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Molecular and Crystal Structure of Azadirachtin-H

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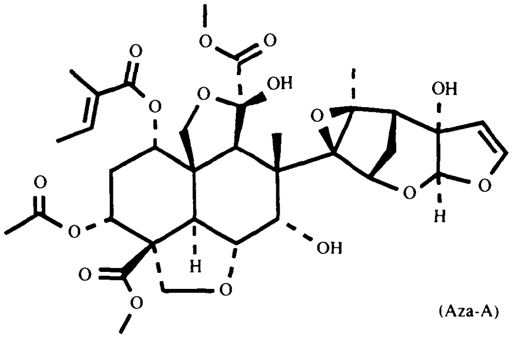
Abstract

Azadirachtin-H, isolated from the seed kernels of *Azadirachta indica* (neem), crystallizes in space group $I4$, $Z = 8$, with disordered ethyl acetate solvent filling channels along the fourfold rotation axes. The crystal structure determination showed that the previously reported molecular structure deduced from NMR studies was correct except for the stereochemistry at C(11). Azadirachtin-H, which belongs to a group of C-*seco*-tetranortriterpenoids (C-*seco*-limonoids) of great interest for their insect antifeedant and ecdysis-inhibiting activity, has some unusual features: the absence of a carbomethoxy group at C(11); the presence of a cyclic hemiacetal function at C(11); the α-orientation of the hydroxyl group on C(11), opposite to that in all other known azadirachtins with a hydroxyl group on C(11), except azadirachtin-I. There is no intramolecular hydrogen bonding. In this crystal the rotation of the two major moieties of the azadirachtin-H molecule about the single connecting C(8)—C(14) bond is quite different from that in azadirachtin-A, whose crystal structure has recently been determined.

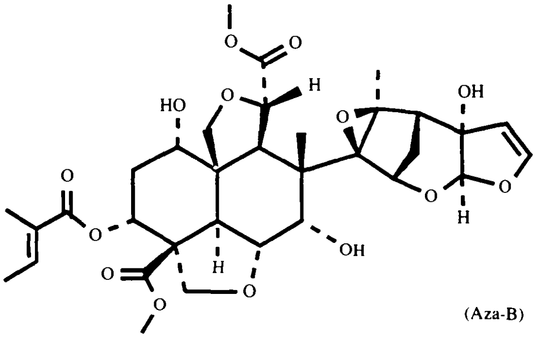
1. Introduction

Of the 50 or so compounds isolated from the seed kernels of *Azadirachta indica* A. Juss [neem tree (Jones, Ley, Morgan & Santafianos, 1989; Hansen, Cuomo, Khan, Gallagher & Ellenberger, 1994)], the azadirachtins form a distinct group of C-*seco*-tetranortriterpenoids (also known as C-*seco*-limonoids) in which two parts, a modified decalin moiety and a modified furan moiety, are connected by a single bond between C(8) and C(14) of the original triterpenoid structure (Ley, Denholm & Wood, 1993). Azadirachtin-A (Aza-A), the most abundant member of this group, has attracted wide attention because of its remarkable antifeedant and ecdysis-inhibiting activity towards more than 200 species of insects and its promise as an environmentally friendly agent for insect control.

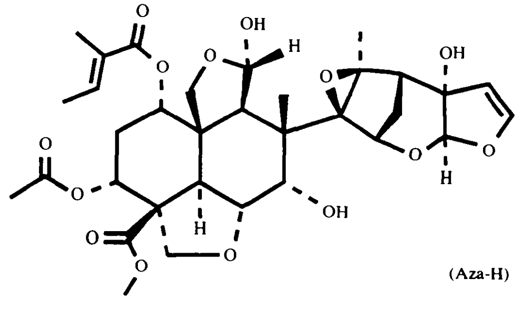
Direct preparative HPLC of neem kernel extract led to the isolation of azadirachtins A, B, D, H and I (Govindachari, Sandhya & Ganesh Raj, 1991). Very recently, Aza-A, which had eluded crystallization for many years, was crystallized successfully (Govindachari, Geetha Gopalakrishnan, Raghunathan & Rajan, 1994) and its structure determined by X-ray diffraction (Kabaleeswaran, Rajan, Govindachari & Geetha Gopalakrishnan, 1994). Earlier, elucidation of the structure of 1-detigloyl-22,23-dihydroazadirachtin-A



(Aza-A)



(Aza-B)



(Aza-H)

(DTA) by X-ray diffraction had been carried out (Broughton, Ley, Slawin, Williams & Morgan, 1986) in order to confirm the structure of Aza-A assigned on the basis of extensive NMR studies (Taylor, 1987; Turner *et al.*, 1987; Bilton *et al.*, 1987). The NMR spectra of Aza-A are temperature-dependent and notoriously difficult to interpret. It was desirable to seek confirmation of the structure of azadirachtin-H (Aza-H) proposed on the basis of NMR data (Govindachari, Sandhya & Ganesh Raj, 1992), especially the location of the tigloyl [*i.e.* (*E*)-2-methyl-2-butenoyl] and acetate groups, and the stereochemistry at C(11).

2. Experimental

Aza-H, obtained by preparative HPLC of neem seed kernel extract, was crystallized by slow evaporation from ethyl acetate. The colorless needles showed a melting point of 531–534 K. Diffraction symmetry showed that the crystals belonged to the unusual tetragonal space group $I4$. Unit-cell parameters were determined by a least-squares fit to the positions of 20 reflections in the θ range 20.6–30.1°. The density, measured by flotation in a mixture of benzene and bromoform, showed that $Z = 8$ and also strongly indicated the presence of some solvent in the crystal.

The structure was solved using the multisolution direct methods algorithms in the program *SHELXS*86 (Sheldrick, 1985). Phases for 316 E values were determined using 6703 triple product relationships and 1000 negative quartets for 200 random phase starting points. The unique successful solution showed all 47 C and O atoms of the Aza-H molecule in the first E-map. Normal least-squares refinement of the Aza-H molecule was carried out using the program *SHELXL*93 (Sheldrick, 1993). C and O atom coordinates were refined independently, with anisotropic displacement parameters assigned to these atoms.* H-atom geometry was idealized and a riding model used for H-atom motions. CH and CH_2 group geometries were fixed; CH_3 group geometry was fixed, but rotation was allowed about the C—CH_3 bond; OH group geometry was fixed, but rotation was allowed about the C—OH bond. U_{iso} for each H was a fixed multiple of U_{eq} for the atom bonded to H (1.2 for CH or CH_2; 1.5 for CH_3 or OH).

The packing of Aza-H in this crystal leaves open channels along the fourfold rotation axes. The crystal density made it evident that solvent was included and the significant electron density clearly seen in a difference Fourier synthesis implied the presence of ethyl acetate loosely held in the channels of the crystal, with at least fourfold disorder. Due to the disorder, the solvate atoms are of course unresolved in Fourier syntheses; nevertheless, some model to account for this electron density was necessary in order to refine the structure.

A plausible fit of disordered ethyl acetate molecules to the difference electron density was constructed and then refined by imposing bond length and angle restraints, as well as a planarity restraint on the C(C=O)O group, but no torsion angle restraints. All intermolecular contact distances between ethyl acetate and Aza-H and between ethyl acetate molecules at different heights z in each channel were restrained to be not less than the sum of van der Waals radii (C 1.7, O 1.5 and H 1.2 Å), to prevent the ethyl acetate from approaching too closely either the walls of the channel or any other solvent molecules above and below it. The motion of the disordered solvent in the channel was modeled as a single overall anisotropic displacement of the molecule as a whole. H atoms were treated as in Aza-H. The occupancy of the ethyl acetate was kept fixed at 0.25.

Refinement was carried out in two blocks to avoid underestimating the uncertainties in the parameters of azadirachtin-H, because the disordered ethyl acetate model would not refine without some damping. In the final cycles, the diagonal elements of the least-squares matrix block for ethyl acetate were multiplied by 1.180 before inversion. Refinement was continued for each block until convergence, as evidenced by oscillation of the parameters between two values. The displacement of C(5) is almost isotropic; Δ/σ for U_{13} of C(5) oscillated between +1.023 and −1.037 in the final refinement cycles. Further experimental details on the crystal, data collection and refinement are given in Table 1.

3. Results and discussion

From the X-ray diffraction data obtained from these crystals the structure of Aza-H was definitively established. The absolute stereochemistry was assumed to conform to the reported absolute stereochemistry of azadirachtin-A and its congeners assigned from the analysis of combined chemical degradation, NMR and X-ray studies (Ley, Lovell & Williams, 1992).

Fig. 1 gives two different perspective views of this complex natural product, including all H atoms, and shows the atomic numbering scheme. Atomic coordinates and equivalent isotropic displacement parameters are listed in Table 2, and bond lengths and angles in Table 3. Results for the disordered ethyl acetate molecule are given in Table 4. *SHELXL*93 (Sheldrick, 1993) generates floating origin restraints, so no atom need have a fixed z coordinate. The bond lengths and angles of Aza-H are all normal and similar to those observed in other azadirachtins (Broughton, Ley, Slawin, Williams & Morgan, 1986; Kabaleeswaran, Rajan, Govindachari & Geetha Gopalakrishnan, 1994). The conformations of the rings in Aza-H (Fig. 1) are also similar to those observed in other azadirachtins. Defining the conformations by

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* Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: CR0491). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Experimental details*

Crystal data	
Chemical formula	$C_{33}H_{42}O_{14}.0.25(C_4H_8O_2)$
Chemical formula weight	684.71
Cell setting	Tetragonal
Space group	$I4$
a (Å)	29.145 (3)
c (Å)	7.695 (1)
V (Å^3)	6536.4 (13)
Z	8
D_x (Mg m^{-3})	1.392
D_m (Mg m^{-3})	1.38 (2)
Radiation type	Cu $K\alpha$
Wavelength (Å)	1.54178
No. of reflections for cell parameters	20
θ range (°)	20.6–30.1
μ (mm^{-1})	0.874
Temperature (K)	298
Crystal form	Needles
Crystal size (mm)	0.40 × 0.10 × 0.10
Crystal color	Colorless
Data collection	
Diffractometer	Enraf–Nonius CAD-4
Data collection method	ω–2θ
Absorption correction	Empirical, ψ scans
$T_{\min}$	0.88
$T_{\max}$	0.96
No. of measured reflections	6175
No. of independent reflections	3016
No. of observed reflections	2290
Criterion for observed reflections	$F_o > 4\sigma(F_o)$
$R_{\rm int}$	0.0313
$\theta_{\max}$ (°)	69.74
Range of h, k, l	$-24 \rightarrow h \rightarrow 25$ $0 \rightarrow k \rightarrow 34$ $0 \rightarrow l \rightarrow 8$
No. of standard reflections	3
Frequency of standard reflections	200
Intensity variation (%)	2
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0512
$wR(F^2)$	0.1525
S	1.095
No. of reflections used in refinement	3016
No. of parameters used	460
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.097P)^2 + 0.48P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{\max}$	1.023
$\Delta\rho_{\max}$ (e Å^{-3})	0.57
$\Delta\rho_{\min}$ (e Å^{-3})	−0.57
Extinction method	$F_c[1 + 2.58 \times 10^{-6}F_c^2/\sin(2\theta)]^{-1/4}$
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C)

how closely the torsion angles in the ring approximate ideal values and symmetries (Duax, Weeks & Rohrer, 1976), we find in the six-membered rings that C(1)—C(2)—C(3)—C(4)—C(5)—C(10) is a chair, C(5)—C(6)—C(7)—C(8)—C(9)—C(10) is a chair and O(15)—C(15)—C(16)—C(17)—C(20)—C(21) is a flattened chair. All the five-membered rings have envelope conformations.

The structure of Aza-H determined by X-ray diffraction confirmed the structure proposed earlier on the basis of NMR studies, in particular, the presence of a tigloyl group at C(1) and an acetate group at C(3), except for the stereochemistry at C(11) (Govindachari, Sandhya & Ganesh Raj, 1992). This X-ray study shows that the dihedral angle H(9)—C(9)—C(11)—H(11) in Aza-H is −92 (1)°. Hence, H(11) is β-oriented and the coupling with H(9) should be very small, as in azadirachtin-B (Aza-B) (Klenk, Bokel & Kraus, 1986). However, on the basis of an observed coupling of 4.4 Hz with H(9), Govindachari, Sandhya & Ganesh Raj (1992) had proposed earlier that H(11) was α-oriented. Redetermination of the NMR spectrum in fresh $CDCl_3$ showed H(11) as a singlet at 5.45 p.p.m.; in acetone-d_6, H(11) was also seen as a singlet, at 5.33 p.p.m. These NMR data thus indicate that H(11) in Aza-H is indeed β-oriented, as seen in the structure determined by X-ray diffraction. It is surmised that the earlier NMR determination could have been vitiated by the presence of trace acid in the $CDCl_3$ used, which probably brought about an opening of the labile cyclic hemiacetal ring and reclosure to a cyclic structure with H(11) in an α-configuration, with a coupling to H(9) in that structure of 4.4 Hz.

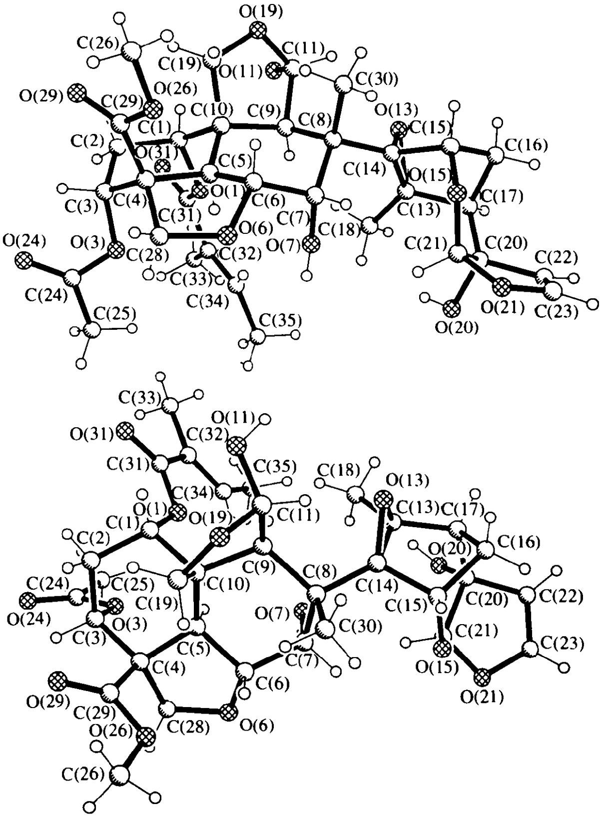

Fig. 1. The azadirachtin-H molecule, seen from two different perspectives.

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}
C(1)	0.8125 (2)	0.5861 (2)	1.0098 (9)	0.049 (1)
O(1)	0.8321 (1)	0.5580 (1)	0.8735 (5)	0.046 (1)
C(31)	0.8741 (2)	0.5399 (2)	0.9003 (9)	0.049 (1)
O(31)	0.8945 (1)	0.5443 (2)	1.0328 (7)	0.074 (1)
C(32)	0.8914 (2)	0.5139 (2)	0.7460 (9)	0.048 (1)
C(33)	0.9381 (2)	0.4939 (3)	0.7677 (13)	0.079 (2)
C(34)	0.8662 (2)	0.5108 (2)	0.6024 (9)	0.054 (1)
C(35)	0.8794 (3)	0.4871 (3)	0.4396 (11)	0.078 (2)
C(2)	0.8311 (2)	0.6349 (2)	0.9982 (9)	0.058 (2)
C(3)	0.8180 (2)	0.6634 (2)	0.8380 (10)	0.056 (2)
O(3)	0.8408 (1)	0.6452 (2)	0.6869 (7)	0.067 (1)
C(24)	0.8816 (2)	0.6628 (3)	0.6445 (13)	0.079 (2)
O(24)	0.8985 (2)	0.6937 (2)	0.7200 (13)	0.134 (3)
C(25)	0.9031 (3)	0.6376 (4)	0.5014 (4)	0.112 (4)
C(4)	0.7658 (2)	0.6610 (2)	0.8079 (9)	0.048 (1)
C(29)	0.7428 (2)	0.6926 (2)	0.9376 (10)	0.060 (2)
O(29)	0.7618 (2)	0.7132 (2)	1.0515 (9)	0.094 (2)
O(26)	0.6979 (1)	0.6948 (1)	0.9159 (8)	0.074 (2)
C(26)	0.6727 (3)	0.7246 (3)	1.0331 (17)	0.101 (3)
C(5)	0.7517 (2)	0.6108 (2)	0.8174 (7)	0.035 (1)
C(6)	0.7064 (2)	0.6080 (1)	0.7325 (7)	0.035 (1)
O(6)	0.7122 (1)	0.6373 (1)	0.5828 (6)	0.050 (1)
C(28)	0.7473 (2)	0.6709 (2)	0.6194 (10)	0.056 (2)
C(7)	0.6962 (2)	0.5584 (2)	0.6857 (7)	0.034 (1)
O(7)	0.7319 (1)	0.5390 (1)	0.5843 (5)	0.040 (1)
C(8)	0.6939 (2)	0.5300 (2)	0.8594 (6)	0.033 (1)
C(30)	0.6528 (2)	0.5477 (2)	0.9659 (8)	0.045 (1)
C(9)	0.7405 (2)	0.5345 (2)	0.9610 (7)	0.035 (1)
C(10)	0.7598 (2)	0.5840 (2)	0.9832 (7)	0.037 (1)
C(19)	0.7371 (2)	0.6001 (2)	1.1524 (8)	0.051 (1)
O(19)	0.7235 (2)	0.5592 (2)	1.2437 (5)	0.064 (1)
C(11)	0.7356 (2)	0.5188 (2)	1.1505 (8)	0.050 (1)
O(11)	0.7771 (2)	0.5015 (2)	1.2121 (6)	0.068 (1)
C(13)	0.7120 (2)	0.4424 (2)	0.7361 (9)	0.050 (1)
C(18)	0.7618 (2)	0.4423 (2)	0.6845 (12)	0.066 (2)
O(13)	0.7038 (1)	0.4443 (1)	0.9245 (6)	0.054 (1)
C(14)	0.6837 (2)	0.4793 (2)	0.8134 (7)	0.039 (1)
C(15)	0.6341 (2)	0.4654 (2)	0.7711 (8)	0.046 (1)
C(16)	0.6356 (2)	0.4134 (2)	0.7558 (10)	0.059 (2)
C(17)	0.6792 (2)	0.4084 (2)	0.6508 (9)	0.055 (2)
C(20)	0.6672 (2)	0.4233 (2)	0.4660 (10)	0.060 (2)
O(20)	0.7066 (2)	0.4244 (2)	0.3572 (8)	0.078 (2)
C(21)	0.6447 (2)	0.4717 (2)	0.4588 (8)	0.053 (2)
O(15)	0.6202 (1)	0.4856 (1)	0.6095 (6)	0.049 (1)
C(22)	0.6300 (3)	0.3959 (3)	0.3715 (12)	0.079 (2)
C(23)	0.6020 (3)	0.4242 (3)	0.3007 (13)	0.091 (3)
O(21)	0.6111 (2)	0.4696 (2)	0.3237 (7)	0.081 (2)

Table 3. *Geometric parameters* (Å, °)

C(1)—O(1)	1.447 (7)	C(7)—C(8)	1.572 (7)
C(1)—C(2)	1.526 (8)	C(8)—C(30)	1.541 (7)
C(1)—C(10)	1.553 (7)	C(8)—C(14)	1.549 (6)
O(1)—C(31)	1.349 (6)	C(8)—C(9)	1.572 (7)
C(31)—O(31)	1.187 (7)	C(9)—C(11)	1.534 (8)
C(31)—C(32)	1.497 (9)	C(9)—C(10)	1.560 (7)
C(32)—C(34)	1.329 (9)	C(10)—C(19)	1.534 (8)
C(32)—C(33)	1.489 (8)	C(19)—O(19)	1.441 (8)
C(34)—C(35)	1.482 (10)	O(19)—C(11)	1.422 (7)
C(2)—C(3)	1.535 (10)	C(11)—O(11)	1.394 (7)
C(3)—O(3)	1.442 (8)	C(13)—O(13)	1.470 (8)
C(3)—C(4)	1.541 (7)	C(13)—C(14)	1.479 (7)
O(3)—C(24)	1.336 (8)	C(13)—C(18)	1.504 (8)
C(24)—O(24)	1.179 (10)	C(13)—C(17)	1.526 (8)
C(24)—C(25)	1.464 (13)	O(13)—C(14)	1.454 (6)
C(4)—C(29)	1.514 (9)	C(14)—C(15)	1.536 (7)
C(4)—C(5)	1.523 (6)	C(15)—O(15)	1.435 (7)
C(4)—C(28)	1.574 (10)	C(15)—C(16)	1.520 (7)
C(29)—O(29)	1.199 (8)	C(16)—C(17)	1.511 (9)
C(29)—O(26)	1.321 (7)	C(17)—C(20)	1.527 (10)
O(26)—C(26)	1.451 (9)	C(20)—O(20)	1.422 (8)
C(5)—C(6)	1.475 (7)	C(20)—C(22)	1.530 (9)
C(5)—C(10)	1.513 (7)	C(20)—C(21)	1.557 (9)
C(6)—O(6)	1.444 (6)	C(21)—O(15)	1.420 (7)
C(6)—C(7)	1.519 (6)	C(21)—O(21)	1.429 (8)
O(6)—C(28)	1.445 (6)	C(22)—C(23)	1.280 (12)
C(7)—O(7)	1.418 (6)	C(23)—O(21)	1.361 (9)
O(1)—C(1)—C(2)	110.3 (5)	C(11)—C(9)—C(8)	111.7 (4)
O(1)—C(1)—C(10)	105.8 (4)	C(10)—C(9)—C(8)	116.2 (4)
C(2)—C(1)—C(10)	112.3 (4)	C(5)—C(10)—C(19)	119.4 (4)
C(31)—O(1)—C(1)	117.9 (4)	C(5)—C(10)—C(1)	104.2 (4)
O(31)—C(31)—O(1)	123.0 (5)	C(19)—C(10)—C(1)	107.6 (4)
O(31)—C(31)—C(32)	124.5 (5)	C(5)—C(10)—C(9)	109.2 (4)
O(1)—C(31)—C(32)	112.5 (5)	C(19)—C(10)—C(9)	102.8 (4)
C(34)—C(32)—C(33)	124.8 (6)	C(1)—C(10)—C(9)	114.0 (4)
C(34)—C(32)—C(31)	120.5 (5)	O(19)—C(19)—C(10)	106.2 (4)
C(33)—C(32)—C(31)	114.7 (6)	C(11)—O(19)—C(19)	111.8 (4)
C(32)—C(34)—C(35)	126.3 (5)	O(11)—C(11)—O(19)	110.1 (5)
C(1)—C(2)—C(3)	117.6 (5)	O(11)—C(11)—C(9)	110.6 (5)
O(3)—C(3)—C(2)	109.4 (4)	O(19)—C(11)—C(9)	104.9 (4)
O(3)—C(3)—C(4)	108.5 (5)	O(13)—C(13)—C(14)	59.1 (4)
C(2)—C(3)—C(4)	110.0 (5)	O(13)—C(13)—C(18)	114.6 (6)
C(24)—O(3)—C(3)	117.8 (6)	C(14)—C(13)—C(18)	130.1 (5)
O(24)—C(24)—O(3)	123.1 (9)	O(13)—C(13)—C(17)	110.3 (5)
O(24)—C(24)—C(25)	125.1 (7)	C(14)—C(13)—C(17)	107.2 (4)
O(3)—C(24)—C(25)	111.7 (8)	C(18)—C(13)—C(17)	119.4 (6)
C(29)—C(4)—C(5)	115.7 (5)	C(14)—O(13)—C(13)	60.8 (3)
C(29)—C(4)—C(3)	108.1 (5)	O(13)—C(14)—C(13)	60.2 (3)
C(5)—C(4)—C(3)	107.7 (4)	O(13)—C(14)—C(15)	108.6 (4)
C(29)—C(4)—C(28)	110.1 (5)	C(13)—C(14)—C(15)	104.3 (4)
C(5)—C(4)—C(28)	97.4 (4)	O(13)—C(14)—C(8)	117.3 (4)
C(3)—C(4)—C(28)	117.9 (5)	C(13)—C(14)—C(8)	132.7 (4)
O(29)—C(29)—O(26)	121.8 (6)	C(15)—C(14)—C(8)	118.7 (4)
O(29)—C(29)—C(4)	125.5 (6)	O(15)—C(15)—C(16)	110.5 (5)
O(26)—C(29)—C(4)	112.7 (5)	O(15)—C(15)—C(14)	109.9 (4)
C(29)—O(26)—C(26)	116.8 (6)	C(16)—C(15)—C(14)	104.6 (4)
C(6)—C(5)—C(10)	118.9 (4)	C(17)—C(16)—C(15)	99.3 (4)
C(6)—C(5)—C(4)	105.9 (4)	C(16)—C(17)—C(13)	103.5 (5)
C(10)—C(5)—C(4)	119.6 (5)	C(16)—C(17)—C(20)	106.2 (5)
O(6)—C(6)—C(5)	102.4 (3)	C(13)—C(17)—C(20)	111.1 (5)
O(6)—C(6)—C(7)	113.4 (4)	O(20)—C(20)—C(17)	111.8 (6)
C(5)—C(6)—C(7)	109.4 (4)	O(20)—C(20)—C(22)	107.8 (6)
C(28)—O(6)—C(6)	109.2 (4)	C(17)—C(20)—C(22)	117.2 (6)
O(6)—C(28)—C(4)	107.3 (4)	O(20)—C(20)—C(21)	107.4 (5)
O(7)—C(7)—C(6)	111.4 (4)	C(17)—C(20)—C(21)	112.7 (5)
O(7)—C(7)—C(8)	106.8 (3)	C(22)—C(20)—C(21)	99.0 (6)
C(6)—C(7)—C(8)	107.9 (4)	O(15)—C(21)—O(21)	105.2 (5)
C(30)—C(8)—C(14)	107.0 (4)	O(15)—C(21)—C(20)	116.2 (5)
C(30)—C(8)—C(9)	112.3 (4)	O(21)—C(21)—C(20)	106.0 (5)
C(14)—C(8)—C(9)	111.0 (4)	C(21)—O(15)—C(15)	116.6 (4)
C(30)—C(8)—C(7)	108.0 (4)	C(23)—C(22)—C(20)	108.5 (6)
C(14)—C(8)—C(7)	108.4 (4)	C(22)—C(23)—O(21)	116.5 (7)
C(9)—C(8)—C(7)	110.1 (3)	C(23)—O(21)—C(21)	105.6 (6)
C(11)—C(9)—C(10)	101.8 (4)		

As a necessary concomitant of the β-orientation of H(11) in Aza-H, the OH group on C(11) has an α-configuration, opposite to that in all other known azadirachtins with a hydroxyl function at C(11) except Aza-I [identical to Aza-H save that at C(4) it has a methyl rather than a carbomethoxy group]. The configuration at C(11) is therefore *S*. The α-orientation of hydroxyl O(11) means that it cannot act as a donor in any intramolecular hydrogen bond; the nearest potential acceptor, O(13), is 3.498 (6) Å away (Fig. 1). Therefore, in Aza-H the two portions of the molecule are free to rotate about the C(8)—C(14) bond and adopt different conformations in solution.

Table 4. *Final parameters for the disordered ethyl acetate model*

Occupancy fixed at 0.25. One overall anisotropic displacement of the molecule as a whole.

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j. \quad U_{eq}\,(\text{Å}^2 \times 10^3) = 551\,(45).$$

Atomic coordinates ($\times 10^4$)

	x	y	z
C(41)	4925 (5)	4929 (5)	3416 (10)
C(42)	5095 (2)	5106 (4)	5119 (9)
O(41)	5440 (3)	5319 (4)	5318 (22)
O(42)	4808 (4)	5000 (9)	6406 (8)
O(43)	4980 (4)	5043 (8)	8170 (10)
C(44)	4672 (7)	4745 (7)	9279 (15)

Bond lengths (Å)

	Refined value	Target value
C(41)—C(42)	1.493 (12)	1.497 (3)
C(42)—O(41)	1.192 (13)	1.196 (3)
C(42)—O(42)	1.333 (13)	1.336 (3)
O(42)—C(43)	1.453 (11)	1.452 (3)
C(43)—C(44)	1.512 (24)	1.513 (3)

Bond angles (°)

	Refined value	Target value
O(41)—C(42)—O(42)	123.8 (7)	123 (1)
O(41)—C(42)—C(41)	125.0 (7)	126 (1)
O(42)—C(42)—C(41)	111.3 (6)	111 (1)
C(42)—O(42)—C(43)	117.2 (7)	118 (1)
O(42)—C(43)—C(44)	105.8 (6)	108 (1)

Table 5. *Hydrogen-bonding data* (Å, °)

D—H···A	H—A	D···A	D—H···A
O(7)—H(O7)···O(19^{i})	2.698 (6)	1.92 (2)	159 (6)
[O(7)—H(O7)···O(6^{ii})	2.922 (4)	2.67 (5)	100 (3)]
[O(11)—H(O11)···O(24^{iii})	3.119 (7)	2.38 (3)	151 (6)]
[O(11)—H(O11)···O(20^{iv})	3.241 (7)	2.65 (5)	131 (6)]

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

The overall conformations in the crystal of the three azadirachtin structures so far determined differ significantly. The dihedral angle C(9)—C(8)—C(14)—O(13) that characterizes the relative orientation of the two major parts of the molecule is +26 (1)° in Aza-H, +162 (1)° in Aza-A and −27° in DTA [consistently using the sign convention in *SHELXL*93 (Sheldrick, 1993)]. In the crystal of DTA, there is a strong intramolecular hydrogen-bond between hydroxyl O(11), which is β-oriented, and the epoxide O(13). Interestingly, Aza-A itself, which could also form such an intramolecular hydrogen bond, crystallizes such that all the hydrogen bonds are intermolecular: O(11)···O(13) 4.39 (1), O(11)···O(20) 4.19 (1) and O(11)···O(15) is 3.14 (1) Å, but no hydrogen bond is formed because the H atom points in another direction. In the crystal of DTA, there is another very weak intramolecular hydrogen bond, from O(20) to O(7), with the O···O distance 3.13 Å. In crystalline Aza-A, these two hydroxyl groups point away from each other in completely opposite directions, so O(7)···O(20) is 6.69 (1) Å. This potential intramolecular hydrogen bond is not formed in the crystal of Aza-H either; the O(7)···O(20) distance of 3.840 (6) Å is far too long (Fig. 1).

The geometric data pertinent to defining the hydrogen-bonding scheme in Aza-H are given in Table 5. Note that all calculated O—H distances were artificially shortened by *ca* 0.1 Å to fit the X-ray data better, that is, to account better for the electron density rather than the position of the H nuclei; this systematic underestimate of the O—H internuclear distances thus also overestimates any of these H···O distances involved in hydrogen-bonding.

The packing of the Aza-H molecules in the unit cell is shown in Figs. 2 and 3. Only one strong hydrogen bond is formed, and it is intermolecular, with hydroxyl O(7) donating to the ring oxygen O(19) of the cyclic hemiacetal group of an Aza-H molecule related by translation along *c* (Fig. 3). All other possible intermolecular and intramolecular hydrogen-bonding interactions are very weak or non-existent, as evidenced by the data in Table 5.

The packing of Aza-H in this tetragonal crystal leaves open channels along the fourfold rotation axes (Fig. 2). Ethyl acetate, at least fourfold disordered, is loosely held

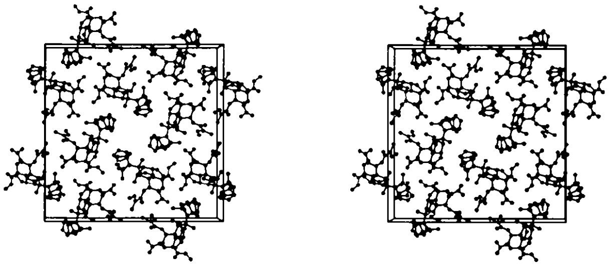

Fig. 2. Packing of the azadirachtin-H molecules, shown looking down **c**. No solvent is shown in the channels along the fourfold rotation axes.

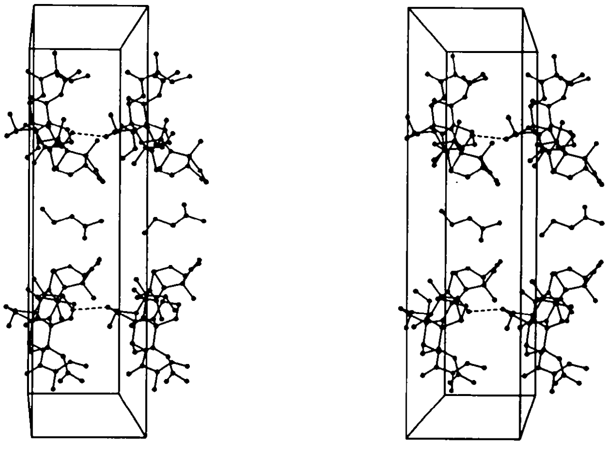

Fig. 3. Packing in the crystal, shown looking down **a**. The single strong intermolecular hydrogen bond is indicated by a dashed line. Two of the four possible orientations of the disordered ethyl acetate molecule (whose length is just equal to that of the *c* axis) are shown.

in the channels. The final refined model for the disordered ethyl acetate has excellent molecular geometry, of course, since this was imposed by the restraints, and no unacceptably short intermolecular contacts, either with the Aza-H molecules constituting the walls of the channel or with other ethyl acetate molecules above or below in the channel, in any of the four possible orientations assumed. While this model might not be complete or correct in all details, we consider it quite satisfactory. Table 4 lists the final parameters for the ethyl acetate model. Fig. 3 shows the fit of the ethyl acetate molecule in the channel, in two of its four possible orientations.

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