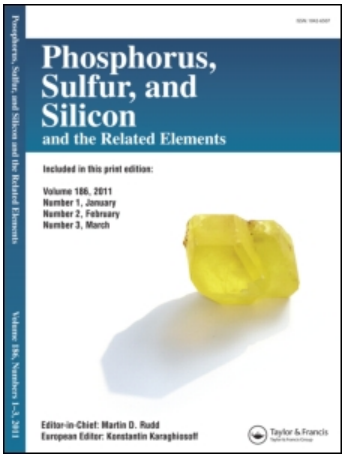

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The Aza-α-aminophosphonate Macrocycle

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The Aza-α-aminophosphonate Macrocycle

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In order to combine the properties of aza-macrocycles and aminophosphonates, a new tetraaminophosponic macrocyclic molecule has been synthesized. This potential receptor for organic molecules as well as for metal cations was obtained by condensation, hydrophosphonylation, and deprotection. The second synthetic step was performed using di(trimethylsilyl) phosphite, which enabled us to obtain the final product in high yield. NMR studies strongly suggested that the α-aminophosphonate macrocycle was reached as a symmetric meso*-derivative.*

Keywords Macrocyclic ligands; NMR spectroscopy

INTRODUCTION

The discovery of a family of macrocyclic compounds was a milestone in chemistry and opened new frontiers in the synthesis of supramolecular host molecules. This group of compounds has been recognized as a source of receptors for many chemical species, such as metal cations, inorganic and organic anions, and structurally variable organic molecules.[1] Therefore they are widely used for construction of metal sequestering agents, selective sensors, mimetics of enzymes, or carriers for transport through membranes.[2–10] On the other hand, aminophosphonates have been found to be not only good enzyme inhibitors, but also a promising group of metal ion chelators, and as such, they are used in many branches of industry (e.g., agricultural, pharmaceutical,

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.
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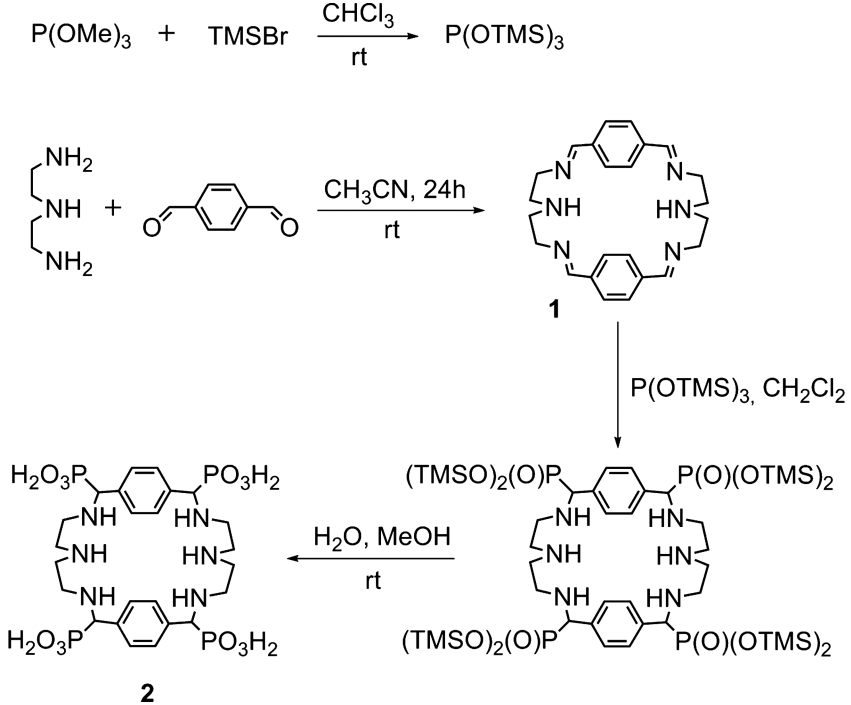
and chemical industry).[1] The tandem structure of macrocyclic polyaza groups including phoshonate entities recently has been extensively investigated as potential contrast agents for MRI spectroscopy.[11] Recently we have shown that some di(aminomethylphosphonic)phenylenes compounds exhibit interesting properties towards basic amino acids (Lys, Arg) and metal ions,[12,13]

RESULTS AND DISCUSSION

In this article, we present the synthesis of a new group of aza-α - aminophosphonate macrocycles represented by compound **2**, which combines features of both macrocyclic and phosphonic entities (Scheme 1). As a substrate recently described, macrocyclic compound **1** was used based on the assumption that the introduction of four phosphonic groups placed into a carefully tailored cavity should result in the new synthetic receptor of possible use in chelation of biologically important molecules and metal ions.[2]



SCHEME 1

The macrocycle **1** was synthesized according to a standard [2+2] condensation reaction that gave the desired Schiff base in a satisfactory yield.[14] When applying the standard procedure for the addition of diethylphosphite to this Schiff base **1**, the course of reaction was non-satisfactory, most likely due to its low solubility in organic solvents and leading to a mixture of many organophosphorus products. Therefore another agent, trimethylsilyl phosphite, generated in situ, was used.[15,16]

However, after only one purification step, a single and narrow signal is present in the ^{31}P NMR spectra of the obtained moiety (see Figures 1 and 2). This is really surprising when considering the relatively high yield of the final product at 95%. This may suggest conversion of kinetically controlled products into a thermodynamically stable *meso*-stereoisomer. The inspection of ^{13}C NMR spectra for α - CH and CH_2 groups of the purified compound reveal the presence of one major stereoisomer accompanied by minute amounts of minor stereoisomers (Figure 2), which supports predominant formation of a *meso*-derivative. A similar assumption was reached from inspection of the ^{1}H NMR spectra. However, the addition of *R* (+) methylbenzylamine to compound **2** shows the presence of two small signals at 14.78 and 15.83 ppm and one main at 15.51 ppm in ^{31}P NMR spectra, which suggests the formation of *meso* forms. Additional confirmation of the suggested *meso* form of compound **2** is a capillary electrophoresis diagram in which only one signal is visible.

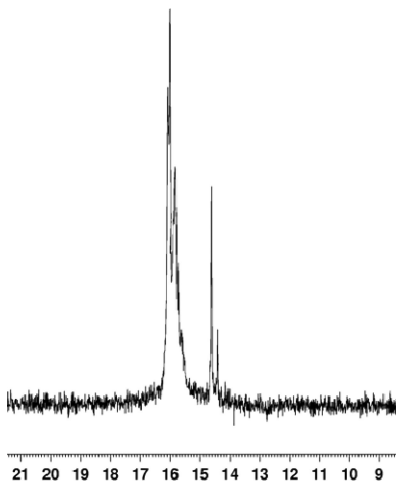


FIGURE 1 The ^{31}P NMR spectrum of a crude compound **2**.

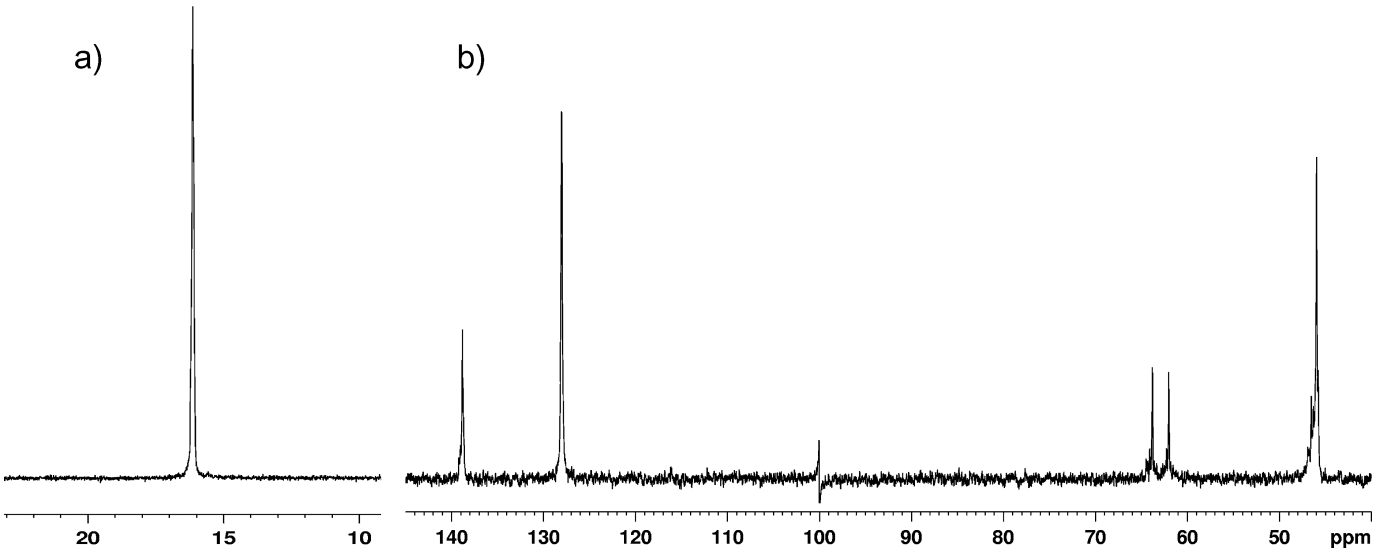


FIGURE 2 The ^{31}P (a) and ^{13}C NMR (b) spectra of a purified compound **2**.

It is worth stressing that the obtained macrocycle **2**, in contrast to simple aminophosphonic acids, is weakly soluble in water at neutral pH. In order to increase solubility of this compound in water, its conversion into salts is required either by addition of an amine (e.g., benzylamine) or by transformation the acid into its sodium or ammonium salt. The MS studies performed for macrocycle **2** sodium salt revealed a complete dissociation of sodium ions and species of molecular masses of 729 $[M\text{-}H]^-$ and 364 $[M\text{-}2H]^{2-}$ was observed, indicating the presence of mononegative and dinegative anionic forms of the compound **2**.

In conclusion, the simple synthesis of aza-α -aminophosphonate compound, a promising agent in supramolecular chemistry, was described.

EXPERIMENTAL

Preparation of a Macrocyclic Schiff Base 1

This compound was synthesized according to the procedure in the literature.[14] The solution of terephthal-aldehyde (22 mmol, 3 g) in 370 mL of CH_3CN was added dropwise to the solution of diethylenetriamine (22 mmol, 2.42 mL) in 630 mL of CH_3CN. The mixture was stirred for 24 h at room temperature, and a white precipitate was formed. It was filtered off and washed with 10 mL of CH_3CN and 3 $\times$ 10 mL of diethyl ether. The ^1H NMR spectra of the isolated product revealed chemical shifts that are in a good agreement with the data in the literature.[14]

Yield: 34%; 1.54 g; 0.0038 mol; 1H NMR (300 MHz, CDCl3): 1.87 (s, 2H, NH); 3.00 (t, 8H, CH_2—NH); 3.79 (t, 8H, CH_2—N=C); 7.55 (s, 8H, Ar); 8.31 (s, 4H, CH=N).

Preparation of a Macrocyclic Compound 2

A mixture of trimethyl phosphite (0.65 mL, 0.678 g, 5,5 mmol) and trimethylsilyl bromide (3.3 mL, 3.278 g, 24.84 mmol) in 30 mL of dried $CHCl_3$ was cooled to –5°C and stirred for 45 min. The solution became yellow and clear. In a separate flask, a Shiff base **1** (0.500 g, 1.242 mmol) was suspended in 15 mL of dried $CHCl_3$ and also cooled to –5°C. After 45 min, it was added to the above solution. The mixture was stirred for 48 h in a room temperature. After that, all volatiles were evaporated, and next the orange residue was treated with 30 mL of methanol containing 5% of water and stirred overnight to give a pale precipitate. A crude product was filtered off and dissolved in 1M solution of sodium hydroxide. Then a 3M hydrochloric acid was dropped in until the white precipitate was formed, which was next filtered off

and washed with diethyl ether to yield a yellow solid, 95%, 0.860 g, mp 255–257°C.

^{1}H NMR (300 MHz, D_2O + NaOH): 1.81–1.92 (m, 16H, CH_2); 3.20 (d, 4H, α –CH, $J = 17.3$ Hz); 6.89 (s, 8H, Ar); ^{31}P NMR (300 MHz, D_2O + NaOH) δ ppm: 16.15 (s, P–CH). ESI-MS (-): $m/z = 729$ $[M\text{-}H]^-$; 364 $[M\text{-}2H]^{2-}$.

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