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Synthesis of New Tetraethyl(*N*-alkyl-1-aminoethan-1,1-diyl)bisphosphonates and ESR Analysis of Chemical Exchange of Derived Nitroxides of Acyclic Aminobisphosphonates.

Short Title: ESR analysis of nitroxides of aminobisphosphonates

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Abstract

The synthesis and the full characterization of two new linear bisphosphonates (tetraethyl(*N*-*tert*butyl-1-aminoethan-1,1-diyl)bisphosphonate and tetraethyl(*N*-*sec*butyl-1-aminoethan-1,1-diyl)bisphosphonate) and the first analysis of the ESR spectra of the corresponding nitroxides is reported. The preliminary results of theoretical calculations on model compounds suggest a small B_0 (in the McConnell equation). The results of bisphosphonate ester and bisphosphonic

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acid are similar. The discrepancies of P coupling for the diphosphorus compound stems from B_2 that is different when the dihedral angle is larger than 90 degree.

Keywords

Bisphosphonates; diphosphorylation; ESR; nitroxide; theoretical calculations; McConnell equation

INTRODUCTION

The radical polymerization has interesting property as it is more tolerant towards trace impurities than ionic or coordination polymerization.^[1] It requires absence of oxygen but can be carried out in the presence of water.^[2] Unfortunately, the control over the macromolecules is worse in radical polymerization than in ionic polymerization.^[2] To increase the polymerization control, the use of nitroxides has been suggested.^[1] Nitroxyl radicals are observed to result in a better control of the molecular weight, polydispersity and termination processes. The action of a nitroxyl radical occurs through a reversible coupling between the nitroxide and the growing polymeric chain. (Scheme 1)

Insert scheme 1

To clarify the role of nitroxyl radical in the polymerization process, some information about its conformational behavior needs to be known. We have already demonstrated it for geminally diphosphorylated pyrrolidinoxyl radicals^[3] where the combination of ring pseudo-rotation with the internal rotation of phosphoryl groups produces at least four nonequivalent sites.

In this paper, we describe the synthesis of two new bisphosphonates, namely the tetraethyl(*N*-*tert*butyl-1-aminoethan-1,1-diyl)bisphosphonate **1** and the tetraethyl(*N*-*sec*butyl-1-aminoethan-1,1-diyl)bisphosphonate **2** molecules (Scheme 2) and perform the full ESR^[4] analysis of the chemical exchange of various nitroxides formed from the oxidation of **1** and **2**. (Scheme 2)

Insert Scheme 2

RESULTS AND DISCUSSION

Synthesis

The synthesis of **1** and **2** is described in Scheme 3. It uses a one step reaction that has been described elsewhere.^[5-7] At -7.5 °C under nitrogen atmosphere POCl₃ (2 mol.) is slowly added to a mixture of the corresponding amide (1 mol. eq) and triethylphosphite (2 mol. eq). After stirring the mixture for one hour at room temperature, it is poured over a cold aqueous solution saturated with NH₄OH. After work-up, the corresponding aminobisphosphonates are obtained with several yields. (Table I) Compounds **3** and **4** are prepared using the procedure of Lessard^[8] and of Sagar^[9], respectively.

Insert Scheme 3

Insert Table I

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Using the same procedure, Grimaldi^[10] prepared the tetraethyl *N*-*tert*butyl aminomethylene bisphosphonate **5** with a yield of 56%. Compared to **1** and **2**, which have one additional methyl group on the carbon bearing the two phosphonate groups, the yield is twice higher with **5**.

ESR Study

Analysis of the radical derived from **1**

The main lines of the spectra can be interpreted as a doublet of a triplet ($A_P = 53.2$ G, $A_N = 13.8$ G) and all lines show a further small doublet with a $A_X = 1.7$ G coupling (Figure 1). Even at high temperature, there is no sign of line width alternation (LWA). In principle, this lack and the very small second phosphorus coupling could be explained by a rigid geometry. However, this contradicts our observations for other geminally diphosphorylated nitroxide radicals where a chemical exchange always occurs. No other example with the phosphorus in beta position can be found in the literature where the coupling is smaller than 20 G, which fact is caused by the anomeric effect stabilizing the axial preference of the CP bond. Furthermore, the spectra contain additional satellites of low intensity that can be attributed to a radical with two phosphorus couplings of 40 G on average; the lines reveal the usual LWA. The major product is thus assigned to a mono-phosphorylated radical (**1aNO**), whereas the satellites are interpreted as the lines of the radical (**1bNO**). The assignment of **1aNO** is supported by the small coupling of 1.7 G typical for *N*-methin hydrogen. This attribution is sustained by the appearance of the impurity lines present in the spectra of the nitroxide obtained by the oxidation of **5** in pentane, which have parameters similar to the major product in the spectra of **1**. A computer simulation of the alternating lines^[11] from **1bNO** gives data

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as $A_N = 14.1$ G, $A_{P'} = 55.2$ G, $A_{P''} = 14.5$ G, $\tau = 0.525$ ns (exchange time at 293 K) and $\Delta E = 15$ kJ/mol (potential barrier computed from the slope on the Arrhenius plot (not shown)).

Using the simplified McConnell equation^[12] ($A_p = B_p \cos^2 \theta$ (Scheme 4) and $A_H = B_H \cos^2 \theta$, with $B_p = 56$ G and $B_H = 24$ G for linear nitroxide^[13]) we found $\theta_p = 12.9^\circ$ and $\theta_H = 72.9^\circ$ for **1aNO**, $\theta_{p'} < 6^\circ$ and $\theta_{p''} = 59.4^\circ$ for **1bNO**.

Insert Scheme 4

Insert Figure 1

A more elaborate study of this thermal evolution and a discussion of the coalescences and the frozen states will be published elsewhere.

Analysis of the radical derived from **2**^[14]

Above room temperature, the ESR spectra show nine major lines (See Figure 9 in ref ^[14] and Figure 2 in this paper). The phosphorus central lines have smaller amplitudes than the outer lines, revealing a fast chemical exchange. At 363 K in toluene the outer triplet splits into a smaller doublet pattern of 1.44 G that can be attributed to the beta proton of the *sec*-butyl group. The three central lines display a 1:2:1 triplet which is credited with the chirality of the *sec*-butyl group. Plain simulations have provided $A_N = 13.96$ G, $A_{P1} = 35.63$ G and $A_{P2} = 38.20$ G coupling constants.

Insert Figure 2

A significant line broadening is noticed at lower temperatures; the corresponding two coalescences happen below 333 K and at 293 K in toluene, below 343 K and at 283 K in dichloromethane (Figure 2). Starting from 213 K in toluene and 203 K in dichloromethane, the spectra have an anisotropic behavior due to the presence of frozen conformers.

In order to see small coupling, new experiments using pump-freeze cycle instead bubbling helium, as well as new oxidants reagents (like lead dioxide or silver dioxide) will be carried out.

Theoretical calculations

Many simulations were performed to analyze the ESR spectra. All simulated spectra show a perfect fit with the experimental ones. However their interpretation is more complicated.

The presence of two different phosphorus atoms allows to determine separately B_0 and B_2 in the dihedral relation of McConnell^[12] by analysis of P-hfs couplings, if the Θ PCP angle is known^[14] B_0 and B_2 are estimated to be 25 and 35 G, respectively if $\Theta = 120^\circ$. B_0 describes direct and indirect polarization, and B_2 describes hyperconjugation.^[15] This contradicts the values of $B_0 = 0$ and $B_2 = 60$ G that were proposed by Tordo *et al.* indicating a significant angular distortion of the PCP group.^[14] According to quantum chemical computations, B_0 should actually be small, i.e., never larger than 6 G.^[16]

To investigate an alternative possibility causing anomalous B_0 and B_2 values, we performed several *ab initio* calculations on model molecules similar to **1bNO** and **2NO** using the Gaussian 98^[17] software. Model molecules are $\text{CH}_3\text{-NO-CH}_2\text{-PO}_3\text{H}_2$ **6**, $\text{CH}_3\text{-NO-CH}_2\text{-PO}_3(\text{CH}_3)_2$ **7** for monophosphonated species and $\text{CH}_3\text{-NO-CH}(\text{PO}_3\text{H}_2)_2$ **8** for

diphosphonated species. All results were obtained after full optimization at UHF(6-31G) level but constraining the value of the dihedral angle θ .^[18,19] In **6**, the PO₃H₂ hydrogen atoms were oriented to avoid hydrogen bonding with the NO oxygen. This configuration was maintained in all the compounds. The second molecule was studied in order to establish that the previous results are independent of the nature of the substituents.

The preliminary results show that i) B_0 is generally small, ii) the values of the energy or of the spin density at 0° and 180° and at 90° and 270° are slightly different, iii) the results for **6** and **7** are very similar, and iv) in case of two (PO₃H₂) groups (compound **8**), result ii) is more important (Figure 3) and the behavior of the two groups is sensibly different, leading to different B_0 and B_2 in the McConnell relation (compared to monophosphonated species).

Insert Figure 3

These results are in agreement with a model in which B_2 is different for the angles larger than 90°. This model can explain the discrepancies of P coupling for the diphosphorus compound even if small B_0 is assumed. Since the B_2 asymmetry is supposed to be related to the level of pyramidal distortion, it was interesting to look into this property. Three angles - the valence angles (C(H₃)-N-O (A_1) and C(P)-N-O (A_2) completed by the elevation angle at the O atom above the CNC plane (B) - are reported here for the most stable structures:

$$\mathbf{6} \quad A_1 = 119.0, A_2 = 117.2, B = 13.2$$

$$\mathbf{7} \quad A_1 = 119.0, A_2 = 117.3, B = 13.6$$

$$\mathbf{8} \quad A_1 = 119.8, A_2 = 117.0, B = 12.0$$

The model we developed^[14] is now supported by the quantum chemical calculations.

Ab initio calculations on **1bNO** and **2NO** are under way and all relevant results will be published in a forthcoming paper.

CONCLUSION

In this paper we have described the synthesis and the full characterization of two new linear bisphosphonates and the preliminary results of the analysis of the ESR spectra of the corresponding nitroxides. We also report the results of theoretical calculations on model compounds. With this approach we can claim that B_0 is generally small and that the results of bisphosphonate ester and bisphosphonic acid are similar. Because of the asymmetry, at 0° and 180° for example, the constants in the McConnell relation are different in the case of mono and diphosphorylated species. For diphosphonate molecules, the constant for the simplified relation must be determined. The discrepancies of P coupling for the diphosphorus compound stems from B_2 that is different when the sign of dihedral angle is changed.

EXPERIMENTAL

NMR spectra were acquired on a Bruker AM 400 (^1H , 400 MHz; ^{13}C , 100.61 MHz; ^{31}P , 161.98 MHz) spectrometer. The chemical shifts (δ) are given in ppm and referred to internal TMS for ^1H and ^{13}C and to external 85 % H_3PO_4 for ^{31}P . ^{15}N NMR spectra were recorded on a Varian Inova 500 at 50.649 MHz (Inverse gated method) and the δ values in ppm are referred to external CD_3NO_2 . All J values are given in Hz. Elemental analyses were performed at the Eindhoven University of Technology. UV spectra were acquired on a HP 8453 UV-Vis spectrophotometer. IR spectra were acquired on a Mattson Polaris spectrophotometer. Raman

spectra were acquired on a Labram Dilor spectrophotometer. Index of refraction were determined on an Atago refractometer at 20 °C. ESR measurements were performed on a Bruker ESP 300E spectrometer equipped with a X-band resonator (9.41 GHz). All ESR spectra were recorded at 100 kHz magnetic field modulation. Solvents were purchased from Biosolve. Phosphorus oxychloride, ammonia solution (ca. 28-30 %), hydrochloric solution (ca 32 %), triethyl phosphite and all compounds for the synthesis of **3** and **4** were used as purchased from Aldrich. *m*-CPBA (*m*-chloroperbenzoic acid) (70-75 %) was used as purchased from Acros. Sodium hydroxide was used as purchased from Fluka.

General procedure

In a double walled flask, under nitrogen, phosphorus oxychloride (20 mL, 0.22 mol) was added during 1 h to a mixture at -7.5 °C of amide **3** or **4** (0.11 mol) and triethylphosphite (34.9 g, 0.21 mol). The reaction mixture was stirred for 1 h at room temperature and then poured over a mixture of ice (200 g) and ammonia 30 % (400 mL). The aqueous layer was extracted with methylene chloride (3 x 100 mL) and then the latter was removed to obtain a yellow oil. The oil was dissolved in 100 mL of methylene chloride. An aqueous solution of hydrochloric acid (10 mL of 32 % HCl solution, 190 mL of water) was added (pH 1) and the aqueous layer was washed with methylene chloride (3 x 100 mL). A solution of sodium hydroxide (20 g of NaOH in 200 mL of water) was added up to pH 10 and the aqueous layer was extracted with methylene chloride (4 x 100 mL). The organic layer was dried over sodium sulfate and filtered. Removal of the solvent afforded **1** or **2**.

Tetraethyl(*N*-*tert*butyl-1-aminoethan-1,1-diyl)bisphosphonate **1**

(11.3 g, 29 %). ¹H NMR (CDCl₃): δ 1.24 (s, 9H, CH₃C), 1.33 (t, J = 7.0, 12H, CH₃CH₂O), 1.74 (t, J = 18.4, 3H, CH₃CP₂), 2.70 (s, 1H, NH), 4.1-4.3 (m, 8H, CH₃CH₂O). ¹³C NMR

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(CDCl₃): δ 15.8 (t, J = 5.5, CH₃CP₂), 16.3 (t, J = 3.5, CH₃CH₂O), 32.4 (CH₃C), 52.6 (t, J = 5.7, CH₃C), 58.9 (t, J = 145.0, CP₂), 62.5 (t, J = 4.1, CH₃CH₂O), 64.0 (t, J = 3.7, CH₃CH₂O).
³¹P NMR (CDCl₃): δ 22.5. ¹⁵N NMR (C₆D₆): δ -324.3 (t, J_{P-N} = 6.1). IR (CCl₄): 3466 (ν_{NH}), 1251 (P=O), 1164 (POC₂H₅) cm⁻¹. Raman: 2978 (ν_{CH₃} As.); 2934 (ν_{CH₂} As.); 2908 (ν_{CH₃} Sym.); 2875 (ν_{CH₂} Sym.); 2776; 2726; 1479; 1456 (δ_{CH₃sp₃} As.); 1446; 1396 or 1369 (δ_{CH₃sp₃} Sym.); 1288; 1239 (P=O); 1099 (ν_{C-N}); 1028; 923; 767; 686; 639; 537; 313; 213 cm⁻¹. Anal. Calcd for C₁₄H₃₃NO₆P₂: C, 45.04; H, 8.91; N, 3.75. Found: C, 44.80; H, 8.49; N, 3.55. UV (Ethanol, 25 °C, 10⁻³ M): λ_{max} 207 (ε_{max} 492 mol⁻¹.dm³.cm⁻¹), 260 (ε_{max} 309 mol⁻¹.dm³.cm⁻¹) nm. n_D²⁰ 1.4463. d₂₁²¹ 1.12. MR_{Exp} 88.9.

Tetraethyl(N-secbutyl-1-aminoethan-1,1-diyl)bisphosphonate 2

(9.0 g, 23 %). ¹H NMR (CDCl₃): δ 0.68 (t, J = 7.4, 3H, CH₃CH₂CH), 0.87 (d, J = 6.4, 3H, CH₃CH), 1.05 (m, 1H, CH₃CH_aH_bCH), 1.15 (t, J = 7.2, 12H, CH₃CH₂O), 1.35 (m, 1H, CH₃CH_aH_bCH), 1.41 (t, J = 17.4, 3H, CH₃CP₂), 2.9 (m, 1H, CHN), 4.02 (m, 8H, CH₃CH₂O).
¹³C NMR (CDCl₃): δ 10.1 (CH₃CH), 15.6 (t, J = 4.2, CH₃CP₂), 16.2 (t, J = 3.0, CH₃CH₂O), 22.3 (CH₃CH₂CH), 32.1 (CH₃CH₂CH), 48.4 (t, J = 6.1, CHN), 57.5 (t, J = 143.0, CP₂), 62.3 (t, J = 3.8, CH₃CH₂O), 63.2 (t, J = 3.8, CH₃CH₂O). ³¹P NMR (CDCl₃): δ 23.3. ¹⁵N NMR (C₆D₆): δ -330.8 (t, J_{P-N} = 5.2). IR (CCl₄): 3447 (ν_{NH}), 1246 (P=O), 1163 (POC₂H₅) cm⁻¹. Raman: 2975 (ν_{CH₃} As.); 2934 (ν_{CH₂} As.); 2905 (ν_{CH₃} Sym.); 2875 (ν_{CH₂} Sym.); 2773; 2723; 1481; 1457 (δ_{CH₃sp₃} As.); 1371; 1292; 1249 (P=O); 1100 (ν_{C-N}); 1031; 949; 844; 813; 765; 648; 535; 327; 242 cm⁻¹. Anal. Calcd for C₁₄H₃₃NO₆P₂.H₂O: C, 42.96; H, 9.01; N, 3.58. Found: C, 42.91; H, 8.50; N, 3.64. UV (Ethanol, 25 °C, 10⁻³ M): λ_{max} 204 (ε_{max} 1202 mol⁻¹.dm³.cm⁻¹) nm. n_D²⁰ 1.4461. d₂₁²¹ 1.13. MR_{Exp} 88.1.

ESR Study of Nitroxides 1aNO, 1bNO and 2NO

Compounds **1** or **2** (0.03 mmol) were dissolved in 100 μ L of solvent (dichloromethane or toluene). *m*-CPBA (7.2 mg, 0.03 mmol) was added and the spectrum was recorded immediately after helium bubbling.

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Captions

Scheme 1: Controlled radical polymerization involving nitroxides

Scheme 2: Compounds studied

Scheme 3: Reaction pathway for the one pot procedure of bisphosphonates

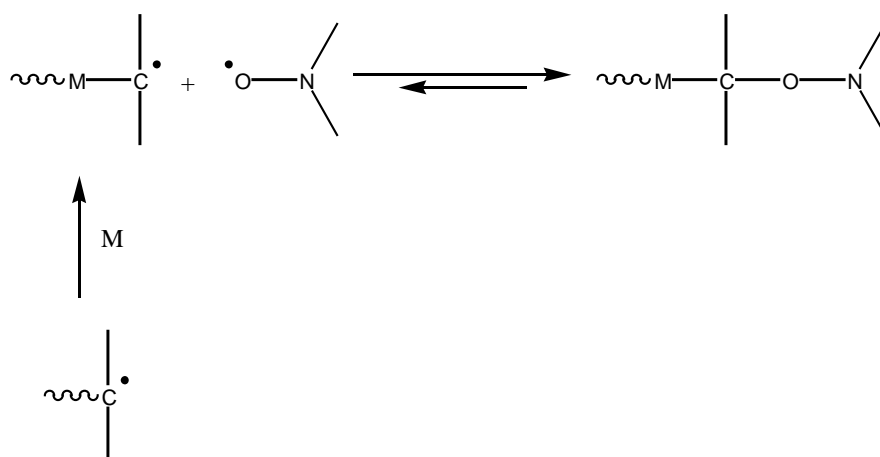
Scheme 4: Explanation of θ in the McConnell equation

Table 1: Yields and ^{31}P chemical shifts for some aminobisphosphonates

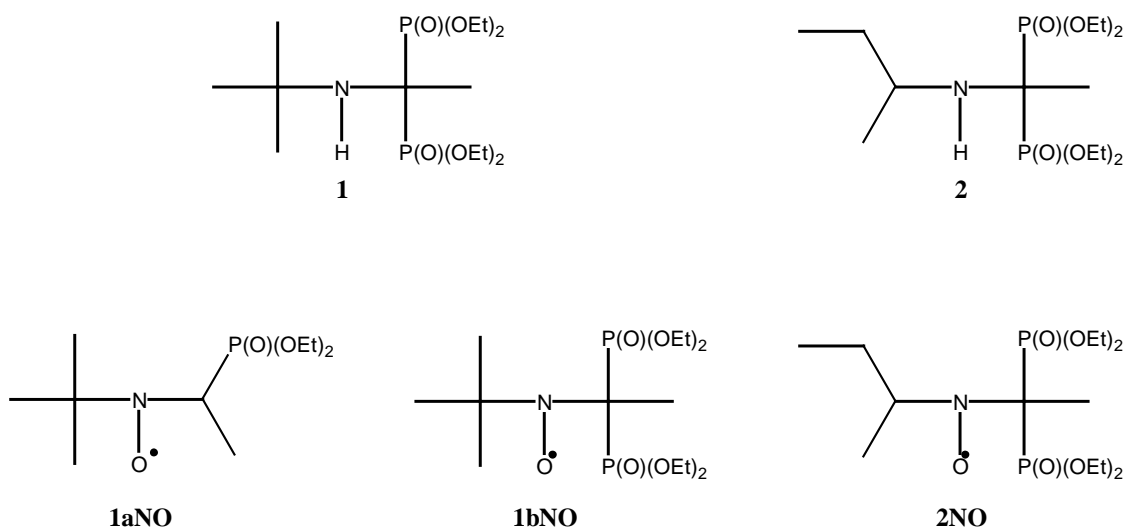
Figure 1: Experimental ESR spectra of radical obtained during the oxidation of **1** in toluene at 213 and 363 K

Figure 2: Experimental ESR spectra of radical **2** in dichloromethane at selected temperatures (in K)

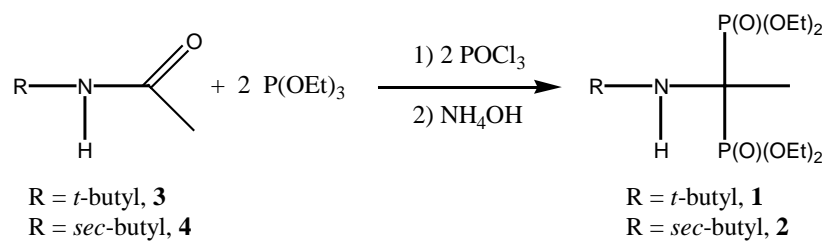
Figure 3: Calculated spin density of the two phosphorus atoms (a) and energy (in kJ/mol) (b) as a function of θ (in degree) for **8**



SCHEME 1



SCHEME 2



SCHEME 3

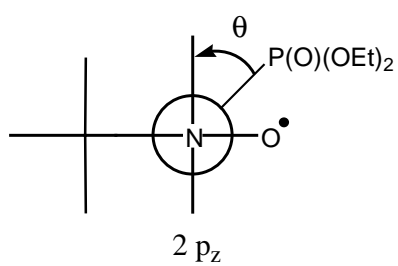
**SCHEME 4**

TABLE I - Yields and ^{31}P Chemical Shifts for Some Aminobisphosphonates

Product	Yield / % (isolated compound)	$\delta^{31}\text{P}$ / ppm in CDCl_3
1	29	22.5
2	23	23.3
5	56	See ref [6] or [10]

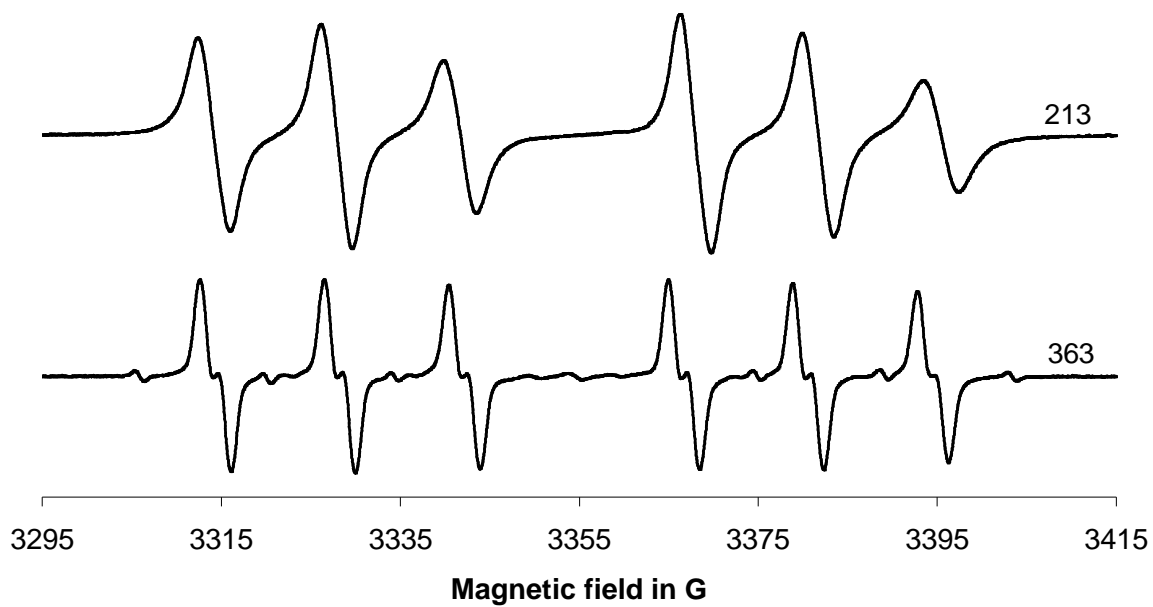


Figure 1 Experimental ESR spectra of radical obtained during the oxidation of **1** in toluene at 213 and 363 K

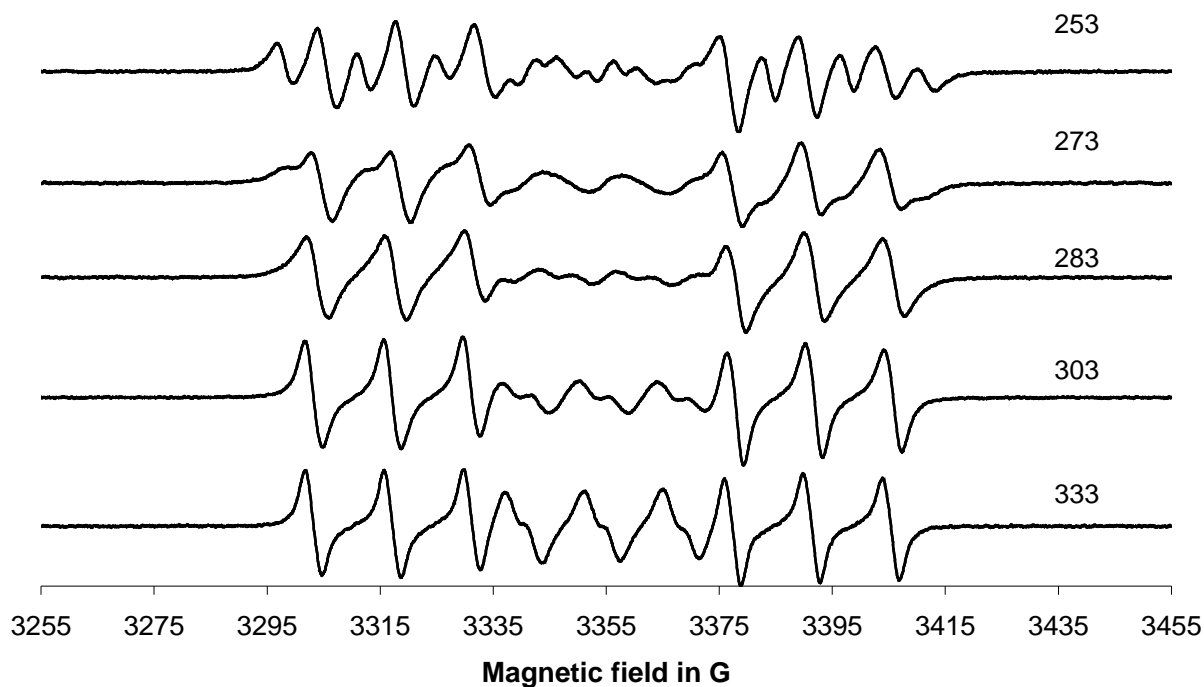
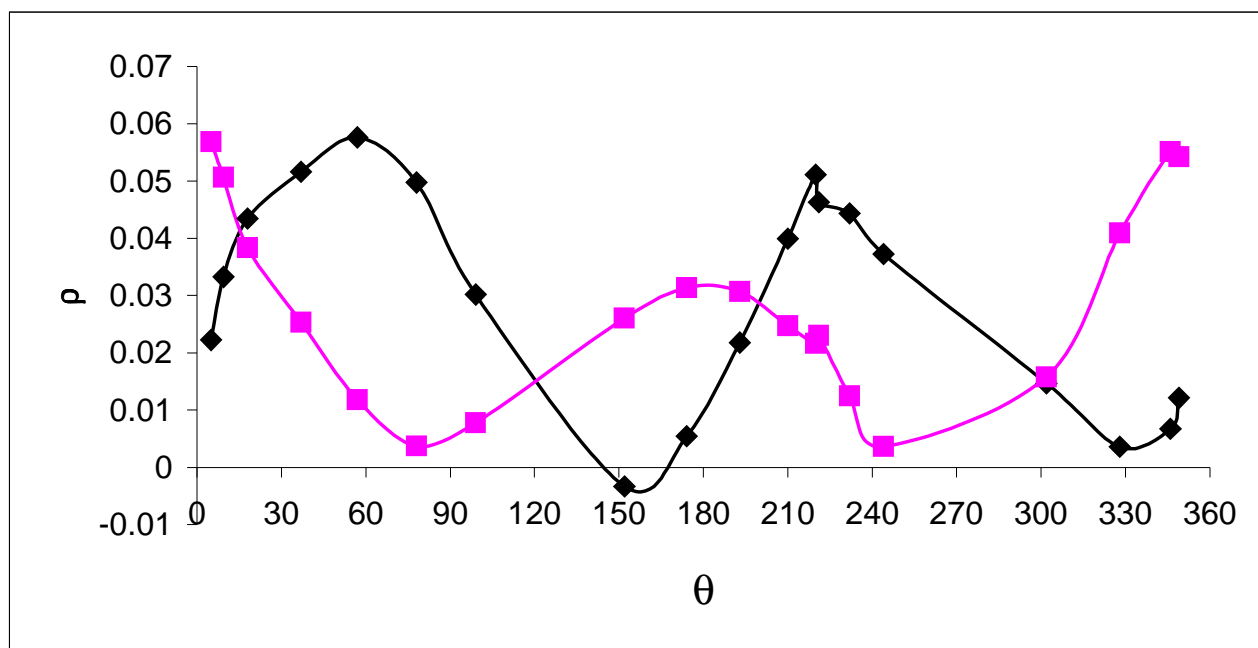


Figure 2 Experimental ESR spectra of radical during oxidation of **2** in dichloromethane at selected temperatures (in K).

(a)



(b)

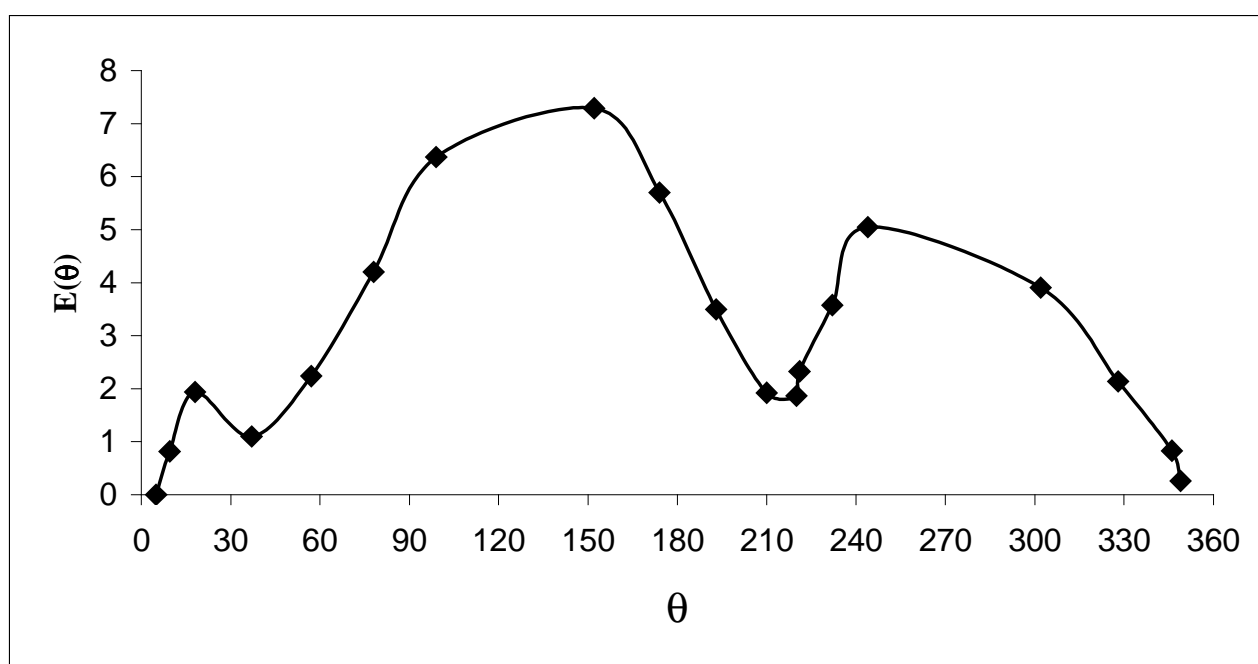


Figure 3 Calculated spin density of the two phosphorus atoms (a) and energy (in kJ/mol) (b) as a function of θ (in degree) for **8**.