

PENICILLAMINE DISULFIDE (PNS) AND ALKALINE CATIONS

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Summary – *D*-penicillamine disulfide (PNS) shows protolytic properties and is able to form complexes with cations, because it has two aminic groups and two carboxylic groups. The four protonation constants of its deprotonated species were determined by means of electromotive force (e.m.f.) measurements of a galvanic cell involving a glass electrode at 25°C and in a constant ionic medium constituted by $\text{N}(\text{CH}_3)_4\text{Cl}$ 3.00 or 1.00 mol dm⁻³. At 25°C and in 3.00 mol dm⁻³ $\text{N}(\text{CH}_3)_4\text{Cl}$ as ionic medium, equilibria taking place between PNS and lithium, sodium and potassium ions were investigated. Experimental data, again obtained from e.m.f. measurements, were explained by assuming the formation of species of the type MH_2PNS ed $\text{M}_2\text{H}_2\text{PNS}$, where M indicates a cation. Stability constants for each proposed species were calculated. A comparison with cystine is discussed.

Riassunto – Il *D*-disolfuro di penicillamina (PNS) essendo un composto che possiede due gruppi amminici e due carbossilici mostra proprietà protolitiche e capacità di formare complessi con i cationi metallici. Mediante misure di forza elettromotrice (f.e.m.) di una cella galvanica con l'uso di elettrodo di vetro, sono state determinate le quattro costanti di protonazione della specie completamente deprotonata a 25°C ed in mezzo ionico costante costituito da $\text{N}(\text{CH}_3)_4\text{Cl}$ 3,00 e 1,00 mol dm⁻³. In mezzo ionico costituito da $\text{N}(\text{CH}_3)_4\text{Cl}$ 3,00 mol dm⁻³ ed a 25°C, sono stati studiati gli equilibri che hanno luogo tra PNS e ioni litio, sodio e potassio. I dati sperimentali ottenuti anche questa volta da misure di f.e.m. sono stati spiegati assumendo la formazione di specie del tipo MH_2PNS ed $\text{M}_2\text{H}_2\text{PNS}$, in cui M indica un catione alcalino. Per ogni specie proposta sono state calcolate le costanti di stabilità. È stato effettuato un confronto con il comportamento della cistina.

INTRODUCTION

The behaviour of aminoacids as ligands of cations has long been a subject of investigation by many researchers.¹⁻³ Most of them studied the more common aminoacids, including those containing more aminic and carboxylic groups.

On the contrary, aminoacids containing sulphur received little attention, probably for their low stability in light and air. Furthermore, some of them have slight solubility in water.

Among aminoacids containing S, cysteine was accurately studied as ligand of cadmium (II) by electromotive force measurements (e.m.f.) carried out by means of glass and cadmium amalgam electrodes and polarographic measurements, DP50 polarography.⁴

In spite of its slight solubility in aqueous solution, cystine was studied both to determine its protonation constants⁵ and to evaluate its ability to bind cations of alkaline metals, i.e. lithium, sodium and potassium.⁶

D-penicillamine disulfide (PNS) is a compound similar to cystine and its behaviour as ligand of cations has been very little studied. Also the protolytic properties are not exhaustively studied.

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The structural formula of PNS is represented in Fig. 1, in the form H_2L ($C_{10}H_{20}O_4N_2S_2$).

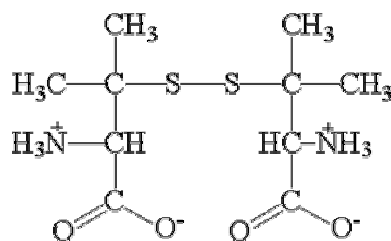


Fig. 1 - The structural formula of D – Penicillamine disulfide.

In 1995, Berthon⁷, by commenting upon research performed on amino acids containing S atoms, believed that the attempts for the determination of the protonation constants of cystine were few for its low solubility. In the same report, nothing is reported about PNS.

Only two papers proposed values for the four protonation constants of PNS.

S.H. Laurie et al.⁸ determined these constants at 25°C and in 0.15 mol dm⁻³ LiCl or NaCl from e.m.f. measurements carried out by means of a glass electrode for hydrogen ion and proposed the values $\log k_1 = 8.72$; $\log k_2 = 7.77$; $\log k_3 = 1.98$ and $\log k_4 = 1.01$.

In 1988, K. Varnagy et al.⁹ studied the protonation of PNS at 25°C and in 0.20 mol dm⁻³ KCl, and its complex formation with cobalt (II), copper (II), nickel (II) and zinc (II) by using the same method of S.H. Laurie et al. These authors proposed the following protonation constants: $\log k_1 = 8.75$; $\log k_2 = 7.76$; $\log k_3 = 2.09$ and $\log k_4 = 1.54$.

Among the literature data, a remarkable difference can be observed for the values of the protonation constants in particular for $\log k_3$ and $\log k_4$, even if the different experimental conditions (i.e. KCl, LiCl and NaCl concentrations.^{8,9}) are taken into account.

The lack of literature information^{1-3, 7} and the possibility of comparison between the behaviour of PNS and cystine induced us to study in this paper the PNS protonation and the equilibria taking place between PNS and cations of alkaline metals, i.e. lithium, sodium and potassium at 25°C and in $N(CH_3)_4Cl$ as constant ionic medium.

Two concentrations of $N(CH_3)_4Cl$ (1.00 and 3.00 mol dm⁻³) were used to investigate the PNS protonation, whereas the equilibria between PNS and lithium, sodium and potassium were investigated only in 3.00 mol dm⁻³ $N(CH_3)_4Cl$.

3.00 mol dm⁻³ $N(CH_3)_4Cl$ was selected as ionic medium because it was expected that $N(CH_3)_4^+$ should be bound by PNS weaker than lithium, sodium and potassium ions. Furthermore, as according to Biedermann e Sillèn,¹⁰ in constant ionic medium activities can be substituted by concentrations, its high concentration allows us to investigate a wide range (up to 0.400 mol dm⁻³) of cation concentration. The formation of weak complexes could take advantage of a high cation concentration.

METHOD OF INVESTIGATION

Preliminary approaches were carried out to evaluate solubility of PNS in comparison with that of cystine.

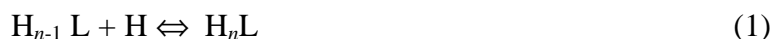
It was observed, as expected, that the neutral form of PNS ($H_2L = C_{10}H_{20}N_2O_4S_2$), corresponds to the lowest solubility, while at either lower or higher hydrogen ion concentration, solubility increases. However, PNS is much more soluble than cystine, because clear solutions 0.025 mol dm⁻³ of PNS could be easily prepared.

Penicillamine Disulfide and Alkaline Cations

The following description of the investigation method is divided in two sections, because, first, protonation was studied and then investigation was focused on the equilibria between PNS and lithium, sodium and potassium ions.

Protonation of PNS

The general form of protonation equilibria can be written, charges omitted, as follows:



Equilibrium (1) was studied at 25°C and in two ionic media: $N(CH_3)_4Cl$, $W = 3.00 \text{ mol dm}^{-3}$ and $N(CH_3)_4Cl$, $W = 1.00 \text{ mol dm}^{-3}$.

The ionic medium method adoption allows us to define the protonation constant k_n , relative to equilibrium (1), as follows:

$$k_n = c_{H_n L} / (c_H c_{H_{n-1} L}) \quad (2)$$

In the expressions (1) and (2) and in the following $n \geq 1$ and c_x indicates the free concentration of the species x which appears as deponent.

Equilibrium (1) was investigated by measuring the e.m.f. of the following galvanic cell:



as a function of $0 \leq C_H \leq 0.100 \text{ mol dm}^{-3}$ and $0.010 \leq C_L \leq 0.020 \text{ mol dm}^{-3}$. C_H and C_L represent the analytical excess of hydrogen ion and the total concentration of PNS.

Solution S1 had the following general composition:

$C_H \text{ mol dm}^{-3}$ in H^+ ; $C_L \text{ mol dm}^{-3}$ in PNS; $(W - C_H) \text{ mol dm}^{-3}$ in $N(CH_3)_4^+$ and $W \text{ mol dm}^{-3}$ in Cl^- , where C_x indicates the total concentration of the species x .

In a constant ionic medium, the e.m.f. of the cell (I) at 25°C and in mV units, can be written as follows:

$$E_I = E^\circ_I + 59.16 \log c_H + E_j \quad (3)$$

where E°_I is a constant determined in the first part of each measure in the absence of PNS, i.e. $C_H = c_H$. E_j is the liquid junction potential depending on the hydrogen ion and it was found, according to Biedermann and Sillén¹⁰, $E_j = -j c_H$. The j value depends on the ionic medium concentration (W) and it increases by decreasing W .

It was found that the contribution of E_j in the here investigated alkaline solutions ($-\log c_H \leq 10$) was negligible, while it was remarkable in the acid solutions, in particular at $W = 1.00 \text{ mol dm}^{-3}$. It was found at $W = 1.00 \text{ mol dm}^{-3}$, $j = 61 \pm 2 \text{ mV}$ and at $W = 3.00 \text{ mol dm}^{-3}$, $j = 16 \pm 1 \text{ mV}$.

After the determination of E°_I and E_j , a solution containing PNS, in the deprotonated form (i.e. in alkaline solution), was added to reach the selected value of concentration and C_H was gradually increased by keeping C_L constant. For each point, c_H could be obtained from the e.m.f. of cell (I).

Equilibria between PNS and lithium, sodium and potassium ions.

Equilibria taking place between PNS and cations of alkaline metals, in particular lithium, sodium and potassium, were investigated by studying the following general equilibrium, where charges were omitted for simplicity:



In equilibrium (4) $q \geq 1$, $p \geq 0$, $r \geq 1$, M indicates one of the three cations, whereas L corresponds to the deprotonated form of the ligand PNS ($L^- = C_{10}H_{18}N_2O_4S_2$).

If $p > 0$, protonated species are formed, while if $p < 0$, the formation of species with loss of protons (or acquisition of OH^-) takes place.

In a constant ionic medium (in this case $3.00 \text{ mol dm}^{-3} \text{ N}(\text{CH}_3)_4\text{Cl}$), the constant of eq. (4), can be defined as follows:

$$\beta_{q,p,r} = c_{\text{Mq H}_p \text{L}_r} / (c_{\text{M}}^q c_{\text{H}}^p c_{\text{L}}^r) \quad (5)$$

The aim of this investigation is to find the prevailing values assumed by q , p , and r and of the relative constants $\beta_{q,p,r}$.

For this purpose, the e.m.f. of the following cell was measured:



In the cell (II), symbols have the same previous meaning and Solution S2 had the following general composition:

$C_{\text{H}} \text{ mol dm}^{-3}$ in H^+ ; $C_{\text{M}} \text{ mol dm}^{-3}$ in M^+ ; $C_{\text{L}} \text{ mol dm}^{-3}$ in PNS; $(3.00 - C_{\text{H}} - C_{\text{M}}) \text{ mol dm}^{-3}$ in $\text{N}(\text{CH}_3)_4^+$ and 3.00 mol dm^{-3} in Cl^- .

The e.m.f. of the cell (II) at 25°C and in mV units, can be written as follows:

$$E_{\text{II}} = E^\circ_{\text{II}} + 59.16 \log c_{\text{H}} + E_{\text{j}}$$

where E°_{II} is a constant determined in the first part of each measure in the absence of PNS, i.e. $C_{\text{H}} = c_{\text{H}}$ and $C_{\text{M}} = c_{\text{M}}$. E_{j} is the liquid junction potential previously determined.

After the determination of E°_{II} and E_{j} , a solution containing the ligand was added so that C_{L} could be gradually increased, by keeping C_{H} and C_{M} constant. Titrations were interrupted at about $-\log c_{\text{H}} \approx 10$. Back titrations were carried out by increasing stepwise C_{H} , by keeping C_{L} and C_{M} constant. As direct and back titrations gave agreeing results, it could be assumed that solutions S2 were at real equilibrium.

EXPERIMENTAL

Materials and analysis

A Sigma Penicillamine disulfide (PNS) (purity $\geq 98\%$) product was used without purification. The check of its melting point provided a value in agreement within $\pm 1^\circ\text{C}$ with the theoretical value. Hydrochloric acid, sodium chloride, tetramethylammonium hydroxide and tetramethylammonium chloride were prepared and analysed as previously described.^{11, 12} A C. Erba RP potassium chloride product was kept at 300°C for two hours and then stored in a desiccator. Its stoichiometric composition was checked by argentometric titration according to Mohr. A concentrated LiCl solution was prepared from a C. Erba RP product and was analysed argentometrically according to Mohr. Results of many determinations agreed within $\pm 0.1\%$. The absence of protolytic impurities was checked by potentiometric titrations carried out according to Gran.¹³

Apparatus

Electromotive force (e.m.f.) measurements were carried out by means of a Radiometer pHM64 or Metrohm mod. 654 electronic voltmeters equipped with glass electrodes from the same firm. The potentiometric salt bridge and the reference electrode [R.E. = $\text{Ag}, \text{AgCl} / 3.00 \text{ mol dm}^{-3} \text{ N}(\text{CH}_3)_4\text{Cl}$ saturated with $\text{AgCl} / 3.00 \text{ mol dm}^{-3} \text{ N}(\text{CH}_3)_4\text{Cl}$] were similar to those described previously.¹⁴

The measured e.m.f. values were constant within a few minutes after each addition and remained constant within $\pm 0.2 \text{ mV}$ overnight. Solutions checked thoroughly the day after that of the measure remained perfectly clear, otherwise the corresponding e.m.f. data were discarded.

Penicillamine Disulfide and Alkaline Cations

All measurements were performed at 25°C. Ultrapure N₂ was bubbled through the solutions as previously described.¹¹ The response of the glass electrode for hydrogen ion (G.E.) was checked and corrected as previously described.⁶

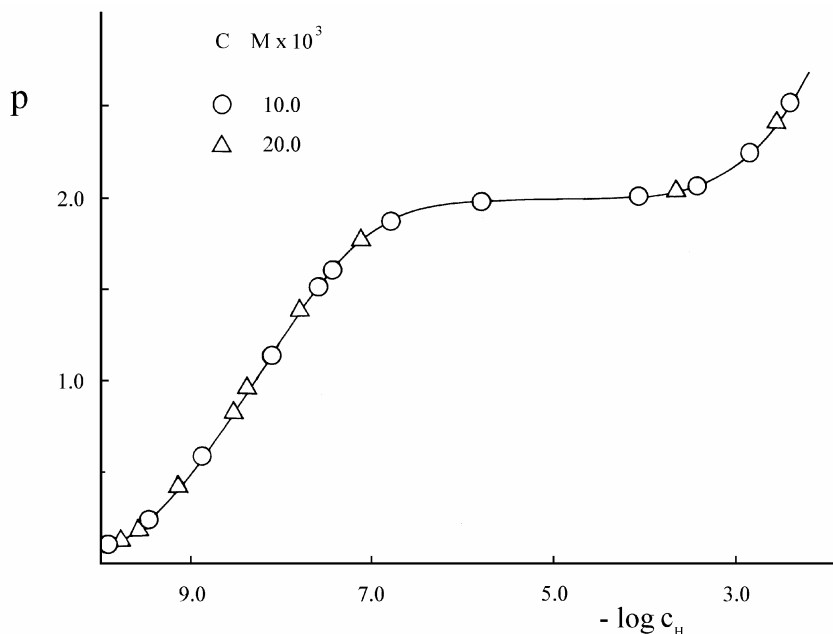


Fig. 2 - Protonation function of PNS, **p**, versus $-\log c_H$. The curve is the normalized one in the position of best fit. Concentrations of the reagents are expressed in $M = \text{mol dm}^{-3}$.

RESULTS

Protonation of PNS

Two different total concentrations of PNS (i.e. $C_L = 0.010$ e $0.020 \text{ mol dm}^{-3}$) were used. For each of them, several series of measurements were carried out.

The knowledge of the c_H value, obtained for each point from e.m.f. measurements, together with the total concentration of PNS, C_L and of the analytical excess of hydrogen ions, C_H , allowed us to calculate the protonation function **p**, representing the average number of protons bound per PNS, according to the following equation:

$$\mathbf{p} = (C_H - c_H) / C_L \quad (6)$$

In Fig. 2, the protonation function **p** (some points of direct and back titration as an example) is plotted as a function of $-\log c_H$ for the data obtained in $3.00 \text{ mol dm}^{-3} \text{N}(\text{CH}_3)_4\text{Cl}$. Fig. 2 shows that all the points fall on the same curve independently of C_L , **p** can reach values higher than 2 and the curve at **p** = 2 (corresponding to the formation of the species H_2L) in a wide range is independent of $-\log c_H$. As **p** is independent of C_L , no appreciable amount of polynuclear species exists, whereas the shape of the curve indicates that the ratio between the second and the third protonation constant is rather high.

A similar trend of experimental points was obtained in the case of $1.00 \text{ mol dm}^{-3} \text{N}(\text{CH}_3)_4\text{Cl}$.

To obtain the values of the protonation constants, experimental data were computed both by the normalized curve method proposed by Sill  n¹⁵ and by a calculation program for PC.¹⁶ In Tab. 1 the results obtained by both methods are collected. The agreement is good. The values proposed for the constants were used to calculate the curve of Fig. 2.

TABLE 1 - Protonation constants values, k_n , of PNS at 25°C and in 1.00 and 3.00 mol dm⁻³ N(CH₃)₄Cl, as ionic medium, respectively.

| | Method | 1.00 mol dm ⁻³ | 3.00 mol dm ⁻³ |
|-----------|----------------|---------------------------|---------------------------|
| Log k_1 | Graph | 8.87 ± 0.02 | 8.99 ± 0.03 |
| | BSTAC | 8.86 ± 0.01 | 9.00 ± 0.01 |
| | Proposed value | 8.86 ± 0.03 | 9.00 ± 0.03 |
| Log k_2 | Graph | 7.37 ± 0.01 | 7.58 ± 0.02 |
| | BSTAC | 7.38 ± 0.01 | 7.60 ± 0.01 |
| | Proposed value | 7.38 ± 0.02 | 7.60 ± 0.02 |
| Log k_3 | Graph | 1.97 ± 0.04 | 2.38 ± 0.03 |
| | BSTAC | 2.00 ± 0.02 | 2.40 ± 0.02 |
| | Proposed value | 1.99 ± 0.05 | 2.40 ± 0.05 |
| Log k_4 | Graph | 0.82 ± 0.07 | 0.99 ± 0.06 |
| | BSTAC | 0.79 ± 0.06 | 1.01 ± 0.05 |
| | Proposed value | 0.80 ± 0.10 | 1.00 ± 0.10 |

The limits of error represent the maximum possible shift of the normalized curve and the experimental points for which agreement was still acceptable.

The good agreement between points and curve shown in Fig. 2 supports the validity of the procedure and the correctness of the results.

By applying a similar treatment to the e.m.f. measurements carried out in 1.00 mol dm⁻³ N(CH₃)₄Cl the results collected in Table 1 were obtained.

Complex formation

The investigated concentration values of the reagents are collected in Table 2. For each value, several series of direct and back e.m.f. measurements of cell (II) were carried out.

TABLE 2 - C_M and C_H values (in mol dm⁻³ × 10³) of the investigated solutions. For each of them, PNS concentration increased gradually.

| | C_M | | | | | |
|-----------|-------|-----|-----|-----|-----|-----------|
| C_H | 100 | 150 | 200 | 300 | 400 | variabile |
| 10 | + | + | + | + | + | |
| 25 | + | + | + | + | + | |
| variabile | | | | | + | + |

Penicillamine Disulfide and Alkaline Cations

The set of experimental data was constituted by the total concentrations of the reagents analytically known and by the free concentration of hydrogen ions deduced from the e.m.f. measurement of cell (II).

The material balance of the analytical excess of hydrogen ion, by taking into account the mass action law, can be written as follows:

$$C_H = c_H + k_1 c_H c_L + 2 k_1 k_2 c_H^2 c_L + 3 k_1 k_2 k_3 c_H^3 c_L + 4 k_1 k_2 k_3 k_4 c_H^4 c_L + \sum \sum \sum p \beta_{q,p,r} c_M^q c_H^p c_L^r. \quad (7)$$

In eq. (7) symbols have the same meaning as before, L indicates PNS completely deprotonated and the values of k_n , obtained in the same experimental conditions [25°C and 3.00 mol dm⁻³ N(CH₃)₄Cl], are collected in Table 1.

Eq. (7) can be used to calculate the free concentration of the ligand, c_L , when its last term is known or negligible.

By taking into account the results obtained in a previous work,⁶ relative to the interaction between cystine and the same alkaline cations studied here, it seems reasonable to suppose that, in the first approximation, the last term of eq. (7) can be neglected.

From the inspection of eq. (7) and of the PNS protonation function (v. Fig. 2), it can be supposed that the concentration of the species H₃PNS ed H₄PNS (omitted charges) can be neglected in alkaline range ($10 \geq -\log c_H \geq 7$), without a loss of accuracy in the elaboration of the experimental data. In the same way, the concentration of the species PNS ed HPNS can be neglected without loss of accuracy in the range $4 \geq -\log c_H \geq 2$. It can be deduced that the ligand acts as L in the former range and as H₂L in the latter one.

The material balance relative to PNS can be written differently in the acid range [eq. (8)] and in the alkaline one [eq. (9)], as follows:

$$C_L = c_L + k_1 c_H c_L + k_1 k_2 c_H^2 c_L + \sum r Z' C_{alk} \quad (8)$$

$$C_L = c_{H_2L} + k_3 c_H c_{H_2L} + k_3 k_4 c_H^2 c_{H_2L} + \sum r Z C_{alk} \quad (9)$$

In eq.s (8) and (9), Z' and Z are the formation function, defined as the average number of PNS bound to the central group constituted by the alkaline cation, which concentration is indicated with C_{alk} .

By applying eq. (8) to the experimental points obtained in the alkaline range, it can be calculated that the last term of eq. (8) is zero for all the obtained points. The meaning of this result indicates that in the selected experimental conditions no appreciable amount of complex is formed.

On the contrary, by applying eq. (9) to the experimental points obtained in the acid range, positive values of Z are obtained even if they are very low.

Fig.s 3, 4 and 5, where most of the experimental points are plotted as examples, show the dependence of Z on $-\log c_{H_2L}$ for lithium, sodium and potassium ions, respectively. The trend of the points is similar in the three figures.

Points obtained at different C_L fall on the same curve, whereas points obtained at different C_{alk} fall on different curves. Z is a function of the total concentration of the cations, but is not a function of the total concentration of the ligand. This means that complexes are formed with $r = 1$, but q can be ≥ 1 . For each species only one PNS is present, but one or more cations can be present.

On the basis of this evidence, the formation function can be written as follows:

$$Z = \sum \beta_{q,2,1} c_{alk}^q c_{H_2L} / C_{alk} \quad (10)$$

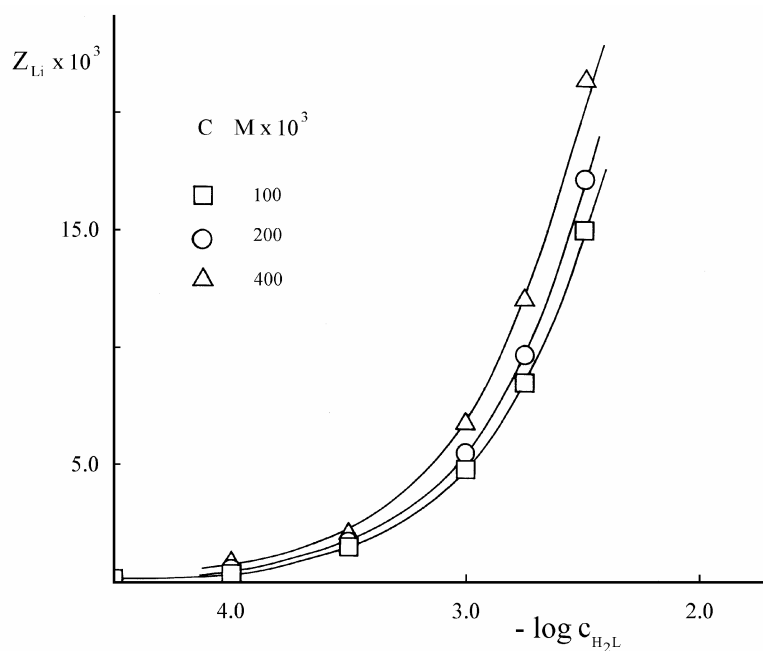


Fig. 3 - The formation function, Z_{Li} , versus $-\log c_{H_2L}$, for lithium ion. Concentrations of the reagents are expressed in $M = \text{mol dm}^{-3}$.

By taking into account the C_{alk} values and the low Z obtained values and shown in Fig. 3, 4 and 5, it can be deduced that the formed complex concentration is very low. It is acceptable to assume that the free concentration of each cation can be substituted by its total concentration in the numerator of eq. (10).

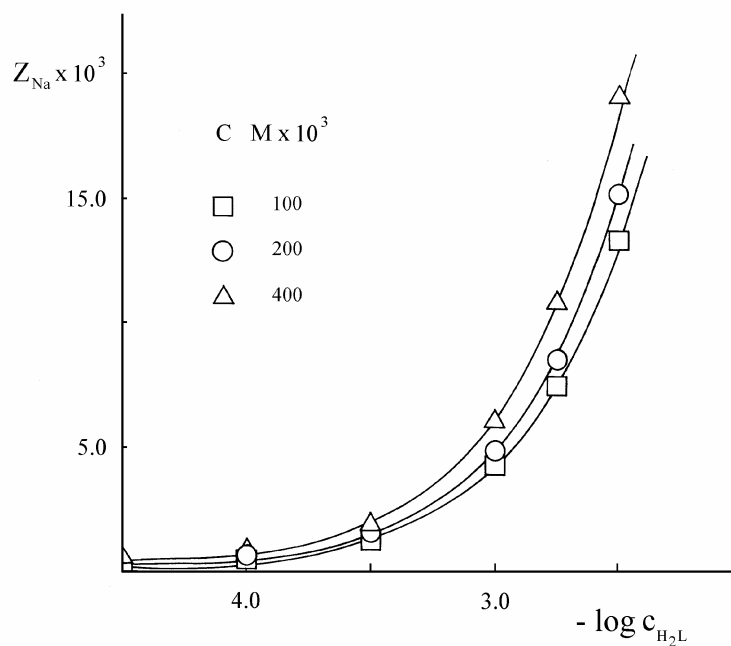


Fig.4 - The formation function, Z_{Na} , versus $-\log c_{H_2L}$, for sodium ion. Concentrations of the reagents are expressed in $M = \text{mol dm}^{-3}$.

With such approximation, eq. (10) can be written:

$$Z = c_{H_2L} \sum \beta_{q,2,1} C_{alk}^{q-1} \quad (11)$$

By introducing in the eq. (11), a conditional constant, γ (where $\gamma = \sum \beta_{q,2,1} C_{alk}^{q-1}$), which remains constant at constant C_{alk} , it can be written:

$$Z = \gamma c_{H_2L} \quad (12)$$

Experimental points of Fig. 3, 4 and 5 can be treated with graphic methods according to Sill  n.¹⁵ The obtained values of γ still depend on the total concentration of the cation. By plotting them as a function of C_{alk} , the prevailing values of q and the corresponding values of the equilibrium constants can be obtained.

In Fig. 6, where this dependence is shown, it can be seen that all the points for each cation fall on the same straight line indicating that q can assume the values 1 or 2. The intercept on the ordinate provides the values of $\beta_{1,2,1}$ and the slope those of $\beta_{2,2,1}$, for each cation.

The primary experimental data were elaborated independently by means of a program BSTAC¹⁶ for PC and the same results were obtained. In Table 3 the results of the two methods are collected and compared.

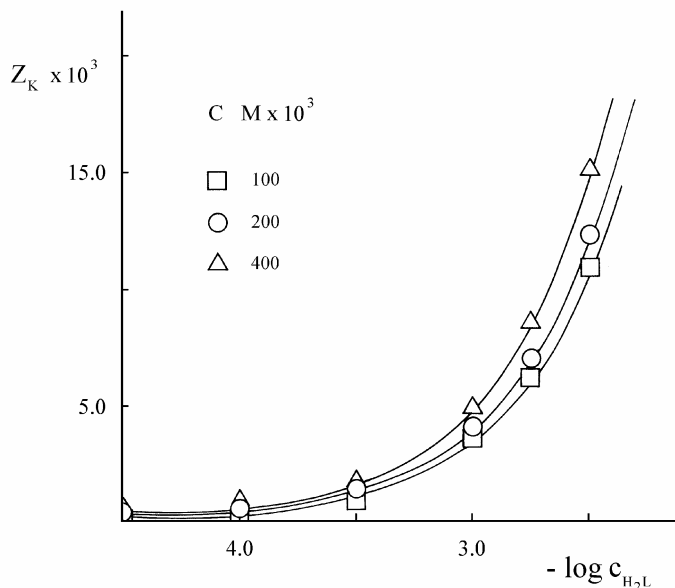


Fig. 5 - The formation function, Z_K , versus $-\log c_{H_2L}$, for potassium ion. Concentrations of the reagents are expressed in $M = \text{mol dm}^{-3}$.

DISCUSSION

From the here obtained results and from those obtained in previously published papers,^{5,6} it can be deduced that both cystine and PNS have four possibilities of protonation, as expected from the formula of Fig. 1.

As was found in this paper, the higher solubility of PNS than that of cystine allowed to increase the PNS concentration. The possibility to investigate solutions with higher ligand concentration was particularly advantageous, because the PNS complexes are weaker than those formed by cystine.

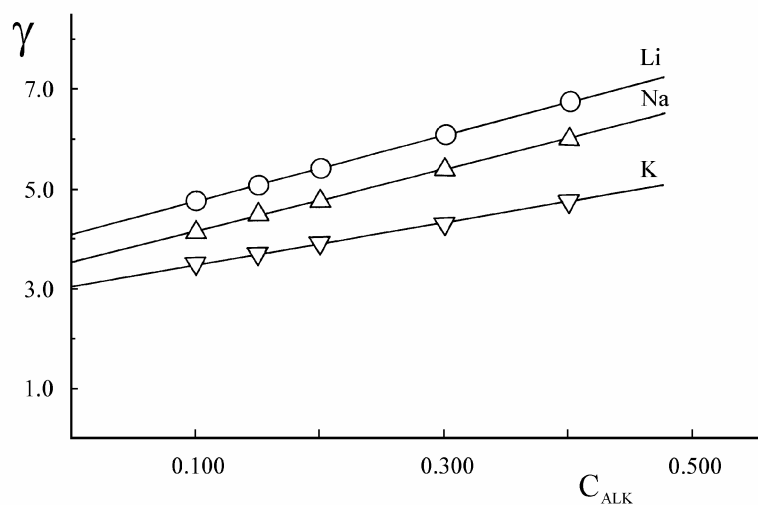


Fig. 6 - The dependence of γ on the total concentration of the cations expressed in $M = \text{mol dm}^{-3}$.

TABLE 3 - Stability constants ($\log \beta_{q,p,r}$) of the complexes formed between PNS and lithium (I), sodium (I) and potassium (I), respectively.

| Species | Method | Li^+ | Na^+ | K^+ |
|--------------------------------|--------|-----------------|-----------------|-----------------|
| MH_2L | Graph | 0.61 ± 0.06 | 0.55 ± 0.06 | 0.48 ± 0.06 |
| | BSTAC | 0.62 ± 0.02 | 0.55 ± 0.01 | 0.47 ± 0.02 |
| $\text{M}_2\text{H}_2\text{L}$ | Graph | 0.83 ± 0.05 | 0.80 ± 0.05 | 0.64 ± 0.05 |
| | BSTAC | 0.83 ± 0.01 | 0.79 ± 0.02 | 0.64 ± 0.02 |

The limits of error represent the maximum possible shift of the normalized curve and the experimental points for which agreement was still acceptable.

By taking into account the results obtained for PNS (this paper) and for cystine,^{5,6} the data can be more reasonably explained by assuming the complex formation rather than by thinking of activity coefficient variation.

From an inspection of the results of this paper, it could appear a contradiction.

Experimental data obtained in the alkaline range can be explained without assumption of complex formation between PNS and the three studied cations. The total concentration of the ligand corresponds to the sum of the contribution of the protonated species.

However, experimental data obtained in acid range cannot be explained without the assumption of the complex formation shown in Table 3.

Penicillamine Disulfide and Alkaline Cations

The explanation can be easily found by thinking that in both cases the experimental data were obtained from a competition for the ligand between each cation and protons.

It is well known that the aminic -NH_2 groups are more basic than the carboxylic ones. As an example, the protonation constants of glycine⁵ ($\text{G}^- = \text{CH}_2(\text{NH}_2) - \text{COO}^-$), at 25°C and in $1.00 \text{ mol dm}^{-3} \text{ N}(\text{CH}_3)_4\text{Cl}$ are $\log k_1 = 9.60$ e $\log k_2 = 2.70$. The former corresponds to the protonation of the aminic nitrogen, while the latter to the carboxylic group.

That means that already in basic range ($-\log c_{\text{H}} \approx 9$) about 50 % of the aminic groups of glycine are protonated, whereas the carboxylic groups are completely deprotonated.

It may be possible that lithium, sodium and potassium ions already in basic range are bound to the carboxylic groups, but in that range cannot interfere in the material balance of the ligand.

Even if ions of the alkaline metals were bound by the forms L^- and HL of PNS, the formation of the corresponding species could not be observed by means of the e.m.f. measurements of the cell (II), because this procedure, based on the competition between H^+ and alk^+ (where alk^+ can be alternatively lithium, sodium or potassium ions), would be applied in the alkaline range where the competition does not exist.

On the contrary the competition takes place in the acid range where carboxylic groups tend to bond either protons or lithium, sodium or potassium ions. In this range the formation function, Z , assumes positive values and increases by increasing the free concentration of the ligand.

Such considerations are similar to those formulated in a previously published paper⁶ where the complex formation between cystine and the same cations studied here was investigated. In the previously performed work⁶, a set of measurements carried out with a glass electrode for sodium proved that although the complex formation took place in the alkaline range, it was not possible to appreciate their presence by using only a glass electrode for protons.

Although e.m.f. measurements are not able to give structural information, from the results obtained here it seems reasonable to suppose that lithium, sodium and potassium are bound to the carboxylic groups of cystine and PNS and not to aminic groups.

By comparing the results obtained for cystine and PNS, it can be deduced that the species assumed to explain the experimental data are similar in both cases. Also for PNS, species containing only one PNS per complex are found, whereas such species can contain one or two cations. The constants found for PNS are lower than those found for cystine and the complex formation could be appreciated because PNS, even in the form H_2L , is much more soluble (more than ten times) than cystine so that it was possible to have more concentrated solutions in the ligand and higher values of Z could be reached.

TABLE 4 - A comparison between the PNS and cystine protonation constants obtained in the same experimental conditions [25°C and $3.00 \text{ mol dm}^{-3} \text{ N}(\text{CH}_3)_4\text{Cl}$].

| | Cystine | PNS |
|-----------|---------|------|
| Log k_1 | 9.14 | 9.00 |
| Log k_2 | 8.61 | 7.60 |
| Log k_3 | 2.82 | 2.40 |
| Log k_4 | 1.89 | 1.00 |

The protonation constants of Table 1 are influenced by the ionic medium. The trend is similar to the one previously observed for cystine^{5,6}. The constant values increase by raising the ionic medium concentration. It is hard to compare the obtained values with the few existing values^{8,9} because of the wide difference of the experimental conditions.

Table 4 shows a comparison between the values of the PNS protonation constants and the analogous ones of the cystine obtained in the same experimental conditions [25°C e 3.00 mol dm⁻³ N(CH₃)₄Cl]. The former are remarkably lower than the latter, in particular for the value of log k_3 .

The formation of complexes between alkaline metals cations and compounds containing carboxylic groups was assumed by other authors for several compounds.

Schwarzenbach et al.¹⁷ assumed the presence of complexes between aminobarbituric acid – N,N – diacetic acid and lithium ions (log β = 5.40) and sodium ions (log β = 3.32). The same authors¹⁸ by investigating the behaviour of ammoniatriacetic acid, explain their experimental data by assuming the formation of complexes with lithium ions (log β = 3.28) and with sodium ions (log β = 2.15).

More recently¹⁹ the complex formation with lithium (log β = 2.79) and sodium (log β = 1.66) ions was assumed also in the case of EDTA.

The results of the literature studies show a trend similar to the one here found, because lithium is more strongly bound to the carboxylic group than sodium.

More recently also Daniele et al.²⁰ assumed the complex formation between EDTA and alkaline cations with stability constants similar to those proposed here.

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