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The 293 K structure of tetradehydrohaliclonacyclamine A

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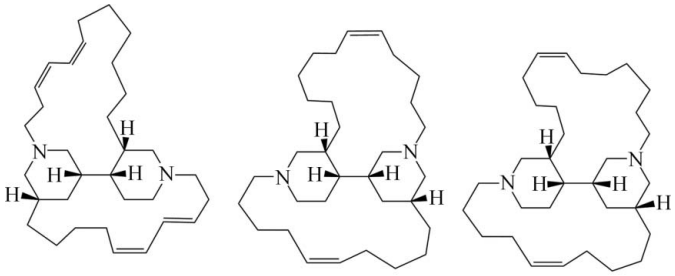
The polycyclic title compound {systematic name: (1*S*,16*S*,17*S*,31*S*)-3,20-diazatetracyclo[15.15.0^{1,17}.1^{3,31}.1^{16,20}]tetratriaconta-6,8,23,25-tetraene}, $C_{32}H_{52}N_2$, has recently been isolated and characterized structurally, in solution by NMR spectroscopy and in the solid state by X-ray crystallography. At 130 K the structure is monoclinic ($P2_1$, Z = 4) and comprises two molecules in the asymmetric unit with distinctly different conformations in the twelve-C-atom bridging chains. We report that, at 250 K, a phase change from monoclinic to orthorhombic ($P22_12_1$, Z = 4) occurs. The higher-temperature phase is structurally characterized herein at 293 K. The two different conformers resolved in the monoclinic low-temperature form merge to give a single disordered molecule in the asymmetric unit of the high-temperature phase.

Comment

From both a structural and a biosynthetic perspective, 3-alkylpiperidines are among the most intriguing of metabolites isolated from marine sponge extracts. Over 30 different carbon skeletons have been documented, with the haliclonacyclamine/arenosclerin skeleton providing more than ten examples from Indo-Pacific, Brazilian and Red Sea sponges (Berlinck, 2007). Our recent isolation of a crystalline sample of tetradehydrohaliclonacyclamine A, (I), from a sponge specimen provisionally identified as *Halichondria* sp. (Mudianta *et al.*, 2010) afforded an opportunity to determine the absolute configuration of this sponge metabolite crystallographically, and to compare it with our earlier structural data for the haliclonacyclamines A, (II), and B, (III) (Charan *et al.*, 1996; Clark *et al.*, 1998; Mudianta *et al.*, 2009).

Previously we have reported the absolute structure determinations of haliclonacyclamines A, (II), and B, (III) (Mudianta *et al.*, 2009), isolated from a *Haliclona* species collected at Heron Island (Australia). Absolute structures of compounds from this family are few and these provide an important link with optical rotation data that cannot be relied upon for absolute structure assignment alone. This is evident from our report that (−)-haliclonacyclamine A, (II), and (+)-haliclonacyclamine B, (III), each share the same absolute configuration of 2*R*,3*R*,7*R*,9*R* (Mudianta *et al.*, 2009). Interestingly, the closely related unsaturated analogue, (I), from the Indonesian sponge *Halichondria* sp., has an opposite absolute configuration 2*S*,3*S*,7*S*,9*S*, as shown by a recent low-temperature crystallographic structure determination (Mudianta *et al.*, 2010). A full characterization of this compound was reported, including its NMR solution structure. During the course of our crystallographic study we observed a totally reversible phase change at *ca* 250 K from a monoclinic form ($P2_1$, Z = 4) to an orthorhombic (higher-temperature) lattice. We report here the details of this higher-temperature form and identify the molecular features that are altered upon conversion to the higher-symmetry lattice at room temperature.



The crystal structure of (I) was determined at 293 K. The compound crystallizes in the orthorhombic space group $P22_12_1$ and all molecules occupy general sites. Discussion of the structure is aided by comparison with its low-temperature form. Note that we report the variant $P22_12_1$ form (instead of the standard setting $P2_12_12$) to aid comparison with the monoclinic structure where the axes are conserved. Inspection of the lattice dimensions of the high- and low-temperature forms illustrates the most significant changes between the two structures. The phase change from monoclinic to orthorhombic is subtle and the unit cells are very similar. In the monoclinic form at 130 K, the cell dimensions are a = 9.8074 (1) Å [*cf.* 9.8895 (3) Å at 293 K], b = 15.9505 (2) Å [*cf.* 16.1689 (5) Å at 293 K], c = 18.3186 (2) Å [*cf.* 18.4642 (7) Å at 293 K] and β = 92.449 (1)°, which is naturally 90° at 293 K. The unit-cell dimensions were measured at various temperatures between 130 and 293 K and an approximate phase transition at a temperature of 250 K was determined. When the phase change is complete, the new crystallographic twofold screw axis parallel to c and the twofold rotation axis parallel to a emerge, and the two independent molecules found in the monoclinic phase become symmetry related.

The gross features of the orthorhombic structure of (I) at 293 K are similar to those found in the low-temperature (130 K) monoclinic phase. In the low-temperature phase, two independent molecules exhibiting different conformations in the region spanned by methylene atoms C17–C20 were identified. In the high-temperature phase, all molecules are disordered between two different conformations (Fig. 1*a*). The

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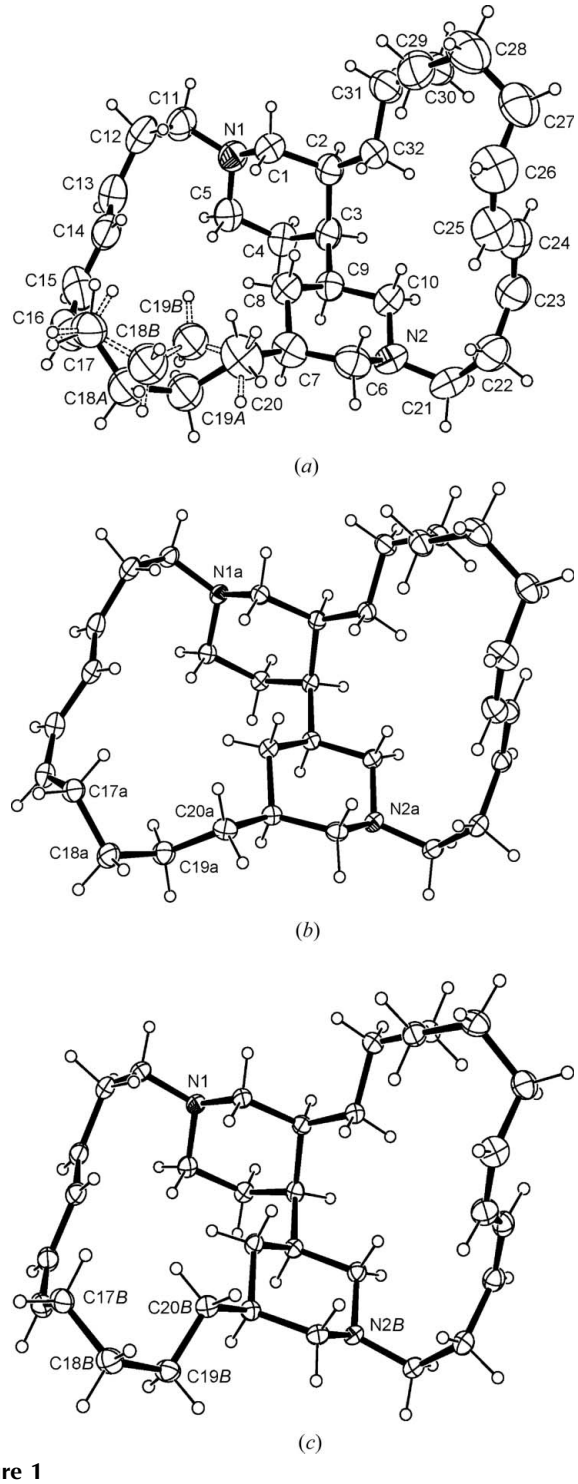

Figure 1
(*a*) The structure of (I), showing the atom-numbering scheme and the methylene-group disorder between atoms C17 and C20; the C—C and C—H bonds of the minor contributor are shown as dashed lines. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Parts (*b*) and (*c*) show the crystallographically independent molecules of (I) in the 130 K structure (Mudianta *et al.*, 2010).

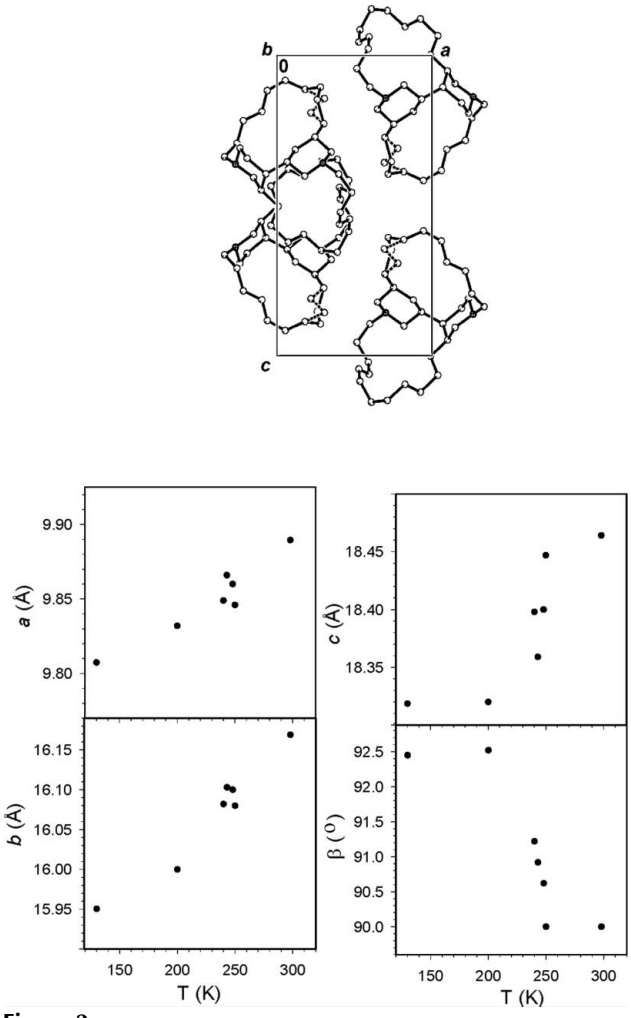

Figure 2
PLUTON plot (Spek, 2009) of the 293 K orthorhombic unit cell of (I), viewed in the [010] direction, and the variations in unit-cell dimensions as a function of temperature.

A conformer in the high-temperature phase closely resembles the *A* conformer seen in the monoclinic form shown in Fig. 1(*b*) (Mudianta *et al.*, 2010). The C17*A*—C18*A*—C19*A*—C20*A* torsion angles are 81.6 (12) and 85.2 (2)°, respectively. The minor *B* conformer in the high-temperature phase has a *trans* conformation [C17—C18*B*—C19*B*—C20 = 171.8 (2) Å]. Interestingly, the occupancies of the two conformers in the high-temperature form are significantly different (0.65 for molecule *A* and 0.35 for molecule *B*), while the ratio of the two conformers in the monoclinic low-temperature phase is necessarily 1:1.

The absolute structure of (I) was established previously at 130 K (Mudianta *et al.*, 2010) by Bijvoet pair analysis (Hooft *et al.*, 2008) implemented within the *PLATON* program (Spek, 2009). The same crystal previously examined at 130 K (Mudianta *et al.*, 2010) was used here for the 293 K structure.

The transformation between the low-temperature monoclinic form of (I) and the high-temperature orthorhombic phase is totally reversible. As the temperature is raised, β decreases gradually until at *ca* 250 K the orthorhombic form is dominant. Concurrently, the three unit-cell lengths all increase with temperature, as illustrated in Fig. 2. As we have shown, this is coupled with the relative proportions of the two distinct molecular conformations of (I). At 250 K and above, one

conformer (indicated by the suffix *A* in Fig. 1*a*) becomes dominant (65%) and disorder is found in all molecules. At low temperature, two crystallographically distinct molecules exist in equal proportions and are locked into their respective conformations with no disorder.

This work has identified an interesting phase transformation between two crystal systems linked to an actuation of conformational disorder in the higher-temperature phase and a redistribution of the proportions of these distinct conformers.

Experimental

Compound (I) was obtained from a CH_2Cl_2–MeOH (1:1 *v*/*v*) extract from a sponge sample (500 g wet weight) of *Halichondria* sp. (order Halichondrida) collected at Tulamben Bay, Bali (Indonesia), as described by Mudianta *et al.* (2010). The same crystal structurally characterized at 130 K (Mudianta *et al.*, 2010) was used here for studying both the phase transition temperature and the higher-temperature structure.

Crystal data

$C_{32}H_{52}N_2$
M_r = 464.76
Orthorhombic, $P22_12_1$
a = 9.8895 (3) Å
b = 16.1689 (5) Å
c = 18.4642 (7) Å
V = 2952.47 (17) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 0.44 mm^{-1}
T = 293 K
0.3 × 0.2 × 0.2 mm

Data collection

Oxford Diffraction Gemini S Ultra diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)
T_{min} = 0.820, T_{max} = 1.000
8051 measured reflections
2628 independent reflections
1427 reflections with $I > 2\sigma(I)$
R_{int} = 0.036

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.148
S = 0.88
2628 reflections
307 parameters
2 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.12 e Å^{-3}

A conclusive absolute structure determination was not possible with the 293 K data set and the chirality of (I) was assigned on the basis of the previously reported 130 K structure using the analysis of Hooft *et al.* (2008). The Flack (1983) parameter was also indeterminate in the absence of any atoms heavier than nitrogen, so all Friedel equivalent reflections were merged prior to refinement. The three most intense reflections (202, 122 and 004) were omitted from the data set.

Alkyl and olefinic H atoms were included at estimated positions using a riding model, with C—H = 0.93–0.98 Å and with U_{iso}(H) = 1.2U_{eq}(C). Disorder in the methylene groups from C17 to C20 was identified. Alternate positions for atoms C18 and C19 were resolved and their complementary occupancies were refined to a ratio of 0.65 (1):0.35 (1), with isotropic displacement parameters. The disorder led to alternate positions for all H atoms attached to atoms C17–C20 inclusive on the basis of their different torsion angles. Restraints were applied to keep the C18*A*—C19*A* and C18*B*—C19*B* bond lengths the same (and corresponding angles involving attached H atoms) to aid refinement. Despite this, some anomalies still exist in a couple of the geometric parameters within the disordered region, but further application of restraints did not yield a worthwhile improvement in the model.

Data collection: *CrysAlis Pro* (Oxford Diffraction, 2008); cell refinement: *CrysAlis Pro*; data reduction: *CrysAlis Pro*; program(s) used to solve structure: *SHELXS86* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3354). Services for accessing these data are described at the back of the journal.

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