New (α-Hydroxyalkyl)phosphorus Amphiphiles: Synthesis and Dissociation Constants

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Direct synthesis of free (α-hydroxyalkyl)phosphinic acid amphiphiles **1** can be readily realized by sonication of the heterogeneous mixture of 50% aqueous hypophosphorous acid and long-chain aldehydes in the presence of catalytic amounts of hydrochloric acid. Oxidation of these phosphinic acids by DMSO in the presence of catalytic amounts of iodine quantitatively leads to the corresponding phosphonic acids **3**. IR spectra of the phosphinic acids **1** in the condensed phase and in solution reveal the presence of intra- and intermolecular associations. Dissociation constants of the phosphorus acids **1** and **3** determined by potentiometric and ^{31}P NMR titrations show a good correlation between the two methods. The phosphinic acid amphiphiles **1** are slightly stronger than the corresponding phosphonic acids **3**. (α-Hydroxyalkyl)phosphonium chlorides are prepared in good yields from the phosphine PH_3 and long-chain aldehydes in acidic media.

Introduction

In recent years, the preparation of α-hydroxyphosphoryl derivatives (phosphonic and phosphinic acids, esters and salts) has attracted significant attention, due to their potential biological activities with broad applications as enzyme inhibitors (renin,[1] EPSP synthase,[2] HIV protease,[3] and PTPase[4]) or as dinucleotide analogues having antiviral properties.[5] In addition, they are useful intermediates in the synthesis of other α- and γ-substituted phosphorus compounds.[6] Their usefulness is also well-known as extractants in the recovery and separation of some metal ions.[7] Furthermore, the (α-hydroxyalkyl)-phosphorus substrates (phosphines, phosphine oxides, and phosphonium salts) can be considered as starting materials for the synthesis of organophosphorus polymers possessing flame-resistant and ion-exchange properties and resins for the production of corrosion-resistant films on metal surfaces.[7]

Known preparations of (α-hydroxyalkyl)phosphorus acids included the Pudovik addition reactions of dialkyl-H-phosphonates, phosphites, or phosphines to carbonyl compounds under base-catalyzed[8−13] or under anhydrous strong acidic conditions are reported.[14,15] More recently, the synthesis of α-hydroxy phosphonates by the combinatorial method on the Wang resin has been described.[16]

Our previous works are focused on the study of the reactivity of amorphous red phosphorus.[17,18] Recently, we have demonstrated that red phosphorus can react with aromatic and α,β-ethylenic aldehydes in basic media via the phosphine, PH_3, and in acidic media via hypophosphorous acid, H_3PO_2, leading to (α-hydroxyalkyl)-phosphinic acids (Scheme 1).[19]

Pursuing our investigation into the reactivity of the P−H labile phosphorus derivatives,[20] and in view to the preparation of (α-hydroxyalkyl)phosphorus acid amphiphiles, we wish to report here the reactivity of

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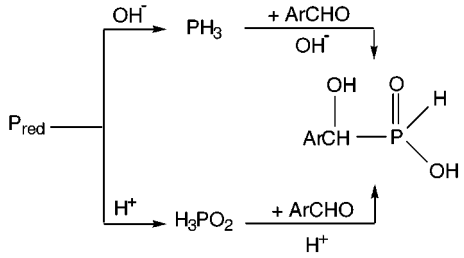
Scheme 1



hypophosphorous acid and phosphine, PH_3, toward long-chain aldehydes in acidic media. To the best of our knowledge, no (α-hydroxyalkyl)phosphinic acid amphiphiles have been already described. Furthermore, the presence of hydrophobic substituents must widen their application fields by enhancing their coordinating and biological properties since the hydrophilic and the hydrophobic groups coexist in the molecule.[21,22]

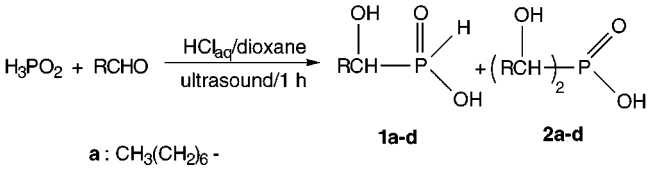
Results and Discussion

Synthesis of (α-Hydroxyalkyl)phosphinic Acid Amphiphiles. The addition reaction of hypophosphorous acid to carbonyl compounds has already been described.[23] It often requires crystalline hypophosphorous acid, and it occurs upon prolonged heating under acid catalysis, affording the mono- and bis(α-hydroxyalkyl)phosphinic acids.[23]

We have optimized the reaction conditions of hypophosphorous acid with a series of aliphatic aldehydes bearing C_8-C_{14} fatty chains by use of commercially available 50 wt % aqueous hypophosphorous acid and catalytic amounts of hydrochloric acid under ultrasonic irradiation. Actually, the efficiency of ultrasound is well-known in the case of heterogeneous reactions,[20,24] and this technique allows one to reduce the reaction time to 1 h with respect to classical heating (2−4 h at 80 °C) (Scheme 2).

Indeed, the reaction of 50 wt % aqueous hypophosphorous acid with 1.2 equiv of aldehyde in the presence of 0.2−0.5 equiv of hydrochloric acid in dioxane under sonication for 1 h affords the mono(α-hydroxyalkyl)-phosphinic acids **1** as the main product (60−85%), accompanied by the corresponding bis-adducts **2** (3−7%) as side products. The use of an excess of hypophosphorous acid (3 equiv) allows one to avoid the formation of the bis-adduct **2**. The (α-hydroxyalkyl)phosphinic acids **1** are easily purified and obtained in good yields (Table 1).

Scheme 2



a : $CH_3(CH_2)_6$ -
b : $CH_3(CH_2)_8$ -
c : $CH_3(CH_2)_{10}$ -
d : $CH_3(CH_2)_{12}$ -

Table 1. Yields and NMR Parameters of (α-Hydroxyalkyl)phosphinic Acids 1 and 2

compd no.	R	%[a,b]	$\delta(^{31}P)(^1J_{PH})$[c,d]	$\delta(^{13}C)$ $(^1J_{CP})$[d]	$\delta(^1H)$[d]
1a	$CH_3(CH_2)_6$	60[a] / 51[b]	34.6 (548)[c] / 31.5 (516)[d]	68.2 (111)	3.48
2a		7[a]	49.7; 48.5[c]		
1b	$CH_3(CH_2)_8$	80[a] / 76[b]	35.0 (546)[c] / 32.8 (516)[d]	69.0 (112)	3.02
2b		5[a]	49.1; 47.6[c]		
1c	$CH_3(CH_2)_{10}$	85[a] / 75[b]	35.0 (543)[c] / 32.9 (517)[d]	67.7 (113)	3.48
2c		5[a]	48.5; 47.0[c]		
1d	$CH_3(CH_2)_{12}$	70[a] / 62[b]	34.2 (532)[c] / 32.9 (517)[d]	68.2 (112)	3.45
2d		3[a]	48.7; 47.2[c]		

[a] Initial yields of **1** and **2** determined by ^{31}P NMR analysis of the crude reaction mixture. [b] Isolated yields of **1**. [c] ^{31}P NMR spectra of the crude mixture; *J* in Hz. [d] ^{31}P, ^{13}C, and ^1H NMR data for the methyne groups of isolated products in DMSO-d_6.

For the mono(α-hydroxyalkyl)phosphinic acids **1**, two diastereomers are expected due to the presence of two asymmetric centers: (1) the carbon bonded to the phosphorus atom and (2) the phosphorus atom bearing four different substituents. However, the later loses its asymmetric character due to the rapid prototropic transfer of the acidic proton between the phosphoryl (P═O) and the acidic (P−OH) sites.[25] The ^{31}P NMR spectra of **1** are characterized by chemical shifts about 32 ppm (single signal for $^{31}P\{^1H\}$ NMR spectra) and a coupling constant $^1J_{PH}$ about 516 Hz. The chemical shift of the carbon atom in the α position of phosphorus ($\delta(^{13}C) \sim 68$) and its coupling constant with the phosphorus atom ($^1J_{CP} \sim 112$ Hz) are consistent with the presence of an (α-hydroxyalkyl)phosphinic moiety. The methyne proton resonates in most cases as a multiplet about 3.5 ppm.

The bis(α-hydroxyalkyl)phosphinic acids **2** obtained as byproducts are only characterized by ^{31}P NMR spectroscopy of the reaction mixture. They exist in three diastereomeric forms (two meso and one racemic form), depending on the chirality of the two carbon atoms bonded to the phosphorus atom, which is itself a pseudo-asymmetric center.[8d,25] However, as in the case of monosubstituted acids **1**, the ^{31}P NMR spectra of **2** exhibit degeneracies due to the rapid prototropic transfer of the acidic proton, and only two signals are observed with a diastereomeric ratio 2:1, as revealed by means of ^{31}P NMR spectroscopy.[8d,25]

Hydrogen Bonding in (α-Hydroxyalkyl)phosphinic Acids. The (α-hydroxyalkyl)phosphinic acids are eminently suited to intra- and intermolecular hydrogen bonding leading to cyclic dimers.[26,27] We have studied

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Table 2. IR Spectroscopic Data for (α-Hydroxyalkyl)phosphinic Acids 1c,e

		ν_{OH} (cm^{-1})			$\nu_{P=O}$ (cm^{-1})		ν_{P-H} (cm^{-1})	
compd no.	conditions	monomer	intra	inter	monomer	inter	monomer	inter
1c	KBr		3395	3303		1089	2450	2365
	$CDCl_3$			3334		1180	2382	
	DMF (0.1 M)	3548	3466	3303	1218	1174	2348	2339
	DMF (0.01 M)	3550	3484	3310	1218	1170	2348	2339
1e	KBr		3420	3237		1192	2442	2252
	$CDCl_3$		3415	3357	1197	1176	2385	
	DMF (0.1 M)	3549	3480	3302	1237	1178	2353	2340
	DMF (0.01 M)	3549	3490	3311	1237	1178	2353	2340

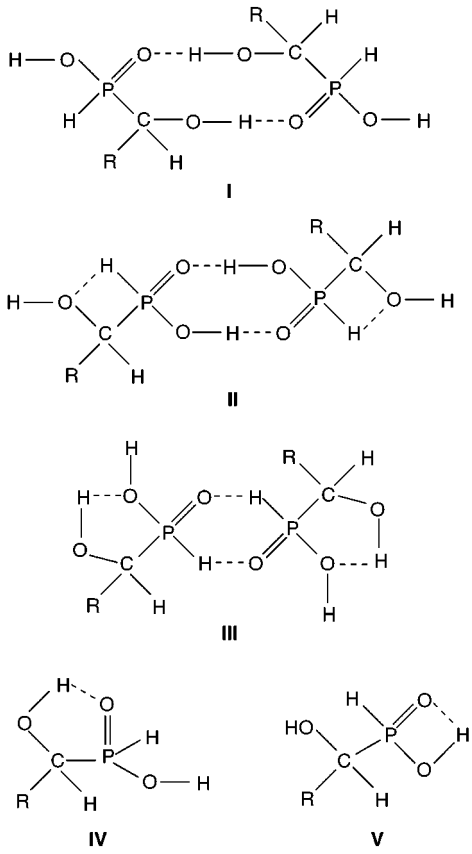
the IR spectra of (α-hydroxydodecyl)- and (α-hydroxybenzyl)phosphinic acids, **1c**,**e**, respectively, in the condensed phase (KBr) and in solution ($CDCl_3$ and DMF), to determine the nature of these intra- and intermolecular associations and to observe a possible influence of the long-chain upon their self-association. The H-bond vibration frequencies observed concern the hydroxyl (ν_{OH}), the phosphoryl ($\nu_{P=O}$), and the P−H (ν_{PH}) regions (Table 2).

The hydroxyl absorption of the condensed phase for the two acids **1** (ν_{OH} *assoc*) is represented by two broad intense bands in the range 3237−3303 and 3395−3420 cm^{-1}. As the substances are diluted with $CDCl_3$ or DMF (due to the insolubility of **1c** in $CDCl_3$), the intensity of the band at 3303 cm^{-1} decreases as a function of concentration in favor of band at 3550 cm^{-1}. This permits an assignment of the absorption ν_{OH} *inter* to the former band and the ν_{OH} *monomer* to the later. At a concentration of 0.01 M, ν_{OH} *inter* remains in the form of a weak band (3310 cm^{-1}), with ν_{OH} *monomer* as a strong band (3550 cm^{-1}) with concomitant appearance of a band at 3484 cm^{-1} whose intensity remains unchanged as a function of concentration. We can attribute this band to the absorption ν_{OH} *intra*. However, in this case H-bonding with the solvent cannot be excluded. The phosphoryl absorption bond at ~1190 cm^{-1} ($\nu_{P=O}$ *inter*) in the condensed phase undergoes at dilute solution a splitting into two bands at ~1170 cm^{-1} ($\nu_{P=O}$ *inter*) and ~1218 cm^{-1} ($\nu_{P=O}$ *monomer*) for **1c**, confirming the participation of the P═O bond in the association processes. We observe the same variations that above for the P−H absorption bands. However, the nature of these associations is complex owing to the presence of the phosphoryl (P═O), acidic hydroxyl (P−OH), α-hydroxyl (C−OH), and P−H groups (Scheme 3).

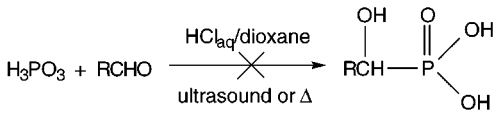
In conclusion, associated molecules of (α-hydroxyalkyl)-phosphinic acids in the condensed phase and in solution exist in the form of cyclic dimers with intermolecular hydrogen bonds. They exist in various forms of free monomer molecules in dilute solutions and are stabilized by intramolecular H-bonds. The behavior of the (α-hydroxydodecyl)- and the (α-hydroxybenzyl)phosphinic acids **1c**,**e**, as studied by IR spectroscopy, present no noticeable differences.

Synthesis of (α-Hydroxyalkyl)phosphonic Acid Amphiphiles. The reaction of phosphorous acid with

Scheme 3



Scheme 4



3

imines has been already described. This reaction affords the corresponding (α-aminoalkyl)phosphonic acids under strongly acidic conditions and prolonged heating.[28] To find conditions that would allow the direct synthesis of free (α-hydroxyalkyl)phosphonic acids, we attempted the addition reaction of phosphorous acid to aldehydes under heating or sonication (Scheme 4). Whatever the reaction conditions, all attempts were unsuccessful. The phosphorous acid is much less reactive toward aldehydes than hypophosphorous acid, as already observed for alkenes.[29]

Since the (α-hydroxyalkyl)phosphinic acids **1** can be easily prepared in good yields from hypophosphorous acid

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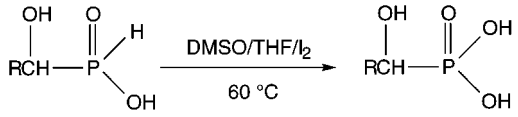
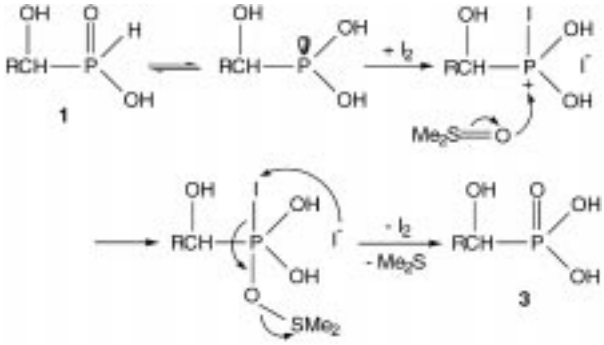
Scheme 5



1a-d **3a-d**

Scheme 6



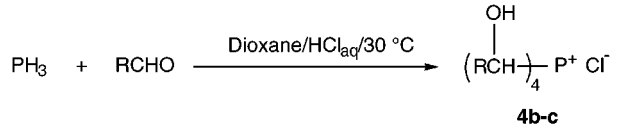
and various long-chain aldehydes, we have undertaken the oxidation of their P−H bond by several methods. The oxidation of phosphinic acid in water in the presence of mercuric oxide has already been described.[23c,d] Our attempts for oxidation of the P−H bond of the acids **1** with 30% aqueous hydrogen peroxide failed. Since the oxidizing power of the sulfoxide group is well-known in the oxidation of trivalent phosphorus compounds[30] or cyclic P−H phosphoranes,[31] we attempted the oxidation of the phosphinic acids **1** in the presence of a stoichiometric amount of DMSO and a catalytic amount of iodine at 60 °C. The reaction time required is 4−5 h (Scheme 5).

The (α-hydroxyalkyl)phosphonic acids **3** are obtained in good yields. The oxidation might proceed by formation of a phosphonium iodide intermediate resulting from the electrophilic attack of iodine to trivalent phosphorous acids **1** (phosphonate−phosphite tautomeric equilibrium),[32] which undergoes the addition of the oxygen atom of DMSO to afford a phosphorane intermediate. The nucleophilic attack of the iodide anion to the later and the departure of methyl sulfide lead to the (α-hydroxyalkyl)phosphonic acids **3** (Scheme 6).

The ^{31}P NMR spectra of **3** are characterized by chemical shifts about 24 ppm. The oxidation of phosphinic acids to phosphonic homologues involves a shielding of the P nucleus ($\Delta\delta(^{31}P) \sim 10$). The chemical shift of the α-carbon ($\delta(^{13}C) \sim 67$) does not undergo a significant variation, but its coupling constant with the phosphorus atom ($^1J_{CP} \sim 160$ Hz) increases about 50 Hz with respect to phosphinic acids **1**.

Synthesis of Tetrakis(α-hydroxyalkyl)phosphonium Salts from Phosphine, PH_3. The phosphonium salts are widely studied and have significant interest due to their numerous applications.[7,33] Examples of formation of (α-hydroxyalkyl)phosphonium salts are considerably rarer. Such compounds have been synthesized from

Scheme 7



4b-c

b : R = $CH_3(CH_2)_8$ -

c : R = $CH_3(CH_2)_{10}$ -

the nucleophilic addition of a phosphine to the carbonyl compounds in the presence of electrophilic trapping agents.[7,33−35] The reactions of phosphine PH_3 with aldehydes yield various products depending on their structure, the catalysts, and the solvent. Thus, with formaldehyde the corresponding phosphonium salt is obtained, whereas with other aldehydes various compounds are formed.[7a,35] The pecularity of these reactions is mostly due to transformations of unstable intermediate products of the condensation of one or two aldehyde molecules with the phosphine.[19,36,37]

The addition of phosphine PH_3, generated by basic hydrolysis of red phosphorus or acidic hydrolysis of zinc phosphide,[17−19] to long-chain aldehydes in acidic media at 30 °C involves the appearance of an insoluble product almost immediately upon the passage of phosphine. The precipitate is collected by filtration and isolated in yields of 54% (**4b**) and 70% (**4c**) (Scheme 7).

Their physical (melting points and elemental analyses) and spectroscopic (^{31}P, ^{1}H, ^{13}C NMR, mass, and infrared spectra) data are consistent with the tetrakis(α-hydroxyalkyl)phosphonium chlorides. The phosphonium salt **4c** has already been described and characterized by its melting point and elemental analysis,[38] but no spectroscopic data have been reported.

The tetrakis(α-hydroxyalkyl)phosphonium chlorides **4b**−**c** contain four asymmetric carbon atoms, so they must be exist in 16 stereoisomeric forms. The tetrahedral geometry of the molecule, together with the presence of four identical substituents bonded to the phosphorus atom, renders some structures equivalent,[25] affording three groups of isomers: group I (*RRRR*/*SSSS*); group II (*RRSS*/*SSRR*; *RSRS*/*SRSR*; *RSSR*/*SRRS*); group III (*RRRS*/*SSSR*; *RRSR*/*SSRS*; *RSRR*/*SRSS*; *SRRR*/*RSSS*). The theoretical percentages of stereoisomers in the groups I/II/III are in a ratio of 12.5/37.5/50.0, respectively. The ^{31}P NMR spectra analysis of **4b**−**c** in $CDCl_3$ exhibited three signals in a relative ratio nearly identical with the calculated values (Table 3).

Dissociation Constants of (α-Hydroxyalkyl)phosphinic and -phosphonic Acid Amphiphiles. Owing

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Table 3. Isolated Yields and ^{31}P NMR Parameters of Tetrakis(α-hydroxyalkyl)phosphonium Chlorides 4

compd no.	yield (%)	$\delta(^{31}P)$ ($CDCl_3$)	rel intensities	
			calcd (%)	found (%)
4b	54	23.4	50	50
		22.9	12.5	20
		21.9	37.5	30
4c	70	23.5	50	50
		22.9	12.5	16
		22.0	37.5	34

to their high complexing ability, organophosphorus acid compounds can be used as extractants for liquid−liquid extraction of metallic cations.[7,39] Among these, alkylphosphinic acids have been reported to possess higher separation factors for lanthanides,[40] actinides,[41] heavy rare earth elements,[42] cobalt and nickel,[43] and other transition metal ions.[44] For such an application, the compounds must not be too soluble in water, and for this reason, the presence of a long alkyl chain inducing a hydrophobic character in these molecules is suitable. Actually, various organophosphorus derivatives are known as phase-transfer catalysts for two-phase reactions.[45]

The knowledge of the acidity constants is essential in order to estimate their extractant properties. Dissociation constants of various phosphinic and phosphonic acids have already been determined in water,[46] in 75% and 95% ethanol,[47] in *tert*-butyl alcohol and pyridine,[48] and in DMSO, DME, and ethylene glycol.[49,50] To determine the influence of the polar head (phosphinic and phosphonic acid) and the alkyl structure upon the acidity constants, we have measured the p*K* values of the acids **1b**−**c** and **3b**−**c**. The water insolubility of the long-chain (α-hydroxyalkyl)phosphorus acids **1** and **3** prevents the determination of p*K* values in water. DMF, an aprotic polar solvent with high dielectric constant ($\epsilon = 36.7$) and high dipolar moment ($\mu = 3.86$ D),[51] is a good solvent for all of the acids. It does not solvate the anions (absence of hydrogen bonding)[52] but strongly solvates the cations due to the negative charge located at oxygen atom.[53] To have estimated p*K* values in water, we compared their dissociation constants in DMF to the p*K* values in DMF of the (α-hydroxybenzyl)phosphinic and -phosphonic acids, **1e** and **3e**, and the hypophosphorous acid for which the p*K* values have been already determined in water.[54] DMSO could not be used as solvent since hypophosphorous acid is oxidized by it.[49]

Table 4. Evaluation of the p*K* Values of the Phosphorus Acids in DMF by Potentiometric and ^{31}P NMR Titrations

method	p*K* of phosphorus acids						
	H_3PO_2	**1c**	**1b**	**1e**	**3c**	**3b**	**3e**
potentiometric[a]	9.40 (1.1)[b,53]	8.80	9.70	9.45 (1.4)[b,53]	11.00	10.75	10.80
^{31}P NMR[c]		8.70		9.60	11.10	10.80	11.00

[a] In DMF at 20 °C. [b] In water at 20 °C. [c] In DMF at 30 °C.

Potentiometric Titration. For the potentiometric titration in DMF at 20 °C, the calibration into pH units of the glass electrode was carried out with 2,4-dinitrobenzoic and 2,6-dihydroxybenzoic acids as buffers neutralized by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). These mixtures were utilized in lieu of either dichloroacetic or picric acids neutralized by triethylamine that had previously been used to determine p*K* values of some organoboron and organophosphorus compounds.[55] The former acids are anhydrous cristalline materials that are easier for handling than the latter ones, whereas DBU is a stronger base than triethylamine.[56] The p*K* value of 2,4-dinitrobenzoic acid has already been reported in DMSO (6.52) and in DMF (8.16).[57] The p*K* value of 2,6-dihydroxybenzoic acid was determined potentiometrically in DMF and DMSO by DBU.[58] Observed values 2.4 (DMF) and 0.4 (DMSO) do not agree with reported parameters 3.56 (DMF)[57] and 3.1 (DMSO).[59] Nevertheless, the weak difference between the two last p*K* values is abnormal since a difference of 1.5 to 2 p*K* units is systematically observed between the two solvents. Moreover, neutralization curves of 2,6-dihydroxybenzoic acid and picric acid are almost superimposable.[58]

Dissociation constants calculated from potentiometric technique are presented in Table 4. All the p*K* values obtained in DMF are in the range 8.8−11.0. We observe that the (α-hydroxyalkyl)phosphinic and -phosphonic acids are weakly dissociated in DMF and they can be considered as weak acids in this solvent. However, their p*K* values are very similar to the p*K* value in DMF of the hypophosphorous acid, which is a strong acid in water ($pK_{water} = 1.1$).[54a]

The P−H phosphinic and phosphonic acids are in tautomeric equilibrium with their trivalent isomers, phosphorus and phosphonous acids, respectively, but owing to the strength of the phosphoryl group, the equilibrium shifts to the left (Scheme 8).[32]

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Scheme 8

Table 5. Influence of pH upon the $\delta(^{31}P)$ and $^1J_{PH}$ (Hz) of the (α-Hydroxyalkyl)phosphinic Acids 1

phosphinic acid	pH	$\delta(^{31}P)$	$^1J_{PH}$ (Hz)
1c	5.3	31.4	512
	10.0	28.1	500
	17.9	23.3	467
1e	5.1	28.0	530
	9.1	25.8	506
	17.9	22.4	485

Table 6. Influence of the Concentration upon the $\delta(^{31}P)$ and $^1J_{PH}$ (Hz) of (α-Hydroxydodecyl)phosphinic Acid (1c) in DMF

	concentration (M)		
	0.1	0.01	0.005
$\delta(^{31}P)$	31.6	31.5	31.4
$^1J_{PH}$ (Hz)	516	517	523

Therefore, acids **1** and **3** exist largely in the tetracoordinate form, and they are considered as mono- and diacids, respectively. The P−H acidities of hydrophosphoryl compounds have been investigated in detail by the potentiometric method in 95% ethanol and by the indicator spectrophotometric method in DMSO and DME.[50] They vary over a wide range (pK_{DMSO} from 20.8 to 28.0), depending on the nature of substituents on the phosphorus atom, and they show the very weak acidic character of the P−H tetracoordinated phosphoryl compounds. During the titration, we have never observed a second acidity due to the P−H bond for the phosphinic acids **1** or due to the second P−OH group for the phosphonic acids **3**. In the later case, it is well-known that the second acidity is about 5 p*K* units higher than the first acidity.[54a]

We observe that the phosphinic acids are slightly stronger than the corresponding phosphonic acids (Table 4). A similar observation has been made for other phosphinic and phosphonic acids.[46a,54c,60] These are monoacids, and no evidence for secondary ionization (P−H acidity) is obtained. The nature of the substituents (H, Ph, or long-chain alkyl) does not have a significant influence on the dissociation constants of these acids. Consequently, the increase of the acidity could arise from the α-hydroxyl group.

^{31}P NMR Titration. As in amino- and hydroxy-substituted phosphonic acid compounds,[61] the ^{31}P-chemical shifts of the α-hydroxyalkyl acids **1** and **3** are strongly dependent on the pH of the solution (Table 5).

An increase in the solution pH causes a shielding of the phosphorus nucleus by approximately 6−8 ppm and a decrease of the $^1J_{PH}$ values of about 40 Hz. In contrast, the ^{31}P NMR data in DMF appear insensitive to the concentration (Table 6).

To make a direct comparison between the p*K* values obtained by the potentiometric technique and by ^{31}P NMR titration,[62] we have operated at 8 mM concentration. The dissociation constants were determined directly from the plot of $\delta(^{31}P)$ against pH in which the p*K* is equal to the pH at half-neutralization (point of inflection). It has recently been reported that the p*K* values of phosphonic acids are invariable with temperature.[46b] The measures of p*K* were made at 30 °C for the NMR titration and at 20 °C for the potentiometric method. Good agreement is obtained between the two methods for the phosphinic and phosphonic acids **1** and **3** (Table 4). The parallelism of the two series is even closer if the fact that p*K* measures only the acidity due to the ionization of the most easily removed proton is taken into account.

Consequently, the (α-hydroxyalkyl)phosphinic and -phosphonic acid amphiphiles **1** and **3** having pH-dependent ^{31}P resonance signals lend themselves to ^{31}P NMR titration, and the dissociation constants obtained by this method closely correlate with those determined by the potentiometric technique. Whereas the (α-hydroxyalkyl)phosphinic and -phosphonic acid amphiphiles **1** and **3** are weakly dissociated in DMF, they can be considered as relatively strong acids in water since their p*K* values are very close to the dissociation constant in DMF of hypophosphorous acid for which the p*K* value in water is about 1.1. The complexing properties and the molecular agregation of these functionalized phosphorus acid amphiphiles are under investigation.

Conclusions

The direct synthesis of free (α-hydroxyalkyl)phosphinic acids from long-chain aldehydes and aqueous hypophosphorous acid, which is a cheap and safe raw material, under sonication for 1 h constitutes a general and convenient procedure for the preparation of new phosphorus acid amphiphiles. The ready oxidation of (α-hydroxyalkyl)phosphinic acids to the corresponding phosphonic acids by DMSO in the presence of catalytic amounts of iodine can be also considered of synthetic interest. The presence of intra- and intermolecular associations by hydrogen bonding is demonstrated by IR spectroscopy in the condensed phase and in solution for the (α-hydroxyalkyl)phosphinic acids. Owing to the presence of the phosphoryl, acidic hydroxyl, α-hydroxyl, and P−H groups, these acids exist in the form of cyclic dimers (intermolecular H-bond) and free monomers stabilized by intramolecular hydrogen-bonding. Dissociation constants of (α-hydroxyalkyl)phosphinic and -phosphonic acids determined in DMF by potentiometric and ^{31}P NMR titrations reveal a good correlation between the two methods. The P−H (α-hydroxyalkyl)phosphinic acids are slightly stronger than the corresponding phosphonic ones. Their p*K* values are very close to the dissociation constant of hypophosphorous acid, and they can be considered as relatively strong acids with potential complexing properties due probably to the presence of a P−H bond and the effect of the α-hydroxyl group. Finally, the tetrakis(α-hydroxyalkyl)phosphonium chloride surfactants are easily prepared in acidic media from the long-chain aldehydes and the phosphine, PH_3, generated by basic hydrolysis of red phosphorus or acid hydrolysis of zinc phosphide. Their applications as intermediates in synthesis or as phase-transfer catalysts are under investigation.

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Experimental Section

General Comments. Red phosphorus (Prolabo), zinc phosphide (Strem), 50% aqueous hypophosphorous acid and aldehydes (Aldrich), 2,6-dihydroxybenzoic acid and 2,4-dinitrobenzoic acid (Fluka), and (α-hydroxybenzyl)phosphinic acid (**1e**) (Janssen) were used as received without prior purification. DMF, reagent grade product, was maintained over 4 Å molecular sieves and stored in a dark bottle protected from moisture. Elemental analyses were performed by the Microanalytical Service Laboratory of the "Laboratoire de Chimie de Coordination" of Toulouse, France. An ultrasound generator, consisting of a 13-mm probe fitted to a Bioblock Vibracell 600 W (20 kHz) generator, was dipped into the solution.

General Procedure for the Synthesis of (α-Hydroxyalkyl)phosphinic Acids (1). Hypophosphorous acid (50% aqueous) (4.3 mmol) was added to a solution of aldehyde (5.16 mmol, 1.2 equiv) in dioxane (6 mL) and hydrochloric acid (37% aqueous) (0.05 mL). The resulting heterogeneous mixture was stirred under reflux for 2−4 h or sonicated for 1 h. Solvents were removed under vacuum. After addition of distilled H_2O to the residue, products were extracted with Et_2O. The organic phase was evaporated to dryness. The white solid residue was washed with *n*-hexane and then filtered off and dried under vacuum.

(α-Hydroxyoctyl)phosphinic acid (1a): yield 51%; mp 63−65 °C (from hexane); ^{31}P NMR (32.44 MHz, DMSO-d_6) δ 31.5 (d, $^1J_{PH}$ = 516 Hz); ^{1}H NMR (80.13 MHz, DMSO-d_6) δ 6.70 (d,$^1J_{HP}$ = 517 Hz, 1H), 5.30 (m, 1H), 3.48 (m, 1H), 1.47−1.26 (m, 12H), 0.85 (m, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 68.22 (d, $^1J_{CP}$ = 111 Hz), 31.14 (s), 29.25 (s), 28.71 (s), 28.52 (s), 24.91 (s), 21.98 (s), 13.84 (s); IR (KBr, cm^{-1}) 3340.0 (OH), 2952.0−2847.7 (P−OH), 2398.4 (P−H), 1085.3 (P═O); MS (DCI/NH_3) *m*/*z* 195 (M + 1)$^+$, 213 (M + 1 + NH_4)$^+$, 389 (2M + 1)$^+$. Anal. Calcd for $C_8H_{19}O_3P$: C, 49.48; H, 9.86. Found: C, 49.64; H, 9.87.

(α-Hydroxydecyl)phosphinic acid (1b): yield 76%; mp 74−75 °C (from hexane); ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 32.8 (d, $^1J_{PH}$ = 516 Hz); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 6.57 (m, 1H), 6.22 (d, $^1J_{HP}$ = 518 Hz, 1H), 3.02 (m, 1H), 1.02−0.77 (m, 16H), 0.37 (m, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 69.03 (d, $^1J_{CP}$ = 112 Hz), 32.13 (s), 30.12 (s), 29.81 (s), 29.69 (s), 29.56 (s), 25.91 (s), 25.72 (s), 22.92 (s), 14.69 (s); IR (KBr, cm^{-1}) 3395.4−3306.9 (OH), 2916.4−2850.1 (P−OH), 2364.8 (P−H), 1090.1 (P═O); MS (DCI/NH_3) *m*/*z* 240 (M + NH_4)$^+$. Anal. Calcd for $C_{10}H_{23}O_3P$: C, 54.04; H, 10.43. Found: C, 53.80; H, 10.54.

(α-Hydroxydodecyl)phosphinic acid (1c): yield 75%; mp 82−83 °C (from hexane); ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 32.9 (d, $^1J_{PH}$ = 517 Hz); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 6.7 (d, $^1J_{HP}$ = 518 Hz, 1H), 6.42 (m, 1H), 3.48 (d, $^2J_{HP}$ = 8.8 Hz, 1H), 1.53−1.24 (m, 20H), 0.85 (t, $^3J_{HH}$ = 6 Hz, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 67.74 (d, $^1J_{CP}$ = 113 Hz), 31.25−22.0 (m), 13.80 (s); IR (KBr, cm^{-1}) 3395.4−3302.6 (OH), 2915.5−2848.8 (P−OH), 2449.8−2365 (P−H), 1089.5 (P═O); MS (DCI/NH_3) *m*/*z* 268 (M + NH_4)$^+$, 251 (M + 1)$^+$. Anal. Calcd for $C_{12}H_{27}O_3P$: C, 57.58; H, 10.87. Found: C, 57.58; H, 10.96.

(α-Hydroxytetradecyl)phosphinic acid (1d): yield 62%; mp 90−92 °C (from EtOH); ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 32.9 (dd, $^1J_{PH}$ = 517 Hz, $^2J_{PH}$ = 9.7 Hz); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 6.7 (dd, $^1J_{HP}$ = 517 Hz, $^3J_{HH}$ = 1.2 Hz, 1H), 3.45 (m, 1H), 1.49−1.24 (m, 24H), 0.85 (t, $^3J_{HH}$ = 6.6 Hz, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 68.20 (d, $^1J_{CP}$ = 112 Hz), 31.21−22.0 (m), 13.82 (s); IR (KBr, cm^{-1}) 3393.8−3306.1 (OH), 2914.8−2848 (P−OH), 2403.8 (P−H), 1090 (P═O); MS (DCI/CH_4) *m*/*z* 279 (M + 1)$^+$, 307 (M + C_2H_5)$^+$. Anal. Calcd for $C_{14}H_{31}O_3P$: C, 60.41; H, 11.22. Found: C, 60.73; H, 11.05.

General Procedure for the Synthesis of (α-Hydroxyalkyl)phosphonic Acids 3. A solution of (α-hydroxyalkyl)-phosphinic acid **1** (2.9 mmol), DMSO (0.22 g, 2.9 mmol, 1 equiv), and iodine (0.002 g, 0.01 equiv) in THF (5 mL) was stirred under heating at 60 °C for 5 h. The completion of the reaction was followed by ^{31}P NMR. The mixture was evaporated to dryness. The residue was washed several times with dichloromethane, and then the insoluble material was filtered off and recrystallized from THF to give a white powder.

(α-Hydroxydecyl)phosphonic acid (3b): yield 80%; mp 145−147 °C (from THF);[63] ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 23.9 (dt, $^2J_{PH}$ = 9.3 Hz, $^3J_{PH}$ = 6.7 Hz); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 8.00−5.50 (m), 3.43 (m, 1H), 1.56−1.25 (m, 16H), 0.86 (t, $^3J_{HH}$ = 6.6 Hz, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 66.9 (d, $^1J_{CP}$ = 161.3 Hz), 33.7−22.0 (m), 13.8 (s); IR (KBr, cm^{-1}) 3202.5−2920.5 (OH), 2850.6 (P−OH), 1123 (P═O); MS (DCI/NH_3) *m*/*z* 238 (M)$^{+\bullet}$, 256 (M + NH_4)$^+$, 440 (2M − 2H_2O)$^{+\bullet}$. Anal. Calcd for $C_{10}H_{23}O_4P$: C, 50.41; H, 9.73. Found: C, 50.62, H, 9.68.

(α-Hydroxydodecyl)phosphonic acid (3c): yield 89%; mp 148−150 °C (from THF); ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 23.8 (m); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 7.10 (m, 3H), 3.44 (m, 1H), 1.53−1.24 (m, 20H), 0.85 (t, $^3J_{HH}$ = 6.1 Hz, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 66.8 (d, $^1J_{CP}$ = 161.2 Hz), 31.2−22.0 (m), 13.8 (s); IR (KBr, cm^{-1}) 3211.8 (OH), 2919.1 (P−OH), 1122.2 (P═O); MS (DCI/NH_3) *m*/*z* 284 (M + NH_4)$^+$. Anal. Calcd for $C_{12}H_{27}O_4P$: C, 54.12; H, 10.22. Found: C, 54.27, H, 10.25.

(α-Hydroxytetradecyl)phosphonic acid (3d): yield 55%; mp 152−154 °C (from THF); ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 24.0 (m); ^{1}H NMR (250.13 MHz, DMSO-d_6) δ 6.27 (m, 3H), 3.43 (m, 1H), 1.49−1.24 (m, 24H), 0.85 (t, $^3J_{HH}$ = 5.3 Hz, 3H); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 66.9 (d, $^1J_{CP}$ = 161.4 Hz), 31.2−22.0 (m), 13.8 (s); IR (KBr, cm^{-1}) 3215.2 (OH), 2918.3−2850.1 (P−OH), 1008.3 (P═O); MS (DCI/NH_3) *m*/*z* 295 (M + 1)$^+$, 312 (M + NH_4)$^+$. Anal. Calcd for $C_{14}H_{31}O_4P$: C, 57.12; H, 10.61. Found: C, 57.24, H, 10.44.

(α-Hydroxybenzyl)phosphonic acid (3e): yield 90%; mp 161−163 °C (from CH_2Cl_2);[23d] ^{31}P NMR (81.01 MHz, DMSO-d_6) δ 19.5 (d, $^2J_{PH}$ = 15.4 Hz); ^{1}H NMR (200.13 MHz, DMSO-d_6) δ 9.00−8.00 (m, 2H), 7.45−7.22 (m, 6H), 4.69 (d, $^2J_{HH}$ = 13.9 Hz); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 140.0 (s), 127.4−126.7 (m), 70.3 (d, $^1J_{CP}$ = 159.5 Hz); IR (KBr, cm^{-1}) 3224.6 (OH), 2839.9 (P−OH), 1006.0 (P═O); MS (DCI/NH_3) *m*/*z* 188 (M)$^{+\bullet}$, 207 (M + 1 + NH_4)$^{+\bullet}$, 224 (M + 1 + N_2H_7)$^+$, 392 [2(M − 1) + NH_4]$^+$. Anal. Calcd for $C_7H_9O_4P$: C, 44.69; H, 4.82. Found: C, 44.61, H, 4.52.

General Procedure for the Synthesis of (α-Hydroxyalkyl)phosphonium Salts 4. The reaction was carried out under an argon atmosphere. Phosphine (PH_3) was generated by basic hydrolysis of red phosphorus or acid hydrolysis of zinc phosphide. To zinc phosphide (0.32 g, 1.24 mmol) in distilled H_2O or red phosphorus (0.31 g, 0.01 mol), stirred and heated at 50 °C, was added dropwise an aqueous solution of sulfuric acid or potassium hydroxide, respectively. The generated phosphine was bubbled through the stirred solution of aldehyde (7.5 mmol) in dioxane (6 mL) and 37% aqueous hydrochloric acid (0.72 mL) at 30 °C for 1.5 h. The insoluble product was formed immediately upon the passage of PH_3. The mixture was maintained under stirring at 30 °C for an additional 1 h. The white solid was collected by filtration, washed several times with *n*-hexane, and dried under vacuum.

Tetrakis(α-hydroxydecyl)phosphonium chloride (4b): yield 54%; mp 112−115 °C (from hexane); ^{31}P NMR (81.01 MHz, $CDCl_3$) δ 23.4 (50%), 22.9 (20%), 21.9 (30%); ^{1}H NMR (80.13 MHz, C_6D_6) δ 5.12 (m, 4H), 4.81 (m, 4H), 1.84−1.33 (m, 64H), 0.97 (m, 12H); ^{13}C NMR (62.90 MHz, C_6D_6) δ 60.00 (d, $^1J_{CP}$ = 130 Hz), 43.84−22.26 (m), 14.43 (s); MS (positive FAB/MNBA) *m*/*z* 659 (M)$^+$; IR (KBr, cm^{-1}) 3262.7 (OH). Anal. Calcd for $C_{40}H_{84}ClO_4P$: C, 69.08; H, 12.17; Cl, 5.10; P, 4.45. Found: C, 68.80; H, 12.06; Cl, 4.97; P,4.46.

Tetrakis(α-hydroxydodecyl)phosphonium chloride (4c): yield 70%; mp 109−111 °C (from hexane);[37] ^{31}P NMR (81.01 MHz, $CDCl_3$) δ 23.5 (50%), 22.9 (16%), 22.0 (34%); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 5.30 (m, 4H), 4.78 (m, 4H), 1.26 (m, 80H), 0.88 (m, 12H); ^{13}C NMR (62.90 MHz, C_6D_6) δ 62.84 (d, $^1J_{CP}$ = 139.4 Hz), 43.92−22.09 (m), 14.10 (s); MS (positive FAB/glycerol) *m*/*z* 771 (M)$^+$; IR (KBr, cm^{-1}) 3265.3 (OH). Anal. Calcd for $C_{48}H_{100}ClO_4P$: C, 71.37; H, 12.48. Found: C, 71.30; H, 12.50.

(63) Fitch, S. J.; Moedritzer, K. *J. Am. Chem. Soc.* **1962**, *84*, 1876.

Determination of the Dissociation Constants of Phosphorus Acids. For all emf measurements a Schott Gerate, CG832, pH-meter equipped with a reference electrode, B220 (saturated solution of LiCl in methanol/KCl 2M), and a glass electrode, Schott H 11280 DIN, 200 MΩ (Ag/AgCl) was used. The calibration was carried out by titration of 2,6-dihydroxybenzoic acid ($pK_{DMF} = 2.4$) and 2,4-dinitrobenzoic acid ($pK_{DMF} = 8.16$) in DMF (8×10^{-3} M) with a solution of DBU in DMF (0.1 M) at 20 °C. The acidity constants of different phosphorus acids were determined under the same conditions. In general, stable potentials were obtained within 10 min. A Bruker AC200 was used for ^{31}P NMR titration. The concentrations were the same than above, but the measurements were carried out at 30 °C. The accuracy of this method is within 0.1−0.2 p*K* unit.

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