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

Gilles Olive, Antal Rockenbauer, Xavier Rozanska, Alain Jacques, Daniel Peeters, Anton German

To cite this version:


HAL Id: hal-00662558
https://hal.archives-ouvertes.fr/hal-00662558
Submitted on 24 Jan 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Short Title: ESR analysis of nitroxides of aminobisphosphonates

Gilles Olive†, Antal Rockenbauer‡, Xavier Rozanska§, Alain Jacques‖, Daniel Peeters‖ and Anton German†

† Department of Polymer Chemistry and Coatings Technology, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands. ‡ Institute of Structural Chemistry, Chemical Research Center, Budapest, P. O. Box 17, H-1525 Hungary. § Schuit Institute of Catalysis, Laboratory of Inorganic Chemistry and Catalysis, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands. ‖ Unité CSTR, Université catholique de Louvain, Bâtiment Lavoisier, Place Louis Pasteur, 1, B-1348 Louvain-la-Neuve, Belgium

Abstract

The synthesis and the full characterization of two new linear bisphosphonates (tetraethyl(N-tertbutyl-1-aminoethan-1,1-diyl)bisphosphonate and tetraethyl(N-secbutyl-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
acid are similar. The discrepancies of P coupling for the diphosphorus compound stems from B\textsubscript{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.\cite{1} It requires absence of oxygen but can be carried out in the presence of water.\cite{2} Unfortunately, the control over the macromolecules is worse in radical polymerization than in ionic polymerization.\cite{2} To increase the polymerization control, the use of nitroxides has been suggested.\cite{1} Nitroxy radicals are observed to result in a better control of the molecular weight, polydispersity and termination processes. The action of a nitroxy radical occurs through a reversible coupling between the nitroxide and the growing polymeric chain. (Scheme 1)

To clarify the role of nitroxy 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\cite{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-tertbutyl-1-aminoethan-1,1-diyl)bisphosphonate $\textbf{1}$ and the tetraethyl(N-secbutyl-1-aminoethan-1,1-diyl)bisphosphonate $\textbf{2}$ molecules (Scheme 2) and perform the full ESR$^{[4]}$ analysis of the chemical exchange of various nitroxides formed from the oxidation of $\textbf{1}$ and $\textbf{2}$. (Scheme 2)

RESULTS AND DISCUSSION

Synthesis

The synthesis of $\textbf{1}$ and $\textbf{2}$ 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 POCl$_3$ (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 NH$_4$OH. After work-up, the corresponding aminobisphosphonates are obtained with several yields. (Table I) Compounds $\textbf{3}$ and $\textbf{4}$ are prepared using the procedure of Lessard$^{[8]}$ and of Sagar$^{[9]}$, respectively.
Using the same procedure, Grimaldi\cite{10} prepared the tetraethyl $N$-ter$t$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 ($1a\text{NO}$), whereas the satellites are interpreted as the lines of the radical ($1b\text{NO}$). The assignment of $1a\text{NO}$ 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\cite{11} from $1b\text{NO}$ gives data
as $A_N = 14.1 \text{ G}$, $A_P' = 55.2 \text{ G}$, $A_P'' = 14.5 \text{ G}$, $\tau = 0.525 \text{ ns}$ (exchange time at 293 K) and $\Delta E = 15 \text{ kJ/mol}$ (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 $B_p = 56 \text{ G}$ and $B_H = 24 \text{ G}$ 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.

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 $A_N = 13.96 \text{ G}$, $A_{P1} = 35.63 \text{ G}$ and $A_{P2} = 38.20 \text{ G}$ coupling constants.
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 $\Theta$ 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 CH$_3$-NO-CH$_2$-PO$_3$H$_2$ 6, CH$_3$-NO-CH$_2$-PO$_3$(CH$_3$)$_2$ 7 for monophosphonated species and CH$_3$-NO-CH-(PO$_3$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 $\theta$.\textsuperscript{[18,19]} In 6, the PO$_3$H$_2$ 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 (PO$_3$H$_2$) 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).

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(H$_3$)-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:

6 $A_1 = 119.0, A_2 = 117.2, B = 13.2$

7 $A_1 = 119.0, A_2 = 117.3, B = 13.6$

8 $A_1 = 119.8, A_2 = 117.0, B = 12.0$

The model we developed\textsuperscript{[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 B₀ 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 B₂ that is different when the sign of dihedral angle is changed.

EXPERIMENTAL

NMR spectra were acquired on a Bruker AM 400 (¹H, 400 MHz; ¹³C, 100.61 MHz; ³¹P, 161.98 MHz) spectrometer. The chemical shifts (δ) are given in ppm and referred to internal TMS for ¹H and ¹³C and to external 85% H₃PO₄ for ³¹P. ¹⁵N 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 CD₃NO₂. 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 phosphate 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 triethyl phosphate (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-tertbutyl-1-aminoethan-1,1-diyl)bisphosphonate 1**

(11.3 g, 29 %). $^1$H NMR (CDCl$_3$): $\delta$ 1.24 (s, 9H, CH$_3$C), 1.33 (t, J = 7.0, 12H, CH$_3$CH$_2$O), 1.74 (t, J = 18.4, 3H, CH$_3$CP$_2$), 2.70 (s, 1H, NH), 4.1-4.3 (m, 8H, CH$_3$CH$_2$O). $^{13}$C NMR
G. Olive et al., Synthesis of New Tetraethyl(N-alkyl-1-aminoethan-1,1-diyl)bisphosphonate 2

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

(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 (CDCl₃): δ -324.3 (t, J = 6.1). IR (CCl₄): 3466 (νNH), 1251 (P=O), 1164 (POC₂H₅) cm⁻¹. Raman: 2978 (νCH₃ As.); 2934 (νCH₂ As.); 2905 (νCH₃ Sym.); 2875 (νCH₂ Sym.); 2776; 2726; 1749; 1456 (δCH₂p₃ As.); 1446; 1396 or 1369 (δCH₂p₃ Sym.); 1288; 1239 (P=O); 1099 (νC=N); 1028; 923; 767; 686; 639; 537; 313; 213 cm⁻¹. Anal. Calcd for C₁₄H₃₅NO₆P₂: 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.


**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, CH₂CH), 1.05 (m, 1H, CH₃CH₂H₃CH), 1.15 (t, J = 7.2, 12H, CH₃CH₂O), 1.35 (m, 1H, CH₃CH₂H₃CH), 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, CH₂CH₂O), 63.2 (t, J = 3.8, CH₂CH₂O). ³¹P NMR (CDCl₃): δ 23.3. ¹⁵N NMR (CDCl₃): δ -330.8 (t, J = 5.2). IR (CCl₄): 3447 (νNH), 1246 (P=O), 1163 (POC₂H₅) cm⁻¹. Raman: 2975 (νCH₃ As.); 2934 (νCH₂ As.); 2905 (νCH₃ Sym.); 2875 (νCH₂ Sym.); 2773; 2723; 1481; 1457 (δCH₃ As.); 1371; 1292; 1249 (P=O); 1100 (νC=N); 1031; 949; 844; 813; 765; 648; 535; 327; 242 cm⁻¹. Anal. Calcd for C₁₄H₃₅NO₆P₂·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.

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

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

We thank the Hungarian Scientific Research Fund OTKA T-046953 for the financial support.
We also thank M. David Riffont from EICVN for his help.

REFERENCES

G. Olive et al., Synthesis of New Tetraethyl(N-alkyl-1-aminoethan-1,1-diyl....


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

1aNO  

1bNO  

2NO
SCHEME 3

R = t-butyl, 3
R = sec-butyl, 4

R = t-butyl, 1
R = sec-butyl, 2
SCHEME 4
### TABLE I - Yields and $^{31}\text{P}$ Chemical Shifts for Some Aminobisphosphonates

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield / % (isolated compound)</th>
<th>$\delta^{31}\text{P}$ / ppm in CDCl$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>22.5</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>23.3</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>See ref [6] or [10]</td>
</tr>
</tbody>
</table>
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).
Figure 3 Calculated spin density of the two phosphorus atoms (a) and energy (in kJ/mol) (b) as a function of \( \theta \) (in degree) for 8.