NEW CHELATING AGENTS BASED ON 8-HYDROXYQUINOLINE

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By

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SCOPE AND CONTENTS:

Several new potentially terdentate chelating agents based on the 8-hydroxyquinoline structure have been synthesized and characterized. Protonation constants of these ligands and formation constants of their chelates with selected metal-ions have been determined. Where possible, the chelates have been characterized by elemental analysis and other means.

The results show that the ligand 2-(2'-thienyl)-8-hydroxyquinoline acts as a sterically hindering bidentate donor; the unusual relationship found between the formation constants of its bis-chelates ($K_1 < K_2$) has been explained on the basis of steric effects.

The results of studies involving 4-amino-5-hydroxyacridine and 4,5-dihydroxyacridine indicate that these ligands act as terdentate and bidentate donors, respectively. The failure of 4,5-dihydroxyacridine to act as a terdentate

donor is explained in terms of chelate-ring strain.

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INTRODUCTION

Since the discovery by Tschugaeff[1] in 1905 that dimethylglyoxime is a highly selective precipitant for nickel(II)-ion, the development of specific and selective organic reagents for the detection and determination of metal-ions has been a main objective of research in analytical chemistry.

Feigl[2] has defined the terms "specific" and "selective" in relation to analytical reagents. A specific reagent is one which, under specified experimental conditions, yields an analytically useful reaction with only one metal-ion; a selective reagent gives an analytical reaction with a limited number of metal-ions under the stated conditions.

That a particular analytical reagent is selective or specific for a certain metal-ion may be the result of one or more factors. For example, the judicious control of pH, or the use of appropriate complexing agents to "mask" interfering ions, often allows the requisite selectivity to be achieved for such inherently non-selective reagents as 8-hydroxyquinoline[3] and ethylenediaminetetraacetic acid[4].

Often, the basis of the selectivity of a reagent resides in differences in the solubility of its metal complexes. This effect is best illustrated by the selectivity of dimethylglyoxime toward nickel(II)-ion. In the solid state, the nickel(II) chelate is polymeric, the molecular units likely being held together by nickel-nickel bonding[5]. The solid complexes of other first-row transition metal-ions with dimethylglyoxime are not polymeric (although the copper(II) complex is dimeric[6]) and, as a result, are considerably more soluble than the nickel(II) complex. This effect of metal-complex solubility in providing the basis of selectivity is all the more remarkable in view of the fact that the solution stability* of the copper(II) complex is greater than that of the nickel(II) complex[7].

Enhanced selectivity may also be achieved when a reagent which reacts with several metal-ions produces a coloured species with one or only a few metal-ions. For example, metalphthalein is a useful indicator for calcium(II), strontium(II) and barium(II) with which it forms highly coloured chelates[8]. Except for magnesium(II), which gives a weak colour, the other metal complexes of

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*The stability of a metal complex, ML_n, in solution is measured by the equilibrium constant K_n for the reaction

$$ML_{n-1} + L \rightleftharpoons ML_n.$$

This equilibrium constant is termed the stability constant or the formation constant. As implied by the subscripts, complex formation occurs in a stepwise fashion.

metalphthalein are colourless. In instances where several coloured complexes are formed, selectivity may still be achieved if the spectral regions of absorption are sufficiently well separated.

Improved selectivity may also occur if some but not all of the complexes formed by a particular reagent are fluorescent. Thus, 8-hydroxyquinoline is a somewhat more selective reagent for gallium when used fluorometrically than it is when employed in other methods[9].

Perrin[10] has commented that another factor which deserves consideration in the development of selective reagents is the possibility of devising methods for estimating a metal-ion in the presence of others by exploiting differences in the rates of formation and dissociation of complexes. Although kinetic effects have been used to advantage in chemical analysis[11], there appears to be no outstanding example of enhanced selectivity toward metal-ions based on rate differences.

Finally, selectivity may result from differences in the solution stabilities of the complexes formed between a particular ligand* and a series of metal-ions. In the extreme, a reagent which forms a very stable complex with one metal-ion but unstable complexes with other metal-ions will be specific. Unfortunately, from the large amount of data that has been accumulated[12],

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*The terms "ligand" and "reagent" are used interchangeably throughout.

it is apparent that the stability differences among complexes of different metal-ions with the same ligand are usually not large enough to provide specificity. Indeed, it seems probable that a specific reagent for each metal-ion is unlikely to be discovered. However, a small number of ligands have assumed importance as analytical reagents because differences in solution stability of their metal complexes have provided enhanced selectivity, if not specificity. Although only modest, this success has stimulated an unusually large amount of research in this area.

With the realization that selectivity in some instances reflects differences in the stability of metal complexes, much of the research mentioned above has been directed towards determining factors that govern their solution stability. Most compounds studied have been metal chelates since with few exceptions, organic reagents are chelating agents. Some of the more important factors that affect metal-chelate stability (and therefore reagent selectivity) are (a) the nature of the ligand donor atoms, (b) the basicity of the ligand donor atoms, and (c) steric effects which influence the formation of the metal chelate. These factors* are discussed below.

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*It is difficult to ignore the nature of the metal-ion when ascribing selectivity to factors (a) and (c). Such properties as charge, size and preferred stereochemistry of the ion are intimately related to the effects of factors (a) and (c). Hence, one should properly speak of the selectivity of a reaction rather than the selectivity of a reagent.

(a) The Nature of the Ligand Donor Atoms. Ahrland, Chatt and Davies[13] have described metal-ions in the periodic table as being either class (a) or class (b). Class (a) metal-ions form their most stable complexes with ligands containing the more electronegative donor atoms such as nitrogen or oxygen; class (b) metal-ions form their most stable complexes with ligands containing the more polarizable donor atoms such as phosphorus, arsenic, sulfur or selenium. Class (a) metal-ions include members of the alkali metals, alkaline earths, lanthanides, actinides, the beginning members of the transition series, and aluminium(III) and gallium(III), i.e., the more electropositive ions. The class (b) metal-ions are found generally within the triangle described by lines joining copper to tungsten and to polonium, i.e., those ions whose complexes have considerable covalent or π-bonding character. (A number of metal-ions do not have distinct class (a) or class (b) character and have been termed borderline ions.) By designing a ligand containing, say, sulfur donor atoms, the number of stable complexes formed may be restricted to the relatively small number of ions within the triangle mentioned above. It is obvious that a considerable measure of selectivity may be achieved by a suitable choice of donor atoms.

(b) The Basicity of the Ligand Donor Atoms. Many studies have shown that for a closely related group

of ligands and a particular metal-ion (e.g., salicylaldehyde derivatives and copper(II)-ion[14]), the stability of the metal chelate increases with increasing basicity of the donor atoms. In most cases, an approximate linear relationship exists between the logarithm of the formation constant of the metal chelate (log K_n) and the logarithm of the protonation constant of the ligand (log K^H). For ligands with more than one type of basic centre, correlations have usually been made with the protonation constant of the most basic centre, although some authors prefer to use the sum of the protonation constants of all the basic centres involved in complex formation.

(c) Steric Effects. Since this factor is more pertinent to the contents of this thesis than factors (a) and (b), it will be discussed in greater detail. Irving and Rossotti[15] have shown that the expected linear relationship between the logarithm of the formation constant and the logarithm of the ligand protonation constant holds for a series of derivatives of 8-hydroxyquinoline and a particular metal-ion, but only for those derivatives that are unsubstituted in the position alpha to the coordinating nitrogen. For ligands which are substituted in this position, the stability of the chelate is substantially less than would be predicted from the linear relationship between log K_n and log K^H. The decrease in stability has been ascribed to steric hindrance

by the alpha substituent to chelate formation. Such steric effects have been exploited analytically in the design of reagents with enhanced selectivity. This enhancement arises largely from the fact that the preferred stereochemical configurations (e.g., tetrahedral, square planar, octahedral) of different metal-ions may vary markedly, even though their affinity for a particular donor atom differs only to a small degree.

The effects of steric hindrance on chelate stability can best be illustrated by examples. The familiar analytical reagent 8-hydroxyquinoline, although a very unselective reagent, is widely used for the gravimetric determination of aluminium(III), with which it forms an insoluble yellow tris-complex. Substitution of a methyl group alpha to the coordinating nitrogen, however, results in a reagent which does not precipitate an aluminium(III) chelate, although it still forms precipitates with most other metal-ions[16]. The fact that 2-methyl-8-hydroxyquinoline does not form a precipitate with aluminium(III)-ion (in fact, in aqueous solution not even a 1:1 complex can be detected[17]) has been attributed to at least three factors[18], the most important of which appears to be a substantial decrease in the stability of the aluminium(III) chelate due to steric hindrance. This decreased stability allows hydroxyl-ion to compete effectively with the ligand for aluminium(III)-ion, as the pH of the solution is

raised to bring about metal-chelate formation. Ultimately, aluminium hydroxide precipitates. Even though 2-methyl-8-hydroxyquinoline still forms complexes with other metal-ions, these complexes are also less stable than the corresponding 8-hydroxyquinoline chelates[19], although not to the point where precipitation of the stoichiometric chelate is prevented.

The chelating agent 1,10-phenanthroline forms stable, water-soluble chelates with many metal-ions. (The formation of the highly coloured tris-chelate with iron(II) is the basis of a well known analytical procedure for the determination of small amounts of iron.) On the other hand, 2,9-dimethyl-1,10-phenanthroline is a specific reagent for copper(I), with which it forms a stable, highly coloured bis-chelate, extractable into organic solvents[20]. The specific nature of this reagent (and of the analogous chelating agent 2,2'-biquinoline) has been demonstrated by tests with many other metal-ions, none of which formed a coloured complex[20,21]. This remarkable specificity stems from the fact that complexes of metal-ions which prefer square planar or octahedral coordination are sterically destabilized[22]. In the copper(I) complex, the metal-ion is tetrahedrally coordinated, the two ligand molecules being held in planes mutually at right angles. In this configuration, steric hindrance caused by the substituents alpha to the coordinating nitrogen atoms is

virtually eliminated.

The linear tetradentate ligand triethylenetetramine forms a very stable square-planar complex with copper(II)-ion[23]. The donor atoms of the isomeric ligand 2,2',2"-triaminotriethylamine prefer a tetrahedral arrangement and as a result, the copper(II) complex of this ligand is less stable[24]. Zinc(II), however, readily forms tetrahedral complexes and as a result its complex with 2,2',2"-triaminotriethylamine is more stable than its complex with the linear polyamine[23,24].

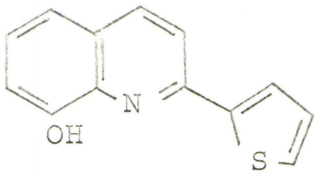
A final example is provided by calcichrome[25], which is a selective metallochromic indicator for calcium(II) in the presence of other alkaline-earth ions. Calcichrome is a macrocyclic ligand that derives its selectivity from the fact that its donor atoms are arranged in a "chelate cage" of such dimensions that, of the alkaline-earth ions, only calcium(II) can enter.

These examples illustrate different steric effects. The substituted compounds 2-methyl-8-hydroxyquinoline and 2,9-dimethyl-1,10-phenanthroline form chelates of lower stability than those of the parent compounds with metal-ions favouring square-planar or octahedral coordination. Here, selectivity is obtained by modifying an analytical reagent by the substitution of sterically hindering groups near the coordination sites. In the third example, the steric relationship of donor atoms within a single

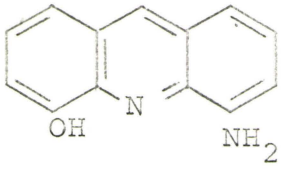
ligand favours the formation of chelates with metal-ions having a certain configuration. The final example illustrates the use of a ligand which is able to discriminate between ions of differing size.

Thus, the introduction of suitable steric constraints in a ligand may result in increased selectivity. To effect the maximum discrimination between metal-ions of different configurations, the ligand should have a rigid orientation of donor atoms, i.e., the ligand should not be able to distort to meet the steric demands of the metal-ion, but should impose its own steric demands upon the metal-ion. The converse, of course, also holds true. Multidentate ligands with completely flexible structures are highly unselective (e.g., ethylenediaminetetraacetic acid, which reacts with virtually every metal-ion).

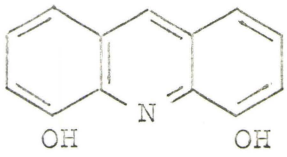
In the present work, the chelating properties of the following potentially terdentate ligands are examined: 2-(2'-thienyl)-8-hydroxyquinoline(I), 4-amino-5-hydroxyacridine(II), 4,5-dihydroxyacridine(III) and 4,5-diaminoacridine(IV). All are new compounds, with the exception of 4,5-diaminoacridine. The ligand 2-(2'-thienyl)-8-hydroxyquinoline was prepared with the expectation that the sulfur atom of the thienyl substituent might coordinate, as in the copper(II) complex of 2-(2'-thienyl)-pyridine[26]. In 2-(2'-thienyl)-8-hydroxyquinoline, only two of the potential coordinating atoms in the ligand



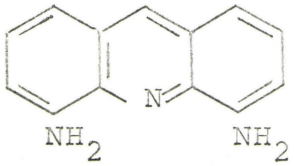
I



II



III



IV

are fixed since the thienyl group has some freedom of motion. In the acridine ligands, the three donor atoms are fixed in a rigid planar framework.

As shown by the construction of molecular models, these ligands should favour complex formation with metal-ions which prefer a planar or octahedral configuration. In these cases, planar mono-chelates or octahedral bis-chelates, respectively, could be formed. Here, the ligands should be terdentate and able to span three co-ordination positions in a plane. With metal-ions which prefer tetrahedral coordination, the ligands would at best be bidentate and hence the complexes would be of consider-ably lower stability.

The new ligands studied in this work are based on the 8-hydroxyquinoline structure; in fact they can be viewed as 2-substituted derivatives of 8-hydroxyquinoline. The formation constants of chelates of several 2-substi-

tuted 8-hydroxyquinolines have been reported, where the 2-substituents are alkyl[19,27] or phenyl[19]. In addition, qualitative tests with 8-hydroxyquinoline-2-carboxylic acid[28], and very recently, with 2-aminomethyl-8-hydroxyquinoline[29] have been reported. These two ligands, and the new ligands described in the present work, are unique in that the 2-substituent, normally expected to be sterically hindering, contains a donor atom which potentially can coordinate with the metal-ion.

The determination of equilibrium constants for the formation of metal chelates has long been used as a means for assessing structural effects of ligands. The chelate formation constant, K_n, is the equilibrium constant for the corresponding stepwise reaction

$$ML_{n-1} + L \rightleftharpoons ML_n.$$

Thus, for a system in which the highest complex formed is ML_N, there are N stepwise equilibria and N formation constants, K_1, K_2 .... K_N. L is the chelating form of the ligand; for some ligands (e.g., ethylenediamine) L is neutral, for others containing acidic protons (e.g., 8-hydroxyquinoline) it is anionic.

In the present work, formation constants were determined by a modified form of the Bjerrum[30] method. This method, applicable to ligands whose chelating form is basic, involves measurement of the hydrogen-ion con-

centration in solutions containing metal-ion, ligand and hydrogen-ion. Protonation of the ligand provides a means of varying the concentration of free ligand, L, over a very wide range. Bjerrum introduced the use of the quantity, $\bar{n}$, the average number of ligands bound to a metal-ion at a particular concentration of L. In the Bjerrum method, measurements are made over a range of concentrations of free ligand, such that $\bar{n}$ varies from zero to N, its maximum value. Bjerrum developed general equations and methods for the calculation of the N formation constants of the complex ML_N from the data $\bar{n}$,[L]. These equations have found widespread use in the study of metal chelates as well as complexes with monodentate ligands.

Although the potentiometric method is very widely applicable, it has a number of limitations. Since most metal-ions undergo hydrolysis, the upper pH limit of the method is determined by the pH of hydrolysis of the metal-ion. This is generally in the vicinity of pH 7 for divalent transition metal-ions[31]. The lower pH limit is about three because, in solutions of higher acidity, the hydrogen-ion released upon chelation is virtually undetectable. A further limitation is that valid measurements cannot be made in the presence of a solid phase containing either metal-ion or ligand. Thus, systems that involve ligands or chelates of low solubility cannot be studied by this method. Other techniques

which may be used to determine chelate formation constants include spectrophotometry, polarography, solvent extraction, ion-exchange and the use of radioactive tracers[32].

The modifications to the Bjerrum method which were used in the present study were introduced by Calvin and Wilson[14]; these workers used a titration technique in which an acidified solution of ligand and metal-ion was titrated with a solution of standard base. (Bjerrum employed a "batch" or one-point technique.) Calvin and Wilson also introduced the use of the mixed solvent dioxane-water to overcome the problems associated with the limited aqueous solubility of many metal chelates. This solvent system has found wide application in the study of the solution chemistry of metal complexes, and many workers have attempted to put equilibrium measurements in aqueous dioxane (and in other aqueous-organic solvents) on a firmer theoretical basis. Van Uitert and Haas[33] compared the behaviour of the glass electrode and the hydrogen electrode in aqueous dioxane and showed that the glass electrode functioned linearly with respect to the hydrogen electrode. The latter electrode was assumed to give a true measure of the hydrogen-ion activity in the mixed solvent. These workers also found that when the glass electrode was used to measure the hydrogen-ion activity of hydrochloric acid solutions in aqueous dioxane, the pH meter reading, R, was given by

$$R = -\log[H^+] - \log U$$

where $[H^+]$ is the stoichiometric concentration of hydrogen-ion*. It was found that U, a correction factor, was a function of the mole fraction of dioxane in the solvent and of the ionic strength of the medium, but was independent of the hydrogen-ion concentration. This permits the use of log U to correct pH meter readings (closely related to hydrogen-ion activity) to hydrogen-ion concentrations. For a given solvent composition and ionic strength, the correction factor is a constant which allows the glass electrode-reference electrode combination to be used as a hydrogen-ion concentration probe.

In order to minimize changes in activity coefficients of the ionic species involved in the reactions, the use of a "background electrolyte" has been recommended[32]. It has been shown by many workers that the activity coefficient of an ionic solute is essentially independent of its concentration, provided that its concentration is negligible compared to that of an inert electrolyte in the solution. Unfortunately, many workers concerned with the determination of formation constants in aqueous-organic solvents have not employed an inert electrolyte. In the present work, in which the solvent was 50% $^{v}/_{v}$ dioxane-water, 0.1M sodium perchlorate was

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*It was assumed that the hydrochloric acid is completely dissociated in each solvent mixture used.

used as a background electrolyte. The Van Uitert and Haas correction factor has been determined for this medium.

This thesis is concerned with several new potentially terdentate chelating agents which embody a rigid or partly rigid orientation of donor groups, and describes their synthesis and characterization. In addition, the protonation constants of these compounds, required for the calculation of metal chelate formation constants, are determined.

The effect of the structural design on the selectivity of the ligands is examined both qualitatively (by noting the occurrence of reactions with many metal-ions) and quantitatively (by the determination of formation constants with selected* metal-ions.) Where possible, the metal complexes formed by the new ligands are characterized.

An attempt to explain the results on the basis of steric effects is made.

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*The ions customarily selected in studies of this kind are manganese(II), iron(II), cobalt(II), nickel(II), copper(II) and zinc(II), since the operation of unusual effects (e.g., steric effects) often disrupts the order of stability of complexes of these ions. In the present work, formation constants for the manganese(II) complexes could not be obtained because the complexes were too unstable. Formation constants for the iron(II) complexes were not determined because of oxidation of iron(II). Cadmium(II) was studied to provide a further example of a metal-ion which exhibits tetrahedral coordination.

EXPERIMENTAL AND RESULTS

Apparatus

Calibrated volumetric ware was used throughout this work whenever this was appropriate.

Infrared spectra were recorded with a Beckman IR-5 infrared spectrometer (Beckman Instruments Inc., Fullerton, California). Visible and ultraviolet spectra were recorded with a Cary Model 14 Spectrophotometer (Applied Physics Corp., Monrovia, California). Other spectrophotometric measurements in the visible and ultraviolet were made using a Hitachi Perkin-Elmer Model 139 Spectrophotometer (Perkin-Elmer Corp., Norwalk, Connecticut), the cell compartment of which was maintained at 25°C.

Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6A mass spectrometer. Samples were introduced through an all-glass inlet system maintained at 200°C. Nuclear magnetic resonance spectra were recorded with a Varian A-60 nuclear magnetic resonance spectrometer (Varian Associates, Palo Alto, California).

The potentiometric titration apparatus for the determination of protonation constants and chelate formation constants consisted of a titration cell, a pH meter, two ten-milliliter microburettes and a constant-tempera-

ture water bath. The pH meter was a Radiometer Model PHM4 (Radiometer, Copenhagen, Denmark) equipped with Beckman saturated calomel and E-3 (low sodium-ion error) glass electrodes.

The Gouy balance consisted of a Sartorius Electrono I microbalance (Sartorius-Werke AG., Göttingen, West Germany) and an electromagnet and associated power supply (Alpha Scientific Laboratories Inc., Berkeley, California) providing 4 kilogauss at 6.6 amperes.

Reagents

All common laboratory chemicals were either analyzed grade or of sufficient purity for the purpose for which they were used. A few organic reagents obtained from commercial sources were recrystallized before use.

Reagent-grade 1,4-dioxane was purified by refluxing over sodium for at least 24 hours, followed by fractional distillation through a 1-meter column packed with glass helices. The fraction boiling in the range 100.5-101.0°C was collected as required and used within 24 hours.

Carbonate-free sodium hydroxide for use in potentiometric titrations was prepared by the following method[34]: a 50 wt% solution of sodium hydroxide was prepared and allowed to stand in a tightly closed polyethylene bottle for 24 hours, after which time the precipitated sodium carbonate had settled to the bottom. An

appropriate volume of this solution was added to 4 litres of freshly boiled distilled water in a polyethylene bottle. The solution, approximately 0.1M, was standardized by titrating against 10-ml. portions of standard potassium hydrogen phthalate solution; the end-point was detected potentiometrically. The required amount of boiled water to make the solution exactly 0.100M was then added, and the solution was re-standardized. The value obtained was 0.1001M ± 0.0001M. A solution of sodium hydroxide, approximately 0.010M, for use in the titration of very dilute solutions, was also prepared and standardized in the same manner. The titre of this solution was 0.0101 ± 0.0001M.

Solutions of perchloric acid, approximately 0.01M in perchloric acid and 0.21M in sodium perchlorate, were prepared for use in potentiometric titrations. The hydrogen-ion concentrations of these solutions were determined by titration with standard sodium hydroxide solution. The end-point was determined potentiometrically. A similar solution, 0.001M in perchloric acid and 0.22M in sodium perchlorate, was prepared and standardized as above.

Metal-ion solutions for potentiometric titrations were prepared from the perchlorate salts (G. F. Smith Chemical Company, Columbus, Ohio). The solutions were 0.01M in metal-ion and were standardized by titration

with EDTA, following accepted methods[4]. The EDTA solution was standardized by titration against standard zinc solution.

Metal-ion solutions for spectrophotometric measurements were prepared by accurate ten-fold dilution of the standard metal-ion solutions used in the potentiometric titrations.

Metal-ion solutions for spot-tests were prepared as approximately 0.02M solutions. The solutions of manganese(II), iron(II), cobalt(II), nickel(II), copper(II), zinc(II), mercury(II) and thallium(III) were prepared from the perchlorate salts. Those of magnesium(II), calcium(II), strontium(II), barium(II), lead(II), cadmium(II), aluminium(III), gallium(III), indium(III), scandium(III), yttrium(III), lanthanum(III), chromium(III), thorium(IV), zirconium(IV) and uranium(VI) were prepared from the nitrate salts, and those of palladium(II), rhodium(III) and cerium(III) were prepared from the chloride salts.

Synthesis of Acridine Ligands

The acridine ligands were prepared by a method established for the synthesis of other acridine derivatives[35]. Ullman condensation of an appropriately substituted 2-halobenzoic acid and an appropriately substituted aniline yielded a substituted diphenylamine-6-carboxylic acid. This compound was cyclized in 98% sulfuric acid to yield a substituted acridone, which was

reduced with sodium amalgam to give the acridine compound. The complete reaction sequence is shown in Figure 1, and the procedures are described in detail below.

The synthesis of 4,5-diaminoacridine is based on the procedures of Goldberg and Kelly[36], and Klein and Lahey[37].

2-Nitro-2'-Methoxydiphenylamine-6-Carboxylic Acid. Fifty grams of 2-bromo-3-nitrobenzoic acid[38], 90 ml. of o-anisidine, 20 g. of anhydrous sodium carbonate and 0.5 g. of copper powder were heated at 135°C for 2 hours, or until the mixture solidified. After cooling, the mixture was extracted with 100 ml. portions of hot benzene. The insoluble sodium salts were separated by filtration, air-dried and taken up in 500 ml. of warm water. The solution was filtered and then adjusted to pH 4 with 6M hydrochloric acid. The precipitated 2-nitro-2'-methoxydiphenylamine-6-carboxylic acid was filtered and dried in air. Yield, 24-25 g. (41-43%).

Recrystallization from 95% ethanol yielded orange-red crystals, m.p. 227-228°C.

4-Nitro-5-Methoxyacridone. Twenty-four grams of 2-nitro-2'-methoxydiphenylamine-6-carboxylic acid were dissolved in 150 ml. of 98% sulfuric acid. The solution was heated at 100°C for 15 minutes with stirring, and then poured into 1.5 ℓ. of water. The resulting suspension of 4-nitro-5-methoxyacridone was stirred overnight

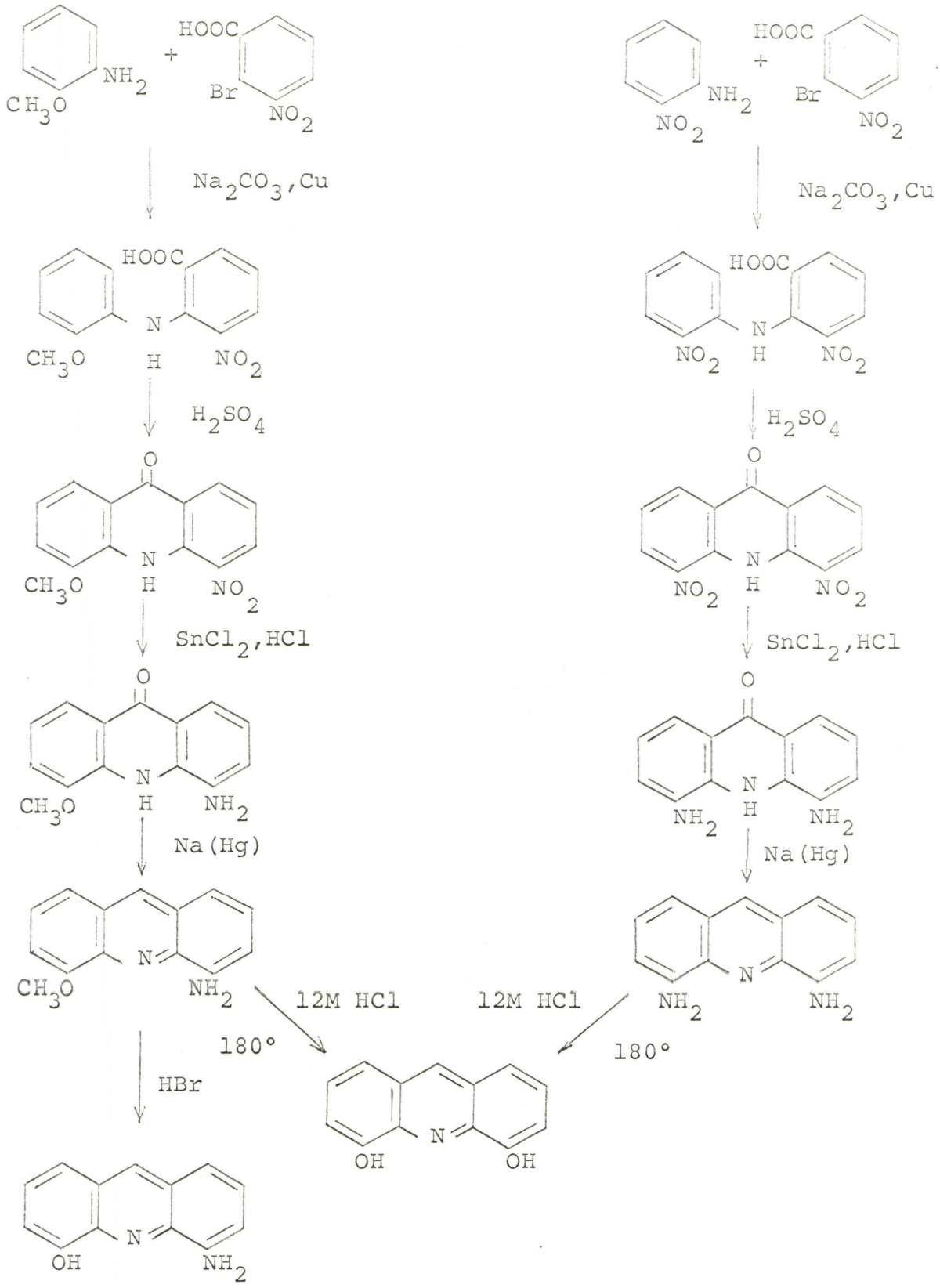

Figure 1. Synthesis of Acridine Ligands.

at approximately 60°C, then filtered and the solid washed with a small amount of dilute aqueous ammonia.

4-Amino-5-Methoxyacridone. The moist 4-nitro-5-methoxyacridone from the preceding step was transferred to a 1-ℓ. flask; 125 g. of stannous chloride and 300 ml. of concentrated hydrochloric acid were added, and the mixture was refluxed for 4 hours. After cooling, the solid was filtered by suction, washed with a small volume of concentrated hydrochloric acid, and dissolved in 1 ℓ. of hot, 1M sodium hydroxide solution. The solution was filtered, and then adjusted to about pH 10 with 6M hydrochloric acid. The precipitated 4-amino-5-methoxyacridone was collected by filtration and dried in air overnight. Yield, 15 g. (74%, based on 2-nitro-2'-methoxydiphenylamine-6-carboxylic acid).

4-Amino-5-Methoxyacridine. Fifteen grams of 4-amino-5-methoxyacridone were placed in a 2-ℓ., 3-neck flask fitted with a mechanical stirrer, and a gas inlet tube, and dissolved in a solution consisting of 500 ml. of 1M sodium hydroxide and 800 ml. of 95% ethanol. The dark green solution was adjusted to pH 8 with approximately 80 ml. of 6M hydrochloric acid. A stream of carbon dioxide was passed into the solution and 650 g. of 4% sodium amalgam were added. The mixture was stirred vigorously for 1 hour without heating, and then at 70-80°C for 2 hours. At the end of this period, the mixture

had become almost colourless. Heating and stirring were continued for a further 2 hours while air was passed into the mixture. The dark solution was filtered hot and the solid material in the flask was extracted several times with hot 95% ethanol. The filtrate and extracts were combined and evaporated to a volume of approximately 500 ml. with frequent additions of water. The precipitated 4-amino-5-methoxyacridine was separated by filtration, washed with water and dried in air. The solid was dissolved in hot benzene, the solution filtered, and the solvent removed in a current of air. Yield, 3 g. of yellow-orange plates (22%).

Recrystallization of a small sample from benzene-petroleum ether yielded orange-yellow needles, m.p. 169-170°C.

Calculated for $C_{14}H_{12}N_2O$: 74.98%C, 5.39%H, 12.49%N

Found*: 74.82%C, 5.55%H, 12.51%N

4-Amino-5-Hydroxyacridine. Six grams of 4-amino-methoxyacridine were dissolved in 100 ml. of 48% hydrobromic acid and refluxed for 24 hours. The solution was cooled, and the precipitated hydrobromide salt of 4-amino-5-hydroxyacridine was obtained by filtration. The solid was dissolved in 200 ml. of hot water and the solution

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*All microanalyses reported in this thesis were performed by Alfred Bernhardt Microanalytisches Laboratorium, Mülheim-Ruhr, West Germany.

made basic with sodium hydroxide. A small amount of insoluble material was removed by filtration; the filtrate was neutralized by the slow addition of 6M hydrochloric acid to the vigorously stirred solution. The precipitated 4-amino-5-hydroxyacridine was filtered, washed with water and dried in air. Yield, 4 g. (72%).

Repeated recrystallization from 50% ethanol yielded the pure material as orange-brown needles, m.p. 195-197°C.

Calculated for $C_{13}H_{10}N_2O$: 74.27%C, 4.79%H, 13.33%N

Found: 73.76%C, 5.09%H, 13.08%N

4,5-Diaminoacridine. This compound was prepared by a series of reactions similar to those described above. 2,2'-Dinitrodiphenylamine-6-carboxylic acid was prepared by heating a mixture of 50 g. of 2-bromo-3-nitrobenzoic acid, 50 g. of o-nitroaniline, 20 g. of anhydrous sodium carbonate and 0.5 g. of copper powder at 190-210°C for 4 hours. The reaction mixture was extracted with benzene and the insoluble sodium salts were dissolved in water. Concentration of the solution to a volume of approximately 200 ml. followed by cooling in an ice-bath yielded the sodium salt of 2,2'-dinitrodiphenylamine-6-carboxylic acid. The sodium salt was dissolved in water and the solution was acidified. The precipitated acid was recrystallized from 95% ethanol to yield yellow needles, m.p. 248-250°C (literature 246°C[36], 252-254°C[37]).

Twenty-two grams of 2,2'-dinitrodiphenylamine-6-carboxylic acid were cyclized in 98% sulfuric acid and the resulting acridone was reduced, first with stannous chloride and then with 4% sodium amalgam, to yield 4,5-diaminoacridine in yellow-brown needles, m.p. 178-179°C (literature 177°C[36], 182°C[37]).

Calculated for $C_{13}H_{11}N_3$: 74.62%C, 5.30%H, 20.08%N

Found: 74.75%C, 5.68%H, 19.77%N

4,5-Dihydroxyacridine. A solution of 2.5 g. of 4-amino-5-methoxyacridine in 25 ml. of 12M hydrochloric acid was sealed in a heavy-walled Pyrex tube and heated for 8 hours at 180°C. After cooling, the contents of the tube were dissolved in 200 ml. of water. The solution was filtered and then made basic with sodium hydroxide. A small amount of insoluble material was removed and the solution was then neutralized with 6M hydrochloric acid. The precipitated 4,5-dihydroxyacridine was collected by filtration. Repeated recrystallization from aqueous ethanol gave light yellow needles, m.p. 265-267°C. The yield was not calculated.

4,5-Dihydroxyacridine could also be prepared from 4,5-diaminoacridine by heating with concentrated hydrochloric acid in a sealed tube at 180°C for 24 hours.

Calculated for $C_{13}H_9N_2O$: 73.92%C, 4.30%H, 6.63%N

Found: 73.81%C, 4.68%H, 6.82%N

4-Hydroxyacridine. 2-Nitrodiphenylamine-6-carboxylic acid was prepared in the usual manner by refluxing a mixture of 50 g. of 2-bromo-3-nitrobenzoic acid, 140 ml. of aniline, 20 g. of anhydrous sodium carbonate and 0.5 g. of copper powder for 1 hour. The precipitated sodium salts were washed with benzene, dried in air and dissolved in water. Acidification yielded the free acid.

The acid was cyclized in 98% sulfuric acid and the resulting 4-nitroacridone was reduced, first with stannous chloride and then with sodium amalgam, to yield 4-aminoacridine. 4-Hydroxyacridine was prepared by heating 3.0 g. of 4-aminoacridine with 15 ml. of concentrated hydrochloric acid in a sealed tube at 200°C for 6 hours. The compound was isolated and purified as described for 4,5-dihydroxyacridine. Yield, 0.54 g. (18%), m.p. 115-115.5°C (literature 116-117°C[39]).

Synthesis of 2-(2'-Thienyl)-8-Hydroxyquinoline

The method employed for this synthesis has been used for the preparation of many 2-aryl-8-hydroxyquinolines[40]. It involves the addition of the appropriate aryllithium compound to the —N=C— bond of the quinoline ring, followed by oxidation of the 2-substituted 1,2-dihydroquinoline compound to the fully aromatic compound. Although these 1,2-dihydroquinoline compounds are readily oxidized (air oxidation during the isolation of

the product generally being sufficient), nitrobenzene was used as an additional oxidizing agent[41] in the present work.

8-Methoxyquinoline. This compound was prepared by the Skraup reaction following the procedure of King and Sherred[42]. After two distillations at reduced pressure, the product was obtained as a clear yellow oil boiling at 160-161°C at 8mm. Hg. (Literature 174-176°C at 29 mm.[42]). Yield, 50 g. (40%).

2-(2'-Thienyl)-8-Methoxyquinoline. A solution of 17 g. of thiophene (previously dried over sodium hydroxide) in 200 ml. of dry ether was placed in a 1-ℓ. flask equipped with a nitrogen inlet, a reflux condenser and a rubber serum cap. The flask was placed in a cold-water bath while 125 ml. of a 1.6M solution of n-butyllithium in hexane was added dropwise by means of a syringe. A solution of 32 g. of 8-methoxyquinoline in 200 ml. of dry ether was then added dropwise with stirring over a period of 1 hour, after which stirring was continued for a further 2 hours. The reaction mixture was hydrolyzed by the addition of 300 ml. of water, the ether layer separated, and the aqueous layer extracted several times with ether. The combined ether extracts were evaporated on a steam plate overnight, leaving a deep red oil. To the oil was added 100 ml. of nitrobenzene, and the solution was boiled for approximately fifteen minutes. The solu-

tion was distilled under vacuum; the product was obtained as a viscous yellow oil boiling at 230°C at 8 mm. Hg. Yield, 32.5 g. (68%).

The solidified product crystallized from ether as light yellow needles, m.p. 110.5-111.0°C.

Calculated for $C_{14}H_{11}ONS$: 69.68%C, 4.61%H, 5.81%N, 13.29%S

Found: 69.53%C, 4.66%H, 5.89%N, 13.56%S

2-(2'-Thienyl)-8-Hydroxyquinoline. A solution of 17.5 g. of 2-(2'-thienyl)-8-methoxyquinoline in 150 ml. of 48% hydrobromic acid was refluxed for 24 hours. Upon cooling, the hydrobromide salt precipitated; this was filtered and dissolved in warm water. The solution was filtered, made basic with sodium hydroxide, and filtered to remove a small amount of insoluble material. Neutralization of the filtrate yielded 2-(2'-thienyl)-8-hydroxyquinoline, which was separated by filtration, washed with water and dried in air. Yield, 6.0 g. (38%).

Repeated recrystallization from aqueous ethanol gave the pure compound, m.p. 71.5-72.0°C.

Calculated for $C_{13}H_9ONS$: 68.68%C, 4.00%H, 6.16%N, 14.11%S

Found: 68.97%C, 3.71%H, 6.28%N, 14.35%S

Characterization of Ligands

In addition to the elemental analyses given above, the new ligands were further characterized by infrared, nuclear magnetic resonance and mass spectrometry. The

infrared spectra (obtained by the potassium bromide pellet technique) showed absorption bands in the regions characteristic of the functional groups (-OH, $-NH_2$ and $-OCH_3$). The NMR spectra were recorded at 60Mc, with dioxane as solvent except as otherwise noted; chemical shifts are with respect to hexamethyldisiloxane as internal reference. The spectra are summarized in Table I and are reproduced in Appendix I. Further comment is given in the Discussion. The mass spectra were recorded using an ionization potential of 80 eV and an ionizing current of 50 μA. For each ligand, the m/e ratio of the parent ion agreed with the calculated molecular weight.

Reactivity of the Ligands toward Metal-ions

Before the determination of chelate formation constants, spot-tests with 29 metal-ions were performed, to determine the general reactivity of the ligands toward metal-ions. The procedure was as follows: 1.0 ml. of aqueous buffer* and 1.0 ml. of a 0.1% solution of ligand in 95% ethanol were mixed in a test-tube. Then three drops (0.1 ml.) of metal-ion solution were added. A colour change or the formation of a precipitate was noted. The results were interpreted in the light of "blank" tests, and are presented in Appendix II.

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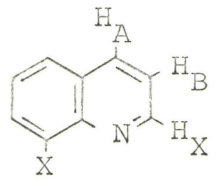
*The buffers were prepared as follows: the pH 5 buffer was acetic acid-sodium acetate, 0.1M in total acetate; the pH 10 buffer was 0.025M sodium tetraborate.

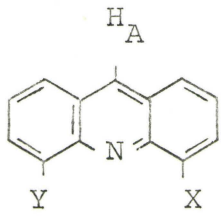
TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF LIGANDS

(Solvent: 1,4-Dioxane, except as noted)



Compound	Chemical Shifts p.p.m. X	H_X	H_A	Coupling Constants (c/s) J_{AB}	J_{BX}	J_{AX}
8-Hydroxyquinoline	9.08	8.77	8.04	8.5	4.0	1.5
2-(2'-Thienyl)-8-Hydroxyquinoline	8.40	-	8.10	8.5	-	-
2-(2'-Thienyl)-8-Methoxyquinoline*	3.87	-	7.64	8.5	-	-



Compound	Chemical Shifts (p.p.m.) 4-Substituent (X)	5-Substituent (Y)	H_A
4,5-Diaminoacridine	5.67	5.67	8.53
4,5-Dihydroxyacridine	9.09	9.09	8.70
4-Amino-5-Hydroxyacridine	5.83	8.95	8.60
4-Amino-5-Methoxyacridine	5.77	4.00	8.64

*In carbon tetrachloride

Preparation of Solid Chelates

Chelates of 4,5-dihydroxyacridine and 2-(2'-thienyl)-8-hydroxyquinoline with cobalt(II), nickel(II), copper(II) and zinc(II), and of 4-amino-5-hydroxyacridine with cobalt(II), nickel(II) and zinc(II) were prepared and isolated in the following manner: 10 ml. of 0.01M metal perchlorate solution and 200 ml. of water were heated to 80°C. The solution was stirred magnetically and 50 ml. of a dioxane solution of the ligand were added. The chelate was precipitated by the dropwise addition of 2.0 ml. of 0.1M sodium hydroxide solution. In the case of the 4,5-dihydroxyacridine chelates, precipitation occurred without the addition of base. The chelates were digested for 1-2 hours at 80°C, then filtered, washed with warm 20% dioxane and dried overnight in a vacuum desiccator at 60°C.

The copper(II) chelate of 4,5-diaminoacridine was prepared as follows: 10 ml. of a 0.01M solution of anhydrous cupric bromide in 50% v/v tetrahydrofuran-dioxane was added to 10 ml. of a 0.020M solution of the ligand in dioxane. Precipitation occurred immediately. The mixture was allowed to stand for a week in order to effect some increase in the particle size of the precipitate, then the solid was separated by suction filtration, washed with a small volume of dioxane, and dried in a vacuum desiccator at 60°C.

Elemental analyses of the chelates are given in Appendix III.

Spectrophotometric Determination of Protonation Constants and the Order of Protonation of Ligand Donor Sites

1. Procedure

The second protonation constants of 2-(2'-thienyl)-8-hydroxyquinoline and 4,5-diaminoacridine were determined spectrophotometrically, since the pH range in which protonation occurs is too low for the potentiometric method (see below) to be applicable. The first protonation constant of 4,5-dihydroxyacridine was determined spectrophotometrically since the pH range of protonation is near the upper limit of the potentiometric method (pH 12-13). Proton formation constants for the ligands 4-amino-5-hydroxyacridine and 4-amino-5-methoxyacridine were also determined spectrophotometrically, although in some cases these could be determined potentiometrically. Approximate values of the third protonation constant of 4-amino-5-hydroxyacridine and the second protonation constant of 4-amino-5-methoxyacridine, which were observable only in rather concentrated acid solution (e.g., 1-5M), were obtained.

Preliminary spectra of the compounds at various pH values were recorded in the visible and ultraviolet ranges. These spectra were required in order to find suitable wavelengths for measurement. They were also used, in the case of 4-amino-5-hydroxyacridine and 4-amino-5-methoxyacridine (in conjunction with the spectra of 4-hydroxy-

acridine) to determine the order of protonation of the ligand donor sites. Solutions of the ligands (2×10^{-5}M for spectra in the range 200-350 mμ, 1×10^{-4}M for spectra in the range 300-600 mμ) were prepared in 50% v/v dioxane-water; pH values were chosen to yield solutions containing, if possible, only one of the protonated forms of the ligand. The spectra are summarized in the following table, and the spectra of the acridine compounds are shown in Appendix IV.

Solutions for the determination of the protonation constants were prepared as follows: 5.00 ml. portions of a dioxane solution of the ligand to be studied were pipetted into 50-ml. volumetric flasks containing 25.0 ml. of aqueous solutions of appropriate pH and 20.0 ml. of dioxane. The required pH values were maintained by acetate or phosphate buffers*, or by perchloric acid or sodium hydroxide solutions. The ionic strength of the solutions was adjusted to 0.10 by the addition of sodium perchlorate†. The flasks were equilibrated at 25.0°C and the solution volume was adjusted to 50.0 ml. with 50% v/v dioxane-water. Absorbance measurements were made on these solutions in 1.00-cm. fused-silica absorption cells at the appropriate wavelength (Table II).

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*The buffers were prepared such that their contribution to the ionic strength of the final solution was less than 0.005. The acetate buffers were 0.005M in total acetate, and the phosphate buffers were 0.001M in total phosphate.

†In the solutions of pH 1 or less, the ionic strength was not controlled.

TABLE II

SPECTRAL DATA OF LIGANDS

(Solvent: 50% v/v dioxane-water; temperature: 25°C)

Ligand	Species	pH	Absorption Maxima, mμ (log ε in parentheses)
4-Amino-5-Hydroxyacridine	H_3L^{++}	4M $HClO_4$	343(3.70), 362(3.95), 450(3.18)
	H_2L^{+}	1	263(4.79), 341(3.40), 358(3.52), 396(3.43)
	HL	7	267(4.74), 430(3.49)
	L^{-}	13	278(4.77), 353(3.31), 371(3.34), 452(3.56)
4-Amino-5-Methoxyacridine	H_2L^{++}	4M $HClO_4$	343(3.79), 360(4.09), 450(3.32)
	HL^{+}	2	339(3.40), 354(3.56), 386(3.48)
	L	7	424(3.52)
4-Hydroxyacridine	H_2L^{+}	2	270(4.77), 345(3.78), 361(4.11), 441(3.35)
	HL	7	259(4.89), 340(3.43), 358(3.63), 395(3.53)
	L^{-}	13	285(4.65), 460(3.37)
4,5-Diaminoacridine	H_2L^{++}	4M $HClO_4$	337(3.77), 353(3.95)
	HL^{+}	2	278(4.52), 434(3.36)
	L	7	275(4.84), 441(3.60)
4,5-Dihydroxyacridine	H_3L^{+}	1	267(4.73), 279(2.92), 365(3.53), 469(3.23)
	H_2L	7	266(5.07), 400(3.60), 418(sh)*
	HL^{-}	11	282(4.74), 450(3.45)
	$L^{=}$	14	280(4.83), 455(3.62)

TABLE II (Cont'd)

Ligand	Species	pH	Absorption Maxima, mμ (log ε in parentheses)	
2-(2'-Thienyl)-8-Hydroxyquinoline	H_2L^+	0	305(4.34)	373(4.32
	HL	7	295(4.49)	338(4.04)
	L^-	13	308(4.56)	402(3.54)

* sh = shoulder

2. Calculations

Protonation constants were calculated using the equations

$$\log K_1^H = p_cH + \log \frac{A_L - A}{A - A_{HL}} \quad (1)$$

$$\log K_2^H = p_cH + \log \frac{A_{HL} - A}{A - A_{H_2L}} \quad (2)$$

where $p_cH = -\log [H^+]$, A_L, A_{HL}, A_{H_2L} represent the absorbance of the neutral, monoprotonated and diprotonated forms of the ligand, respectively, and A represents the absorbance of a mixture of L and HL^+, or HL^+ and H_2L^{++}. These equations hold only if the pH range of protonation of the donor site under consideration does not overlap appreciably with that of another. The data are presented in Appendix V.

The pH ranges for the addition of the first and second protons to 4,5-diaminoacridine did overlap appreciably, and as a result a plot of absorbance (at 275 mμ) versus pH did not exhibit a region in which only the monoprotonated species, HL^+, absorbed, although the absorbance of the pure species L and H_2L^{++} could readily be obtained. The absorbance of the monoprotonated species was obtained in the following manner. From equation (1)

$$1/K_1^H = \frac{[H^+]\ (A - A_{HL})}{(A_L - A)} \quad (3)$$

which, upon rearranging, becomes

$$A\left[\frac{1}{K_1^H} + [H^+]\right] = [H^+]\,A_{HL} + A_L/K_1^H \qquad (4)$$

In the pH region in which only the species L and HL^+ exist in appreciable concentrations, a plot of the left-hand side of equation (4) (using the values of K_1^H obtained potentiometrically as described below) versus $[H^+]$ yielded a straight line with slope $A_{HL}+$.

Using this value of $A_{HL}+$ and equation (2), $\log K_2^H$ was calculated from data in the pH region in which only HL^+ and H_2L^{++} exist in appreciable concentrations. Figure 2 shows the agreement between the calculated curve of absorbance versus pH and the experimental points.

In a similar manner, the value of $\log K_1^H$ for 4,5-dihydroxyacridine was obtained, using the value of $\log K_2^H$ determined potentiometrically. Figure 3 shows the agreement between the calculated curve and the experimental points.

The values of the protonation constants are given in Table III.

Potentiometric Determination of Protonation Constants

1. Procedure

Potentiometric titrations were performed in a 200-ml. jacketted titration cell; water at 25.0 ± 0.1°C was circulated through the outer jacket. The cell was fitted with a Lucite cover, with holes for the glass and

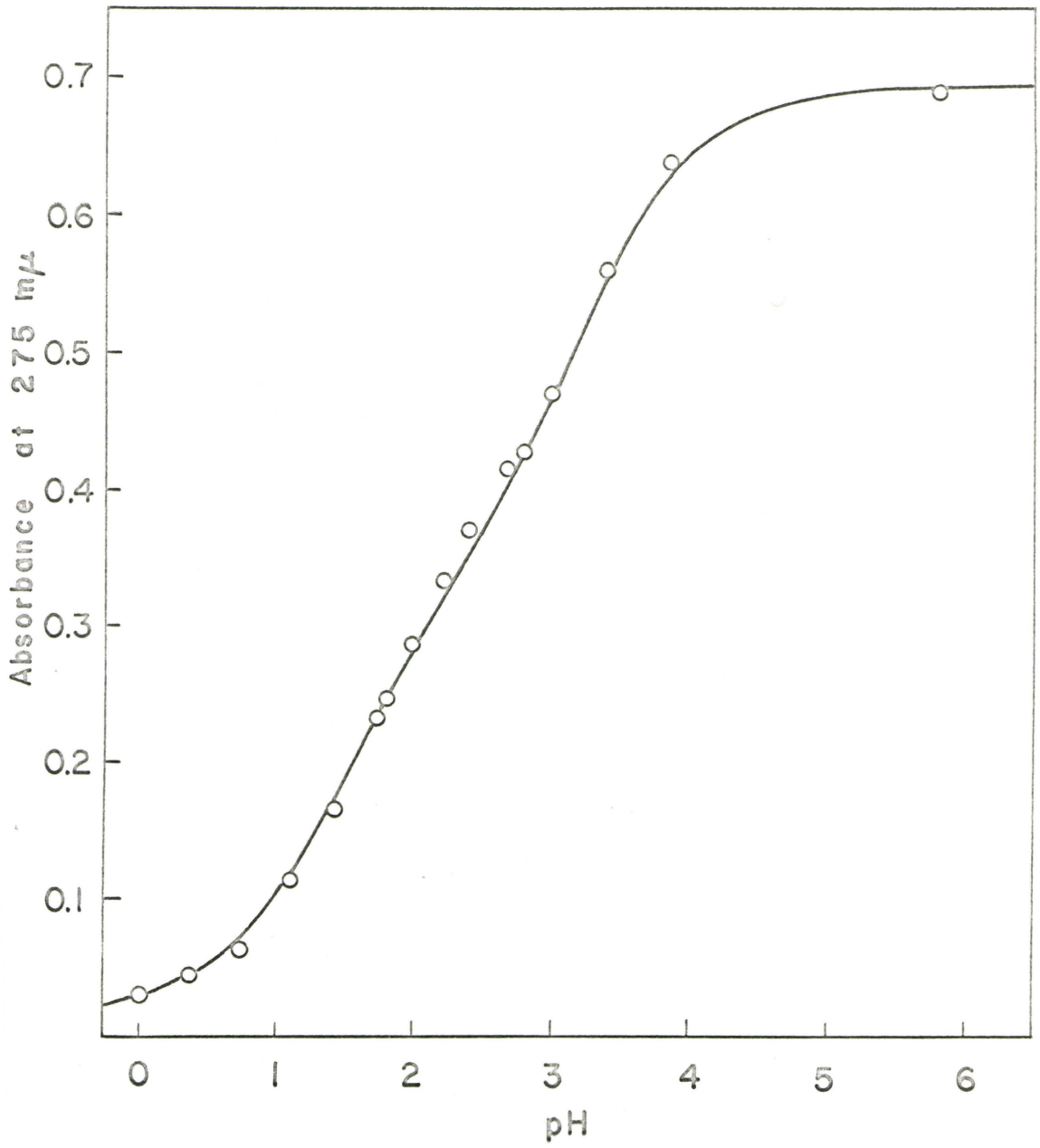

Figure 2. Absorbance versus pH for 4,5-Diaminoacridine. The circles are experimental points; the solid line is calculated from the concentration of ligand, the molar extinction coefficients, and the protonation constants.

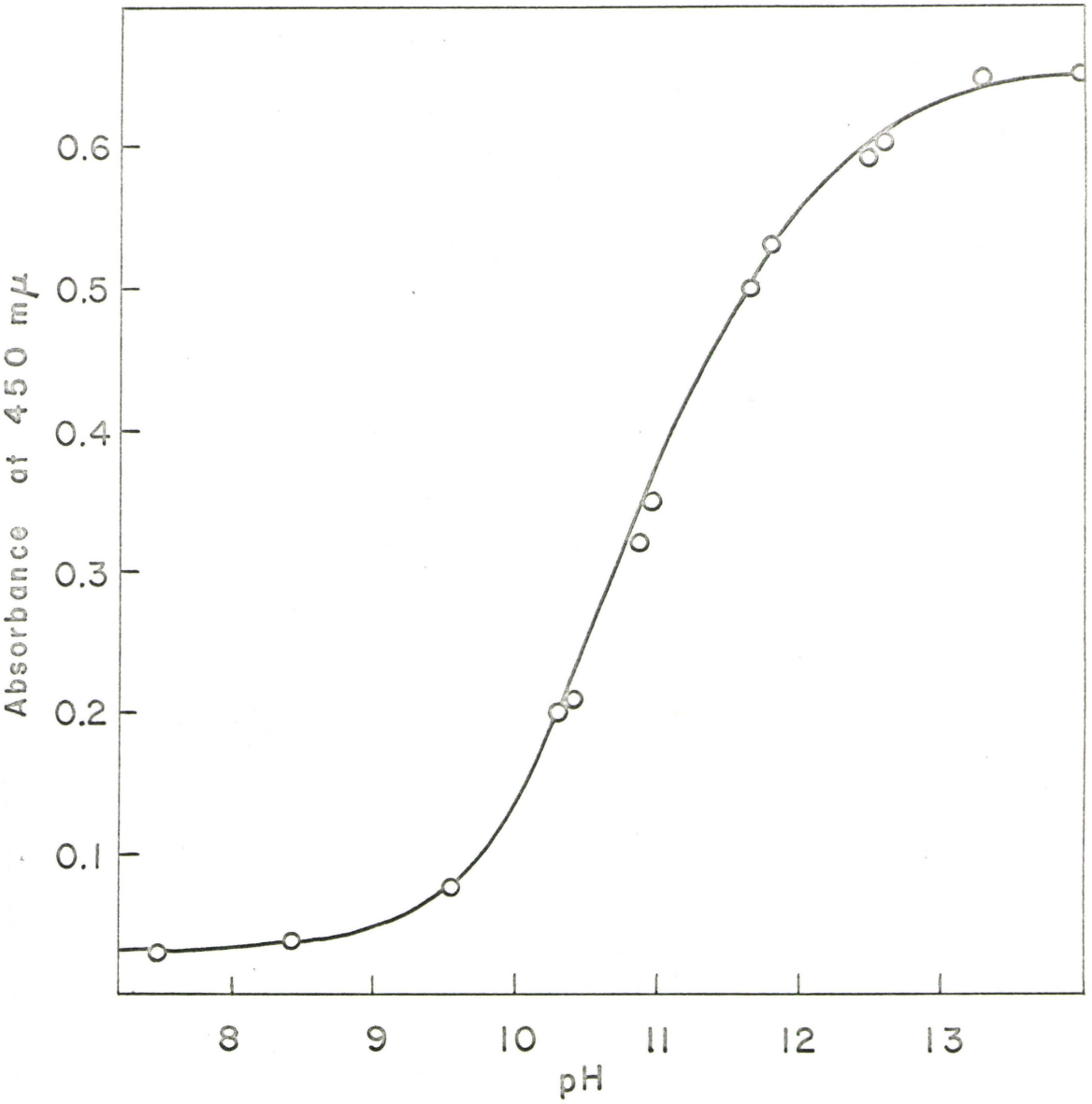

Figure 3. Absorbance versus pH for 4,5-Dihydroxyacridine. The circles are experimental points; the solid line is calculated from the concentration of ligand, the molar extinction coefficients, and the protonation constants.

reference electrodes, nitrogen inlet tubes, thermometer and burettes. Purified-grade nitrogen was bubbled through the solution and an atmosphere of nitrogen was maintained above the solution during the titration. The contents of the cell were stirred magnetically. The tip of the sodium hydroxide burette was drawn out into a fine capillary, and titrations were performed with the tip of the burette below the surface of the solution. The burette was filled by gravity from a 4-ℓ. polyethylene bottle, and the contents of the bottle and of the burette were protected from atmospheric carbon dioxide by absorption tubes filled with Drierite and Ascarite.

The pH meter was standardized before use with Beckman buffers of pH 4.01, 7.00 and 10.00.

The titration procedure was as follows: a weighed amount of the ligand (previously dried overnight in vacuo) was placed in the titration cell and dissolved in 5.0 ml. of dioxane. Next, 5.0 ml. of water and 50.0 ml. of standard 0.01M perchloric acid solution (0.21M in sodium perchlorate) were pipetted into the cell, followed by 50.0 ml. of dioxane. The electrodes were inserted into the solution, and nitrogen gas was bubbled through the solution for 5-10 minutes while the contents of the cell reached 25.0°C.

The titration was then performed by the addition of small increments of sodium hydroxide. With each

addition of base, an equal volume of dioxane was added, and the pH of the solution was recorded. Attainment of equilibrium was rapid in every titration.

The glass electrode was calibrated as a hydrogen-ion concentration probe by titrating 50.0 ml. of the perchloric acid solution plus 50.0 ml. of dioxane. At each point on the titration curve the measured pH was compared with $-\log [H^+]$, calculated from the molarities of acid and base, the volume of base added, and the total volume of solution. In the pH range 2-3 (0-80% neutralization) the Van Uitert and Haas correction factor $\log U_H$, where

$$R + \log U_H = p_cH \qquad (5)$$

was constant and equal to -0.08 ± 0.01. In equation (5), R is the pH meter reading (see Introduction).

From the same titration, the value of p_cK_W was obtained in the following manner: at each point on the titration curve past the equivalence point (110-170% neutralization), the measured pH value was corrected for the sodium-ion error, using the data available for aqueous systems[43]. (The sodium-ion corrections applied were very small, the maximum being less than 0.03 pH units.) The Van Uitert and Haas correction factor was then applied, giving the value of $p_cH = -\log [H^+]$. From the volume of base added, the value of $p_cOH = -\log [OH^-]$ was calculated.

Then

$$p_cK_W = p_cH + p_cOH \qquad (6)$$

was calculated for each point. The value obtained was 15.33 ± 0.02.

These values are in good agreement with those reported by Takamoto, Fernando and Freiser[44], who obtained values of -0.10 and 15.38 for the correction factor and p_cK_W, respectively.

2. Calculations

The variable $\bar{p}$, the average number of protons bound to each ligand molecule, was calculated for each point on the titration curves.

At any point in a titration, the stoichiometric concentration of available protons is equal to the sum of the concentrations of dissociable protons from the ligand, from added strong acid, and of hydrogen-ion arising from the ionization of water, less the concentration of added strong base. Thus for a neutral ligand H_kL, of concentration C_L, total concentration of available protons $= k \cdot C_L + [ClO_4^-] + [OH^-] - [Na^+]$.

$$\text{Let } \bar{p} = \frac{\text{total concentration of protons bound to ligand}}{\text{total ligand concentration}} . \qquad (7)$$

$$\text{Thus } \bar{p} = \frac{[\text{total available protons}] - [\text{free hydrogen-ion}]}{[\text{total ligand}]} \qquad (8)$$

$$= \frac{k \cdot C_L + [ClO_4^-] + [OH^-] - [Na^+] - [H^+]}{C_L} \qquad (8a)$$

where [ ] signifies moles/litre.

For most ligands with which this study is concerned, the protonation equilibria did not overlap. The protonation constants were calculated from the appropriate expressions[45] below:

$$\log K_1^H = p_cH + \log \left[\bar{p} / (1-\bar{p}) \right] \quad (9)$$

$$\log K_2^H = p_cH + \log \left[(\bar{p}-1) / (2-\bar{p}) \right] \quad (10)$$

$$\log K_3^H = p_cH + \log \left[(\bar{p}-2) / (3-\bar{p}) \right] \quad (11)$$

Values of $\bar{p}$ in the range 0.2 - 0.8, 1.2 - 1.8 and 2.2 - 2.8 were used to calculate K_1^H, K_2^H and K_3^H, respectively. Calculations were performed with the aid of an IBM computer.

For the two phenolic dissociations of 4,5-dihydroxyacridine, the two protonation equilibria overlapped. The two protonation constants were obtained from the $\bar{p}$, pH data by the following method. From equation (7)

$$\bar{p} = \frac{[HL^-]+2[H_2L]}{[L^=] + [HL^-] + [H_2L]} \quad (12)$$

$$= \frac{K_1^H[H^+][L^=]+2K_1^H K_2^H[H^+]^2[L^=]}{[L^=] + K_1^H[H^+][L^=] + K_1^H K_2^H[H^+]^2[L^=]} \quad (13)$$

$$= \frac{K_1^H[H^+]+2K_1^H K_2^H[H^+]^2}{1 + K_1^H[H^+] + K_1^H K_2^H[H^+]^2} \quad . \quad (14)$$

Equation (14) may be arranged to give the equation

$$\frac{\bar{p}}{(\bar{p}-1)[H^+]} = K_1^H K_2^H \frac{(2-\bar{p})[H^+]}{(\bar{p}-1)} - K_1^H \qquad (15)$$

or $$Y = K_1^H K_2^H X - K_1^H \qquad (16)$$

where $$Y = \frac{\bar{p}}{(\bar{p}-1)[H^+]}$$

and $$X = \frac{(2-\bar{p})[H^+]}{(\bar{p}-1)} .$$

The values of K_1^H and K_2^H were obtained from the slope and intercept of the least-squares fit of equation (16) to the data. Values of $\bar{p}$ in the range 0.2 - 0.8 and 1.2 - 1.8 were used in the calculations, which were performed with the aid of an IBM computer. Representative titration data for each compound are presented in Appendix VI.

The values of the protonation constants are given in Table III. The constants are the result of at least three titrations (except those for acridine and 4-hydroxyacridine, which are the result of two titrations). The precision is expressed as the 95% confidence limits of the mean. These limits are given by $\pm ds/\sqrt{N}$, where s is the pooled estimated standard deviation, N is the total number of experimental observations, and d is the corresponding value of Student's "t" for a confidence limit of 95%.

TABLE III

PROTONATION CONSTANTS OF LIGANDS

(determined in 50% v/v% dioxane-water, 25.0°C, ionic strength 0.1)

Ligand	$\log K_1^H$	$\log K_2^H$	$\log K_3^H$
Acridine	4.22±0.01†		
4-Hydroxyacridine	11.27±0.01	4.24±0.01	
4-Amino-5-Hydroxyacridine	11.50±0.01	2.57±0.01 2.51±0.01*	~ -0.5
4-Amino-5-Methoxyacridine	2.89±0.03*	~-0.5	
4,5-Diaminoacridine	3.18±0.01	1.42±0.05*	
4,5-Dihydroxyacridine	12.12±0.02 12.03±0.05*	10.58±0.01	2.56±0.01
2-(2'-Thienyl)-8-Hydroxyquinoline	11.66±0.01	1.48±0.03*	

* Value determined spectrophotometrically

† The limits shown are the 95% confidence limits.

Potentiometric Determination of Metal Chelate Formation Constants

1. Procedure

The titration procedure was similar to that used for the determination of the protonation constants of the ligands, with the following differences: the ligand was introduced as a 5.00-ml. portion of a standard solution in dioxane, and 5.00 ml. of a standard metal-ion solution was added in place of 5.00 ml. of water. As in the determination of the ligand protonation constants, the ionic strength was 0.10 and the temperature was 25°C.

2. General Calculations

The general equations of Hearon and Gilbert[46] for the calculation of metal chelate formation constants from potentiometric data were used. These equations are

$$[L] = \frac{-Z_L \cdot C_L - Z_M \cdot C_M - \Sigma Z_i [I_i]}{\sum_{j=o}^{J} j \beta_j^H [H^+]^j} \qquad (17)$$

and

$$\bar{n} = \frac{C_L - [L] \sum_{j=o}^{J} \beta_j^H [H^+]^j}{C_M} \quad . \qquad (18)$$

These equations are developed fully in Appendix VII.

The quantity [L] is the molar concentration of the chelating form (charge omitted) of the ligand. The quantity $\bar{n}$ is the average number of ligands bound to a metal-ion at a particular value of [L]. The other

quantities in equations (17) and (18) are defined in Appendix VII and are readily calculated or determined experimentally.

From values of $\bar{n}$, [L] it is possible to calculate the formation constants for the system under study. The constants may be obtained by any one of a number of graphical or numerical methods; a few of these methods are discussed in Appendix VII.

Equations (17) and (18) are general equations and require modification for each combination of metal-ion and ligand. The modified equations are given in the sections below.

Representative titration data are presented in Appendix VIII.

3. Formation Constants of 2-(2'-Thienyl)-8-Hydroxyquinoline Chelates

Titration curves of the metal chelates of 2-(2'-thienyl)-8-hydroxyquinoline are shown in Figure 4. The end-point of the titration curve for each metal chelate is displaced from the end-point of the titration of perchloric acid and ligand by a volume of base equivalent to the release of two hydrogen-ions per metal-ion. Since each ligand molecule releases one hydrogen-ion upon chelation, this displacement indicates that the metal chelates of 2-(2'-thienyl)-8-hydroxyquinoline have the stoichiometry ML_2. This stoichiometry is confirmed by the results

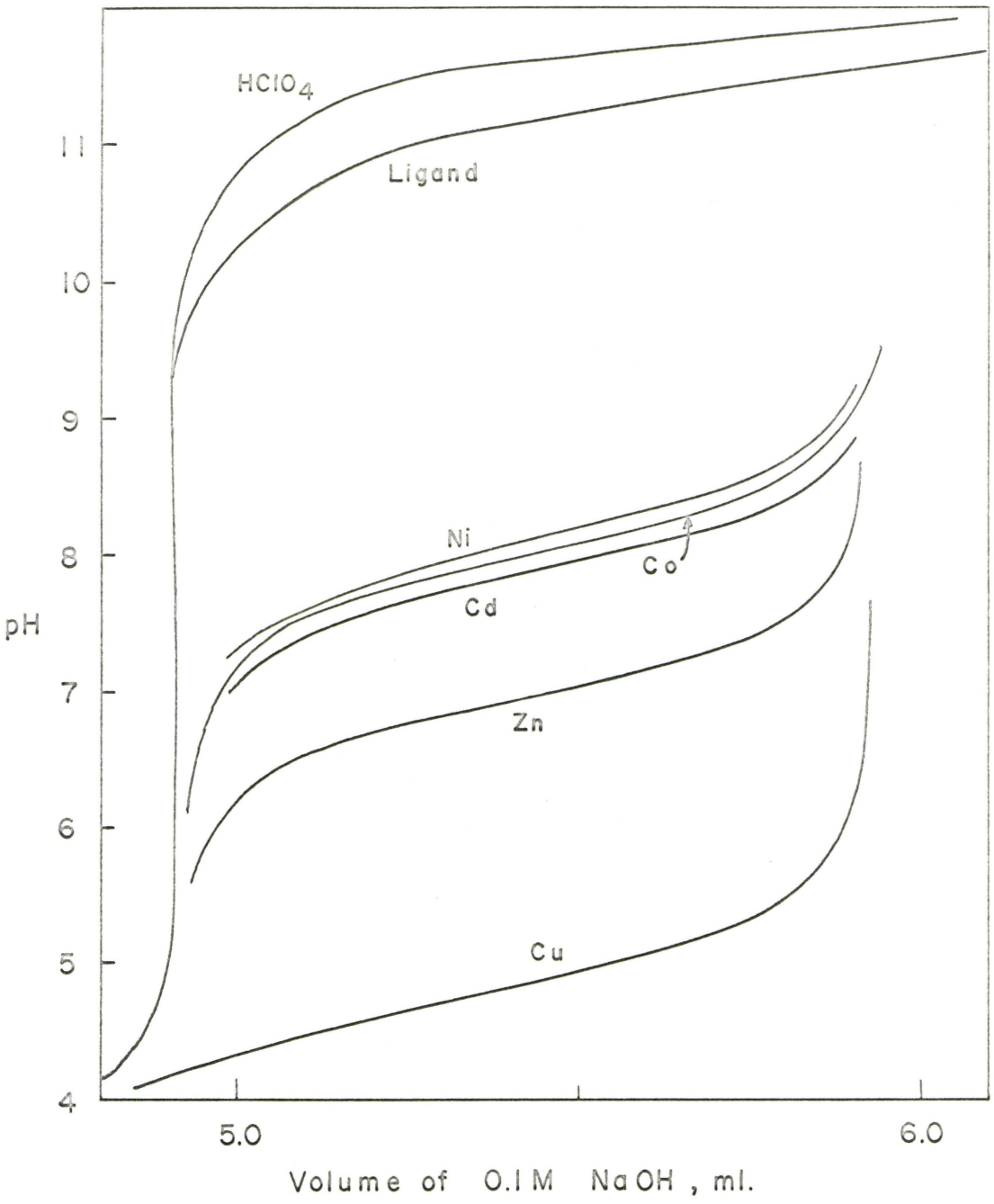

Figure 4. Titration curves of 2-(2'-Thienyl)-8-Hydroxyquinoline Chelates.

of elemental analyses of the solid chelates (Table I, Appendix III).

Values of [L] and $\bar{n}$ were calculated from the appropriate form of equation (17) and equation (18):

$$[L] = \frac{C_L - 2C_M - [H^+] - [Na^+] + [ClO_4^-] + [OH^-]}{K_1^H[H^+] + 2K_1^H K_2^H [H^+]^2} \qquad (19)$$

$$\bar{n} = \frac{C_L - [L]\left[1 + K_1^H[H^+] + K_1^H K_2^H[H^+]^2\right]}{C_M} \qquad (20)$$

The $\bar{n}$ values (as a function of pL, where pL = -log [L]) reached a maximum value of 2.0 in each case, further indicating the stoichiometry ML_2.

The stepwise formation constants were obtained by a linear least-squares fit of equation (17), Appendix VII, to the $\bar{n}$, [L] data. Values of $\bar{n}$ in the ranges 0.2 - 0.8 and 1.2 - 1.8 were used in these calculations, since the coefficients X and Y in this equation are sensitive to experimental error for values of $\bar{n}$ near 0, 1 and 2 (see Appendix VII). The stepwise and overall formation constants are given in Table IV; the constants are the result of at least three titrations, and the precision is expressed as the 95% confidence limits of the mean.

The titrations were performed at a molar ratio of ligand-to-metal of approximately 6:1, except for copper(II), where the ratio was 4:1. Since the pH region

TABLE IV

FORMATION CONSTANTS OF METAL CHELATES OF

2-(2'-THIENYL)-8-HYDROXYQUINOLINE

(determined in 50% v/v dioxane-water, 25.0°C, ionic strength 0.1)

Metal-ion	log K_1	log K_2	log β_2
Co(II)	5.83±0.09[†]	7.08±0.09	12.91±0.01
Ni(II)	5.94±0.07	6.77±0.07	12.70±0.01
Cu(II)	8.84±0.18	11.01±0.18	19.85±0.01
Zn(II)	6.61±0.06	8.38±0.06	14.99±0.01
Cd(II)	6.15±0.07	7.03±0.07	13.19±0.01

[†]The limits shown are the 95% confidence limits.

in which complex formation occurred was about pH 7 for all metal-ions except copper(II), the possibility existed of erroneous results being obtained because of hydrolysis of the metal-ion. To demonstrate that hydrolysis was not interfering, titrations at a molar ratio of ligand-to-metal of 20:1 were also done. The formation constants from these titrations were not significantly different from those obtained at the lower ratio.

The formation curves for the chelates are shown in Figure 5. The curves are calculated from the formation constants obtained at a 6:1 ligand-to-metal ratio, or, in the case of copper(II), at a 4:1 ratio.

4. Formation Constants of 4-Amino-5-Hydroxyacridine Chelates

Titration curves of metal chelates of 4-amino-5-hydroxyacridine are shown in Figure 6. Titrations were performed at a ligand-to-metal ratio of approximately 6:1, except for copper(II), which will be considered separately. As with the 2-(2'-thienyl)-8-hydroxyquinoline chelates, chelate formation occurred at about pH 7. Since in most cases precipitation of the metal chelate occurred before chelate formation was complete, titrations were not done at a higher ligand-to-metal ratio. However, as demonstrated in the previous section, hydrolysis of the metal-ions is not likely at these pH values.

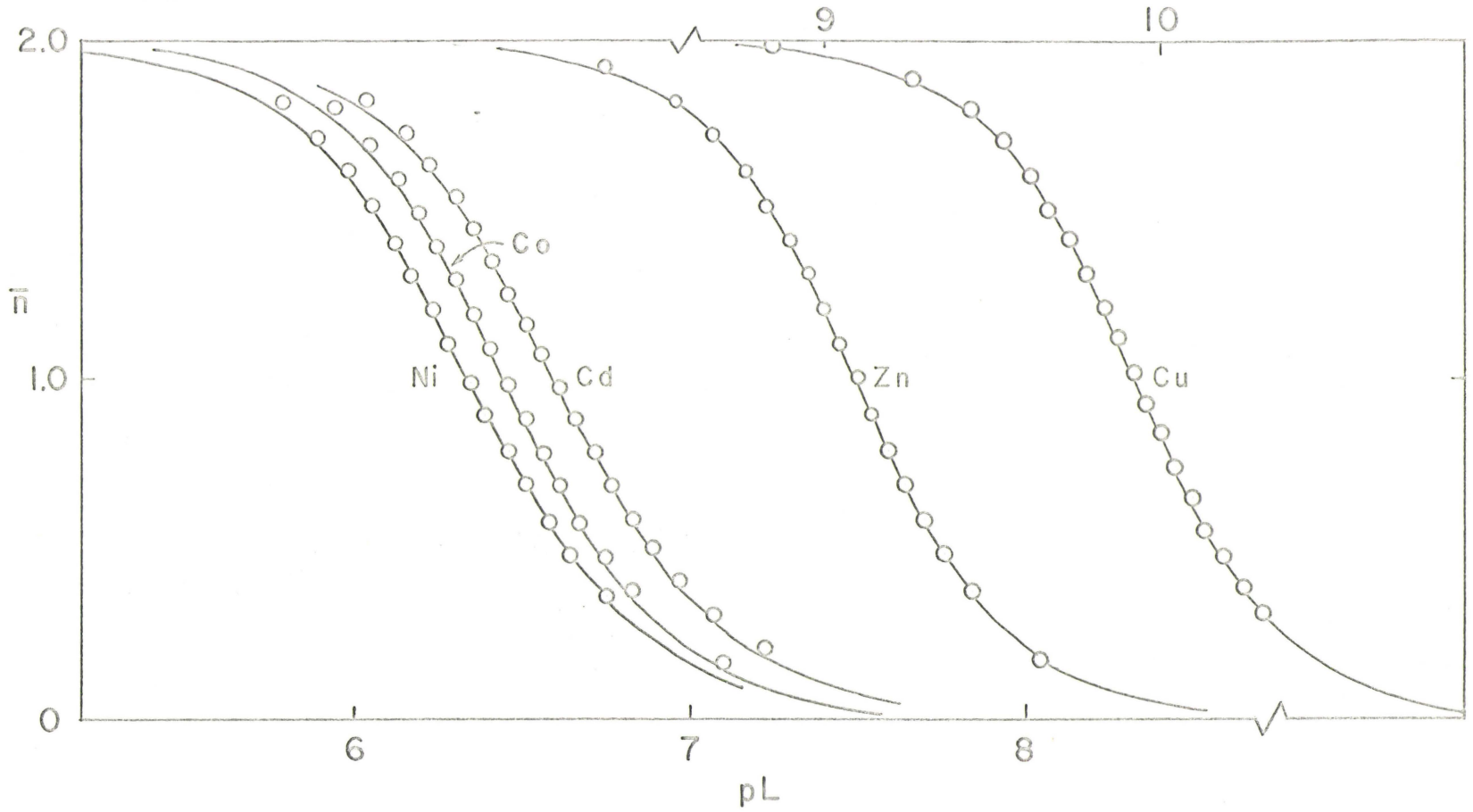

Figure 5. Formation Curves of 2-(2'-Thienyl)-8-Hydroxyquinoline Chelates. The circles are experimental values; the solid lines are calculated from the values of log K_1 and log K_2.

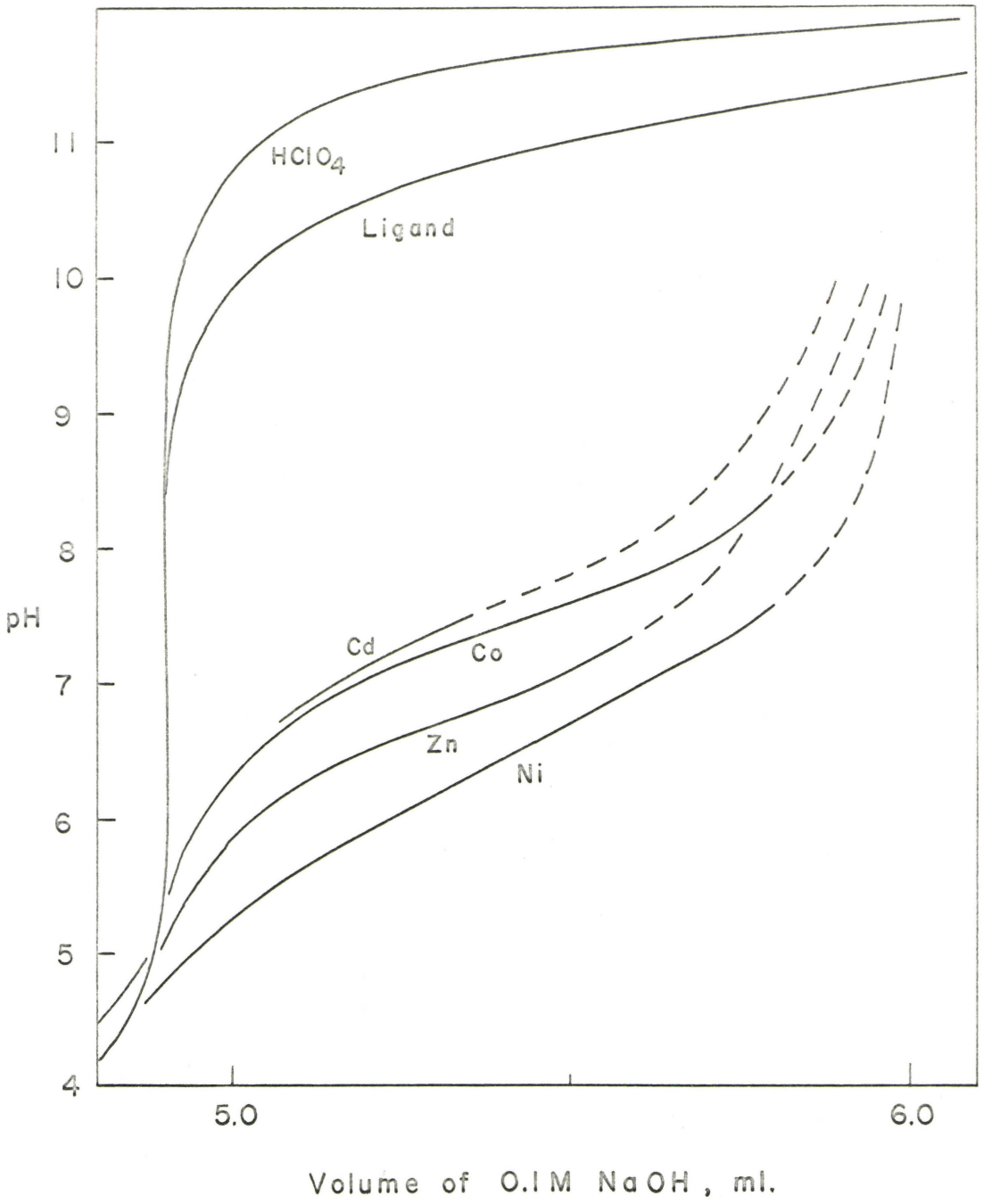

Figure 6. Titration curves of the Cobalt(II), Nickel(II), Zinc(II) and Cadmium(II) Chelates of 4-Amino-5-Hydroxy-acridine. The broken line indicates the formation of a precipitate.

In the titration of the cobalt(II) and zinc(II) systems, the displacement of the end-point of the titration curve from that of perchloric acid plus ligand corresponds to the release of two hydrogen-ions per metal-ion. Since each ligand releases one hydrogen-ion upon chelation, the complex must have the stoichiometry ML_2. This agrees with the results of elemental analyses of the solid chelates (Table II, Appendix III). Precipitation of the chelates of nickel(II) and cadmium(II) occurred before the end of the titration; the titration curves of these metal-ions also indicated that two hydrogen-ions per metal-ion were released upon chelation. This was confirmed in titrations (not used in the calculation of stability constants) in which the concentration of metal-ion was reduced to a level such that precipitation did not occur.

Values of [L] and $\bar{n}$ were calculated from the appropriate form of equations (17) and (18), respectively:

$$[L] = \frac{C_L - 2\,C_M - [H^+] - [Na^+] + [ClO_4^-] + [OH^-]}{K_1^H[H^+] + 2\,K_1^H\,K_2^H[H^+]^2} \qquad (21)$$

$$\bar{n} = \frac{C_L - [L]\left[1 + K_1^H[H^+] + K_1^H\,K_2^H[H^+]^2\right]}{C_M} \qquad (22)$$

The third protonation constant of the ligand, K_3^H, was omitted from the calculations since $K_1^H K_2^H K_3^H[H^+]^3$ is

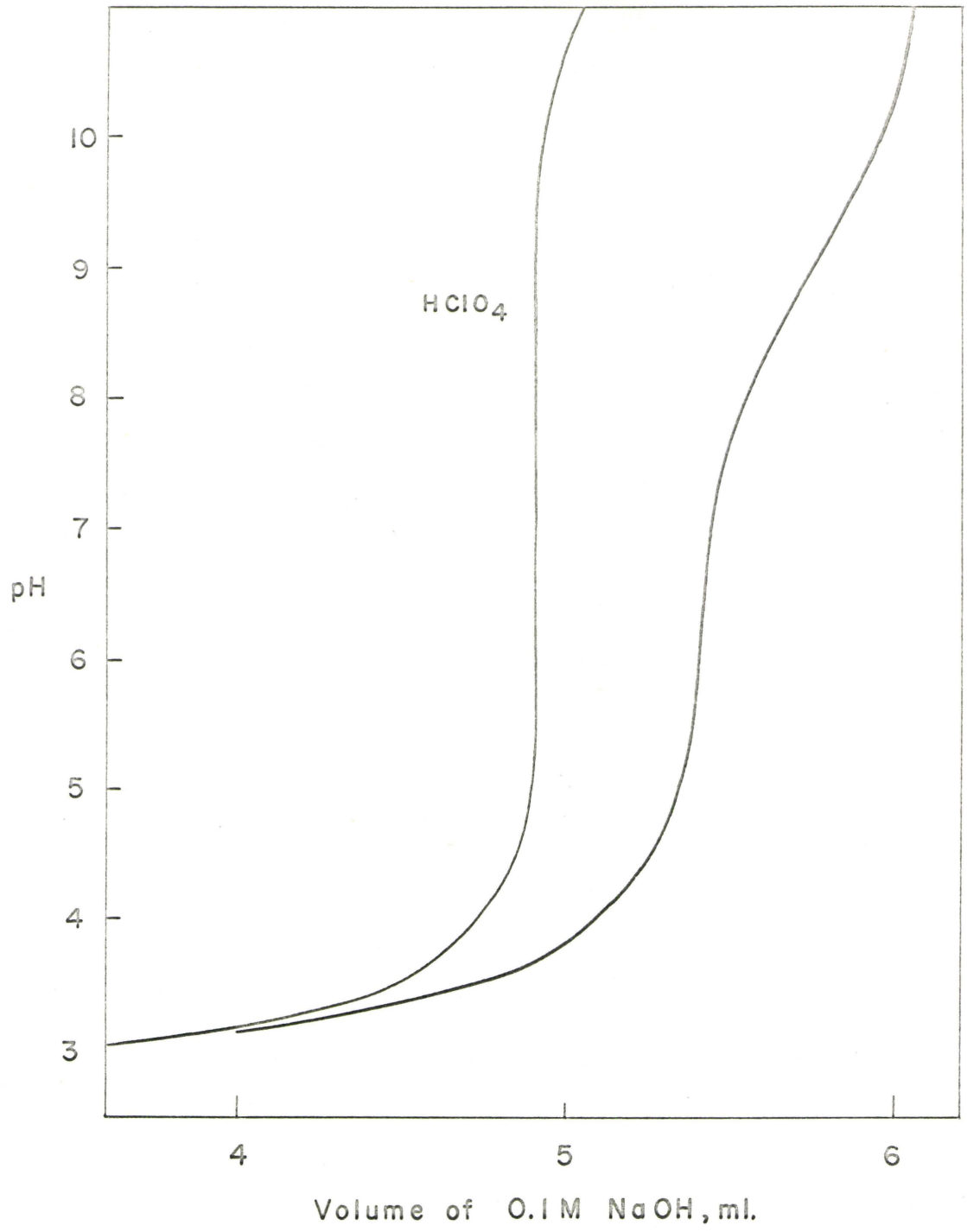

Figure 7. Titration Curve of the Copper(II) Chelate of 4-Amino-5-Hydroxyacridine.

much less than $K_1^H K_2^H [H^+]^2$ throughout the titration.

Titration of copper(II) at a ligand-to-metal ratio of approximately 4:1 yielded a titration curve in which one hydrogen-ion per metal-ion was released upon chelation. Therefore, the stoichiometry of this complex is 1:1. A second region of proton release occurred at higher pH values (pH 7-10); this second buffer region was also observed when the ligand-to-metal ratio was 1:1 (Figure 7). This buffer region is almost certainly due to proton release from a coordinated water molecule (i.e., the complex has the formula $CuL \cdot H_2O$) and not to the addition of a second ligand molecule. The acid dissociation constant K_a of this water molecule, where K_a refers to the reaction

$$[CuL \cdot H_2O]^+ \rightleftharpoons CuL \cdot OH + H^+$$

was obtained directly from the titration curve as the pH of half-neutralization.

A number of bidentate and terdentate ligands were titrated in the presence of an equimolar concentration of copper(II)-ion. The first acid dissociation constant of coordinated water in these complexes was determined in the same manner as described above. The results of these titrations, together with data available in the literature for systems studied in 50% v/v dioxane-water, are shown in Table V.

TABLE V

ACID DISSOCIATION CONSTANT OF COORDINATED WATER

IN 1:1 COPPER(II) CHELATES

(25.0°C, 50% v/v dioxane-water)

Chelating Ligand	Number of Donor Groups	pK_a	Reference
4-Amino-5-Hydroxyacridine	3	8.9	this work
4-(2'-pyridylazo)-resorcinol	3	10.1	(47)
4-(2'-thiazolylazo)-resorcinol	3	10.1	(47)
Pyridine-2-aldehyde-2-quinolylhydrazone	3	9	(48)
Pyridine-2-aldehyde-2-benzothiazolylhydrazone	3	9	(48)
glycylglycine	3	10.0	this work
iminodiacetate	3	9.6	"
1,10-Phenanthroline	2	7.0	"
α,α'-Bipyridyl	2	6.9	"
8-Hydroxyquinoline	2	7.1	"

The chelate formation constants for the cobalt(II), nickel(II), zinc(II) and cadmium(II) chelates were calculated from the least-squares fit of equation(17), Appendix VII, to the $\bar{n}$, [L] data. The formation constant of the copper(II) chelate was calculated using equation (15), Appendix VII. Values of $\bar{n}$ in the ranges 0.2 -0.8 and 1.2 - 1.8 were used. The constants are reported in Table VI. The values are the result of at least three titrations; the precision is expressed as the 95% confidence limits of the mean.

Formation curves for the chelates are shown in Figure 8. The curves are calculated from the formation constants reported in Table VI.

5. Formation Constant of the Copper(II) Chelate of 4,5-Diaminoacridine

Titrations of the copper(II)-4,5-diaminoacridine system were performed at molar ratios of ligand to metal of 6:1, 2:1 and 1:1. The titration curves obtained are shown in Figure 9. Values of [L] and $\bar{n}$ were calculated from the appropriate form of equation (17) and equation (18) respectively:

$$[L] = \frac{-2\ C_M - [H^+] - [Na^+] + [ClO_4^-] + [OH^-]}{K_1^H[H^+] + 2\ K_1^H\ K_2^H[H^+]^2} \qquad (23)$$

$$\bar{n} = \frac{C_L - [L]\left[\ 1 + K_1^H[H^+] + K_1^H\ K_2^H[H^+]^2\ \right]}{C_M} \qquad (24)$$

TABLE VI

FORMATION CONSTANTS OF METAL CHELATES OF

4-AMINO-5-HYDROXYACRIDINE

(determined in 50% v/v dioxane-water, 25.0°C, ionic strength 0.1)

Metal-ion	log K_1	log K_2	log β_2
Co(II)	6.97±0.02†	6.55±0.03	13.52±0.02
Ni(II)	8.29±0.02	7.22±0.02	15.51±0.02
Cu(II)	11.76±0.01	-	-
Zn(II)	7.69±0.04	7.15±0.04	14.83±0.02
Cd(II)	7.05±0.05	6.03±0.14	13.08±0.12

†The limits shown are the 95% confidence limits.

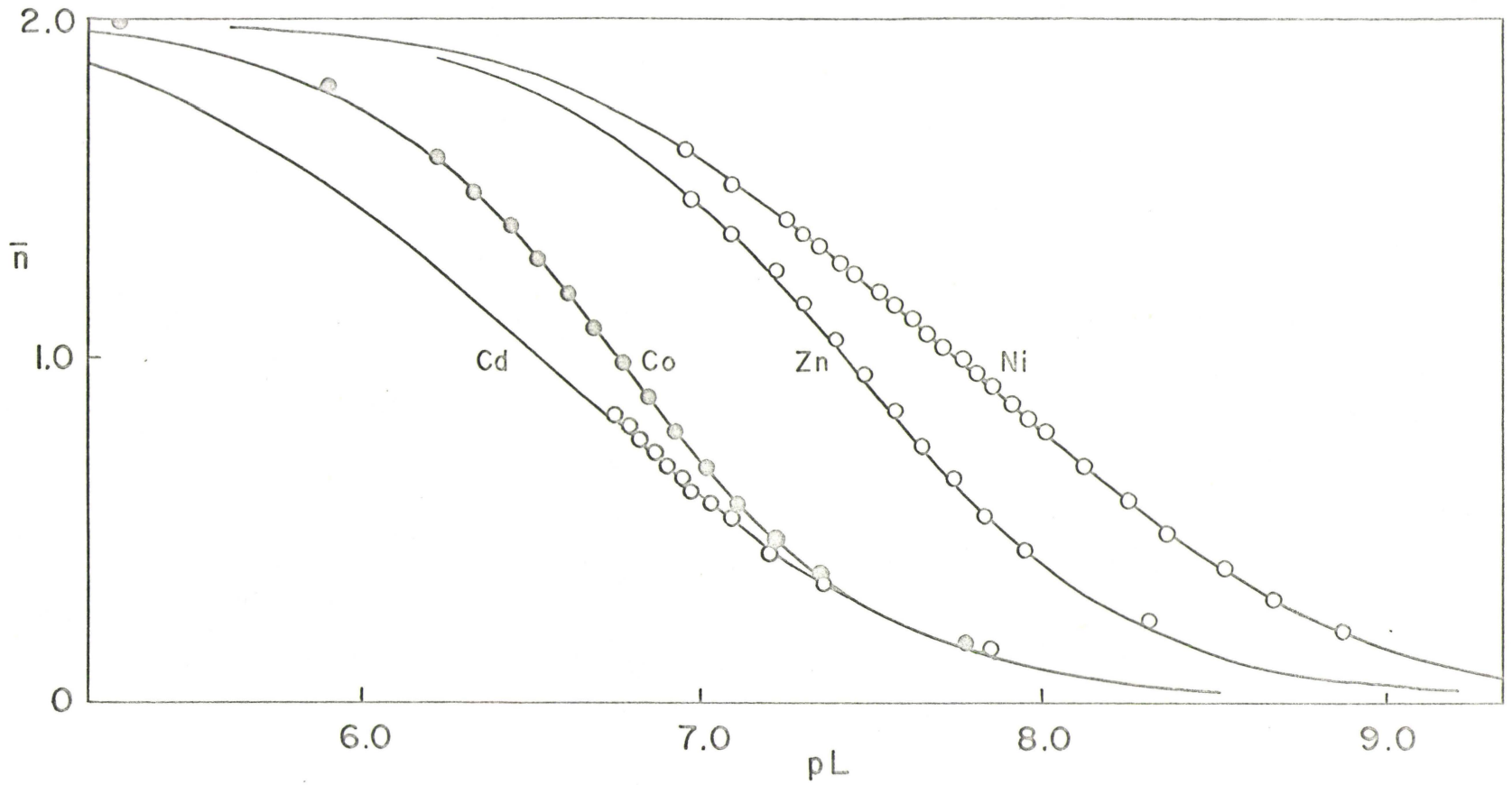

Figure 8. Formation Curves of the Bis-Chelates of 4-Amino-5-Hydroxyacridine. The circles are experimental values; the solid lines are calculated from the values of log K_1 and log K_2.

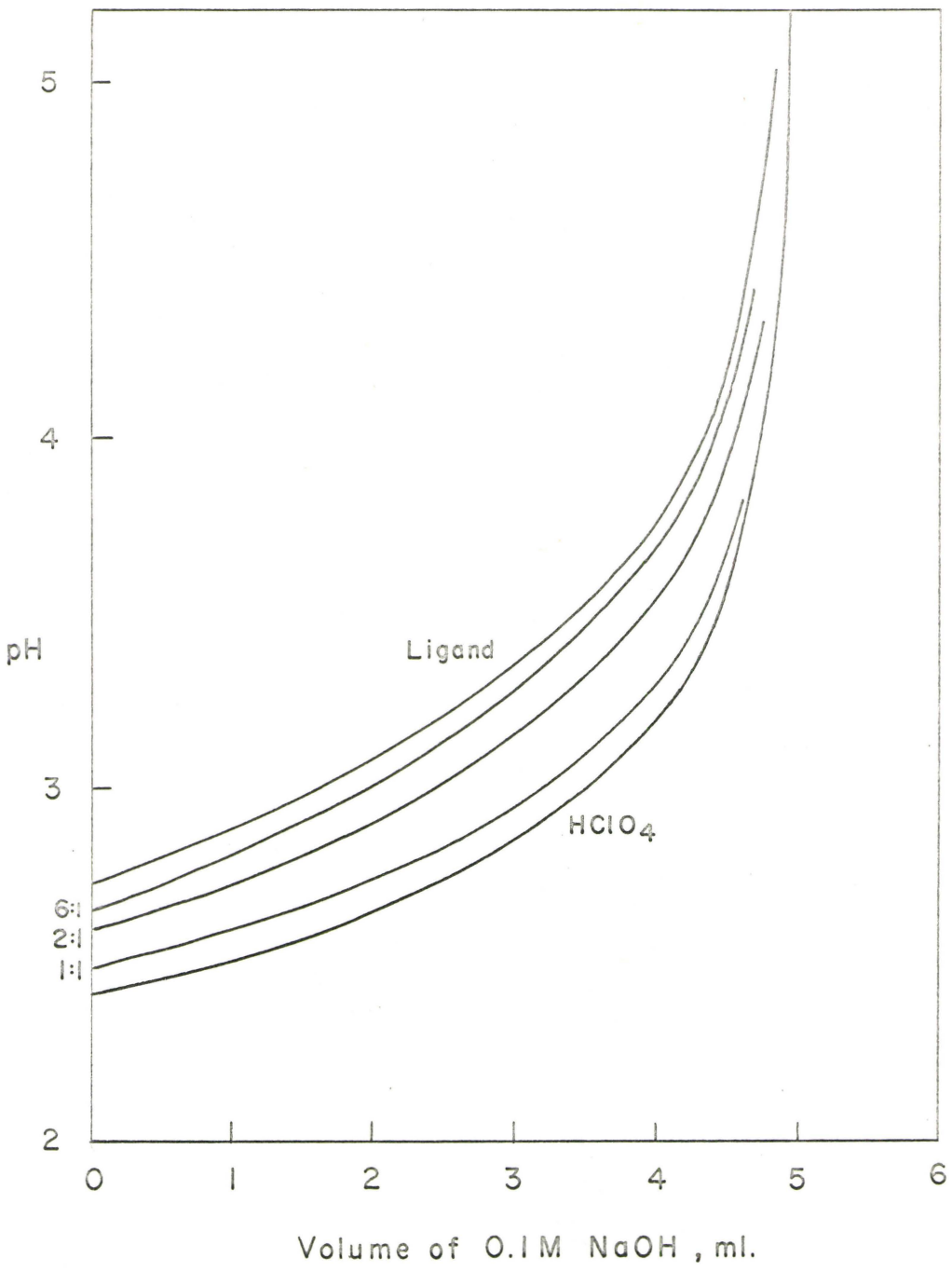

Figure 9. Titration Curve of the Copper(II) Chelate of 4,5-Diaminoacridine. Figures at the left of the curves indicate the molar ratio of ligand to metal.

The third protonation constant was omitted from the calculations, since $K_1^H K_2^H K_3^H [H^+]^3$ would be expected to be much less than $K_1^H K_2^H [H^+]^2$ throughout the titration.

In titrations in which the ligand-to-metal ratio was 2:1 or 1:1, $\bar{n}$ reached a maximum of 1.0, indicating a stoichiometry of 1:1 for the copper(II) chelate. This stoichiometry is supported by the results of the elemental analyses of the chelate (Table III, Appendix III), although the data are not entirely satisfactory. When the ligand-to-metal ratio was 6:1, the calculated $\bar{n}$ values indicated that chelate formation was complete at the beginning of the titration. The formation constant was calculated from the $\bar{n}$, [L] data obtained for a ligand-to-metal ratio of 1:1, using equation (15), Appendix VII. The value obtained was $\log K_1 = 4.7 \pm 0.2$.

6. Metal Chelates of 4,5-Dihydroxyacridine

Formation constants of the metal chelates of 4,5-dihydroxyacridine could not be determined by the usual potentiometric method, since precipitation of the metal chelate occurred at the beginning of the titration (copper(II)-ion), or upon neutralization of the perchloric acid (cobalt(II)-, nickel(II)- and zinc(II)-ions). Nevertheless, titration in the presence of these precipitates (in solutions in which the ligand-to-metal ratio was 2:1) showed that two protons were released per metal-ion. Since each ligand contains two potentially

replaceable protons, the release of two protons per metal-ion is consistent with either the formation of a mono-chelate, in which the di-anion of 4,5-dihydroxy-acridine acts as a terdentate ligand, or the formation of a bis-chelate, in which the mono-anion of 4,5-dihydroxy-acridine acts as a bidentate ligand. Precipitation of a solid phase is also consistent with either compound, since each is electrically neutral. Titration of solutions containing ligand and metal-ion in a 1:1 molar ratio also resulted in precipitation. These titration curves appeared to contain two buffer regions, each corresponding to the release of one proton per metal-ion.

The most reasonable interpretation of the titration curve is that the lower buffer region is caused by the formation of the bis-chelate by one-half of the metal-ion present, according to the equation

$$M^{2+} + H_2L \longrightarrow \tfrac{1}{2}\, M(HL)_2 + H^+ + \tfrac{1}{2}\, M^{2+} \quad ,$$

and the higher buffer region to hydrolysis of the remaining unchelated metal-ion, according to the equation

$$\tfrac{1}{2}\, M^{2+} + H_2O \longrightarrow \tfrac{1}{2}\, M(OH)_2 + H^+ \quad .$$

Elemental analysis of the solid chelates (prepared at a ligand-to-metal ratio in excess of 2:1) showed that the stoichiometry of the solid was indeed $M(HL)_2$.

It was observed that in strongly basic solution

(about pH 12), the solid metal chelates dissolved, giving highly coloured red-brown solutions. For each metal-ion, the stoichiometry of the absorbing species was determined by the method of Job[49]. The procedure was as follows: a series of solutions was prepared, each containing V ml. of 0.001M metal-ion solution and (10-V) ml. of a 0.001M solution of 4,5-dihydroxyacridine in dioxane. The solutions were made alkaline by the addition of 1.0 ml. of 0.1M sodium hydroxide, and were then diluted to 50.0 ml. with 50% v/v dioxane-water. The final pH of the solutions was 12.5 - 12.8. Spectra of the solutions in the visible region were recorded. An absorption maximum due to the metal chelate was observed in the region 470 - 490 mμ. The data were plotted in the following manner: for each solution, the absorbance which would have been observed at the analytical wavelength if the metal-ion and ligand had not reacted* was subtracted from the measured absorbance. The corrected absorbance was plotted against the quantity $[L]/([L] + [M])$. For each of the metal-ions studied, a maximum was observed in this plot at the point $[L]/([L] + [M]) = 0.67$. This indicates that the absorbing species contains two ligands per metal-ion and further supports that data referred to above. The absorption maxima and the logarithms of the extinction coefficients

*This absorbance is essentially the absorbance of the reagent alone.

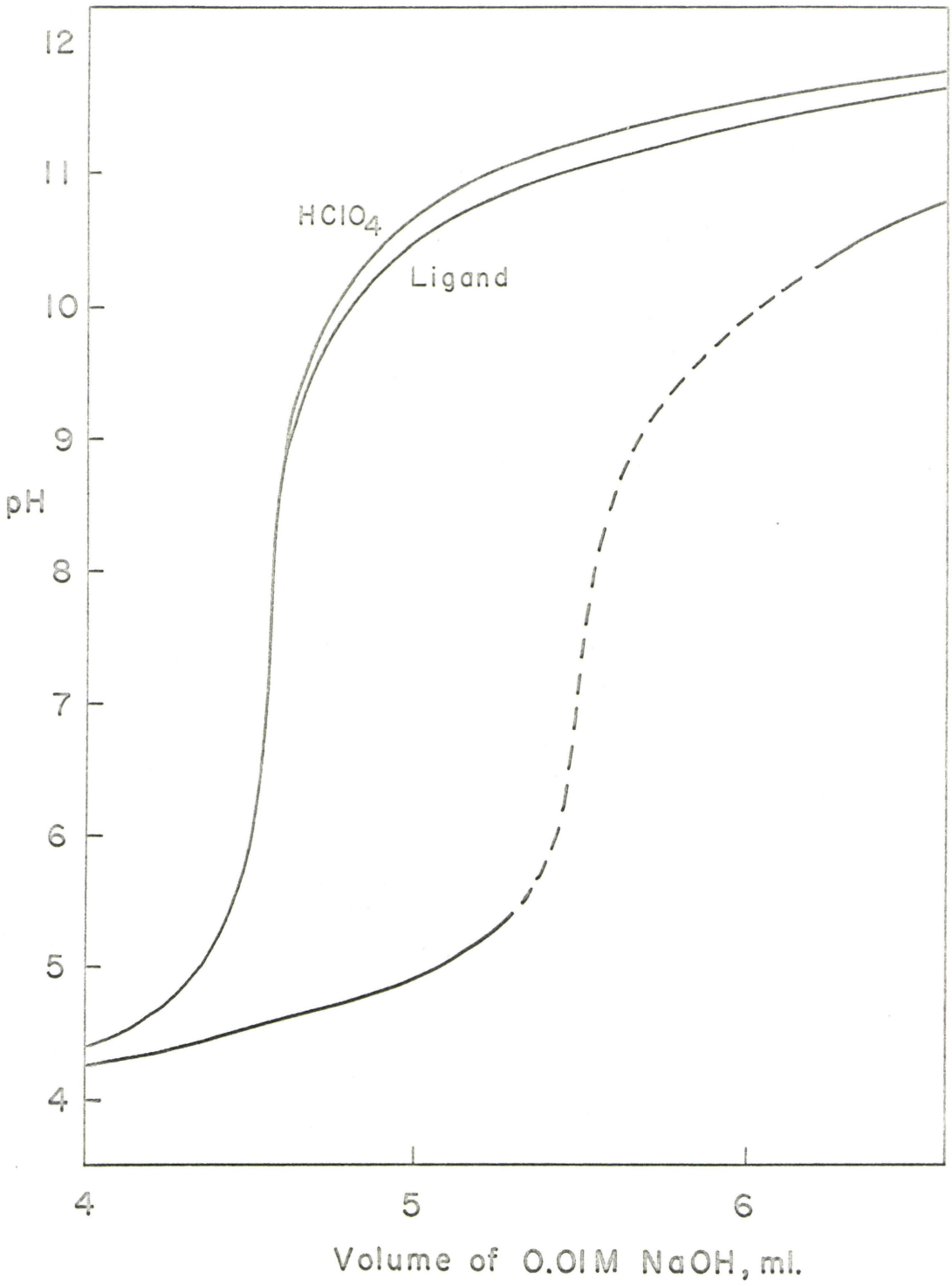

Figure 10. Titration Curve of the Copper(II) Chelate of 4,5-Dihydroxyacridine. The broken line indicates the formation of a precipitate.

are given in Table VII.

TABLE VII

ABSORPTION MAXIMA AND EXTINCTION COEFFICIENTS OF ANIONIC BIS-CHELATES OF 4,5-DIHYDROXYACRIDINE

(pH = 12.5 - 12.8)

Metal-ion	Absorption Maximum, mμ	log ε
Co(II)	488	3.95
Ni(II)	488	3.97
Cu(II)	471	3.81
Zn(II)	483	3.88

Potentiometric titrations were also performed in which the concentrations of metal-ion, ligand, acid and base were reduced by a factor of ten from the concentrations normally used. The ligand-to-metal ratio was 2:1. At this lower concentration, the copper(II) chelate remained in solution until the late stages of the titration, but the chelates of cobalt(II), nickel(II) and zinc(II) again precipitated at an early stage. The titration curve of the copper(II) chelate is shown in Figure 10.

For each metal-ion, two protons per metal-ion were released on chelation (as was observed in the previous titrations). Above pH 7, a second buffer region, corresponding to the titration of two protons, was observed.

Proton loss in this region resulted in the formation of a soluble complex (vide supra) and is probably due to the dissociation of the remaining protons on the chelated ligands, thus

$$M(HL)_2 \longrightarrow ML_2^{=} + 2H^{+} .$$

Since the titration mixture was heterogeneous over almost the whole of this buffer region, protonation constants of the metal chelates could not be calculated. However, the acidity of the phenol groups appears to have been increased somewhat by chelate formation.

Values of $\bar{n}$ and [L] for the copper(II) chelate were calculated using equations (25) and (26) of Appendix VII. The pH regions of chelate formation and dissociation of the protons of the metal chelate were well separated, permitting the calculation of $\bar{n}$, [L] data without knowledge of the protonation constants of the metal chelate. Values of the formation constants were obtained from the formation curve by interpolation at $\bar{n} = 0.5$ and $\bar{n} = 1.5$, followed by correction of the constants according to the method described in Appendix IX. The values obtained were $\log K_1 = 9.1$ and $\log K_2 = 11.3$. These values are reported to only one decimal place since titrations involving very low concentrations of ligand and metal-ion are less precise.

Formation constants for the chelates of cobalt(II),

nickel(II) and zinc(II) with 4,5-dihydroxyacridine could not be obtained, since precipitation occurred early in the titration.

Determination of the Magnetic Susceptibilities of the Cobalt(II) and Nickel(II) Chelates of 2-(2'-Thienyl)-8-Hydroxyquinoline

The magnetic susceptibilities of the cobalt(II) and nickel(II) complexes of 2-(2'-thienyl)-8-hydroxyquinoline were determined at room temperature (23°C) by the Gouy method. Measurements were made on approximately 200 mg. of sample contained in a Pyrex tube of 2 mm. inside diameter. The tube was calibrated using $HgCo(CNS)_4$ as standard, from which the "tube calibration constant", β, was found to be 1.88. The molar susceptibility[†] was corrected for diamagnetism of the ligands by the use of Pascal's constants[(50)].

The magnetic moments, μ_{eff}, of cobalt(II) and nickel(II) in their 2-(2'-thienyl)-8-hydroxyquinoline chelates were found to be 4.50 B.M. and 3.21 B.M., respectively.

[†]The molar susceptibilities were 4075 x 10^{-6} c.g.s. units for the nickel(II) chelate and 8410 x 10^{-6} c.g.s. units for the cobalt(II) chelate.

DISCUSSION

Synthesis and Characterization of New Ligands

One of the ligands originally considered for study was 2-aminomethyl-8-hydroxyquinoline, but it could not be prepared. Three synthetic routes were considered: (a) reaction of o-aminophenol and a suitably substituted α,β-unsaturated aldehyde, (b) preparation of 8-hydroxyquinoline-2-aldehyde by oxidation of 2-methyl-8-hydroxyquinoline with selenium dioxide, followed by oximation of the aldehyde and reduction of the oxime group to $-CH_2NH_2$, and (c) preparation of 8-hydroxyquinoline-2-carboxamide from 8-hydroxyquinoline-2-carboxylic acid and reduction of the amide group to $-CH_2NH_2$. Method (a) was discarded because the appropriate α,β-unsaturated aldehydes were not commercially available. Method (b) yielded red oils with either 2-methyl-8-hydroxyquinoline or 2-methyl-8-methoxyquinoline. Attempts to isolate the aldehyde failed, and eventually the method was abandoned. Later, a report in the literature stated that 2-aminomethyl-8-hydroxyquinoline had been prepared from 8-hydroxyquinoline-2-aldehyde[29]. The aldehyde was apparently prepared by selenium dioxide oxidation of 2-methyl-8-acetoxyquinoline.

Method (c) was the most thoroughly investigated. 8-Methoxyquinoline-2-carboxylic acid was prepared by the procedure of Irving and Pinnington[51]. From this, the methyl ester and the amide were prepared in succession. The amide (white solid, m.p. 181°C) was characterized by infrared (N-H stretching bands at 3100 and 3450 $cm.^{-1}$). Direct reduction of the amide with lithium aluminium hydride, sodium borohydride or sodium borohydride-aluminium chloride-diglyme[52] was unsuccessful. Dehydration of the amide to yield the nitrile appeared promising, since 2-cyanopyridine has been reduced successfully to 2-amino-methylpyridine with various reagents[53,54]. Dehydration with thionyl chloride[55] proved unsuccessful; heating a mixture of the amide and phosphorus pentoxide in vacuo[56] yielded a very small amount of a white crystalline material by sublimation, but extensive decomposition also occurred. The characteristic C≡N stretching band at 2450 $cm.^{-1}$ indicated that the product was 8-methoxyquinaldonitrile. Because of the small yield, however, this method was also abandoned and attention was turned to the synthesis of 2-(2'-thienyl)-8-hydroxyquinoline and the acridine derivatives. These were synthesized without undue difficulty, although the overall yield of the acridine derivatives was small because of the number of steps involved in the synthesis.

The nuclear magnetic resonance spectra of the acridine ligands are of interest, since only a few spectra of substituted acridines have been reported in the litera-

ture[57]. Although the spectrum of acridine itself is complicated[57], the spectra of the disubstituted acridines studied in the present work are somewhat simpler (Table I and Appendix I).

The synthesis of 2-(2'-thienyl)-8-hydroxyquinoline is not unambiguous, since the possibility existed of substitution of the thienyl ring in the 7-position, ortho to the oxygen. The nuclear magnetic resonance spectrum of the final product showed that substitution had occurred in the 2-position. For both pyridine and quinoline, the signal from the hydrogen alpha to the heterocyclic nitrogen is shifted strongly downfield[58]. The same effect has been observed for 8-hydroxyquinoline[59]. Comparison of the spectra of 8-hydroxyquinoline and 2-(2'-thienyl)-8-hydroxyquinoline (Figure 1, Appendix I) shows that the resonance assigned to the alpha hydrogen in 8-hydroxyquinoline is absent in the spectrum of 2-(2'-thienyl)-8-hydroxyquinoline. In addition, there is no splitting of the H_A resonance by H_X.

Reactivity of the Ligands toward Metal-ions

Of the 29 metal-ions for which tests were performed, eleven reacted with 2-(2'-thienyl)-8-hydroxyquinoline at pH 10 and only five reacted at pH 5 (Table I, Appendix II). Therefore, at pH 5 the ligand is selective

in its reactions with metal-ions and is potentially a useful analytical reagent. Its selectivity is in contrast to that of the parent ligand, 8-hydroxyquinoline, which is very unselective at about the same pH value. The increase in selectivity is due to a decrease in metal-chelate stability, caused by the sterically hindering substituent. The effect of this substituent on formation constants is discussed in a later section.

The ligand 4,5-diaminoacridine is even more selective. Three ions reacted at pH 5 and three at pH 10 (Table II, Appendix II). Twenty-four ions did not react at either pH value. Although 4,5-diaminoacridine appears to be highly selective, the low value of the formation constant of its copper(II) chelate ($\log K_1 = 4.7$) indicates that complexes formed by this ligand are too unstable for it to be of much value as an analytical reagent.

4-Amino-5-hydroxyacridine is considerably less selective. Reaction occurred with twelve metal-ions at pH 10 and nine at pH 5 (Table III, Appendix II). 4,5-Dihydroxyacridine is unselective (Table IV, Appendix II). Twenty-two ions reacted at pH 10 and twenty-three at pH 5.

It is noteworthy that aluminium(III) does not give a reaction with any of the above ligands at either pH value. This is consistent with the observation that other 2-substituted 8-hydroxyquinolines do not react

with aluminium(III)-ion in aqueous solution (see Introduction).

Protonation of Ligand Donor Atoms

The visible and near-ultraviolet spectra of the acridine ligands and some model compounds were studied as a function of pH to determine the order of protonation of the basic centres in the molecules. Often, for a compound having more than one basic centre, the order of protonation can be assigned without ambiguity. For example, the two protonation constants of 8-hydroxyquinoline (log K_1^H = 9.81, log K_2^H = 4.91[60]) may be assigned to the protonation of the phenoxide ion and the quinoline nitrogen, respectively, simply from a knowledge of the protonation constant of quinoline (log K^H = 4.90[61]) and 1-naphthol (log K^H = 9.92[62]). Such a method fails, however, in the case of a molecule such as 8-aminoquinoline. Both centres would be expected to have comparable basicity, since log K^H = 4.90 for quinoline and log K^H = 3.90 for 1-naphthylamine[61].

The order of protonation of the isomeric monoaminoacridines has been decided on the basis of their absorption spectra[63]. The spectrum of acridine is very similar to that of anthracene[64], in agreement with the general observation that replacement of a CH group by a nitrogen atom in an aromatic hydrocarbon results in only

minor changes in the absorption spectrum[65]. The spectrum of the acridine cation differs somewhat from that of the neutral molecule. In particular, a band centred at about 440 mμ is observed[63,66]. This feature is characteristic of acridine cations in which the ring nitrogen is protonated and is important in the discussion below. Also important is the observation that although primary aromatic amines absorb at longer wavelengths than the parent hydrocarbons, because of conjugation of the amino group with the ring, protonation of the amino group prevents such conjugation, giving rise to a spectrum characteristic of the parent hydrocarbon. Thus the spectrum of anilinium-ion is almost identical to that of benzene[67].

Craig and Short[66] and Turnbull[63] found that the spectra of the neutral and singly protonated forms of the isomeric monoaminoacridines were not similar to the spectra of either acridine or the acridinium-ion, but that the spectra of the doubly protonated forms were almost identical to that of the acridinium-ion. From these results it was concluded that the ring nitrogen was protonated first and the primary amino group second. However, 4,5-diaminoacridine was found to differ from the monoaminoacridines in that the primary amino groups were protonated first[68]. This conclusion was based on the observation that the spectrum of the doubly protonated species (in 5M hydrochloric acid) was almost identical to

that of neutral acridine, and the spectrum of the triply protonated species (in 9M sulfuric acid) was almost identical to that of the acridinium-ion (i.e., a new band appears near 450 mμ). Similar behaviour was observed in the protonation of 4-amino-5-methylacridine in ethanolic hydrochloric acid (although in aqueous hydrochloric acid, the spectra indicated that the ring nitrogen was protonated first).

The reversal of protonation order, caused by the low basicity of the ring nitrogen atom in these two compounds, was attributed to steric hindrance by the substituents to the approach of hydronium-ions[68]. More correctly, the substituents prevent solvation of the protonated ring nitrogen and hence its basicity is decreased. (Steric inhibition of solvation is now recognized as an important factor in acid-base phenomena, e.g., in the reduced base strength of 2,6-di-t-butylpyridine and the reduced acid strength of 2,6-di-t-butylphenol[69]). A similar decrease in basicity due to steric hindrance has been observed in the case of 4,5-dimethylacridine[70] (log K^H = 2.88 compared to log K^H = 4.11 for acridine, in 50% v/v ethanol-water at 20°C).

Although the value of the protonation constant for the ring nitrogen of 4,5-diaminoacridine is not known, it must be extremely low, since protonation requires 9M

sulfuric acid. This additional decrease in basicity is caused by electrostatic repulsion by the two protonated amino groups.

Comparison of the spectra of 4-amino-5-hydroxyacridine and 4-amino-5-methoxyacridine with that of 4-hydroxyacridine (Appendix IV) permits the elucidation of the protonation order of the two amino-substituted acridines. The order of protonation of 4-hydroxyacridine is unambiguous. The spectra of singly protonated 4-amino-5-hydroxyacridine (H_2L^+) and 4-amino-5-methoxyacridine (HL^+) are almost identical to the spectrum of neutral 4-hydroxyacridine (HL). The spectra of doubly protonated 4-amino-5-hydroxyacridine (H_3L^{++}) and 4-amino-5-methoxyacridine (H_2L^{++}) are almost identical to the spectrum of the 4-hydroxyacridinium-ion (HL^+); a band at about 450 mμ, characteristic of the acridinium-ion, is observed in the spectra of all three compounds. These results show that the primary amino group is protonated first and the ring nitrogen second.

The protonation constants of these two molecules may now be assigned as follows: for 4-amino-5-hydroxyacridine, the first protonation constant ($\log K_1^H = 11.50$) refers to protonation of the phenolate oxygen. The second protonation constant of 4-amino-5-hydroxyacridine ($\log K_2^H = 2.57$) and the first protonation constant of

4-amino-5-methoxyacridine (log K_1^H = 2.89) refer to protonation of the primary amino group, and the final protonation constant (approximately -0.5 in each case) refers to the protonation of the aromatic nitrogen atom. The lowering of the basicity of the aromatic nitrogen atom to the point where the amino nitrogen is protonated in preference to the ring nitrogen is caused by steric hindrance. The basicity of the aromatic nitrogen atom is further reduced by electrostatic repulsion.

In the case of 4,5-dihydroxyacridine, the sequence of protonation is unambiguous. The basicity of the ring nitrogen atom (log K_3^H = 2.56) is lowered considerably from that of acridine (log K^H = 4.22) or 4-hydroxyacridine (log K_2^H = 4.24) but the effect is caused completely by steric hindrance and is uncomplicated by electrostatic repulsions.

The separation between the protonation constants of the phenolate oxygens of 4,5-dihydroxyacridine results from the same electrostatic repulsion (between the two negative charges on the di-anion) as is encountered in the di-cation of 4,5-diaminoacridine. Since the charged centres are separated by approximately the same distance, it is not surprising that the difference in protonation constants for 4,5-dihydroxyacridine (log K_1^H-log K_2^H = 1.54) is similar to that for 4,5-diaminoacridine(log K_1^H-log K_2^H=1.76).

In summary, steric inhibition of protonation of the

ring nitrogen occurs in all the 4,5-disubstituted acridines studied, resulting in a significant decrease in the protonation constant. If the substituents are basic and comparable in strength to the ring nitrogen, these centres are protonated first. A further decrease in the protonation constant then results because of electrostatic repulsions. In the presence of such powerful effects, the rôle of normal inductive and resonance effects of the substituents is obscured.

The protonation constant of the quinoline nitrogen in 2-(2'-thienyl)-8-hydroxyquinoline (log K_2^H = 1.48) is also lowered considerably (compare to log K_2^H = 3.97 for 8-hydroxyquinoline[71] in 50% v/v dioxane-water at 25°C). This decrease is also the result of a steric effect since the inductive effect of the thienyl group is small. Steric effects of comparable magnitude have been observed in other 2-substituted quinolines, for example in 2-phenyl-8-hydroxyquinoline (log K_2^H = 2.07[19]) and 2-(o-hydroxyphenyl)-quinoline (log $K_2^H \sim 2$[71]).

A complete list of protonation constants is given in Table III of Experimental and Results. These constants have been used in calculating the metal-chelate formation constants discussed in the following sections.

Metal Chelates of 2-(2'-Thienyl)-8-Hydroxyquinoline

The stoichiometry of the metal chelates of 2-(2'-thienyl)-8-hydroxyquinoline was established by elemental

analysis of the solid chelates and by the number of protons released per metal-ion upon chelation (see Experimental and Results). The ligand formed bis-chelates with each of the metal-ions studied.

As shown by the formation constants (Table IV), the metal chelates of 2-(2'-thienyl)-8-hydroxyquinoline are much less stable than the chelates of 8-hydroxyquinoline[71] (log β_2 is from 4 to 9 log units lower). This lower stability suggests that the sulfur atom is not serving as a donor, and that the thienyl group is hindering the formation of the metal chelates. A better comparison is made with the chelates of 2-phenyl-8-hydroxyquinoline[19], since the phenyl group is about the same size as the thienyl group and the logarithms of the protonation constants of the two ligands are similar (11.66 and 1.48 for the thienyl derivative and 11.87 and 2.07 for the phenyl derivative[19]). The latter fact is significant since the formation constants, in the absence of other effects, are approximately linear functions of the protonation constants (see Introduction). The overall formation constants of the 2-(2'-thienyl)-8-hydroxyquinoline chelates are somewhat smaller than those of the 2-phenyl-8-hydroxyquinoline chelates (e.g., by 2.4 log units for the copper chelates). It must be concluded that the thienyl ring is acting solely as a sterically hindering

group, since there is no increase in stability as is observed in the case of the 2-(2'-thienyl)-pyridine chelate with copper(II)[26].

The failure of the sulfur in 2-(2'-thienyl)-8-hydroxyquinoline to coordinate is likely caused by at least two factors. First, the thienyl sulfur atom is a very weak donor (log K_1 = 0.33 for the copper(II)-thiophene complex in 90% dioxane[26]). Secondly, the formation of a terdentate chelate by 2-(2'-thienyl)-8-hydroxyquinoline would require some distortion of normal bond angles in the chelate rings, leading to chelate-ring strain. With the bidentate ligand 2-(2'-thienyl)-pyridine, this ring strain would be virtually non-existent.

The formation constants of the 2-(2'-thienyl)-8-hydroxyquinoline complexes are unusual, in that K_2 is much greater than K_1. Very few examples of this behaviour are to be found in the literature. For the iron(II)-1,10-phenanthroline system, K_3 is much greater than either K_1 or K_2[72]; this is probably caused by spin-pairing of electrons on the addition of the third ligand. This explanation is substantiated by magnetic measurements, which show that the tris-complex is diamagnetic while the mono- and bis-complexes are paramagnetic[73,74].

For complexes of silver(I) with ammonia, many

alkyl- and arylamines, pyridine and many substituted pyridines, K_2 is greater than K_1. This has been explained as being caused by a change in stereochemistry[75]. The bis-complex AgL_2^+ has a linear structure, while in the 1:1 complex, the ligand replaces a water molecule in what is probably a tetrahedral aquo complex.

The cobalt(II) complex of 1-nitroso-2-naphthol may provide a further example. K_2 was reported to be larger than K_1, but this anomaly may be caused by oxidation of cobalt(II) to cobalt(III)[76]. Other examples include the nickel(II) chelate of 2,3-dimethyl-2,3-diaminobutane* and the cadmium(II), nickel(II) and zinc(II) chelates of some S-alkyl carboxylic acids**. No explanation has been advanced for the behaviour of these complexes.

For a series of substituted pyrazolones[79-81], K_2 is greater than K_1 for the chelates of cobalt(II), nickel(II), copper(II) and zinc(II). The explanation that the bis-chelates are more symmetrical than the mono-chelates and moreover are neutral, is erroneous. In fact, the neutralization of metal-ion charge by an anionic ligand decreases coulombic attraction between

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*The copper(II) chelate is normal; so are the nickel(II) chelates of other substituted ethylenediamines[77].

**The copper(II) and lead(II) chelates are normal[78].

the chelated metal-ion and successive ligands and actually increases the separation between stepwise constants.

The fact that K_2 is greater than K_1 for the chelates of 2-(2'-thienyl)-8-hydroxyquinoline is best explained as the result of a steric effect. As stated in the Introduction, substitution of a methyl group in the 2-position of 8-hydroxyquinoline (or in the corresponding position in analogous compounds, including 1,10-phenanthroline) results in steric destabilization of the metal chelates. This can be of two kinds: (a) destabilization arising from the interaction of the 2-substituent with water molecules in the coordination sphere of the metal-ion, and (b) destabilization arising from interaction between bound ligands. The former effect is shown by a decrease in the magnitude of the first formation constant, compared to that of the parent compound; a decrease in the magnitude of subsequent formation constants may be the result of steric destabilization of the latter type. Ligand-ligand interference has been advanced as the reason for the non-precipitation of aluminium(III) by 2-methyl-8-hydroxyquinoline[39], but since no evidence has been found for a 1:1 chelate in aqueous solution[17], steric interaction between the ligand and coordinated water must be a more important factor, as has been stated recently[18].

the copper(II)-ion, the structure of the mono-ligand aquo complex is distorted from a planar towards a tetrahedral arrangement of ligands, in which there is less steric interaction. That energy is required to distort the structure is shown by a decrease in the first formation constant. Substitution of the second ligand in an already distorted structure occurs without any serious decrease in stability. As the degree of steric interaction increases, the separation between the two constants decreases, with some suggestion (Table VIII) that K_1 may become even less than K_2.

In the case of the 2-(2'-thienyl)-8-hydroxyquinoline complexes, steric interaction between the thienyl substituent and the adjacent water molecule in the plane of the chelate ring is very large. (This interaction is indicated by the construction of models; in fact, the ligand was designed such that the sulfur might coordinate in the position occupied by the water molecule.) As a result, distortion of the structure of the mono-ligand aquo complex must occur, and the first formation constant becomes smaller than the second.

The formation constants of the metal chelates of 2-phenyl-8-hydroxyquinoline support this hypothesesis.

The corrected values* of log K_1 and log K_2 for the metal chelates of this ligand are 10.2 and 12.1 for copper(II), 7.1 and 7.4 for nickel(II) and 7.0 and 10.5 for zinc(II). Further confirmation of this 2-substituent effect is derived from the work of Kaneko and Ueno[27], who determined the formation constants of the nickel(II), copper(II), zinc(II) and cadmium(II) chelates of several 2-alkyl-8-hydroxyquinolines. The results of this study are shown in Table IX.

The data show that as the size of the 2-substituent increases, the difference between log K_1 and log K_2 decreases and eventually log K_1 becomes smaller than log K_2 (in the case of every metal-ion except cadmium). This effect, for which Kaneko and Ueno could offer no explanation, is dramatic support of the hypothesis that steric hindrance between the 2-substituent and an adjacent coordinated water molecule causes distortion of the monoligand chelate, and facilitates entry of the second ligand.

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*The constants reported in the literature[19] are those obtained by interpolation of the formation function at $\bar{n}=0.5$ and $\bar{n}=1.5$. The values reported here have been converted to the true values by means of the expression

$$K_1 = K_1' - 3\,K_2' \quad \text{and} \quad K_2 = \frac{K_1'\,K_2'}{K_1}$$

where K_1' and K_2' are the interpolated values.

Derivation of this equation and its application to incorrect values in the literature are described in Appendix IX.

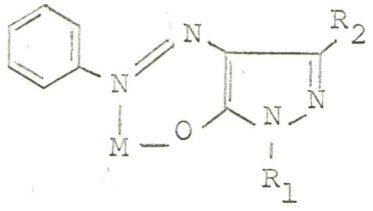
TABLE IX

FORMATION CONSTANTS OF SOME 2-ALKYL-8-HYDROXYQUINOLINE CHELATES

2-Substituent		Ni(II)	Cu(II)	Zn(II)	Cd(II)
-H	log K_1*	11.40	13.17	9.83	9.40
	log K_2*	9.98	13.05	9.03	7.71
$-CH_3$	log K_1	9.35	12.43	9.89	9.18
	log K_2	8.91	11.46	9.22	8.21
$-C_2H_5$	log K_1	8.69	12.05	9.66	8.66
	log K_2	9.05	11.28	9.30	8.31
$-\underline{n}-C_3H_7$	log K_1	9.01	12.06	8.96	8.84
	log K_2	9.46	11.81	10.49	8.70
$-\underline{n}-C_4H_9$	log K_1	9.18	12.05	9.75	9.28
	log K_2	9.89	12.23	10.24	8.98

*Data of reference (67) corrected according to the equations of Appendix IX.

The fact that K_2 is greater than K_1 for metal chelates of the substituted pyrazolones can also be explained on the same basis. The structure of the chelates is shown below. The



phenyl ring is substituted in a position such that it can

interfere with an adjacent coordinated water molecule.

Additional studies were made (with the cobalt(II) and nickel(II) complexes) in the hope of obtaining supporting evidence for distortion of structure. If the bis-chelates were tetrahedral, their absorption spectra and magnetic moments should indicate this.

The absorption spectra* in the region 400-750 mμ did not exhibit the strong absorptions characteristic[83] of tetrahedral cobalt(II) and nickel(II) complexes. However, this in itself is not proof of the lack of distortion since recently it has been shown that planar copper(II) complexes which have undergone moderate distortion toward a tetrahedral structure may give an absorption spectrum characteristic of the planar complex[84].

In interpreting the magnetic moments of the cobalt(II) and nickel(II) chelates, the only structures that need be considered are planar, distorted tetrahedral and pseudo-octahedral, in which the metal-ion in a planar complex is associated with coordinated water or donor atoms of neighbouring complexes. Chelates of 8-hydroxyquinoline with many divalent transition metals precipitate from aqueous solution as dihydrates[85]; x-ray studies have shown that the water molecules are coordinated to the

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*Spectra were determined using 50% v/v dioxane-water as solvent, to permit comparison with the equilibrium measurements.

metal-ion, at least in the chelates of copper(II) and zinc(II)[86-88]. The water molecules are lost at approximately 125°C[85]. Since no loss in weight was observed on drying the 2-(2'-thienyl)-8-hydroxyquinoline complexes at 150°C, it can be assumed that they are anhydrous.

Since the magnetic moment of the nickel(II)-ion in the 2-(2'-thienyl)-8-hydroxyquinoline chelate is 3.21 B.M., the planar structure, which would be diamagnetic, can be eliminated. Although the magnetic moment is less than expected for true tetrahedral complexes of nickel(II)(e.g., for $NiCl_4^{=}$, μ_{eff} = 3.87 B.M. at room temperature[89]), Sacconi _et al._[90] have found that the magnetic moments of complexes containing nickel(II) in a distorted tetrahedral environment are also less than expected for a true tetrahedral complex. For example, bis(N-_iso_ propylsalicylaldiminato)nickel(II) has a magnetic moment of 3.34 B.M.[90] and has been shown by x-ray studies to be distorted toward a tetrahedral structure by the branched alkyl groups[91]. Similarly, bis(N-butylsalicylaldiminato)cobalt(II) has a magnetic moment at room temperature of 4.47 B.M.[92] and is tetrahedral[92,93]. The magnetic moment of the 2-(2'-thienyl)-8-hydroxyquinoline chelate is 4.50 B.M.

However, since the observed magnetic moments of

the 2-(2'-thienyl)-8-hydroxyquinoline chelates can also be the result of pseudo-octahedral coordination, the question can only be resolved by determination of the structures by x-ray methods.

Metal Chelates of 4-Amino-5-Hydroxyacridine

Evidence that the copper(II) chelate of 4-amino-5-hydroxyacridine is terdentate is obtained from the stoichiometry of the chelate, the dissociation constant of the coordinated water molecule, and the magnitude of the formation constant. The 1:1 stoichiometry was obtained by analysis of the titration curve (Figure 7). There is no evidence for the formation of a chelate of stoichiometry higher than 1:1, even when the ligand is in threefold excess. The second buffer region (pH 7-10) has been attributed to proton loss from a coordinated water molecule, since it is observed even when the ligand-to-metal ratio is 1:1. The stoichiometry of the chelate could not be confirmed by elemental analysis, because the complex was too soluble to isolate.

The magnitude of the dissociation constant of the coordinated water molecule in other 1:1 copper(II) chelates appears to offer a useful test for the number of coordinated donor groups of a chelating ligand. Martell et al.[94] showed that in aqueous solution at 25°C, the pK_a of coordinated water in 1:1 copper(II) chelates of

twelve bidentate ligands was 7.2 ± 0.6*. The magnitude of the acid dissociation constant is apparently not sensitive to the charge and the stability of the complex. For 1:1 copper(II) chelates with terdentate ligands, the pK_a of the coordinated water molecule was in the range 9.0 - 9.2. No region of proton loss from coordinated water was observed for copper(II) chelates in which four or more donor groups of a chelating ligand were coordinated. Martell and his co-workers did not state the obvious conclusion, that the acid dissociation constant provides a method for distinguishing between bidentate, terdentate and higher-dentate ligands in copper(II) chelates. In the present work, the first acid dissociation constants of coordinated water in the copper(II) chelates of some bidentate and terdentate ligands were determined in 50% v/v dioxane-water (Table V). Exactly the same effect was noted. For the chelates of bidentate ligands, the pK_a values are in the range 6.9 - 7.1, while for the chelates of terdentate ligands, the values are in the range 9-10. For the copper(II) chelate of 4-amino-5-hydroxyacridine, the pK_a value indicates that the ligand is terdentate.

Several studies have shown that a terdentate ligand forms more stable chelates than a similarly con-

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*This value is for the dissociation of the first water molecule. The pK_a for the dissociation of a second water molecule is about 9.

stituted bidentate ligand[95]. Thus it is surprising to find that log K_1 for the copper(II) chelate of 4-amino-5-hydroxyacridine (11.76) is significantly lower than log K_1 for the 8-hydroxyquinoline complex (13.17). On the basis of the formation constant alone, 4-amino-5-hydroxyacridine might at first be considered to be bidentate. However, if this were the case, the third donor group* would be sterically hindering, probably to a greater extent than the thienyl group in the 2-(2'-thienyl)-8-hydroxyquinoline chelate. In the latter chelate there is the possibility of partial relief of steric hindrance by distortion of the bond linking the thienyl substituent and the quinoline ring, or by rotation of the thienyl group out of the plane of the quinoline ring. The analogous effects cannot occur in the chelates derived from 4-amino-5-hydroxyacridine. Thus, if the third donor group were not coordinated, the chelate should be of comparable or lower stability than the 2-(2'-thienyl)-8-hydroxyquinoline chelate. As before, the difference in protonation constants must be considered. The protonation constants of the phenolate oxygens are

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*It is assumed that if the ligand acted as a bidentate donor, the primary amino group would likely be uncoordinated, since it is much less basic than the phenolate-ion. Coordination of the aromatic nitrogen is favoured by the formation of a very stable five-membered ring involving it, the metal-ion and the phenolate-ion.

similar (log K_1^H = 11.50 for the acridine ligand, log K_1^H = 11.66 for the quinoline ligand). The protonation of the aromatic nitrogen in 4-amino-5-hydroxyacridine is complicated by electrostatic repulsion; it is assumed that the intrinsic basicity of the aromatic nitrogen in the two compounds is similar. Since log K_1 for the 4-amino-5-hydroxyacridine chelate (11.76) is much greater than that for the 2-(2'-thienyl)-8-hydroxyquinoline chelate (8.84), the ligand must be terdentate in the copper(II) chelate of the acridine ligand.

The decrease in stability of the terdentate chelate from that of the bidentate 8-hydroxyquinoline chelate is likely due to chelate-ring strain caused by the coordination of the third donor group. This ring strain is indicated by molecular models and has been introduced previously to explain the failure of the sulfur to coordinate in the chelates of 2-(2'-thienyl)-8-hydroxyquinoline. Ring strain would be an even more important factor in the 4-amino-5-hydroxyacridine chelates, since the donor atoms are held in position by the rigid acridine ring system. No other rigid terdentate ligands have been studied by other workers, but similar effects have been postulated in metal chelates of terpyridyl and quaterpyridyl[96], and have been observed in the structures of ethylenediaminetetraacetic acid chelates[97] and the zinc(II) chelate of terpyridyl[98].

The cobalt(II), nickel(II), zinc(II) and cadmium(II) chelates of 4-amino-5-hydroxyacridine are also less stable than the corresponding 8-hydroxyquinoline chelates. Elemental analyses showed that the isolated solid complexes had a ligand-to-metal ratio of 2:1. However, the stoichiometry of the chelates cannot be used to decide whether the ligand is terdentate or bidentate, since bis-chelates are possible in either case. The acid dissociation constant of coordinated water in 1:1 chelates of these metal-ions cannot be used to determine the number of ligand donor atoms that are coordinated, since data in the literature[12] suggest that the pK_a values for chelates containing bidentate and terdentate ligands are not sufficiently different.

However, as reasoned for the copper(II) chelate, if the third donor group is not coordinated, it must behave as a sterically hindering group, and the chelates should be of comparable stability to the 2-(2'-thienyl)-8-hydroxyquinoline chelates. Furthermore, K_1 should be less than K_2, for the reasons noted previously. Neither of these two effects is observed. The values of log K_1 are greater for the 4-amino-5-hydroxyacridine chelates than for the 2-(2'-thienyl)-8-hydroxyquinoline chelates (although by about only one log unit). More important, K_1 is greater than K_2.

In reactions with several 2-substituted 8-hydroxy-

quinolines, it has been shown that nickel(II) is more susceptible to steric hindrance than copper(II), cobalt(II) and zinc(II). The observed order of stability for the metal chelates of 8-hydroxyquinoline with these metal-ions is

Cu > Ni > Co > Zn*

while for 2-methyl-8-hydroxyquinoline the order is

Cu > Zn > Co > Ni.

This latter order is observed for the metal chelates of 2-(2'-thienyl)-8-hydroxyquinoline and several 2-alkyl-8-hydroxyquinolines[27] (Table IX). The cause of this preferential destabilization of nickel(II) chelates is not well understood, but may be related to a greater resistance to distortion than the other metal-ions.

Examination of the formation constants of chelates of several terdentate ligands[12] showed that a stability series comparable in generality to the Irving-Williams order for bidentate ligands cannot be written. The following limited series, however, seems to apply.

Cu > Ni > (Co, Zn).

For the chelates of 4-amino-5-hydroxyacridine, the stability order which is observed is

Cu > Ni > Zn > Co

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*This is in agreement with the Irving-Williams stability order[99].

which is the order observed for terdentate chelates and not for complexes of 2-substituted 8-hydroxyquinolines. This order suggests that the 4-amino-5-hydroxyacridine chelates are terdentate.

The Copper(II) Chelate of 4,5-Diaminoacridine

Little evidence is available concerning the number of donor groups which are coordinated to copper(II) in the 4,5-diaminoacridine chelate. The 1:1 stoichiometry, as shown by potentiometric titration and elemental analysis*, suggests that the ligand is terdentate. The magnitude of the formation constant ($\log K_1 = 4.7$) is of little use, since the formation constants of the copper(II) chelate of 8-aminoquinoline in 50% v/v dioxane-water are not available for comparison. Determination of these constants was attempted, but a precipitate (probably $CuL_2(ClO_4)_2$) formed upon mixing the reagents. When the anions of the background electrolyte and strong acid were changed from perchlorate to nitrate, precipitation (probably of $CuL_2(NO_3)_2$) again occurred. Each of these compounds has been prepared in aqueous solution[100].

The formation constants of several metal chelates of 8-aminoquinoline in water have been determined by

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*The results of the elemental analysis(Table III, Appendix III) are not entirely satisfactory, but differentiate between a 1:1 and a 1:2 complex.

Yasuda[101]. The logarithm of the overall formation constant, β_2, of the copper(II) chelate was found to be approximately 10. It has been shown that for chelate systems involving nitrogen donors, the formation constants are relatively insensitive to the changing organic content of a mixed solvent[15]. Hence, log β_2 for the copper(II) chelate of 8-aminoquinoline in 50% v/v dioxane-water may be approximately 10. Assuming, then, that log K_1 is about five, the stability of the 4,5-diaminoacridine chelate does not seem to be too different from that of the 8-aminoquinoline chelate. This suggests that the ligand is terdentate, since if it were bidentate, steric hindrance by the non-coordinated amino group should result in the chelate being much less stable than the 8-aminoquinoline chelate.

Metal Chelates of 4,5-Dihydroxyacridine

The extremely low solubility of the 4,5-dihydroxyacridine chelates prevented both the potentiometric and spectrophotometric study of the solution equilibria with all ions tried except copper(II), even at a concentration of 5×10^{-5}M (one-tenth the normal concentration).

The potentiometric titration curves could be used, however, to determine that the ligand formed bischelates, and this conclusion is confirmed by the results of elemental analysis. The insolubility of the bis-

chelates suggests their formulation as the electrically neutral species $M(HL)_2$, where HL^-, the mono-anion of 4,5-dihydroxyacridine, is a bidentate ligand.

This conclusion is surprising, since the phenol group is a strong donor group and in the 4,5-dihydroxyacridine chelates, is held close to the metal-ion. The fact that for the copper(II) chelate, log K_1 (9.2) is less than log K_2 (11.3) and that these values are almost identical* to those for the copper(II) chelate of 2-(2'-thienyl)-8-hydroxyquinoline (log K_1 = 8.84 and log K_2 = 11.01) suggests that the phenol group is sterically hindering.

It should be noted that the observation that K_2 is greater than K_1 strengthens the argument made previously in favour of the terdentate nature of 4-amino-5-hydroxyacridine. For the chelates of this ligand, with cobalt(II), nickel(II), zinc(II) and cadmium(II), K_1 is greater than K_2.

The reason that 4,5-dihydroxyacridine can be bidentate and 4-amino-5-hydroxyacridine terdentate is not readily apparent. Perhaps chelate-ring strain developed by coordination of the third donor group would be greater in the 4,5-dihydroxyacridine chelates since, in many

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*The protonation constants of the two ligands are sufficiently similar (Table III) to allow comparisons between chelate formation constants.

transition-metal chelates, metal-oxygen bonds are shorter than metal-nitrogen bonds[102]. Molecular models indicate that some strain opposing coordination of the third donor group should be experienced with either ligand. Another reason may be that when the tendency of the phenolate oxygen and amino group to bond to the metal-ion is reduced by the rigid nature of the ligand, the phenolate oxygen can satisfy its coordination requirements by protonation.

At high pH values, the neutral complexes of 4,5-dihydroxyacridine are deprotonated to yield anionic chelates, $ML_2^{=}$. The buffer region in the pH range 9-11 (Figure 10) is indicative of this. Whether 4,5-dihydroxyacridine acts as a terdentate ligand in these anionic chelates is unknown.

A few examples of metal chelates in which a potential donor group does not coordinate with the metal-ion are known. In the nickel(II) and copper(II) chelates of ethylenediaminetetraacetic acid, one carboxylic acid group is not coordinated[97]. Examples of complexes containing more than one free carboxylic acid group also are known[103]. In the bis-histidino chelates of zinc(II) and cadmium(II), the two nitrogen donors of each ligand are strongly coordinated but the carboxylate oxygen is only loosely associated[104-107].

Selectivity of the New Ligands

Modification of the 8-hydroxyquinoline structure has resulted in a significant increase in selectivity for only 2-(2'-thienyl)-8-hydroxyquinoline and 4,5-diaminoacridine. In each case, the improved selectivity arises from the reduced stability of the metal chelates. The stability of the 2-(2'-thienyl)-8-hydroxyquinoline chelates is lowered because the non-coordinating thienyl group inhibits chelate formation; the stability of the 4,5-diaminoacridine chelates is reduced mainly because of the absence of a strongly bonding donor group such as phenoxide. The chelates of 4,5-diaminoacridine are so unstable that the ligand is not useful analytically; on the other hand, some metal chelates of 2-(2'-thienyl)-8-hydroxyquinoline are sufficiently stable for analytical purposes, lending potential to this ligand as an analytical reagent.

The selectivity of the terdentate ligand 4-amino-5-hydroxyacridine is not much greater than that of 8-hydroxyquinoline. This small increase in selectivity is probably the result of decreased chelate stability. It was hoped that with a fixed arrangement of donor groups such as is present in 4-amino-5-hydroxyacridine, a large difference in stability would be found between octahedral or planar complexes, in which the ligand could be ter-

dentate, and tetrahedral complexes, in which the ligand could at best be bidentate. However, the results of the present work show that the ligand is terdentate with all the metal-ions studied, even with zinc(II) and cadmium(II), which often form tetrahedral complexes. Thus, it appears that rigid planar terdentate ligands will not be useful analytical reagents.

4,5-Dihydroxyacridine is highly unselective. Since it acts as a sterically hindering bidentate ligand toward the metal-ions studied in this work, its complexes should be of lower stability than those of 8-hydroxyquinoline, and indeed its copper(II) chelate is much less stable. Although this reduction in stability should increase the selectivity of 4,5-dihydroxyacridine, this effect is overshadowed by the very low solubility of the metal chelates. As a result, the ligand is unselective.

Discussion of Errors

This discussion is limited to the errors peculiar to the determination of protonation constants and chelate formation constants. The largest source of error arises from the measurement of pH, and affects both the spectrophotometric and potentiometric methods. Recent improvements in the design of pH meters and electrodes permit measurements of pH with a precision of a few one-thousandths of a pH unit, so that the largest error in pH

measurement results from the uncertainty in the values of the standard buffer solutions used to calibrate the pH meter. This uncertainty is of the order of 0.01 pH unit.

Errors due to activity coefficients are eliminated by the use of a background electrolyte and the Van Uitert and Haas correction factor. The correction factor allows conversion of hydrogen-ion activities to stoichiometric hydrogen-ion concentrations. This means that the equilibrium constants determined in the present work are concentration constants. These constants are valid only for 50% v/v dioxane-water and an ionic strength of 0.1.

The calculation of chelate formation constants involves both measurement of pH and the use of ligand protonation constants, which are also based on pH measurements. A detailed analysis of error has not been performed, but experience has shown that a constant error in pH values results in an error of the same magnitude in the value of the protonation constant; similarly, an error in the value of the protonation constant results in an error of the same magnitude in log K_1 and log K_2 for the metal chelate.

Although uncertainties in the pH scale and the values of the ligand protonation constants exist, these are essentially constant for titrations involving the

same ligand and a series of metal-ions. Therefore, formation constants resulting from such titrations can be compared with some certainty.

The formation constants reported in the present work were calculated by least-squares fit of the best line to a linear form of the formation function. This method uses a large amount of the experimental data and also eliminates the subjective factor. Other methods which have been proposed[108] often use only a small portion of the data or require graphical procedures which may introduce subjective errors, or both.

The uncertainties in the values of log K_1 and log K_2 also depend on the magnitude of the quantity K_1/K_2. This quantity determines the slope of the formation curve at the mid-point[109]. When K_1/K_2 is much less than unity, the shape of the formation curve is insensitive to variations in K_1 and K_2 and as a result, the uncertainty in K_1 and K_2 is large. The chelates of 2-(2'-thienyl)-8-hydroxyquinoline provide examples of this type of behaviour (Table IV).

Suggestions for Further Work

The findings of the present work suggest further research in three areas. First, the effect of bulky 2-substituents in 8-hydroxyquinoline on the relationship between K_1 and K_2 should be studied further. Specifically,

the effect of branched alkyl substituents (e.g., iso-propyl and tert-butyl) would complement the findings of Kaneko and Ueno[27], who studied only linear alkyl groups.

Secondly, the synthesis of further derivatives of 8-hydroxyquinoline which contain 2-substituents bearing potential coordinating groups should be investigated. In the light of the results reported in this work, it appears that a flexible substituent should permit coordination without the development of undue strain in the resulting chelate ring. Additional ligands of this type include 2-aminomethyl-8-hydroxyquinoline and 2-(2'-pyridyl)-8-hydroxyquinoline. Preliminary experiments with the former ligand have already been reported by Stevenson and Freiser[29].

Lastly, further attempts to determine the formation constants of metal chelates of 4,5-dihydroxyacridine should be made. Because of the extremely insoluble nature of these chelates, the only experimental technique which appears to be applicable is the solubility method involving radioactive tracers[32].

SUMMARY

1. The following new compounds have been synthesized and characterized: 2-(2'-thienyl)-8-hydroxyquinoline, 4-amino-5-hydroxyacridine, 4-amino-5-methoxyacridine and 4,5-dihydroxyacridine. The protonation constants of these compounds, and of 4,5-diaminoacridine, 4-hydroxyacridine and acridine, have been determined in 50% v/v dioxane-water at 25°C. The order of successive sites of protonation of 4-amino-5-hydroxyacridine and 4-amino-5-methoxyacridine has been elucidated.

2. The chelate formation constants for the reaction of 2-(2'-thienyl)-8-hydroxyquinoline and 4-amino-5-hydroxyacridine with cobalt(II), nickel(II), copper(II), zinc(II) and cadmium(II), and of 4,5-diaminoacridine and 4,5-dihydroxyacridine with copper(II) have been determined in 50% v/v dioxane-water at 25°C.

3. The 2-(2'-thienyl)-8-hydroxyquinoline chelates have been formulated as sterically hindered complexes in which the ligand is bidentate. The unusual relationship, $K_1 < K_2$, for these complexes has been attributed

to a decrease in the ease of formation of the first complex, ML^+, resulting from steric interaction between the bulky substituent and an adjacent coordinated water molecule.

4. The 1:1 stoichiometry and the acid dissociation constant of the water molecule in the copper(II) chelate of 4-amino-5-hydroxyacridine indicate that in this complex the ligand is terdentate. It is suggested that the magnitude of the first acid dissociation constant of coordinated water in 1:1 copper(II) chelates provides a useful method for determining the number of coordinated donor atoms in a chelating ligand.

The fact that the formation constant of the copper(II) chelate of 4-amino-5-hydroxyacridine is lower than that of the copper(II) chelate of 8-hydroxyquinoline is interpreted to indicate that chelate-ring strain is developed upon coordination of the third donor group.

5. On the basis of the normal relationship of the formation constants ($K_1 > K_2$) and the normal chelate stability order (Cu > Ni > Zn > Co), the chelates of 4-amino-5-hydroxyacridine studied in this work have been formulated as complexes in which the ligand is terdentate. It is suggested that the decrease in stability of these chelates relative to the stability

of the corresponding 8-hydroxyquinoline chelates is the result of chelate-ring strain caused by the coordination of the third donor group.

6. On the basis of its stoichiometry and the magnitude and unusual relationship ($K_1 < K_2$) of its formation constants, the copper(II) chelate of 4,5-dihydroxyacridine has been formulated as a chelate in which the ligand is bidentate. The copper(II) chelate of 4,5-diaminoacridine has been tentatively formulated as a chelate in which the ligand is terdentate. No direct evidence other than the 1:1 stoichiometry is available concerning the number of coordinated donor atoms in this ligand.

7. A useful equation has been derived for the correction of temporary formation constants obtained by interpolation of the formation curve at $\bar{n} = 0.5$ and $\bar{n} = 1.5$. This equation provides values of K_1 and K_2 that more closely approximate the true values, and is useful for the correction of values in the literature which have been obtained by interpolation.

8. Except for 2-(2'-thienyl)-8-hydroxyquinoline, a useful increase in selectivity was not observed for any of the other ligands based on 8-hydroxyquinoline. In the light of the results reported in this thesis, suggestions have been made for further research.

APPENDIX I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF LIGANDS

All spectra were recorded with 1,4-dioxane as solvent and hexamethyldisiloxane as internal reference.

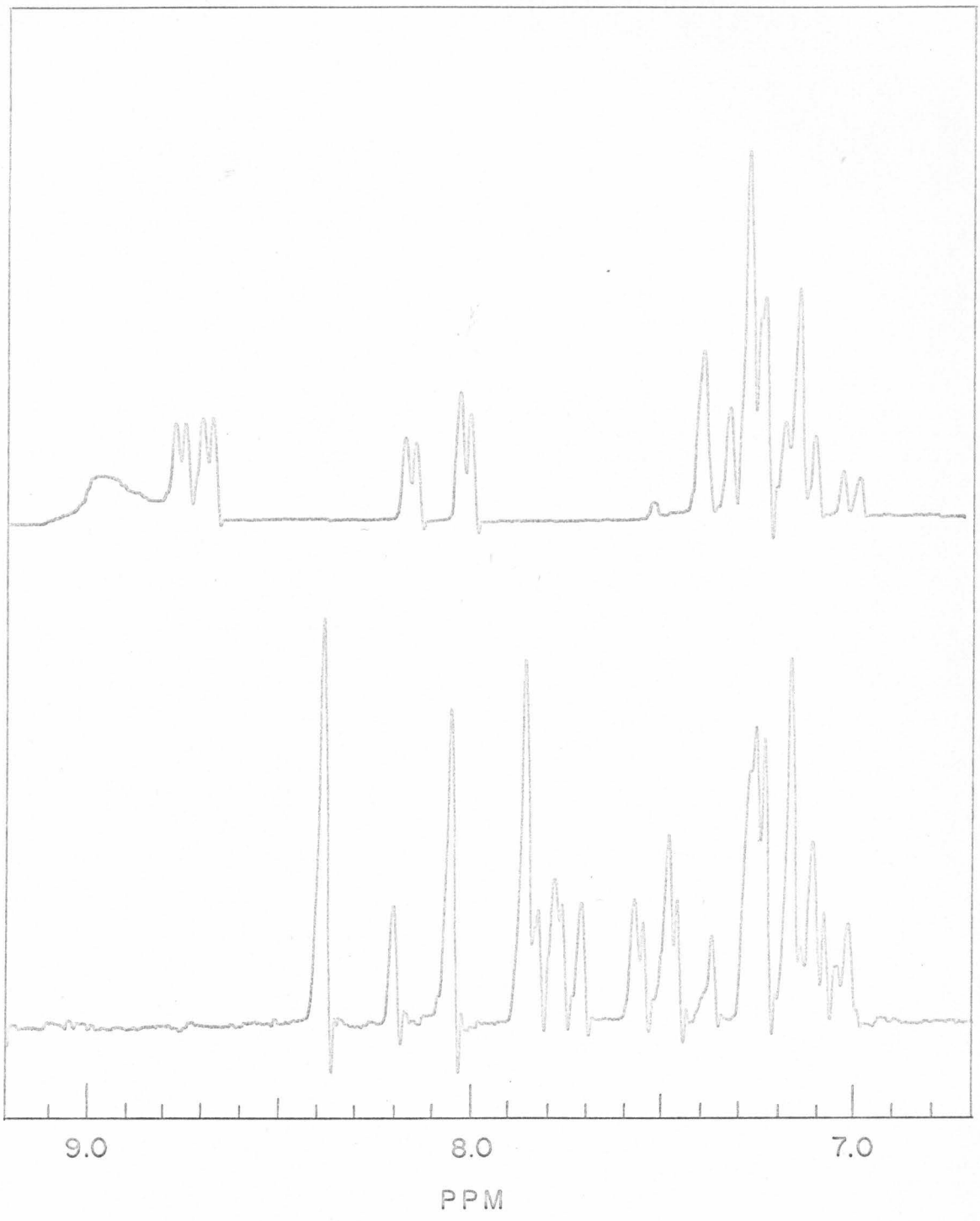

Figure 1. Nuclear Magnetic Resonance Spectra of 8-Hydroxyquinoline(upper) and 2-(2'-Thienyl)-8-Hydroxyquinoline(lower).

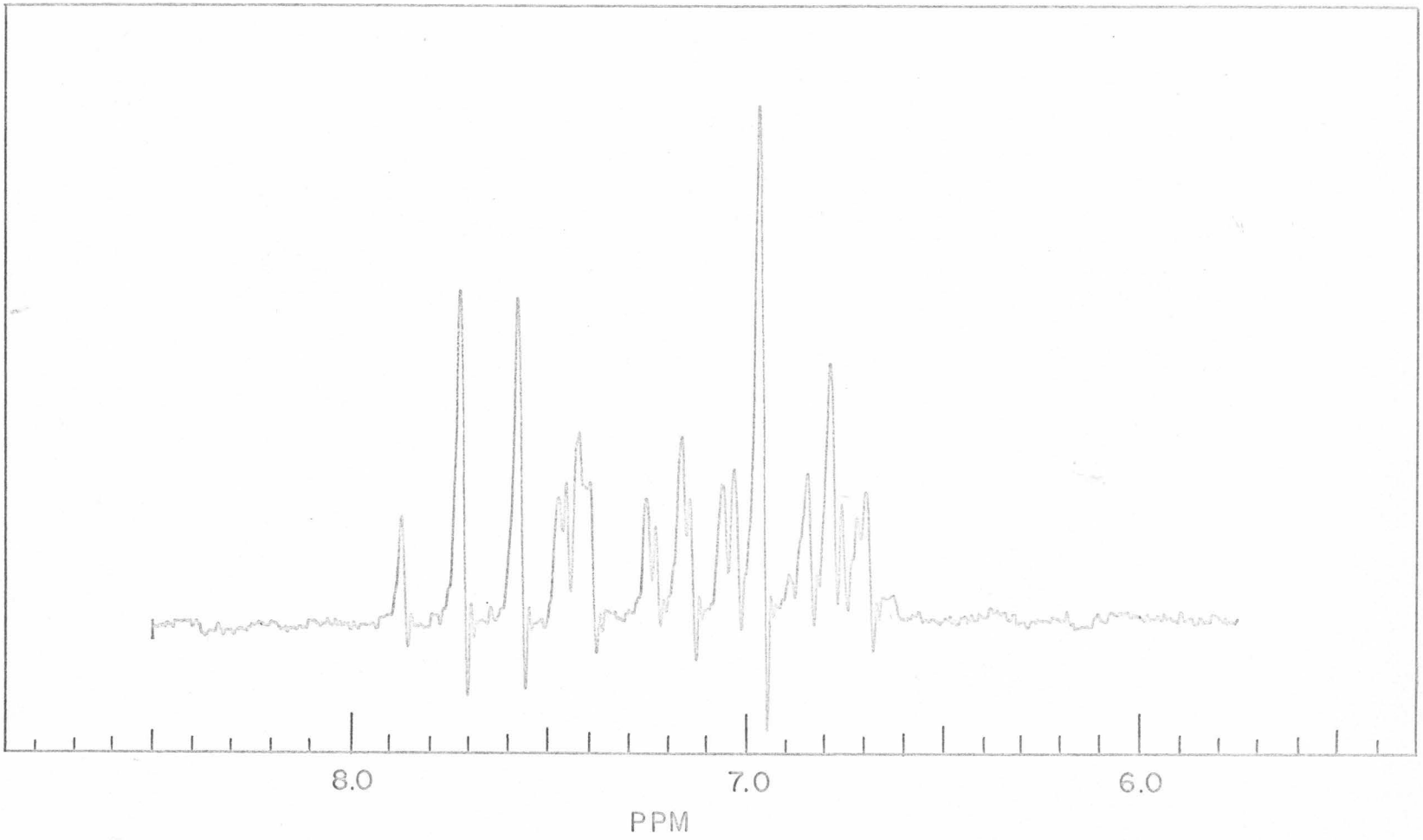

Figure 2. Nuclear Magnetic Resonance Spectrum of 2-(2'-Thienyl)-8-Methoxyquinoline.

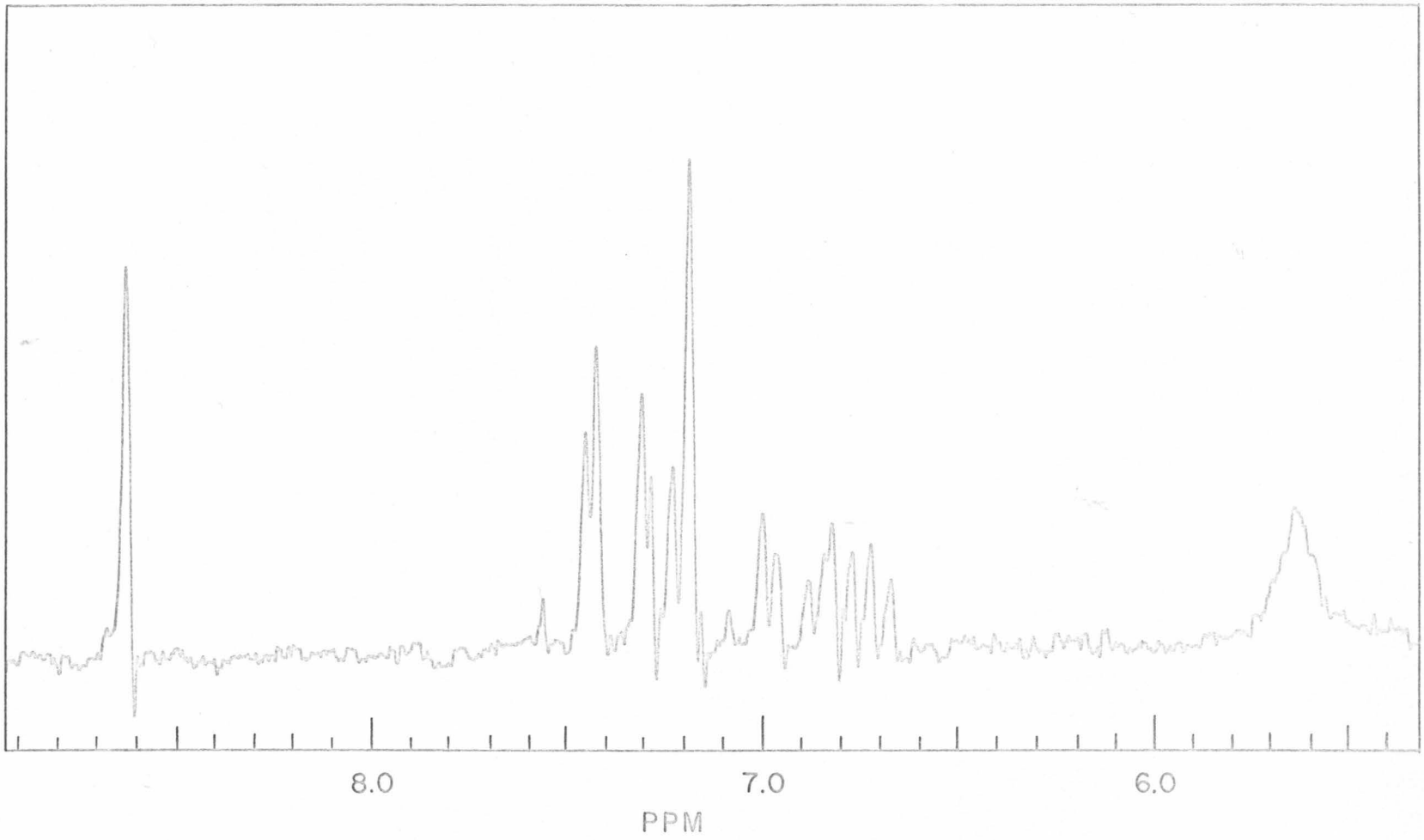

Figure 3. Nuclear Magnetic Resonance Spectrum of 4-Amino-5-Methoxyacridine.

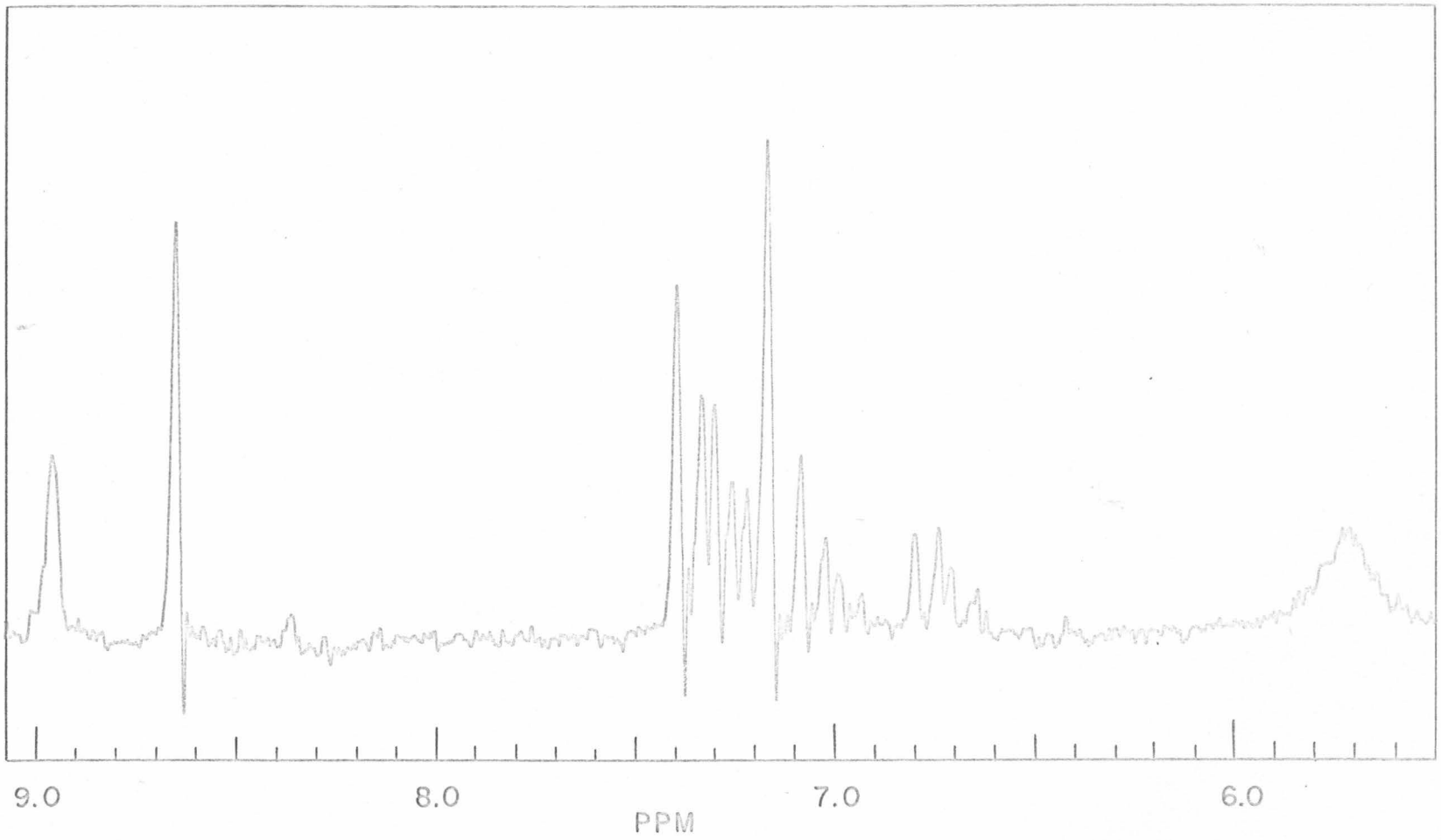

Figure 4. Nuclear Magnetic Resonance Spectrum of 4-Amino-5-Hydroxyacridine.

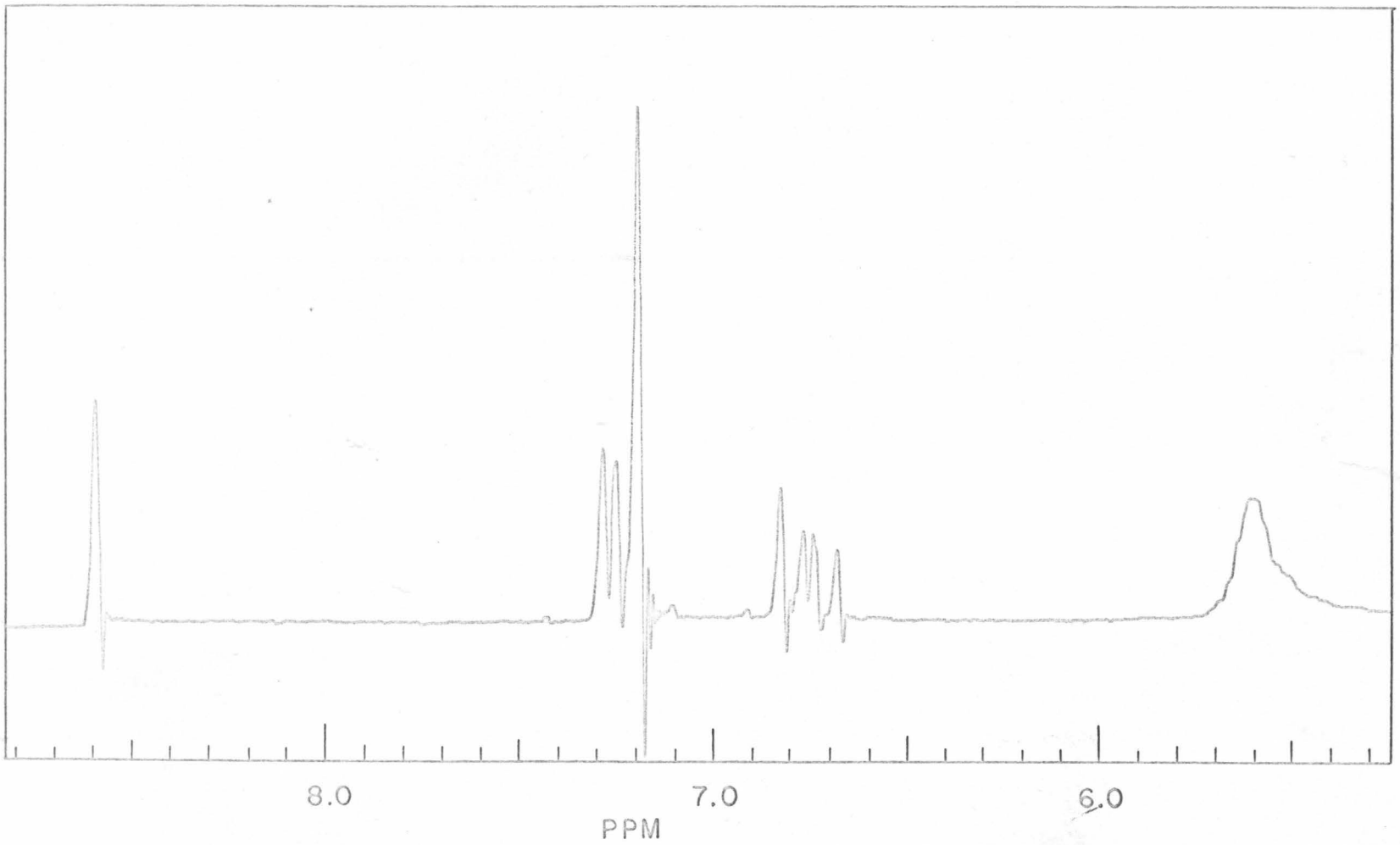

Figure 5. Nuclear Magnetic Resonance Spectrum of 4,5-Diaminoacridine.

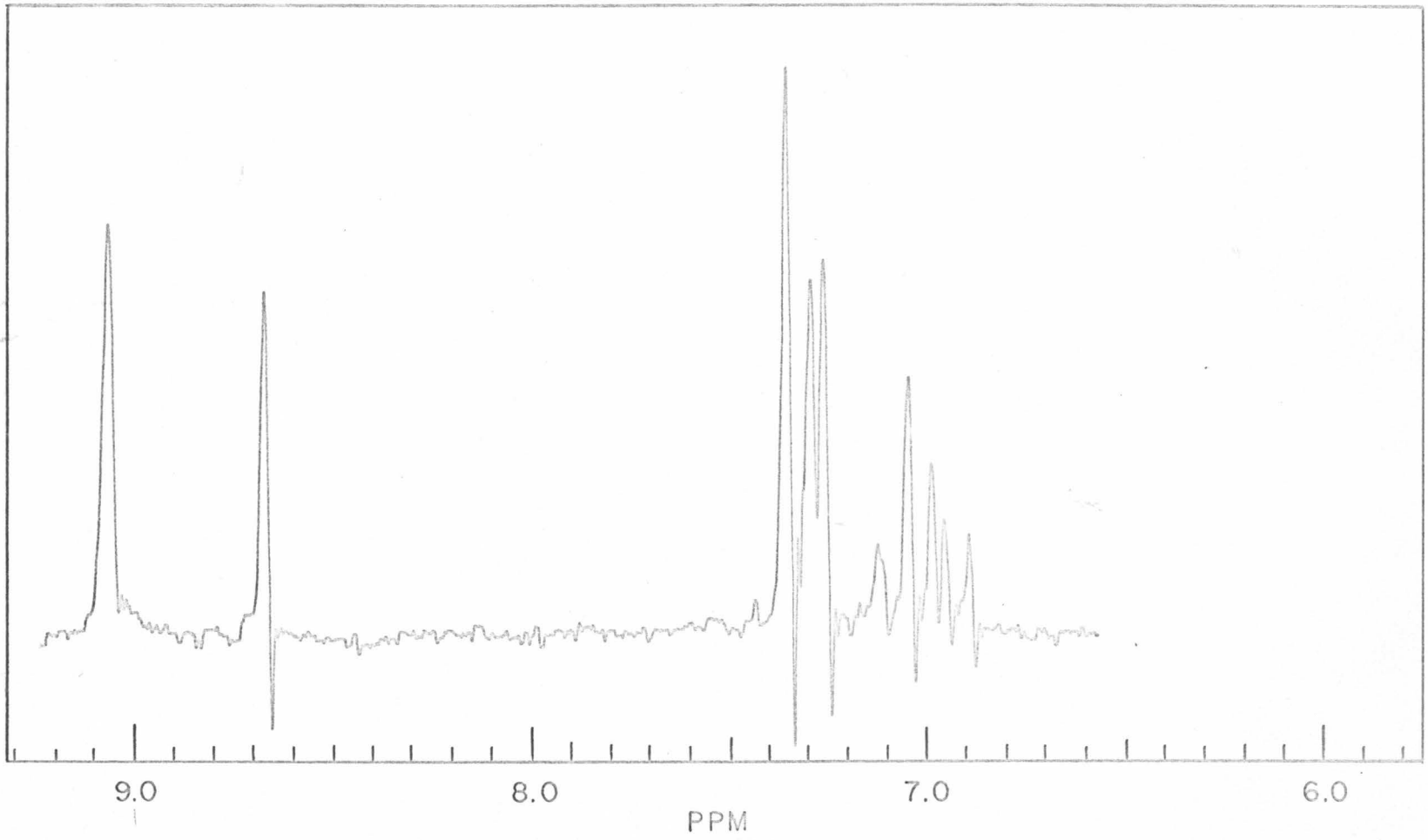

Figure 6. Nuclear Magnetic Resonance Spectrum of 4,5-Dihydroxyacridine.

APPENDIX II

REACTIVITY OF LIGANDS TOWARD METAL-IONS

TABLE I

SPOT-TESTS WITH 2-(2'-THIENYL)-8-HYDROXYQUINOLINE

Metal-ion	Acetate Buffer (pH 5)	Borate Buffer (pH 10)
Mn(II)	*	yellow colour
Fe(II)		orange precipitate
Co(II)		yellow colour
Ni(II)		yellow colour
Cu(II)	yellow-green colour	yellow-green colour
Zn(II)		yellow colour
Cd(II)		yellow precipitate
Pb(II)		yellow precipitate
Hg(II)	orange turbidity	orange turbidity
Pd(II)	orange colour	orange colour
Fe(III)	orange colour	
Rh(III)	yellow colour	yellow colour

* No entry indicates "no observable reaction".

No reaction with: Mg(II), Ca(II), Sr(II), Ba(II), Sc(III), Y(III), La(III), Al(III), Ga(III), In(III), Tl(III), Cr(III), Ce(III), Cu(I), Zr(IV), Th(IV), U(VI).

TABLE II

SPOT-TESTS WITH 4,5-DIAMINOACRIDINE

Metal-ion	Acetate Buffer (pH 5)	Borate Buffer (pH 10)
Cu(II)	yellow-green colour	*
Hg(II)	red gelatinous precipitate	red gelatinous precipitate
Tl(III)	yellow colour	
Rh(III)		yellow-green precipitate
Pd(II)		yellow-green precipitate

* No entry indicates "no observable reaction".

No reaction with: Mg(II), Ca(II), Sr(II), Ba(II), Sc(III). Y(III), La(III), Al(III), Ga(III), In(III), Mn(II), Fe(II), Co(II), Ni(II), Zn(II), Cd(II), Pb(II), Fe(III), Cr(III), Ce(III), Cu(I), Zr(IV), Th(IV), U(VI).

TABLE III

SPOT-TESTS WITH 4-AMINO-5-HYDROXYACRIDINE

Metal-ion	Acetate Buffer (pH 5)	Borate Buffer (pH 10)
Mn(II)	*	orange-red precipitate
Co(II)		orange-red precipitate
Ni(II)		orange-red precipitate
Cu(II)	orange colour	brown precipitate
Zn(II)		orange-red precipitate
Cd(II)		orange-red precipitate
Pb(II)	orange colour	orange-red precipitate
Hg(II)	orange-red precipitate	orange-brown precipitate
Pd(II)	orange colour	orange precipitate
Ga(III)	orange colour	
In(III)	orange colour	
Tl(III)		orange-brown precipitate
Fe(III)	red-brown precipitate	red-brown colour
Rh(III)	yellow-orange colour	orange colour
U(VI)	orange colour	

* No entry indicates "no observable reaction".

No reaction with: Fe(II), Mg(II), Ca(II), Sr(II), Ba(II), Sc(III), Y(III), La(III), Al(III), Cr(III), Ce(III), Cu(I), Zr(IV), Th(IV).

TABLE IV

SPOT-TESTS WITH 4,5-DIHYDROXYACRIDINE

Metal-ion	Acetate Buffer(pH 5)	Borate Buffer (pH 10)
Mg(II)	*	orange precipitate
Ca(II)		orange colour
Sr(II)		yellow precipitate
Ba(II)		yellow precipitate
Sc(III)	orange precipitate	orange precipitate
Y(III)	orange precipitate	orange precipitate
La(III)	orange precipitate	orange precipitate
Ga(III)	orange colour	orange colour
In(III)	orange precipitate	orange precipitate
Tl(III)	red-brown precipitate	red-brown precipitate
Mn(II)	yellow precipitate	yellow precipitate
Fe(II)	orange colour	brown precipitate
Co(II)	orange precipitate	orange precipitate
Ni(II)	orange precipitate	orange precipitate
Cu(II)	orange precipitate	red-brown precipitate
Zn(II)	orange precipitate	orange precipitate
Cd(II)	orange precipitate	orange precipitate
Pb(II)	red-orange precipitate	orange precipitate
Hg(II)	red-brown precipitate	red-brown precipitate
Pd(II)	orange precipitate	
Fe(III)	purple-black precipitate	purple colour
Rh(III)	orange colour	
Cr(III)	orange-brown colour	
Ce(III)	yellow precipitate	yellow precipitate
Zr(IV)	orange precipitate	orange precipitate
Th(IV)	orange precipitate	
U(VI)	yellow-orange colour	

* No entry indicates "no observable reaction".

No reaction with: Al(III), Cu(I).

APPENDIX III

ELEMENTAL ANALYSIS OF METAL CHELATES

TABLE I

METAL CHELATES OF 2-(2'-THIENYL)-8-HYDROXYQUINOLINE

	% C	% H	% N	% S
Calculated for $Co(C_{13}H_8ONS)_2$	61.05	3.15	5.47	12.53
Found	62.59	3.60	5.39	11.90
Calculated for $Ni(C_{13}H_8ONS)_2$	61.09	3.15	5.48	12.54
Found	60.84	3.31	5.59	12.33
Calculated for $Cu(C_{13}H_8ONS)_2$	60.51	3.11	5.43	12.42
Found	62.10	3.24	5.20	11.65
Calculated for $Zn(C_{13}H_8ONS)_2$	60.30	3.11	5.41	12.38
Found	61.08	3.22	5.18	11.94

TABLE II

METAL CHELATES OF 4-AMINO-5-HYDROXYACRIDINE

	% C	% H	% N
Calculated for $Co(C_{13}H_9ON_2)_2$	65.42	3.79	11.73
Found	65.95	4.10	11.27
Calculated for $Ni(C_{13}H_9ON_2)_2$	65.44	3.79	11.73
Found	65.23	4.02	11.52
Calculated for $Zn(C_{13}H_9ON_2)_2$	64.55	3.74	11.58
Found	64.25	4.05	11.59

TABLE III

COPPER(II) CHELATE OF 4,5-DIAMINOACRIDINE

	% C	% H	% N	% Br
Calculated for $Cu(C_{13}H_{11}N_3)Br_2$	36.08	2.57	9.71	36.94
Calculated for $Cu(C_{13}H_{11}N_3)_2Br_2$	48.64	3.46	13.09	24.90
Found	32.97	2.95	8.85	39.93

TABLE IV

METAL CHELATES OF 4,5-DIHYDROXYACRIDINE

	% C	% H	% N
Calculated for $Co(C_{13}H_8O_2N)_2$	65.14	3.36	5.84
Found	64.09	3.49	5.90
Calculated for $Ni(C_{13}H_8O_2N)_2$	65.16	3.36	5.84
Found	64.72	3.61	5.99
Calculated for $Cu(C_{13}H_8O_2N)_2$	64.52	3.33	5.79
Found	63.78	3.41	5.82
Calculated for $Zn(C_{13}H_8O_2N)_2$	64.27	3.31	5.76
Found	63.91	3.45	5.71

APPENDIX IV

VISIBLE AND NEAR-ULTRAVIOLET SPECTRA OF ACRIDINE COMPOUNDS

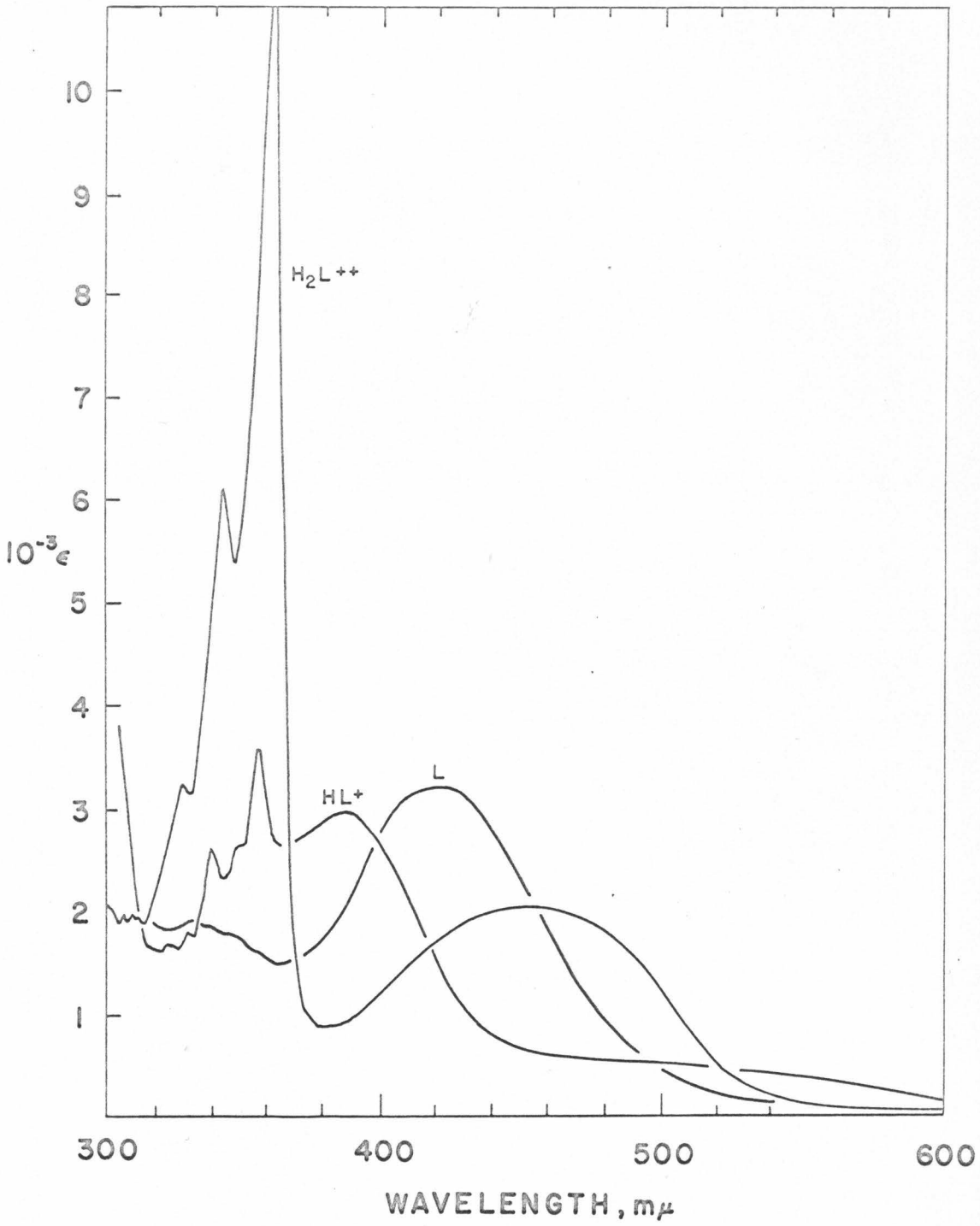

Figure 1. Absorption Spectra of the Neutral and Protonated Forms of 4-Amino-5-Methoxyacridine.

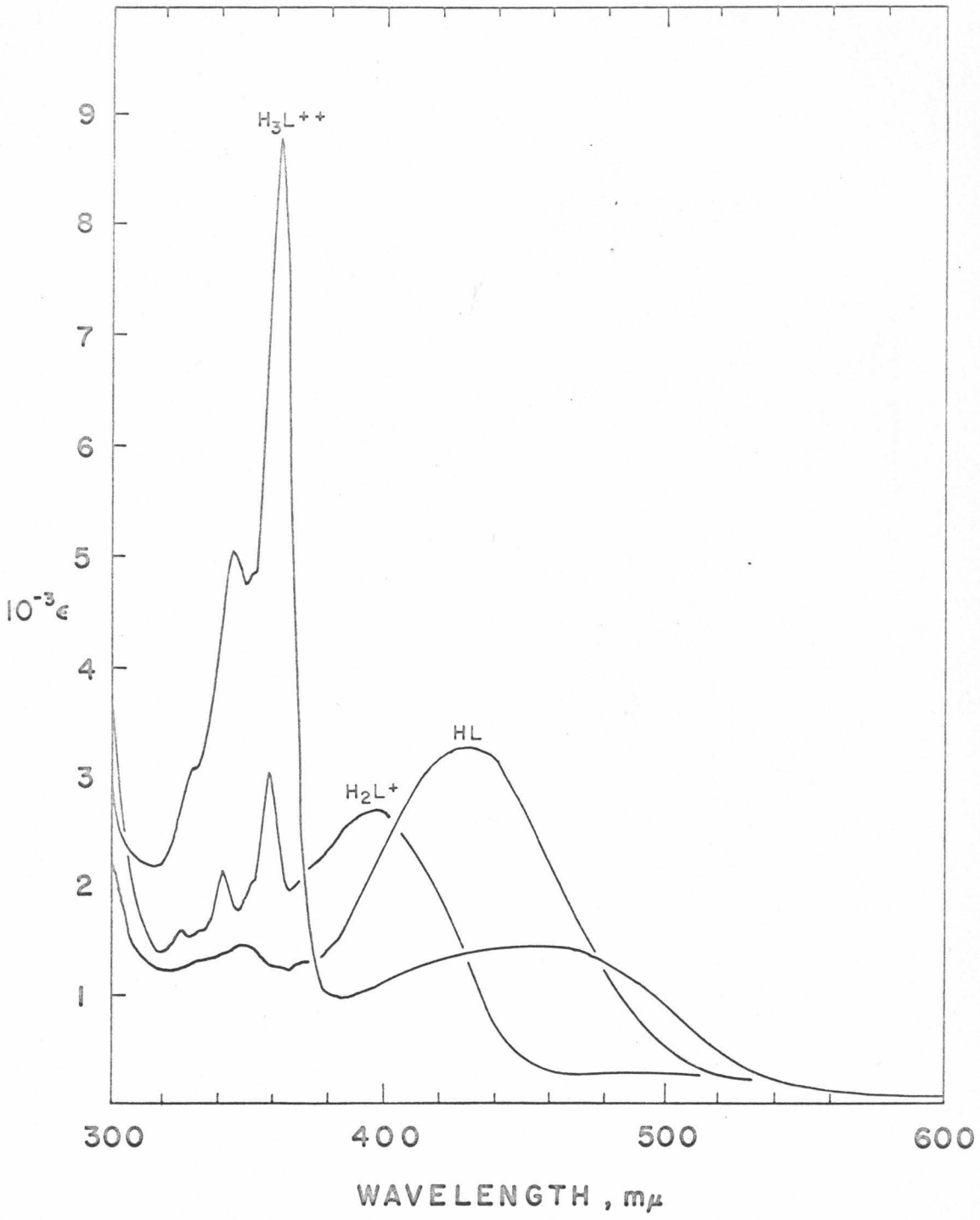

Figure 2. Absorption Spectra of the Neutral and Protonated Forms of 4-Amino-5-Hydroxyacridine.

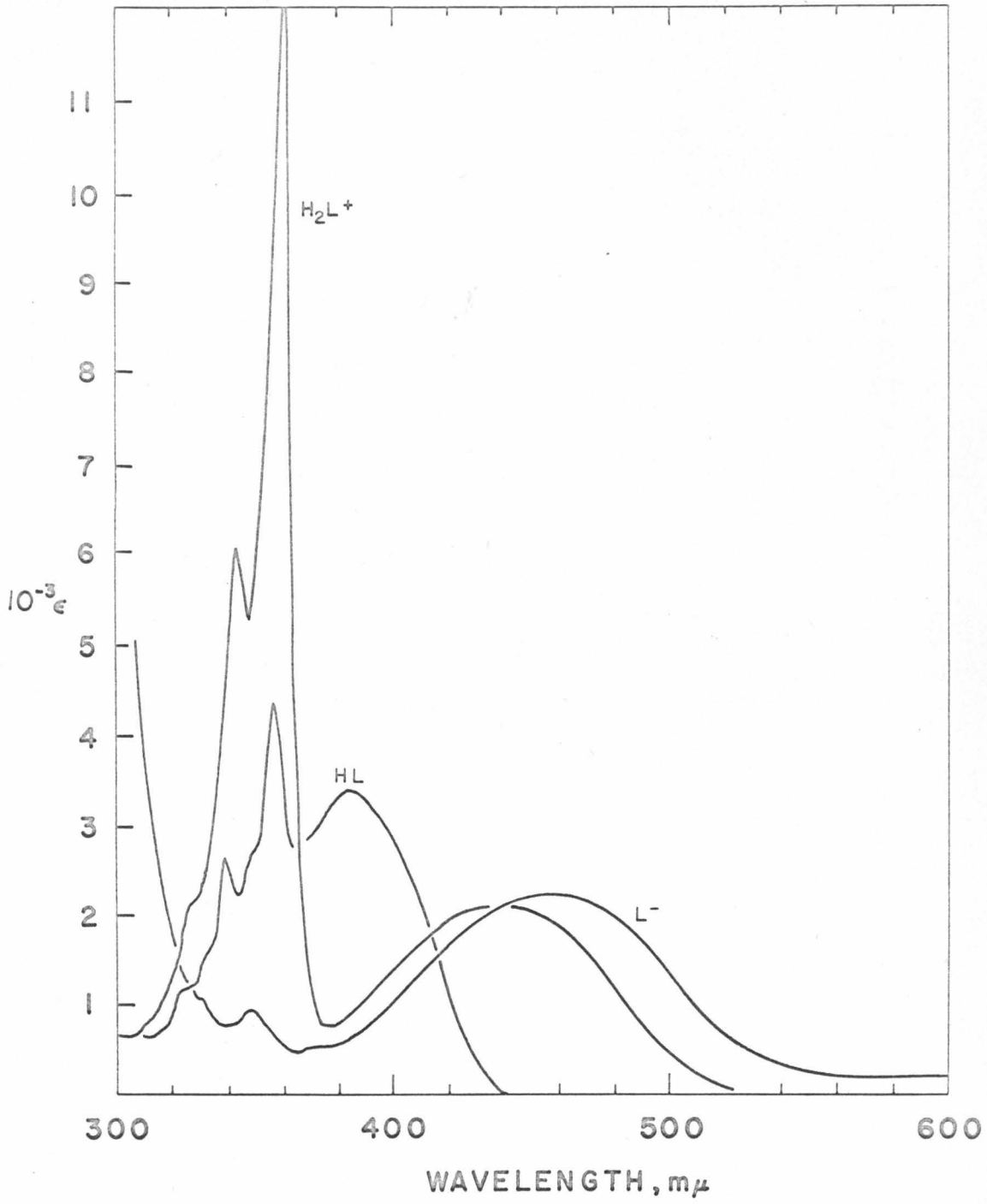

Figure 3. Absorption Spectra of the Anionic, Neutral and Cationic Forms of 4-Hydroxyacridine.

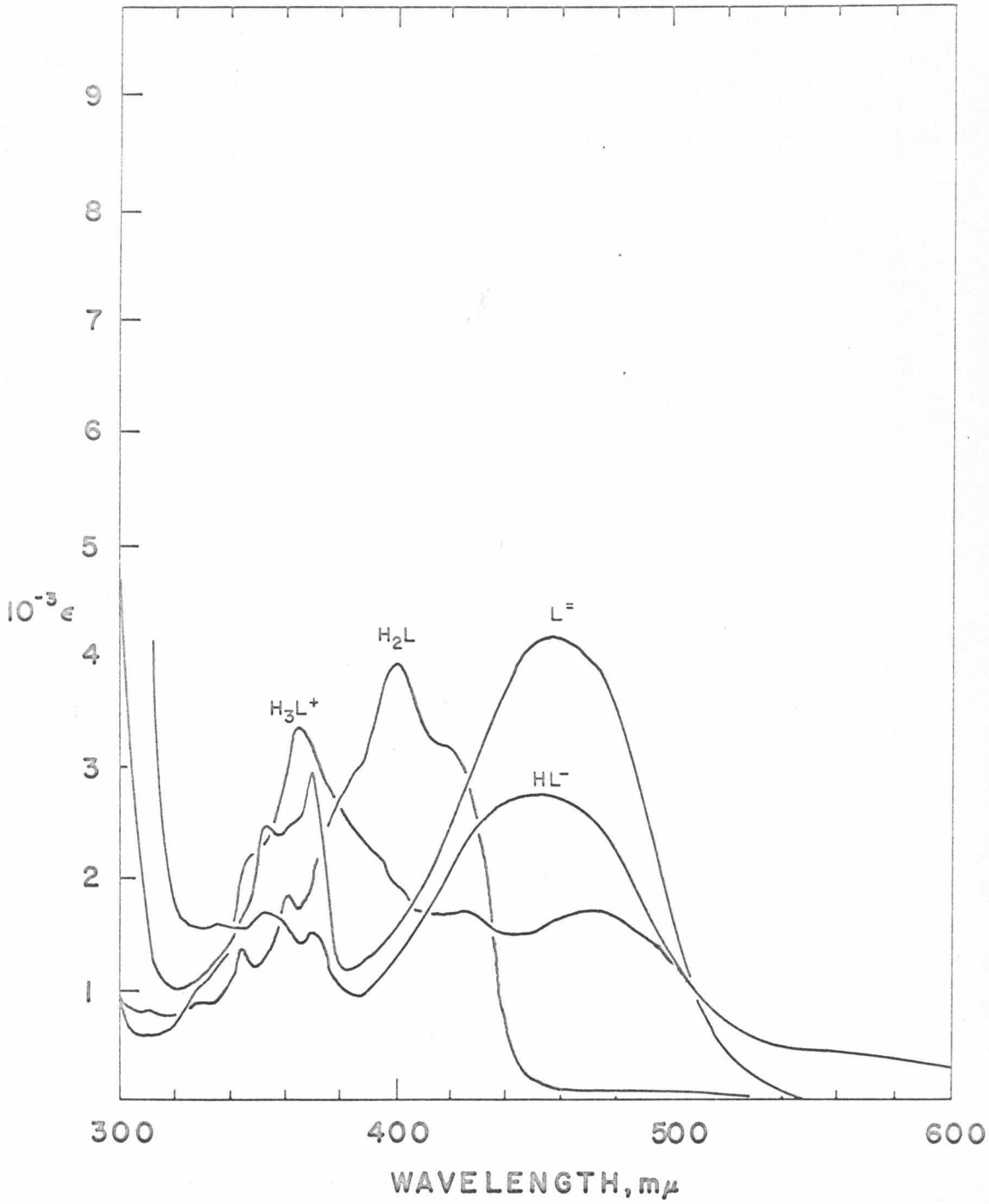

Figure 4. Absorption Spectra of the Anionic, Neutral and Cationic Forms of 4,5-Dihydroxyacridine.

APPENDIX V

SPECTROPHOTOMETRIC DETERMINATION OF PROTONATION CONSTANTS

TABLE I

DETERMINATION OF LOG K_2^H OF 2-(2'-THIENYL)-8-HYDROXYQUINOLINE

Concentration of reagent	4.00×10^{-5}M
Wavelength	373 mμ
Solvent	50% v/v dioxane-water
Temperature	25°C
Ionic Strength	0.1

p_cH	Absorbance	log K_2^H
0	0.837	-
1.43	0.489	1.51
1.71	0.357	1.48
1.97	0.254	1.46
2.36	0.160	1.46
5.30	0.075	-

Mean = 1.48

Std. Dev. = 0.02

TABLE II

DETERMINATION OF LOG K_2^H OF 4-AMINO-5-HYDROXYACRIDINE

Concentration of reagent	1.92×10^{-4} M
Wavelength	433 mμ
Solvent	50% v/v dioxane-water
Temperature	25° C
Ionic strength	0.1

p_cH	Absorbance	log K_2^H
0.41	0.242	-
1.01	0.246	-
1.71	0.286	-
2.00	0.328	2.51
2.24	0.368	2.52
2.41	0.399	2.53
2.53	0.426	2.52
2.70	0.467	2.49
3.03	0.522	2.50
5.80	0.605	-

Mean = 2.51

Std. Dev. = 0.01

TABLE III

DETERMINATION OF LOG K_1^H OF 4-AMINO-5-METHOXYACRIDINE

Concentration of reagent	1.73×10^{-4}M
Wavelength	427 mμ
Solvent	50% v/v dioxane-water
Temperature	25° C
Ionic strength	0.1

p_cH	Absorbance	log K_1^H
1.00	0.153	-
2.00	0.188	-
2.52	0.274	2.92
2.73	0.323	2.88
2.79	0.350	2.85
3.23	0.447	2.88
3.44	0.479	2.92
5.80	0.577	-

Mean = 2.89

Std. Dev. = 0.03

TABLE IV

DETERMINATION OF LOG K_1^H AND LOG K_2^H OF 4,5-DIAMINOACRIDINE

Concentration of reagent	0.99×10^{-5} M
Wavelength	275 mμ
Solvent	50% v/v dioxane-water
Temperature	25° C
Ionic strength	0.1

p_c^H	Absorbance
0.0	0.029
0.37	0.045
0.73	0.062
1.10	0.113
1.42	0.166
1.73	0.232
1.78	0.247
1.99	0.287
2.21	0.333
2.38	0.370
2.67	0.415
2.79	0.432
2.98	0.470
3.38	0.560
3.86	0.638
5.80	0.687

TABLE V

DETERMINATION OF LOG K_1^H AND LOG K_2^H OF 4,5-DIHYDROXYACRIDINE

Concentration of reagent	1.55×10^{-4}
Wavelength	450 mμ
Solvent	50% v/v dioxane-water
Temperature	25° C
Ionic strength	0.1

p_cH	Absorbance
7.48	0.032
8.42	0.037
9.56	0.077
10.30	0.200
10.39	0.209
10.87	0.320
10.95	0.349
11.65	0.502
11.78	0.530
11.79	0.520
12.48	0.590
12.61	0.602
13.27	0.648
14.0	0.650

APPENDIX VI

POTENTIOMETRIC DETERMINATION OF PROTONATION CONSTANTS

TABLE I

PRØTØNATIØN CØNSTANT EVALUATIØN

PRØTØNATIØN ØF ACRIDINE

VØL. NAØH	PCH	P	PKC
0.000	2.847	0.932	
1.000	3.210	0.896	
1.200	3.310	0.879	
1.400	3.412	0.854	
1.600	3.520	0.824	
1.800	3.632	0.789	4.204
2.000	3.732	0.747	4.202
2.200	3.840	0.703	4.214
2.400	3.940	0.655	4.219
2.600	4.038	0.605	4.224
2.800	4.134	0.554	4.228
3.000	4.228	0.501	4.231
3.200	4.324	0.448	4.233
3.400	4.422	0.394	4.235
3.600	4.526	0.339	4.237
3.800	4.639	0.284	4.238
4.000	4.762	0.229	4.235
4.200	4.916	0.173	
4.400	5.110	0.118	
4.600	5.396	0.062	
4.800	6.150	0.006	

LØG K1 = 4.225 LØG K2 = ******* LØG K3 = *******

STD.DEV. = 0.013 STD.DEV. = ******* STD.DEV. = *******

TABLE II

PROTONATION CONSTANT EVALUATION

PROTONATION OF 4-HYDROXYACRIDINE

VOL. NAOH	PCH	P	PKC
0.800	3.011	1.941	
1.000	3.082	1.929	
1.200	3.161	1.913	
1.400	3.254	1.896	
1.600	3.351	1.871	
1.800	3.462	1.842	
2.000	3.578	1.807	
2.200	3.695	1.764	4.206
2.400	3.815	1.717	4.219
2.600	3.927	1.665	4.225
2.800	4.039	1.610	4.233
3.000	4.150	1.553	4.242
3.200	4.257	1.493	4.245
3.400	4.365	1.433	4.247
3.600	4.482	1.371	4.254
3.800	4.604	1.309	4.255
4.000	4.744	1.247	4.260
4.900	9.640	0.962	
5.100	10.252	0.899	
5.200	10.400	0.868	
5.300	10.525	0.837	
5.400	10.621	0.806	
5.500	10.710	0.775	11.249
5.600	10.789	0.745	11.254
5.700	10.859	0.714	11.257
5.800	10.925	0.684	11.261
5.900	10.985	0.654	11.262
6.000	11.043	0.624	11.263
6.100	11.101	0.594	11.267
6.200	11.154	0.565	11.268
6.300	11.208	0.536	11.270
6.400	11.258	0.507	11.270
6.500	11.309	0.479	11.273
6.600	11.357	0.451	11.272
6.700	11.407	0.424	11.273
6.800	11.455	0.397	11.274
6.900	11.504	0.371	11.276
7.000	11.551	0.346	11.274
7.200	11.647	0.298	11.274

LOG K1 = 11.267 LOG K2 = 4.239 LOG K3 = *******

STD.DEV. = 0.008 STD.DEV. = 0.017 STD.DEV. = *******

TABLE III

PRØTØNATIØN CØNSTANT EVALUATIØN

PRØTØNATIØN ØF 4-AMINØ-5-HYDRØXYACRIDINE

VØL. NAØH	PCH	P	PKC
0.800	2.632	1.461	2.564
1.000	2.659	1.444	2.561
1.200	2.689	1.429	2.565
1.400	2.717	1.407	2.554
1.600	2.749	1.390	2.554
1.800	2.782	1.370	2.550
2.000	2.820	1.353	2.558
2.200	2.856	1.331	2.549
2.400	2.898	1.311	2.553
2.600	2.946	1.293	2.564
2.800	2.998	1.274	2.576
3.000	3.050	1.250	2.573
3.200	3.109	1.226	2.574
3.400	3.179	1.203	2.586
3.600	3.256	1.178	
3.800	3.334	1.146	
4.000	3.440	1.118	
4.800	6.380	0.993	
4.900	9.717	0.961	
5.000	10.184	0.929	
5.200	10.586	0.867	
5.400	10.824	0.806	
5.500	10.924	0.775	11.462
5.600	10.994	0.745	11.460
5.700	11.079	0.715	11.479
5.800	11.145	0.686	11.484
5.900	11.202	0.656	11.483
6.000	11.259	0.627	11.485
6.100	11.316	0.599	11.490
6.200	11.369	0.571	11.493
6.300	11.419	0.543	11.493
6.400	11.469	0.516	11.496
6.500	11.516	0.489	11.496
6.600	11.562	0.462	11.497
6.700	11.608	0.437	11.499
6.800	11.652	0.412	11.497
6.900	11.697	0.389	11.500
7.000	11.740	0.366	11.501
7.200	11.825	0.322	11.502
7.400	11.911	0.285	11.511

LØG K1 = 11.490 LØG K2 = 2.563 LØG K3 = *******

STD.DEV. = 0.013 STD.DEV. = 0.011 STD.DEV. = *******

TABLE IV

PRØTØNATIØN CØNSTANT EVALUATIØN

PRØTØNATIØN ØF 4,5-DIAMINØACRIDINE

VØL. NAØH	PCH	P	PKC
0.800	2.780	0.731	3.214
1.000	2.815	0.711	3.205
1.200	2.852	0.689	3.198
1.400	2.892	0.668	3.196
1.600	2.933	0.644	3.190
1.800	2.975	0.617	3.183
2.000	3.019	0.589	3.175
2.200	3.067	0.560	3.172
2.400	3.122	0.532	3.178
2.600	3.173	0.498	3.169
2.800	3.233	0.465	3.171
3.000	3.296	0.429	3.172
3.200	3.363	0.391	3.170
3.400	3.436	0.352	3.172
3.600	3.522	0.311	3.176
3.800	3.615	0.268	3.178
4.000	3.725	0.224	3.184
4.500	4.147	0.107	

LØG K1 = 3.183 LØG K2 = ******* LØG K3 = *******

STD.DEV. = 0.013 STD.DEV. = ******* STD.DEV. = *******

TABLE V

PRØTØNATIØN CØNSTANT EVALUATIØN

PRØTØNATIØN ØF 4,5-DIHYDRØXYACRIDINE

VØL. NAØH	PCH	P	PKC
0.000	2.482	2.541	2.554
0.200	2.502	2.520	2.538
0.400	2.524	2.503	2.530
0.600	2.549	2.492	2.536
0.800	2.575	2.480	2.541
1.000	2.601	2.464	2.539
1.200	2.628	2.447	2.536
1.400	2.658	2.434	2.542
1.600	2.690	2.420	2.550
1.800	2.719	2.395	2.534
2.000	2.752	2.375	2.529
2.200	2.792	2.362	2.546
2.400	2.832	2.344	2.551
2.600	2.876	2.326	2.560
2.800	2.922	2.304	2.563
3.000	2.974	2.284	2.572
3.200	3.032	2.263	2.584
3.400	3.090	2.234	2.574
3.600	3.160	2.208	2.578
3.800	3.247	2.184	
4.000	3.344	2.155	
4.200	3.468	2.126	
4.400	3.630	2.094	
4.600	3.888	2.062	
4.800	4.520	2.027	
5.000	9.150	1.958	
5.100	9.420	1.916	
5.200	9.621	1.874	
5.300	9.783	1.832	
5.400	9.927	1.790	10.503
5.500	10.042	1.749	10.515
5.600	10.142	1.707	10.524
5.700	10.232	1.665	10.530
5.800	10.315	1.624	10.535
5.900	10.387	1.582	10.532
6.000	10.460	1.541	10.531
6.100	10.527	1.500	10.527
6.200	10.593	1.459	10.521
6.300	10.659	1.418	10.516
6.400	10.719	1.377	10.502
6.500	10.784	1.337	10.490
6.600	10.844	1.297	10.470
6.700	10.906	1.257	10.446
6.800	10.971	1.218	10.417
6.900	11.032	1.179	
7.000	11.092	1.141	
7.100	11.152	1.103	
7.200	11.213	1.066	
7.300	11.270	1.030	
7.400	11.325	0.994	
7.500	11.387	0.960	

TABLE V (Continued)

7.600	11.435	0.924	
7.700	11.477	0.889	
7.800	11.530	0.857	
7.900	11.578	0.824	
8.000	11.625	0.793	12.209
8.100	11.684	0.766	12.200
8.200	11.727	0.737	12.175
8.300	11.775	0.711	12.165
8.400	11.825	0.687	12.167
8.500	11.854	0.656	12.135
8.600	11.906	0.638	12.152
8.700	11.954	0.619	12.165
8.800	11.991	0.598	12.164
8.900	12.024	0.576	12.158
9.000	12.063	0.559	12.167
9.100	12.091	0.538	12.157
9.200	12.131	0.526	12.176

LØG K1 = ******* LØG K2 = ******* LØG K3 = 2.550

STD.DEV. = ******* STD.DEV. = ******* STD.DEV. = 0.017

PRØTØNATIØN CØNSTANTS BY LEAST SQUARES

LØG K1 = 12.084 LØG K2 = 10.553

STD.DEV. = 0.062 STD.DEV. = 0.040

TABLE VI

PRØTØNATIØN CØNSTANT EVALUATIØN

PRØTØNATIØN ØF 2-THIENYL-8-HYDRØXYQUINØLINE

VØL. NAØH	PCH	P	PKC
0.800	2.483	1.110	
1.000	2.509	1.110	
4.900	10.210	0.962	
5.000	10.523	0.930	
5.100	10.713	0.899	
5.200	10.847	0.868	
5.300	10.961	0.837	
5.410	11.057	0.803	
5.500	11.132	0.776	11.672
5.600	11.203	0.746	11.672
5.700	11.266	0.716	11.668
5.800	11.325	0.687	11.666
5.900	11.385	0.658	11.669
6.000	11.437	0.630	11.668
6.100	11.488	0.602	11.668
6.200	11.537	0.574	11.667
6.300	11.583	0.548	11.666
6.400	11.628	0.521	11.665
6.500	11.667	0.495	11.657
6.600	11.709	0.470	11.656
6.700	11.752	0.445	11.656
6.800	11.796	0.423	11.661
6.900	11.834	0.400	11.659
7.000	11.878	0.380	11.666
7.100	11.914	0.359	11.663
7.200	11.953	0.340	11.665

LØG K1 = 11.665 LØG K2 = ******* LØG K3 = *******

STD.DEV. = 0.005 STD.DEV. = ******* STD.DEV. = *******

APPENDIX VII

GENERAL EQUATIONS FOR THE CALCULATION OF FORMATION CONSTANTS FROM POTENTIOMETRIC DATA

The following derivation of general equations for the determination of stability constants is based on the derivation of Hearon and Gilbert[45]. In the present work, the equations are formulated using more familiar symbols, only the most commonly used and most convenient methods of calculation are presented, and equations for complex formation by a ligand which chelates in a form which is not fully deprotonated have been added.

The equilibria studied are

$$ML_n + L \rightleftharpoons ML_{n+1} \qquad n = 0,1,2.....N \qquad (1)$$

where M, the metal-ion has charge Z_M and L, the chelating form of the ligand, has charge Z_L. (Z_M and Z_L have the algebraic sign of the charge on the species, e.g., for 8-hydroxyquinoline, $Z_L = -1$). The chelating form of the ligand is generally the completely ionized form of the neutral species H_kL, and is formed in the equilibria

$$H_{j+1}L \rightleftharpoons H_jL + H^+ \qquad j = 0,1,2...J \qquad (2)$$

(For simplicity, charges on the metal-ion, ligand and

metal complexes have been omitted.) The maximum number of protons coordinated to the ligand, and of ligands to the metal-ion, are denoted by J and N, respectively.

The following derivation excludes polynuclear (e.g., M_mL_n, where m>1) and mixed-ligand complexes (e.g., MA_mL_n, where m>0 for all ligands other than those derived from the solvent). Proton-bearing complexes (e.g., $M(H_jL)_n$, where j>0) will be discussed later.

The material balance for the ligand and metal-ion are

$$C_L = \sum_{j=0}^{J} [H_jL] + \sum_{n=0}^{N} n\,[ML_n] \qquad (3)$$

and

$$C_M = \sum_{n=0}^{N} [ML_n] \qquad (4)$$

where C_L and C_M are the analytical or total concentrations of the ligand and metal-ion, respectively, in moles per litre and the square brackets signify molar concentrations.

The charge balance (i.e., the condition of electroneutrality) is given by

$$\sum_{j=0}^{J} (j+Z_L)[H_jL] + \sum_{n=0}^{N} (Z_M+nZ_L)[ML_n] + \Sigma Z_i[I_i] = 0 \qquad (5)$$

where Z_i and $[I_i]$ are the charge and concentration of the ith ion which contains neither M or L. This quantity is assumed to be known; it contains the anions of metal salt and strong acid, and the cation of base, as well as

$[H^+]$ and $[OH^-]$.

From (3), (4), and (5) one obtains

$$Z_L C_L + Z_M C_M + \sum_{j=0}^{J} j[H_jL] + \Sigma Z_i[I_i] = 0 \qquad (6)$$

The material balance for the concentration of ligand not bound to M (i.e., $\sum_{j=0}^{J} [H_jL]$) can be written in terms of the overall protonation constants, β_j^H, where

$$\beta_j^H = \frac{[H_jL]}{[L][H^+]^j} = K_1^H K_2^H \ldots\ldots K_j^H \qquad (7)$$

and $$\beta_o^H = 1. \qquad (7a)$$

Thus $$\sum_{j=0}^{J} [H_jL] = [L] \sum_{j=0}^{J} \beta_j^H [H^+]^j \qquad (8)$$

and from (6) and (8)

$$[L] = \frac{-Z_L C_L - Z_M C_M - \Sigma Z_i[I_i]}{\sum_{j=0}^{J} j\,\beta_j^H\,[H^+]^j} \qquad (9)$$

In the present study, which involves divalent metal-ions, equation (9) becomes

$$[L] = \frac{-Z_L C_L - 2C_M - [H^+] - [Na^+] + [ClO_4^-] + [OH^-]}{\sum_{j=0}^{J} j\,\beta_j^H\,[H^+]^j} \qquad (9a)$$

Here, $[ClO_4^-]$ = (concentration of $HClO_4$ added) + (concentration of ClO_4^- added as the transition-metal perchlorate). The concentration of sodium and perchlorate ions added to adjust the ionic strength were omitted from these calculations.

Now, as pointed out in the Introduction,

$$\bar{n} = \frac{\text{total concentration of ligand bound to metal-ion}}{\text{total concentration of metal-ion}} \qquad (10)$$

$$= \frac{[\text{total ligand}] - [\text{ligand not bound to metal-ion}]}{[\text{total metal-ion}]} \qquad (10a)$$

From equation (8)

$$\bar{n} = \frac{C_L - [L] \sum_{j=0}^{J} {}^{H}\beta_j [H^+]^j}{C_M} \qquad (11)$$

where [L] is given by equation (9).

Calculation of values of $\bar{n}$ and corresponding values of [L] from the experimental quantities provides the data from which formation constants may be calculated. For convenience, the data are usually expressed as $\bar{n}$, pL where pL = -log [L]. A plot of $\bar{n}$ versus pL yields the characteristic formation curve.

For systems in which the formation constants differ greatly in magnitude (e.g., $K_n / K_{n+1} > 100$), the stepwise formation constants can be read directly from the formation curve. Bjerrum[30] has shown that

$$K_n = 1 / [L]_{\bar{n}=n-0.5} \qquad (12)$$

or $$\log K_n = pL \text{ at } \bar{n} = n-0.5 \qquad (12a)$$

When the constants are not well separated, this method yields only "conditional" constants which must be refined by iteration.

For 1:1 chelates, the interpolation method is always applicable, and equation (12a) may be used to obtain the formation constant. However, this method does not make full use of the experimental data. For 1:1 chelates, a value of the formation constant can be calculated at each point on the titration curve. Thus, from equation (10)

$$\bar{n} = \frac{[ML]}{[M] + [ML]} \tag{13}$$

$$= \frac{K_1[L]}{1 + K_1[L]} \tag{14}$$

from which $K_1 = \frac{\bar{n}}{(1-\bar{n})[L]}$ (15)

or $$\log K_1 = \log \frac{\bar{n}}{(1-\bar{n})} + pL. \tag{15a}$$

For systems in which the highest chelate formed is ML_2, equation (10) becomes

$$\bar{n} = \frac{[ML] + 2[ML_2]}{[M] + [ML] + [ML_2]} \tag{16}$$

Suitable substitution for [ML] and $[ML_2]$ and cancellation of [M] gives

$$\bar{n} = \frac{K_1[L] + 2\,K_1K_2[L]^2}{1 + K_1[L] + K_1K_2[L]^2} \tag{16a}$$

This equation can be rearranged to

$$\frac{\bar{n}}{(1-\bar{n})[L]} = \frac{(2-\bar{n})[L]}{(1-\bar{n})}\,K_1K_2 + K_1 \tag{17}$$

or $$Y = K_1K_2\,X + K_1 \tag{17a}$$

where $Y = \frac{\bar{n}}{(1-\bar{n})[L]}$

and $X = \frac{(2-\bar{n})[L]}{(1-\bar{n})}$

A plot of Y versus X yields a straight line with slope K_1K_2 and intercept K_1. The slope and intercept of the line of best fit can be determined by the method of least squares. Irving and Rossotti[108] have suggested that this method is superior to other graphical or algebraic methods since it avoids subjective factors and utilizes a large amount of the available data. A limitation of the method is that the coefficients X and Y are sensitive to experimental error in $\bar{n}$ for values of $\bar{n}$ near 0, 1 and 2.

For a system in which the chelating form of the ligand is not fully deprotonated (i.e., the chelating form of the ligand is H_KL), the derivation is similar to that already described and hence will be treated in less detail. Only the case where subsequent proton loss from the metal chelate does not interfere with chelate formation will be discussed here.

The mass and charge balance relationships are

$$\sum_{j=0}^{J} [H_jL] + \sum_{n=0}^{N} n\,[M(H_KL)_n] = C_L \qquad (18)$$

$$\sum_{n=0}^{N} [M(H_KL)_n] = C_M \qquad (19)$$

$$\sum_{j=0}^{J} (j+Z_L)[H_jL] = \sum_{n=0}^{N} (Z_M+nZ_K)[M(H_KL)_n] + \Sigma Z_i[I_i] = 0 \qquad (20)$$

where the chelating form of the ligand H_KL has charge Z_K and the fully deprotonated form has charge Z_L.

Expanding equation (20), substituting (18) and (19) and utilizing the relationship

$$Z_L = Z_K - K \tag{21}$$

yields the equation

$$\sum_{j=0}^{J} (j-K)[H_jL] + Z_MC_M + Z_KC_L + \Sigma Z_i[I_i] = 0 \tag{22}$$

from which is obtained

$$\sum_{j=0}^{J} [H_jL] = \frac{-Z_MC_M - Z_KC_L - \Sigma Z_i[I_i]}{(j-K)} \quad . \tag{23}$$

Now it can readily be shown that

$$\sum_{j=0}^{J} [H_jL] = \frac{[H_KL] \sum_{j=0}^{J} \beta_j^H [H^+]^j}{\beta_K^H [H^+]^K} \quad . \tag{24}$$

$$\text{Thus} \qquad [H_KL] = \frac{\left[- Z_MC_M - Z_KC_L - \Sigma Z_i[I_i]\right] \beta_K^H [H^+]^K}{\sum_{j=0}^{J} (j-K)\, \beta_j^H [H^+]^j} \tag{25}$$

From (10a) and (24)

$$\bar{n} = \frac{C_L - [H_KL] \sum_{j=0}^{J} \beta_j^H [H^+]^j \Big/ \beta_K^H [H^+]^K}{C_M} \tag{26}$$

Note that when K=0, equations (25) and (26) reduce to equations (9) and (11), respectively.

APPENDIX VIII

POTENTIOMETRIC DETERMINATION OF CHELATE FORMATION CONSTANTS

TABLE I

METAL CHELATES OF 2-THIENYL-8-HYDROXYQUINOLINE

(LIGAND PROTONATION CONSTANTS 11.66 , 1.48)

COBALT STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.173	7.102
2	0.376	6.830
3	0.477	6.748
4	0.579	6.682
5	0.680	6.620
6	0.782	6.567
7	0.883	6.510
8	0.985	6.463
9	1.086	6.409
10	1.188	6.363
11	1.289	6.309
12	1.391	6.259
13	1.492	6.198
14	1.593	6.139
15	1.694	6.045
16	1.795	5.951
17	1.896	5.802
18	1.994	5.534

LOG K1 =	5.829	LOG K2 =	7.091	LOG BETA2 =	12.920
STD.DEV.=	0.185	STD.DEV.=	0.186	STD.DEV.=	0.018

NICKEL STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.174	7.062
2	0.379	6.749
3	0.481	6.650
4	0.584	6.582
5	0.686	6.517
6	0.788	6.455
7	0.891	6.393
8	0.993	6.346
9	1.095	6.284
10	1.198	6.236
11	1.300	6.173
12	1.402	6.131
13	1.505	6.059
14	1.607	5.992
15	1.709	5.898
16	1.810	5.795

LOG K1 =	5.935	LOG K2 =	6.755	LOG BETA2 =	12.690
STD.DEV.=	0.184	STD.DEV.=	0.186	STD.DEV.=	0.029

TABLE I (Continued)

COPPER STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.316	10.301
2	0.394	10.240
3	0.478	10.187
4	0.563	10.132
5	0.653	10.090
6	0.743	10.042
7	0.836	10.000
8	0.929	9.956
9	1.023	9.915
10	1.117	9.869
11	1.213	9.826
12	1.308	9.776
13	1.405	9.729
14	1.501	9.669
15	1.599	9.609
16	1.695	9.525
17	1.793	9.431
18	1.890	9.258
19	1.986	8.846

LOG K1 =	8.878	LOG K2 =	10.967	LOG BETA2 =	19.845
STD.DEV.=	0.168	STD.DEV.=	0.168	STD.DEV.=	0.006

ZINC STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.176	8.040
2	0.381	7.835
3	0.484	7.758
4	0.586	7.703
5	0.689	7.641
6	0.792	7.591
7	0.895	7.537
8	0.997	7.497
9	1.100	7.447
10	1.203	7.401
11	1.306	7.347
12	1.408	7.299
13	1.511	7.231
14	1.614	7.170
15	1.717	7.072
16	1.819	6.964
17	1.922	6.754
18	2.017	5.544

LOG K1 =	6.584	LOG K2 =	8.406	LOG BETA2 =	14.990
STD.DEV.=	0.185	STD.DEV.=	0.186	STD.DEV.=	0.008

TABLE I (Continued)

CADMIUM STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.104	7.652
2	0.217	7.218
3	0.311	7.071
4	0.405	6.969
5	0.499	6.886
6	0.594	6.826
7	0.688	6.766
8	0.782	6.715
9	0.877	6.657
10	0.971	6.613
11	1.065	6.561
12	1.159	6.518
13	1.254	6.463
14	1.348	6.418
15	1.442	6.362
16	1.536	6.306
17	1.630	6.233
18	1.724	6.155
19	1.818	6.042
20	1.912	5.891
21	1.948	5.786
22	1.984	5.632

LOG K1 =	6.169	LOG K2 =	7.038	LOG BETA2 =	13.207
STD.DEV.=	0.186	STD.DEV.=	0.188	STD.DEV.=	0.029

TABLE II

METAL CHELATES OF 4-AMINO-5-HYDROXYACRIDINE

(LIGAND PROTONATION CONSTANTS 11.50 , 2.57)

COBALT STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.175	7.773
2	0.377	7.349
3	0.478	7.207
4	0.579	7.109
5	0.681	7.005
6	0.782	6.923
7	0.884	6.836
8	0.985	6.766
9	1.087	6.680
10	1.188	6.610
11	1.290	6.515
12	1.391	6.440
13	1.493	6.326
14	1.594	6.217
15	1.795	5.903
16	1.988	5.286

LOG K1 =	6.952	LOG K2 =	6.554	LOG BETA2 =	13.505
STD.DEV.=	0.040	STD.DEV.=	0.047	STD.DEV.=	0.024

NICKEL STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.207	8.869
2	0.297	8.665
3	0.394	8.528
4	0.492	8.370
5	0.592	8.260
6	0.692	8.120
7	0.793	8.013
8	0.834	7.955
9	0.874	7.908
10	0.915	7.851
11	0.956	7.812
12	0.996	7.768
13	1.037	7.709
14	1.078	7.666
15	1.119	7.614
16	1.160	7.564
17	1.201	7.516
18	1.241	7.454
19	1.282	7.406
20	1.323	7.354
21	1.364	7.295
22	1.405	7.250
23	1.507	7.091
24	1.610	6.950

TABLE II (Continued)

LOG K1 =	8.294	LOG K2 =	7.202	LOG BETA2 =	15.496
STD.DEV.=	0.040	STD.DEV.=	0.053	STD.DEV.=	0.035

CADMIUM STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.163	7.852
2	0.350	7.366
3	0.444	7.203
4	0.538	7.087
5	0.575	7.034
6	0.613	6.986
7	0.651	6.949
8	0.688	6.900
9	0.726	6.866
10	0.764	6.820
11	0.802	6.787
12	0.839	6.748

LOG K1 =	7.026	LOG K2 =	6.106	LOG BETA2 =	13.131
STD.DEV.=	0.041	STD.DEV.=	0.083	STD.DEV.=	0.072

ZINC STABILITY CONSTANT, PERCENT DIOXANE = 50.0

NO.	N-BAR	PL
1	0.243	8.307
2	0.445	7.948
3	0.547	7.827
4	0.649	7.737
5	0.751	7.645
6	0.854	7.567
7	0.957	7.479
8	1.059	7.404
9	1.162	7.300
10	1.264	7.219
11	1.367	7.092
12	1.470	6.970

LOG K1 =	7.707	LOG K2 =	7.150	LOG BETA2 =	14.857
STD.DEV.=	0.096	STD.DEV.=	0.116	STD.DEV.=	0.066

TABLE II (Continued)

CØPPER STABILITY CØNSTANT, PERCENT DIØXANE = 50.0

NØ.	N-BAR	PL	LØG K
1	0.419	11.976	11.834
2	0.446	11.881	11.788
3	0.495	11.787	11.779
4	0.521	11.729	11.764
5	0.560	11.677	11.781
6	0.593	11.606	11.769
7	0.629	11.519	11.748
8	0.682	11.431	11.762
9	0.709	11.373	11.759
10	0.741	11.312	11.768
11	0.770	11.224	11.749
12	0.807	11.124	
13	0.855	11.022	
14	0.908	10.871	
15	0.969	10.635	
16	1.046	10.223	

LØG K1 = 11.773 STD.DEV.= 0.024

TABLE III

METAL CHELATES ØF 4,5-DIAMINØACRIDINE

(LIGAND PRØTØNATIØN CØNSTANTS 3.18 , 1.42)

CØPPER STABILITY CØNSTANT, PERCENT DIØXANE = 50.0

NØ.	N-BAR	PL	LØG K
1	0.814	4.086	4.726
2	0.819	4.079	4.736
3	0.821	4.064	4.725
4	0.826	4.055	4.731
5	0.831	4.045	4.736
6	0.839	4.044	4.760
7	0.847	4.043	4.787
8	0.854	4.036	4.803
9	0.859	4.026	4.810
10	0.860	4.005	4.795
11	0.872	4.011	4.844
12	0.874	3.989	4.831
13	0.882	3.984	4.858
14	0.881	3.951	4.821
15	0.886	3.933	4.823
16	0.893	3.922	4.842
17	0.894	3.891	4.818
18	0.899	3.866	4.815
19	0.902	3.836	
20	0.908	3.812	
21	0.910	3.771	
22	0.914	3.733	
23	0.917	3.687	
24	0.914	3.613	
25	0.885	3.451	
26	0.712	3.096	

LØG K1 = 4.704 STD.DEV.= 0.306

TABLE IV

METAL CHELATES ØF 4,5-DIHYDRØXYACRIDINE

(LIGAND PRØTØNATIØN CØNSTANTS 12.12 , 10.58 , 2.56)

CØPPER STABILITY CØNSTANT, PERCENT DIØXANE = 50.0

NØ.	N-BAR	PL
1	0.709	10.935
2	0.495	10.712
3	0.506	10.493
4	0.575	10.398
5	0.715	10.317
6	0.887	10.226
7	1.110	10.138
8	1.240	10.096
9	1.369	10.039
10	1.502	9.964
11	1.634	9.841
12	1.781	9.675

APPENDIX IX

DETERMINATION OF THE TRUE FORMATION CONSTANTS K_1 AND K_2 FROM VALUES INTERPOLATED AT $\bar{n} = 0.5$ AND $\bar{n} = 1.5$

Many formation constants reported in the literature have been obtained by interpolation of the formation curve at half-integral $\bar{n}$ values. The "Bjerrum half-$\bar{n}$ method" utilizes the relationships

$$K_1' = {}^{1}\!/_{[L]_{\bar{n}=0.5}} \qquad (1)$$

and

$$K_2' = {}^{1}\!/_{[L]_{\bar{n}=1.5}}. \qquad (2)$$

These constants, denoted "conditional constants" by Bjerrum[30], are equal to the true constants K_1 and K_2 only if log K_1 is greater than log K_2 by at least 2-3 units[108,110]. Bjerrum intended the conditional constants to be used only as initial values of a series of successive approximations.

Many of the formation constants reported in the literature have been obtained by the half-$\bar{n}$ method, and have been reported without further refinement, even though the logarithms of these constants have differed by less than one unit.

The method described below presents a simple procedure by which the true constants (or at least good approximations to the true constants) may be calculated from the reported (i.e., conditional) values for systems where the highest complex formed is ML_2.

The conditional constants, K_1' and K_2', provide two points on the formation curve defined by the coordinates $\bar{n} = 0.5$, $[L] = {}^{1}/_{K_1'}$ and $\bar{n} = 1.5$, $[L] = {}^{1}/_{K_2'}$. For a bis-complex, the formation function is given by

$$\bar{n} = \frac{K_1[L] + 2\,K_1K_2[L]^2}{1 + K_1[L] + K_1K_2[L]^2} \tag{3}$$

from which the equation

$$K_1 = \frac{\bar{n}}{(1-\bar{n})[L]} + \frac{(\bar{n}-2)[L]}{(1-\bar{n})}\,K_1K_2 \tag{4}$$

is obtained. Substituting the values $\bar{n} = 0.5$ and $[L] = {}^{1}/_{K_1'}$ into equation (4) yields

$$K_1 = K_1' - \frac{3\,K_1K_2}{K_1'}\,. \tag{5}$$

Since the formation curve is symmetrical about its midpoint, such that

$$K_1'K_2' = \beta_2 = K_1K_2 \tag{6}$$

then $$K_1 = K_1' - 3\,K_2' \tag{7}$$

and $$K_2 = \frac{K_1'K_2'}{K_1}\,. \tag{8}$$

Hence the conditional constants may readily be converted into the true constants by means of equations (7) and (8). Examples which illustrate the agreement between the formation constants obtained in this manner and the constants obtained by the least-squares method described earlier in this work are given in Table I.

TABLE I

FORMATION CONSTANTS OF METAL CHELATES OF 2-(2'-THIENYL)-8-HYDROXYQUINOLINE

	Conditional Values		Corrected Values		Least-Squares Values	
Metal-ion	Log K_1'	Log K_2'	Log K_1	Log K_2	Log K_1	Log K_2
Co(II)	6.73	6.19	5.86	7.07	5.83	7.08
Ni(II)	6.64	6.06	5.94	6.76	5.94	6.77
Cu(II)	10.17	9.67	8.9	10.9	8.84	11.01
Zn(II)	7.75	7.24	6.60	8.39	6.61	8.38
Cd(II)	7.08	6.60	5.0	8.7	6.15	7.03

Recently, a paper by Schrøder[111] described the same method of correcting conditional constants obtained by the half-$\bar{n}$ method. These corrected values were used as initial values in a series of successive approximations, utilizing all of the $\bar{n}$, pL data and resulting in more reliable values for the constants.

From equation (7) it can be seen that K_1' is always larger than the true value, K_1, by an amount $3K_2'$. When K_2' is much smaller than K_1', the required correction is small and K_1' approaches the true value. Similarly K_2' is always smaller than the true value. From equation (7)

$$K_1 = K_1' \left[1 - \frac{3K_2'}{K_1'} \right] \tag{9}$$

from which $$\log K_1 = \log K_1' - C \tag{10}$$

where $$C = -\log \left[1 - \frac{3K_2'}{K_1'} \right] . \tag{11}$$

Similarly, from equations (8), (9) and (11)

$$\log K_2 = \log K_2' + C. \tag{12}$$

The correction term C depends only on the ratio of the two constants and not on their absolute magnitudes. Values of C may be tabulated as a function of $\log K_1' - \log K_2'$; Figure 1 illustrates this relationship graphically and provides a convenient method for obtaining the corrected values, $\log K_1$ and $\log K_2$.

Figure 1 shows that for some minimum value of $\log K_1' - \log K_2'$, the correction C approaches infinity. From equation (11) it can be seen that this occurs as K_1' approaches $3K_2'$. Hence the minimum possible difference between conditional constants is 0.447 log units. Figure 1 also indicates that if the conditional constants

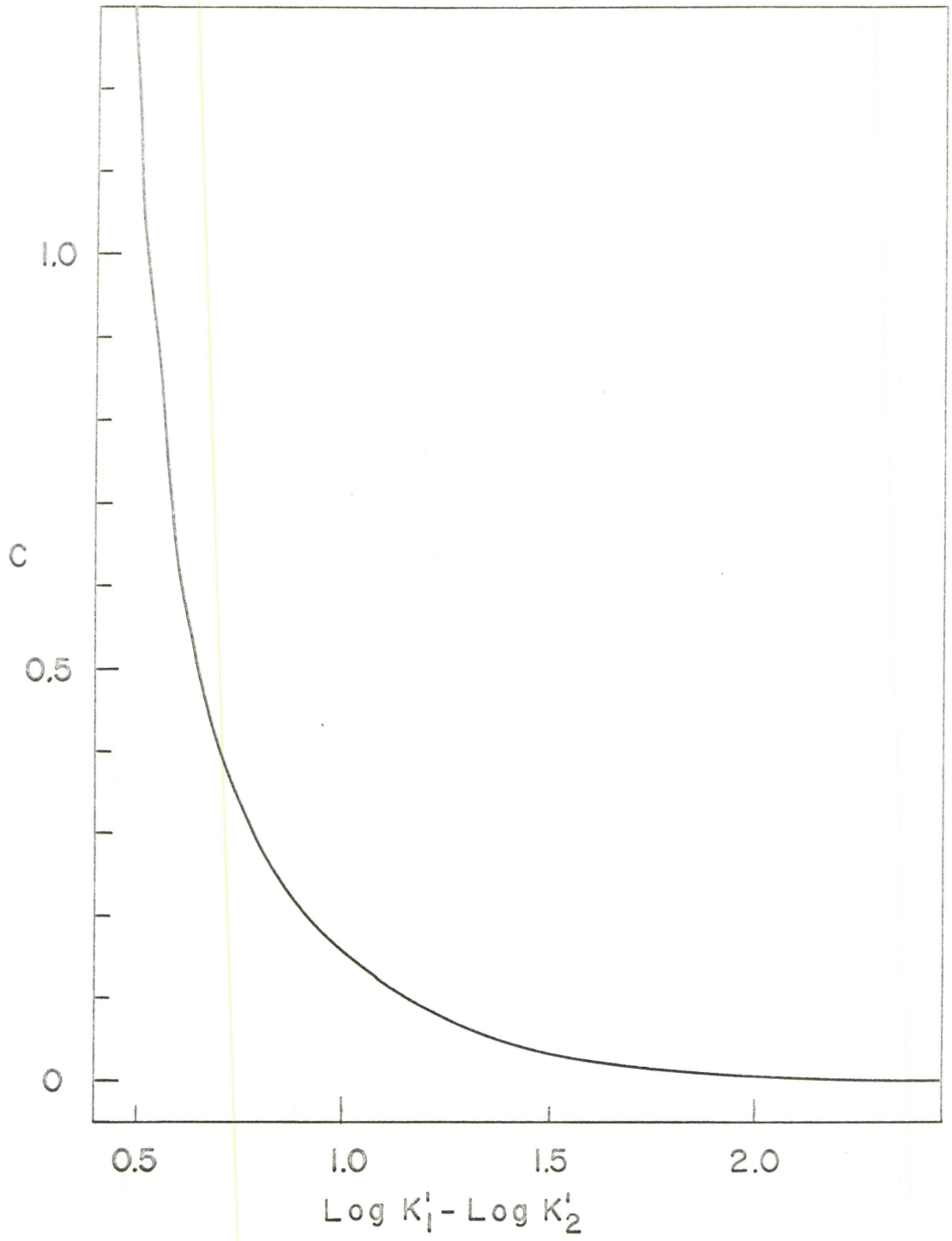

Figure 1. The Relationship between the Correction Term, C, and the Difference between the Logarithms of the Conditional Constants, K_1' and K_2'.

differ by 2.5 log units or greater, the correction to be applied is less than 0.005 log units. Under these circumstances, the Bjerrum half-$\bar{n}$ method yields the true constants.

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