X-Ray Crystal Structure of Ascidiacyclamide, a Cytotoxic Cyclic Peptide from Ascidian

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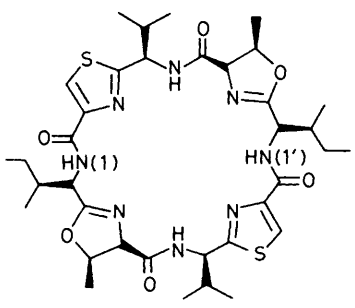
The first direct *X*-ray crystal structure determination of a cytotoxic cyclic peptide from ascidian, ascidiacyclamide, has shown a molecular conformation responsible for its biological activity.

Lipophilic cyclic peptides from marine organisms are of increasing interest owing to their highly potent antineoplastic and/or cytotoxic activities.[1] Ascidiacyclamide (**1**) is a cytotoxic cyclic peptide isolated from ascidian.[2] Its structure, containing thiazole and oxazoline rings, was confirmed by our synthesis,[3] which also determined the absolute configuration. The unusual ring structure found in (**1**) has also been observed in other cyclic peptides of marine origin such as ulithiacyclamide,[4,5] ulicyclamide,[4,6] patellamides A,[7,8] B,[7,9,10] and C,[7,9] which exhibit potent cytotoxic activities against L1210 murine leukaemia cells.[7] Therefore this ring structure may be necessary for the emergence of activity, although up to now little is known about the mode of its biological reaction.

Since a detailed knowledge of the spatial geometry of a molecule is essential for an understanding of its biological reactions at the molecular level, the stereostructure of (**1**) has been elucidated by *X*-ray crystallography; to our knowledge, this is the first *X*-ray study of cytotoxic cyclic peptides from tunicates.† Measurement of Bijvoet pairs [$|F(hkl)|$ and $|F(\bar{h}\bar{k}\bar{l})|$] clearly demonstrated the absolute configuration of



(**1**)

† *Crystal data* for (**1**): crystals, as colourless prisms, were grown from benzene; $C_{36}H_{52}N_8O_6S_2 \cdot 2C_6H_6$, M = 913.2, monoclinic, space group $C2$, a = 15.909(6), b = 13.150(6), c = 12.754(5) Å, β = 101.13(2)°, U = 2618(2) Å^3, $F(000)$ = 976, D_m = 1.152 (flotation in H_2O–saturated KI solution), D_c = 1.158 g cm^{-3}, Z = 2, μ(Cu-K_α) = 12.93 cm^{-1}. The molecule has two-fold symmetry which corresponds with that of space group $C2$. The structure was solved by a combination of heavy atom method and successive Fourier syntheses. Refinement with anisotropic thermal parameters for non-H atoms and isotropic ones for H atoms converged at R = 0.08 and R_w = 0.07 for 2346 observed reflections. A crystal of dimensions 0.3 × 0.3 × 0.4 mm^3 was used. Independent reflections ($2 \leq 2 \leq 130°$) were collected using the ω–2θ scanning mode on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu-K_α radiation. Intensities were corrected for Lorentz and polarization factors, but not for absorption, because of the small crystal size and the lack of significant fluctuation of intensity in the ϕ scanning of the (0k0) reflection at χ = 90°. *X*-Ray analysis was carried out using the UNICS program.[11] Some of the bonding parameters concerning the side chain atom (C_δ) of the isoleucine moiety deviated significantly from the standard values, probably owing to its large thermal motion. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, see Notice to Authors, Issue No. 1.

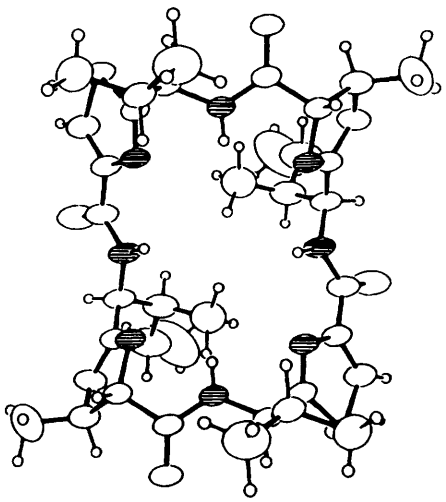


Figure 1. ORTEP[12] perspective drawing of ascidiacyclamide, viewed along a two-fold axis passing through the centre of the molecule. Shaded circles represent nitrogen atoms.

the ascidiacyclamide molecule to be as shown in (**1**); it is identical to that previously determined by the synthetic method.[3]

The molecular conformation established by the *X*-ray study is illustrated in Figure 1. The cyclic peptide chain takes a saddle-shaped conformation, and is cylindrically curved along the line joining two nitrogen atoms N(1) and N(1'). Thiazole and oxazoline rings are located alternately at each corner of the rectangular ring. There are no intramolecular hydrogen bonds, although the observed intermolecular ones between neighbouring molecules stabilize the crystal packing. The most important feature in this molecular conformation is that all the N–N bonds are directed toward the interior of the ring. It is interesting to note that N–H bonds of amide groups and N atoms of thiazole and oxazoline rings are arranged alternately around the ring at equal intervals, and the N–H bonds and N lone pairs are all directed towards a point at the centre of the molecule.

Although it is unclear at present, this characteristic atomic arrangement may be related to the emergence of biological activity. Furthermore we suspect that the related cyclic peptides, mentioned above, are likely to share the same conformation.

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