

## Synthesis and reactivity of platinum and palladium complexes with $\alpha$ -amino acids, peptides and derivatives thereof: platinum (II) as amino protecting group

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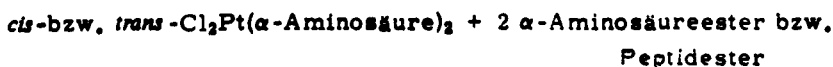
**Abstract** - Platinum(II) has been proven to be an effective amino protecting group of  $\alpha$ -amino acids. A series of reactions at the carboxylic group of N-coordinated  $\alpha$ -amino acids has been carried out to give platinum(II) complexes with peptide esters,  $\alpha$ -amino acid amides and anhydrides and very reactive  $\alpha$ -amino acid chlorides as ligands. Peptide synthesis at platinum(II) and removal of platinum(II) by hydrogenation with hydrogen proceeds practically without racemisation. Platinum(II) and palladium(II) complexes of derivatives of  $\alpha$ -amino acids have been prepared, containing Schiff bases, N-glycosides from monosaccharides and  $\alpha$ -amino acids, N-chloro amino acid esters, N-diphosphino, N-dithiocarboxy amino acids,  $\alpha$ -imino acids, the three functional ligands  $\alpha,\beta$ - and  $\gamma,\delta$ -dehydro amino acids and N-carboxy- $\alpha$ -dehydroamino acid anhydrides (Leuchs anhydrides). In *cis*-Cl<sub>2</sub>Pd(allylglycine) the  $\gamma,\delta$ -dehydro- $\alpha$ -amino acid is coordinated via the amino and C=C groups. Representatives of the new complexes have been characterized by crystal structure determination.

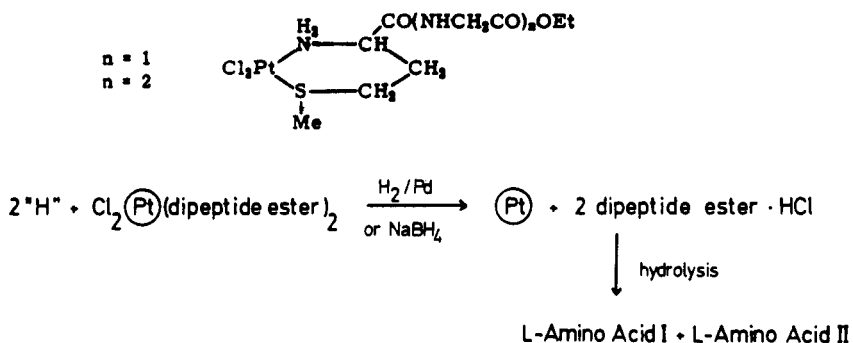
### INTRODUCTION

Platinum complexes of  $\alpha$ -amino acids are classic compounds and have been known for almost 100 years (ref.1); they have a long tradition in Russia. Extensive studies have been carried out particularly by Volshtein and his coworkers (ref.2). Our group in Munich (ref.3) has been interested in the synthesis and reactivity of metal complexes of  $\alpha$ -amino acids and peptides also with the idea that naturally occurring ligands might act as carrier ligands for the selective transport of antitumor active *cis*-platinum compounds. Active research on platinum and palladium complexes of  $\alpha$ -amino acids is going on in many groups (ref.4).

### PLATINUM AS AMINO PROTECTING GROUP

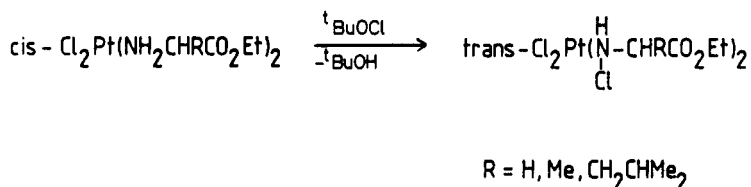
We have found that with complexes *cis*- and *trans*- Cl<sub>2</sub>Pt(NH<sub>2</sub>CHRCO<sub>2</sub>H)<sub>2</sub> (ref.1, 2,5) a series of reactions can be carried out at the free carboxyl group without cleavage of the platinum-nitrogen bond (ref.3). Due to the stable Pt-NH<sub>2</sub> bond platinum acts as an effective amino protecting group for peptide synthesis (ref.3,6). It is of great advantage to use a water soluble carbodiimide which makes the isolation of the dipeptide complexes *cis,trans*-X<sub>2</sub>Pt(peptide ester)<sub>2</sub> easy (ref.3h). Also some palladium(II) complexes which contain N-bound  $\alpha$ -amino acids with free carboxylic group have been similarly used (ref.6,7). Peptide synthesis at the platinum also has been carried out using platinum complexes of activated  $\alpha$ -amino acid esters (ref.3b). A similar method has been applied to link carrier molecules to *o*-catecholato platinum(II) complexes (ref.8) and for the synthesis of metal labeled antigens (ref.9). Removal of platinum(II) as amino protecting group in complexes Cl<sub>2</sub>Pt(peptide ester)<sub>2</sub> can be carried out most conveniently by reduction with hydrogen which gives the metal and the free peptide hydrochloride. Peptide synthesis at the metal and removal of Pt(II) proceed without racemisation (ref.3h).





Complexes of  $\alpha$ -amino acid, peptide esters (ref.3f,10a,11,12) and dipeptides (ref.13) also can be directly obtained from  $\text{PtCl}_4^{2-}$ . Due to the trans effect of the halide ligands usually the cis-platinum complexes  $\text{X}_2\text{Pt}(\text{NH}_2\text{CHRCO}_2\text{R}')_2$ ,  $\text{X}_2\text{Pt}(\text{peptide ester})_2$  are formed. From Pd(II) and  $\alpha$ -amino acid esters the trans-complexes  $\text{Cl}_2\text{Pd}(\alpha\text{-amino acid ester})_2$  have been obtained (ref.10,11). The IR,  $^{15}\text{N}$ - and  $^{195}\text{Pt}$ -NMR-spectra of several of these Pt(II)- and Pt(IV) complexes have been studied (ref.14,3g). A series of cis-platinum complexes described above with variation of the ester group (e.g. with monosaccharides, ref.3i) and the sequence of the peptide ligand has been tested for antitumor activity. Some of the complexes show high activity in in vitro tests but in vivo they are less active (ref.15). Using neutron activation analysis it could be shown that cis- $\text{Cl}_2\text{Pt}(\text{glyglyOEt})_2$  is accumulated in tumor cells of rats (ref.16). Several other platinum(II) complexes have been tested for antitumor activity (ref.17). Tert.-butylamine has been introduced in platinum(II) complexes of  $\alpha$ -amino acids in order to increase the liposolubility of the compounds (ref.18). Platinum complexes with diamino propionic acid ester (ref.19) and aminomalonate (ref.20) as ligands reveal antineoplastic activity.

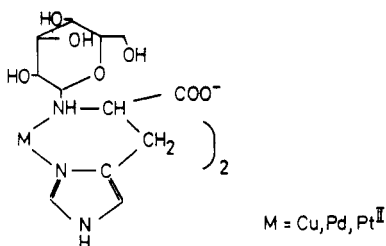
Platinum(II) proved to be a very strong amino protecting group. Even reactive  $\alpha$ -amino acid chlorides can be introduced as ligands (ref.3,7,21). Using t-butyl hypochlorite chlorination at the amino group occurs without cleavage of the platinum-nitrogen bond (ref.22).



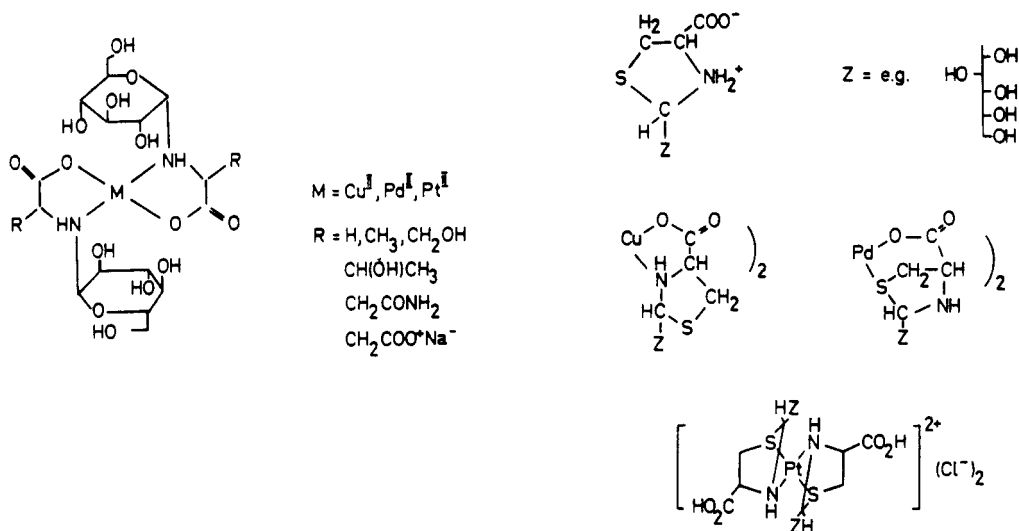
Reaction of  $\alpha$ -amino acidato complexes  $\text{Pt}(\text{NH}_2\text{CHRCOO})_2$  with nitrosyl salts leaves the amino group unaffected and gives blue nitrosyl complexes  $[(\text{ON})\text{Pt}(\text{NH}_2\text{CHRCOO})_2]^+\text{X}^-$  (ref.23), the XPS-spectra of which indicate Pt(III) species. Presumably they have a tetragonal pyramidal structure as has been found for the complex  $[\text{ONPt}(\text{C}_6\text{Cl}_5)_4]^-$  (ref.24).

#### Platinum(II) and palladium(II) complexes of derivatives and precursors of $\alpha$ -amino acids

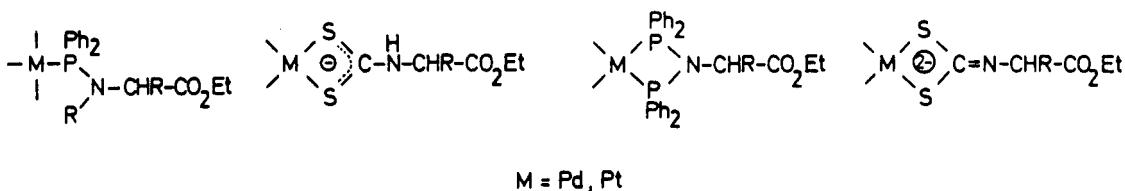
Various derivatives and precursors of  $\alpha$ -amino acids have been used as ligands. These include complexes of 1-amino-1-cyclopropane carboxylic acid (ref.25) and of various Schiff bases from  $\alpha$ -amino acids and amide acetals (ref.26). A contribution to the mechanism of the Akabori reaction has been made (ref.26). Condensation products from  $\alpha$ -amino acids and monosaccharides (N-glycosides) form a series of chelate complexes (ref.27).



More stable N-glycosides are the condensation products from cysteine and mono-saccharides. The thiazolidine ligands with polyhydroxy substituents may form chelate rings via the amino and carboxylate group, the carboxylate oxygen and sulfur atom or via the amino and thio group, respectively. The IR-spectra indicate the following bonding modes for Cu(II), Pd(II) and Pt(II) complexes (ref.27,28).

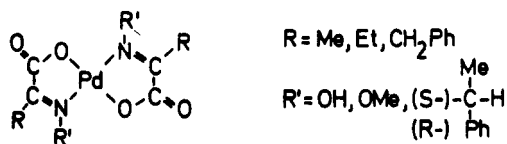
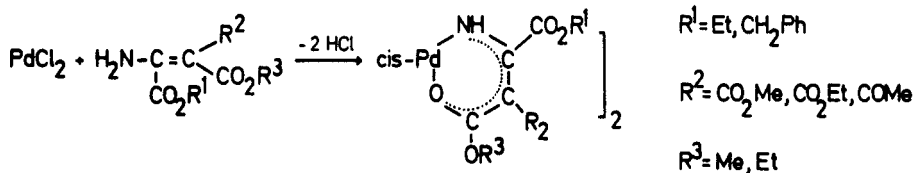
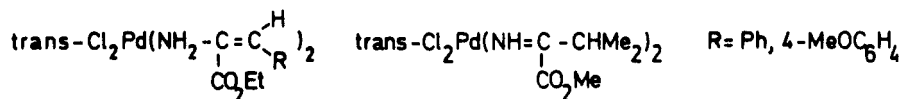


Stronger coordination compared to the amino group can be obtained by introduction of sulfur or phosphorus donor atoms. Thus metal complexes of phosphino amines (ref.29), dithiocarbamates (ref.30) and dithiocarbimates (ref. 31) with  $\alpha$ -amino acids as amine component have been prepared.

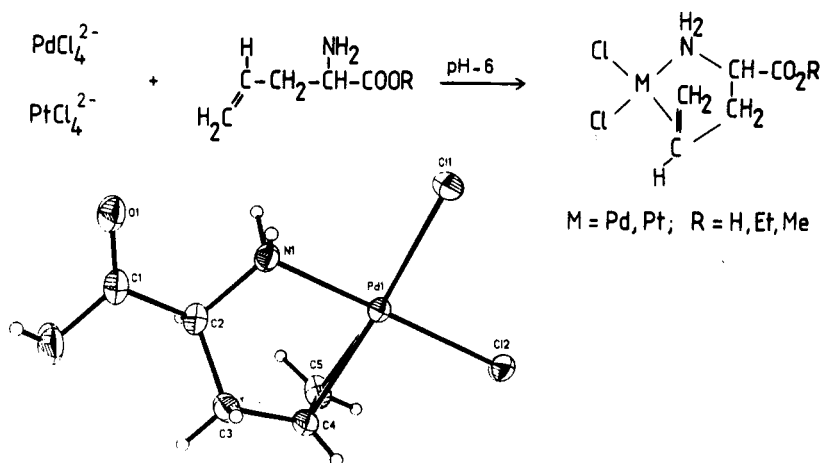


$\alpha, \beta$ -Dehydro- $\alpha$ -amino acids and  $\alpha$ -imino acids are important starting compounds for the asymmetric synthesis of  $\alpha$ -amino acids (ref.32). Palladium complexes with dehydro amino acids and  $\alpha$ -imino esters which coordinate through the nitrogen donor could be obtained (ref.22).

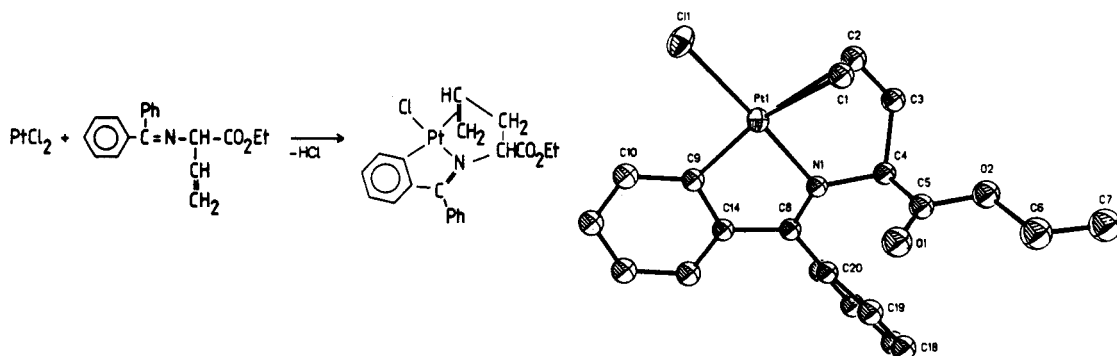
Dehydro amino acids which have two ester groups react with  $\text{PdCl}_2$  to give imino ketonato like chelate complexes; their structure has been confirmed by X-ray diffraction (ref.22).



The three-functional allylglycine coordinates to Pd(II) and Pt(II) via the amino group and the C=C- bond and forms a stable 5 1/2 membered chelate ring (ref.33). The C=C double bond lies almost perpendicular to the coordination plane as it is usual found for Pd(II) and Pt(II) alkene complexes.

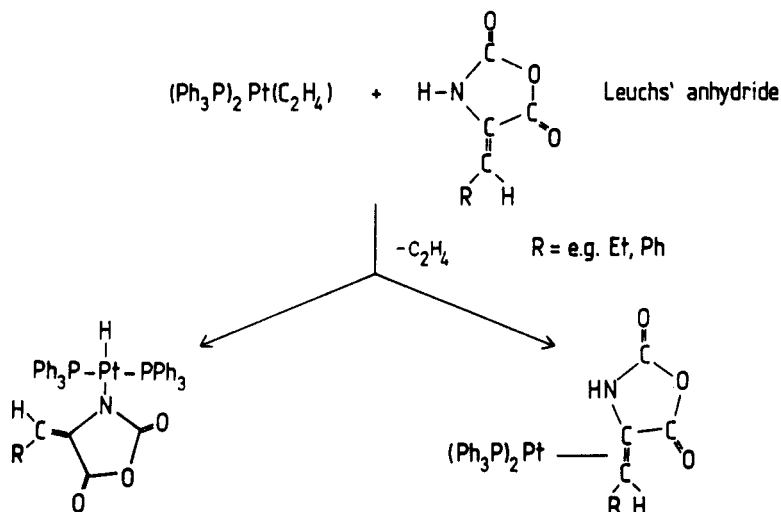


A similar structure has been found for the product of ortho metallation from  $\text{PtCl}_2$  and the Schiff base from allylglycine and diphenylketone (ref.33).



Several  $\alpha$ -amino acid complexes which contain a metal-carbon- $\sigma$ -bond have been reported (ref.34).

The reaction of unsaturated Leuchs anhydride to zerovalent platinum proceeds both by oxidative addition of the N-H group and coordination of the C=C-bond (ref.22).



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