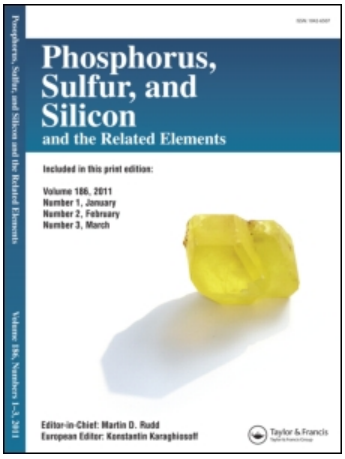

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PYRIDIN-2-YL-(I-PROPYLAMINO)-METHANE PHOSPHONIC ACID - PROTONATION AND METAL COMPLEX FORMATION - NMR-CONTROLLED TITRATION

A. Bier[a]; S. Failla[b]; P. Finocchiaro[b]; G. Hägele[a]; M. Latronico[b]; E. Libertini[b]; J. Ollig[a]
[a] Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf;, Germany [b] Istituto Chimico, Facolta di Ingegneria, Universita di Catania, Catania, Italy

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PYRIDIN-2-YL-(I-PROPYLAMINO)-METHANE PHOSPHONIC ACID – PROTONATION AND METAL COMPLEX FORMATION – NMR-CONTROLLED TITRATION

A. BIER[a], S. FAILLA[b], P. FINOCCHIARO[b], G. HÄGELE[a*], M. LATRONICO[b], E. LIBERTINI[b] and J. OLLIG[a]

[a]*Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, D-40225-Düsseldorf, Germany and* [b]*Istituto Chimico, Facolta di Ingegneria, Universita di Catania, Viale A. Doria 6, 1–95125 Catania, Italy*

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Dissociation and stability constants for protolytic and complex formation equilibria of a polyfunctional ligand are determined. Deprotonation is monitored by NMR controlled titrations. Macroscopic and microscopic concepts are discussed. Nickel complexes are more stable than those of Ca and Mg.

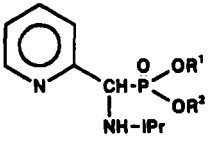
Keywords: Aminophosphonic Acid; Potentiometric Titration; NMR controlled Titration

INTRODUCTION

Recently we reported [1] on the synthesis of 1-amino-1-aryl-methane phosphonic acids and corresponding diethyl esters. Particular attention was paid to structures possessing heteroaryl substituents especially pyridine rings attached to the methine carbon bearing the phosphonate unit [2]. The leading idea was, to form flexible multidentate ligands with oxygen and nitrogen atoms of specific donor properties. Corresponding compounds are accessible e. g. by addition of diethylphosphite to Schiff bases. Star-

* Correspondence Authors.

ting off from pyridyl substituted Schiff bases we obtained a series of compounds [2], and among them **1** was selected for our studies presented here. Alkaline hydrolysis of the diethylester **1a** lead to the mono ester **1b** while acidolysis of **1a** yielded the parent acid **1c.**



1a: $R^1=R^2=Et$; **1b**: $R^1=Et$, $R^2=H$; **1c**: $R^1=R^2=H$.

In this note we report on the dissociation constants and stability constants for protonation and metal complex formation equilibria of **1c,** the neutral form of a bivalent acid H_2L which in solid state or solution might exist in three different betainic structures (see **Scheme 1**). The most likely form will be deduced from NMR-studies below. **1c** was obtained as a dihydrate, a white solid, with m.p. 205°C, stable in the air, easily soluble in water.

A PC-guided apparatus **MINI_T** [3] is used to determine the protonation and complex formation constants of **1c** by precision titration. In addition **NMR_T** [4] a set-up for NMR controlled titrations will be used to elucidate the deprotonation sequence of the bivalent cationic acid form of **1c** conveniently abbreviated as H_4L^{2+}.

The macroscopic deprotonation scheme is shown below involving the five protolytic partners H_iL^{i-2} (i=0–4) and the four dissociation constants K_i (i=1–4) expressed as pK_i-values:

$$(1) \qquad H_4L^{2+} \overset{pK_1}{\longleftrightarrow} H_3L^{+} \overset{pK_2}{\longleftrightarrow} H_2L \overset{pK_3}{\longleftrightarrow} HL^{-} \overset{pK_4}{\longleftrightarrow} L^{2-}$$

$$(2) \qquad H_{5-i}L^{3-i} \longleftrightarrow H^{+} + H_{4-i}L^{2-i} \qquad (i = 1 \text{ to } 4)$$

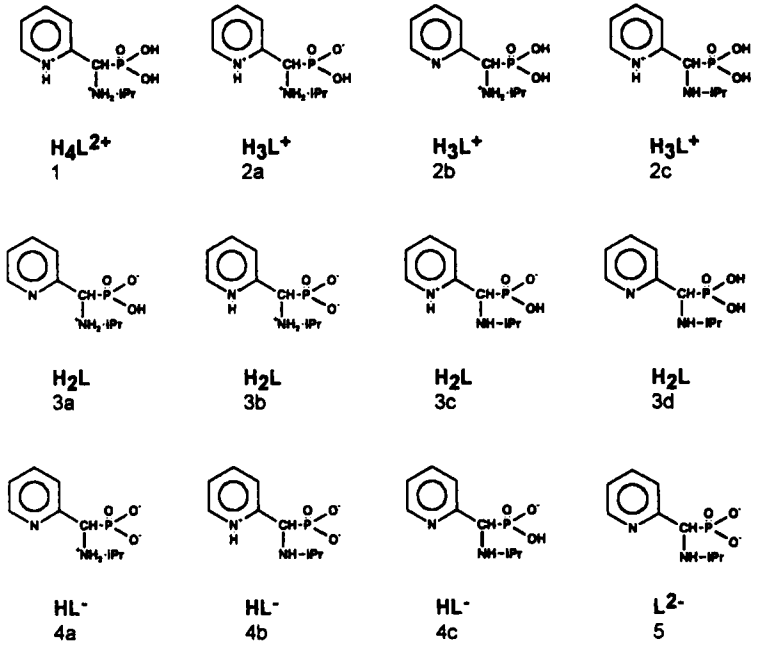
$$(3) \qquad K_i = \frac{C_{H^+} \cdot C_{H_{4-i}L^{2-i}}}{C_{H_{5-i}L^{3-i}}} \qquad (i = 1 \text{ to } 4)$$

An alternative description uses the stability concept and brutto stability constants β_i reflecting upon re-protonation of the bivalent anion L^{2-} of **1c**:

$$(4) \qquad iH^{+} + L^{2-} \longleftrightarrow H_iL^{i-2} \qquad (i = 1 \text{ to } 4)$$

$$\beta_{H_iL^{i-2}} = \frac{C_{H_iL^{i-2}}}{C^i_{H+} \cdot C_{L^{2-}}} \qquad (i = 1 \text{ to } 4) \tag{5}$$

The microscopic protonation scheme is more complex. The five macroscopic species H_iL^{i-2} comprise of a total of 12 microscopic species as given in **Scheme 1**.



SCHEME 1 Macroscopic and microscopic protonation species of **1c**. Enumeration of species 1 to 5 as used in Figures 1 and 2

The formation of metal complexes – as observed – is described by a macroscopic concept:

$$M^{2+} + jL^{2-} \longleftrightarrow ML_j^{2-2j} \qquad (j = 1 \text{ to } 2) \tag{6}$$

$$\beta_{ML_j^{2-2j}} = \frac{C_{ML_j^{2-2j}}}{C_{M^{2+}} \cdot C^j_{L^{2-}}} \qquad (j = 1 \text{ to } 2) \tag{7}$$

RESULTS

Dissociation constants and stability constants

Dissociation constants and stability constants for protonation equilibria are given in **Table I**:

TABLE I Dissociation constants and stability constants for protolytic equilibria of **1c**

pK_1	pK_2	pK_3	pK_4
1.20 (0.15)	1.88 (0.15)	5.22 (0.17)	9.90 (0.07)
$\log\beta_1$	$\log\beta_2$	$\log\beta_3$	$\log\beta_4$
9.90 (0.07)	15.12 (0.10)	17.00 (0.05)	18.20 (0.10)

Corresponding diagrams for the titration and the molar fractions of protonation species are given in **Figures 1** to **3**:

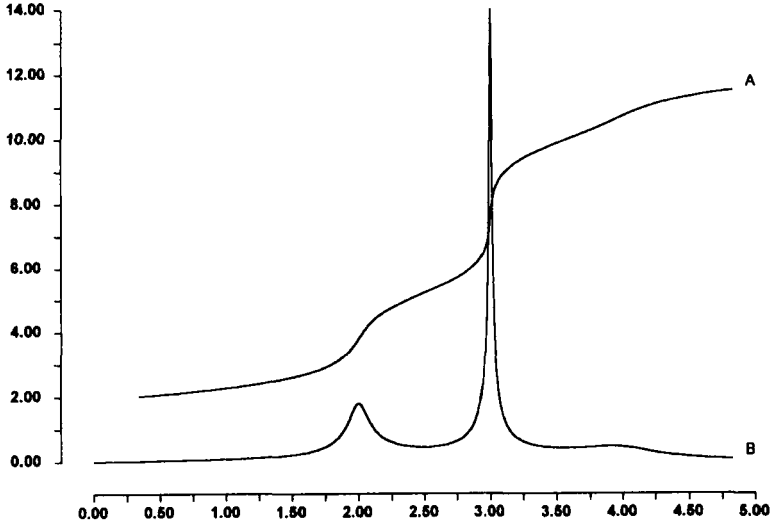


FIGURE 1 Titration of **1c** + 2 HNO_3 vs. NaOH. x-axis: degree of titration τ; y-axis: pH. A: pH vs. degree of titration. B: first derivative $dpH/d\tau$ of A

Stability constants for metal complex formation

While magnesium and calcium formed one type of complex only, [MgL] and $[CaL_2]^{2-}$, for Nickel both forms of complexes [NiL] and $[NiL_2]^{2-}$ were derived. The experimental data did not yield any evidence for the formation of protonated metal complexes. Corresponding stability constants are listed in **Table II**:

TABLE II Stability constants for complex formation of **1c** with Mg^{2+}, Ca^{2+} and Ni^{2+}

M	$\log\beta_{ML}$	$\log\beta_{ML2}$
Mg	3.34 (0.06)	-
Ca	-	5.87 (0.09)
Ni	9.85 (0.05)	16.78 (0.12)

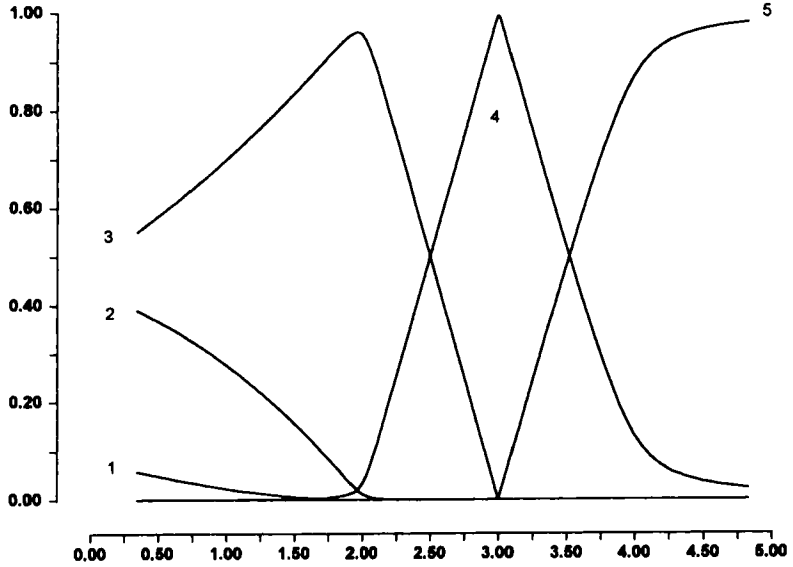


FIGURE 2 Molar fraction of protonation species for the protolytic equilibria of **1c**: x-axis: degree of titration τ. y-axis: molar fraction. 1: H_4L^{2+}. 2: H_3L^{+}. 3: H_2L. 4: HL^{-}. 5: L^{2-}

Diagrams for the complex formation equilibria of Ni^{2+} with **1c** are given in **Figures 4** to **6**:

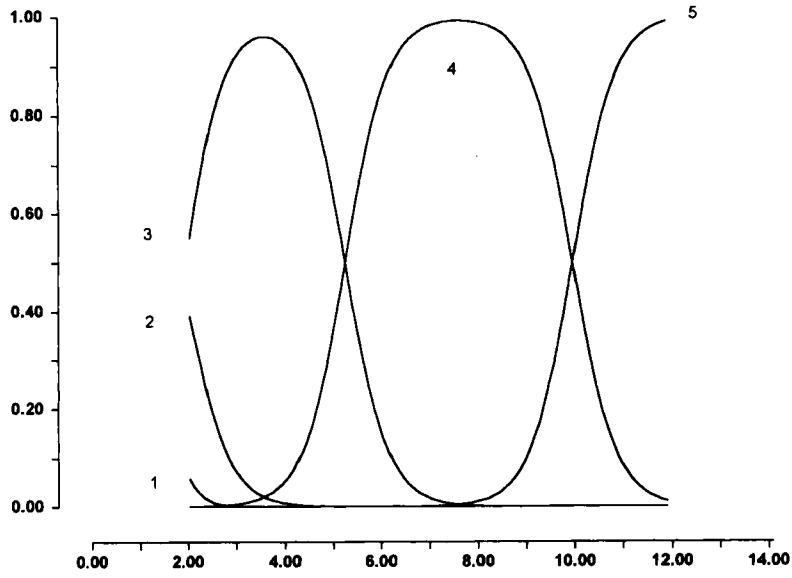


FIGURE 3 Molar fraction of protonation species for the protolytic equilibria of **1c**: x-axis: pH. y-axis: molar fraction. 1: H_4L^{2+}. 2: H_3L^{+}. 3: H_2L. 4: HL^{-}. 5: L^{2-}

NMR controlled titrations

NMR controlled titrations of **1c** vs. NaOH deduced the most likely path of microscopic deprotonation sequence. The analytical principles, hard and soft ware set-up for this technique were described in [4]. Since protonation equilibria are rapid on the NMR time scale, a dynamic NMR parameter δ is observed during titration. δ is the weighted average of ion specific parameter δ_{H_iL} following eq. (8):

$$\delta = \sum x_{H_iL} \cdot \delta_{H_iL} \tag{8}$$

Figure 7, a so-called $\tau - \delta$ diagram, correlates the chemical shift δ_P with the degree of titration τ. τ is defined by eq. (9) as the ratio of equivalents of base added (n_{NaOH}) to global amount of ligand calculated as totally protonated form ($n_{H_4L^{2+}}$)

$$\tau = \frac{n_{NaOH}}{n_{H_4L^{2+}}} \tag{9}$$

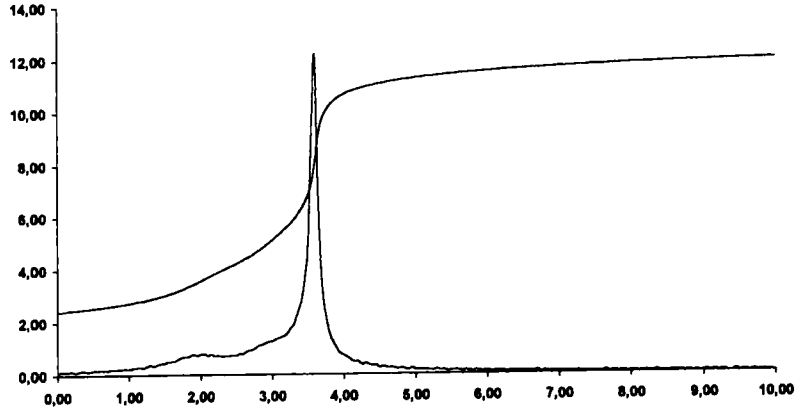


FIGURE 4 Titration of **1c** + 2 HNO_3 + $Ni(NO_3)_2$ vs. NaOH. x-axis: volume of titrator [ml]. y-axis: pH

In the starting phase only minute contributions from $\mathbf{H_4L^{2+}}$–1 and small contributions from $\mathbf{H_3L^{+}}$–2a exist and so the $\mathbf{H_2L}$–3a dominates. The first two equivalents of NaOH are used to deprotonate H_3O^+ and the pyridinium cationic site of $\mathbf{H_3L^{+}}$–2a to form the betain $\mathbf{H_2L}$–3a. This process is indicated by a typical low field shift of δ_P within the interval $0 < \tau < 2$. For $2 < \tau < 3$ the remaining POH function of $\mathbf{H_2L}$–3a is deprotonated to PO^- in $\mathbf{HL^-}$–4a as deduced from the high field shift of δ_P. The final deprotonation takes place at the i-propyl-ammonium cationic site of $\mathbf{HL^-}$–4a to form $\mathbf{L^{2-}}$–5 accompanied by a low field shift of δ_P for $\tau > 3$. The latter two deprotonation steps are consistent with findings from both the α- and the β-phosphaalanines $CH_3CH(NH_2)PO_3H_2$ and $H_2NCH_2CH_2PO_3H_2$ resp. as described in [4c,4g]. Henceforth the dominating deprotonation sequence of **1c** together with ion specific chemical shift data for δ_P is given by **Table III**:

TABLE III Macroscopic and microscopic species with ion specific chemical shifts δ_P [ppm].

Macroscopic	$\mathbf{H_4L^{2+}}$	↔	$\mathbf{H_3L^{+}}$	↔	$\mathbf{H_2L}$	↔	$\mathbf{HL^-}$	↔	$\mathbf{L^{2-}}$
Microscopic	1	↔	2a	↔	3a	↔	4a	↔	5
Ion specific chemical shift δ_P	6.0*		6.1		9.1		8.8*		16.0*

* δ_P not iterated.

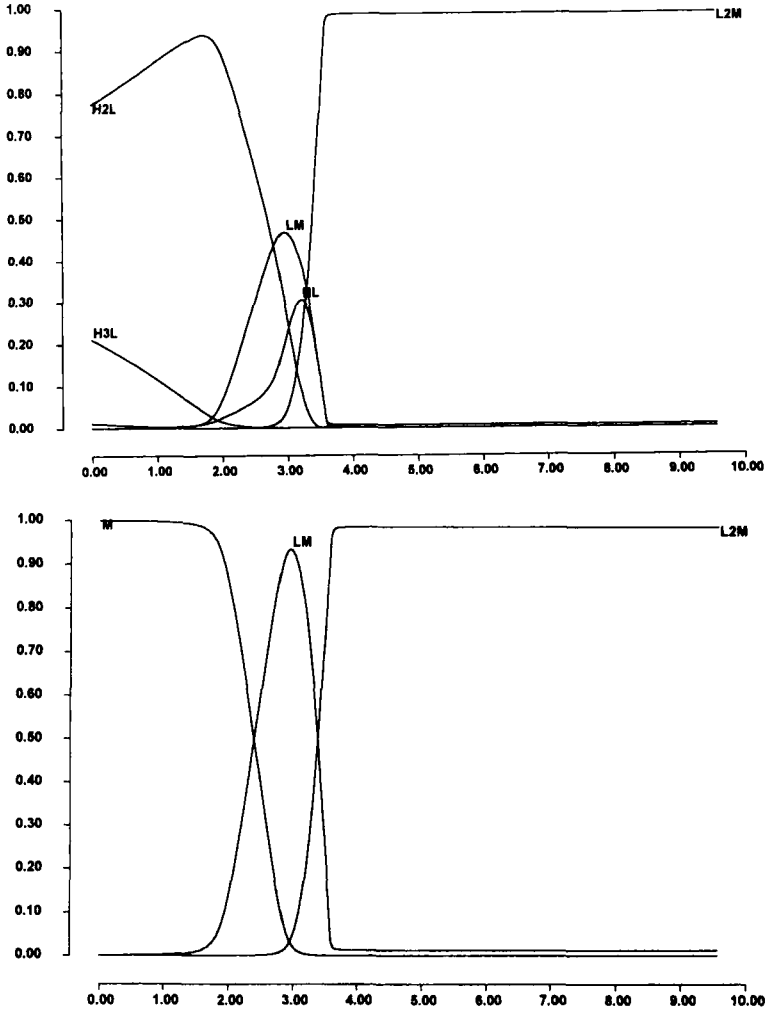


FIGURE 5 Molar fraction of protonation and complex species for the protolytic and complex formation equilibria of **1c** with Ni^{2+}: x-axis: degree of titration τ. y-axis: molar fraction. H3L: H_3L^+. H2L: H_2L. HL: HL^-. LM: NiL. L2M: NiL_2^{2-}. upper: molar fraction with respect to ligand L. lower: molar fraction with respect to metal M

The deprotonation sequence of both N-containing cationic sites, the pyridinium and the alkylammonium sites, in **1** is consistent with results from studies on 2-amino-methylpyridine [5]. From simultaneous observa-

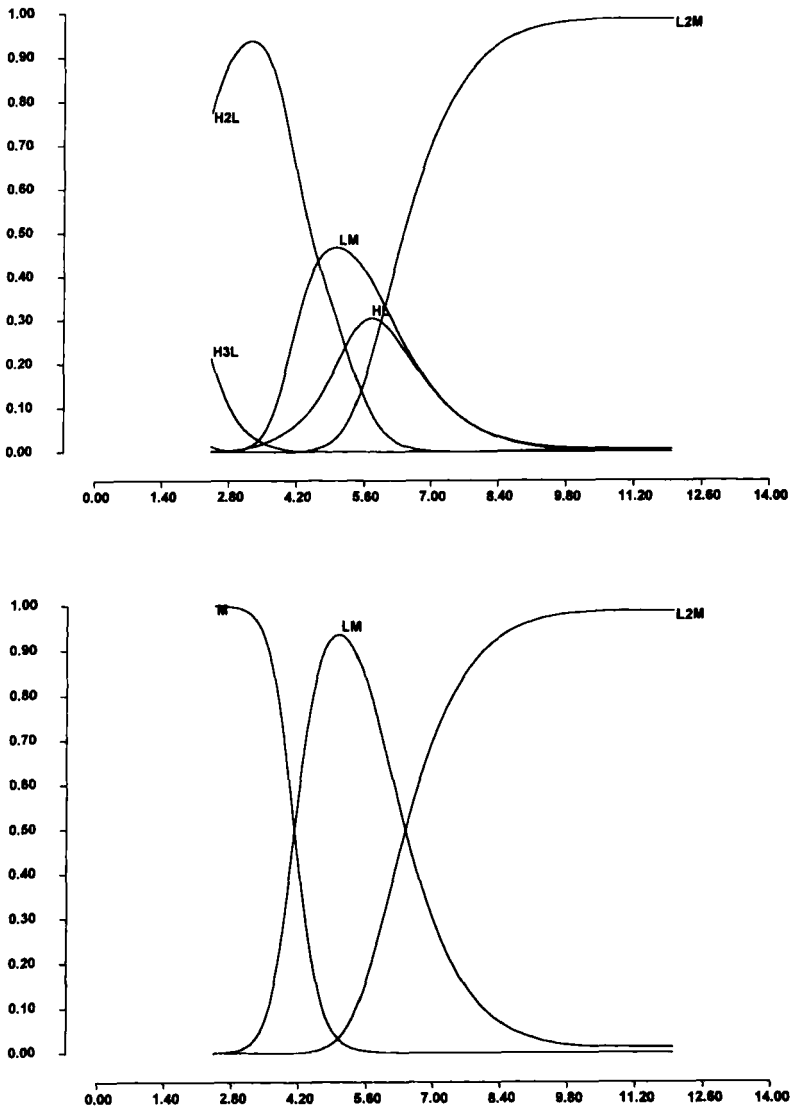


FIGURE 6 Molar fraction of protonation and complex species for the protolytic and complex formation equilibria of **1c** with Ni^{2+}: x-axis: pH. y-axis: molar fraction. H3L: H_3L^+. H2L: H_2L. HL: HL^-. LM: NiL. L2M: NiL_2^{2-}. upper: molar fraction with respect to ligand L. lower: molar fraction with respect to metal M

tion of pH and chemical shift via NMR controlled titrations so-called pH-δ diagrams may be calculated as shown in **Figure 8**:

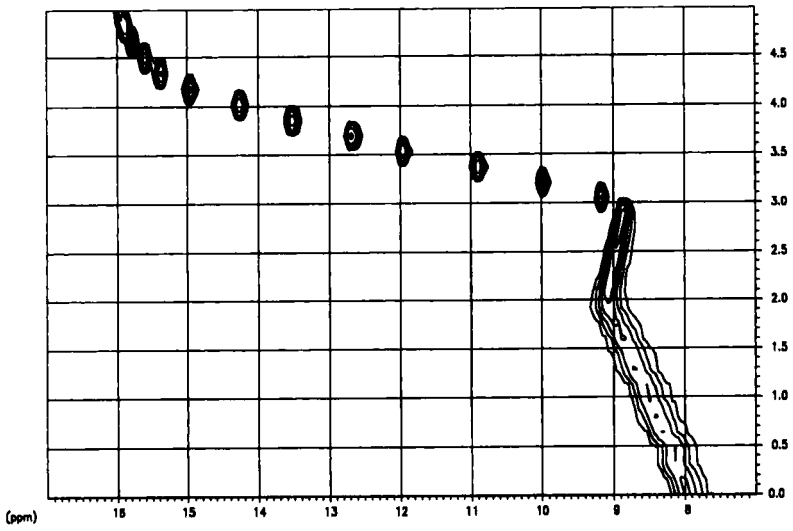


FIGURE 7 τ-δ diagram of a NMR controlled titration of **1c** vs. NaOH. x-axis: Chemical shift δ_P [ppm]. y-axis: degree of titration τ

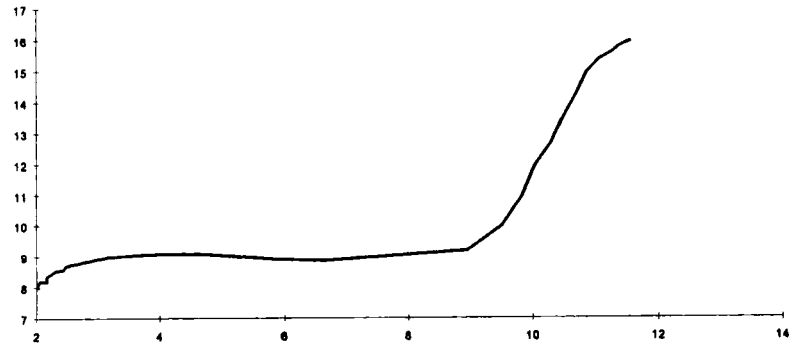


FIGURE 8 pH-δ diagram for a NMR controlled titration of **1c** vs. NaOH. x-axis: pH. y-axis: Chemical shift δ_P [ppm]

From **Figure 8** follows, that the gradient $\Delta\delta_P/\Delta pH$ is significant in the range close to pH 2 and in the range for pH from 9 to 12. Between pH 3

and pH 9 the chemical shift is less sensitive, an analogue to a "buffer plateau" exists.

EXPERIMENTAL

Synthesis

Compound **1c** was obtained following procedures given in [2].

Analytics

Dissociation and stability constants were determined using the programs MINI_T [3] and ITERAX [3]. A) 50 ml of a an aqueous solution holding 0.4 mmol **1c,** 1 mmol HNO_3 and 1 mmol $NaNO_3$ were titrated vs. 0.1 m NaOH in intervals of 0.05 ml. B) Similarly 50 ml of a solution holding 0.08 mmol **1c,** 0.2 mmol HNO_3, 0.04 mmol $Me(NO_3)_2$ (Me = Mg, Ca, Ni) and 5 mmol $NaNO_3$were titrated vs. 0.1 m NaOH in intervals of 0.05 ml. Volumetric and potentiometric data from a combined glasselectrode were recorded (MINI_T) and iterated (ITERAX) [3]. Stability constants quoted in this text are averaged from three experiments.

NMR controlled titration

Detailed descriptions of methods used are given in reference [4]. 0.1658 mmol of **1c** and 0.310 mmol HNO_3 were dissolved in 23 ml H_2O and titrated vs. 0.09972 m NaOH. pH was monitored by a combined glasselectrode. Individual $^{31}P\{^1H\}$-FIDs were registered for 36 specific and equidistant steps of τ. τ, the degree of titration, is defined negative for excess of acid with respect to the amphiprotic ligand H_2L but positive for addition of base to H_2L. NMR: Spectrometer: BRUKER AM200SY operating for ^{31}P at 81 MHz. For the evaluation of NMR controlled titrations a specially designed program system NMR_T [4] was used.

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