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N-(1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinium–Hydrogen Maleate (1/1), Enalapril (MK-421)

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Abstract. $C_{20}H_{29}N_2O_5^+.C_4H_3O_4^-$, $M_r = 492{\cdot}5$, monoclinic, $P2_1$, $a = 11{\cdot}224$ (4), $b = 6{\cdot}645$ (2), $c = 17{\cdot}824$ (5) Å, $\beta = 105{\cdot}52$ (3)°, $V = 1280{\cdot}9$ (7) Å^3, $Z = 2$, $D_x = 1{\cdot}27$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 1{\cdot}06$ cm^{-1}, $F(000) = 524$, $T = 293$ K, final $R = 0{\cdot}089$ for 1187 observed reflections. The title compound (MK-421) is a potent orally active inhibitor of angiotensin-converting enzyme. The molecule is observed with Ala NH_2^+ as a positively charged group. The backbone shows an extended conformation at Ala. The crystal-structure conformation is compared with the proposed biologically active conformation of enalapril and with the crystal conformation of captopril (SQ 14,225).

Introduction. Much attention focuses on the renin–angiotensin system in relation to mechanisms controlling blood pressure. The discovery of captopril (Ondetti, Rubin & Cushman, 1977) and enalapril (Patchett *et al.*, 1980) as potent orally active inhibitors of angiotensin-converting enzyme led to the development of novel molecules with similar biological activity (Condon *et al.*, 1982; Thorsett, Harris, Aster, Peterson, Taub & Patchett, 1983).

As yet, however, the only crystal-structure analysis of angiotensin-converting enzyme flexible inhibitor reported in the literature concerns captopril (Fujinaga & James, 1980).

The present study was undertaken to determine precise molecular and conformational parameters for MK-421 which may be of use in the understanding of conformational requirements for ACE (angiotensin-converting enzyme) inhibition. The observed crystal-structure conformation is compared with the biologically active conformation proposed by Andrews, Carson, Caselli, Spark & Woods (1985) and with the conformation of captopril.

Experimental. Crystals grown with vapour-diffusion technique with methanol as solvent and diethyl oxide as precipitating agent. Plate-like crystal, dimensions $0{\cdot}05 \times 0{\cdot}20 \times 0{\cdot}40$ mm; Enraf–Nonius CAD-4 diffractometer; Mo $K\alpha$ radiation, graphite monochromator. Lattice parameters from least-squares adjustment to setting angles of 25 reflections with $9 < 2\theta < 18°$. Correction for Lorentz and polarization effects; ω–2θ scans. $\theta_{max} = 25°$; range of hkl: h: $-12 \rightarrow 12$; k: $0 \rightarrow 7$; l: $0 \rightarrow 21$. Intensity variation of three standard reflections <2%. 2459 unique reflections measured; 1187 with $I > 2\sigma(I)$. Solution by direct methods (*MITHRIL*; Gilmore, 1984). Refinement on F by block-diagonal least squares; anisotropic non-H atoms, fixed parameters for H atoms [located in ΔF map except at C(5) and at the carboxyl groups]. $R = 0{\cdot}089$, $wR = 0{\cdot}092$ (poor quality of crystal and hence of intensity data); $w = 1/\sigma^2(F_o)$ based on counting statistics; $S = 1{\cdot}10$; $\Delta/\sigma_{max} = 0{\cdot}5$; $\Delta/\sigma_{mean} = 0{\cdot}1$. Max. and min. heights in final $\Delta\rho$ map $+0{\cdot}3$ and $-0{\cdot}2$ e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974)

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for non-H atoms and from Stewart, Davidson & Simpson (1965) for H atoms. Local programs *CRISAFFI, CRISUTIL*; Mini-6 92 Bull computer.*

* Lists of structure factors, anisotropic parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42859 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

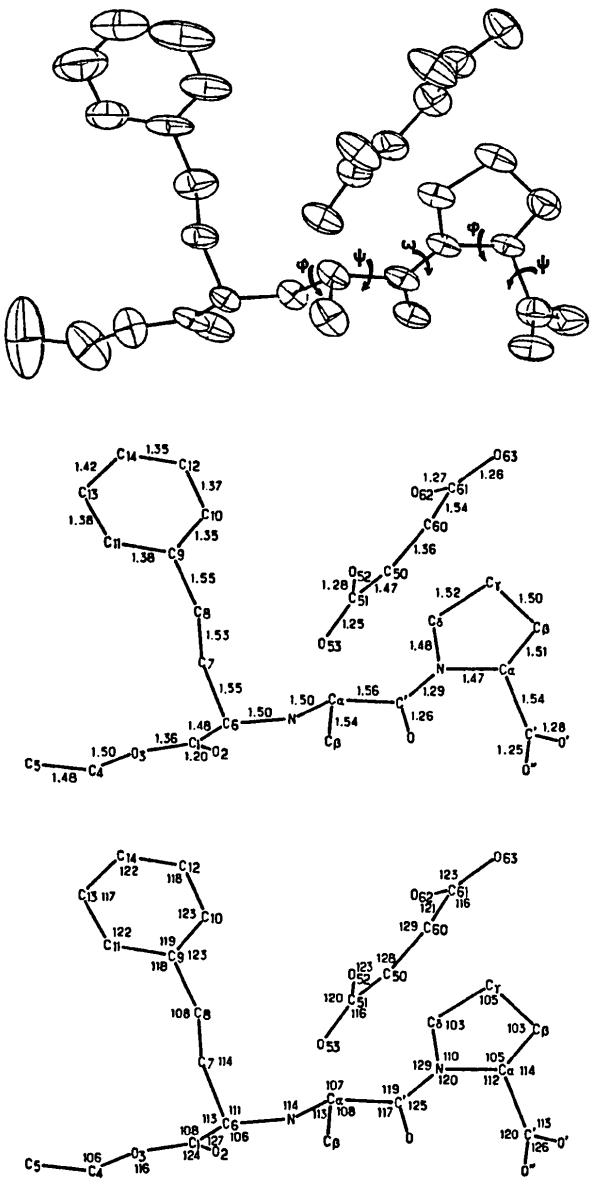

Fig. 1. Projection of the molecular structure with the thermal ellipsoids drawn at 50% probability. The numbering scheme and Bond lengths ($\bar{\sigma} = 0.01$ Å) and angles ($\bar{\sigma} = 1°$) are given.

Discussion. Bond lengths and angles are shown in Fig. 1, together with the conformation of the molecule and the numbering of the atoms. These values are in good agreement with those reported previously for amino acids and peptides (Marsh & Donohue, 1967). The positional and thermal parameters of the non-hydrogen atoms are listed in Table 1.

Two of the four maleate O atoms show considerable deviations from planarity. The distances of these O atoms from the mean plane of the molecules are: O(53) 0·11 (2), O(63) 0·17 (2) Å. These differences are observed in other structures (Marsau & Cotrait, 1976) and have to be attributed to hydrogen bonding and packing effects.

Enalapril exists in the crystal with the alanyl N protonated. The alanyl nitrogen is hydrogen bonded to the maleate atom O(53) [2·76 (1) Å] and its distance from the carboxyl oxygen atom O''(Pro) of a related molecule $(1-x, -\frac{1}{2}+y, 2-z)$ is 3·14 (1) Å (Fig. 2). An additional hydrogen bond links the enalapril oxygen O′ to the maleate oxygen O(63): O′···O(63)$(2-x, -\frac{1}{2}+y, 2-z) = 2{\cdot}66$ (1) Å. Apart from these hydrogen bonds, all other intermolecular contacts correspond to normal van der Waals interactions.

Table 1. *Positional parameters* ($\times 10^4$) *and equivalent isotropic temperature factors* (Å^2)

$$U_{eq} = (\tfrac{1}{6}\pi^2)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
C(1)	2994 (11)	−2920 (22)	7339 (7)	0·2 (1)
O(2)	3684 (8)	−4328 (16)	7480 (6)	0·3 (1)
O(3)	1824 (8)	−2992 (16)	6867 (6)	0·2 (1)
C(4)	1416 (17)	−4975 (29)	6474 (12)	0·2 (1)
C(5)	265 (22)	−4557 (54)	5862 (17)	0·8 (3)
C(6)	3247 (10)	−836 (21)	7628 (7)	0·2 (1)
C(7)	3183 (11)	697 (24)	6966 (8)	0·3 (1)
C(8)	3968 (13)	140 (28)	6418 (8)	0·5 (1)
C(9)	3790 (13)	1802 (26)	5790 (8)	0·4 (1)
C(10)	4435 (15)	3543 (29)	5895 (9)	0·5 (1)
C(11)	2913 (15)	1492 (31)	5094 (10)	0·4 (1)
C(12)	4257 (17)	5014 (31)	5335 (11)	0·7 (2)
C(13)	2699 (20)	2894 (49)	4502 (12)	0·8 (2)
C(14)	3393 (20)	4700 (40)	4652 (12)	0·7 (2)
Alanyl				
N	4505 (9)	−861 (18)	8196 (6)	0·1 (1)
C^{α}	4907 (11)	1150 (20)	8557 (8)	0·2 (1)
C′	6161 (11)	823 (23)	9179 (7)	0·2 (1)
O	6374 (7)	−922 (15)	9454 (5)	0·2 (1)
C^{β}	3991 (12)	2052 (27)	8975 (9)	0·3 (1)
Proline				
N	6896 (9)	2329 (16)	9376 (6)	0·2 (1)
C^{α}	8109 (11)	2047 (23)	9940 (7)	0·2 (1)
C′	8004 (12)	1027 (25)	10697 (9)	0·3 (1)
O′	8855 (8)	−274 (20)	10957 (6)	0·5 (1)
O′′	7260 (9)	1685 (17)	11046 (5)	0·4 (1)
C^{β}	8685 (12)	4113 (27)	10064 (8)	0·2 (1)
C^{γ}	8140 (13)	5128 (25)	9295 (9)	0·3 (1)
C^{δ}	6811 (11)	4374 (23)	9032 (8)	0·2 (1)
Maleate				
C(50)	8500 (11)	−1809 (26)	7662 (8)	0·3 (1)
C(51)	7282 (11)	−978 (25)	7651 (7)	0·2 (1)
O(52)	7061 (8)	912 (18)	7656 (7)	0·3 (1)
O(53)	6459 (8)	−2223 (16)	7675 (6)	0·3 (1)
C(60)	9567 (12)	−792 (26)	7698 (8)	0·2 (1)
C(61)	9813 (13)	1487 (25)	7760 (8)	0·2 (1)
O(62)	8935 (9)	2736 (18)	7699 (7)	0·4 (1)
O(63)	10930 (8)	2003 (18)	7925 (6)	0·3 (1)

The pyrrolidine ring of Pro has the C^{γ}-*exo* conformation following the classification by Balasubramanian, Lakshminarayanan, Sabesan, Tegoni, Venkatesan & Ramachandran (1971) and Ashida & Kakudo (1974). C^{γ}-*exo* is the slightly preferred conformation for Pro and is observed in many other structures such as Tyr-Pro-Asn-Gly (Précigoux, Geoffre, Hospital & Leroy, 1982) or SQ 14,225 [1-(D-3-mercapto-2-methylpropionyl)-L-proline] (Fujinaga & James, 1980).

At Ala, the peptide main chain in standard nomenclature (IUPAC–IUB Commission on Biochemical Nomenclature, 1971) is described by the φ, ψ and ω angles, respectively equal to 175 (2), 156 (2), −178 (2)°, which correspond to a nearly fully extended conformation.

To compare the observed conformation with the biologically active conformation proposed by Andrews *et al.* (1985) and with the captopril conformation, the main conformational angles are listed in Table 2.

Captopril is an alanylproline analogue with the NH_2 terminal group replaced by CH_2SH. By analogy with the peptide nomenclature, the S–C–C^{α}–C′ dihedral angle is called φ Ala.

As far as the alanylproline-like fragment is concerned, the three conformations in Table 2 are very similar. Thus, the zinc-binding sulfur atom of captopril has a spatial localization comparable to that observed for C(6) in the enalapril structure.

The conformation of the phenethyl group in the proposed biologically active model is consistent with the situation observed crystallographically.

The main difference appears in the orientation of the phenethyl group defined by the C(8)–C(7)–C(6)–N angle. However, the carboxyl terminal, the carbonyl oxygen and the ethyl ester group (enalapril) or the second carboxyl group (model) are situated on the same side of the molecule. On the contrary, as seen in an *ORTEP* drawing of the crystalline conformation of enalaprilat [the X-ray crystallographic structure determination of the active form of enalapril was done by Springer and is partly described by Patchett & Cordes (1985)], the carboxyl groups are oriented in opposite directions.

We thank the Merck Sharp & Dohme-Chibret Laboratory for the gift of the sample.

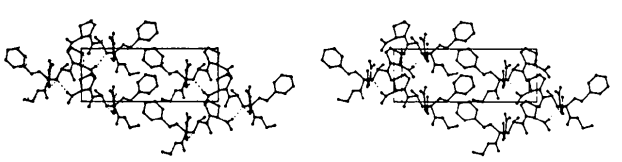

Fig. 2. Packing diagram for enalapril maleate. The *c* axis is horizontal; *b* is vertical. Dotted lines indicate hydrogen bonds.

Table 2. *Main dihedral angles: observed for enalapril* ($\bar{\sigma} = 2°$), *proposed for the biologically active conformation of enalaprilat* (*Andrews et al.*, 1985) *and observed for captopril* (*Fujinaga & James*, 1980)

The φ Ala value for captopril is defined by S–C–C^{α}–C′.

	Enalapril	Proposed biologically active conformation	Captopril
C(10)–C(9)–C(8)–C(7)	84	90	
C(9)–C(8)–C(7)–C(6)	179	180	
C(8)–C(7)–C(6)–N	68	180–240	
C(7)–C(6)–N–C^{α}	57		
Alanyl			
φ	175		−171
ψ	156	160–170	138
ω	−178	180	173
Proline			
φ	−53	−60	−67
ψ	140		162

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