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

Anvarhusein A. Isab *, Mohamed I.M. Wazeer

Contribution from Department of Chemistry, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

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Abstract

Complexation of Ag^+ with captopril, 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline, has been studied by ^1H and ^{13}C-NMR spectroscopy. The equilibrium constants for the *trans* to *cis* isomers of captopril bound to Ag^+ were measured by ^1H NMR spectroscopy. It is observed that the *trans* isomer of the drug binds more strongly to Ag^+ between pH 5 and 8, as shown by the broadening of the *trans* isomer's resonances in ^{13}C NMR spectra on complexation. A monodentate complexation of the *trans* captopril with Ag^+ 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 *Heterotrotropic Plate Counts* (HPC), *Pseudomonas aeruginosa* and *Fecal streptococcus* bacteria.

Keywords: Captopril; Ag(I)–captopril complex; CP MAS of Ag(I)–captopril; Antimicrobial Activity

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^{2+} 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^{2+} 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 ^1H and ^{13}C NMR spectroscopy offers a powerful tool to distinguish between the isomers [17].

In the present paper, we report the pH* titration of captopril with Ag^+ by ^1H and ^{13}C NMR in solution, in an effort to identify which isomer is binding preferentially to Ag^+. Solid-state ^{13}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_2O, 36%

* Corresponding author. Tel.: +966 3 8602645; fax: +966 3 8604277.
E-mail addresses: aisab@kfupm.edu.sa (A.A. Isab), miwazeer@kfupm.edu.sa (M.I.M. Wazeer).

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