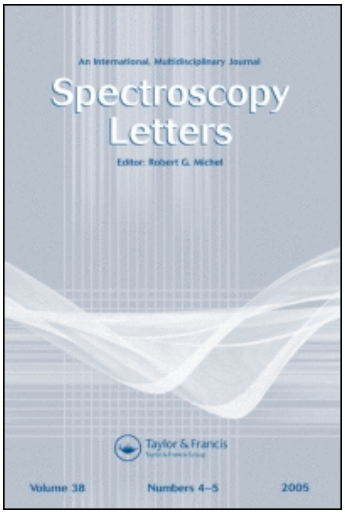

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Captopril and Its Disulfide Metabolite: ^{13}C NMR Assignments and Preferred Conformations

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CAPTOPRIL AND ITS DISULFIDE METABOLITE: ^{13}C NMR ASSIGNMENTS AND PREFERRED CONFORMATIONS

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Key Words: Captopril; antihypertensive agent; disulfide metabolite; ^{13}C nmr assignments; preferred conformations.

Abstract

The ^{13}C nmr assignments for captopril (1) and its disulfide mammalian metabolite (2) were made. Evidence was presented for the preferred conformations of these compounds to be in the trans forms.

Introduction

As a part of our ongoing study of the fungal metabolites* of the antihypertensive agent captopril, chemically known as 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl)]-L-proline (1), it was decided to assign all carbon signals in its ^{13}C nmr spectrum. This study, it was thought, should provide valuable information that would help identify the resulting metabolites. This investigation was also extended to include the ^{13}C nmr assignments of the major known[1] mammalian metabolite of captopril (1), namely 1,1'[dithio-bis-(D-2-methyl-1-oxopropane-3,1-diyl)]-bis-

*This study was undertaken to compare the fungal metabolites with those isolated from mammalian sources. Numerous analogous examples in the literature[3] point to the possibility that fungi might produce metabolites from drugs identical to those produced by mammals. This route should provide an easy source to produce these compounds for biological evaluations.

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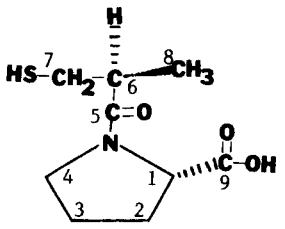
[L-proline] (2), as it was also readily available by chemical oxidation. Furthermore, it was expected that the study should present evidence for the preferred conformations of these compounds in view of what has been reported[2] about the occurrence of cis and trans isomers of proline amides.

Results and Discussion

The study of the ^{13}C nmr assignments of captopril (1) and its metabolite 2 was based on the use of (±)-acetylproline (3) as a model compound. The pyridine-d_5 spectrum of this compound exhibited major signals assigned as shown on its structure. The position of the carboxyl carbonyl was relatively more shielded in comparison to that of cyclopentane-carboxylic acid (180.7 ppm)[4] presumably due to the shielding γ-effect of the acetyl group. The assignment of the remaining signals was straightforward and was based on the chemical shifts rules and the multiplicities in the off-resonance spectrum.

The ^{13}C nmr spectrum of 3 showed, in addition, less intense (25-30% less) signals at δ 60.8 (d), 46.6 (t), 31.6 (t) and 23.1 (t); these were ascribed to the α-, δ-, β- and α-carbon signals of the minor cis-isomer where the two carbonyl groups are anti with respect to each other (distiniction from the syn relationship shown in 3). In the cis-isomer, due to the shielding effect of the amide carbonyl, the signals due to the γ-and the δ-carbon atoms are located further upfield from the corresponding signals of the trans-isomer; while those of the α- and β-carbon atoms occur at lower field positions[2]. This difference helped distinguish the signal due the β-carbon from that of the γ-carbon.



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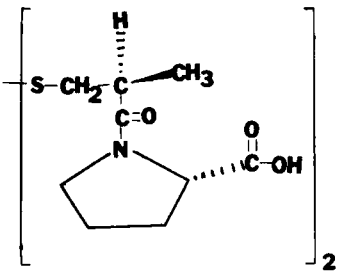

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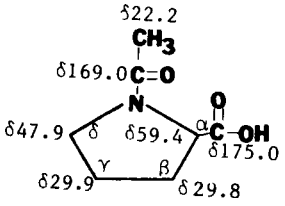

3

With the carbon signals of 3 assigned, the similarly located carbon signals of captopril (1) and its metabolite 2 were designated (Table 1).

As shown in Table 1, the amide carbon signal in both 1 and 2 are more deshielded than that in 3. This can be ascribed to the β-effect of the methyl group of the side chain.

TABLE 1

^{13}C NMR[a] Assignments of Captopril (1) and its Metabolite (2).

Carbon Number	Captopril (1)[b]	2[c]
1	59.3 (d)	59.5 (d)
2	29.4 (t)	29.5 (t)
3	25.0 (t)	25.0 (t)
4	47.2 (t)	47.2 (t)
5	173.5 (s)	173.3 (s)
6	42.4 (d)	42.2 (d)
7	28.1 (b)	38.2 (t)
8	17.1 (q)	17.2 (q)
9	174.7 (s)	174.8 (s)

[a]The spectra were taken in pyridine-d_5. The methanol-d_4 spectra were essentially similar except that the carbonyl region was less satisfactorily resolved.

[b]Additional less intense signals (10% or less) were also observed at δ 60.0 (d, C-1), 46.0 (t, C-4), 31.5 (t, C-2) and 23.0 (t, C-3). These were attributed to the minor cis-isomer.

[c]Additional less intense signals (10% or less) were also observed at δ 59.8 (d, C-1), 46.2 (t-C_4), 31.5 (t, C-2) and 22.9 (t, C-3). These were attributed to minor cis-isomer.

It should be noted that the assignment of C-7 (Table 1) of captopril (1) was based on subtracting the spectrum of 3 from that of 1. This same signal was found to shift downfield by 10.1 ppm in the metabolite 2. This is comparable in magnitude to the downfield shift observed when carbon-bearing hydroxyl functions are converted to endoperoxides[5]. It is also worthy to note that carbons bearing thiol groups are much

less deshielded than those carrying oxygen or nitrogen functional groups.

In conclusion the ^{13}C nmr spectra of captopril (1) and its metabolite 2 suggest that they exist predominately as drawn, in trans forms, with the carbonyl groups of the amide and carboxyl groups syn to each other.

Experimental

Captopril (1) and its disulfide metabolite (2) were gifts to one of us (FSE) from The E.R. Squibb & Sons, Inc., the Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08540, U.S.A. The ^{13}C nmr spectra were obtained at 15.03 MHz on a Jeol-FX60 FT NMR Spectrometer, using TMS as internal standard and pyridine-d_5 as solvent, unless otherwise stated. The proton-noise decoupled spectra were obtained using a 45° pulse, 5-s repetition and 8,192 datum points. Single frequency off-resonance spectra were conducted by centering the decoupling frequency 1100 Hz downfield from the signal for TMS. The abbreviations s, d, t, and q denote singlet, doublet, triplet and quartet, respectively.

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