Conformational Similarities of Angiotensin-converting Enzyme Inhibitors: *X*-Ray Crystal Structures

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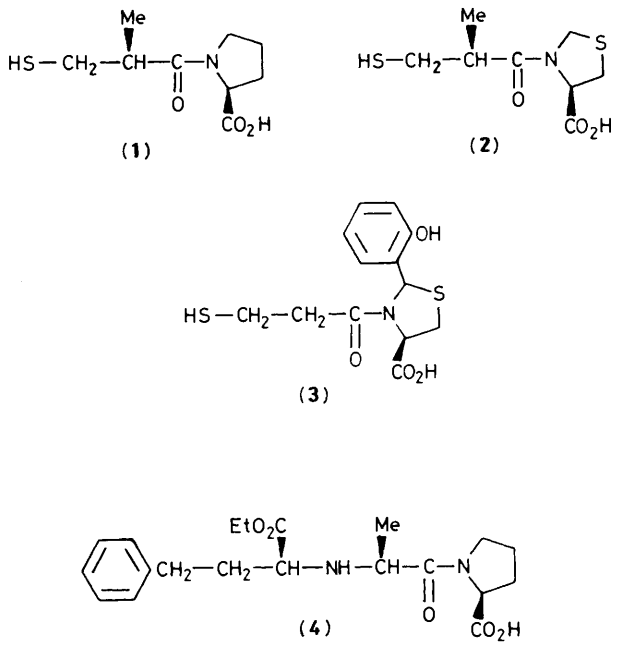
Crystal structures of enalapril (MK-421) and two mercaptoalkanoyl derivatives (YS-980 and SA-446) which are potent angiotensin-converting enzyme inhibitors have shown that they have a common conformation.

Since the development of captopril (**1**) by Ondetti *et al.*[1] numerous reports on angiotensin-converting enzyme (ACE) inhibitors have appeared. Clinical studies have shown ACE inhibitors to be useful for the control of hypertension and congestive heart failure.

The conformational studies of ACE inhibitors are useful as an aid in the design of new drugs. Therefore we have analysed the crystal structures of YS-980 (**2**), SA-446 (**3**), and enalapril (**4**). These compounds have recently been demonstrated as useful ACE inhibitors having antihypertensive activities.[2]

Crystal data: (**2**) $C_8H_{13}NO_3S_2$, M = 235.3, orthorhombic, space group $P2_12_12_1$, a = 15.498(3), b = 12.066(3), c = 5.806(1) Å, U = 1085.7(4) Å^3, Z = 4, D_c = 1.439, D_m = 1.435(6) g cm^{-3}; (**3**) $C_{13}H_{15}NO_4S_2$, M = 313.4, orthorhombic, space group $P2_12_12_1$, a = 7.091(2), b = 11.940(5), c = 17.082(8) Å, U = 1447(1) Å^3, Z = 4, D_c = 1.439, D_m = 1.425(1) g cm^{-3}; (**4**) as maleate salt, $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$, M = 492.5, monoclinic, space group $P2_1$, a = 17.838(4), b = 6.640(2), c = 11.649(3) Å, β = 106.29(2)°, U = 1324.4(8) Å^3, Z = 2, D_c = 1.235, D_m = 1.235(1) g cm^{-3}. Independent reflections ($\sin\theta/\lambda \leq 0.588$ Å^{-1}) were collected on a Rigaku AFC-5 diffractometer using graphite-monochromated Cu-K_α radiation. The structures were solved by direct and Fourier methods and refined by block diagonal least-squares including



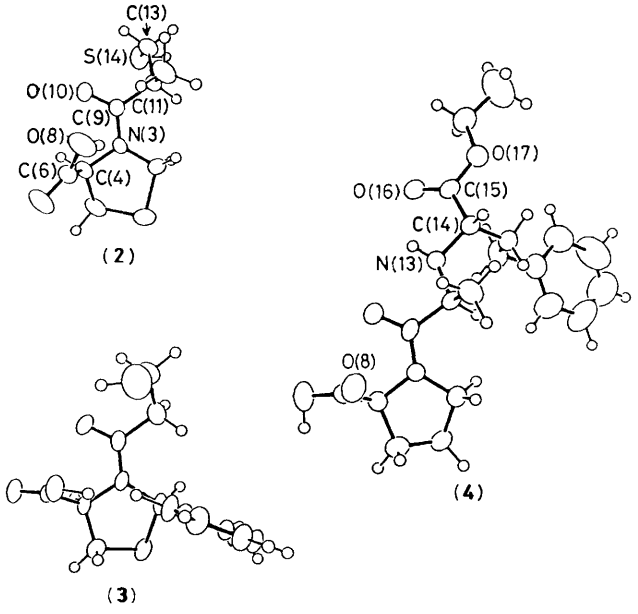


Figure 1. Molecular conformations observed in the crystals of (**2**), (**3**), and (**4**).

Table 1. Comparison of selected torsion angles (°).

Torsion angle[a]	(1)	(2)	(3)	(4)
ϕ_1	189.4	−63.6	67.3	175.2
ψ_1	138.2	151.9	220.5	157.4
ω_1	173.3	166.3	181.6	182.2
ϕ_2	−67.3	−79.1	−53.4	−56.8
ψ_2	−17.0	19.1	−43.4	−43.7
θ_1				178.3
θ_2				−173.4

[a] ϕ_1: 9–11–13–14, ψ_1: 3–9–11–13, ω_1: 4–3–9–11, ϕ_2: 6–4–3–9, ψ_2: 8–6–4–3, θ_1: 11–13–14–15, θ_2: 13–14–15–17.

hydrogen atoms. Final *R* factors of (**2**), (**3**), and (**4**) are 0.059, 0.065, and 0.079 for 1102, 1445, and 2374 reflections with $|F_o|>\sigma(F_o)$.†

The molecular structures of (**2**), (**3**), and (**4**) are illustrated in Figure 1. Their selected torsion angles are listed in Table 1, in which the values of captopril (**1**)[3] are also given for comparison. Two torsion angles, ω_1 and ϕ_2, defining the spatial orientations of amide carbonyl and carboxy groups which are important for the binding with the active site of ACE[1,4] are all restricted in the *antiperiplanar* and *synclinal* regions respectively, implying that this conformation is required for activity. Further a common conformation is seen in the torsion angles of ψ_1 (*trans*) and ψ_2 (*cis*), although these have large conformational freedom compared with ω_1 and ϕ_2. Consequently all compounds adopt a common conformation with a *trans* zigzag fashion of the C(4)–N(3)–C(9)–C(11)–C(13)[N(13)] bond sequence and a *cis* orientation between the carboxy and amido carbonyl groups. In captopril and the thiol analogues being studied, (**2**) and (**3**), the position of the sulphur atom is not constant; the rotation around ϕ_1 being near 60° (**3**), 180° (captopril), or −60° (**2**). Respective regions were shown to be stable by conformational energy calculations.[5] From comparison of the spatial orientation of the sulphur atom with that of the carboxy oxygen atom [O(16)] in (**4**), both of which are key atoms for the interaction with the active site zinc atom of ACE,[1,6] the active conformation is likely to be that in which ϕ_1 is near the −60° region. This has also been inferred from energy calculations[5] and computer graphic studies.[7]

It is interesting to note that the polar atoms of carboxy, amide carbonyl, and zinc-binding groups are all located on one side of the C(4)–N(3)–C(9)–C(11)–C(13)[N(13)] bond sequence, while the hydrophobic groups are on the opposite side.

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† The atomic co-ordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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