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Stereoselective electrochemical thioalkylation of glycine in Ni(II) coordination environment

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ABSTRACT

One-pot method for direct stereoselective (S)-α-thioalkylation of glycine in Ni(II) coordination environment was elaborated. The reaction of electrochemically deprotonated Ni(II) glycine/Schiff-base complex containing (S)-o-[N-(N′-benzylprolyl)amino]benzophenone as an auxiliary chiral moiety with alkyl thiocyanates leads to the α-thioalkylated derivatives in a practical ca.70% chemical yield and stereoselectivity (de 80%).

Introduction

Targeted electrochemical activation of the certain reaction sites in the reactants is a powerful tool which allows significantly broadening the scope of chemical transformations available [1]. This approach is in line with the modern sustainable chemistry requirements and, nowadays, it is becoming popular among synthetic community. To implement this approach, redox active compounds are necessary. Transition metal complexes which are redox active both in anodic and cathodic area are good candidates for this type of chemical transformations. Performing electrochemically induced reactions in metal complexes with chiral ligands creating an efficient asymmetric environment around the metal center allows combination of the benefits of electrochemical activation with common methods of chirality induction in homogeneous reactions.

Metal complexes with asymmetric coordination environment are widely used for various types of stereoselective synthesis (see, e.g., review [2]). The rational design of a metal coordination environment based on the non-covalent secondary interactions between a metal center and chiral ligand affords high level of stereoinduction.

Square-planar Ni(II) complexes with the ligands of a Schiff base type containing (S)-o-[N-(*N*-benzylprolyl)amino]benzophenone [(*S*)-BPB] as an auxiliary chiral moiety are convenient objects for performing stereoselective reactions with amino acids coordinated to Ni(II) center. These complexes are known since 1980s[3]; they are stable, operationally simple and can be easily disassembled using HCl in methanol releasing a functionalized enantiopure amino acid; the chiral auxiliary (S)-BPB can be almost quantitatively recovered [3], in line with chiral economy strategy. A lot of research has been already performed with these complexes (for review, see [4–8]), but electrochemical activation has been applied to these compounds only in our recent publications [9–12] and turned out to be highly efficient. We have demonstrated that varying the type of electrochemical activation (anodic vs. cathodic vs. application of electrogenerated base), it turns possible to activate different redox-active sites in the coordination environment of the metal center, giving rise to various targeted regio- and stereo selective modifications of the amino acid moiety yielding different types of functionalized mono- and binuclear Ni(II) complexes [9–11].

The present paper is the further development of this research. It is aimed at the elaboration of the practical electrochemical method for stereoselective thioalkylation of glycine in the Ni(II) coordination environment. To the best of our knowledge, direct insertion of a sulfur-containing fragment in the α-position of amino acids has not been elaborated yet whereas β-thioalkylated complexes

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have been reported [13]. To form reactive nucleophilic species, the starting Ni(II) Schiff base glycine complex with (*S*)-o-[N-(*N*-benzylprolyl)amino]benzophenone (**Gly-Ni**, see Scheme 1) was subjected to electrochemical deprotonation and was further involved in the reaction with alkyl thiocyanate.

Organic thiocyanates are interesting objects for performing reactions with nucleophiles. They can be applied as sulfur transfer reagents in organic transformations [14,15]. Electrochemical investigation of these compounds showed that the nucleophilic attack can be performed at different centers [16] resulting in the R-S or S-CN bond cleavage, as dependent on the type of the substituent and reaction conditions. For benzyl thiocyanate, regioselective reductive S-CN bond cleavage was observed [16]. Consequently, one can expect that it can be used as a thiolating agent for the stereoselective insertion of the RS- moiety at the α- glycine carbon atom in Ni(II) coordination environment.

Novel Schiff-base Ni(II) complexes obtained will be of interest as the starting materials for further oxidative modification of the thioalkyl moiety leading to precursors for the practically important optically pure sulfur-containing amino acids as well as their derivatives.

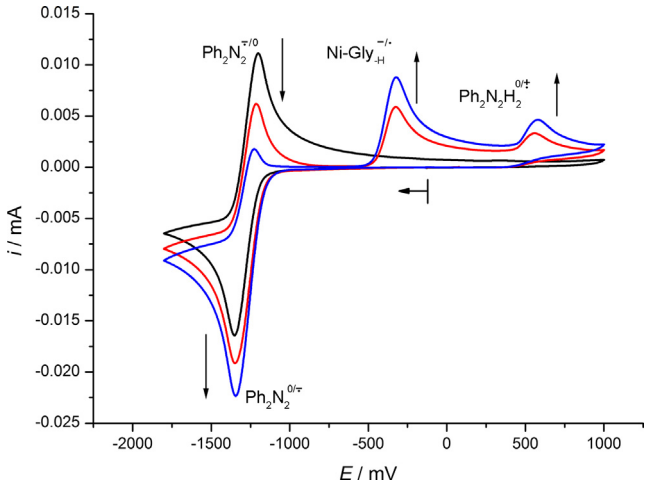
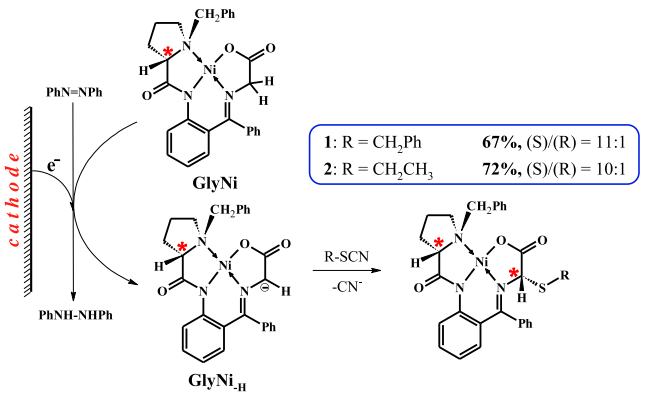


Fig. 1. CV monitoring of the **Gly-Ni** deprotonation with azobenzene (10 mM) radical anion in DMF at various **Gly-Ni**/Ph_2N_2 ratio. Black curve–Ph_2N_2 solution without **Gly-Ni** additive; red curve – 0.8: 1 **Gly-Ni**/Ph_2N_2 molar ratio; blue curve – 1.5:1 **Gly-Ni**/Ph_2N_2 molar ratio (100 mV/s, Pt, DMF, 0.05 M Bu_4NBF_4, vs. Ag/AgCl, $KCl_{(sat.)}$).

Results and discussion

In order to activate the starting **Gly-Ni** complex, it was deprotonated using electrochemically generated base - azobenzene radical-anion which was formed at the potential of −1.35 V (peak potential, vs. Ag/AgCl, $KCl_{(sat.)}$). Electrochemical approach instead of application of common bases was chosen since it ensured a precise control on concentration of a base [17,18] and its *in situ* reaction with the complex leading to the quantitative deprotonation of the latter. An excess of the base can be easily eliminated via electrochemical oxidation; thus, further epimerization of the enantiomers formed [19] can be avoided.

Preparative **Gly-Ni** deprotonation was carried out in dimethylformamide in a two-compartment cell at the potential of −1.40 V (which is more positive than the potential of **Gly-Ni** reduction but is sufficient for efficient production of $Ph_2N_2^{0/-}$ redox couple) using glassy carbon plate as a working electrode and a Fe wire as a counter electrode. **Ni-Gly-$_H$** formation can be monitored using voltammetry (by detecting the characteristic oxidation peak, −0.32 V vs. Ag/AgCl, $KCl_{(sat.)}$, Fig. 1) and spectroelectrochemical method (UV/Vis, λ=458 nm). As it is clearly seen from Fig. 1, gradual addition of **Gly-Ni** to the azobenzene solution results in decrease in the reverse peak corresponding to oxidation of azobenzene radical anions. At **Gly-Ni**/Ph_2N_2 = 1:1 M ratio, it disappears almost completely indicating that all azobenzene radical anions produced in the electrode vicinity are consumed for deprotonation of the starting complex. Simultaneously, an oxidation peak corresponding to the deprotonated **Ni-Gly-$_H$** complex appears in the voltammogram and is gradually increased until equimolar **Gly-Ni**/Ph_2N_2 ratio in solution is achieved. In the bulk experiments, the orange solution of the starting complex became almost black after passing the ca.1.2 M equivalents of charge. The electrolysis was stopped when the further increase in the amount of the electricity passed did not lead to the enhancement of the peak current corresponding to **Ni-Gly-$_H$**. To eliminate the small excess of the base (if present), the potential of the working electrode was switched to -1 V and bulk potentiostatic electrolysis was performed until all Ph_2N_2 radical anions were reoxidized. The peak current corresponding to **Ni-Gly-$_H$** stayed constant indicating that concentration of **Ni-Gly-$_H$** in solution was not changed. The obtained solution of the quantitatively deprotonated **Gly-Ni** was subjected to the reaction with the electrophile.



Scheme 1.

An equimolar amount of benzyl thiocyanate was added to the solution of **GlyNi** after its complete deprotonation. The color of solution gradually changed from black to reddish-orange indicating formation of the neutral complex. The reaction between **Ni-Gly-$_H$** and alkyl thiocyanate can occur as a single electron transfer (SET) process or via nucleophilic attack at the carbon or sulfur atom. To choose between these two options, the reduction potential for benzyl thiocyanate was measured in the conditions of **Ni-Gly-$_H$** formation. Though the value obtained (−2.18 V, Pt, acetonitrile, vs. Ag/AgCl/KCl) might be somewhat different from the standard potential for $PhCH_2SCN$ reduction (electron transfer is followed by S-CN bond cleavage [16]), the electrochemical potential gap between **Ni-Gly-$_H$** oxidation and $PhCH_2SCN$ reduction is too broad (1.80 V) for an outer sphere electron transfer to occur. Thus, nucleophilic attack seems to be preferential.

The reaction product **1** was isolated using column chromatography. HRMS data showed intensive $M+H^+$ (620.1510) and $M+Na^+$ (642.1337) peaks indicating that $PhCH_2S$ fragment was inserted in the **Ni-Gly-$_H$** complex. The structure of the product **1** was confirmed by ^1H and ^{13}C NMR (see SI).

The methyne proton of the α-amino acid fragment appears as a singlet at 4.31 ppm. Comparison with the chemical shift of the α-methyne proton in the similar Schiff-base Ni(II) complex formed of (*S*)-alanine (3.85 ppm, [20]) indicates that electron-withdrawing group in the new S-containing complex is bound to the α- amino acid carbon. A singlet type of the signal evidences for an absence