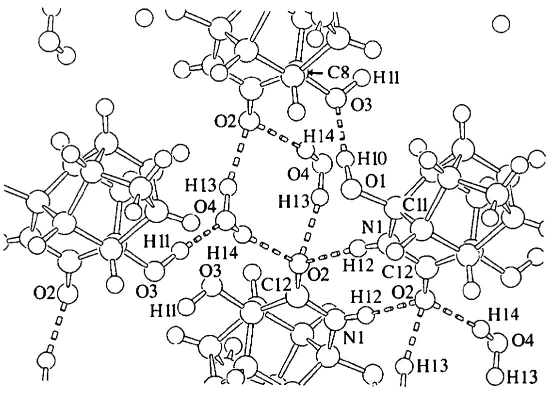


Fig. 2. Drawing of the hydrogen-bond network, showing hydrogen bonds in fragmented style.

Table 4. *Hydrogen-bonding parameters (Å, °)*

D—H···*A*	*D*···H	H—*A*	*D*···*A*	*D*—H···*A*
O1—H10···O3$^{\rm i}$	0.95 (3)	1.82 (3)	2.761 (2)	173 (3)
O3—H11···O4$^{\rm ii}$	0.98 (3)	1.68 (3)	2.652 (2)	174 (3)
O4—H13···O2$^{\rm i}$	0.99 (5)	1.99 (5)	2.950 (2)	164 (4)
O4—H14···O2$^{\rm iii}$	0.83 (3)	2.01 (3)	2.812 (2)	163 (3)
N1—H12···O2$^{\rm iii}$	0.91 (2)	2.06 (2)	2.945 (3)	165 (2)

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

oxygen O2 has three hydrogen bonds, in distorted tetrahedral array around the carbonyl bond and directed towards two separate water molecules and a neighbouring —NH— group. The amino group N1—H12 connects through its H atom to the O2 atom of a neighbouring carbonyl hydroxy group, which is bonded through its hydrogen to a water molecule. To achieve this it is necessary for the functional groups of all lactams in corresponding asymmetric units to have the same orientation with respect to the water of hydration. This requirement does not differentiate between enantiomers, with the consequence that both forms are incorporated. The end effect is that only the upper halves of the enantiomers, remote from the functional groups, have different orientations and this is the source of the observed disorder.

Details of the molecular geometry are given in Table 3 and some important metrical parameters pertaining to the hydrogen-bond network are summarized in Table 4. These values are not seriously affected by the disorder at the other end of the molecule and are presented with confidence. It now becomes clear why the hydrate is only formed at high pH. Its formation depends on the network of hydrogen bonds, which is not possible with protonated water (H_3O^+) at low pH.

As a final check on the feasibility of the proposed disorder, all non-bonded contacts around the disordered region were examined. The closest contacts are $d(\mathrm{H1'—O1},\ 1 - x, y, \frac{3}{2} - z) = 2.66$ and $d(\mathrm{H3'—O1},\ \frac{1}{2} + x, \frac{1}{2} + y, z) = 2.84$ Å, which are interpreted as showing that sufficient room exists for the alternative placements.

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