THE DIRECT EXPERIMENTAL EVIDENCE OF INTERMOLECULAR SALT-BRIDGE IN GASEOUS PROTONATED PEPTIDES

Shibdas Banerjee, Shyamalava Mazumdar*
Department of Chemical Sciences, Tata Institute of Fundamental Research, Homi Bhabha Road, Colaba, Mumbai 400005, India
shibchem@tifr.res.in

The elecetrospray ionization mass spectrometric (ESI-MS) investigation of a series of synthetic octapeptides containing six alanine and two lysine residues differing only by their positions showed that formation of intermolecular dimers of the peptide ions in the gaseous phase. We have investigated the nature of interaction between two monomers involved in the formation of such dimers. The dimer was found to be formed without loss of any small molecules (such as water). Decrease in polarity of the solution from water to alcohol showed enhanced propensity of formation of the dimer indicating that the electrostatic interaction plays a crucial role to stabilize the dimer. Chemical derivatizations like esterification of the carboxylic acid group or acylation of amine groups of all the peptides exhibited the collapse of dimer which indicated that these functional groups are responsible for the stability of the dimers. Furthermore selective functionalization studied showed that the ε-NH₂ (of lysine) and C-terminal carboxylic acid facilitate the dimerization through intermolecular hydrogen bonding/ salt bridge formation. To the best of our knowledge, this is the first report of detection of an intermolecular salt bridge between small peptide ions in gas phase by electrospray ionization mass spectrometry.
EFFECT OF HETERO CY CLIC THIOLS ELIMINATED DURING THE HYDROLYSIS OF CEPHALOSPORINS ON METALLO-β-LACTAMASE AND PEROXIDASE ACTIVITIES

A. Tamilselvi and Govindasamy Mugesh*
Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560 012, India.
atselvi@ipc.iisc.ernet.in

Hydrolysis of β-lactam antibiotics by β-lactamases is one of the major bacterial defense systems. The active site of β-lactamases includes a serine residue (serine-β-lactamases) or zinc ions (metallo-β-lactamases, mβl) and these enzymes have the ability to catalyze the hydrolysis of a variety of antibiotics including the latest generation of cephalosporins, cephemcyins and imipenem. [1,2] While the penicillin-based antibiotics can be hydrolyzed by both serine- and metallo-β-lactamases, the hydrolysis of cephalosporins by the metalloenzymes is somewhat more efficient than that of the serine-β-lactamases (Scheme 1).

In this poster, the effect of various side chains attached to the β-lactam moiety on the hydrolysis of some commonly used antibiotics by metallo-β-lactamase (mβl) from B. cereus will be described. It is observed that the cephalosporins having heterocyclic thiol side chains are more resistance to mβl-mediated hydrolysis than the antibiotics that do not have such side chains. This is partly due to the inhibition of enzyme activity by the thiol moieties eliminated during the hydrolysis. It is also observed that the heterocyclic side chains in pure form inhibit the β-lactamase activity of mβl as well as its synthetic mimic. The mode of binding of these heterocyclic side chains to zinc will also be:

Scheme 1

Figure 1
presented with the help of model complexes (Figure 1). [3,4] However, these thiones produced in the reactions effectively inhibit LPO-catalyzed iodination reactions, indicating that the hydrolysis of antibiotics having heterocyclic thiol side chains leads to the generation of antithyroid agents. [5] The inhibition of LPO-catalyzed iodination reaction by these thiones is found to be very similar to that of the commonly used antithyroid drug methimazole. These observations suggest that some of the latest generation of antibiotics may show negative effects on thyroid gland upon hydrolysis and an ideal side chain could be the one that irreversibly inhibits β-lactamase activity, but does not have any effect on peroxidase-catalyzed reactions.

References

Disulfiram is a well-known inhibitor of aldehyde dehydrogenase (ALDH). It has been used as a drug for the treatment of alcoholism for more than 50 years. In normal condition, alcohol is oxidized to aldehyde in liver by alcohol dehydrogenase (ADH). The aldehyde generated in this reaction is further oxidized to the corresponding carboxylic acid by ALDH. Disulfiram inhibits ALDH activity and stops the alcohol metabolism in the intermediate stage. [1,2] In the present study, a number of disulfiram analogues have been synthesized and studied for the inhibition of aldehyde dehydrogenase activity. Furthermore, we have studied the mechanistic pathway of inhibition of aldehyde dehydrogenase by these disulfiram analogues. As thiols have good affinity towards Zn(II) ion, these compounds may inhibit the ADH activity by binding to the active site Zn(II) of alcohol dehydrogenase (Figure 1A) [3] In view of this, we have carried out a detailed inhibition study of alcohol dehydrogenase by disulfiram and its analogues. This study suggests that, in addition to the inhibition of aldehyde dehydrogenase activity, disulfiram and its analogues inhibit alcohol dehydrogenase activity.
A closer look at the chemical structure of disulfiram and thiourea-based antithyroid drugs indicates the presence of similar thiourea pharmacophore. Therefore, we have studied the antithyroid activity of these disulfiram compounds by following the inhibition of LPO-catalyzed iodination of L-tyrosine. [4] This study suggests that the disulfiram and its analogues exhibit activity very similar to that of the commonly used antithyroid drugs.

References

P-033

SYNTHESIS, CHARACTERIZATION, DNA BINDING AND NUCLEASE ACTIVITY OF NICKEL(II) COMPLEXES OF THIOSEMICARBAZONES

P. MURALI KRISHNA and K. HUSSAIN REDDY

1Department of Chemistry, M. S Ramaiah Institute of Technology, Bangalore-560 054, India
2Department of Chemistry, Sri Krishnadevaraya University Anantapur-515003, India.
muralikp21@gmail.com

Nickel(II) complexes of thiosemicarbazones derived from cinnamaldehyde and substituted thiosemicarbazides NH$_2$NHC(S)NHR, where R = H, Me, Et, Ph have been synthesized and characterized by elemental analysis, conductivity measurements, magnetic moments, electronic, IR, $^1$H-NMR and crystallography. The spectral data suggested that all the nickel complexes are presumably have distorted square planar structure in solid state, but in coordinating solvents like DMSO, the complexes may assume octahedral structure due to the binding of solvent molecules to metal in axial position. Cyclic voltammetric studies indicate that quasi-reversible one electron electrochemical reduction (Ni$^{II}$ and Ni$^{III}$) in the potential regions -0.45 to -0.51V and -1.11 to -1.38 V against Ag/AgCl reference electrode. The DNA binding interactions of nickel(II) complexes with calf thymus DNA has been investigated using absorption spectrophotometry. The complexes on reactions with pUC18 plasmid DNA show nuclease activity.

References

UNIQUE O₂-ACTIVATION BY COPPER(I) COMPLEXES WITH N-ALKYLATED CIS,CIS-1,3,5-TRIAMINOCYCLOHEXANE LIGANDS

Jun Matsumoto, Yuji Kajita, and Hideki Masuda
Department of Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Showa-ku, Nagoya, 466-8555, Japan
chn13310@stn.nitech.ac.jp

Hemocyanin, tyrosinase, and catechol oxygenase contain two copper ions at their active centers, and react with dioxygen to form a μ-η²:η²-peroxodicopper complex as a reaction intermediate. Although many synthetic model compounds to these proteins have previously been synthesized and reported, the activation mechanism has not been clarified yet in detail. We have also reported that three copper(I) complexes with cis,cis-1,3,5-triaminocyclohexane derivatives react with dioxygen to form bis(μ-oxo)dicopper(III) complexes[1].

At this stage, we have prepared a novel copper(I) complex with \(N,N',N''\)-triisopropyl-cis,cis-1,3,5-triaminocyclohexane (iPr₃ TACH) ([Cu(MeCN)(iPr₃ TACH)]SbF₆ (1)). The crystal structure of 1 has been determined by X-ray structure analysis (Figure 1). The colorless acetone or THF solution of 1 reacted with dioxygen at -72 °C to give purple solution. Although it was stable at -72 °C, this species was decomposed at ambient temperature. The purple species gave the absorption bands at 361 and 527 nm which were assigned to \(\pi_\sigma^* \rightarrow d_{xy}\) and \(\sigma^* \rightarrow d_{xy}\) charge-transfer bands originating from the oxide to the Cu(II) in the (μ-η²:η²-peroxo)dicopper(II) species, respectively, they gave the \(v(\text{O}^{16}_\text{O}-\text{O}^{16}_\text{O})\) stretching vibration at 757 cm\(^{-1}\) (Δν = 42 cm\(^{-1}\)) by resonance Raman spectral measurement. It was ESR silent. Thus, this species was assigned to be a μ-η²:η²-peroxodicopper(II) complex \([\text{Cu}_2(\mu-\eta^2:\eta^2\text{-O}_2)(\text{iPr}_3\text{TACH})_2][\text{SbF}_6]_2\) (2). Compound 2 released \(\text{O}_2\) by Ar-bubbling for a short time at 0 °C to form complex 1, which was regenerated by \(\text{O}_2\)-bubbling at -72 °C (Scheme 1). In this presentation, we will discuss about the difference in \(\text{O}_2\)-activity by substituent effects on the basis of the results of crystal structures and electronic absorption and resonance Raman spectral measurements.
References