EPR Properties of Two New Cyclic Phosphinylhydrazyl Radicals and of Their Inclusion Complexes with Cyclodextrins

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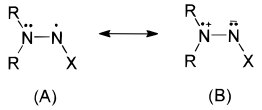
Two phosphorus-containing hydrazines, namely morpholin-4-ylphosphoramidic acid diethyl ester (**1a**) and (2,2,6,6-tetramethylpiperidin-1-yl)phosphoramidic acid diethyl ester (**2a**), have been synthesized. The corresponding hydrazyl radicals (**1b** and **2b**) have been obtained, by in situ oxidation, and their properties have been investigated by EPR spectroscopy. The **1b** radical shows spectra strongly dependent on temperature due to the inversion of the morpholin ring and to rotation about the N−N bond. Since, in the investigated temperature range, both motions take place in the EPR time scale, a kinetic study of these process could be made by analyzing the spectral line-shape variations. The **2b** radical is highly persistent and shows a strong temperature and solvent dependence of the phosphorus splitting. The latter property was usefully exploited to study the guest−host interaction of this radical with cyclodextrins. A method is also proposed for the determination of affinity constants for cyclodextrins of nonparamagnetic compounds.

The study of hydrazyl radicals by electron paramagnetic resonance (EPR) spectroscopy has been a productive field of research for a long time, and a variety of variously substituted hydrazyls have been investigated in solution.[1−3] A peculiarity of these persistent radicals is the great sensitivity to the nature of the substituents of the distribution of spin density between the two nitrogen atoms, which is related to the relative importance of the mesomeric structures A and B.



Ingold and co-workers[2] in their studies of mono-, di-, and trialkyl ^{15}N-labeled hydrazyls have shown that the divalent nitrogen may or may not be responsible for the larger of the two nitrogen splittings depending on the number, position, and electronic properties of the substituents, although the larger a_N value is generally associated with it.

In 1986, Tordo and co-workers[4] reported the generation and the characterization by EPR of phosphinylhydrazyl radicals, $R_2NN(^{\cdot})P(O)R'_2$, obtained by oxidation of the corresponding hydrazines with thermally or photolytically produced *tert*-butoxyl radicals. In this case, the larger of the two nitrogen splittings is due to the tervalent nitrogen atom, the assignment being based on ^{15}N-labeling experiments. Phosphinylhydrazyl radicals exist in equilibrium with their diamagnetic dimers, and some of them are very persistent. Their greater stability, compared to that of trialkylhydrazyl radicals, has been attributed to the electron-withdrawing effect of the phosphinyl group, which stabilizes the resonance structure B and to the fact that the absence of hydrogen atoms in the position β to the divalent nitrogen prevents radical decay by disproportionation.

In the present work, we describe the synthesis of the hydrazine precursors **1a** and **1b**, the generation of the corresponding cyclic phosphinylhydrazyl radicals **2a** and **2b,** and an EPR investigation of their properties.

It will also be shown that the more persistent one (**2b**) can easily form inclusion complexes with cyclodextrin hosts and that the large spectral changes observed upon complexation make this radical a particularly suitable probe to investigate host−guest interactions in supramolecular chemistry.

Results and Discussion

Synthesis of the Phosphinyl Hydrazines. 4-Aminomorpholine and 1-amino-2,2,6,6-tetramethylpiperidine were synthesized by $LiAlH_4$ reduction of the corresponding nitrosoamines.[5] The phosphinyl hydrazine **1a** was prepared by simply reacting diethylchlorophosphate with 4-aminomorpholine (see Scheme 1) similarly to what was reported for preparing analogous phosphinyl hydrazines.[4] The synthesis of the hydrazine **2a** was less straightforward since 1-amino-2,2,6,6-tetramethylpiperidine did not react with diethylchloro phosphate presumably for steric reasons (vide infra). To synthesize **2a**, the hindered

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(2) (a) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 6110. (b) Lunazzi, L.; Ingold, K. U. *Ibid.* **1974**, *96*, 5558. (c) Malatesta, V.; Ingold, K. U. *Ibid.* **1974**, *96*, 3949. (d) Kaba, R. A.; Lunazzi, L.; Lindsay, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1975**, *97*, 6762.

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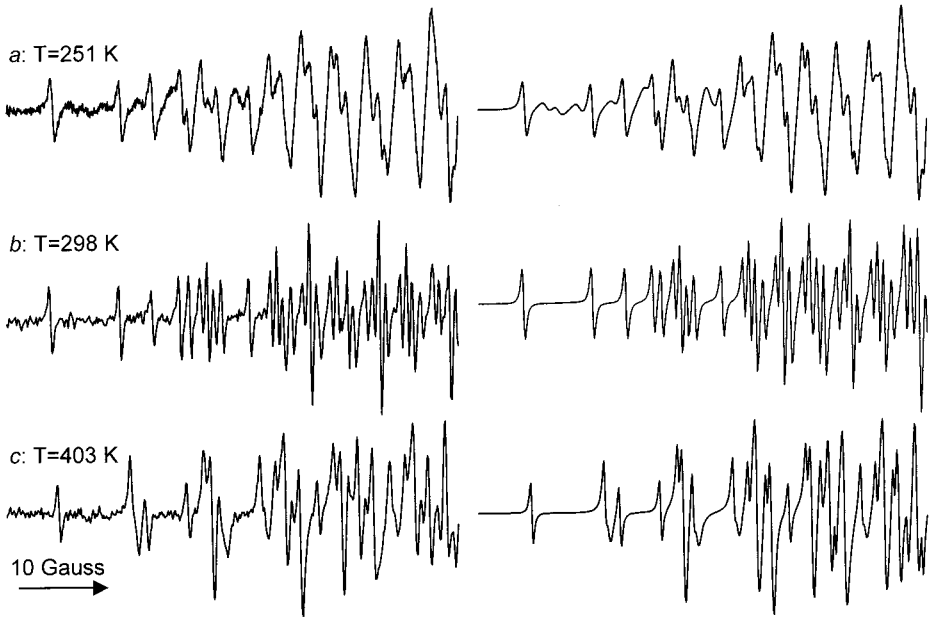
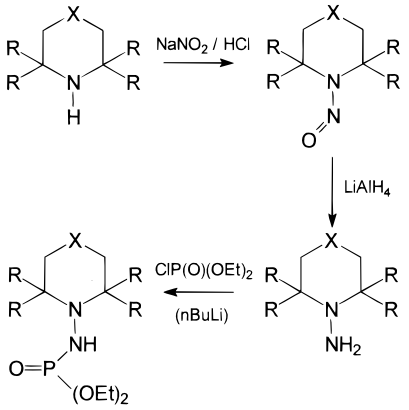


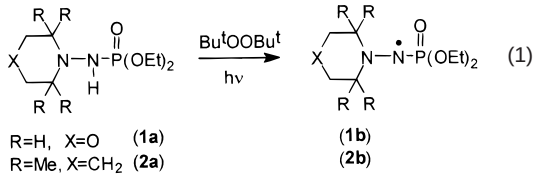
Figure 1. Low-field half EPR spectra of radical **1b** in chlorobenzene at −22 °C (a), 25 °C (b) and 130 °C (c). On the right side are shown the corresponding simulations obtained by using the rate constants reported in the text.

Scheme 1



hydrazine was treated with butyllitium before carrying out the reaction with the chlorophosphate.

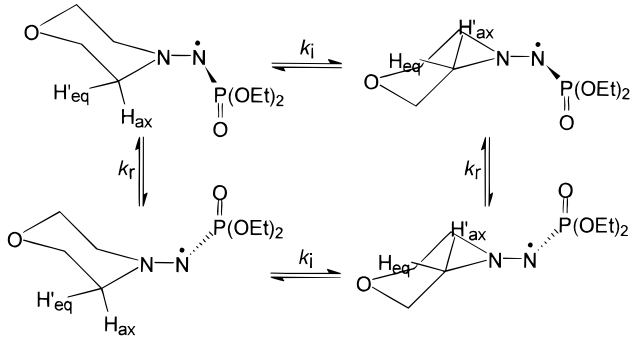
Hydrazyl Radicals. The hydrazyl radicals **1b** and **2b** were produced in deoxygenated *tert*-butylbenzene or chlorobenzene solutions by oxidation of the corresponding hydrazines with *tert*-butoxy radicals photolytically generated from di-*tert*-butyl peroxide (eq 1). The two radicals were characterized by very different persistency since **1b** disappeared immediately when stopping the irradiation while **2b** had a half-life time of ca. 15 h at room temperature, its decay following good first-order kinetics. Thus, sterical protection of the radical center greatly increases the persistency of the hydrazyl radical, consistent with previous data reported for similar systems.[2]



(1)

The EPR spectrum of **1b** showed selective line broadening effects and was strongly dependent on temperature

Scheme 2



as shown in Figure 1. This is not surprising in view of the fact that this radical can exist in four equivalent conformations (see Scheme 2) that may interconvert both by rotation about the N−N bond (k_{rot}) and by inversion of the six-membered morpholine ring (k_{inv}) which, in the isoelectronic morpholine-4-oxyl radical,[6] is known to adopt either of the chair conformations depicted in Scheme 2.

If assuming that the two different internal motions are frozen in the EPR time scale, the spectrum of **1b** should result from the coupling of the unpaired electron with a phosphorus, two nitrogens, and four different β-protons. This is actually what was observed at −22 °C in PhCl (see Figure 1a and Table 1) or at −30 °C in Me_3CPh; no coupling to the γ-protons of the morpholine ring was instead detected. When the sample was heated, some of the lines became too broad to be observable (Figure 1b), and by further increasing the temperature new lines appeared at spectral positions corresponding to the averages of the axial and equatorial β-proton splittings, which became progressively sharp (Figure 1c and Table 1). At 130 °C, the inversion of the morpholine ring was fast in the EPR time scale while the rotation about the N−N bond was still too slow to completely average the

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Table 1. Hyperfine Splitting Constants (Gauss = 0.1 mT) and *g*-Factors of the Hydrazyl Radicals 1b and 2b

radical	*T* (°C)	solvent	$a_{N(1)}$	$a_{N(2)}$	a_P	$a_{H(\beta)}$	*g* factor
1b	−30	Me_3CPh	7.51	14.37	11.67	2.37 (H_{eq}), 14.26 (H_{ax})	
						3.70 (H_{eq}), 14.50 (H_{ax})	
	25	Me_3CPh	7.66	14.37	11.05	16.62 ($a_{eq} + a_{ax}$)	2.0038
						18.14 ($a_{eq} + a_{ax}$)	
	130	Me_3CPh	8.04	14.35	9.80	8.53 (4H)	
2b	25	Benzene	8.83	14.22	4.22		2.0038
	25	ACN	8.27	14.53	4.96		
	25	MeOH/H_2O (1:1)	8.02	14.98	11.76		
	25	H_2O	8.01	15.29	17.17		

couplings at the β-protons cis and trans to the phosphinyl group. This could be inferred from the presence of selective broadening of some spectral lines even at high temperature. Simulation of the experimental EPR spectra by using well-established procedures[7] based on the density matrix theory[8] allowed us to estimate the rate constants for ring inversion and internal rotation. Thus, good simulations of the spectra recorded in PhCl were obtained by using the splitting constant reported in Table 1 and the following rate constants: at −22 °C $k_{inv} = 8 \times 10^6$ s^{-1} and $k_{rot} < 10^5$ s^{-1}, at 110 °C $k_{inv} = 5 \times 10^8$ s^{-1} and $k_{rot} \leq 5 \times 10^5$ s^{-1}, and at 130 °C $k_{inv} = 9 \times 10^8$ s^{-1} and $k_{rot} = 1 \times 10^6$ s^{-1}. From these rate constants, the activation parameters for ring inversion were calculated as $E_{a,inv} \cong 6.3$ kcal mol^{-1} and log $A = 12.4$, which compares favorably with the E_a value of 6.1 kcal mol^{-1} reported for the ring inversion of the morpholine-4-oxyl radical.[6] For the internal rotation of the phosphinyl group, by assuming the same log *A* value, i.e., 12.4, the rate constant at 130 °C provides an activation energy of ca. 12 kcal mol^{-1}, which is close to the E_a value of ≅10 kcal mol^{-1} determined by Tordo and co-workers[4] in the phosphinylhydrazyl radical $Me_2NN(^{\cdot})P(O)(OEt)_2$. A more detailed kinetic EPR study of the internal rotation in **2b** could not be done because in the accessible temperature range the exchange broadening due to ring inversion is so strong to hide any other effect.

The nonequivalence of the β-proton splittings, observed even at temperatures where ring inversion was fast enough to average the axial and equatorial coupling constants, is a clear indication that the phosphinyl group is coplanar with the average molecular plane, i.e., lies on the nodal plane of the $2p_z$ orbital of the divalent nitrogen N_1. Also consistent with this interpretation is the temperature dependence of a_P, whose absolute value decreases by heating the sample (see Figure 2). This dependence can be explained as follows; the phosphorus coupling is a balance of two contributions of opposite sign, a negative one due to spin polarization (structure A) and a positive one due to hyperconiugation (structure B).[9] When the temperature is raised, the increasing libration of the phosphinyl group out of the molecular plane increases the total spin density on the P atom. Thus, the hyperconiugative term becomes larger and the phosphorus coupling becomes less negative giving rise to the observed temperature dependence of the a_P. A similar behavior has been reported by Tordo et al. in the 1,1-dimethylphosphinylhydrazyl radical as shown in Figure 2.[4]

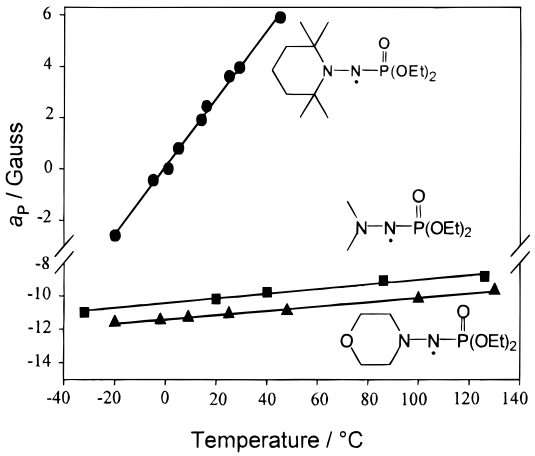

Figure 2. Temperature dependence of phosphorus hyperfine splitting constants for **1b** (▲), **2b** (●), and dimethylphosphinylhydrazyl (■) in toluene. The latter data were taken from ref 4.

Figure 2 reports also the experimental a_P values of the hydrazyl radical **2b** in toluene. In this case, the phosphorus splitting shows a dramatic temperature dependence also changing sign above 5 °C. The difference with respect to **1b** can be explained in terms of the larger crowding around the radical center, due to the four methyl groups in positions 2 and 6 of the piperidine ring. The large sterical interactions are expected to keep the phosphinyl group partially out of the molecular plane even in the minimum energy conformation and to lower the height of energy barrier to rotation about the N−N bond, with the result that the higher librational states of $P(O)(OEt)_2$ will be more populated than in **1b** at high temperatures. The larger crowding around the nitrogen is also confirmed by the low reactivity of 1-amino-2,2,6,6-tetramethylpiperidine toward diethyl chlorophosphate.

Large changes in the magnitude of the phosphorus coupling of **2b** were also observed by changing the nature of the solvent as shown in Table 1. Especially remarkable is the fact that the value of a_P undergoes at room temperature a 4-fold increase on passing from a scarcely polar solvent such as benzene (4.22 G) to water (17.17 G), this change being even larger than that observed for the nitrogen coupling in the neutral 4-acetyl-1-methylpyridinyl radical.[10]

Inclusion of 2b in Cyclodextrins. One of the major problems usually met when studying inclusion effects by EPR spectroscopy is the low sensitivity of the spectral parameters to complexation with the consequent difficulty in distinguishing the signals of the free and included species.[11] Since the cyclodextrin cavity is characterized by a different polarity from that of water, good differentiation of the signals due to the free and included radical is obtained when the value of hyperfine splitting constant is sensitive to the environment polarity. Thus, the strong sensitivity to solvent polarity found for radical

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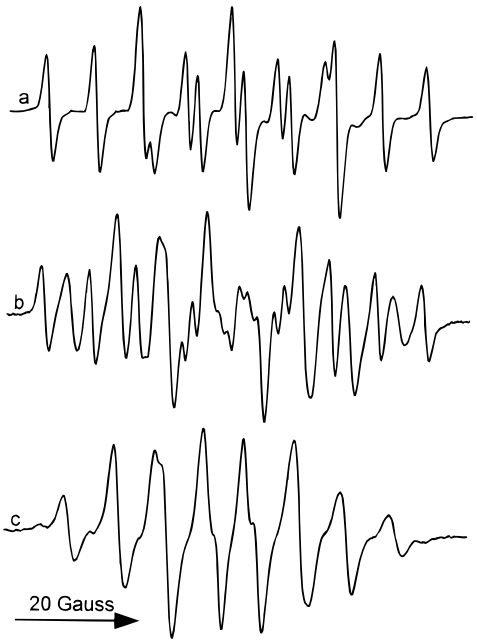
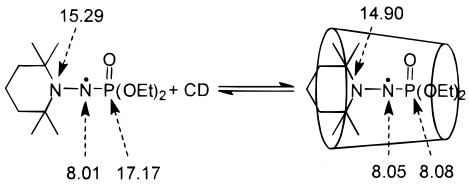


Figure 3. EPR spectra of radical **2b** in water (a) and in the presence of CD 6.5 mM (b) and 70 mM (c) at 25 °C.

Scheme 3



2b prompted us to investigate its behavior in water in the presence of cyclodextrins.

Figure 3 shows the EPR spectra of this hydrazyl radical recorded in pure water (Figure 3a) and in a water solution containing 6.5 mM heptakis(2,6,-*O*-dimethyl)-*β*-cyclodextrin (CD) (Figure 3b). In the latter one are present additional signals that we attribute to the radical included in the CD, since by increasing the concentration of the complexing species the spectrum of the included radical became dominant (Figure 3c). The measured hyperfine splitting constants for the free and complexed species are reported in Scheme 3; it should be pointed out that the effect of inclusion is almost negligible on the values of the nitrogen coupling, while the phosphorus splitting decreases dramatically upon complexation (from 17.17 to 8.08 G at room temperature).

It should be noted that although phosphorus-containing nitroxide radicals have been used to investigate biphasic systems characterized by different polar environments, such as micelles,[12] the strong variation observed in the phosphorus splitting when passing from water to CD is peculiar of radical **2b**. Actually, in the related *tert*-butyl phosphinyl nitroxide, the $Me_3CN(O^{\cdot})P(O)(OEt)_2$, the a_P value for the free and CD-included species are 13.95 and 13.31 G, respectively, a difference comparable to the line width.[13] This means that hydrazyl radical **2b** represents an useful probe for investigating inclusion effects by EPR spectroscopy, because of the strong sensitivity of the phosphorus coupling to complexation.

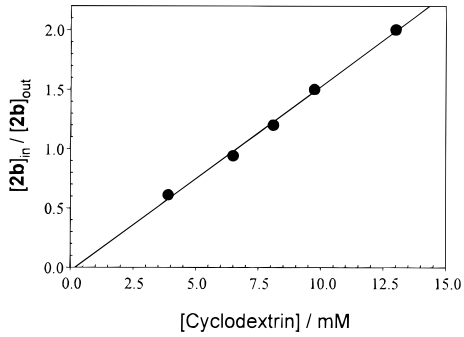


Figure 4. Plot of the ratio between the CD-included and the free radical **2b** versus the concentration of CD in water at 25 °C.

The value of the room-temperature binding constant of **2b** with CD was determined by plotting (Figure 4) the ratio between the concentrations of the free and included radical as function of the cyclodextrin concentration in water. This means that in eq 2 defining K_2 it is assumed that $[CD] = [CD]_0 - [RCD^{\cdot}] \cong [CD]_0$, $[CD]_0$ being the total concentration of CD in solution. The above assumption is justified by the fact that the radical concentration employed ($\leq 1 \times 10^{-4}$ M) is much smaller that of CD (on the order of 10^{-2} M). The ratio between complexed and uncomplexed radicals was determined by best fit simulations of the digitized experimental EPR spectra, and the resulting plot afforded the affinity constant of **2b** for CD as $K_2 = 153 \pm 10\ M^{-1}$.

$$R^{\cdot} + CD \underset{}{\overset{K_2}{\rightleftharpoons}} RCD^{\cdot} \quad K_2 = \frac{[RCD^{\cdot}]}{[R^{\cdot}][CD]} \quad (2)$$

Due to the persistency and sensitivity to environment of the hydrazyl radical **2b**, we tried to use it as probe in competitive inclusion experiments for the determination of affinity constants for cyclodextrins of nonparamagnetic compounds. The knowledge of this parameter is especially useful in the case of certain drugs for which cyclodextrins are used as carriers to deliver the right amount of drug to the target site for a given period of time, to overcome the undesirable properties of the drug molecule.[14] The validity of the method was checked by using diclofenac (i.e., sodium[*o*-[(2,6-dichlorophenyl)amino]phenyl]acetate), a widely used antiinflammatory drug for which the affinity constant for CD has been reported to be 370 M^{-1}.[15]

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This determination was carried out by adding a known amount of the diamagnetic compound A to water solutions containing CD and the hydrazyl radical **2b**. Under these conditions (eq 3), the affinity constant of A, K_4, can be calculated from eq 5 by using the [CD] value obtained by introducing in eq 2 the known value of K_2 and the experimental ratio [RCD•]/[R•] measured in the solution containing A.

$$R\bullet + A + CD \rightleftharpoons RCD\bullet + ACD \quad (3)$$

$$A + CD \overset{K_4}{\rightleftharpoons} ACD \quad (4)$$

$$K_4 \cong \frac{[CD]_0 - [CD]}{([A]_0 - [CD]_0 + [CD])[CD]} \quad (5)$$

Actually, when adding diclofenac to the solution, the spectral lines due to the included radical showed a marked decrease proportional to the quantity of drug from which a binding constant K_4 of 470 M^{-1} could be calculated. Since this value is close to that reported in the literature for diclofenac, it is concluded that the competition method here described can be usefully employed to determine binding constants of drugs for cyclodextrins in those cases where traditional methods such as NMR and UV−vis spectroscopy cannot be applied.

Experimental Section

General Methods. NMR spectra were recorded on a Bruker AMX 300 MHz spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN in the Ciba Specialty Chemical laboratory. Mass spectra were carried out on a Hewlett-Packard HP 5973 spectrometer. EPR spectra were obtained using a Bruker ESP 300 spectrometer equipped with an NMR gaussmeter for field calibration and a Hewlett-Packard 5350B microwave frequency counter for the determination of the *g*-factors, which were referenced to that of the perylene radical cation in concentrated H_2SO_4 ($g = 2.002\,58$). The sample temperature was controlled with a standard variable-temperature accessory and was monitored before and after each run using a copper−constantan thermocouple. Digitized EPR spectra were transferred to a personal computer and were analyzed using digital simulations carried out with a program developed in our laboratory and based on a Monte Carlo procedure.[16] Radicals **1b** and **2b** were generated in organic solvents by reacting the corresponding hydrazine with photolytically produced *tert*-butoxyl radicals. CD-included radical **2b** was generated by a flash of intense UV irradiation of a sample containing hydrazine **2a** in benzene/di-*tert*-butyl peroxide (10:1 (v/v)). The solvent was removed under reduced pressure, and the residue was dissolved in water containing variable amounts of cyclodextrin. Samples were then transferred in capillary tubes (1 mm i.d.), and EPR spectra were recorded.

Morpholin-4-yl-phosphoramidic Acid Diethyl Ester (1a). To a solution of 39.7 g (0.389 mol) of *N*-aminomorpholine and 39.3 g (0.389 mol) of triethylamine in 1000 mL of methylene dichloride under nitrogen, cooled to 0 °C, was slowly added 172.6 g (0.398 mol) of diethyl chlorophosphate. The temperature was kept during the addition at 0 °C. After the addition, the temperature was allowed to reach room temperature, and the solution was stirred for an additional 1 h. A white precipitate was formed. The mixture was washed twice with 50 mL of water and twice with a 10% solution of K_2CO_3. The organic layer was separated and dried under sodium sulfate, and the solvent was removed in a vacuum. A total of 79.7 g of a white powder was recovered in 93% yield. The compound was recrystallized from diisopropyl ether: mp 101−103 °C; MS (EI) *m*/*z* 238 (M^+, 5); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 1H), 4.09 (m, 4H), 3.69 (m, 4H), 2.71 (m, 4H), 1.30 (td, $^3J_{H-H} = 7.0$ Hz, $^4J_{P-H} = 0.9$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 66.53 (s), 62.93 (d,$^2J_{P-C} = 5.7$ Hz), 58.73 (d,$^3J_{P-C} = 6.9$ Hz), 16.15 (d,$^3J_{P-C} = 6.9$ Hz). Anal. Calcd for $C_8H_{19}N_2O_4P$: C, 40.34; H,7.98; N, 11.76. Found: C, 40.20; H, 8.01; N, 11.58.

(2,2,6,6-Tetramethylpiperidin-1-yl)phosphoramidic Acid Diethyl Ester (2a). (A) Synthesis of 2,2,6,6-Tetramethyl-1-nitrosopiperidine. To a solution of 23.5 g (0.167 mol) of 2,2,6,6-tetramethylpiperidine in 200 mL of water. HCl (10 mL, 37%) was added. The solution was heated at 75 °C, and a solution of 63 g (0.9 mol) of sodium nitrite in 200 mL of water was slowly added. The solution was allowed to react for 3 h at 75 °C and for an additional 10 h at 100 °C. The reaction mixture was cooled at room temperature and treated twice with 300 mL of diethyl ether. The organic layer was then washed with 100 mL of a water solution of 2 N HCl and with 100 mL of a saturated water solution of Na_2CO_3. The organic phase was then dried under anhydrous sodium sulfate, and the solvent was removed under vacuum. An orange oil was recovered in 98% yield: MS (EI) *m*/*z* 170 (M^+, 25); ^{1}H NMR ($CDCl_3$) δ 1.60 (broad s, 12H), 1.40 (broad m, 6H); ^{13}C NMR ($CDCl_3$) δ 62.08, 60.66, 41.58, 38.89, 31.90, 26.11, 16.24. **(B) Synthesis of 2,2,6,6-Tetramethylpiperidin-1-ylamine.** To a solution of 15 g of $LiAlH_4$ in 250 mL of anhydrous dibutyl ether cooled at 0 °C was slowly added 30 g of the compound from part A dissolved in 75 mL of dibutyl ether. The temperature was increased to 95 °C (reflux temperature), and the mixture was allowed to react for 3 h. The mixture was cooled at about 0 °C, and 50 mL of water was slowly added. The organic layer was recovered and dried under sodium sulfate. The solvent was removed under vacuum. A yellow oil was recovered at 73% yield: MS (EI) *m*/*z* 156 (M^+, 12); ^{1}H NMR ($CDCl_3$) δ 1.40 (broad s, 6H), 0.95 (broad m, 12H); ^{13}C NMR ($CDCl_3$) δ 57.02, 40.52, 25.52, 17.60. **(C).** To a solution of 6 g (38.5 mmol) of the compound from part B in 60 mL of anhydrous THF cooled at −78 °C was slowly added 15.2 mL of a solution of butyllithium 2.5 N in *n*-hexane. After the addition, the temperature was increased to room temperature and the mixture allowed to react for 30 h. The mixture was then cooled again at −78 °C, and 6.6 g (38 mmol) of diethyl chlorophosphate was slowly added. After 30 h, the solution was heated at room temperature. The solvent was removed under vacuum and the residue dissolved in methylene chloride, washed with water, and dried with sodium sulfate. A white powder recovered with 40% yield was then crystallized by *n*-hexane: mp 136−138 °C; MS (EI) *m*/*z* 292 (M^+, 15); ^{1}H NMR ($CDCl_3$) δ 4.06 (m, 4H), 3.67 (d, $^2J_{P-H} = 32$ Hz, 1H), 1.50 (broad s, 6H), 1.26 (td, $^3J_{H-H} = 7.0$ Hz, $^4J_{P-H} = 0.9$ Hz, 6H), 1.00 (broad m, 12H); ^{13}C NMR ($CDCl_3$) δ 63.24 (d,$^2J_{P-C} = 6.0$ Hz), 59.10 (s), 40.48(s), 33.61 (broad s), 18.42 (broad s), 17.63 (s), 16.58 (d,$^3J_{P-C} = 7.2$ Hz). Anal. Calcd for $C_{13}H_{29}N_2O_3P$: C, 53.4; H, 9.93; N, 9.59. Found: C, 53.3; H, 10.10; N, 8.93.

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