Acyclic β-Phosphonylated Nitroxides: A New Series of Counter-Radicals for "Living"/Controlled Free Radical Polymerization

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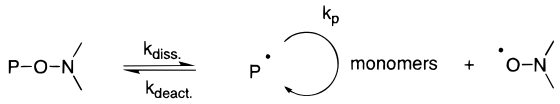
ABSTRACT: Oxidation of α-(*N*-alkylamino) phosphonic acid esters, carrying one or two alkyl groups as substituents on their α-carbon, by *m*-chloroperbenzoic acid afforded the corresponding stable β-phosphonylated nitroxides. The nitroxides derived from α-mono-*tert*-butyl α-alkylaminophosphonic acid esters are stable compounds despite the presence of a hydrogen atom on the α-carbon bound to the nitroxyl group. The ESR study of these nitroxides in solution showed that this β-hydrogen atom lies in the nodal plane to the nitroxyl function. These β-phosphonylated nitroxides were found to efficiently control the free radical polymerization reaction of styrene, with a much faster rate of propagation than that observed in TEMPO-mediated systems.

Introduction

The concept of "living"/controlled free radical polymerization is based on the reversible deactivation of growing polymeric radicals by stable radicals such as nitroxide but also by halogenated forms of metallic complexes, transition metal compounds, etc.... Since the initial report by Rizzardo and Solomon[1] on the use of nitroxides to control free radical polymerization, much progress has been made, and the field is now better understood. Key publications in the domain of nitroxide-mediated polymerization include the contributions of Georges, Matyjaszewski, Hawker, Fukuda, Fischer, and others.[2−15]

One method to bring about "living"/controlled polymerization is to use a conventional thermal initiator such as azobis(isobutyronitrile) (AIBN) or dibenzoyl peroxide (BPO), along with commercially available nitroxides, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). A second method is to resort to alkoxyamines prepared beforehand which can be directly used to trigger polymerization. Both approaches, although technically different, share the same mechanistic concept: growing polymeric radicals go through successive deactivation−dissociation cycles whereby they are alternatively transformed into dormant alkoxyamines and activated into active radicals by thermal homolysis.Nitroxide-mediated polymerizations have been successfully used to control the polymerization of styrene and derivatives so that samples exhibiting rather narrow polydispersities can now be obtained. However, one has to recognize that the rate of polymerization in such systems is sluggish: the constant of equilibrium ($K = k_{diss}/k_{deact}$) is very low and polymerization proceeds because the polystyryl radicals that are independently produced by autopolymerization help to shift the above equilibrium toward active species. The use of additives such as camphorsulfonic acid, benzoic acid, etc., along with TEMPO, results in a higher rate of polymerization of styrene, but the samples obtained in this way are ill-defined.

Scheme 1



Since the ease of homolysis of dormant species is a key point in nitroxide-mediated polymerizations, alkoxyamines that would exhibit higher rates of dissociation than the one based on TEMPO would be highly desirable. Thinking along this line, Moad and Rizzardo[13] demonstrated that the substituents present on the positions α, α′ to the nitroxide function have a significant effect on the homolysis rate constant (k_{diss}) of the corresponding alkoxyamines and showed that the BDE of the NO−C bond could be qualitatively predicted using molecular orbital calculations. Puts and Sogah[14] reported that the polymerization of styrene carried out in the presence of 2,5-dimethyl-2,5-diarylpyrrolidin-1-oxy gives a better molar mass control than TEMPO-mediated systems and is faster.

The overall structure of nitroxides was shown to influence also their rate of coupling with active radicals. Kazmaier et al.[10a] observed that di-*tert*-butylnitroxide allows a faster controlled polymerization of styrene as compared to TEMPO. This difference can be accounted for by a faster rate of homolysis of the dormant species and a lower trapping rate of the active polymer radicals. Thus, acyclic nitroxides appear to be better suited than cyclic homologues to this end.

Despite all these improvements, nitroxide-mediated polymerization still remains of limited applicability: for instance, the level of control that was so far achieved

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in the polymerization of (meth)acrylic monomers is rather poor.[12] To overcome these limitations, the development of novel and more efficient nitroxides would be highly desirable. In this context, stable nitroxides carrying bulky phosphonate substituents in β-position to the nitrogen atoms appear interesting: one nitroxyl radical of this family, namely N-*tert*-butyl-N−(1-diethylphosphono-2,2-dimethyl)propylnitroxyl (**8**), not only was shown to control the free radical polymerization of styrene and *n*-butyl acrylate—which is a major step forward—but it was also demonstrated to foster a much faster rate of propagation than that observed in TEMPO-mediated processes.

This contribution describes the synthesis of a series of original acyclic β-phosphonylated nitroxides that were obtained using a chemistry recently developed by us.[16] The effectiveness of these nitroxides as moderators of free radical polymerization and promoters of a truly "living"/controlled process has then been investigated. Using styrene as the reference monomer, the results obtained with these nitroxides as counter-radicals have been compared with the data generated for TEMPO-mediated systems. In particular, the two criteria of the controlled character, which are the linear variation of $\ln[M]_0/[M]$ as a function of time and the linear evolution of $\bar{M}_n$ with conversion, have been thoroughly checked as well as the efficiency of the initiation step.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 200 or 100 MHz and ^{13}C NMR were run at 50.32 MHz. The chemical shifts (δ) in ppm are referred to internal Me_4Si. Proton-decoupled ^{31}P NMR spectra were recorded at 40.54 MHz, and the chemical shifts (δ) in ppm are referred to external 85% phosphoric acid. ^{19}F NMR spectra were run at 94.22 MHz. Melting points were recorded on a Büchi apparatus B510 and are uncorrected. Mass spectra were recorded on a Varian Mat 311 spectrometer equipped with a direct probe apparatus. Low- and high-resolution mass spectra were measured at 70 eV (EI). Elemental analyses were performed by Service Commun de Microanalyse, Faculté des Sciences et Techniques de Saint Jérôme, Avenue Escadrille Normandie Niemen, F-13397 Marseille Cedex 13, France. ESR spectra were recorded on a Bruker ESP 300 equipped with an ER 035N NMR gaussmeter for field calibration and an HP 5350B microwave frequency counter. Hyperfine splitting coupling constants are given in gauss (G). Chromatographic separations were performed using Silicagel 60, 230−400 mesh, for column chromatography.

General Procedure for the Preparation of α-Aminophosphonates 1, 4, 5, and 6. A mixture of the amine (50 mmol) and the aldehyde or ketone (50 mmol) was stirred at 40 °C for 1 h under nitrogen atmosphere. After addition of diethyl phosphite (100 mmol) at room temperature, the solution was stirred at 40 °C for 24 h. The reaction mixture was then diluted with diethyl ether (100 mL) and washed with 5% aqueous HCl until pH 3. The aqueous phase was extracted with diethyl ether. Sodium hydrogen carbonate was added to the aqueous phase until pH 8 and the aqueous phase was then extracted with diethyl ether (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Distillation of the solvent under reduced pressure afforded the pure α-aminophosphonate.

Diethyl 2,2-Dimethyl-1-(1,1-dimethylethylamino)propylphosphonate (1): 60% yield; colorless oil. ^{31}P NMR ($CDCl_3$): δ 29.84. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99 (s, 9H), 1.06 (s, 9H), 1.28 (t, 6H, J_{HH} = 7.1 Hz), 2.69 (d, 1H, J_{HP} = 17.9 Hz), 4.06 (m, 4H, J_{HH} = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 16.49 (d, J_{CP} = 5.5 Hz), 27.90 (d, J_{CP} = 6.1 Hz), 30.74 (s), 35.24 (d, J_{CP} = 9.6 Hz), 50.93 (s), 59.42 (d, J_{CP} = 132.9 Hz), 61.39 (d, J_{CP} = 7.1 Hz). Anal. Calcd for $C_{13}H_{30}NO_3P$: C, 55.89; H, 10.82; N, 5.01. Found: C, 55.87; H, 10.89; N, 5.04.

Diethyl 1-(1,1-Dimethylethylamino)(2-methylpropyl)-phosphonate (4): 21% yield, colorless oil. ^{31}P NMR ($CDCl_3$): δ 28.08. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (dd, 6H, J_{HP} = 4 Hz, J_{HH} = 8 Hz), 1.09 (s, 9H), 1.32 (t, 6H, J_{HH} = 6.2 Hz), 2.05 (m, 1H), 2.90 (dd, 1H, J_{HP} = 19.2 Hz, J_{HH} = 3 Hz), 4.07−4.17 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 16.33 (d, J_{CP} = 6 Hz), 18.63 (d, J_{CP} = 3 Hz), 19.44 (d, J_{CP} = 4.5 Hz), 30.16 (s), 31.50 (d, J_{CP} = 6.5 Hz), 50.69 (d, J_{CP} = 6 Hz), 54.55 (d, J_{CP} = 144.5 Hz), 61.25 (d, J_{CP} = 8.5 Hz), 61.81 (d, J_{CP} = 6 Hz). Anal. Calcd for $C_{12}H_{28}NO_3P$: C, 54.32; H, 10.64; N, 5.28. Found: C, 54.08; H, 10.49; N, 5.13.

Diethyl Cyclohexyl-1-(1-phenylethylamino)phosphonate (5): 78% yield; colorless oil. ^{31}P NMR ($CDCl_3$): δ 30.23. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.14−1.80 (m, 19H), 4.14−4.33 (m, 5H), 7.29−7.47 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.49 (d, J_{CP} = 2.52 Hz), 16.61 (d, J_{CP} = 2.52 Hz), 19.77 (d, J_{CP} = 13.08 Hz), 19.98 (d, J_{CP} = 13.08 Hz), 25.42 (s), 26.93 (s), 28.07 (d, J_{CP} = 5.53 Hz), 32.64 (d, J_{CP} = 3.02 Hz), 52.39 (s), 56.26 (d, J_{CP} = 137.4 Hz), 61.30 (d, J_{CP} = 8.05 Hz), 61.65 (d, J_{CP} = 8.05 Hz), 126.01 (s), 126.48 (s), 127.86 (s), 148.72 (s). Anal. Calcd for $C_{18}H_{30}NO_3P$: C, 63.70; H, 8.91; N, 4.13. Found: C, 62.32; H, 9.17; N, 4.28.

(*S*)-(−)-Diethyl Cyclohexyl-1-(1-phenylethylamino)-phosphonate) ((−)-5). Purification by silica gel chromatography (dichloromethane−ethanol 9:1) afforded compound **(−)-5** (13% yield) as a colorless oil. ^{31}P NMR ($CDCl_3$): δ 30.27. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04−1.79 (m, 19H), 4.10 (m, 4H), 4.39 (dq, 1H, J_{HH} = 6.4 Hz, J_{HP} = 4 Hz), 7.15−7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 16.43 (d, J_{CP} = 6 Hz), 19.61 (d, J_{CP} = 12 Hz), 19.90 (d, J_{CP} = 9.5 Hz), 25.31 (s), 26.81 (s), 27.97 (d, J_{CP} = 4.5 Hz), 32.51 (s), 52.32 (s), 57.14 (d, J_{CP} = 137 Hz), 61.17 (d, J_{CP} = 8.5 Hz), 61.52 (d, J_{CP} = 8 Hz), 125.89 (s), 126.35 (s), 127.74 (s), 148.58 (s). $[\alpha]_D^{20}$ = −75° (*c* 0.14 g/100 mL, EtOH). Anal. Calcd for $C_{18}H_{30}NO_3P$: C, 63.70; H, 8.91; N, 4.13. Found: C, 63.71; H, 8.87; N, 4.11.

Diethyl 1-(4-*tert*-Butylphenylamino)-1-methylethylphosphonate (6): 54% yield; light yellow crystals; mp 121 °C. ^{31}P NMR ($CDCl_3$): δ 29.57. ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.25 (t, 6H, J_{HH} = 5.68 Hz), 1.27 (s, 9H), 1.48 (d, 6H, J_{HP} = 15.63 Hz), 3.63 (s, 1H), 4.08 (dq, 4H, J_{HH} = J_{HP} = 5.68 Hz), 6.90 (d, 2H, J_{HH} = 8.53 Hz), 7.19 (d, 2H, J_{HH} = 8.53 Hz). ^{13}C NMR ($CDCl_3$): δ 16.50 (d, J_{CP} = 5.7 Hz), 24.07 (s), 31.52 (s), 34.09 (s), 54.85 (d, J_{CP} = 154.1 Hz), 62.44 (d, J_{CP} = 7.4 Hz), 121.47 (s), 125.48 (s), 142.17 (d, J_{CP} = 8 Hz), 144.22 (s). Anal. Calcd for $C_{17}H_{30}NO_3P$: C, 62.37; H, 9.24; N, 4.28. Found: C, 62.25; H, 9.11; N, 4.24.

Dibenzyl 2,2-Dimethyl-1-(1,1-dimethylethylamino)propylphosphonate (2). A mixture of *tert*-butylamine (4.38 g, 60 mmol) and pivalaldehyde (5.16 g, 60 mmol) dissolved in pentane (50 mL) was stirred at 40 °C for 1 week, with azeotropic distillation of the water with the help of a Dean−Stark apparatus. Dibenzyl phosphite (15.73 g, 60 mmol) was then added under nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 4 h. A white precipitate was filtered off and the mixture was washed with water (50 mL) and dried over anhydrous Na_2SO_4. Distillation of the solvent under reduced pressure afforded the title compound **2** (4.8 g, 20%) as a pale yellow oil. ^{31}P NMR ($CDCl_3$): δ 30.66 ppm. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05 (s, 18H), 2.83 (d, 1H, J_{HP} = 17.8 Hz), 4.94 (d, 4H, J_{HP} = 7.6 Hz), 7.31 (s, 5H). ^{13}C NMR ($CDCl_3$): δ 27.92 (d, J_{CP} = 6.6 Hz), 30.61 (s), 35.28 (d, J_{CP} = 10 Hz), 50.92 (s), 59.94 (d, J_{CP} = 131.5 Hz), 67.01 (t, J_{CP} = 8.5 Hz), 127.97 (s), 128.12 (s), 128.47 (s), 136.74 (s). Anal. Calcd for $C_{23}H_{34}NO_3P$: C, 68.81; H, 8.03; N, 3.49. Found: C, 68.53; H, 8.10; N, 3.32.

Bis(2,2,2-trifluoroethyl) 2,2-Dimethyl-1-(1,1-dimethylethylamino)propylphosphonate (3). A mixture of *tert*-butylamine (4.38 g, 60 mmol) and pivalaldehyde (5.16 g, 60 mmol) dissolved in pentane (50 mL) was stirred at 40 °C for 5 days, with azeotropic distillation of the water with the help of a Dean−Stark apparatus. Bis(2,2,2-trifluoroethyl) phosphite (14.8 g, 60 mmol) was then added at room temperature, under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 2 h. The solvent was distilled under

reduced pressure to give **3** (15.66 g, 67%) as a colorless oil. ^{31}P NMR ($CDCl_3$): δ 30.09. ^{19}F NMR (94.22 MHz, $CDCl_3$): δ −75.53 (J_{HF} = 5.75 Hz). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.12 (s, 9H), 3.05 (d, 1H, J_{HP} = 15.2 Hz), 4.37 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 27.66 (d, J_{CP} = 7.2 Hz), 30.34 (s), 34.91 (d, J_{CP} = 10.3 Hz), 51.18 (d, J_{CP} = 3.2 Hz), 60.72 (d, J_{CP} = 140.1 Hz), 62.04 (m), 123.55 (m). Anal. Calcd for $C_{13}H_{24}F_6NO_3P$: C, 40.32; H, 6.25; N, 3.62. Found: C, 40.26; H, 6.26; N, 3.57.

Diethyl 1-(4-*tert*-Butylphenylamino)ethylphosphonate (7). A solution of 4-*tert*-butylaniline (0.72 g, 5 mmol) and acetaldehyde (0.21 g, 5 mmol) in dry dichloromethane (10 mL) was stirred at room temperature for 15 min. Formation of *N*-(4-*tert*-butylphenyl)ethylidenylimine (**17**) was checked by NMR. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 9H), 2.16 (m, 3H), 6.61 (d, 2H, J_{HH} = 8.01 Hz), 7.16 (d, 2H, J_{HH} = 8.01 Hz), 7.95 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 22.89, 31.40, 33.77, 114.80, 125.89, 141.23, 143.66, 161.56. Under a dry atmosphere of nitrogen, diethyltrimethylsilyl phosphite (1.25 mL, 5.5 mmol) was added dropwise. The solution was left at room temperature for 2 days. The reaction mixture was then poured into water (20 mL), and the organic products were extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and distilled under reduced pressure. Purification of the residue by silica gel column chromatography (diethyl ether) afforded compound **7** (0.32 g, 20%) as a white solid, mp 68 °C. ^{31}P NMR ($CDCl_3$): δ 26.21. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.27 (t, 6H, J_{HH} = 3.10 Hz), 1.4−1.6 (m, 4H), 3.30 (s, 1H), 4.13 (dq, 4H, J_{HH} = J_{HP} = 7.81 Hz), 6.61 (d, 2H, J_{HH} = 8.71 Hz), 7.20 (d, 2H, J_{HH} = 8.71 Hz). ^{13}C NMR ($CDCl_3$): δ 15.82 (s), 16.40 (d, J_{CP} = 6.34 Hz), 31.45 (s), 33.82 (s), 46.49 (d, J_{CP} = 158.49 Hz), 62.0 (d, J_{CP} = 7.55 Hz), 62.89 (d, J_{CP} = 7.55 Hz), 113.39 (s), 125.98 (s), 141.08 (s), 143.98 (s). Anal. Calcd for $C_{16}H_{28}NO_3P$: C, 61.32; H, 9.01; N, 4.47. Found: C, 61.38; H, 9.06; N, 4.48.

General Procedure for the Oxidation of the α-Aminophosphonates into the β-Phosphonylated Nitroxides. A solution of *m*-chloroperbenzoic acid (8 mmol) in dichloromethane (20 mL) was added at 0 °C to a solution of the α-aminophosphonate (8 mmol) in dichloromethane (10 mL). The mixture was stirred for 6 h at room temperature. Then a saturated aqueous solution of sodium hydrogen carbonate was added until pH neutral. The organic phase was successively washed with water, 1 M aqueous sulfuric acid, water, saturated aqueous sodium hydrogen carbonate, and water and dried over anhydrous Na_2SO_4. Distillation of the solvent under reduced pressure afforded an oil which was purified by silica gel chromatography (dichloromethane−THF−pentane 1:1:2).

***N*-*tert*-Butyl-*N*-[1-diethylphosphono(2,2-dimethylpropyl)]nitroxide (8):** 48% yield; orange oil; MS *m*/*z* 294 (M^+, 1), 238 (2), 57 (100); HRMS (EI, 70 eV) exact mass calculated for $C_{13}H_{29}NO_4P$ $[M]^+$ 294.1834, found 294.1837. Anal. Calcd for $C_{13}H_{29}NO_4P$: C, 53.06; H, 9.93; N, 4.76. Found: C, 53.01; H, 9.91; N, 4.73.

***N*-*tert*-Butyl-*N*-[1-dibenzylphosphono-(2,2-dimethylpropyl)]nitroxide (9):** 25% yield; yellow crystals; mp 66 °C; MS *m*/*z* 294 (M^+, 1), 238 (2), 57 (100); HRMS (EI, 70 eV) exact mass calculated for $C_{23}H_{33}NO_4P$ $[M]^+$ 418.2147, found 418.2159. Anal. Calcd for $C_{23}H_{33}NO_4P$: C, 66.01; H, 7.95; N, 3.35. Found: C, 66.07; H, 7.89; N, 3.40.

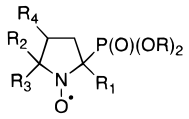
***N*-*tert*-Butyl-*N*-(1-diethylphosphono-2-methylpropyl)-nitroxide (11):** 42% yield; orange oil. Anal. Calcd for $C_{12}H_{27}NO_4P$: C, 51.42; H, 9.71; N, 5.00. Found: C, 51.34; H, 9.66; N, 5.03.

***N*-(1-Methylbenzyl)-*N*-[1-cyclohexyl-1-(diethylphosphono)]nitroxide (12):** 37% yield; orange oil. Anal. Calcd for $C_{18}H_{29}NO_4P$: C, 61.00; H, 8.25; N, 3.95. Found: C, 61.07; H, 8.27; N, 3.83.

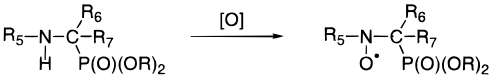
(+)-*N*-(1-Methylbenzyl)-1-cyclohexyl-1-(diethylphosphono)nitroxide (+)-(12): 42% yield; orange oil; $[\alpha]_D^{20}$ = +14° (*c* 0.22 g/100 mL, EtOH). Anal. Calcd for $C_{18}H_{29}NO_4P$: C, 61.00; H, 8.25; N, 3.95. Found: C, 60.87; H, 8.24; N, 3.91.

***N*-(4-*tert*-Butylphenyl)-1-diethylphosphono-1-(methylethyl)nitroxide (13):** 91% yield; red paste. Anal. Calcd for $C_{17}H_{29}NO_4P$: C, 59.63; H, 8.54; N, 4.09. Found: C, 59.57; H, 8.52; N, 4.03.

Scheme 2



Scheme 3



1: R_5 = *t*-Bu; R_6 = H; R_7 = *t*-Bu; R = Et **8**
2: R_5 = *t*-Bu; R_6 = H; R_7 = *t*-Bu; R = $PhCH_2$ **9**
3: R_5 = *t*-Bu; R_6 = H; R_7 = *t*-Bu; R = CF_3CH_2 **10**
4: R_5 = *t*-Bu; R_6 = H; R_7 = *i*-Pr; R = Et **11**
5: R_5 = PhCH(Me); R_6, R_7 = $(CH_2)_5$; R = Et **12**
6: R_5 = 4-*t*-BuC_6H_4; R_6 = R_7 = Me; R = Et **13**
7: R_5 = 4-*t*-BuC_6H_4; R_6 = H; R_7 = Me; R = Et **14**

Polymerization Experiments. Azobis(isobutyronitrile) (AIBN) (Aldrich) was recrystallized from its ether solution. Styrene (Aldrich) was distilled under reduced pressure prior to use. The polymerizations were carried out in a dry Schlenk tube. Nitroxide, monomer, and the required amount of initiator were introduced into the reaction tube, under inert atmosphere. The mixture was thoroughly degassed before being heated to the desired temperature. Aliquots were removed at different time intervals and characterized by gel permeation chromatography (GPC) with THF as eluent, using TSK columns calibrated with polystyrene standards. The conversion was determined by gravimetry after precipitation of the sample by MeOH.

Results and Discussion

Stable β-phosphonylated pyrrolidinoxy radicals, such as the family of 2-dialkylphosphono-2,5,5-trialkylpyrrolidinoxy type compounds (Scheme 2), have been synthesized, using a chemistry recently developed in our laboratory.[16]

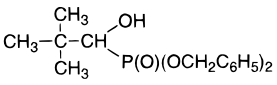
These nitroxides were obtained by oxidation of the corresponding 1-aminoalkylphosphonic acid esters, the synthesis of which involves a cyclization reaction by intramolecular aminomercuration of the appropriate alkenylaminophosphonates followed by reduction with sodium borohydride.

Following a similar approach, we have synthesized a series of acyclic β-phosphonylated nitroxides (Scheme 3) by oxidation of the appropriate acyclic α-aminophosphonates and studied their ESR characteristics.

Synthesis of the α-Aminophosphonates 1−7. α-Aminophosphonic acid and their derivatives exhibit a variety of biological activities. Therefore, a large number of studies on the synthesis of acyclic α-aminophosphonates and their corresponding acids has been reported.[17] Three major types of synthetic approaches have been developed to this end: (a) the one-pot reaction of a carbonyl compound with an amine and a dialkyl phosphite (referred to as the Kabachnik−Fields reaction),[18] (b) the addition of a phosphorus reagent [$(EtO)_2POR$] to an imine,[19,17a] or (c) the addition of phosphorus trichloride to a α-hydroxyamine derivative.

The Kabachnik−Fields reaction has been frequently used for the synthesis of acyclic α-aminophosphonic acid derivatives.[18] The alternative procedure, which involves the in situ generation of an imine followed by reaction with the appropriate trivalent phosphorus reagent, generally affords high yields of α-aminophosphonic acid

Scheme 4



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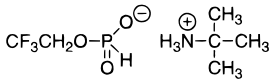
Scheme 5



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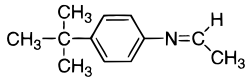
Scheme 6



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derivatives.[19,17a] To prepare the diethylphosphono derivatives **1**, **4**, **5**, and **6**, we resorted to a modification of the Kabachnik−Fields reaction. A mixture of equimolar amounts of amine and carbonyl compound was stirred for 1 h at room temperature. A small excess of diethyl phosphite was then added. After workup, the compounds **1**, **4**, **5**, and **6** were isolated in yields ranging from modest (**4**: 21%) to relatively good (**5**: 78%) values. However, when using this procedure for the synthesis of aminophosphonates **2** and **3**, an unexpected result was obtained. In the case of the reaction of pivalaldehyde with *tert*-butylamine and dibenzyl phosphite, the major product formed was dibenzyl (2,2-dimethyl-1-hydroxypropyl)phosphonate (**15**). This compound is actually the product of the direct addition of dibenzyl phosphite to pivalaldehyde (Scheme 4).[20]

In the case of the reaction of pivalaldehyde with *tert*-butylamine and bis(2,2,2-trifluoroethyl) phosphite, the expected aminophosphonate **3** was not obtained. Instead, the major product formed appeared to be *N*-*tert*-butylammonium mono(2,2,2-trifluoroethyl) phosphite (**16)** (Scheme 5). This product results from the hydrolysis of the phosphite catalyzed by *tert*-butylamine.[21,22]

To avoid these drawbacks, we came to generate the imine in situ, the water formed being removed from the reaction mixture by azeotropic distillation. After formation of the imine, the phosphite reagent was added to the mixture. In this way, the α-aminophosphonate **2** could be obtained, although in a poor 20% yield, the phosphite used in this case being dibenzyl phosphite; as to the α-aminophosphonate **3**, it was obtained in 67% yield by reaction of the same imine with bis(2,2,2-trifluoroethyl) phosphite. When applied to the synthesis of the aminophosphonate **7**, which derives from acetaldehyde, 4-*tert*-butylaniline, and diethyl phosphite, both procedures were found unsuccessful. Formation of the corresponding *N*-(4-*tert*-butylphenyl)ethylidenylimine (**17**) was confirmed by NMR (Scheme 6) but all attempts to isolate it failed. However, treatment of a solution of **17** in anhydrous dichloromethane with diethyl trimethylsilyl phosphite at room temperature afforded the expected aminophosphonate **7** in a modest 20% yield.

Oxidation of the α-Aminophosphonates 1−7. Treatment of the α-aminophosphonates **1**, **2**, **4**, **5**, and **6** with 1 mol equiv of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane gave the corresponding nitroxides **8**, **9**, **11**, **12**, and **13**. Nitroxides **8**, **11**, **12**, and **13** were isolated as oils in 48, 42, 37, and 91% yields, respectively. The nitroxide **9** was obtained in 25% yield as a solid. Because of the nature of the starting amine, the nitroxide **12** could also be prepared as an optically active compound. Oxidation of the chiral α-aminophosphonate **(*S*)-(−)-5** $\{[\alpha]_D^{20} = -75°$ (*c* 0.14 g/100 mL, EtOH)$\}$, resulting from the reaction of cyclohexanone with (*S*)-(−)-1-phenylethylamine and diethyl phosphite, led to the chiral nitroxide **(+)-12** $\{[\alpha]_D^{20} = +14°$ (*c* 0.22 g/100 mL, EtOH)$\}$ in 42% yield. The nitroxide **8** was also obtained in 45% yield through oxidation of aminophosphonate **1** by oxone in acetone,[23] without distillation of the in situ generated dimethyldioxirane,[24] which served as the effective oxidation agent. In the case of the oxidation of α-aminophosphonate **3**, its reaction with *m*-CPBA or with 30% hydrogen peroxide, catalyzed with sodium tungstate, led to a mixture containing the expected nitroxide **10**, as detected by ESR. Unfortunately, all attempts to isolate it as a pure compound failed. Similarly, oxidation of the aminophosphonate **7** with *m*-CPBA led to a mixture containing the nitroxide **14**. Even though it was detected by ESR, attempts to isolate it were unsuccessful.

Table 1. ESR Features of Nitroxides 8−14 in Dichloromethane at Room Temperature

nitroxide	a_N/G	a_P/G	a_H/G	g
8	14.27	45.26		2.0061
9	14.27	45.88		2.0061
10	14.27	45.26		2.0062
11	14.27	47.76	0.99	2.0061
12	13.96	59.34	2.40	2.0061
13	12.71	36.18	0.87	2.0059
14	14.10	45.09		2.0061

ESR Study and Stability of the Nitroxides. The nitroxides **8**−**14** were studied by ESR, either pure or as crude products. The ESR features of these nitroxides are reported in Table 1.

To measure their stability, the isolated nitroxides were characterized by ESR in dichloromethane solution and the evolution of their ESR was monitored as a function of time. Although they contain an H atom in the β- or β'-position, the nitroxides **8**, **9**, **11**, and **12** are stable compounds which could be isolated and stored either neat or in solution. Despite the presence of a *tert*-butyl group in the *para* position of the aromatic ring in order to avoid possible decomposition reactions,[25] nitroxides **13** and **14** were only persistent for a short period of time (24 h to a few days). Nitroxide **14** appeared to exhibit a limited stability, as its ESR signal disappeared completely after 24 h at ambient temperature.

The a_N and a_P couplings in **8**, **9**, **10**, and **11** are similar, thus providing evidence that all these nitroxides adopt similar conformations. Furthermore, the β-couplings in phosphonylated nitroxides follow the McConnell relation: $a_H = B_H \cos^2 \theta_H$ and $a_P = B_P \cos^2 \theta_P$. θ_H is the dihedral angle between the planes $N-C_\alpha-H_\beta$ and $C_\alpha-N-2p_z$ whereas θ_P is the dihedral angle between the planes $N-C_\alpha-P_\beta$ and $C_\alpha-N-2p_z$, $2p_z$ being the principal direction of the $2p_z$ orbital of the nitrogen atom in the nitroxide. On the basis of force field calculations,[26] a value close to 60 G was proposed for B_P in acyclic β-diethylphosphono nitroxides.[16d,27] In the nitroxides **8**, **9**, **10**, and **11**, the hydrogen in the β-position was "invisible" as indicated by a θ_H angle close to 90° and, consequently, a θ_P angle close to 30° (Figure 1). This last value, combined with the phosphorus−hfs value of 45 G, corresponds to $B_P = 60$ G which is in good agreement with our previously reported value.

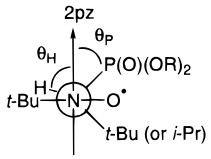

Figure 1. Conformation of the nitroxides **8**, **9**, **10**, and **11**.

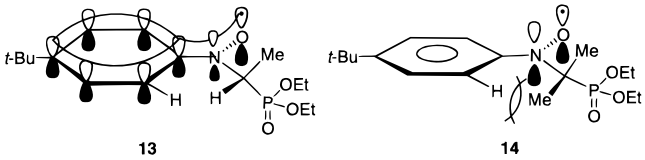

Figure 2. Steric effects on the electron spin delocalization in nitroxides **13** and **14**.

These results allowed us to assume for the nitroxides **8**, **9**, **10**, and **11** the existence of a largely predominant conformer at ambient temperature in which the H atom of the α-carbon bound to the nitroxide moiety is eclipsed by a bulky alkyl group. This conformation explains their stability, preventing the disproportionation of these nitroxides. The influence of steric hindrance due to the two *tert*-butyl groups was also reflected in the X-ray structure. Indeed, the X-ray crystallographic structure of nitroxide **9**[28] was characterized by a large C−N−C angle (126.5°), and by long Cα−Cβ (1.55 Å) and Cα−Pβ (1.83 Å) bonds. These experimental data supported our calculations and led to a B_P value of 64 G for the dibenzylphosphononitroxide **9**. The X-ray structure and the ESR study show that the nitroxide **9** adopts a same conformation, in the solid state as well as in solution. This influence of the steric hindrance in nitroxides possessing a β-hydrogen atom was also observed by Reznikov et al.[29] They recently reported the stability of acyclic nitroxides, bearing such a β-hydrogen atom, in which the nitroxyl function is directly linked to a diphenylmethyl group.[29]

In the case of the arylnitroxide **13**, steric interactions between the aromatic ring and the hydrogen present on the α-carbon are negligible. Therefore, the electron density can be delocalized over the aromatic ring, and this results in a rather low value for the a_N coupling constant (12.7 G). In the arylnitroxide **14**, the α-carbon bears two methyl substituents. Steric hindrance between these methyl groups and the *ortho* aromatic hydrogen prevents the conjugation between the aromatic ring and the nitroxide group. Thus, the electron density is no more delocalized and the a_N coupling constant raises to a higher value (14.1 G).

"Living"/Controlled Free Radical Polymerization Mediated by β-Phosphonylated Nitroxides. As discussed earlier, the vast majority of stable radicals investigated in this contribution are acyclic β-hydrogen-bearing nitroxides whose α-carbons carry a phosphonate derivative as substituent. They were all used under the same experimental conditions, AIBN being the initiator chosen for this screening procedure. The polymerizations were carried out at 120 °C and the [monomer] to [initiator] ratio was set so as to obtain samples with $\bar{M}_n$ = 20 000 g/mol at complete conversion, assuming an ideal initiator efficiency of 1. The effectiveness of **8** as moderator of the free radical polymerization of styrene (and also of *n*-butyl acrylate) has already been shown: using AIBN as initiator, polystyrene samples exhibiting expected molar masses and polydispersities in the range 1.1−1.3 could be obtained up to $\bar{M}_n = 10^5$. After their creation, the chains were seen to grow under truly "living"/controlled conditions, a linear relationship being obtained between ln $[M]_0/[M]$ and time on one hand and between $\bar{M}_n$ and conversion on the other.[30,31] For the initiation step to occur with an efficiency close to 1, it was found necessary to use a slight excess of **8** ([**8**]/[AIBN] = 2.5) as compared to the initiating radicals. Under these conditions, almost no radical resulting from the decomposition of AIBN was lost in irreversible termination, the presence of this slight excess of stable radicals helping to artificially secure the so-called "persistent radical effect". In this way, the system could be prevented from generating, by irreversible termination, the excess of stable radicals it requires to proceed under "living" conditions: a controlled process could thus be achieved from the very onset of polymerization (Table 2, Figure 3).

When the same [nitroxide] to [initiator] ratio of 2.5 was applied with TEMPO as the counter-radical, a 2-h-long induction period was observed before the polymerization actually occurred (Figure 3); in the latter case, the chains were found to grow at a much slower pace than that measured for systems mediated by β-hydrogen-containing nitroxides. Samples exhibiting lower molar masses than those actually targeted were

Table 2. Free Radical Polymerization of Styrene Carried out in the Presence of Miscellaneous Nitroxides 8−15, Using AIBN as Initiator ($[AIBN]_0 = 2.2 \times 10^{-2}$ M) and a [Nitroxide] to [AIBN] Ratio of 2.5

nitroxide	time (min)	conversion (%)	$\bar{M}_{n,th}$	$\bar{M}_{n,exp}$	f	I^a
8	100	40	8000	8500	∼0.95	1.12
	210	60	12200	12500	∼1	1.11
	420	80	16700	16000	∼1	1.11
TEMPO	100	∼0				
	450	20	4000	3500	>1	1.2
	620	40	8000	7500	>1	1.18
	960	75	15000	13000	>1	1.16
9	100	29	5800	5800	1	1.07
	210	54	11200	11000	1	1.07
	420	77	14900	10000	∼1	1.08
10	100	50	10000	21000	0.48	1.27
	210	65	13000	24000	0.53	1.40
	420	85	17000	31000	0.54	1.72
12	100	60	12400	18600	0.65	1.39
	210	87	17500	24500	0.7	1.40
	420	>95	20000	29000	0.7	1.42
13	100	20	4000	25000	u[b]	1.27
	210	35	7000	26000	u	1.4
	420	70	14000	26000	u	1.7
18	100	20	4000	4000	1	1.10
	210	40	8000	7000	∼0.9	1.08
	420	60	12000	11900	∼1	1.08

[a] $I = \bar{M}_w/\bar{M}_n$. [b] Uncontrolled; f (=$\bar{M}_{n,th}/\bar{M}_{n,exp}$) is the efficiency of the initiating step.

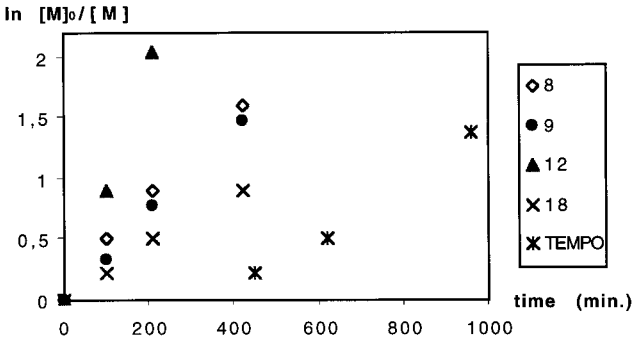

Figure 3. Variation of $\ln[M]_o/[M]$ as a function of time for free radical polymerizations of styrene mediated by miscellaneous nitroxides (see Table 2 for conditions).

obtained, indicating that a substantial amount of chains were created by thermal autopolymerization of styrene.

High values of k_{diss} and small values of k_{deact} (Scheme 1) are the main favorable factors controlling living radical polymerizations.[9c] The differences observed between **8** and TEMPO can be accounted for by the difference in the equilibrium constant ($K = k_{diss}/k_{deact}$) for the reversible homolysis of the dormant species involved in the controlled polymerization. We have determined[32] $K_{\mathbf{8}}$ and K_{TEMPO} for model alkoxyamines obtained by trapping the 2-phenylethyl radical with **8** and TEMPO, respectively. We found that at 123 °C, $K_{\mathbf{8}} = 9.8 \times 10^{-10}$ M and $K_{TEMPO} = 2.1 \times 10^{-12}$ M. Thus, the rate of dissociation of **8**−CH(Me)Ph is about 10 times larger than that of the TEMPO analogue while the rate of trapping of the 2-phenylethyl radical is about 45 times larger with TEMPO.

Quite different is the situation that prevailed when the phosphonylated nitroxides **9**−**12** were used to control the polymerization (Table 2, Figure 3). When considering the results obtained with **8** and **9**, it appears that these two counter radicals behave very similarly. The rate of polymerization of the process mediated by **9** is only marginally smaller than that determined for the system controlled by **8**. On the other hand, the samples obtained in the presence of **9** exhibit an even better degree of control with polydispersities lower than 1.1. The presence of a bulkier phosphonate substituent in **9** seems not to affect significantly its propensity to efficiently recombine with active radicals. Attempts at using a β-hydrogen-bearing nitroxide of the same family, substituted with a bis(trifluoroethyl) phosphonate group (**10**), yielded samples with broader molar mass distributions and poorer degree of control. Obviously, the rate of polymerization is faster with **10** as counter radical in lieu of **8**. On the other hand, the polydispersity indices of the samples tend to increase with the conversion which suggests that a substantial amount of growing chains were lost in irreversible termination throughout polymerization. Considering that the efficiency of the initiation step is not higher than 0.55, this shows that **10** is not as appropriate as **8** or **9** to control the polymerization of styrene under the experimental conditions used. Whether this lack of reactivity of **10** and the poor control that results stem from mere steric hindrance due to the bulkiness of the phosphonate group or from the presence of electron-withdrawing fluorine atoms is an unsettled matter that deserves further investigation. Compared to the previous phosphonylated nitroxides **12** is also an acyclic β-hydrogen-bearing nitroxide but its β-hydrogen atom is not carried by the phosphonate-substituted carbon but by the other α-carbon. The polymerization of styrene carried out in the presence of **12** appears much faster than the one controlled by **8**, all of the monomer being almost exhausted after 7 h. Despite the excess of **12** present in the reaction medium, the initiation step could not be controlled as efficiently as it was with **8**. The initiator efficiency indeed revolves around 0.7, indicating that about 30% of the initiating radicals were lost in irreversible deactivation. This merely reflects the difficulty experienced by **12** to efficiently trap active alkyl radicals, certainly because of steric reasons. This results in a shift of the equilibrium between dormant and active species toward the latter and eventually in a faster rate of propagation. As **12** is not as good as **8** at trapping active radicals, each active chain has more room for growth before being transformed into a dormant species: the samples obtained under these conditions therefore exhibited larger polydispersities.

Besides these β-phosphonylated nitroxides that are all original, other β-hydrogen-carrying nitroxides were also reported to be truly stable. One of them, namely *tert*-butyl(phenylisopropyl)methylnitroxide, **18**, was prepared according to the method of Reznikov and Volodarky[29] and subsequently used to control the polymerization of styrene.[30,31a] Nitroxide **18** appears to be an excellent moderator of free radical polymerization, affording samples of controlled size and rather low polydispersities. However, the rate of polymerization in the process mediated by **18** is slower than that observed for the polymerization controlled by **8**. This indicates that the equilibrium is shifted toward dormant species with **18** as counter radical. Whether this feature results from a faster rate of trapping of active radicals by **18** and/or from a slower rate of decomposition of the corresponding alkoxyamine is a question that could be answered only after carrying out a kinetic investigation.

Moreover, the use of **18** and its 2-phenylethyl radical alkoxyamine in living radical polymerizations has been subsequently reexamined and extended by Benoit et al.[4c]

All the nitroxides so far tried contain a β-hydrogen atom, besides a β-phosphonate group for some of them. To better understand the effect of the nitroxide structure on the success or the failure of "living"/controlled free radical polymerization, a β-phosphonylated nitroxide free of any β-hydrogen atom (**13**) was purposely synthesized. When used to mediate the free radical polymerization of styrene, **13** is found not to bring about a controlled propagation; regardless of the conversion considered, samples with essentially similar molar masses were indeed obtained. This shows that the presence of a non entirely substituted α-tertiary carbon in the nitroxide is essential to obtain "living"/controlled polymerization. As to the β-phosphonate groups that were introduced in the majority of nitroxides investigated, they appear to essentially impart additional steric hindrance around the stable radical, contributing to gently shift the equilibrium toward active species.

Conclusion

A series of original β-phosphonylated nitroxides was prepared following a chemistry recently disclosed and used as moderators in the free radical polymerization of styrene. When TEMPO-mediated processes are compared with these polymerizations, not only is the "living"/controlled character of the latter well established but also their overall rate of propagation is much faster under the same experimental conditions. The nitroxides that are the best suited to this end are those bearing a β-hydrogen atom beside their β-phosphonate substituent. One of them, namely **8**, can even be viewed as a multifaceted counter radical since not only styrene but also *n*-butyl acrylate could be polymerized under "living"/controlled conditions in its presence.

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(20) Compound **15** has been characterized: ^{31}P NMR (d_6-acetone): δ 29.30. ^{1}H NMR (100 MHz, d_6-acetone): δ 1.10 (s, 9H), 3.38 (broad m, 1H), 3.74 (d, 1H, J_{HP} = 8 Hz), 5.09 (m, 4H), 7.35 (m, 10H). Anal. Calcd for $C_{19}H_{25}O_4P$: C, 65.51; H, 7.23. Found: C, 65.72; H, 7.37.
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(22) Compound **16** has been characterized: mp 168 °C. ^{31}P NMR (D_2O): δ 7.40. ^{19}F NMR (94.22 MHz, D_2O): δ −73.09 (J_{HF} = 9.4 Hz). ^{1}H NMR (100 MHz, D_2O): δ 1.36 (s, 9H), 4.3 (m, 2H), 6.81 (d, 1H, J_{HP} = 653.8 Hz). MS: m/z 237 (M^+, 21), 165 (43), 74 (82), 57 (100). Anal. Calcd for $C_6H_{15}F_3NO_3P$: C, 30.39; H, 6.38; N, 5.91; F 24.03. Found: C, 30.49; H, 6.27; N, 5.89; F 23.5.
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