Zinc and Silver Ion Coordination by Pyrido[1,2-*a*]pyrimidine Derivatives*

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Abstract

The protonation and zinc and silver ion coordination equilibria of 15 pyrido[1,2-*a*]pyrimidine derivatives were studied by polarographic, potentiometric and spectrophotometric methods. The compositions of the complexes and the corresponding stability constants were determined by computer evaluation of the data. The results reflected the effects of the configuration and the degree of saturation of the ring system of the ligand, the basicities of the donor atoms, chelate formation and the presence of substituents at different positions on the stabilities of the complexes.

Introduction

Certain types of pyrido[1,2-*a*]pyrimidine derivatives have valuable pharmacological properties and are therefore used as pharmaceutical preparations. Changes in the substituents on the pyrido[1,2-*a*]-pyrimidine skeleton result in changes in the biological activity, and different derivatives in this group of compounds serve as antipyretic, tranquillizer, analgesic, anti-inflammatory, anti-allergic, anti-artherosclerotic or antibacterial drugs. Other derivatives are used as additives in photographic materials, sensitizing silver halide emulsions and photoconductor layers.

Because of the numerous practical applications of pyrido[1,2-*a*]pyrimidine derivatives, several research groups have been engaged in the study of the synthesis, reactions and physicochemical characterization of these compounds. The results of these investigations were reviewed in 1961 by Mosby [1] and in 1983 by Hermecz and Mészáros [2].

Pyrido[1,2-*a*]pyrimidine derivatives contain nitrogen and oxygen donor atoms, some of them with a basic character. The protonation constants of these groups have been determined by means of spectrophotometric [3] and potentiometric [4] equilibrium measurements. The formation of a water-insoluble zinc complex was observed in the case of only one derivative [5]. No systematic coordination chemical study has yet been performed on these systems.

Since metal coordination by such molecules may result in significant changes in their chemical behaviour, and in particular in their stability in solution, a systematic study of the metal–ligand interactions in this system may lead to results of practical importance as concerns the preparation of pharmaceutical products containing pyrido[1,2-*a*]pyrimidine derivatives as active substances.

The results of studies of the protonation, and the zinc and silver coordination equilibria of a series of pyrido[1,2-*a*]pyrimidine derivatives shown in Fig. 1 are reported below.

Experimental

Protonation Studies

The protonation equilibria of the nitrogen donor atom at position 1 were studied by means of photometric equilibrium measurements in aqueous solution with a Unicam SP 800 spectrophotometer. The pH-dependences of the UV absorption spectra of an unsaturated, a tetrahydro and a hexahydro derivative are presented in Figs. 2–4, respectively. Other derivatives with similar degrees of saturation exhibit similar spectral behaviour.

The protonation of the carboxylate groups at position 3 or 9 (latter as acetate) of the bicyclic skeleton was studied by means of potentiometric equilibrium measurements, using the computer-controlled on-line automatic titration device constructed in our laboratory and described previously [6]. These measurements were performed in aqueous solution and in 50% *v/v* water–acetone as solvent. The data indicated the presence of carboxylate

*This paper is dedicated to Professor Dr. Viktor Gutmann (Technical University, Vienna) on the occasion of his 65th birthday.

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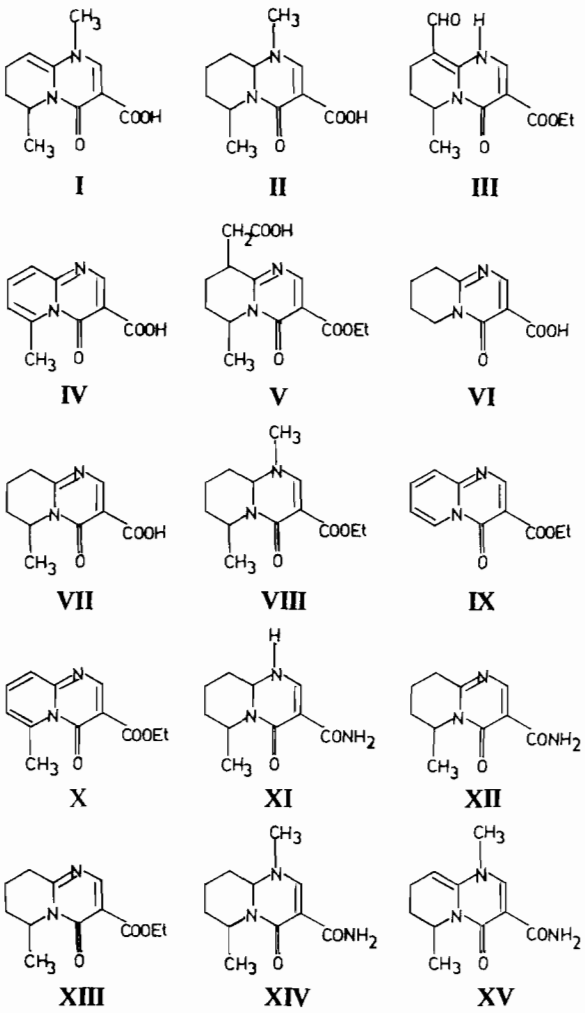


Fig. 1. Pyrido[1,2-*a*]pyrimidine derivatives investigated.

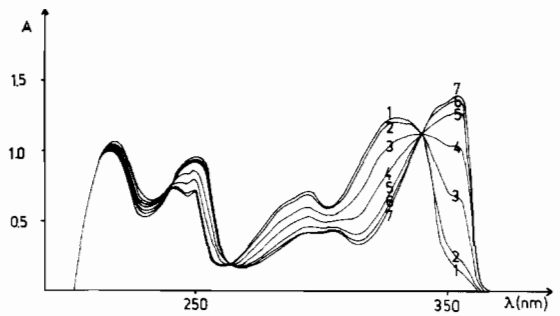


Fig. 2. pH-Dependence of the ultraviolet spectrum of **IX** in aqueous solution. Concentration = 1.09×10^{-4} mol dm^{-3}; $d = 1$ cm; pH: (1) 0.7; (2) 1.23; (3) 1.60; (4) 2.0; (5) 2.6; (6) 3.0; (7) 4.0.

groups with surprisingly different basicities. Typical titration curves characteristic of a carboxylate group with pK = 8.23 (curve 2) and one with pK = 4.17 (curve 3) are shown in Fig. 5. The protonation con-

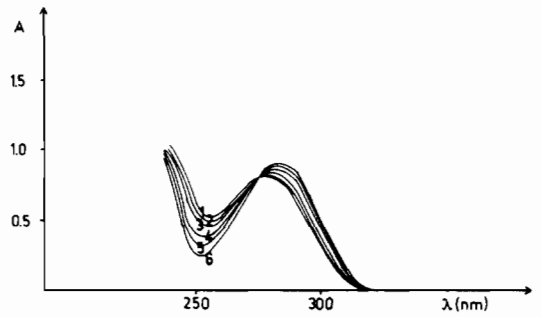


Fig. 3. pH-Dependence of the ultraviolet spectrum of **I** in aqueous solution. Concentration = 1.53×10^{-4} mol dm^{-3}; $d = 1$ cm; pH (1) 4.0; (2) 3.0; (3) 2.6; (4) 2.0; (5) 1.6; (6) 0.7.

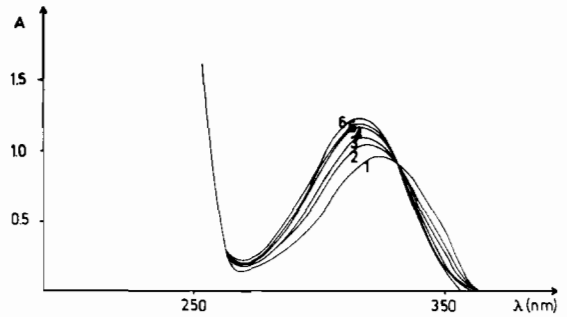


Fig. 4. pH-Dependence of the ultraviolet spectrum of **VIII** in aqueous solution. Concentration = 2.04×10^{-4} mol dm^{-3}; $d = 1$ cm; pH: (1) 0.3; (2) 0.7; (3) 1.23; (4) 1.42; (5) 1.67; (6) 2.02.

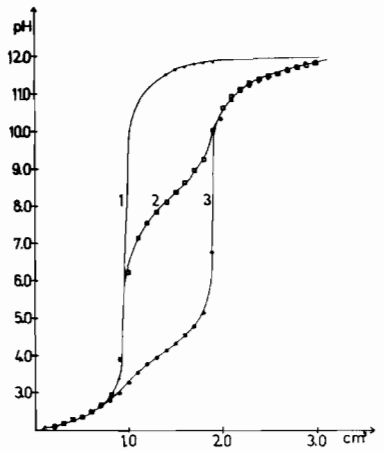


Fig. 5. Titration curves for determination of the log K values of the carboxylate groups in **II** and **VII**. (1) Titration curve of 0.01014 mol dm^{-3} standard HNO_3 solution. (2) Titration curve of 0.0101 mol dm^{-3} **II** in the presence of 0.01014 mol dm^{-3} standard HNO_3 solution. (3) Titration curve of 0.0098 mol dm^{-3} **VII** in the presence of 0.01014 mol dm^{-3} standard HNO_3 solution.

stants calculated from the spectrophotometric and potentiometric data with a computer program are shown in Table I.

TABLE I. Protonation Constants of the Pyrido[1,2-*a*]-pyrimidine Derivatives

Compound	log K_0[a]		log K_N[b]
	In water	In 50% *v/v* acetone–water	In water
I	8.64	7.80	2.25
II	8.23	9.16	2.10
III	7.09	6.86	1.37
IV	4.72	5.60	2.23
V	4.28	5.40	1.34
VI	4.26	5.10	1.65
VII	4.17	4.97	1.75
VIII			1.2
IX			1.81
X			2.60
XI			<1
XII			2.0
XIII			1.95
XIV			1.2
XV			<1

[a]Reproducibility: ±0.05. [b]Reproducibility ±0.1.

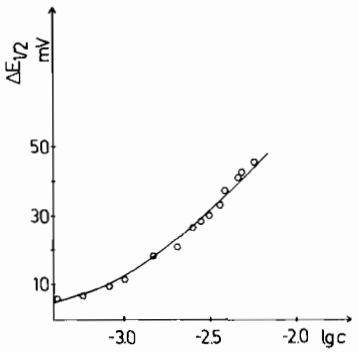


Fig. 6. Measured and calculated $\Delta E_{1/2}$ values plotted as a function of the logarithm of the total ligand concentration for zinc ion coordination by IV. Circles are experimental data; the full line represents the calculated values.

Zinc Ion Coordination Studies

Since pyrido[1,2-*a*]pyrimidine derivatives contain not only the basic donor atoms, but also donor groups which do not participate in protonation–deprotonation equilibria, zinc ion coordination was studied by means of polarographic equilibrium measurements, which reflect the overall effect of the binding of zinc ions in pH-dependent and pH-independent processes. The compositions of the complexes formed and the corresponding stability constants were determined from the ligand concentration-dependence of the half-wave potential ($E_{1/2}$ *vs.* log c_A curves) of zinc in the system. The measurements and the evaluation of the experimental data were performed as reported previously [7]. For control of the correctness of the equilibrium constants derived by computer evaluation of the data, the computer program simulated the experimental curves on the basis of these equilibrium constants.

The good agreement between the experimental and simulated values proved the reliability of the evaluation method (Fig. 6). The complex stability constants are listed in Table II.

TABLE II. Stability Constants (log β values) of the Zinc Complexes: $\beta_1 = K_1$; $\beta_2 = K_1K_2$; $\beta_3 = K_1K_2K_3$

Compound	log β_1	log β_2	log β_3
II			9.50 ± 0.1
IV	2.96 ± 0.05	5.89 ± 0.06	
V	0.74 ± 0.3	3.32 ± 0.07	
VI	1.66 ± 0.12	4.28 ± 0.1	
VII	2.40 ± 0.13	4.99 ± 0.12	
VIII	2.89 ± 0.04	5.22 ± 0.08	
X	1.75 ± 0.06		
XIV	1.52 ± 0.03		

TABLE III. Stability Constants (log β values[a]) of the Silver Complexes

Compound	log β_{21}	log β_{11}	log β_{12}
II	2.22 ± 0.04	0.66 ± 0.06	
VI		1.26 ± 0.01	
VII		1.22 ± 0.03	
IX		1.08 ± 0.01	2.75 ± 0.03
X		1.33 ± 0.02	
XII		1.55 ± 0.01	
XIII		1.46 ± 0.01	

[a]$\beta_{21} = [Ag_2L]/([Ag^+]^2[L])$; $\beta_{11} = [AgL]/([Ag^+][L])$; $\beta_{12} = [AgL_2]/([Ag^+][L]^2)$ (Charges of the ligands are neglected in the above equations.)

Silver Ion Coordination Studies

Because of the low water-solubility of the silver complexes of pyrido[1,2-*a*]pyrimidine derivatives, the silver ion coordination studies were performed in 50% *v/v* water–acetone as solvent by means of potentiometric equilibrium measurements with the computer-controlled on-line automatic titration device used for the pH-metric studies. First-order silver electrodes served as both analytical electrode and reference electrode, the latter being situated in a Wilhelm bridge. The stability constants of the silver complexes were determined by computer analysis of the potentiometric data (Table III).

Results and Discussion

Protonation of the Donor Atoms

The data in Table I show that two of the pyrido-[1,2-*a*]pyrimidine derivatives (**I** and **II**) have sur-

prisingly high carboxylate protonation constants (in aqueous solution log $K > 8.2$). The decrease in the polarity of the solution when 50% *v/v* acetone–water was used as solvent instead of water was accompanied by a decrease in the carboxylate protonation constant of **I**, and in an increase in that of **II**. The extremely high protonation constants suggested that the carboxyl groups of compounds **I** and **II** form intramolecular hydrogen-bonds which hinder the release of the carboxyl proton. The carbonyl oxygen at position 4 and the ring nitrogen at position 1 may both serve as pillar atoms for the hydrogen-bond with the carboxyl group at position 3, resulting in the formation of six-membered chelate rings. In the former case, the hydrogen-bond formation results in partial enolization of the carbonyl group. This causes an increase in the polarity of the molecule.

The hydrogen-bond formation between the carboxyl at position 3 and the nitrogen at position 1 does not cause a significant polarity change.

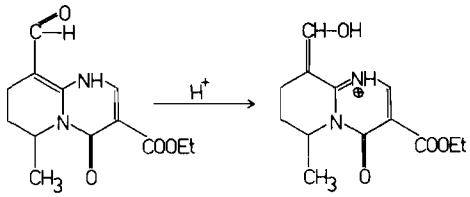
The different solvent dependence of the protonation constants of compounds **I** and **II** indicated the presence of different type of hydrogen-bonds in the two systems.

Since the decrease in the relative permittivity of the solvent hinders the polarity increase of the solute, the decreased protonation constant of **I** in the solvent mixture indicates that the hydrogen-bond formation in **I** is accompanied by a polarity increase of the molecule due to the mentioned partial enolization. Thus in **I** the hydrogen-bond connects the carboxyl at position 3, probably with the carbonyl oxygen at position 4.

A decrease in the relative permittivity of a solution generally favours the formation of neutral species. This is the reason why in **II**, and in all the other investigated pyrido[1,2-*a*]pyrimidine derivatives except **I**, the carboxylate protonation constants proved to be higher in the solvent mixture than in aqueous solution. In these systems the protonation of the molecule is not accompanied by significant polarity changes. The extremely high protonation constant of **II** has to be attributed therefore to hydrogen-bond formation not leading to polarity change, e.g. to enolization of the compound. Thus, this hydrogen-bond probably connects the carboxyl at position 3 with the ring nitrogen at position 1.

In compound **III**, which has a carboxyl ethyl ester at position 3, the protonation of the molecule (log K = 7.09) results in the enolization of the formyl group [8] at position 9, according to Scheme 1.

The protonation constants of the other carboxylate-containing molecules (**IV**–**VII**) did not indicate intramolecular hydrogen-bond formation. Compound **IV**, which possesses a completely unsaturated ring system, showed the highest log K value (4.72) for this series of molecules. The tetrahydro



Scheme 1.

derivatives (**V**–**VII**) had significantly lower protonation constants (log K values between 4.28 and 4.17). Surprisingly, the basicity of the acetate group at position 9 (**V**) and that of the carboxylate group at position 3 (**VII**) proved to be equal within experimental error.

The effect of the degree of saturation of the ring system on the basicities of the donor atoms is well reflected by the protonation constants of the nitrogen donor atom in position 1. With increasing degree of saturation of the ring system, the log K_N values of the compounds containing the same substituents decrease (*cf.* the pairs **IV** and **VII**, **I** and **II**, **X** and **XIII**, for example). A methyl group bound to the nitrogen donor atom significantly increases the basicity of the latter at the same degree of saturation (*cf.* **XI** and **XIV**). Thus, the electron-shifting property of the methyl group overcompensates its steric effect on the free electron pair of the nitrogen. The data show, however, that the degree of saturation of the ring system has a greater effect on the basicity of the nitrogen in position 1 than does the methyl group attached to it (*cf.* the pairs **VIII** and **XIII**, or **XII** and **XIV**). In unsaturated systems, even a methyl group at position 6 in the ring system significantly increases the basicity of the nitrogen in position 1 (*cf.* pair **IX** and **X**). The latter effect proved to be much smaller in the tetrahydro derivatives (see **VI** and **VII**). Substituents at position 9 naturally also influence the basicity of the nitrogen in position 1 (see **V** and **III**).

Zinc Ion Coordination Equilibria

The polarographic investigations have shown that ten of the fifteen investigated pyrido[1,2-*a*]-pyrimidine derivatives form stable zinc complexes. In the case of eight compounds, the overall stability constants of the complexes could be computed from the ligand concentration-dependence of the half-wave potentials. The logarithms of the stability constants are presented in Table II. For compound **III**, the polarographic behaviour of the system indicated the formation of the zinc complex but, because of the polarographic activity of the formyl group in the organic ligand, the shift of the half-wave potential of zinc due to complex formation could not be established. This prevented determination of the stability constant in the latter system.

A comparison of the data in Tables I and II reveals that the stabilities of the zinc complexes are correlated with the basicities of both the ring nitrogen and the carboxylate oxygen donor atoms. In the complexes containing carboxylate groups with similar basicities (**V**, **VI** and **VII**), the sequence of the complex stability constants parallels the sequence of the basicities of the ring nitrogens.

Thus, in the complexes of **IV**, **V**, **VI** and **VII**, the pyrido[1,2-*a*]pyrimidine derivatives are bifunctional ligands, with one carboxylate oxygen and one ring nitrogen acting as donor atoms. The high stability of the complex of compound **IV** is due to the pseudo-aromatic character of the ring system, which results in increased conjugation in the chelate ring. The stability of the complex of **V** is lower than those of **VI** and **VII** (all three are tetrahydro derivatives), not only because of the lower basicity of the ring nitrogen, but also because compound **V**, which has an acetate group at position 9, forms a seven-membered chelate ring with zinc, whereas **VI** and **VII**, which have a carboxylate group at position 3, form six-membered chelate rings. The stability of the complex of **VII** is higher than that of **VI** because of the electron shift caused by the methyl group at position 6 (also reflected in the basicity of the ring nitrogen in position 1).

The stability constants of the hexahydro derivatives **II**, **VIII** and **XIV** show that in these systems the methyl group on the ring nitrogen in position 1 does not prevent zinc ion coordination.

The heterocycles of the hexahydro derivatives seem to have a configuration [9, 10] which makes the free electron pair of the ring nitrogen in position 5 accessible for the coordination of zinc. The configuration of the less saturated heterocycles (the planarity of the ring system [10]) and the interaction of the free electron pair on the nitrogen with the π electrons of the ring, however, prevent the coordination of this nitrogen.

The effect of the substituent at position 3 on the complex stability is also seen in the case of the hexahydro derivatives. The presence of a carboxyl group (**II**) is the most favourable for complex formation in this system, too; if the ethyl ester of the carboxyl group was at position 3 (**VIII**), the complex stability was lower, and with a carboxamide group at the same position (**XIV**), the stability was still further decreased.

The anomalous sequence of the stepwise stability constants ($K_2 > K_1$) in Table II indicates the preferential formation of bis complexes (**V**, **VI** and **VII**) and, in the case of **II**, the tris complex. The $K_1 - K_2$ differences in the complexes of **IV** and **VIII** proved to be smaller than expected on the basis of statistical considerations, again indicating the stabilization of the bis complexes. This phenomenon may be attributed mainly to π back-donation (an electron shift from non-bonding d orbitals of the zinc to low-energy π antibonding orbitals of the unsaturated heterocycle) in the system. Hydrophobic interaction between the two (or three) ligands bound in the same coordination sphere may also stabilize the bis or tris complexes. The latter interaction may be of greater importance in the complexes of the hexahydro derivatives.

Silver Ion Coordination Equilibria

The zinc ion coordination studies reflected the importance of the nitrogen donor atoms in the metal ion binding of pyrido[1,2-*a*]pyrimidine derivatives. These investigations also indicated the effect of back-donation on the stability of the complexes. Since mostly chelate complexes of zinc were formed in these systems, with the substituents at position 3 or 9 acting as second donor groups, the behaviour of the nitrogen donor atom in itself was next studied in systems where chelate formation was hindered, so that the effect of the second donor atom did not disturb the picture.

In these systems, silver ion forms complexes with a linear coordination sphere. Accordingly, a donor substituent situated at position 3 or 9 of the pyrido-[1,2-*a*]pyrimidine derivatives does not form a chelate ring with a silver ion coordinated by the ring nitrogen in position 1 or 5. Silver ion coordination studies were therefore used for the characterization of the nitrogen donor atoms in the system.

The stability constants presented in Table III reveal significant differences between the zinc and silver ion coordination processes. A comparison of the data in Tables II and III demonstrates that:

(a) In contrast to the zinc ion coordination of the unsaturated and tetrahydro derivatives, the binding of silver ion is prevented not only by a methyl group on the nitrogen in position 1, but also by a bulky substituent at position 9, though the latter does not hinder the coordination of zinc (see e.g. the data on **V**).

(b) The nature of the substituent at position 3 does not influence the binding of silver by the ring nitrogen in position 1. (Derivatives with an acylamide (**XII**) or the ethyl ester of the carboxyl group (**IX**, **X**, **XIII**) at this position form silver complexes with higher stabilities than those containing a free carboxylate group (**VI**, **VII**).) Compounds **IX**, **XII** and **XIII** do not form zinc complexes at all, and the stability of that of **X** is much lower than those of **VI** and **VII**).

(c) The stabilities of the silver complexes are much lower than those of the zinc complexes (even in the solvent with lower dielectric constant, which favours a stability increase). This is due to the stability increase caused by chelate formation in the zinc-

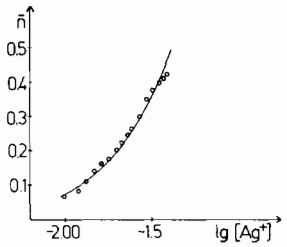


Fig. 7. Formation curve of the silver complex of **II**. Circles are experimental values; the full line was calculated by assuming the formation of two complexes, with metal:ligand ratios of 1:1 and 2:1.

containing systems. Only one compound (**IX**) was shown to form a bis complex with silver, for only in the latter system did the solubility of the ligand permit the use of a ligand excess high enough to ensure bis complex formation. The silver complex of **IV** precipitated from solution in the 50% *v/v* acetone–water solvent, which prevented its equilibrium study.

Compound **II** is the only one which coordinated two silver ions, as shown by the $\bar{n}$ *vs.* $\log[Ag^+]$ curve in Fig. 7. The good fit between the calculated and experimental data proves this behaviour. Thus, in this hexahydro derivative the ring nitrogen in position 5 is accessible not only for the coordination of zinc, but also for that of silver. Compounds **VIII** and **XIV** did not display the same behaviour, indicating that in the case of silver coordination by the ring nitrogen in position 5 the substituent at position 3 may also influence the complex formation process.

Conclusion

These pyrido[1,2-*a*]pyrimidine derivatives served as favourable model systems for study of the factors influencing the coordination chemical behaviour of ring nitrogens in cyclic compounds with different degrees of saturation. The equilibrium studies reflected the effects of the degree of saturation, chelate formation, the basicities of the donor atoms, the presence of substituents at different positions and the configuration of the ring system on the stabilities of the zinc and silver complexes.

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