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Citation for published version (APA):

van Lier, J. J. C., Ven, van de, L. J. M., Haan, de, J. W., & Buck, H. M. (1983). Lithium halide and lithium perchlorate binding to phosphates : a multinuclear nuclear magnetic resonance spectroscopic study. *Journal of Physical Chemistry*, 87(18), 3501-3509. <https://doi.org/10.1021/j100241a029>

DOI:

[10.1021/j100241a029](https://doi.org/10.1021/j100241a029)

Document status and date:

Published: 01/01/1983

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Lithium Halide and Lithium Perchlorate Binding to Phosphates. A Multinuclear Magnetic Resonance Spectroscopic Study

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(Received: June 7, 1982; In Final Form: November 4, 1982)

Previous work in this laboratory indicated the formation of neutral pentacoordinated phosphorus intermediates during dealkylation reactions in salt-phosphate aggregates. In the present paper we describe the retardation in the rate of phosphorylation toward methanol revealed by kinetic data on 2-methoxy-2-oxo-4,5-dimethyl-1,3,2-dioxaphosphol-4-ene (2) upon addition of an equimolar amount of LiX (X = F, Cl, Br) in deuteriochloroform. The nature of interactions of LiX (X = F, Cl, Br, ClO₄) with 2-isopropoxy-2-oxo-5-methyl-1,2-oxaphosphol-4-ene (1), compound 2, triphenyl phosphate (3), and triethyl phosphate (4) in acetone and, in some cases in tetrahydrofuran (THF), were studied by means of multinuclear NMR spectroscopy. The results obtained by the various types of NMR measurements are discussed and put into perspective, both mutually and in relation with the kinetic data. ⁷Li NMR chemical shift and line broadening data reveal complexation of the phosphoryl oxygen atom by the Li⁺ ion. All four phosphorus compounds investigated here show a preference for 1:1 complexation (salt-phosphate). ¹H NMR spectra of 1 in acetone and benzene with lithium bromide reveal moderate changes in the chemical shift of the ring methylene protons. The changes in the geminal coupling constants were small, which indicates negligible differences in the net atomic charges on the phosphorus atom. ³⁵Cl and ⁸¹Br NMR data on salt-phosphate aggregates reveal a fast equilibrium in the complex and a line broadening effect upon complexation. From ³¹P NMR, the absence of covalent PF bonds could be demonstrated for the combination 2/LiF in tetrahydrofuran. Some of our conclusions are corroborated by the results of quantum chemical calculations.

Introduction

Growing recognition of the importance of biologically relevant metal-ion interactions with nucleic acids and nucleotides has stimulated research focused on the chemistry of the complexes formed.¹⁻⁴ Interactions between alkaline-earth metal species and nucleosides (without phosphate groups) are weak and can be explained with only a few specified binding criteria.^{5,6} In nucleic acids, the phosphate-to-metal bonding dominates. Recent ab initio studies of interactions of Li⁺, Na⁺, Be²⁺, and Mg²⁺ with H₂PO₄⁻ reveal significant electron transfer for all complexes, except those involving Na⁺.⁷ This implies that these interactions are not totally electrostatic. On the other hand, ion pairs in organic solvents have been studied thoroughly by combinations of multinuclear NMR techniques.^{8,9} Previous work in this laboratory¹⁰ provided strong evidence for the involvement of neutral pentacoordinated phosphorus intermediates during dealkylation reactions proceeding via salt-phosphate aggregates in media with low dielectric constants. We therefore decided to investigate the nature of the interaction of lithium halides and lithium perchlorate with model phosphates and a model phosphonate in acetone by means of multinuclear NMR.

To gain more insight into the nature of the salt-phosphate interaction, ¹H NMR spectra of the cyclic phosphonate 1 (Figure 1) in a number of organic solvents (with and without lithium salt) would be helpful. Also, ⁷Li, ³⁵Cl, and ⁸¹Br NMR spectra of the salt-phosphate complexes can yield valuable information regarding the nature of the complexes. Here, we report chemical shift data of the ⁷Li nuclei and line width data for ³⁵Cl and ⁸¹Br of salts, dissolved in acetone-phosphate mixtures. These data and the solvent- and salt-dependent nonequivalence of the methylene protons in 2-isopropoxy-2-oxo-5-methyl-1,2-oxaphosphol-4-ene (1, Figure 1) correspond with the close-ion-pair theory of Popov⁸ and Weingärtner and Hertz.⁹ Besides the study of aggregates by physical means, it also appeared worthwhile to investigate the effect of lithium halides on the rate of phosphorylation of model compound 2.

Bromine anions cause a remarkable decrease in the rate of phosphorylation toward methanol in the different cyclic compounds studied.¹¹ In order to establish if this retardation is a more general property of halogen anions in some organic solvents, detailed kinetic data of the complex system LiX (X = F, Cl, Br)/2-methoxy-2-oxo-4,5-dimethyl-1,3,2-dioxaphosphol-4-ene (2, Figure 1)/methanol in deuteriochloroform were determined.

Experimental Section

Reagents. Lithium perchlorate, lithium bromide, lithium chloride, lithium fluoride, and potassium fluoride (Merck AG, Darmstadt) were azeotropically refluxed (benzene) with a special adapter until no water could be removed. Evaporation of the dry solvent in vacuo under nitrogen yielded the dry salt. After drying, all the lithium salts were stored under dry nitrogen atmosphere. 2-Isopropoxy-2-oxo-5-methyl-1,2-oxaphosphol-4-ene (1) was prepared from the corresponding chlorooxaphospholene.¹⁰

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Figure 1. Model compounds 1-4.

2-Methoxy-2-oxo-4,5-dimethyl-1,3,2-dioxaphosphol-4-ene (2) was prepared by the procedure described by Ramirez et al.¹² Triphenyl phosphate (3, Aldrich) was azeotropically dried (benzene solution; water was removed by a special adapter) and evaporated to dryness just before use. Triethyl phosphate (4, Aldrich) and the cyclic organophosphorus compounds (1, 2) were freshly distilled under reduced pressure before use.

Solvents. Acetone (Merck) was distilled over Drierite and further dried over molecular sieves. Methanol (Merck) was first fractionally distilled from calcium hydride in a nitrogen atmosphere and stored over molecular sieves (3 Å). Tetrahydrofuran (Merck) was fractionally distilled from calcium hydride in a nitrogen atmosphere. All deuterated solvents used were stored over molecular sieves.

Solutions. In view of the hygroscopicity of solvents and of lithium salts, all solutions were freshly prepared and the NMR tubes were filled under nitrogen atmosphere. NMR spectra of salt-phosphate complexes were obtained immediately after sample preparation. In this way, the influence of dealkylation reactions on chemical shifts and line width data could be neglected.

NMR Measurements. NMR spectra were obtained by using a Bruker WM-250 multinuclear spectrometer operating at a field strength of 5.7 T. For lithium-7 (97.21 MHz) chemical shift data were measured against an aqueous 4.0 M LiClO₄ solution. Line widths were of the order of 2 Hz. The accuracy of measurement was ± 0.2 Hz.

Chlorine-35 spectra were obtained at a frequency of 24.507 MHz. Line broadening functions in the ranges 3, 10, and 50 Hz were used, depending on the line width to be observed.

Bromine-81 spectra were obtained at a frequency of 67.55 MHz. Line broadening parameters were set at 100 Hz.

Line widths of the chlorine-35 and bromine-81 resonances were determined with an estimated accuracy of $\pm 10\%$ as an average of two to four measurements (each of 100–10 000 pulses). All spectra (except the low-temperature phosphorus-31) were recorded at 298 K.

Phosphorus-31 spectra (101.27 MHz) were obtained with a resolution of 7×10^{-2} Hz. Chemical shifts are reported relative to 85% external H₃PO₄; negative values refer to shielding.

Some of the 250.13-MHz proton spectra were simulated in order to establish accurate values for the coupling constants and chemical shift parameters.

Results and Discussion

Addition of LiX (X = F, Cl, Br, ClO₄) to solutions of 1-4 (Figure 1) in acetone reveals deshielding of the proton resonances in the ¹H NMR as a consequence of the complexation of the phosphoryl oxygen atom with the lithium cation, which results also in a deshielding of the phosphorus atom. These results are in accordance with former

Figure 2. P(V) intermediate in the dealkylation reaction.

TABLE I: Kinetic Data of the System LiX (X = F, Cl, Br)/2/Methanol in Deuteriochloroform at $T = 296$ K^a

salt	$t_{1/2}$, min	r , ^b Å	$10^3 k$, s ⁻¹	k_{rel} ^c
LiF	5.57	1.33	2.15	1.00
LiCl	11.38	1.81	1.02	0.48
LiBr	31.81	1.96	0.36	0.17

^a Concentrations are equimolar (0.3 M). ^b Anionic radius without solvation spheres. ^c $k_{rel} = k/(2.15 \times 10^{-3})$.

work on salt-phosphate aggregates.^{11,13-16} The above-mentioned adducts all disproportionate eventually to the corresponding dealkylated products in the case of LiF, LiCl, and LiBr. The weakly nucleophilic ClO₄⁻ ion is not capable of activating the dealkylation process. Our earlier NMR and kinetic experiments^{10,11} provided strong evidence for the involvement of a pentacoordinated phosphorus intermediate with only a moderate charge separation in the rate-determining step of the dealkylation reaction (Figure 2).

Kinetic Measurements. Addition of 1 equiv of methanol to a 0.5 M solution of 2 in tetrahydrofuran (THF) results in a fast phosphorylation reaction. However, in the presence of 1 equiv of LiBr, almost complete dealkylation is observed.¹¹ In order to elucidate the observed decrease in the rate of phosphorylation we studied the model system LiX (X = F, Cl, Br)/2/methanol in equimolar ratio of the components (0.3 M) in deuteriochloroform. To separate the reaction rates of the combined phosphorylation (path I, Figure 3) and dealkylation (path II, Figure 3) in the system, kinetic measurements in deuteriochloroform were performed on 2/methanol (equimolar ratio, 0.3 M) and 2/LiBr (equimolar ratio, 0.3 M). Considering the poor solubility of LiBr in CDCl₃ at 296 K (8×10^{-3} mol/L), the effective LiBr concentration in solution during the dealkylation process can be regarded as constant and the reaction becomes pseudo first order in phosphate with $k_1 = 3.41 \times 10^{-3}$ L/(mol s).¹⁷ Earlier kinetic measurements of the dealkylation (path II) in the more polar acetone-*d*₆ revealed that the reaction was first order in phosphate and first order in LiBr.¹⁰ In the case of phosphorylation (path

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(17) The reaction rate becomes $-d(P)/dt = k_2(P)$ with $k_2 = k_1(B)$ in which (P) is the concentration of phosphate (mol/L) and (B) is the concentration of LiBr (mol/L). This gives $\ln(P_{\infty}/P_{t=0}) = -k_1(B)t$ with an average $k_1 = 3.41 \times 10^{-3}$ L/(mol s). (B) was estimated at 10^{-2} mol/L (296 K).

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Figure 3. Kinetic pathways of the system LiBr/2/methanol in deuteriochloroform.

Figure 4. Kinetic first-order plots of the system LiX (X = F, Cl, Br)/2/methanol in deuteriochloroform ($T = 296\text{ K}$). The concentrations of the different compounds are equimolar (0.3 M).

I) our kinetic measurements revealed that the reaction was first order in phosphate and of zero order in methanol with an average rate constant of $2.15 \times 10^{-3}\text{ s}^{-1}$. As the phosphorylation proceeds much faster than the dealkylation, it is reasonable to neglect the latter path in case of the phosphate/salt/alcohol system. Therefore, the complex system (Figure 3) can be approximated by a total first-order reaction in phosphate.¹⁸ The kinetic first-order plots of the phosphorylation (Figure 4) reveal that the reaction rate decreases in the order fluoride > chloride > bromide (Table I). The results show a relation between the reaction rate of the phosphorylation and the ionic radius of the different anions studied. The observed relation is not linear because of the different solvent reorientation properties of the halide ions involved.⁹ This creates unique solvation spheres for the various anions. As a result of their ordered solvation spheres, the halide ions, which appear as close-ion pairs⁹ in combination with the metal ion, are capable of screening the phosphorus atom against a nucleophilic attack of the methanol molecule (Figure 5). Consequently, the phosphorylation of methanol is retarded in comparison with the salt-free experiment. Most likely, attack of methanol proceeds by a displacement of the halogen atom followed by a fast intramolecular nucleophilic attack at the phosphorus atom. The kinetic data provide evidence for the proximity of the halide ion with regard to the phosphorus atom (viz., Figure 5).

¹H NMR. In order to improve our knowledge about the location of the Li^+ ion in the salt-phosphate complexes studied here, we took recourse to the paramagnetic Eu^{3+}

TABLE II: Solvent and Salt Effects on the Chemical Shift Difference $\Delta\delta$ of the Methylene Protons of 1^a

close-ion pair ^b	salt	solvent	$\Delta\delta$	
			solvent ^c	salt ^d
		$(\text{CD}_3)_2\text{SO}$	0	
		CD_2Cl_2	0.048	
		CDCl_3	0.100	
yes	LiClO_4	CD_3NO_2	0	0.048
yes	LiCl (satd)	CD_3NO_2	0	0.060
yes	LiCl (satd)	$(\text{CD}_3)_2\text{CO}$	0.01	0.050
yes	LiBr (1 equiv)	$(\text{CD}_3)_2\text{CO}$	0.01	0.286
yes	LiBr (satd)	C_6D_6	0.176 ^e	0.504
no	LiClO_4	SO_2 liq	0	0
no	LiBr (1 equiv)	SO_2 liq	0	0
no	LiBr	$(\text{CD}_3)_2\text{SO}$	≈ 0	0
no	AlCl_3	$(\text{CD}_3)_2\text{CO}$	0.010	0
no	LiBr/kryptofix (1/1) ^f	$(\text{CD}_3)_2\text{CO}$	0.010	0

^a 250.13-MHz ¹H NMR ($T = 298\text{ K}$). ^b According to Popov⁸ and Weingärtner.⁹ ^c Solvent-induced differential shielding. ^d $\Delta\delta(\text{salt})$: measured total effect, containing contributions from both solvent and ion pairs. ^e This large effect can be explained by aromatic-solvent-induced shift (ASIS) which is known for phenyl fragments. ^f Kryptofix 221/LiBr in 1/1 mole ratio.

ion in combination with 1. Addition of $\text{Eu}(\text{fod})_3$ ¹⁹ to a solution of 1 in CDCl_3 reveals deshielding for all the proton resonances in the NMR spectrum due to phosphoryl oxygen complexation by the paramagnetic Eu^{3+} ion (Figure 6). The shift of the tertiary isopropoxy proton (4) shows a high concentration dependence. Obviously, the Eu^{3+} ion is situated in the proximity of this proton. This confirms our earlier observed complexation of the phosphoryl oxygen atom by the Li^+ ion.¹¹ Moreover, the asymmetric ring in the structure causes, via preferred orientation of the $\text{Eu}(\text{fod})_3$ complex, increased shift differences of the isopropoxy methyl groups at higher $\text{Eu}(\text{fod})_3$ concentrations (viz., two resonances (1)). The asymmetric location of the Eu^{3+} ion with respect to the ring methylene protons 3 and 3' causes a different deshielding for both protons. From molecular model building studies one would expect intrinsically inequivalent resonances of the methylene protons. Indeed the 250.13-MHz ¹H NMR spectrum of 1 in acetone- d_6 revealed inequivalent resonances ($\Delta\delta = 2.5\text{ Hz}$; 0.01 ppm; Figure 7). This value appeared to be solvent dependent and should therefore be ascribed to solvent-induced differential shielding effects (Table II). From

(18) The measured rate constant for the phosphorylation is somewhat lower than the real value because of displacement of CDCl_3 by methanol in the inner solvation shell of the lithium cation. As a consequence the amount of free methanol is slightly reduced.

(19) $\text{Eu}(\text{fod})_3$: tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

Figure 5. Stereoscopic drawing of the LiBr-2 aggregate. The closest P-Br distance in the complex was calculated to be 4.0 Å. The different radii used for scaling do not represent solvation.

Figure 6. 60-MHz ^1H NMR results of 1 in CDCl_3 with different concentrations of $\text{Eu}(\text{fod})_3$. δ in ppm vs. Me_4Si ($T = 298\text{ K}$).

earlier research in this laboratory^{10,11} it was established that the shift difference between the methylene protons was dependent on the anion, on the cation, and also on the bulkiness of the exocyclic alkoxy ligand. Comparison with the literature on solutions of alkali halides in organic solvents⁹ revealed that a large $\Delta\delta$ is observed in those cases where the ions of the salts form close pairs and in which one or both ions are surrounded by partially oriented solvent molecules. Therefore, the observed $\Delta\delta$ in the case of close-ion pairs can best be explained by reorientation effects of the solvent structure near the close-ion pair and concomitant electric field effects.

From Table II it is evident that there is no salt-induced $\Delta\delta$ of the methylene protons in the case of fully complexed or solvated cations and anions. Hence, only possible solvent-induced differential shielding can be measured ($\Delta\delta(\text{solvent})$, viz., Table II). In the case of SO_2 we have fully solvated halide anions which prevent salt-induced $\Delta\delta$ of the protons. In the case of AlCl_3 we have a Lewis acid which complexes halide anions.¹¹

^7Li NMR measurements of a 1:2 mixture of kryptofix 221²⁰ and LiBr in acetone reveal two resonances at δ 2.43 and -0.11 which can be attributed to the LiBr in solution and the fully complexed kryptofix 221 $\cdot\text{Li}^+$, respectively. In a 1:1 mixture there is no free LiBr in solution. As a result there is no salt-induced $\Delta\delta$.

Figure 7. 250.13-MHz ^1H NMR spectrum of 1 in acetone- d_6 . δ in ppm vs. Me_4Si ($T = 298\text{ K}$).

Formation of a covalent bond between the Li^+ ion and the phosphoryl oxygen atom would lead to a positively charged phosphorus atom. In order to investigate a possible change in net atomic charge on the phosphorus atom upon addition of lithium salt the accurate values of the $^2J_{\text{HH}}$ geminal coupling constants²¹ had to be determined via computer simulation of the 250.13-MHz ^1H NMR spectra of 1 in acetone- d_6 , with 1 equiv of LiBr in acetone- d_6 and in hexadeuteriobenzene (Figures 8–10). The results are summarized in Table III. From this table it is evident that the difference in $^2J_{\text{HH}}$ between acetone- d_6 and acetone- d_6 with 1 equiv of LiBr is 0.34 Hz. This implies a negligible change in the net atomic charge on the phosphorus atom. Moreover, this conclusion is consistent with the fact that we observed only small (approximately 1 ppm) ^{31}P chemical shift differences upon addition of salt.

^{31}P NMR. Earlier work in this laboratory concerning the kinetics of dealkylation reactions in organophosphorus

(20) Kryptofix 221: 4,7,13,16,21-pentaoxa-1,10-diazabicyclo[8.8.5]tricosane.

(21) Substitution of an electronegative atom in a β -position leads to a negative change in $^2J_{\text{HH}}$. See: "Proton and Carbon-13 NMR Spectroscopy. An Integrated Approach"; Abraham, R. J., Loftus, P., Eds.; Heyden: London, 1978; p 47.

Figure 8. Recorded (a) and simulated (b) 250.13-MHz ^1H NMR spectrum of the methylene protons of **1** in acetone- d_6 . Notice the resemblance of the fine structure in the low-field domain (nearly forbidden transitions).

compounds^{10,11} strongly points to pentacoordinated intermediate structures. We decided to investigate possible intermediate structures by means of low-temperature ^{31}P NMR techniques.

Recent work of Granth et al.²² showed structures intermediate between halophosphoranes (pentacoordinated structure) and phosphonium halides with covalent phosphorus-halogen bonds, which have a very large degree of

Figure 9. Recorded (a) and simulated (b) 250.13-MHz ^1H NMR spectrum of the methylene protons of **1** with 1 equiv of LiBr in acetone- d_6 .

TABLE III: Indirect Coupling Constants (J) and Chemical Shift Values (W) via Computer-Simulated 250.13-MHz ^1H NMR Spectra of **1**

$W,^a \text{ ppm}$ $J, \text{ Hz}$

Acetone- d_6 , Rms Error = 0.042

W(1)		J_{12}	12.64	J_{24}	2.75
W(2)	0.538	J_{13}	15.74	J_{25}	2.55
W(3)	0.548	J_{14}	33.61	J_{34}	3.08
W(4)	3.201	J_{15}	0.80	J_{35}	2.28
W(5)	0	J_{23}	-18.67	J_{45}	1.44

Benzene- d_6 , Rms Error = 0.116

W(1)		J_{12}	13.46	J_{24}	2.72
W(2)	0.681	J_{13}	15.24	J_{25}	2.49
W(3)	0.503	J_{14}	33.54	J_{34}	3.03
W(4)	2.917	J_{15}	0.85	J_{35}	2.30
W(5)	0	J_{23}	-18.41	J_{45}	1.45

Acetone- d_6 /LiBr 1/1 Mole Ratio, Rms Error = 0.167

W(1)		J_{12}	14.28	J_{24}	2.69
W(2)	0.551	J_{13}	15.03	J_{25}	2.48
W(3)	0.656	J_{14}	34.58	J_{34}	2.74
W(4)	3.297	J_{15}	0.74	J_{35}	2.36
W(5)	0	J_{23}	-19.01	J_{45}	1.43

^a W(2) and W(3) may be interchanged.

ionic character. ^{31}P chemical shifts were measured near +40 ppm which points to phosphonium structures. Granth took recourse to electric field induced contributions to explain the deshielding of one of the aromatic protons H_0 (Figure 11). Over such small distances relatively large uncertainties exist in the use of the formalism, both in order of magnitude and in direction.²³ Moreover, an ion

Figure 10. Recorded (a) and simulated (b) 250.13-MHz ^1H NMR spectrum of the methylene protons of **1** in C_6D_6 .

Figure 11. Deshielding of the H_O proton caused by the electric field induced contributions of P-X dipole.

pair suitably oriented with respect to the C-H_O bond could very well have the same effect, i.e., a covalent or ionic P-X bond (X = halogen) is not necessary in order to explain deshielding of the H_O proton. The orientation of the halide anion with respect to the phosphorus atom is probably determined largely by steric factors.

We investigated whether in the salt-phosphate aggregates studied here a stable pentacoordinated structure could be trapped at low temperature. In the case of the bromine anion, **2** revealed the highest rate of dealkylation and thus a concomitant low activation energy ($E_a \approx 12.5$ kJ/mol) to form the pentacoordinated intermediate state.¹¹ Therefore, low-temperature 101.27-MHz ^{31}P NMR spectra of **2** in tetrahydrofuran- d_8 were recorded. The low dielectric constant of THF ($\epsilon = 7.4$; $T = 298$ K) precludes any ion-pair dissociation thus supporting the generation of a pentacoordinated intermediate. Covalent character of the phosphorus-fluoride interaction should be accurately measurable because of the large $^1J_{\text{PF}} \approx 1000$ Hz.²⁴ Addition of 1 equiv of LiF at 213 K to a solution of **2** (0.3 M) in THF- d_8 revealed a line broadening of 1.75 Hz and an upfield shift of 0.40 ppm. No doublet in the ^{31}P resonance could be resolved in the temperature region 213–298 K. The same result was obtained in case of NaF.

Very recently Richman et al.²⁵ published the ^{31}P and ^{19}F NMR results of cyclenfluorophosphoranes and demon-

Figure 12. Different geometries of the LiBr/**2** complex: (a) close-ion-pair structure, (b) phosphonium structure, (c) pentacoordinate structure.

TABLE IV: 97.21-MHz Lithium-7 Chemical Shifts (ppm) of 1/1 Mole Ratio LiBr/Model Compound Aggregates in Acetone at $T = 298$ K^a

LiBr/1		LiBr/3		LiBr/4		LiBr	
<i>M</i> ^b	$\delta(^7\text{Li})^c$	<i>M</i>	$\delta(^7\text{Li})$	<i>M</i>	$\delta(^7\text{Li})$	<i>M</i>	$\delta(^7\text{Li})$
0.11	2.23	0.13	2.41	0.11	2.15	0.09	2.50
0.31	2.04	0.25	2.32	0.26	2.03	0.24	2.48
0.47	1.98	0.50	2.17	0.49	1.89	0.53	2.47
0.94	1.81	1.00	1.95	0.98	1.78	0.94	2.36

^a ^7Li chemical shifts against 4.0 M aqueous LiClO_4 solution.

^b Concentration of model compound (mol/L).

^c Estimated accuracy of $\delta(^7\text{Li})$: 2×10^{-2} ppm.

strated a clear distinction between covalent and ionic structures. In the ionic structures, no $^1J_{\text{PF}}$ was observed whereas in the pentacoordinated structures couplings of 800–900 Hz were measured. Our earlier work gave evidence for generation of pentacoordinated intermediate structures during dealkylation reactions. We argue that, in the salt aggregates studied here, it is possible with NMR techniques to measure the change in solvation but not pentacoordinated intermediate structures with a lifetime short on the NMR time scale.²⁶ In addition, different intermediate geometries of **2** with 1 equiv of LiBr were calculated by the CNDO/2 method.²⁷ Optimization of the different structures a–c (Figure 12) revealed a decreasing stability in the order $a > b > c$. The kinetic data on dealkylation reactions point to pentacoordinate intermediate structures. Combined with our calculations this implies a short-living structure of type c as a result of the interaction of the d orbitals of the phosphorus atom with the unpaired electron pairs of the bromine anion. Structure a seems the most stable, NMR-observed configuration.

^7Li , ^{35}Cl , and ^{81}Br NMR. The results of our ^1H and ^{31}P NMR measurements prompted us to study also the deportment of the Li^+ ions in the salt-phosphate aggregates in acetone by means of ^7Li NMR. With respect to the anionic behavior in the salt-phosphate complexes, we took recourse to ^{35}Cl and ^{81}Br NMR techniques. The data of the ^7Li , ^{35}Cl , and ^{81}Br studies are shown in Figures 13–16 and in Tables IV–VIII.

The properties of ^7Li nuclei are quite favorable for NMR studies. The resonance lines of the Li^+ ion in solutions are exceptionally narrow ($W_{1/2} \approx 2$ Hz)²⁸ and chemical shifts (against 4.0 M aqueous perchlorate solution) can be measured with considerable accuracy. The results available for chlorine and bromine NMR in nonaqueous solvents are limited. Halide ion quadrupole relaxation rates have been reported for methanol,^{9,29,30} dimethyl sulf-

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(26) In our attempt to extend the lifetime of the intermediate structure, we prepared 2-(1,1,1,3,3,3-hexafluoro)isopropoxy-2-oxo-4,5-dimethyl-1,3,2-dioxaphosphol-4-ene. Upon addition of 1 equiv of LiX (X = F, Cl, Br) this compound showed no dealkylation because of the strongly reduced tendency for P=O bond formation from this ligand.

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TABLE V: Limiting Values at $T = 298$ K for Infinite Dilution of Lithium-7 Chemical Shifts (ppm) and Bromine-81 Line Widths (kHz) of 1/1 Mole Ratio Complexes of Model Compound/Salt in Acetone

compd	limiting values	
	$\delta(^7\text{Li})^a$	$W_{1/2}(^{81}\text{Br})^b$
LiBr sec	2.53	6.3
1/LiBr	2.36	8.5
3/LiBr	2.53	6.6
4/LiBr	2.26	7.2

^a Estimated accuracy, 2×10^{-2} ppm; chemical shift in ppm vs. 4.0 M aqueous LiClO_4 solution. ^b Estimated accuracy, 0.5 kHz.

oxide,^{9,29} nitromethane,³¹ formic acid,⁹ *N*-methylformamide,⁹ dimethylformamide,⁹ acetonitrile,⁹ and acetone⁹ and for mixtures of acetonitrile,³² methanol,^{30,33} and acetone³³ with water.

From Table IV it is evident that the ^7Li chemical shifts of lithium bromide are concentration dependent. This concentration dependence can be attributed to the formation of contact ion pairs, i.e., to cases where the anion directly replaces a solvent molecule or molecules in the inner solvation shell of the cation.⁸ It has been previously observed^{34,35} that the contact ion pair equilibrium strongly depends on the donor ability of the solvent molecule as well as on the bulk dielectric constant ϵ of the medium. Acetone has a dielectric constant of 20.7 (298 K), its donor ability is reasonably high, and on Gutmann's scale³⁶ its donor number is 17.0. Contact ion pair formation in acetone occurs likewise in the case of lithium chloride (Table VII). We notice, that the ^7Li chemical shifts are clearly dependent on the counterion (Cl^- , Br^- , ClO_4^-) and on the concentration. The ^7Li chemical shift values agree reasonably well with those reported by Maciel et al.³⁷ and by Akitt and Downs.³⁸ From Table IV we see that addition of 1 equiv of the phosphoryl compounds 1, 3, or 4 to the lithium bromide solution results in shielding of the ^7Li nucleus. This shielding occurs as a result of replacement of at least one of the four carbonyl groups in the inner solvation shell of the lithium ion by a phosphoryl group.³⁹ Addition of small amounts of water results in an analogous replacement by water. Limiting ^7Li chemical shift values for infinite dilution (extrapolation from data in Table IV) are listed in Table V. From our CNDO/2 geometry optimizations of the model compounds 1 and 4 there seems to be a correlation between the dipole moment of the phosphate/phosphonate (8.23 and 8.83 D for 1 and 4, respectively) and the value of the limiting ^7Li chemical shift. A larger dipole moment results in a larger shielding of the ^7Li nucleus. Compound 3 shows a different deportment (dipole, 13.05 D). The results of the ^{81}Br line width measurements of the 1:1 LiBr-model compound complexes are plotted in Figure 13. There is considerable

Figure 13. 67.55-MHz bromine-81 line widths ($W_{1/2}$) of (1:1) LiBr-model compound aggregates in acetone.

broadening of the ^{81}Br resonance with increasing concentration of the complexes in acetone. The observed concentration-dependent broadening of the ^{81}Br resonance is indicative of contact ion pair formation because of asymmetrical solvation of the bromine anion, caused by a contribution of the (Li-O-P) fragment, thus enhancing the electrical anisotropy around the ^{81}Br nucleus. This results in an increase in line width with increasing salt concentration. The contribution of the (Li-O-P) fragment to the electrical anisotropy of the ellipsoidal ^{81}Br nucleus can also account for the difference in limiting values of the ^{81}Br line widths in the 1:1 complexes and in LiBr (viz., Table V). Table IV and Figure 13 reveal that no distinction can be made between the cyclic and the acyclic model compounds. The different behavior of 3 (Figure 13) might be explained by a larger distortion of the solvent structure due to a relatively high molecular weight ($M_v = 326$ vs. 176 and 182 for 1 and 4, respectively) and by the relatively high molecular dipole (our CNDO/2 calculations: 13.05 D). The distortion of the solvent structure in the case of 3 is reflected in an extra line width of the ^{81}Br nucleus with increasing phosphate concentration.

Tables VI-VIII show the influence of increasing model compound concentration on the ^7Li chemical shift with constant concentration of lithium bromide, lithium chloride, and lithium perchlorate, respectively. These tables reveal that the ^7Li chemical shift is dependent on the sort of phosphate molecule involved but independent of the nature of the anion (Cl^- vs. Br^-). The ^7Li measurements reveal a fast equilibrium reaction in the case of the salt-phosphate aggregates. Addition of extra lithium salt and dilution to a former measured concentration results in exactly the same ^7Li chemical shift. The concentration dependence of the ^7Li chemical shift increases with increasing salt concentration.

Addition of water results in shielding of the ^7Li nucleus analogous to the results of Popov.⁸ This shielding increases with decreasing salt concentration and is independent of the anion (Cl^- vs. Br^-). Recent ab initio studies indicate that in the $\text{Li}^+ \cdots \text{H}_2\text{PO}_4^-$ complex hydration of the Li^+ ion does not significantly alter the extent of covalency of the metal-phosphate bond, although it weakens the direct complex formation by partial neutralization of the cation.⁷ The concentration-dependent chemical shift differences in the case of the ^7Li nucleus are in the same range as observed for 1:1 complexes (Table IV). Therefore, in spite of the large excess of model compound, it can be concluded that there is a high preference to replace *only one* of the four carbonyl groups in the inner solvation shell of the lithium cation by a phosphoryl fragment and exclusively 1:1 complexes salt-phosphate have to be considered. In

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TABLE VI: 97.21-MHz Lithium-7 Chemical Shifts (ppm) of Salt/Phosphate Aggregates in Acetone at $T = 298\text{ K}^a$

1				3				4			
M^b	$\delta(^7\text{Li})$	M^c	$\delta(^7\text{Li})$	M^d	$\delta(^7\text{Li})$	M^e	$\delta(^7\text{Li})$	M^f	$\delta(^7\text{Li})$	M^g	$\delta(^7\text{Li})$
0	2.51	0	2.42	0	2.50	0	2.46	0	2.50	0	2.44
0.09	2.23	0.12	2.30	0.13	2.39	0.14	2.36	0.15	1.73	0.16	2.20
0.26	1.84	0.44	2.01	0.27	2.28	0.39	2.21	0.54	1.20	0.49	1.78
0.65	1.33	0.86	1.66	0.57	2.09	0.54	2.13	0.94	0.93	0.85	1.43
1.15	0.98	1.50	1.25	0.94	1.91	0.81	2.00	1.14	0.85	1.17	1.20
1.66	0.75			1.25	1.78	1.14	1.86	1.35	0.77	1.35	1.13
						1.47	1.73				

^a LiBr concentration constant and model compound concentration variable; ⁷Li chemical shifts against 4.0 M aqueous LiClO₄ solution. M is the concentration of the model compound (mol/L); estimated accuracy of $\delta(^7\text{Li})$: 2×10^{-2} ppm.

^b 0.10 M LiBr. ^c 0.58 M LiBr. ^d 0.13 M LiBr. ^e 0.40 M LiBr. ^f 0.11 M LiBr. ^g 0.45 M LiBr.

Figure 14. 24.507-MHz chlorine-35 line widths of salt-phosphate aggregates in acetone. LiCl concentration saturated (0.08 mol/L): (a) 0.08 M LiCl/3, (b) 0.08 M LiCl/4, (c) 0.08 M LiCl/1.

addition, CNDO/2 calculations on the 1:1 salt-phosphate aggregates reveal a concomitant decrease in the net atomic charge of the ⁷Li nucleus (0.3 eu) in comparison with the free lithium salt (close-ion pair). This large decrease in net atomic charge and the increased steric hindrance in the case of 2:1, 3:1, and 4:1 phosphate-salt aggregates suggest that the latter structures become highly unlikely.

Figures 14–16 show ³⁵Cl and ⁸¹Br line widths plotted vs. the model compound concentration, while the salt concentration is kept constant. The model compounds 1 and 4 reveal no extreme concentration dependence in the line widths, whereas 3 shows a different deportment (viz., Figure 14). Compound 3 reveals a high tendency to pen-

TABLE VII: 97.21-MHz Lithium-7 Chemical Shifts (ppm) of Salt/Phosphate Aggregates in Acetone at $T = 298\text{ K}^a$

1		3		4	
M^b	$\delta(^7\text{Li})^c$	M	$\delta(^7\text{Li})$	M	$\delta(^7\text{Li})$
0	2.27	0	2.27	0	2.27
0.19	1.82	0.08	2.21	0.08	2.07
0.34	1.59	0.42	2.07	0.21	1.85
0.68	1.24	0.85	1.93	0.49	1.54
1.01	1.02	1.31	1.81	0.87	1.30
1.33	0.85				

^a LiCl concentration saturated (0.08 mol/L) and model compound concentration variable; ⁷Li chemical shift against 4.0 M aqueous LiClO₄ solution. ^b M is the concentration of the model compound (mol/L). ^c Estimated accuracy of $\delta(^7\text{Li})$: 2×10^{-2} ppm.

etrate into the solvation shell of the anion. This distortion effect is stronger in the case of the chlorine anion (Figure 14) and in the case of the perchlorate anion (Figure 15). With respect to the lithium chloride solution, the electrical anisotropy around the ³⁵Cl nucleus is enhanced because of asymmetrical solvation of the chlorine anion due to a contribution of the (Li–O–P) fragment. Weingartner⁹ was not able to measure ³⁵Cl line widths of lithium chloride in acetone. The aromatic character of 3 probably causes extra ³⁵Cl line broadening via large magnetic anisotropies inherent in aromatic rings.

Observation of the ³⁵Cl line width data with increasing concentration of lithium perchlorate (viz., Figure 15b) suggests that interactions between the lithium cation and the perchlorate anion are involved. These data are in

Figure 15. 24.507-MHz chlorine-35 line widths of salt-phosphate aggregates in acetone. LiClO₄ concentration constant: (a) 0.12 M LiClO₄/1, (b) 0.12 M LiClO₄/3, (c) 0.58 M LiClO₄/3, (d) concentration of LiClO₄ variable; no model compound dissolved.

TABLE VIII: 97.21-MHz Lithium-7 Chemical Shifts (ppm) of Salt-Phosphate Aggregates in Acetone at $T = 298\text{ K}^a$

1				3				4			
M^b	$\delta(^7\text{Li})$	M^c	$\delta(^7\text{Li})$	M^d	$\delta(^7\text{Li})$	M^e	$\delta(^7\text{Li})$	M^f	$\delta(^7\text{Li})$	M^g	$\delta(^7\text{Li})$
0	2.25	0	2.10	0	2.27	0	2.08	0	2.26	0	2.09
0.22	1.71	0.19	1.90	0.19	2.07	0.13	1.98	0.21	1.72	0.21	1.87
0.54	1.22	0.36	1.71	0.40	1.87	0.31	1.85	0.45	1.26	0.37	1.73
0.85	0.95	0.70	1.42	0.59	1.72	0.64	1.63	0.83	0.81	0.62	1.46
1.00	0.85	1.17	1.07	0.89	1.52	0.88	1.50	1.17	0.66	0.88	1.15
1.18	0.75	1.09	0.81	1.26	1.32	1.35	1.28	1.38	0.61	1.34	0.90

^a LiClO_4 concentration constant and model compound concentration variable; ^7Li chemical shifts against 4.0 M aqueous LiClO_4 solution. M is the concentration of the model compound (mol/L); estimated accuracy of $\delta(^7\text{Li})$: 2×10^{-2} ppm. For variable LiClO_4 concentration (mol/L) in acetone without model compound the following ^7Li chemical shifts were measured: 0.05 M, 2.37 ppm; 0.10 M, 2.30 ppm; 0.20 M, 2.23 ppm; 0.40 M, 2.15 ppm; and 0.81 M, 2.05 ppm. ^b 0.13 M LiClO_4 . ^c 0.49 M LiClO_4 . ^d 0.11 M LiClO_4 . ^e 0.57 M LiClO_4 . ^f 0.12 M LiClO_4 . ^g 0.52 M LiClO_4 .

Figure 16. 67.55-MHz bromine-81 line widths of salt-phosphate aggregates in acetone. LiBr concentration constant: (a) 0.11 M $\text{LiBr}/1$, (b) 0.09 M $\text{LiBr}/3$.

contrast with the results of Popov.^{8,39} As we estimate the possible error in our measured ^{35}Cl line widths on the order of 1 Hz in a lithium perchlorate solution, these data suggest an aromatic-solvent-induced contribution in the case of 3. This effect results in increased ^{35}Cl line widths. With respect to 1, at least two contradictory effects must be involved which at present are not clear. Former publications from this laboratory^{40,41} offered the suggestion that knowledge, achieved via physical data on model organophosphorus compounds, can also be applied to the phosphate residues in the helix backbone of the double-stranded DNA molecule. A model was presented for the salt-induced transition of right-handed B-DNA into left-handed Z-DNA assuming long-lived phosphate-salt complexes.^{42,43} Careful study of small DNA fragments in aqueous salt solutions by means of multinuclear NMR techniques may give additional information.

Conclusions

(1) Kinetic experiments revealed that phosphorylation of 2 is retarded by addition of lithium halides. The magnitude of the effect is correlated to the ionic radius as well as to the solvation properties (larger solvation shells result in more efficient screening of the phosphorus atom).

(2) ^1H NMR spectra of $\text{Eu}(\text{fod})_3$ complexes of 1 confirm the intrinsic magnetic inequivalence of the ring methylene protons. In retrospect earlier results from this laboratory¹⁰ can be explained similarly. Addition of lithium halides to solutions of 1 causes effects which are superficially analogous but which are related to solvent reorientation in the vicinity of the ring methylene protons.

(3) Accurate values of $^2J_{\text{HH}}$ determined via computer simulation of ^1H NMR spectra of 1 in different environments (acetone, benzene, acetone/lithium bromide) revealed a negligible change in the net atomic charge on the phosphorus atom. This conclusion seems consistent with the small (~ 1 ppm) ^{31}P chemical shift differences which occur upon addition of salt to the phosphates.

Our low-temperature ^{31}P NMR results (in which 2 and lithium fluoride or sodium fluoride were dissolved in THF) showed no $^1J_{\text{PF}}$ in the temperature range 213–298 K. This indicates that no covalent P–F bonds are formed.

In addition, different geometries of 2 with 1 equiv of LiBr were calculated by the CNDO/2 method (Figure 12, a–c).²⁷ Optimization toward lowest total energy revealed a decreasing stability in the order $a > b > c$. This implies a short-living P^{V} -like structure as a result of the interaction of the d orbitals of phosphorus with the unpaired electron pairs of the bromine (Figure 12c). The close-ion-pair aggregate (Figure 12a) seems the most stable, NMR-observed configuration.

(4) ^7Li NMR spectra of several lithium halides in a number of organic solvents are consistent with earlier work of Popov⁸ and Weingärtner.⁹ The same is true for the ^{35}Cl and ^{81}Br NMR measurements of the anions with the exception of the ^{35}Cl NMR results of lithium chloride in acetone. The ^7Li , ^{35}Cl , and ^{81}Br NMR results can be explained assuming fast equilibria between lithium halides in the complexed (with phosphates) and free forms. There seems to be a preference for 1:1 complexes of lithium halides and the phosphates studied here.

Acknowledgment. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). We thank Mrs. Hanneke Becht, Mr. Jacques Stroucken, and Mr. Piet Traa for their assistance in kinetic experiments and Dr. Gerrit Visser for the stereoscopic drawing (Figure 5).

Registry No. 1, 63630-61-5; 2, 933-43-7; 3, 115-86-6; 4, 78-40-0; LiClO_4 , 7791-03-9; LiBr , 7550-35-8; LiCl , 7447-41-8; LiF , 7789-24-4; $(\text{CD}_3)_2\text{SO}$, 2206-27-1; CD_2Cl_2 , 1665-00-5; CDCl_3 , 865-49-6; CD_3NO_2 , 13031-32-8; $(\text{CD}_3)_2\text{CO}$, 666-52-4; C_6D_6 , 1076-43-3; SO_2 , 7446-09-5.

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