



# Solid and solution NMR studies of the complexation of Ag<sup>+</sup> with the *trans* isomer of captopril: Biological activities of this high blood pressure drug along with its Ag<sup>+</sup> complex

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## Abstract

Complexation of Ag<sup>+</sup> with captopril, 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline, has been studied by <sup>1</sup>H and <sup>13</sup>C-NMR spectroscopy. The equilibrium constants for the *trans* to *cis* isomers of captopril bound to Ag<sup>+</sup> were measured by <sup>1</sup>H NMR spectroscopy. It is observed that the *trans* isomer of the drug binds more strongly to Ag<sup>+</sup> between pH 5 and 8, as shown by the broadening of the *trans* isomer's resonances in <sup>13</sup>C NMR spectra on complexation. A monodentate complexation of the *trans* captopril with Ag<sup>+</sup> via the thiol site is proposed based on the solid-state NMR and IR data. A superior antimicrobial activity is exhibited by the Cap–Ag(I) complex compared to captopril ligand itself against *Heterotrophic Plate Counts* (HPC), *Pseudomonas aeruginosa* and *Fecal streptococcus* bacteria.

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## 1. Introduction

Captopril, 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline, is an orally active drug for the treatment of high blood pressure [1–3]. High blood pressure can result from the production of angiotensin II from inactive angiotensin I, the conversion being catalyzed by angiotensin-converting enzyme [4,5], which is a zinc containing metallo-enzyme [6]. The clinical trials have shown that side effects are sometimes associated with this drug [7,8] especially in patients receiving high doses (~450 mg/d). These side effects include a dry cough, skin rashes, dysgeusia, and neutropenia often associated with zinc and/or copper depletion [9–11].

Hughes et al. [12] have studied the complexation of captopril with Zn(II), Cd(II) and Pb(II) by potentiometric titrations. The log β values of captopril:Zn<sup>2+</sup> ratio of 1:1, 2:1 and 3:1 is found to be 5.38, 11.66 and 15.30, respectively, indicating a stronger complexation at a higher captopril to Zn<sup>2+</sup> ratio.

It is well known that proline-containing peptides normally exist as an equilibrium mixture of *cis* and *trans* isomers with

respect to the peptide bond involving the proline amino group [13–15]. Thus, captopril is expected to be present in aqueous solution as *trans* and *cis* forms, with the relative population of the two forms dependent on the protonation state of the molecule [16–18].

Hassall et al. [19] have assumed that conformationally restricted angiotensin converting enzyme inhibitors require a *trans* amide bond of captopril when binding to enzyme. In view of the above restriction, it is of interest to study the metal-ion binding to captopril, since <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy offers a powerful tool to distinguish between the isomers [17].

In the present paper, we report the pH<sup>\*</sup> titration of captopril with Ag<sup>+</sup> by <sup>1</sup>H and <sup>13</sup>C NMR in solution, in an effort to identify which isomer is binding preferentially to Ag<sup>+</sup>. Solid-state <sup>13</sup>C spectra of the ligand and the complex were also recorded, to identify the nature of the complex in the absence of complications of *cis/trans* equilibria [17].

## 2. Experimental

### 2.1. Chemicals

The captopril was a gift from the Bristol–Myers Squibb Institute for Medical Research, Princeton, NJ. The 99.7% D<sub>2</sub>O, 36%

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