'catemer' mais ne relève pas de cycles à plus de deux fonctions carboxylique.

Il n'existe pas d'autres distances courtes, les liaisons entre les feuillets de molécules reliées par liaison hydrogène étant assurées par des forces de van der Waals.

En conclusion, l'étude de la structure de l'acide ETTA a permis de mettre en évidence un nouveau type d'association de groupements carboxylique par liaison hydrogène et également de confirmer la stéréochimie du groupement thioacétal $\rangle C\langle^{S}_{S}$ dont les caractéristiques moyennes établies en comparaison avec les structures déterminées antérieurement par les auteurs s'établissent aux valeurs suivantes: angle S–C–S: 116,7°; angle C–S–C: 101,9°; distance C–S: 1,805 Å; distance S–S: 3,071 Å.

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Conformation of the Cyclic Tetrapeptide *cyclo*(-L-Leucyl-L-tyrosyl-δ-aminovaleryl-δ-aminovaleryl-) Crystallized from Acetone/H_2O and Comparison with the Crystal from Acetone/DMSO

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cyclo(-L-Leu-L-Tyr-δ-Avaler-δ-Avaler-) (*A*) is a synthetic tetrapeptide which is an effective inhibitor of chymotrypsin. An X-ray diffraction study has already been done on the same molecule crystallized from acetone/DMSO (*B*). The present molecule ($C_{25}H_{39}N_4O_5 . 3{\cdot}6H_2O$), crystallized from an acetone/H_2O mixture, is in the orthorhombic space group $P2_12_12_1$, with $a = 17{\cdot}201$ (3), $b = 18{\cdot}806$ (3), $c = 9{\cdot}327$ (3) Å and $Z = 4$. Although the two crystals are in different space groups, the molecules are quite similar in conformation and packing. Both structures have large cavities, formed by intermolecular hydrogen bonding among four peptide molecules, which accommodate either H_2O molecules or DMSO solvent molecules.

Introduction

cyclo(-L-Leu-L-Tyr-δ-Avaler-δ-Avaler-) (*A*) is a synthetic tetrapeptide which contains an 18-membered ring since it includes two δ amino acids (Avaler = aminovaleryl). It is an effective inhibitor of chymotrypsin (Tsetlin, Shepel, Ivanov & Ovchinnikov, 1975). The conformation of the same molecule crystallized from acetone/DMSO (*B*) has been determined by X-ray diffraction (Karle, 1976). The present crystal was grown from an acetone/H_2O mixture and crystallized in space group $P2_12_12_1$ as opposed to space group $P2_1$ for crystal *B*. The objective of this work was to study any conformational changes in the molecule due to the nature of the solvent.

Experimental

The peptide was synthesized according to the procedure outlined by Tsetlin *et al.* (1975). Information on data collection and physical quantities are presented in Table 1. The solution was accomplished by obtaining a partial structure with the symbolic addition procedure for non-centrosymmetric crystals (Karle & Karle, 1966) which was then developed into the full structure by recycling with the tangent formula (Karle, 1968). The structure was refined by full-matrix least-squares methods using program *ORFXLS*-3 (Busing *et al.*, 1971). The atomic scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962). The function minimized by the least-

squares procedure was $\sum (|F_o| - |F_c|)^2$. All data were used in the refinement. A difference map calculated at an intermediate stage of refinement was used to locate the H atoms. Positions for 33 of the 39 H atoms were found. Five of the H atoms on the C(1$^\alpha$) side chain and the H atom on O(2$^\eta$) were not found. The final R factor for the full set of 2759 reflections was 9·9%. The goodness-of-fit parameter was 2·2. Refined coordinates for the non-hydrogen atoms are listed in Table 2.*

Discussion

Bond lengths and angles for crystal *A* are illustrated in Fig. 1. The bond lengths for the molecule in the different crystal systems agree to within a maximum of 4σ [except for the N(3)–C(2′) bond] and most of the angles agree to within 5σ, where σ represents the standard deviations quoted for the present structure. The angles around C(2′) lie outside this range: N(3)–C(2′)–C(2$^\alpha$) is 116·2° in *B* and 121·2° in *A*, and N(3)–C(2′)–O(2) is 119·4° in *B* and 123·5° in *A*. The conformations of the peptide molecule in crystals *A* and *B* are very similar and no significant differences are noted in the torsion angles (see Table 3) except for ψ_2 [N(2)–C(2$^\alpha$)–C(2′)–N(3)] which is 3° in crystal *A* and 35° in crystal *B*, and φ_3' which is 138° in *A* and 94° in *B*. The flattening of the ring in this area of crystal *A* results in an intramolecular approach between N(3) and O(4) of 4·23 Å compared with 4·59 Å in *B*; however, there is still no intramolecular hydrogen bond even though 4 → 1 hydrogen bonds are often found in cyclic peptides (Karle, 1975).

Even though the crystals were grown from different solvents and crystallized in different space groups they

* Lists of structure factors, anisotropic thermal parameters for non-hydrogen atoms and hydrogen atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33693 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Crystallographic data*

	Crystal *A*	Crystal *B*
Molecular formula	$C_{25}H_{39}N_4O_5.3{\cdot}6H_2O$	$C_{25}H_{39}N_4O_5.(CH_3)_2SO.H_2O$
Space group	$P2_12_12_1$	$P2_1$
a	17·201 (3) Å	9·361 (3) Å
b	18·806 (3)	19·039 (3)
c	9·327 (3)	9·603 (3)
		($2c \sin\beta$) = 17·182 Å
β		116·5 (3)°
Volume	3017·11 Å^3	1531·1 Å^3
Z	4	2
Density (calculated)	1·15 g cm^{-3}	1·24 g cm^{-3}
Source of data	Picker FACS-I diffractometer	
Radiation	Cu $K\alpha$(Ni filter), λ = 1·5418 Å	
Data collection technique	θ–2θ scan	
Maximum sin θ/λ	0·521 Å^{-1}	
Number of independent reflections	2759	2558

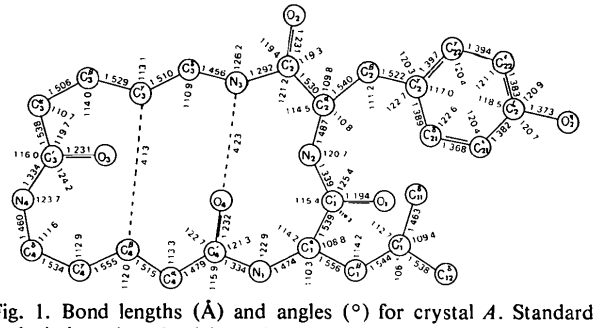

Fig. 1. Bond lengths (Å) and angles (°) for crystal *A*. Standard deviations, based solely on least-squares results, are of the order of 0·011 Å for bonds and 0·7° for the angles.

Table 2. *Fractional coordinates for crystal A*

Standard deviations for the atoms in the peptide molecule, based solely on least-squares results, are 0·0005*a*, 0·0005*b* and 0·0009*c*.

	x	*y*	*z*
N(1)	0·8516	0·3048	0·3531
C(1$^\alpha$)	0·8739	0·3769	0·3998
C(1′)	0·9621	0·3904	0·4009
O(1)	0·9855	0·4498	0·4145
C(1$^\beta$)	0·8408	0·3925	0·5519
C(1$^\gamma$)	0·7512	0·3903	0·5609
C(11$^\delta$)	0·7141	0·4452	0·4736
C(12$^\delta$)	0·7308	0·4023	0·7196
N(2)	1·0067	0·3324	0·3882
C(2$^\alpha$)	1·0927	0·3375	0·4003
C(2′)	1·1332	0·3034	0·2715
O(2)	1·2046	0·2995	0·2697
C(2$^\beta$)	1·1213	0·3023	0·5398
C(2$^\gamma$)	1·0812	0·3342	0·6703
C(21$^\delta$)	1·1105	0·3927	0·7436
C(22$^\delta$)	1·0116	0·3052	0·7210
C(21$^\epsilon$)	1·0738	0·4218	0·8596
C(22$^\epsilon$)	0·9745	0·3344	0·8401
C(2$^\zeta$)	1·0051	0·3930	0·9099
O(2$^\eta$)	0·9677	0·4224	1·0258
N(3)	1·0937	0·2778	0·1655
C(3$^\alpha$)	1·0610	0·0753	−0·1745
C(3′)	0·9745	0·0927	−0·1967
O(3)	0·9549	0·1327	−0·2948
C(3$^\beta$)	1·1061	0·1412	−0·1363
C(3$^\gamma$)	1·0779	0·1780	0·0003
C(3$^\delta$)	1·1255	0·2427	0·0392
N(4)	0·9250	0·0620	−0·1057
C(4$^\alpha$)	0·8110	0·2152	0·1882
C(4′)	0·8417	0·2874	0·2157
O(4)	0·8557	0·3301	0·1189
C(4$^\beta$)	0·8390	0·1837	0·0478
C(4$^\gamma$)	0·8097	0·1062	0·0263
C(4$^\delta$)	0·8408	0·0718	−0·1113
W(1)	0·3297	0·3024	0·4338
W(2)	0·4974	0·3239	0·5827
W(3)	0·5154	0·4525	0·6902
W(4)	0·4642	0·4594	0·6905
W(5)	0·3086	0·4452	0·5719

Table 3. *Comparison of torsional angles* (°)

Standard deviations for the torsion angles for crystal *A* are of the order of 0·9°.

	Crystal *A*	Crystal *B*		Crystal *A*	Crystal *B*
Peptide ring					
φ_1	−86	−96	μ_{33}*	59	64
ψ_1	−13	−5	ψ_3'	−117	−132
ω_1	−175	−171	ω_3	−179	−179
φ_2	−127	−136	φ_4'	−118	−108
ψ_2	3	35	μ_{41}*	66	61
ω_2	−178	−171	μ_{42}*	−177	−176
φ_3'	138	94	μ_{43}*	177	177
μ_{31}*	178	175	ψ_4'	−150	−140
μ_{32}*	177	178	ω_4	−173	−174
Side chains					
χ_{11}	−61	−74	χ_{21}	−55	−48
χ_{12}^1	176	175	χ_{22}^1	−90	−88
χ_{12}^2	−64	−64	χ_{22}^2	90	92

* Torsional angles about the C–C bonds in the two trimethylene moieties in the peptide ring.

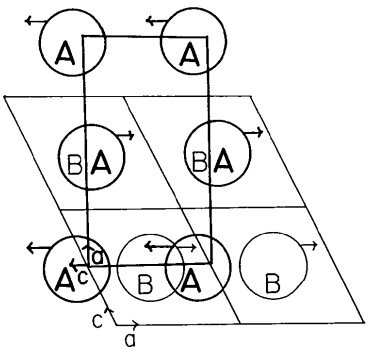

Fig. 2. The relationship of axes and a schematic representation of the packing in the $P2_1$ crystal (case *B*) and the $P2_12_12_1$ crystal (case *A*, bold face). In case *B*, layers of molecules parallel to the horizontal axis are all directed in the same way, whereas in case *A*, the layers of molecules alternate direction. The lengths of the *b* axes for the two crystals are 18·8 Å for the $P2_12_12_1$ cell and 19·0 Å for the $P2_1$ cell.

exhibit definite similarities in intermolecular packing. Fig. 2 shows the relationship of axes in the two crystals as well as a schematic representation of the packing of the molecules. In the $P2_1$ crystal (case *B*) the molecules form hydrogen-bonded layers parallel to the *a* axis and perpendicular to the *ac* plane. The layers, of course, are repeated by translation along the *c* axis. In the $P2_12_12_1$ crystal (case *A*) almost identical layers are formed; however, every other layer reverses direction due to a twofold screw relationship along the *a* axis of that crystal. The stereodiagram in Fig. 3 (Johnson, 1965) further illustrates the reversal of adjacent layers in the $P2_12_12_1$ crystal (case *A*).

A comparison of the peptide and solvent molecules in each layer of crystals *A* and *B* is shown in Fig. 4. Four peptide molecules, connected by hydrogen bonds, form a cavity for the solvent. To form the cavity, there are four intermolecular peptide–peptide hydrogen bonds: two N(4)H···O(1) bonds (labelled **c**) and two O(2^n)H···O(4) bonds (labelled **d**), see Table 4. In addition there is another boundary linkage between peptide molecules through *W*(1) (where *W* designates water) labelled **a** and **f**. In the two crystals the shapes and sizes of the cavity are very similar.

In the $P2_1$ cell, Fig. 4(*b*), the cavity is filled with one molecule of $(CH_3)_2SO$ where the S atom is disordered between two sites. The solvent molecule forms an N(2)H···O=S hydrogen bond with the peptide. The nearest approaches of the non-polar end of the $(CH_3)_2SO$ are between the CH_3 groups and the OH group of the Tyr side chain at 3·51 and 3·60 Å. All other solvent–peptide contacts are much longer. In the $P2_12_12_1$ cell, Fig. 4(*a*), the cavity is filled only with H_2O molecules. In addition to *W*(1), which is present in both crystals, there is *W*(2) at full occupancy which participates in three hydrogen bonds (**b**, **g** and **h**). Sites *W*(3) and *W*(4) are adjacent to each other, see Fig. 3, and cannot be occupied at the same time. However, during refinement they were assigned arbitrary isotropic thermal parameters and their occupancy was allowed to vary. The results indicated that the total occupancy of the two sites is unity. Water molecules in

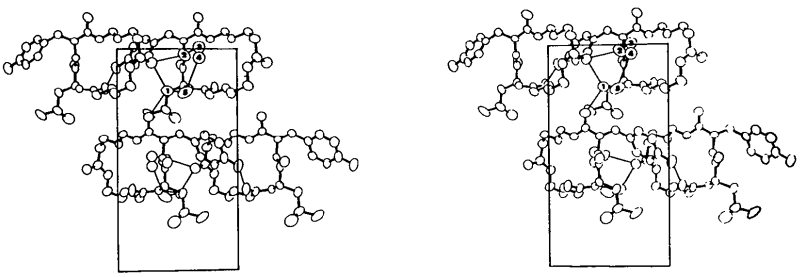

Fig. 3. Stereodiagram of the packing of molecules in the $P2_12_12_1$ crystal of *cyclo*(-L-Leu-L-Tyr-*δ*-Avaler-*δ*-Avaler-). Compare to case *B* in Fig. 2. The directions of the axes are *a*↑, *c*← and *b* directed into the plane of the paper. (The contents for only one-half the cell in the *b* direction are represented.) Atoms labelled 1–5 are H_2O molecules where sites 3, 4 and 5 have partial occupancy.

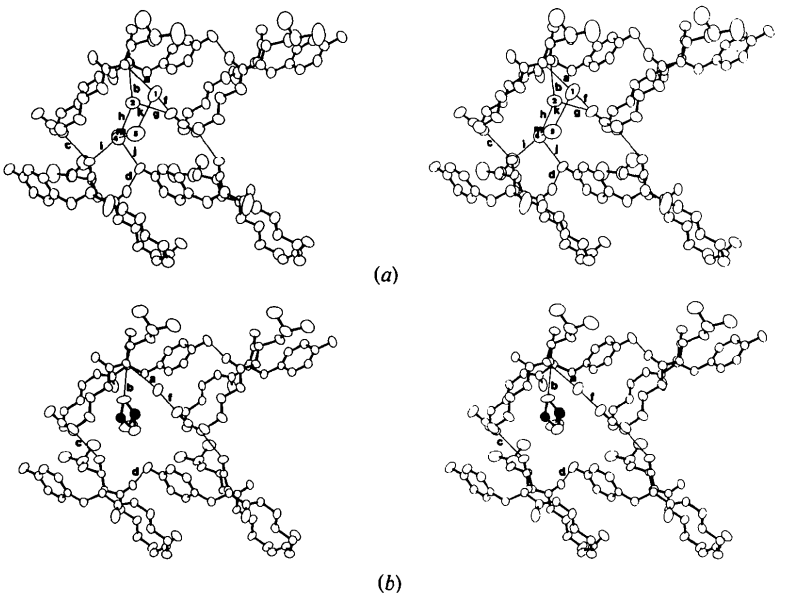

Fig. 4. Cavities formed by groups of four peptide molecules. (*a*) $P2_12_12_1$ crystal with five sites for H_2O molecules in the cavity. Sites 1 and 2 are fully occupied, the total occupancy of sites 3 and 4 is 1·0 (site 3 is hidden behind site 4; both sites cannot be occupied at the same time) and the occupancy of site 5 is ~0·6. (*b*) $P2_1$ crystal with one H_2O and one DMSO in the cavity where the sulfur atom designated by ● is disordered between two sites. Equivalent hydrogen bonds in the two crystals are labelled by the same letter symbols.

Table 4. *Hydrogen bonds for crystal A*

N(3) does not participate in hydrogen bonding.

Donor	Acceptor	Length, Å	Symmetry position of acceptor	Label in Fig. 4(*a*) and (*b*)
N(1)	*W*(1)	2·86	$\frac{1}{2}+x, \frac{1}{2}-y, 1-z$	**a**
N(2)	*W*(2)	2·96	$\frac{1}{2}+x, \frac{1}{2}-y, 1-z$	**b**
N(4)	O(1)	3·16	$2-x, -\frac{1}{2}+y, \frac{1}{2}-z$	**c**
O(2^n)	O(4)	2·73	$x, y, 1+z$	**d**
W(1)	O(2)	2·64	$-1+x, y, z$	**e**
W(1)	O(3)	2·79	$-\frac{1}{2}+x, \frac{1}{2}-y, -z$	**f**
W(2)	O(3)	2·90	$-\frac{1}{2}+x, \frac{1}{2}-y, -z$	**g**
W(2)	*W*(3) 2·64 *W*(4) 2·80		x,y,z	**h**
W(3) *W*(4)	O(1)	2·78 2·83	$\frac{3}{2}-x, 1-y, \frac{1}{2}+z$	**i**
W(3) *W*(4)	O(2^n)	2·82 2·94	$\frac{3}{2}-x, 1-y, -\frac{1}{2}+z$	**j**
W(5)	*W*(1)	3·00	x,y,z	**k**
W(5)	*W*(4)	2·91	x,y,z	**m**

sites *W*(3) or *W*(4) participate in three (**h**, **i**, and **j**) or four (**h**, **i**, **j** and **m**) hydrogen bonds, respectively. The occupancy of site *W*(5) is ~0·6. This water molecule participates in two hydrogen bonds (**k** and **m**), as a donor. The water molecules form hydrogen bonds not only among themselves but also to the peptide molecules surrounding the cavity (*e.g.*, **b**, **g**, **i** and **j**).

Hydrogen bond **e**, not shown in Fig. 4, connects *W*(1) and carbonyl O(2) in an adjacent layer, in both crystals. The length of the N(4)H···O(1) bond (labelled **c**) is near 3·16 Å in both cases; however, it has still been designated as a hydrogen bond since the proton on N(4) is directed towards O(1) and furthermore the bond completes the boundary of the solvent cavity. N(3) does not participate in any hydrogen bonding, although it could have been expected to be a donor to O(4) if a transannular hydrogen bond across a β turn were to form.

Conclusion

It appears that the conformation of *cyclo*(-L-Leu-L-Tyr-δ-Avaler-δ-Avaler-) is intrinsic to the molecule and independent of the solvent. The molecules have the property of aggregation in such a manner that large cavities are created. In turn, the cavities are filled with the available solvent and the appropriate hydrogen bonds between peptide molecules and the polar segments of the solvent molecules are formed. A similar situation has been observed for antamanide crystallized from *n*-hexane/methyl acetate, and from CH_3CN/acetone (Karle & Duesler, 1977) where the peptide molecules with an invariant conformation aggregate to form channels of large diameter which are filled either with non-polar molecules or with water molecules, depending upon the solvent.

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The Constitution of Hector's Base: The Crystal and Molecular Structure of 5-Imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline

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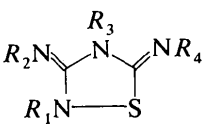
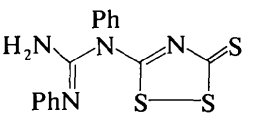
Hector's base, $C_{14}H_{12}N_4S$, is orthorhombic, space group $P2_12_12_1$, $a = 12{\cdot}196\ (2)$, $b = 11{\cdot}027\ (2)$, $c = 9{\cdot}519\ (2)$ Å; $Z = 4$. The structure was solved by direct methods using 2086 diffractometer data and refined by the full-matrix least-squares method to $R = 0{\cdot}0790$. The 89-year controversy concerning the constitution of Hector's base has been resolved: it has been shown to be 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline.

Introduction

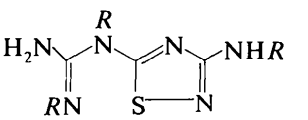
The oxidation of 1-phenylthiourea with H_2O_2 yields a heterocyclic base, $C_{14}H_{12}N_4S$ (Hector, 1889), generally known as Hector's base. Despite considerable recent interest in its chemistry (Kurzer, 1965; Akiba, Tsuchiya & Inamoto, 1976; Butler, 1978), the constitution of this base has never been definitively determined. Six structures, the six possible permutations of two phenyl groups amongst the four distinct N atoms of the 3,5-diimino-1,2,4-thiadiazolidine skeleton (I*a–f*) have been suggested by different authors (Kurzer, 1965): of these structures, (I*c*) has been adopted in the most recent work (Akiba, Tsuchiya & Inamoto, 1976; Butler, 1978), although (I*e*) has also been widely employed (Kurzer, 1965). The reaction of Hector's base with carbon disulphide yields an adduct $C_{15}H_{12}N_4S_3$ (Fromm & Heyder, 1909), whose constitution is (II) (Butler, Glidewell & Liles, 1978) [rather than those suggested earlier (Butler, 1978)]; similarly the bis(4-bromophenyl) analogue of Hector's base forms an adduct with 4-bromophenylcyanamide (Akiba, Tsuchiya, Ochiumi & Inamoto, 1975), whose constitution is (III) (Akiba, Tsuchiya, Inamoto, Onuma, Nagashima & Nakamura, 1976). If (I*c*) properly represents Hector's base, then the formation of both (II) and (III) requires, after ring-opening, a rotation about the C—N(1) bond of the guanidine group, the rationale of which is by no means apparent. The structures (II) and (III) raise the possibility that Hector's base is in fact (I*e*).



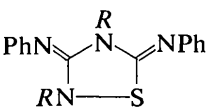
(I*a*)	$R_1 = R_2 = H$	$R_3 = R_4 = Ph$
(I*b*)	$R_1 = R_3 = H$	$R_2 = R_4 = Ph$
(I*c*)	$R_1 = R_4 = H$	$R_2 = R_3 = Ph$
(I*d*)	$R_2 = R_3 = H$	$R_1 = R_4 = Ph$
(I*e*)	$R_2 = R_4 = H$	$R_1 = R_3 = Ph$
(I*f*)	$R_3 = R_4 = H$	$R_1 = R_2 = Ph$



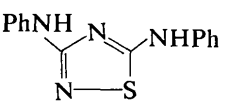
(II)



(III) $R = BrC_6H_4$



(IV*a*) $R = H$
(IV*b*) $R = Me$



(V)

In ethanolic ammonia at 150°C Hector's base forms an isomer (Dost, 1906) usually called Dost's base, for which the constitutions (IV*a*) (Christopherson, Øttersen, Seff & Treppendahl, 1975), (V) (Kurzer & Sanderson, 1963) and (VI) (*Beilstein*, 1937) have been suggested. The molecular structure of (IV*b*) has been

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