Ultrasound Promoted *N*-Benzylation of Metal Glycinato Complexes

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The activation of the methylene group of metal complexed glycine has been utilized by Nakahara *et al.* [1] and Gillard *et al.* [2] in the formation of higher amino acids through alkylation with limited success; generally in only trace amounts.

In an attempt to reinvestigate this reaction, we have employed ultrasound irradiation which is known to enhance many reactions dramatically [3]. We hoped to form phenylalanine in the reaction of $[Cu(gly)]_2 \cdot H_2O$ with benzyl chloride under basic conditions in much improved yield. To our surprise, we isolated high yields of *N*-benzylglycine. We wish to report this result and other results obtained from reactions using different metal ions and substituted benzyl chlorides.

Experimental

Materials

Glycine, benzyl chloride, *p*-chlorobenzyl chloride and α-chloro-*p*-xylene were purchased from Aldrich Chemical Company. Dowex®-50W (50 X 2-100, H^+ form) cation exchange resin was obtained from Sigma Chemical Company, USA.

Preparation of Complexes

Metal glycinato complexes were prepared as previously described, $[Cu(gly)_2] \cdot H_2O$ [4a], $[Ni(gly)_2] \cdot 2H_2O$ [4b] and $[Co(gly)_3] \cdot 2H_2O$ [4c]. All the complexes gave satisfactory analytical and spectral data.

N-Benzylation of cis-Bis-glycinato Cu(II)·H_2O Complex

cis-Bis-glycinato Cu(II)·H_2O (0.06 g, 0.25 mmol) was dissolved in 10 ml 4:1 mixture of water and dimethyl sulphoxide and the pH was adjusted to 11.0 by adding a few drops of freshly prepared 10% sodium methoxide solution in water. To this solution benzyl chloride (0.31 g, 2.5 mmol) was added dropwise and sonicated for 2 h in a Cole Palmer Ultrasound Laboratory Cleaner (model 115 vac, 50/60 Hz) at 45 °C. The pH of 11.0 was maintained throughout by adding sodium methoxide solution.

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The reaction mixture was poured onto a Dowex®-50W column (2 X 20 cm) and washed with 50 ml of water. The amino acids were eluted from the column by washing it with 50 ml of 1 M ammonia. Evaporation of ammonia gave *N*-benzylglycine which was derivatized to its *O*-isopropyl *N*-TFA ester for gas chromatography [5]. Other reactions were carried out in a similar manner.

Gas Chromatography and Gas Chromatography–Mass Spectrometry

GC analyses were performed on a HP 5880A gas chromatograph under isothermal conditions (120 °C) using a 150 ft X 0.02 in stainless steel capillary column coated with a 1:1 mixture of *N*-docosanoyl-L-val-t-butyl amide and *N*-octadecanoyl-L-val-L-val-cyclohexyl ester [6]. The chiral column was employed to detect D- or L-phenylalanine which would result from C-benzylation. Nitrogen was used as the carrier gas.

GC–MS analyses were carried out on a LKB 2091 instrument using a 15 m OV-101 capillary column under split-mode injection. The mass spectrometer was operated at 70 eV in cyclic scan mode.

Results and Discussion

Percent yields of *N*-benzylglycine formed in the reaction employing the Ni(II), Co(III) and Cu(II) glycinato complexes with benzyl chloride are given in Table I. The percent yields reported are based upon the unreacted glycine that appeared in the chromatogram. These reactions were carried out for 2 h at 45 °C and pH 11.0 using ultrasound irradiation. Ultrasound eliminated the need for drastic heating conditions and reduced the extent of complex decomposition, thereby offering two advantages over conventional reactions. These advantages attracted the ultrasound applications in a variety of synthetic preparations with and without metal ions over the past few years [3]. After the reaction, the complex was decomposed by a Dowex®-50W cation

TABLE I. Preparation of *N*-Benzylglycine From Metal Glycinato Complexes by Ultrasound Irradiation[a]

Entry	Starting complex structure	% Yield of *N*-benzylglycine[b]
1	$[Ni(gly)_2] \cdot 2H_2O$	No reaction
2	$[Co(gly)_3] \cdot 2H_2O$	55
3	$[Cu(gly)_2] \cdot H_2O$	92

[a]For details see 'Experimental'. [b]Yield based on gas chromatography of the product mixture after derivatization.

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TABLE II. Preparation of N-substituted Benzylglycines from Cu(II) Glycinato Complex by Ultrasound Irradiation[a]

Entry	Starting complex structure	Starting $X-C_6H_4-CH_2Cl$	% Yield of $X-C_6H_6-CH_2-NH_2-CH_2-COOH$[b]
1	$[Cu(gly)_2]\cdot H_2O$	$C_6H_5CH_2Cl$	92
2	$[Cu(gly)_2]\cdot H_2O$	$(p)Cl-C_6H_4-CH_2Cl$	98
3	$[Cu(gly)_2]\cdot H_2O$	$(p)CH_3-C_6H_4-CH_2Cl$	5

[a]For details see 'Experimental'. [b]Yield based on gas chromatography of the product mixture after derivatization.

(H^+ form) exchange resin. The recovered amino acids were derivatized to their *O*-isopropyl and *N*-TFA esters for analysis by gas chromatography (GC) and GC–MS.

The $[Cu(gly)_2]\cdot H_2O$ complex reacted with benzyl chloride yielding *N*-benzylglycine in 92% yield, Table I. This alternate method of preparation is an improvement over the existing methods [7]. *N*-Benzyl glycine gave a single peak in the chromatogram which was eluted at 45.8 min. It was positively identified by comparing the gas chromatogram of an authentic sample of derivatized *N*-benzylglycine. The utilization of a chiral phase column also established that neither D- nor L-phenylalanine was formed in the reaction mixture. Gillard *et al.* [2] have reported that $[Co(en)_2(gly)]^{2+}$ reacted with benzyl bromide to give phenylalanine in 10% yield by paper chromatography. It was later realized that these authors [2] have indeed formed *N*-benzylglycine rather than phenylalanine as was determined by gas chromatography. Synthesis employing the Co(III) complex afforded a moderate yield of *N*-benzylglycine, while Ni(II) exhibited no reactivity under these experimental conditions, Table I. These results are consistent with those reported for Ni(II) ion reactivity toward racemization [8]. It is most likely that the nickel complex like the copper and cobalt complexes is stable at 45 °C.

Results obtained from the reactions of $[Cu(gly)_2]\cdot H_2O$ with the substituted *N*-benzyl chlorides are shown in Table II. The Cu(II) complexed glycine reacted with *p*-chlorobenzyl chloride nearly quantitatively to yield the corresponding *N*-*p*-chlorobenzylglycine. On the other hand, the electron donating *p*-methyl group substantially retarded the formation of N-substituted glycine, suggesting that this reaction proceeds through the SN^2 mechanism and no carbocation is formed.

The positive identification of the products was accomplished either by comparison of GC retention data with those of authentic samples or by interpretation of their characteristic mass spectral data. Further studies are in progress to establish the generality of this reaction.

In conclusion, the method described here provides a simple alternative to prepare *N*-arylmethylglycines in high yields. This study also offers additional evidence to the fact that the initial attack of RX occurs through an SN^2 mechanism at the NH_2 group of the ligand [9]. It also further establishes the unique unreactive character of the nickel complexes.

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