Sulphonamide Nitrogen-containing N-Protected Amino Acids interacting with Palladium(II). Polarographic and pH-Metric Investigation in Aqueous Solution

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The interaction of *N*-benzenesulphonyl-, *N*-tosyl-, and *N*-dansyl-glycine (dansyl = 5-dimethylaminonaphthalene-1-sulphonyl) with Pd^{II} in aqueous solution was investigated by electrochemical methods. In the pH range 4—11.5 all ligands give rise to the species [Pd(LNO)] and $[Pd(LNO)_2]^{2-}$ (LNO = amino acid dianion). The latter was found to prevail at high pH values, where *N*-dansylglycine, in addition, forms the mixed hydroxo species $[Pd(LNO)(OH)]^-$. These complexes are more stable than the corresponding ones formed by Cu^{II} and Cd^{II}. Palladium(II) is more effective than Cu^{II} and Cd^{II} in promoting amide-nitrogen deprotonation in this class of ligands, as previously observed with peptides.

Transition-metal ions such as Cu^{II}, Pd^{II}, Ni^{II}, Co^{II}, and Zn^{II} are effective in substituting for a peptide hydrogen in oligopeptides and related ligands.[1] In particular, Pd^{II} shows the strongest lowering effect on the pK_a for peptide nitrogen deprotonation and the highest stability constants for the corresponding complexes.[1] Such a metal-promoted deprotonation was not observed for amino acids N-substituted by an RCO group (R = alkyl or aryl group),[2] while it does occur if the N-substituent is an RSO_2 group, with Cd^{II},[3] Cu^{II},[4,5] and Pd^{II},[1] being the only effective metal ions. This peculiar ability of the N–RSO_2 amino acids can be attributed to the more acidic character of the sulphonamide-nitrogen bound hydrogen as compared to the peptide hydrogen of the N–RCO amino acids. The carboxylate group plays a key role in the process acting as a primary binding group ('anchoring group') and decreasing the competition from the metal hydroxide precipitation. Thus, once the metal-promoted nitrogen deprotonation has occurred, these ligands act as bidentate through the deprotonated sulphonamide nitrogen and the carboxylate group. Some preliminary reports[1] and some recent data[6] indicate that also in this case Pd^{II} is the most effective metal ion in substituting for the amide hydrogen. In this paper we report a detailed polarographic investigation of palladium(II)–N–RSO_2-substituted glycine systems with the aim of characterizing the type and stability constants of the complexes, and comparing the results previously obtained with Cu^{II} and Cd^{II}.

Experimental

N-Dansylglycine (dnsgly) (dansyl = 5-dimethylaminonaphthalene-1-sulphonyl) (Sigma), *N*-tosylglycine (tsgly), and *N*-benzenesulphonylglycine (bsgly) were twice recrystallized before use. Doubly distilled water was used throughout. Due to the slow hydrolysis of Pd^{II} at pH $\geqslant 1$, the use of soluble complexes, especially $[PdCl_4]^{2-}$ and $PdCl_2$, as metal-ion source is a commonly adopted procedure.[7] However, the resulting stability constants are conditional constants referring to the ligand exchange, and since they depend on the way the mixed complexes (formed due to the presence of two kinds of ligands) are handled, the values obtained by different authors are often scarcely in agreement.[7] In order to avoid this problem we have studied the systems by dissolving in aqueous solution the solid complexes $Na_2[Pd(LNO)_2]$ (LNO = dianion of amino acid). These complexes were obtained by adding solid $Pd(NO_3)_2 \cdot 2H_2O$ (Fluka) to a water–methanol (4:1, v/v) solution of the ligand (M/L = 1:4) at pH 11 with rapid stirring. The pH dropped to 3.5 and it was corrected to 6 for tsgly and bsgly and to 12 for dnsgly with concentrated NaOH. After a few days at room temperature crystalline compounds separated. Aqueous solutions for the polarographic analysis were prepared by dissolving the solid complexes $Na_2[Pd(LNO)_2]$ up to 5×10^{-4} mol dm^{-3} Pd^{II} and by adding ligand in order to obtain ligand-to-metal ratios in the range 2:1—20:1.

The polarographic measurements were carried out in the pH range 11.5—3.5 by adding small amounts of concentrated aqueous $HClO_4$ (72%) to the starting basic solutions. Below pH 3.5 a slow chemical reduction of Pd^{II} by Hg was detected and this prevents any quantitative analysis. Sodium perchlorate was used as base electrolyte and the ionic strength was kept constant (I = 0.1 mol dm^{-3}). The pH measurements were performed with an Amel-337 pH meter using an Ingold HA 405-60-K1 pH-combined electrode. Polarographic measurements were carried out with an Amel Multipolarograph 472 at 25 ± 0.1 °C. A dropping mercury electrode (d.m.e.) and a 'Norbide' boron carbide electrode[8] were used as working electrodes. A saturated calomel electrode (s.c.e.) was used as a reference and all the $E_{\frac{1}{2}}$ values are referred to it. The counter electrode was a platinum sheet. In order to characterize the electron-transfer process, concentrations of Pd^{II} ranging from 10^{-4} to 5×10^{-4} mol dm^{-3} and dropping times of 1, 2, 3, and 4 s were used. The reversibility of the processes was determined from semilogarithmic analysis of the polarographic waves. The dependence of the limiting current on the dropping time and the depolarizer concentration shows the diffusive nature of the processes. The number of electrons involved in the reduction of the complexes was determined by means of the Ilkovic equation.[9] Potentiometric measurements were performed at 25 ± 0.1 °C with the fully automatic Orion 960 Autochemistry system using a Ross 81028c combined electrode. Carbonate-free sodium hydroxide (Carlo Erba) standardized against phthalate was used as titrant. All the experiments were carried out under a nitrogen atmosphere and the ionic strength was kept constant at 0.1 mol dm^{-3} with $NaClO_4$. The solutions were prepared by dissolving the complex and adding stoicheiometric amounts of $HClO_4$ in order to neutralize the ligand.

Results and Discussion

The palladium(II)–N–RSO_2-substituted glycine systems exhibit closely similar polarographic behaviour. Only one quasi-reversible, two-electron, diffusion-controlled reduction wave is

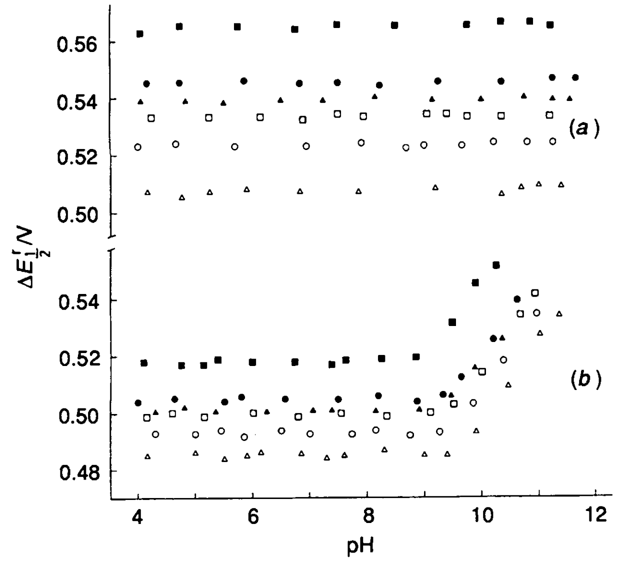


Figure 1. Plots of $\Delta E^{r}_{\frac{1}{2}}$ *vs.* pH at various ligand (L) concentrations: (*a*) tosylglycine; (*b*) dansylglycine. $c_{Pd^{2+}} = 5 \times 10^{-4}$; $c_L = 10^{-3}$ (△), 2×10^{-3} (○), 3×10^{-3} (□), 4×10^{-3} (▲), 5×10^{-3} (●), and 10^{-2} mol dm^{-3} (■). $\Delta E^{r}_{\frac{1}{2}} = (E^{r}_{\frac{1}{2}})_M - (E^{r}_{\frac{1}{2}})_C$, where $(E^{r}_{\frac{1}{2}})_M$ is the reversible half-wave potential of the uncomplexed metal ion and $(E^{r}_{\frac{1}{2}})_C$ that of the complexed metal ion. Benzenesulphonylglycine and tosylglycine show a qualitatively similar behaviour (the reduction potentials at different pH and ligand concentration given by bsgly are invariably about 30 mV more negative than the corresponding values for tsgly): hence, the data for the former ligand are omitted for the sake of clarity

Table. Values * of log β for complexes prevailing in aqueous solution

Complex	bsgly	tsgly	dnsgly
[Pd(LNO)]	18.9	17.8	17.8
$[Pd(LNO)_2]^{2-}$	24.4	23.4	21.8
$[Pd(LNO)(OH)]^-$	—	—	21.6

* β is the overall stability constant.

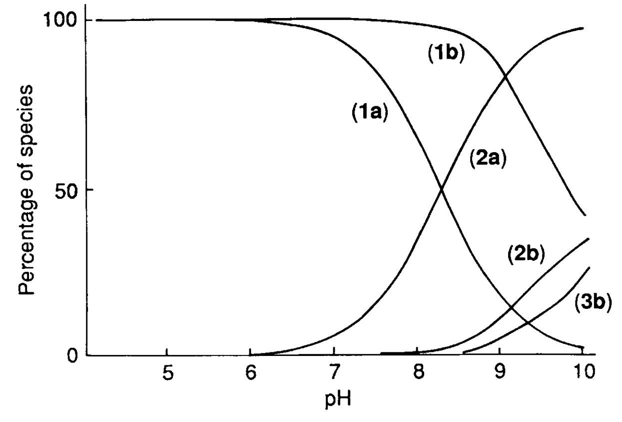


Figure 2. Species distribution curves for Pd^{II}–L systems: (**a**) tosylglycine; (**b**) dansylglycine. Metal-to-ligand ratio 1:4. Benzenesulphonylglycine gives a set of curves superimposable on those of tosylglycine. The curves were obtained with the DISPO program (M. Micheloni, personal communication). Species: (**1**) [Pd(LNO)]; (**2**) $[Pd(LNO)_2]^{2-}$; (**3**) $[Pd(LNO)(OH)]^-$

observed between pH 4 and 11.5 (Figure 1). With increasing ligand concentration, the half-wave potential ($E_{\frac{1}{2}}$) shifts toward more negative values but the diffusion current (i_d) remains nearly constant. The $E_{\frac{1}{2}}$ and i_d values are pH independent, except for the Pd^{II}-dngly system at pH ⩾ 9.6 for which the $E_{\frac{1}{2}}$ value decreases with increasing pH, indicating the formation of mixed hydroxy complexes. A new wave at more positive $E_{\frac{1}{2}}$ values, irreversible and pH-dependent, appears for all systems below pH 4. Its i_d value decreases with time and the wave completely disappears after about 5 h. The concomitant decrease in the intensity of the electronic spectrum ($\lambda_{max.}$ = 355 nm) and the separation of metallic Pd in the electrochemical cell indicate that a chemical reduction of Pd^{II} by the metallic Hg of the electrode takes place under these conditions. The above wave could be attributed to the reduction of the carboxylate complexes (the pH dependence also suggests the presence of mixed hydroxy complexes), but such a chemical reduction prevents any quantitative analysis. As a consequence, we have studied the systems in the pH range 4—11.5, where the ligands act as N, O bidentate dianions, as confirmed by the *X*-ray structure of the complexes obtained in this pH range.[6] The reversible half-wave potentials ($E^{r}_{\frac{1}{2}}$) were determined with the Matsuda–Ayabe procedure[10] and the overall stability constants (β) with the DeFord–Hume equation.[9] The $E^{r}_{\frac{1}{2}}$ of the Pd^{II} on the mercury electrode required by the latter equation cannot be determined directly by polarographic measurements since the reduction wave of the Pd^{II} is masked by the current due to the oxidation of mercury. Therefore we have indirectly evaluated the $E^{r}_{\frac{1}{2}}$ value by assuming that the difference in $E^{r}_{\frac{1}{2}}$ determined with a d.m.e. and with a Norbide electrode, due to the formation of an amalgam with the former, is the same as that evaluated for Cu^{II} and Cd^{II}.[8] The calculated $E^{r}_{\frac{1}{2}}$ value for Pd^{II} on the mercury electrode is +0.430 V *vs.* s.c.e. The Norbide electrode was not used to study the present systems due to the difficulty in obtaining a good data reproducibility.[8] All ligands give rise to the complexes [Pd(LNO)] and $[Pd(LNO)_2]^{2-}$. In addition, the Shaap–McMaster method[9] applied to the Pd^{II}–dnsgly system reveals the presence of the species $[Pd(dnsglyNO)(OH)]^-$ at pH ⩾ 9.6. The overall stability constants are reported in the Table and the species distribution curves in Figure 2. For all ligands the co-ordination number is pH-dependent: the binding of one and two chelating molecules is favoured at low and high pH, respectively. With *N*-dansylglycine, as previously observed for Cu^{II}[4] and Cd^{II},[3a] the co-ordination of only one ligand molecule is favoured. The co-ordination of two *N*-dansylglycinate dianions prevails only at high ligand-to-metal ratios (⩾ 8:1). This behaviour and the concomitant smaller stability of the $[Pd(dnsglyNO)_2]^{2-}$ species as compared to those of the other ligands can be ascribed to the steric hindrance of the bulky naphthalene side chain; such a lower stability of the bis(chelate) complexes justifies the presence of the mixed hydroxo species $[Pd(dnsglyNO)(OH)]^-$ at high pH, not observed for the other ligands. The greater stability of the complexes given by bsgly as compared to those formed by tsgly may be due to a greater strength of the inter- and intramolecular hydrophobic interactions involving the aromatic rings in the former species due to the presence of unsubstituted phenyl rings. This is supported by the *X*-ray structures of $Na_2[Pd(bsglyNO)_2]\cdot H_2O$[6b] and $Na_2[Pd(tsglyNO)_2]$[6a] which show in the former case a more extended and stronger network of hydrophobic interactions. The potentiometric titration curves for the Pd–tsgly system are reported in Figure 3. For all ligands only one titration step is observed. In particular, for tsgly and bsgly the end-point is reached by adding an amount of NaOH corresponding to equation (1), while dnsgly, up to ligand-to-metal ratios of 4:1, closely follows equation (2) (*m* = number of moles). These

$$m_{NaOH} = m_L + 2m_{Pd} \qquad (1)$$

$$m_{NaOH} = m_L + m_{Pd} \qquad (2)$$

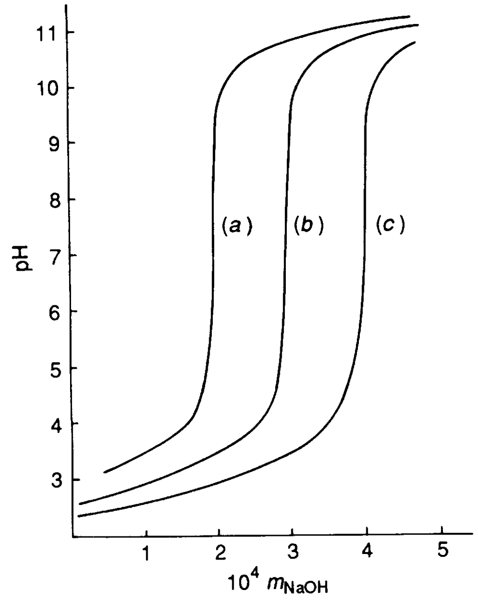
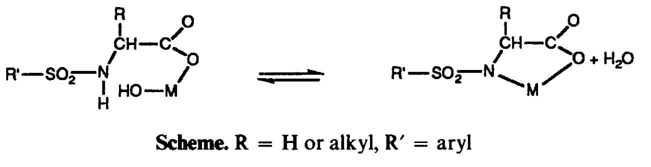


Figure 3. Neutralization curves for tosylglycine in the presence of Pd^{2+} in aqueous solution ($m_{tsgly} = 0.196 \times 10^{-3}$): $m_{Pd^{2+}} = 0$, (*a*) 0.052×10^{-3} (*b*) or 0.0981×10^{-3} (*c*) where m = number of moles



Scheme. R = H or alkyl, R′ = aryl

behaviours are in full agreement with the above polarographic findings regarding the co-ordination number of the species formed by these ligands. Moreover, these titration curves indicate that the pK_a for amide-nitrogen deprotonation is lower than 4, as also shown by the polarographic data. This pK_a is at least four units lower than that observed for Cu^{II} and Cd^{II},[3a,4] and confirms that Pd^{II} is the most effective metal ion not only in promoting peptide-nitrogen deprotonation but also in displacing the nitrogen-bound hydrogen in amino acids N-protected by a sulphonic group. While the difference between the pK_{NH} values induced by Pd^{II} and Cu^{II} in peptides and related ligands is about two units (p$K_{NH} \approx 2$ *vs.* ≈ 4, respectively), such a difference is greatly increased for the present class of ligands (p$K_{NH} \leqslant 4$ *vs.* ≈ 8, respectively). This effect can be attributed to the peculiar ability of Pd^{II} to interact with the aromatic ring[7a] and the S atom of the ligands. Such interactions have been recently observed in the *X*-ray structures of $Na_2[Pd(tsglyNO)_2]$[6a] and $Na_2[Pd(bsglyNO)_2]\cdot H_2O$.[6b] The polarographic stability constants for metal complexes of RSO_2 amino acids follow the order Pd $\gg$ Cu > Cd, as observed for oligopeptides.[1] The experimental evidence that Cd^{II}, Cu^{II} and, possibly, Pd^{II} give rise to mixed hydroxy carboxylate complexes at low pH values suggests that the OH^- ion bound to the metal may act as a Lewis base towards the nitrogen-bound hydrogen in the metal-induced sulphonamide deprotonation (Scheme). We can suggest that the metal ions that are effective in sulphonamide deprotonation are those that form hydroxo species, $[M(OH)]^+$, at low pH (Pd^{II}, and Cu^{II})[11], or undergo metal hydroxide precipitation at high pH (Cd^{II}) so that the metal substitution for the sulphonamide hydrogen *via* the metal-bound hydroxy group may occur without competition from the metal hydroxide precipitation.

Acknowledgements

This work was supported by a grant from the Consiglio Nazionale delle Ricerche (CNR), Rome, and from the Ministero dell' Universita e della Ricerca Scientifica, Rome.

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Received 19*th September* 1989; *Paper* 9/04002A