Heteroatom Chemistry
Volume 11, Number 7, 2000

Syntheses, Characterization, Stereochemistry and Complexing Properties of Acyclic and Macrocyclic Compounds Possessing α-Amino- or α-Hydroxyphosphonate Units: A Review Article

Salvatore Failla,[1] Paolo Finocchiaro,[2] and Giuseppe A. Consiglio[2]

[1]*Dipartimento di Ingegneria Chimica, dei Materiali delle Materie Prime e Metallurgiche, Università di Roma "La Sapienza", Via del Castro Laurenziano, 7, 00161 Rome, Italy*

[2]*Dipartimento di Metodologie Fisiche e Chimiche per l'Ingegneria, Facolta' di Ingegneria, Universita' di Catania, V.le A. Doria, 6, 95125 Catania (IT); pfinocchiaro@ic.ing.unict.it*

Received 15 March 2000; revised 30 June 2000

ABSTRACT: *In this article we shall review the salient aspects concerning the syntheses, characterization, and complexing properties of variously substituted mono- and bis-(α-amino)- and (α-hydroxy)-phosphonates. Characterization of these compounds was mainly achieved by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, by FABMS techniques, and by X-ray diffraction analyses. Hydrolytic cleavage in alkaline solutions of the dialkyl esters gave the corresponding monoesters, which also show good complexing properties toward standard metals and lanthanides.*

The last section of this article is dedicated to a review of the synthesis, characterization and stereochemistry of cyclophanes, and macrocyclic compounds possessing phosphonate units. © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:493–504, 2000

Correspondence to: Paolo Finocchiaro.

Contract Grant Sponsor: Consiglio Nazionale delle Ricerche (CNR).

Contract Grant Sponsor: Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

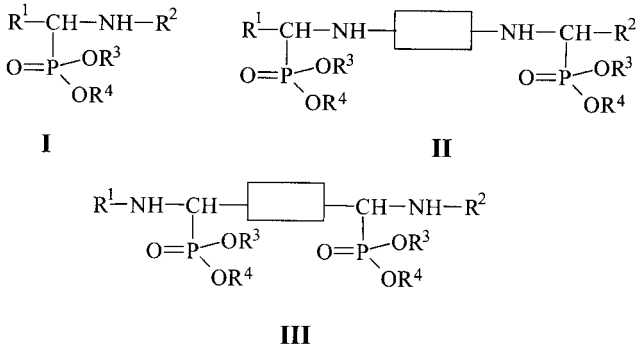
AMINO-PHOSPHONIC ACID DIALKYL- AND MONO-ALKYL ESTERS

α-Aminophosphonic acids are bioisosteres of natural aminoacids that serve as important surrogates in order to modify biological processes to inhibit enzyme activity [1] and bacterial growth [2]. Furthermore, these compounds, as well as their dialkyl and monoalkyl esters, are widely used in agrochemistry as antifungal agents [3], herbicides [4], and as plant regulators. Self-condensation of α-aminophosphonic acids produces phosphonodipeptides and phosphotripeptides, clinically studied as antibiotics [5], and condensation of racemic phosphonate esters with vinblastine gives epimers that show antitumor activity [6].

In addition, α-aminophosphonic acids and their monoalkyl esters are of interest also in hydrometallurgy in order to extract metals [7] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinides [8,9].

Therefore, considering the interest and the wide applications of such compounds, we decided to synthesize a great variety of mono-and bis-α-aminophosphonic acid dialkyl esters, as well as some of

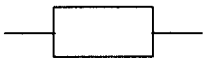
their monoesters, with general structures **I, II, and III** (Chart 1).



I **II**

III

where R^1 and / or R^2 = aryl, heteroaryl, cycloalkyl, alkyl



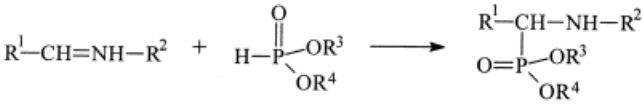
= alkanediyl, cyclohexyl, aryl

R^3 = methyl, ethyl; R^4 = H, methyl, ethyl

In this article we shall review the salient results obtained during our investigations, as well as the novel results that emerged from our studies concerning both characterization and complexation properties.

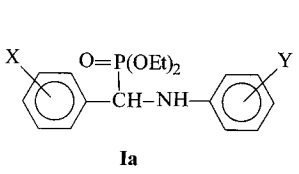
α-Aminophosphonic Acid Derivatives of General Formula **I**

Among the possible different synthetic routes that can yield α-aminophosphonic acid dialkyl esters, we prefer the addition of dialkyl phosphites neat or in solvents (polar or apolar) to the Schiff base precursors, readily available from the condensation of primary amines with aldehydes (Scheme 1).

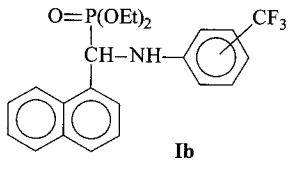


SCHEME 1

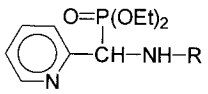
In order to facilitate the addition reaction, a catalytic amount of NaH was used. According to this procedure, we prepared in good yields α-aminophosphonic dialkyl esters **Ia–If**, where the X and Y substituents range from hydrogen, halogens, trifluoromethyl groups, methoxy, carbomethoxy and phenylazo moieties, to free carboxylic groups.



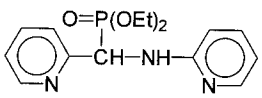
Ia



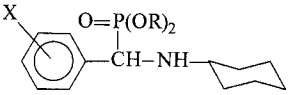
Ib



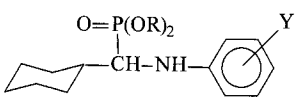
Ic



Id



Ie



If

Dialkyl esters, both methyl as well as ethyl derivatives, in which R^1 and R^2 in **I** consist of unsubstituted or variously substituted aryl or cyclohexyl rings, are white crystalline compounds, soluble in organic solvents. They were mainly characterized by NMR spectroscopy and by fast atom bombardment mass spectrometry (FABMS) analyses. In the ^{1}H NMR spectra, the most diagnostic signals are observed in the alkoxy and in the methyne regions; in fact, the diethyl esters give rise to two distinct doublets of triplets at δ = 1.1 – 1.3 ppm for the methyl groups and a complex multiplet for the methylene protons; the dimethyl esters show two distinct doublets ($^3J_{PH} \cong 10.5$ Hz) for the OCH_3 protons at δ = 3.1 ÷ 3.8 ppm. The nonequivalence of the two OR groups is due to the close proximity of the stereocenter, and the chemical shift difference between the two triplets or the two doublets is very sensitive to the moiety attached to the methyne carbon atom. In particular, going from cyclohexyl to 1-naphthalene substituents at the α-CH-group, the difference in chemical shifts $\Delta\delta$ varies from a few hundredths of a ppm in **If** to 0.7 ÷ 0.8 ppm in **Ib.** This effect is certainly due to the strong anisotropic ring current sensed by one alkoxy group in comparison to the other, allowing speculation on the preferred geometry adopted in solution by these compounds (see below).

The methyne hydrogen of the -CH-P(O)$(OR)_2$ group appears as a sharp doublet ($^2J_{PH} \cong 22 – 24$ Hz) or as a double doublet, due to the additional coupling with the NH proton. The observation of the latter pattern in some derivatives (or in some solvents) is due to a slower exchange of the NH protons. In such cases, the CH resonances give rise to a four line pattern with $^2J_{PH}$ in the range of 18 ÷ 24 Hz and

$^3J_{HH} \cong 8 - 9$ Hz, whereas the NH proton signal appears as a triplet with $^3J_{PH}$ nearly equal to $^3J_{HH}$.

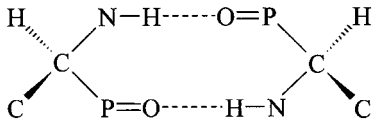
Interesting enough, in phosphonates **Ia, Ie, If,** bearing a carboxy or carbomethoxy group in the *ortho* position, the NH proton resonates below δ = 8.00 ppm, experiencing a dramatic deshielding effect due to the formation of a hydrogen bond between the NH and the ortho carbonyl oxygen, via a six-membered cyclic structure.

The geometry adopted in the solid state by derivative **Ia** (X = Y = H) was investigated by X-ray diffraction [10,11], and the following salient characteristics were found:

1. The hydrogen atoms bonded to the chiral carbon atom and to the nitrogen atom in the H–N–C–H moiety are oriented in the *anti* position, while both phenyl rings show the *syn* conformation. Both rings are slightly twisted in order to relieve steric interactions. The planes of the phenyl rings are practically perpendicular to each other with a dihedral angle of 89.9°. The orientations of the individual P–OEt groups with respect to the aromatic ring plane are as follow: one lies over the phenyl ring attached to the CH and experiences the diamagnetic ring current shielding effect, whereas the other one points toward the NH moiety and is far away from the other phenyl ring; thus, this geometry well explains the chemical shift difference between the two triplets noticed in the ^{1}H NMR spectra.

2. The nitrogen pyramid is considerably flattened with an increased C–N–C bond angle of 121.71°.

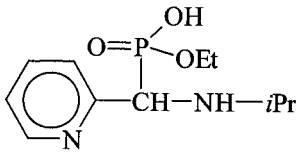
3. Because of the parallel orientation of the N–H and the P=O bonds, cyclic dimers with N–H to O=P hydrogen bridge bonds are formed, as schematically indicated in the following structure.



4. The pair of chiral methyne carbon atoms gives rise to the formation of *S,S* and *R,R* enantiomers in the solid state that are tightly bound together by O–H–N bridges [10]. Considering that the biological activity of chiral compounds depends on the absolute configuration, as reported in several literature examples [12,2a,2d], we developed a direct and efficient enantioselective resolution of some of the phosphonates **Ia–If** using commercially available HPLC chiral columns [13,14]. The interest of such a procedure resides in the fact that we can dispose of optically pure compounds, avoiding the long and tedious conventional procedure of resolving racemic mixtures through the formation of diastereomeric salts and subsequent hydrolytic cleavage, or without recourse to asymmetric syntheses which are quite often not very effective.

A great variety of racemic *N*-arylamino-arylmethylphosphonic acid diethyl esters with various fluorinated substituents in one or both aryl rings (**Ia**, X = H; 4-F; 3-F; 2-F; 3,4-F_2; 4-CF_3; 4-CF_3O; Y = H; 4-, 3-, 2-F; 3,4-F_2; 4-, 3-, 2-CF_3; 4-, 2-CF_3O;) have been resolved by using this technique [14]. We have found that the chiral separation strongly depends on the substitution pattern in the *N*-aryl and/or in the C-aryl moieties, and it increases significantly with the polarity of fluorinated substituents. By constructing a model which takes into account the steric and the hydrogen-bond interactions between the analyte and the stationary chiral phase, we were able to propose a recognition mechanism of the two enantiomers, correlating it with the absolute conformations of the optical isomers and to relate it to the chiroptical behavior [14].

Aminophosphonic acid diethyl esters containing the pyridine moiety (formulas **Ic** and **Id**) were also synthesized by us in good yields, starting from their Schiff base precursors [15]. The aim of preparing such phosphonates containing the heterocyclic ring was to enhance the complexation properties toward metals and toward lanthanides in particular, in order to use such compounds in diagnostic medicine, NMR imaging techniques, and in agrochemistry. Indeed, alkaline hydrolysis of derivatives **Ic** and **Id** gave the corresponding monoethyl phosphonates, which are very versatile complexing agents for transition metals. As an example, from the reaction of the monoester **IV** with copper(II) chloride dihydrate in methanol, a crystalline product has been isolated.



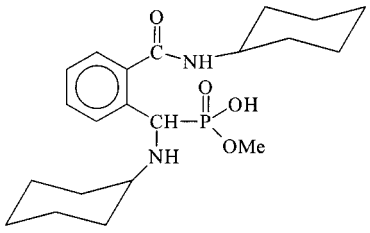
IV

By elemental and LSIMS analyses, the complex was found to be dimeric with formula $Cu_2L_2Cl_2$, where L stands for IV. X-ray structural determinations revealed a novel ligand-bridged centrosymmetric dimeric complex linked by bridging phosphoryl oxygen atoms reinforced by the two strong hydrogen bonds from the amino proton of one ligand to the phosphoryl oxygen of the second [16]. Each copper atom has a distorted square pyramidal coordination, and, for the first time, a metal complex of an ami-

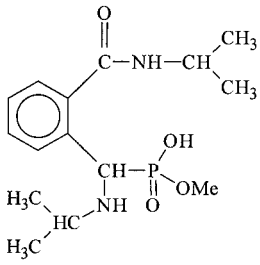
nophosphonate monoester shows limited oligomerization, demonstrating the potential advantages for biological applications of the monoesters in contrast to the diesters and the free acids [16].

In order to enhance the hydrophilicity and the complexing properties towards II° group elements, we introduced in our amino-phosphonate one or more carboxylic groups (**Ia, Ie, If,** X = Y = COOH). Furthermore, the presence of such functionalities should facilitate enantiomer resolution both by HPLC methods or by conventional chemical techniques, and will allow the synthesis of disparate derivatives (amides, amines, nitriles) and of interesting monomers for definite polycondensates bearing the aminophosphono functionality. The compounds obtained are white crystalline materials soluble both in polar organic solvents ($CHCl_3$, CH_3CN, DMSO, alcohols) as well as in water or in slightly alkaline solutions, rendering them attractive for biological applications [17].

The synthesis of the aforementioned compounds containing the free carboxylic group was straightforward starting from the corresponding Schiff base according to Scheme 1. However, when *o*-carboxybenzaldehyde and primary amines, such as cyclohexyl- and isopropylamine, were employed as reagents for the synthesis of Schiff bases, oily products were obtained, which by subsequent addition of dimethyl phosphite produced in very good yields amido-aminophosphonic acid monomethyl esters, very soluble in water and in protic organic solvents (compounds **V** and **VI**) [18].

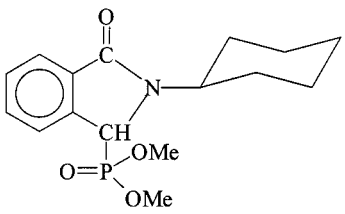


V

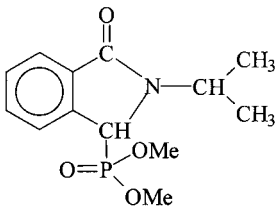


VI

The by-product of this unusual and unexpected addition reaction is a cyclic aminophosphonic acid dimethyl ester (VII or VIII).



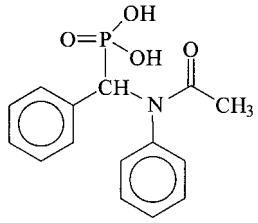
VII



VIII

Characterization of these new compounds was achieved by ^1H and ^{31}P NMR spectroscopy, by FABMS techniques, and by IR spectroscopy [18].

Although, in this case, the phosphorylation reaction is quite complex on the molecular level, there is no doubt that this unexpected course of the reaction is due to the use of *o*-carboxybenzaldehyde, which mainly exists in a cyclic 3-hydroxyphthalide structure. Thus, a possible reaction mechanism leading to the compounds **V–VIII** was outlined, and we stress here that this procedure allows us to obtain in a very convenient way, and by one-pot reactions, good yields of aminophosphonic acid monomethyl esters containing ancillary moieties (the amido group) suitable for complexing metals. Furthermore, in an extended way, the compounds obtained can be thought of as the nonnatural analog of peptides, and therefore they can be of utility in biological tests. Functionalization at the NH group of our aminophosphonates, of general formula **Ia,** was found not to be an easy reaction. Nevertheless, the reaction of an N-phenylaminobenzylphosphonate with an excess of CH_3COCl gave a new amidophosphonic acid **IX** by hydrolyzing the ester groups in situ.



IX

Considering the interest of compounds of type **IX** for biological and practical applications, we performed a detailed study in the solid state by X-ray structural analyses and in solution by ^1H and ^{31}P NMR spectroscopy [19].

Single-crystal X-ray analysis reveals that **IX** is a diprotic acid possessing in the solid state a centrosymmetric space group, consistent with an equal mixture of *R* and *S* enantiomers. The geometry at the phosphorus atom is quite distorted from tetrahedral, and although the compound adopts a conformation that, in featuring a *cisoid* arrangement of the phosphonic acid oxygen and the amide oxygen, is favorable for chelating formation, there is no intramolecular hydrogen bonding in the solid state. In contrast, inspection of the packing of the crystal reveals the importance of intermolecular hydrogen bonding in determining the solid state structure. The compound forms polymeric chains that propagate in the direction of the *a* axis and result from two sepa-

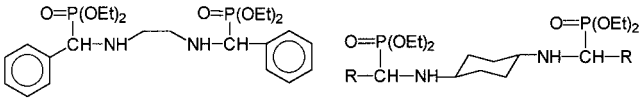
rate four-center interactions across inversion centers.

The ^{1}H and ^{31}P NMR spectra of **IX** in CD_3OD reveal the presence of two discrete species on the NMR timescale that are ascribed to the two rotamers arising from restricted rotation around the amide bond, and integration of ^{1}H and ^{31}P NMR spectra are consistent with populations in the ratio ca. 60:40 of the two rotamers [19].

Preliminary results on complexation behavior reveal that **IX** is able to complex specifically with lanthanides, such Ho^{3+} and Gd^{3+}, rendering this molecule very attractive for use in diagnostic medicine.

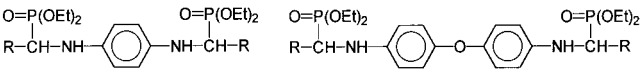
Bisfunctional Aminophosphonates with General Structures II *and* III.

Addition of dialkyl phosphites to bis-imines led us to obtain a variety of aminoarylmethyl diphosphonate alkyl esters in good yields [20]. All compounds (their structures being exemplified by **IIa–d** and **IIIa–c**) are crystalline solids and were characterized by ^{1}H and ^{31}P NMR and by FABMS techniques, which reveal the presence of peaks or fragmentation patterns very useful and diagnostic for constitutional assignments [20]. In the ^{1}H NMR spectra two distinct triplets of equal intensity are in evidence for the methyl protons of the ethoxy group, and a sharp doublet or doublet of doublets is observed for the methyne hydrogen atoms. The interpretation of such multiplicities is analogous to what has already been described for aminophosphonates of general structure **I**.

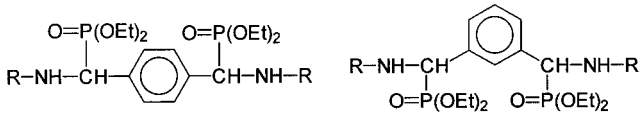


IIa

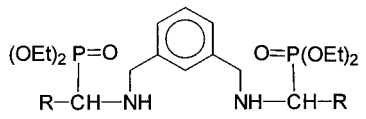
IIb



IIc **IId**



IIIa **IIIb**



IIIc

On the consideration that the addition of diethyl phosphite to bis-imines should generate, owing to the chiralities of the groups present in the diphosphonate molecule, two diastereomeric products (*meso* and racemic forms), the presence of only one signal observed in all compounds for the methyne and ethoxy groups indicates that only one of the two possible diastereomers is formed stereospecifically in our addition reactions. This observation was further confirmed by analysis of the ^{31}P NMR spectra of our compounds, in which only one sharp phosphorus signal is observed in the majority of our samples, indicating that only one diastereomer contributes to the structure [20]. Therefore, we can conclude that the addition of diethyl phosphite to symmetrical bis-imines proceeds stereospecifically with the predominant formation of only one of the two possible diastereomeric forms.

Indeed, X-ray diffraction analyses clearly indicate that **IIa** has a *meso* configuration, and, in the solid-state, the molecular conformation possesses a fully elongated transplanar structure along the P–C–N–C–C–N–P skeleton, with the phenyl ring in a *trans* position one to the other and lying almost perpendicular to the skeleton plane [21]. Furthermore, by using molecular modeling methods, such as Molecular Mechanics (MM), Molecular Dynamic (MD) simulations, and semiempirical methods (MOPAC 6.0 PM3), the conformational aspects of *N*,*N*′-1,2-ethylenediamino-bis-(phenylmethylphosphonic acid diethyl ester) **IIa** were investigated in order to find the most stable conformer [22]. The results of our computational structural analyses are in good agreement with the conformation obtained from the X-ray crystal structure, and the most stable conformation was found to be the *meso* form, with an elongated transplanar structure, as found in the solid state [21].

The FABMS technique indicates that a protonated molecular ion $[M + H]^+$ was observed in high intensity for all compounds, and the $[M + H - 138]^+$ ion or the $[M + H - (2 \times 138)]^+$ ion constitute the base peak. The $[M + H - 138]^+$ ion corresponding to the monoaminophosphonate molecule was generated by the easy loss of diethyl phosphite $HP(O)(OEt)_2$, *m/z* 138. The region at relatively low masses is characterized by the presence of the ion $[M + H - (2 \times 138)]^+$, which is the base peak or the second peak in relative intensity [20].

In all spectra, peaks due to cluster ions $[xM + R]^+$ are observed. A cluster with a peak at *m/z* 23 mass unit above that of the molecular ion strongly indicates cationization of our molecules with Na. A cluster with peak, at *m/z* $[2M + H]^+$ mass unit with relative intensities in the range 1–5% is also present

in all spectra. This latter peak and some other cluster ions may originate from a beam-surface reaction indicating that probably some association occurs among the molecular ion with a neutral molecule and fragments [20].

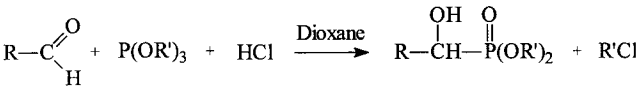
The presence of heteroaromatic rings, such as pyridine or azo-groups (R substituents in structure **II** and **III**), renders such compounds also very attractive for complexation studies towards metals. In this respect, compounds of type **IIIa** and **IIIb** were hydrolysed to the corresponding monoesters in alkaline solution [23]. Such compounds are very soluble in water and strong polar organic solvents. Derivatives possessing a phenylazo group are deeply red-colored, and their absorption maxima are pH-dependent, which suggests a possible use for spectrophotometric titrations in aqueous media and for complexation studies at different pH values.

Characterization of these monoesters by the FABMS technique can be performed only using the negative ion mode. The results indicate that, for all compounds examined, a pseudomolecular ion $[M - Na]^-$ with very high intensity was observed. In comparison with the diesters, the monoesters do not show any fragmentation pattern. In all spectra, peaks due to the cluster ions $[nM - Na]^-$, where $n = 1, 2, 3$, were observed. The region at relative high masses is characterized by the presence of the ion $[2M - Na]^-$, which is the second peak in relative intensity. This interesting peak is very diagnostic for determining the molecular masses of the salt molecules. In fact, the detection of both ions as the anion $[M - X]^-$ and the cluster ion $[2M - X]^-$ (where X is the cation), allows the determination of the relative molecular masses of the salt molecule and its ionic components, that is, anion and cation. A cluster with a peak, at m/z $[3M - Na]^-$ mass unit above that of the molecular ion, with relative intensities in the range 5–10%, is also present in all spectra [23].

α-HYDROXY-PHOSPHONATES

α-Hydroxy phosphoryl compounds (phosphonates and phosphonic acids) are compounds of significant biological activity [24,25] and have been shown to inhibit enzymes such as renin [26], EPSP synthase [27], and HIV protease [28].

In our synthesis, following previous literature reports [29,30] in which 1,2-dihydroxy-1,2-bisphosphonylethanes and 1,4-bis(dialkoxyphosphinyl) benzene were obtained by reacting glyoxal [29] or 1,4-benzenedicarboxaldehyde [30], respectively, with phosphorous acid triesters, the trialkyl phosphite being added, at room temperature, under strong acidic conditions to the corresponding carbonyl compound (R = alkyl, aryl, heteroaryl) dissolved in anhydrous dioxane (Scheme 2):



SCHEME 2

The reaction is quite exothermic and cooling is often needed; a 10–15 minute reaction time is sufficient in order to assure almost quantitative yields in the desired product. The choice of solvent is very crucial: in fact, it is imperative that it must be inert toward the starting aldehyde and should easily dissolve the reactants and the final products, including large quantities of gaseous HCl. Chemical considerations, coupled with the necessity of using strictly anhydrous conditions, led us to select dioxane as the solvent for our reaction.

The addition reaction is quite general and it works well with all kind of aliphatic, aromatic and heteroaromatic mono- and bis-aldehydes. The α-hydroxy phosphonates so obtained are white crystalline compounds, and their complete spectroscopic characteristics (^{1}H NMR, ^{31}P NMR, FABMS, IR) were reported in previous articles [31]. The most important features are as follows:

1. The methyne proton of our hydroxy-phosphonates resonates in $CDCl_3$ solution as a doublet with a negative geminal coupling constant $^2J_{PH}$ in the range 9–12 Hz, which is much lower in comparison with the same coupling constant observed in several 1-amino-phosphonates ($^2J_{PH}$ = minus 18–24 Hz) [20]. In DMSO-d_6 as solvent, additional coupling of the methyne hydrogen with the hydroxylic proton generates an ABX system ($^2J_{PH} = -(12–15)$ Hz and $^3J_{HH}$ = 4–6 Hz). The hydroxylic proton resonates as a doublet of doublets with a coupling costant $^3J_{PH}$ in the range of 10–16 Hz.

2. The alkyl protons of the alkoxy groups are also very diagnostic due to the proximity of the chiral center. The two OR′ groups are diastereotopic, and therefore two distinct doublets are observed for the methoxy groups, and two distinct triplets are observed for the ethoxy groups. The difference in chemical shifts of these signals is a function of the diamagnetic anisotropy of R [20].

3. The ^{31}P{^{1}H}NMR spectra of our mono-α-hydroxy-phosphonates show singlets in the region of δ = 20–25 ppm, a value consistent with the presence of the phosphonic acid diester moiety [20] and very much far apart from the value expected for the corresponding phosphates ($\delta \cong 0$ ppm). The ^{31}P NMR spectra were also extremely useful in determining the diastereomeric purity of bis-α-hydroxyphos-

phonates, which, by virtue of possessing two identical chiral centers, can exist as two diastereomeric pairs (*meso* and racemic). In fact, although the ^{1}H NMR spectra of some bis-α-hydroxy phosphonates show only one signal for the methyne protons, which would imply the presence of only one diastereomer formed in the addition reaction, the $^{31}P\{^{1}H\}$NMR spectrum on the contrary reveals indeed the presence of two singlets, indicating that our reaction is not at all stereoselective [31].

On plotting the methyne proton chemical shifts of our *para*-substituted α-hydroxy-phosphonates against Hammett's σ_p values [32], a linear correlation was observed [31]; in particular, electron-withdrawing substituents exert a deshielding effect, and thus the methyne proton signals are moved to lower fields with respect to the unsubstituted cognate. For the same compounds, an opposite trend was noticed looking at the ^{31}P chemical shifts, although a linear correlation still exists when δ values are plotted against the Hammett's σ_p. Such an effect was already noticed also in α-aminophosphonates [33].

The characterization of our synthesized compounds was also performed by FABMS techniques. The main and general conclusions are as follows: The quasi-molecular peak at $m/z = [M + H]^+$ was always observed, and generally it represents the base peak of our spectrum. Other intense signals always present were the peak at $m/z = [M + H - 18]^+$ generated by a loss of a water molecule; and peaks due to the loss of one molecule of $HP(O)(OC_2H_5)_2$ for the diethyl esters or one molecule of $HP(O)(OCH_3)_2$ for the dimethyl esters, that is, fragments at $m/z = [M + H - 138]^+$ and $m/z = [M + H - 110]^+$, respectively. In all MS spectra, peaks due to the ion at m/z $[M + 23]^+$ were also observed, which indicates that our phosphonates possess a great tendency to interact with the Na^+ cation. More interestingly, cluster peaks due to the ions at m/z $[xM+H]^+$, where x varies between 2 and 5, were always observed, and their intensities are quite remarkable, indicating how easily such molecules yield cluster structures, also in the gas phase, as already observed for other similar compounds [20].

Considering that the absolute configuration in the α-position of substituted phosphonic acids has been shown to be important for biological activity [1a], we performed direct separation of a series of 17 α-hydroxybenzylphosphonate diethyl esters by chiral HPLC on Whelk-O 1 phase, which was proven to be the most effective in comparison with the other two CSPs (α-Burke and Chiralpak AD) [34].

Substituent effects on the enantioselectivity were studied and a chiral recognition model between the Whelk-O 1 phase and the α-hydroxyphosphonates was proposed. The good enantioselectivity and resolution factor allowed us to separate and recover for the first time a few milligrams of the single enantiomers of *para*- and *ortho*-arylsubstituted α-hydroxybenzylphosphonates. An increase of the π-basicity of the aryl group enhances the enantioselectivity: the latter is greater for *para*-substituted compounds with respect to their *ortho*-isomers, and in particular, for *para*-halogen substituted α-hydroxy-phosphonates [34].

The circular dichroism (CD) spectra of the isolated enantiomers were obtained allowing us to establish their absolute configuration and to ascertain, quickly and accurately, the enantiomeric purity of α-hydroxyphosphonates obtained by asymmetric synthesis or enzymatic resolution and without any derivatization into diastereomers as Mosher's esters. In the pharmacological applications, they can offer a method to follow the metabolic pathway of more complex racemic α-hydroxyphosphonate esters used as antiviral prodrugs, since the Whelk-O 1 phase is a rugged material that can be used with a large variety of mobile phases, including aqueous ones.

MACROCYCLES CONTAINING PHOSPHONIC UNITS

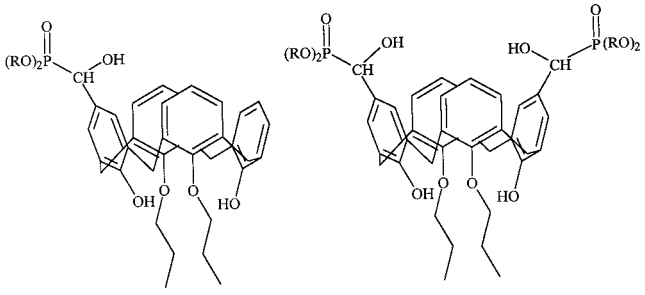
The selective recognition of biologically relevant molecules by synthetic receptors is a very fertile and interesting field in supramolecular chemistry. In particular, high emphasis is devoted to the synthesis of conformationally preorganized building blocks from which hosts with desired properties can be prepared by appropriate and selective functionalization reactions.

On the basis that calixarenes-phenol cyclic oligomers [35] are considered to be a versatile class of macrocyclic hosts because of their remarkable ability to form inclusion compounds [36], we describe herein the synthesis and the stereochemical peculiarity of some calix[4]arenes possessing one or two fragments of α-amino- and α-hydroxy-phosphonic acid diethyl esters [37].

By reacting 5-monoformyl- and 5,17-diformyl-25,27-dipropoxycalix[4]arenes in 1,4-dioxan (or THF) with trimethyl, triethyl, or triisopropyl phosphites in the presence of dry gaseous hydrogen chloride at temperatures of -5 to $+20°C$, calixarenes containing one or two diametrically opposite dialkoxyphosphonylmethylol groups at the upper rim, were synthesized in high yields [37] (compounds **X** and **XI**, Chart 2).

The formyl calixarenes were transformed into monoimino- and diimino-calixarenes obtained by

prolonged boiling with *para*-toluidine in *meta*-xylene solutions in the presence of molecular sieves.

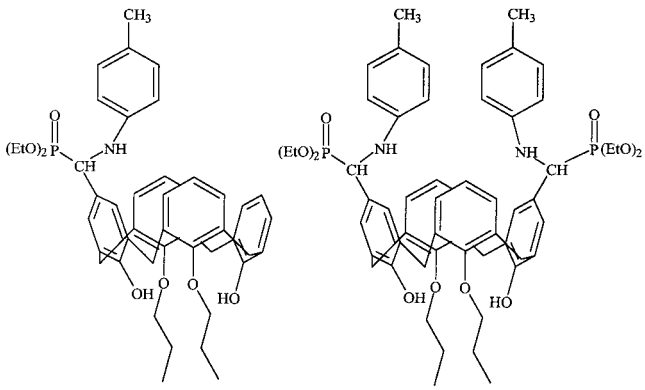


X a-c **XI** a-c

R = CH_3 (a); C_2H_5 (b); *i*- C_3H_7 (c)

CHART 1

Early attempts to use the classical conditions of the Pudovik reaction for the phosphorylation of iminocalixarenes were unsuccessful. In fact, due to the low acidity of diethyl phosphite, the catalytic quantity of Na is bound by the more acidic phenolic OH groups of calixarenes and thus is not available for the nucleophilic addition process. This problem was solved by using a large quantity of sodium sufficient both for the substitution of the phenolic protons of the calixarenes and for the phosphite activation. Under these conditions, the addition reaction leads to good yields of mono- and bis-diethoxyphosphonyl-*N*-*para*-tolylaminomethyl-25,27-dipropoxy-calix-[4] arenes [37] (**XII** and **XIII**).



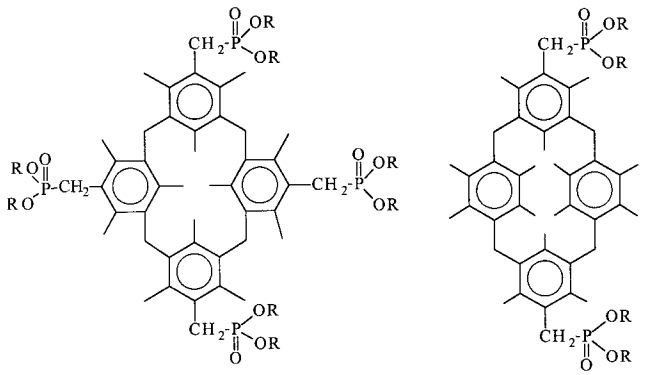
XII **XIII**

CHART 2

α-Hydroxy- and α-amino-phosphonylmethyl derivatives of calixarenes are white solids easily soluble in the majority of organic solvents and insoluble in hexane and water. Upper rim disubstituted calixarenes possessing C_{2v} symmetry show one pair of doublets at δ = 3.40 and 4.30 ppm with a characteristic coupling constant $^2J_{HH}$ of 13 Hz. The spectra of monosubstituted compounds possessing C_{1v} symmetry are more complicated. In this case two pairs of doublets of nonequivalent CH_2 protons with similar chemical shifts and the spin-spin interaction constants are present [37].

The remarkable peculiarity of bis-hydroxyphosphonates and bis-aminophosphonates is due to the presence of two constitutionally identical chiral carbon atoms of methylol or aminomethyl groups at the upper rim of the macrocycle. Thus, after addition of the phosphoryl groups, D,L-racemic and (or) the *meso*-form could be obtained. The presence of only one set of signals in the ^{1}H and ^{31}P NMR spectra of bis-aminophosphonates confirms once again that the addition of diethyl phosphite to C=N bonds is stereospecific with the preponderant formation of one diastereomer [20]. In contrast, to bis-aminophosphonates, two set of signals are observed in the ^{1}H NMR spectra of bis-hydroxyphosphonates. The most characteristic ones are the doubling of the PCH signals, which differ not only by chemical shifts, but also by the spin-spin proton-phosphorus coupling constants and the intensity-ratio change from 35:65 to 65:35 as a function of the size of the alkyl groups at the phosphorus atom. This fact is consistent with the formation of a stereoisomeric mixture of racemic and *meso*-forms in the phosphorylation process.

The second peculiarity of bis-hydroxyphosphonates is the ability to form dimeric structures possessing a ten-membered cyclic architecture due to CH–OH···O=P hydrogen bonds at the upper rim of the macrocycle. These dimeric structures are confirmed by ^{1}H NMR investigations, by FABMS spectra, and by IR spectra in CCl_4 solutions [37].



XIV a-c

a : R = Me
b : R = Et
c : R = *i*-Pr

XV a-c

CHART 3

Macrocycles closely related to calix[4]arenes, that is, tetrameric metacyclophanes possessing four aromatic units connected by methylene bridges are eas-

ily prepared by Friedel-Crafts reactions. Therefore, we functionalized some of such macrocycles by use of the insertion of pendant methylene phosphonic acid dialkyl ester groups, by the Arbuzov reaction starting from the chloromethyl derivatives [38,39]. This was affected in order to make use of robust macrocycles **XIV** and **XV** (Chart 3) that are able to complex cations, and, in particular, lanthanides, useful as luminescent sensors and for diagnostic bioassays [8,9,40] in powerful screening techniques such as magnetic resonance imaging (MRI) and in proton emission computed assisted tomography (SPECT). Macrocycles **XIV** and **XV** were fully characterized by NMR and by FABMS spectroscopy, and their stereochemistry was investigated in solution and also in the solid state for compound **XIVb** [38,39]. The NMR data are consistent with a 1,3-alternated saddle-shaped geometry, and the inner methyl groups are very much upfield shifted by the aromatic ring current effect. Because of this geometry, the methylene phosphonic units are alternatively up and down the cage in strategic positions for complexing with neutral guests.

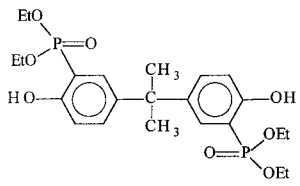
Due to the skeleton symmetry, the bridging methylene protons appear as a sharp singlet in **XIV** and as two doublets in **XV;** the methylene groups attached to the phosphonic groups appear as a sharp doublet due to the coupling with phosphorus ($^2J_{HP}$ = 21.5 Hz), whereas the methyl or methylene protons of the alkyl groups R are diastereotopic when R is *i*-Pr or Et and enantiotopic for R = Me.

A further point of interest in our phosphorylated macrocycles is their tendency to generate clathrate inclusion compounds with small organic molecules in their solid state, a property that may render these compounds also of relevant interest as receptors towards hydrophobic guests, or as water-soluble macrocyclic hosts once the phosphonic group is hydrolized to the corresponding monoester or to the free acid, with pH-dependent binding properties. Rewarding enough, macrocycle **XIVb** was found to form an inclusion compound with cyclohexane, whose stoichiometry, determined both by ^{1}H NMR integration and by X-ray diffraction techniques, was found in the molar ratio 1:2 (macrocycle over guest). The compound **XIVb** was found by ^{1}H NMR spectroscopy to crystallize with some water, and such a finding is very relevant to the molecular architecture of our host. Once again, this finding reveals that the 1,3-alternate conformation of fully aromatic tetrameric macrocycles is very appropriate in order to form a clathrate and can act as molecular receptors.

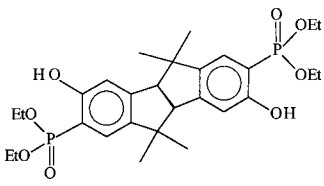
The crystal structure of **XIVb** $\cdot 2C_6H_{12} \cdot H_2O$ has been determined by X-ray analysis at -50°C. The calixarene molecule lies around a twofold rotation axis of the space group, parallel [100], through one pair of opposite methylene C atoms in the inner macrocycle. From the latter, the arene systems are protruding alternately up and down, with the dihedral angle between the two across from each other at 34.8(2)°.

A molecule of water, also present in the crystal structure, is situated on the same type of symmetry axis as the calixarene. The two molecules are consecutively hydrogen-bonded to each other in a one-dimensional array along [010]. The cyclohexane molecule incorporated into the crystal structure, does not appear as a molecular inclusion compound, but rather as a lattice clathrate. Specifically, and as an unusual feature, the cyclohexane molecules are arranged in a tetrahedron-like cluster of four around a 222-D_2 position of the space group at 1/4, 3/4, 1/2 (and 3/4, 1/4, 1/2) [38].

By condensing 2,2-bis(3-diethylphosphono-4-hydroxyphenyl)propane (**XVI**) or the phosphonate spirobisindane monomer (**XVII**) with 1,3- or 1,4-alkanediylarylhalides through the Williamson procedure, we obtained a large variety of macrocycles conformationally mobile or stereochemically rigid, according to the dimension of their cavity [41,42].



XVI

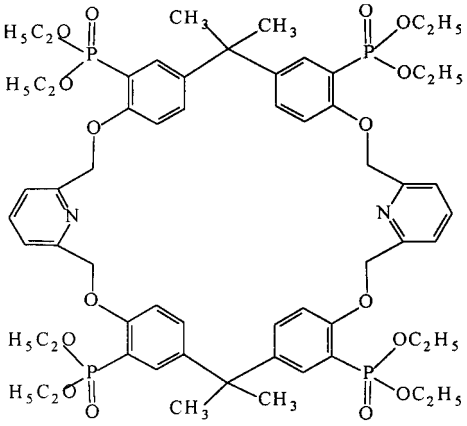


XVII

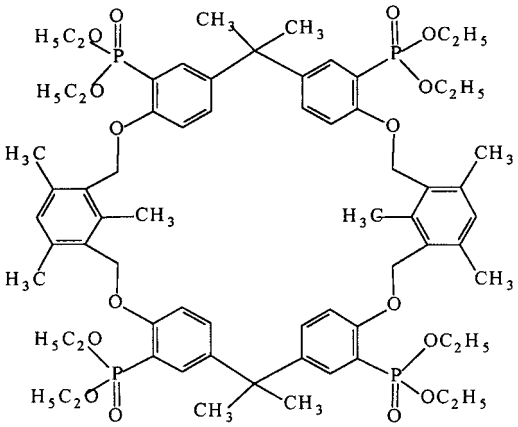
Compound **XVI,** much more mobile than **XVII,** gave as the main product of the cyclization process the [2 + 2] macrocycles **XVIII, XIX,** and **XX,** accompanied by small amount of their higher cyclic oligomers.

The 500 MHz ^{1}H NMR spectrum of macrocycle XVIII at room temperature in $CDCl_3$ solution shows a triplet and a multiplet for the ethoxy groups linked to the phosphorus atoms, a sharp singlet for the methyl group attached to the bridgehead quaternary carbons, a single sharp peak for the benzylic protons linked to the pyridine nuclei and the expected multiplicity for the aromatic hydrogens. This pattern, coupled with the ^{13}C and ^{31}P NMR spectra, clearly indicates a great mobility for macrocycle **XVIII,** which interconverts itself in solution among various possible conformations. Also for macrocycles **XIX** and **XX** ^{1}H, ^{13}C, and ^{31}P NMR spectra can be inter-

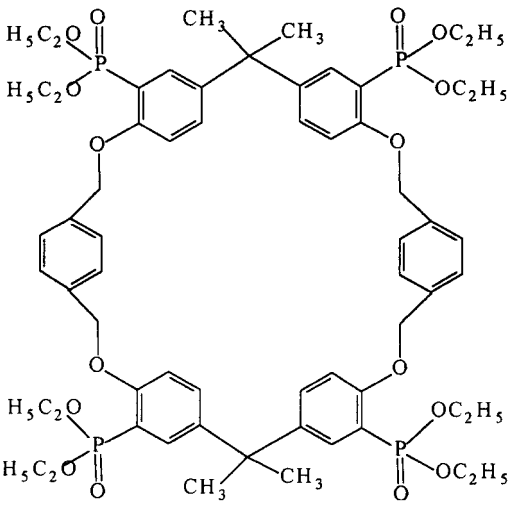
preted in terms of high conformational mobility occurring in solution at room temperature [41].



XVIII



XIX

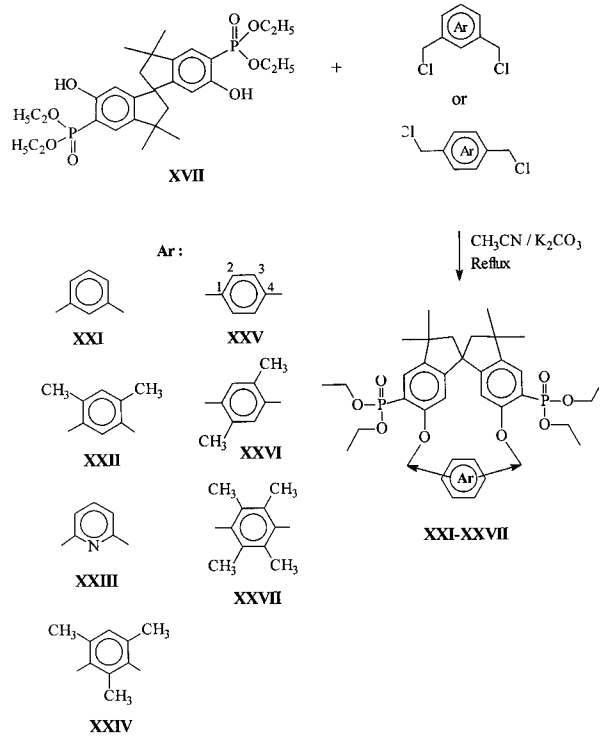


XX

Interesting enough, crystals of **XVIII,** obtained from a cyclohexane/ethyl acetate solution show, in the NMR spectrum, the presence of the saturated hydrocarbon included in a molar ratio 1:1. The structure of **XVIII** included with one molecule of cyclohexane was unequivocally established by a single-crystal X-ray diffraction study. For the most part, bond distances and angles are normal and gave values consistent with other comparable structures. Final refinements confirmed that there is considerable static disorder in molecules of XVIII in that the pendant ethoxy groups of the phosphite moieties have different conformations. The guest cyclohexane molecule fits nicely into the hydrophobic cavity of the cycle **XVIII** host molecule with intermolecular distances which are all less than the van der Waals distances expected, that is, there are no strong intermolecular interactions, only rather weak nonpolar-nonpolar interactions [41].

Contrary to **XVIII,** macrocycles **XIX** and **XX,** which lack the polarity of the pyridine nitrogens, are not able to form inclusion complexes, at least not with the large number of organic solvents that have been tried so far (benzene, toluene, ethyl acetate, cyclohexane). This different behavior can also be ascribed to the *para*-substituted spacer molecules that are not preorganized and thus give more flexibility to the macrocycles.

The Williamson synthetic procedure using the stereochemically constrained monomer **XVII** as condensing agent produced in high yield the [1 + 1] rigid cyclophanes as depicted in Scheme 3.



SCHEME 3

Full characterization in solution of all cyclophanes was performed by proton, carbon, and phosphorus NMR spectroscopy. By NMR analyses, it was shown that **XXI–XXIII** show mobility of the aryl rings, which by π-radians rotation, average the benzylic bridging protons as well as the spirobisindane phosphonic groups [42].

On the contrary, macrocycle **XXIV,** as well as those obtained by condensing the dihydroxy monomer with 1,4-bis-chloromethyl aryl derivatives, that is, compounds **XXV–XXVII**, are all stereochemically rigid on the NMR timescale. In particular, for **XXIV,** restricted rotation of the 1,3 bridged-mesityl ring renders the molecule asymmetric, as evidenced by the fact that all nuclei are chemically and magnetically different, and this is confirmed by ^{1}H, ^{13}C, and ^{31}P NMR observations. Compounds **XXV–XXVII** have a dissymetric structure (point group symmetry C_2), and for all of them, kinetic restricted rotation of the 1,4-bridged aryl ring was observed, as evidenced by the presence of two sets of signals for the nuclei in positions 2 and 3 [42].

The stereochemical pattern in our macrocycles is quite intriguing due to the presence in the same molecule of a C_2-symmetrical spirobisindane unit (which is in itself chiral) and of a xylylene bridging moiety that could impart a planar chirality. It follows that choosing the appropriate unit (that is, the 2,5-disubstituted 1,4-xylylene bridge) under conditions of restricted rotation of this unit, only two different distereomers are possible for macrocycle **XXVI.** In our synthesis, however, only a single diastereomer was isolated with a sharp melting point, which showed only one set of signals for all the diastereotopic nuclei; this indicated a high stereospecificity of such a cyclization reaction [42].

With the aim of elucidating the preferred geometry in the solid state, we undertook an X-ray structure of macrocycles **XXIV,** complexed with two moles of cyclohexane, and also of **XXVI.**

Host **XXIV** is asymmetric (C_1) and the inner mesityl methyl group is pointing inside the cavity under the shielding cone of the spirobisindane aromatic ring. By measuring interatomic distances, we could have an idea of the internal cavity of host **XXIV,** and we found that the cavity is large but not large enough to include small organic solvent molecules such as cyclohexane. This explains why the two molecules of cyclohexane, enclathrated by host **XXIV,** are present in the lattice, exterior to **XXIV** [42].

The X-ray structure of the isolated diastereomer of **XXVI** reveals that the structure is consistent with that deduced by NMR observations in solution and that the *p*-xylyl aryl methyl groups are pointing out of the cavity and are close to the hydrogens of the spirobisindane moiety ortho to the oxygen bridging atom [42].

On consideration of the fact that the spirobisindane phosphonate monomer **XVII** is a preorganized dissymetric molecule that exists as a pair of enantiomers, this compound can be used as a chiral template for building chiral polycondensates or inducing chirality in replicant strands. Having in mind the idea that the resulting macrocycles, as pure enantiomers, could be of interest also for chiral recognition and for chiral discriminations, we performed HPLC separations using chiral columns.

All macrocycles which are stereochemically rigid, namely, compounds **XXIV–XXVII,** are well separated into their enantiomers, and, in some cases it was possible to collect them in order to measure their CD spectra. The CD spectrum of monomer **XVII** showed remarkable Cotton effects (CE). In fact the CD split shows a positive CE ($\Delta\varepsilon$ +60 at 215 nm, $\Delta\varepsilon$ −78 at 205 nm) for the less retained enantiomer. A negative CE is observed for the most retained enantiomer. A similar behavior can be envisaged for compound **XXIV,** although the CD splitting cannot be observed due to the shorter wavelengths of the CD bands [42].

CONCLUSIONS

From this concise review, we can conclude that the syntheses of variously substituted α-amino- and α-hydroxy-phosphonic acid dialkyl esters can be easily performed by addition of dialkyl phosphites to the corresponding mono- or bis-imine or to the carbonyl precursors, respectively. Stereospecific addition is observed in the syntheses of bis-aminophosphonates, and all the reviewed compounds can be of interest in agrochemistry, biological screenings, and/or for pharmaceutical applications.

The corresponding mono-esters of the α-aminophosphonic acids are easily obtained by hydrolytic alkaline reactions and show good complexing properties toward transition metals and lanthanides, rendering them very attractive for complexation studies and for potential use in diagnostic medicine.

Macrocyclic hosts containing phosphonic units show a very interesting stereochemistry, and for some of them, their solid state geometry has been established by X-ray diffraction techniques.

REFERENCES

[1] (a) For comprehensive reviews see: Kafarski, P.; Lejczak, B. Phosphorus Sulfur Silicon 1991, 63, 193; (b) Bartlett, P. A.; Marlowe, C. K.; Giannousis, P. P.; Han-

son, J. E. Cold Spring Harbor Symp Quant Biol 1987, LII, 83; (c) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. J Med Chem 1994, 37, 158; (d) McLeod, D. A.; Brinkworth, R. I.; Asheley, J. A.; Janda, K. D.; Wirshing, P. Bioorg Med Chem Lett 1991, 1, 653.

[2] (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. Nature 1978, 272, 56; (b) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Ringrose, P. S. Antimicrob Agents Chemother 1979, 15, 677; (c) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. Antimicrob Agents Chemother 1979, 15, 684; (d) Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Lloyd, W. J.; Ringrose, P. S. Antimicrob Agents Chemother 1979, 15, 696.

[3] (a) Maier, L.; Diel, P. J. Phosphorus Sulfur Silicon 1994, 90, 259; (b) Maier, L.; Diel, P. J. Phosphorus Sulfur Silicon 1991, 57, 57.

[4] Natchev, I. A. Liebigs Ann Chem 1988, 861.

[5] (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Haga, S.; Sugi, H.; Tanigawa, K.; Suzuki, Y.; Fukawa, K.; Irino, O.; Saita, O.; Yamabe, S. Heterocycles 1981, 16, 1205; (b) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. J Chem Soc Perkin Trans I 1984, 2845; (c) Lejczak, B.; Kafarski, P.; Sztajer, H.; Mastalerz, P. J Med Chem 1986, 29, 2212; (e) Okada, Y.; Iguchi, S.; Mimura, M.; Yagyu, M. Chem Pharm Bull 1980, 28, 1320.

[6] Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A.; Cudennec, C. A.; Pierré, A. J Med Chem 1991, 34, 1998.

[7] Jagovic, V.; Herak, M. J. J Inorg Nucl Chem 1970, 32, 1323.

[8] Bligh, S. W. A.; Choi, N.; Green, D. S. T. C.; Hudson, H. R.; Mc Grath, C. M.; Mc Pianka, M. Polyhedron 1993, 12, 2887, and references therein.

[9] (a) Bulman, R. A. In Trace Metals and Fluoride in Bones and Teeth, Priest, N. O., van de Vyver, F. L. Eds., CRC Press: Boca Raton, FL, 1990; p. 271; (b) Engel, R. Chem Rev 1977, 77, 349.

[10] Ruzic-Toros, Z.; Kojic-Prodic, B.; Sljukic, M. Acta Cryst 1978, B, 34, 3110.

[11] Belsky, V. K.; Finocchiaro, P. Unpublished results. 1992, Moscow.

[12] Atherton, F. R.; Hassall, C. H.; Lambert, R. W. J Med Chem 1986, 29, 29.

[13] Caccamese, S.; Failla, S.; Finocchiaro, P.; Hägele, G.; Principato, G. J Chem Research (S) 1992, 242.

[14] Caccamese, S.; Principato, G.; Gruss, U.; Hägele, G.; Failla, S. Tetrahedron Asym 1994, 5, 141.

[15] Failla, S.; Finocchiaro, P.; Latronico, M.; Libertini, M. Phosphorus Sulfur Silicon 1994, 88, 185.

[16] Bligh, S. W. A.; Choi, N.; Failla, S.; Finocchiaro, P.; Il'Yasov, A.; Libertini, M.; Mc Graft, C. M.; McPartlin, M.; Woodroffe, T. M. J Chem Soc Dalton Trans 1994, 3333.

[17] Failla, S.; Finocchiaro, P. Phosphorus Sulfur Silicon 1995, 101, 261.

[18] Failla, S.; Finocchiaro, P. Phosphorus Sulfur Silicon 1995, 105, 195.

[19] Choi, N.; Failla, S.; Finocchiaro, P.; McPartlin, M.; Scowen, I. J. J Chem Res (S) 1994, 340.

[20] Failla, S.; Finocchiaro, P.; Hägele, G.; Rapisardi, R. Phosphorus Sulfur Silicon 1993, 82, 79.

[21] Failla, S.; Finocchiaro, P.; Belsky, V. K.; Zavodnik, V. E.; Sobolev, A. N. Phosphorus Sulfur Silicon 1993, 80, 75.

[22] Dronia, H.; Failla, S.; Finocchiaro, P.; Hägele, G. J Mol Struct (Theochem) 1995, 334, 179.

[23] Failla, S.; Finocchiaro , P. Phosphorus Sulfur Silicon 1993, 85, 65.

[24] Brienne, M. J.; Jacques, J.; Brianso, M. C.; Surcouf, E. Nouv J Chim 1978, 2, 19.

[25] Abramov, V. S. Zh Obhsch Khim 1952, 22, 647; Chem Abstr 1953, 47, 5351.

[26] (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. Tetrahedron Lett 1990, 31, 5587; (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. Tetrahedron Lett 1990, 31, 5591.

[27] (a) Sikorski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Font, J. L.; Gruys, K. J.; Han, C. Y.; Lin, K. C.; Pansegrau, P. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. Phosphorus Sulfur Silicon 1993, 76, 115; (b) Peterson, M. L.; Corey, S. D.; Sikorski, J. A.; Walker, M. C.; Abstracts of Papers, 203rd American Chemical Society National Meeting, San Francisco, ORGN 469, 1992.

[28] Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. Tetrahedron Lett 1992, 6625; Moore M. L.; Dreyer, G. B. Perspective Drug Discovery Design, (1993), I, 85.

[29] Mikroyannidis, J. A. Phosphorus and Sulfur 1984, 20, 323.

[30] Mikroyannidis, J. A. J Polym Sci 1988, A26, 885.

[31] Consiglio, G.; Failla, S.; Finocchiaro, P. Phosphorus Sulfur Silicon 1996, 117, 37.

[32] Chapman, N. B.; Shorter, J. Advance in Linear Free Energy Relationships; Plenum Press: London, 1972.

[33] Smith, S. J.; Zimmer, H.; Fluck, E.; Fisher, P. Phosphorus Sulfur Silicon 1988, 35, 105.

[34] Caccamese, S.; Failla, S.; Finocchiaro, P.; Principato, G. Chirality 1998, 10, 100.

[35] Gutsche, C. D. Calixarenes; The Royal Society of Chemistry: Cambridge, 1989.

[36] Bohmer, V. J., (Ed.) Calixarenes: A Versatile Class of Macrocyclic Compounds; Kluver Academic Publishers; Dordrecht, 1991.

[37] Markovsky, L. N.; Kalchenko, V. I.; Solovyov, A. V.; Finocchiaro, P.; Failla, S.; Atamas, L. I.; Consiglio, G.; Tsymbal, I. F. Anales de Quimica Int Ed 1998, 94, 164.

[38] Consiglio, G.; Finocchiaro, P.; Failla, S.; Albert, A.; Mootz, D. Phosphorus Sulfur Silicon 1999, 149, 29.

[39] Consiglio, G. A.; Failla, S.; Finocchiaro, P. Mendeleev Commun 1999, 90.

[40] Aime, S.; Batsanov, A. S.; Botta, M.; Dickins, R. S.; Faulkner, S.; Foster, C. E.; Harrison, A.; Howard, J. A. K.; Moloney, J. M.; Norman, T. J.; Parker, D.; Royle, L.; Williams, J. A. G. J Chem Soc Dalton Trans 1997, 3623.

[41] Consiglio, G. A.; Failla, S.; Finocchiaro, P.; Visi, M.; Hardcastle, K. Supramolecular Chemistry 2000, 11, 177.

[42] Consiglio, G. A.; Finocchiaro, P.; Failla, S.; Hardcastle, K. I.; Ross, C.; Caccamese, S.; Giudice, G. Eur J Org Chem 1999, 2799.