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An Improved Synthetic Method and the First Crystal Structures for (Dihalomethylene)bisphosphonate Partial Esters

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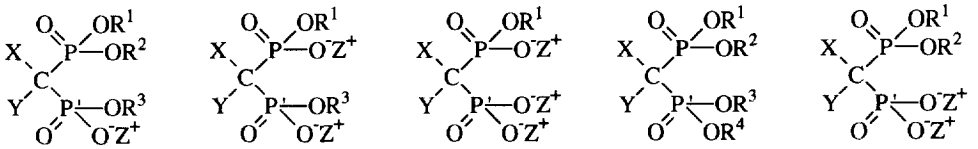
Abstract: A new general and selective strategy for the synthesis of (dihalomethylene)bisphosphonic acid (XYMBP) partial alkyl esters (PE) with high selectivity and purity has been developed. Preparation is started from selected XYMBP tetraesters using tertiary or secondary amines as dealkylating reagents leading to trialkyl or P,P'-dialkyl XYMBP PEs, respectively. The solid state structures are given for three of the compounds: $Cl_2C[P(O)(OPr^i)(O^-Na^+)][P(O)(O^-Na^+)_2]$ and $Cl_2C[P(O)(OPr^i)(O^-X^+)]_2$, where $X=Na^+$ or $H_2N^+(CH_2CH_2)_2O$.

Several methylenebisphosphonic (MBP) acids, their salts and tetraesters have been prepared in order to modify their biological properties by varying the substituents at the bridging carbon.[1] However, little is known about the selective preparation of the intermediate forms, partial MBP esters,[2] due to the difficulties in obtaining pure compounds having exactly one, two or three ester substituents and far less is known about the corresponding halomethylene derivatives[3]. Clodronate (Cl_2MBP) is one of the best documented bisphosphonates used in the treatment of increased bone resorption and malignant hypercalcemia, but both the therapeutic index and absorption are poor, like other tetraacidic bisphosphonates.[4] Bisphosphonates seem to act by binding to the surface of the bone though the precise mechanism of action of these drugs is still largely unknown. In an attempt to tackle some of these problems XYMBP PEs **1-2** and **3** were synthesised from **4** and **5**, respectively. These new bisphosphonate derivatives are expected to be better drugs for the treatment of numerous bone diseases, *e.g.* osteoporosis, which is becoming more and more common in our affluent society. Some biological activity information is already available for the compounds studied and comparative molecular field analysis (CoMFA) have been done to find out three-dimensional quantitative structure activity relationships (QSAR) between the observed biological data and the molecules steric and electrostatic properties.[5]



1 **2** **3** **4** **5**

Theoretically XYMBP PEs can be synthesised by several routes: the separation of XYMBP PE mixtures, building up of bisphosphonates from partial monoester species, halogenation of MBP PEs, or the selective addition[3a] or selective removal[3b] of desired amounts of esters. MBP tetraacids are synthesised by hydrolysis of the corresponding tetraesters,[2b] and reversed tetraesters are prepared from MBP acids with $HC(OR)_3$[6] or by esterification of $H_2C[P(O)Cl_2]$ with alcohols.[7] In all cases PEs appear as the intermediates, but the separation of these mixtures requires laborious chromatographic or fractional crystallisation methods.[3b] The second method is most unlikely since linking two partial monoesters together is troublesome by literature procedures, such as the carbanion method.[8] The next method is possible only for specific PEs, since only some MBP PE starting materials are available.[2] Selective addition of ester groups to XYMBP is also laborious since XYMBP must contain groups, which are converted only to esters (*e.g.*, P-Cl group).[2c] Following the last approach, the previous paper in this series considered the synthesis of some Cl_2MBP PEs from mixed tetraesters containing designated numbers of either methyl or branched esters, which are selectively hydrolysed using trialkylsilylhalide or acids, respectively.[3b] This approach precludes the preparation of some PE combinations, *e.g.* partial methyl esters are difficult to synthesise by this method. The usual method of removing benzyl groups *via* catalytic hydrogenation over Pd/C led to replacement of the halogens by hydrogen with the mixed Cl_2MBP methylbenzyl esters. Moreover, the preparation of mixed tetraesters from toxic monophosphorus compounds as starting materials is tedious.

Here we report a general and selective method for producing tri- and P,P'-dialkyl PEs in good yield without any limitation on the length or shape of the ester substituents, from readily available XYMBP tetraesters using tertiary or secondary amines as dealkylating reagents. Moreover, P,P-dimethyl XYMBP PEs react with secondary amines producing the corresponding monomethyl PE. The progress of these reactions, and the purity and identification of the products were determined using ^{31}P and ^{1}H NMR techniques. For X-ray analysis, crystals of **6e** and **6h** were growth as described earlier.[9] A search of CSD[10] (version 5.06, October 1993) did not reveal any examples of bisphosphonate partial ester crystal structures.

RESULTS AND DISCUSSION

Synthesis. - In seeking a method for the preparation of partial methyl esters of Cl_2MBP, we found that treatment of $Cl_2C[P(O)(OMe)_2]_2$ (**4a**) with amines lead to partial demethylation of **4a**. The degree of demethylation was dependent on the type of amine and the length of the alkyl chains in the amine used. When equimolar amounts of **4a** or **4b** and longer n-alkyl tertiary amines, *e.g.* tributylamine, with CH_3CN as solvent were mixed mono tetraalkyl ammonium salts of XYMBP trimethyl esters were obtained quantitively, whereas only partial conversion was obtained if tertiary amines with shorter chains were used. We also applied this reaction to other XYMBP esters, but no selective reaction was obtained with tertiary n-alkylamines. However,

using the less bulky pyridine, reaction of **4d** to the ethylpyridinium salt of the triethyl ester occurred rapidly, but the hindered isopropyl derivative **4e** required an excess of amine and had to be heated under reflux for 3.5 h before the amount of triisopropyl ester had reached a maximum. The only significant side-reaction with pyridine was formation of the P,P'-diester of XYMBP. Using a large excess of pyridine and prolonged reaction time hydrolysis of two ester groups was achieved (**2h**), but yields was less than 50% and some by-products were also observed.

Table 1. Some representative examples of the preparation of XYMBP PEs with reaction conditions and yield.

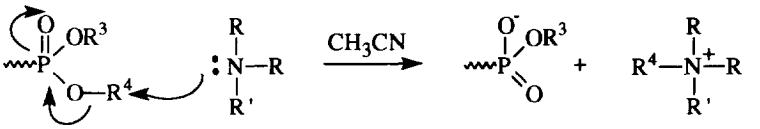
	Starting material					Reaction				Selec-
Nro	X	Y	R^1=R^2	R^3=R^4	Amine[a]	condions	Product	Z	Yield[b]	tivity[c]
4a	Cl	Cl	Me	Me	A	50°/4 h	**1a**	A^+Me	100	100
4b	Br	Br	Me	Me	A	50°/6 h	**1b**	A^+Me	100	100
4c	Cl	Cl	Pr^i	Me	A	60°/4 h	**1c**	A^+Me	100	100
4d	Cl	Cl	Et	Et	B	120°/15 min	**1d**	B^+Et	80	90
4e	Cl	Cl	Pr^i	Pr^i	B	115°/3.5 h	**1e**	B^+Pr^i	80	91
4f	Cl	Cl	Hex	Hex	B	115°/1 h	**1f**	B^+Hex	85	90
4a	Cl	Cl	Me	Me	C	105°/20 min	**2a**	C^+H	100	100
4b	Br	Br	Me	Me	D	105°/20 min	**2b**	D^+H	80	100
4c	Cl	Cl	Et	Et	D	110°/20 min	**2c**	D^+H	90	100
4c	Cl	Cl	Et	Et	C	100°/1 h	**2c'**	C^+H	82	100
4e	Cl	Cl	Pr^i	Pr^i	D	110°/30 min	**2d**	D^+H	83	100
4g	Cl	Cl	2-Pen	2-Pen	D	110°/30 min	**2e**	D^+H	20	100
4h	Cl	Cl	c-Pen	c-Pen	D	130°/2 h	**2f**	D^+H	53	100
4f	Cl	Cl	Hex	Hex	D	110°C/0.5 h	**2g**	D^+H	44	100
4f	Cl	Cl	Hex	Hex	B	115°/24 h	**2h**	B^+H	[d]	50
4i	Cl	Cl	Allyl	Allyl	C	110°C/1 h	**2i**	C^+H	50	100
4j	Cl	Cl	Bu	Pr^i	C	110°/30 min	**2j**	C^+H	43	100
4k	Cl	H	Et	Me	C	105°/4 h	**2k**	C^+H	36	45
4l	Br	H	Hex	Hex	D	110°/5 h	**2l**	D^+H	[d]	40
5a	Cl	Cl	Me	C^+H	D	50°/4 h	**3a**	[e]	100	100

[a]A = Bu_3N, B = pyridine, C = piperidine, D = morpholine. [b]yields are not optimised. [c]Calculated from ^{31}P NMR spectra before isolation. [d]not isolated. [e]counter cations: two C^+H and one D^+H.

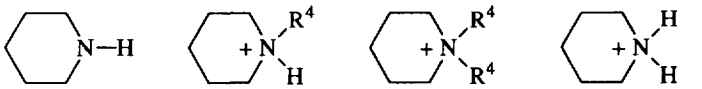
A more convenient route to P,P'-diesters **2** with high selectivity and good yield was developed by treating the XYMBP tetraester at 100°-130° with a large excess of secondary amine, giving instead of the expected trialkylammonium products, dialkylammonium salts. The rate of this reaction was quite insensitive to the nature of the secondary amine used or to the structure of the XYMBP tetraester, all those used giving good yields. The same procedure was used, when P,P-dimethyl Cl_2MDB PE (**5**) was converted to the corresponding mono-

methyl ester **3**; however, as for other P,P-diesters this reaction was unsuccessful. All of these amine salts could be easily converted to their acid form using ion exchange resins, and further to the metal *e.g.*, sodium, salts **6**. However, high pH conditions need to be avoided with n-alkyl PEs, since gradual P-C bond fragmentation occurs above pH 10.

The mechanism of the reaction can be understood by considering that the XYMBP tetraester acts as an N-alkylating reagent. This is a possibility since the bond between the ester carbon and the phosphorus oxygen is weakened due to the electronegative halogen atoms at the bridging carbon. Rearrangement of the electronic structure leads eventually to an ionic bond between the bisphosphonate triester anion and the tetraalkylammonium cation. The rate of this step clearly depends on the number of halogen atoms at the bridging carbon, the best results being obtained with dihaloesters. Only partial conversion is achieved with monohalogenated derivatives (see Table 1 **4k** and **4l**) and no reaction is discernible in the absence of electronegative groups at the bridging carbon.



If secondary rather than tertiary amines are used, the second alkyl group from the adjacent phosphorus is hydrolysed, but surprisingly a dialkyl ammonium salt is formed. We investigated the mechanism of this step by NMR spectroscopy using **4a**, **4d** and **4e** with one, two, four (CD_3CN as co-solvent) and ten equivalents of piperidine as amine and heating under reflux for 30 min. In the case of **4a** the trimethyl PE is initially formed and reacts further to give **2a**. Unexpected is, that in the beginning the countercation is not II as expected, but mixture of III (R^4=CH_3) and IV indicating that initially formed II rearranges quickly to III and IV, of which IV is favoured by being in closer contact with the anionic site and also being less soluble and forming a solid precipitate. However, the total yield of **2a** (containing salt IV) is 100% indicating that salt IV is at least partially formed from III by elimination of two methyl groups probably as ethene.[11]



I **II** **III** **IV**

In the case of **4d** and **4e** the triester PE intermediate was not detected, but products **2c** and **2d** were formed immediately. Initially the countercation is II, which rearranges to IV by elimination of R^4 as the corresponding alkene.[12] In the case of **4e** we were able to absorb some of the propene gas into CD_3COCD_3 at -90°C for NMR analysis. Amine salt IV is highly favoured because of its two amine hydrogens being available to form intermolecular hydrogen bonds (see also crystallographic analysis) and the complex formed with **2** is practically insoluble under the conditions used, leading to a crystalline precipitate. This hydrogen bonding and the steric bulkiness of the tertiary amines used explain, why triesters and diesters of XYMBP are obtained when tertiary and secondary amines are used.

NMR Studies. - ^{31}P NMR spectroscopy was the easiest method for following the formation of bisphosphonate PEs, since unequivalent phosphorus atoms in tri-, mixed P,P'- and monoesters give rise to two separate doublets with equal $^{2}J_{PP}$ coupling constants and the multiplicity of the coupled ^{31}P NMR spectra offer an unambiguous method for determining the numbers and types of substituents on each phosphorus atom. Symmetrical P,P'-diesters were more difficult to identify giving only a single line in decoupled ^{31}P spectra, but their high solubility in water and carbon spectra confirmed the structure.

The appearances of multiplets in the decoupled carbon and proton spectra (the α and β signals) for symmetrical diesters were characteristic but complex, due to the second-order nature of the spectra. The ^{31}P chemical shifts were sensitive to the number of ester groups at the phosphorus atoms, the pH of the solution and the solvent, but only weakly to the shape and length of ester chain. Triesters were easily identified based on ^{31}P shifts, due to the large separation (ca. 10 ppm) between the $(RO)_2P(O)$ (16.5 - 11.1 ppm) and $P(O)(OR)(O^-Z^+)$ (6.6 - 1.3 ppm) fragments of the spectra. For mixed P,P'- and monoesters the shift difference was less than 3 ppm. The $^{2}J_{PP}$ coupling constants were less sensitive to the environment, but the $^{1}J_{CP}$ couplings were more informative being sensitive to both the symmetry and the number of ester groups on phosphorus: ca. 155 Hz for $P(O)(OR)_2$, 135 Hz for symmetric and 120 Hz for asymmetric $P(O)(OR)(O^-Z^+)$ and 110 Hz for $P(O)(O^-Z^+)_2$ fragments. For molecules containing two Pr^i esters on the same phosphorus atom the proton decoupled carbon spectra showed two β-CH_3 doublets, due to the different electronic environments of the β carbons. A corresponding situation with one Pr^i and one cation showed only one signal, obviously due to the rapid walk of the cation between the two anionic oxygens.

In the decoupled carbon spectra, C^{α} and C^{β} shifts for symmetric structures gave second-order quintets consistent with an AA'X (**P'**-C-**P**-O-C^{α} or **P'**-C-**P**-O-C-C^{β}) spin system[7b] rather than two doublets as are observed when the phosphorus shifts are unequal. It is possible to calculate $^{2}J_{PP'}$, $^{2}J_{CP}$, $^{3}J_{CP}$ and $^{4}J_{CP'}$ coupling constants for this system if all of the lines are observed; however the intensities of "satellite" peaks (combination lines) are inversely proportional to $^{2}J_{PP'}$ coupling and for compounds with large $^{2}J_{PP'}$ (≥15 Hz) significantly long pulsing times and concentrated samples are required to distinquish these two lines unambiguously from the background. However, the sums of the J_{CP} couplings (ΣJ_{CP}, the width of the virtual triplet) were well-defined and characteristic for the system, values of which for C^{α} and C^{β} in symmetric molecules are given in the experimental section. Moreover, lines from halogenated carbon atoms are rather small compared to other signals due to long relaxation times (for $X_2\underline{C}P_2$ 30-60 s), and the lack of nuclear Overhauser enhancement (nOe).

X-ray crystallography. - Crystal structures for two symmetrical P,P'-diesters as the disodium **6e** and dimorpholinium salt **2d**, and for one monoester **6h** as a trisodium salt were determined. The sodium salts were exceptionally difficult to crystallise for X-ray structure analysis, the reason for which was understood after the structure of these crystals were solved. The gel technique (tetramethoxysilane) proved to be successful for these water containing sodium salts.[9] In these salts, the bisphosphonate anions are held together in a three dimensional network by sodium atoms, being coordinated with both bisphosphonate and water oxygens, and by O-H···O hydrogen bonds. In the case of ammonium salt **2d**, bisphosphorus molecules are bound to each other by a strong hydrogen bond network *via* amine-N^+H_2. The asymmetric units of the crystallised compounds with their coordination, numbering scheme and packing are depicted in *Figures* 1-3.

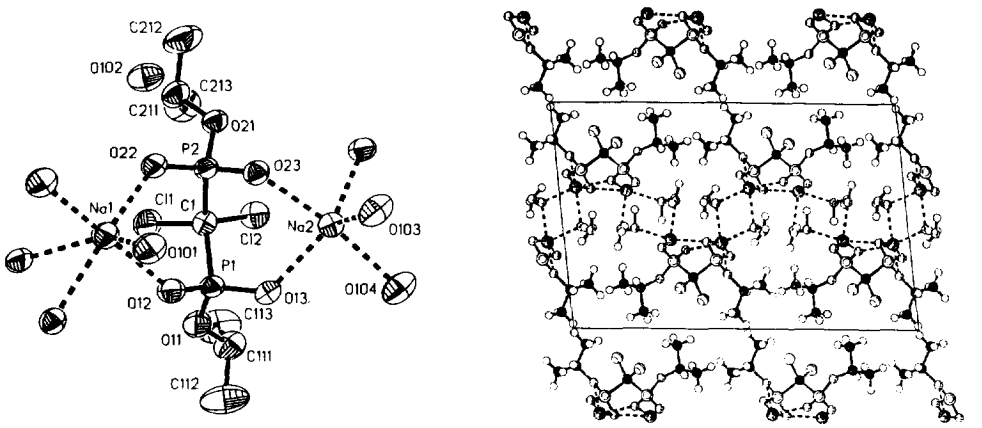


Fig. 1. The structure, numbering scheme and packing of **6e**.

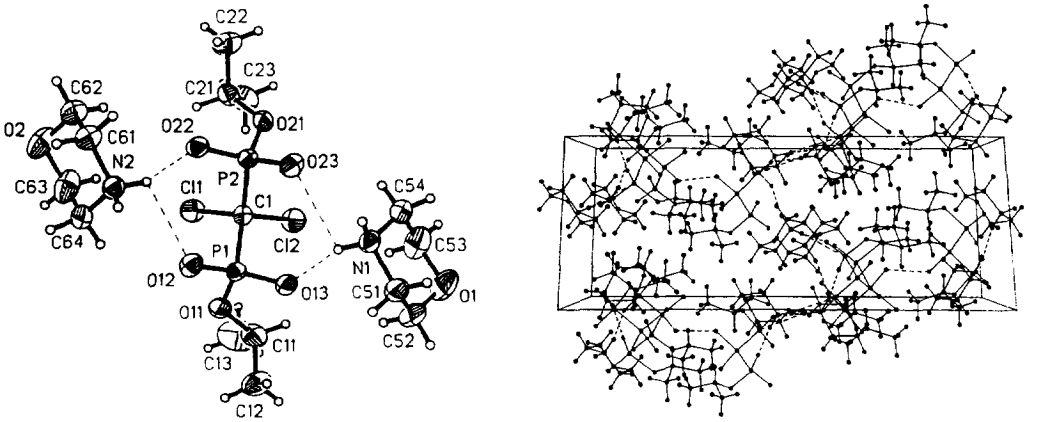


Fig. 2. The structure, numbering scheme and packing of **2d**.

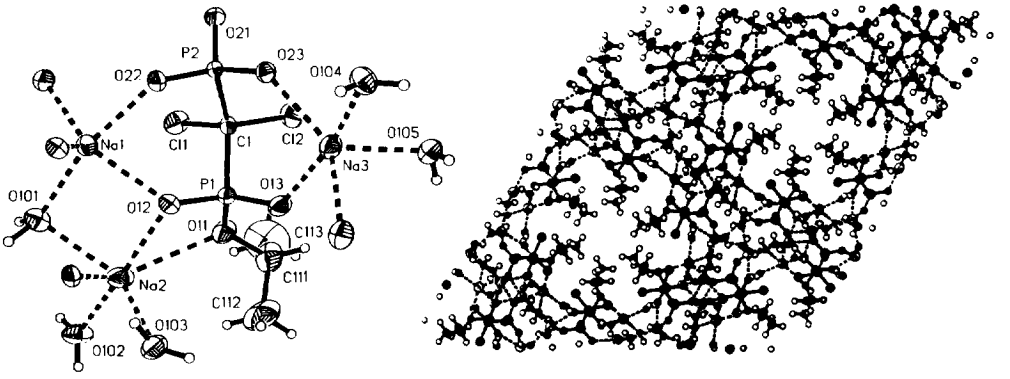


Fig. 3. The structure, numbering scheme and packing of **6h**.

In symmetrical diester disodium salts the structural units are built up from two partial ester molecules which are bound together due to the strong Na···O interactions forming a P-O···Na···$(H_2O)_2$···Na···O-P bridge between molecules. This structural unit forms complex non-bonded layers due to Na···O interactions and hydrogen bonds. The layers are then offset relative to one another such that the perihedral isopropyl groups point out from the layers (see *Fig.* 1). The coordination of Na(1) can be described as a distorted octahedral (Na···O distances within the range 2.349 - 2.726 Å) and the coordination of Na(2) as a distorted square pyramid (Na···O within the range 2.311 - 2.440 Å). Three of the four water molecules are involved in the hydrogen bonding system as donors with H···O distances of 1.71 - 2.11 Å, O···O 2.749-2.907 Å and O–H···O 156 -179°. The shortest Na···Na distances are 3.485 and 3.836 Å.

The corresponding dimorpholinium salt ($C_7H_{14}Cl_2O_6P_2^{2-}$ *$2C_4H_{10}NO^{2+}$) crystallised in the monoclinic space group $P2_1$. The two independent formula units which posses approximately pseudo C_2 symmetry are related to each other by a pseudo mirror plane. The morpholinium cations are in a chair conformation and connect adjacent Cl_2MBP anions together by hydrogen bonds. Each of them form one strong (N···O 2.677 - 2.691 Å) and one weak (N···O 2.965-3.003 Å) hydrogen bond to a Cl_2MBP anion as shown in *Fig.* 2. The other H atom in the morpholinium salt available for hydrogen bonding takes part in a strong hydrogen bond to a adjacent phosphate anion so that each unalkylated phosphonate O atom forms one strong hydrogen bond with a cation. This hydrogen bond network between Cl_2MBP anions forms strands through the crystal and these are interconnected to each other by van der Waals forces.

In the monoester crystals the most obvious structural units are circles, where the isopropyl groups point toward the inversion center contained in the -3 axis (see *Fig.* 3.). Therefore, there is a hole in the crystal lattice along the symmetry element. Due to the space group there are three such holes in the unit cell. The coordination of Na(1) can be described as a distorted square pyramid (Na···O 2.339 - 2.393 Å), that of Na(2) as a distorted octahedral (Na···O 2.277 - 2.897 Å) and of Na(3) as a distorted trigonal bipyramid (Na···O 2.329 - 2.480 Å). All water molecules are involved in a hydrogen bonding system with H···O distances of 1.75-2.03 Å, O···O 2.669 - 2.972 Å and O–H···O 153 - 171°. The shortest Na···Na distances are 3.189 and 3.412 Å.

Values of these parameters for the three molecules studied are compared in Table 2 with those of the corresponding tetraisopropyl ester[7b] (values in parenthesis). The bond lengths of the alkylated P-O bonds are within the limits 1.578 - 1.592 Å (1.554 Å), and 1.481 - 1.526 Å (1.453 Å) in the unalkylated case and the bond angles for the C-P-O fragment 103.6° - 108.6° (99.9°, 104.7° and 112.0°) indicating clearly that the negative charge on the phosphorus atom is delocalised between the oxygens. The other bond lengths and angles are almost the same for all of these molecules.

CONCLUSIONS

A selective and general method for the production of tri- and P,P'-diesters of XYMBP has been developed. Trialkylesters were obtained using a tertiary amine as a deesterification agent giving quantitative yields with tributylamine from short-chain tetraesters. For longer or branched tetraalkyl esters the use of pyridine as base gave the best results. P,P'-diesters were prepared from the tetraester with secondary amines in good yield independent of the shape of the ester groups on the bisphosphonate.

Table 2. X-ray analysis of **6e**, **2d** and **6h** and comparison with Cl_2MDB tetraisopropyl ester **4d**.[7b]

Selected bond lengths (Å), deviation 0.004-0.010 Å:

Bond	6e	2d	6h	4d	Bond	6e	2d	6h	4d
Cl1-C1	1.792	1.798	1.803	1.790	P1-C1	1.865	1.869	1.854	1.854
Cl2-C1	1.793	1.793	1.788	1.790	P2-C1	1.856	1.875	1.869	1.854
P1-O11	1.578	1.588	1.588	1.554	P2-O21	1.592	1.590	1.515	1.554
P1-O12	1.482	1.498	1.494	1.560	P2-O22	1.481	1.491	1.505	1.560
P1-O13	1.487	1.488	1.485	1.453	P2-O23	1.493	1.490	1.526	1.453
O11-C11	1.452	1.456	1.454	1.480					

Selected bond angles (°), deviation 0.2-0.5°:

Angle	6e	2d	6h	4d	Angle	6e	2d	6h	4d
Cl1-C1-Cl2	109.7	108.1	108.1	108.2	P1-C1-P2	112.6	113.7	114.9	115.0
C1-P1-O11	104.4	103.6	105.4	104.7	C1-P2-O21	105.2	106.9	106.3	104.7
C1-P1-O12	106.4	108.2	106.4	99.9	C1-P2-O22	108.6	104.1	105.7	99.9
C1-P1-O13	107.4	106.8	108.0	112.0	C1-P2-O23	105.7	106.3	104.6	112.0
P1-C1-Cl1	108.6	108.9	107.4	109.9	P1-C1-Cl2	108.6	108.5	109.2	106.9
P2-C1-Cl1	109.5	108.8	107.9	109.9	P2-C1-Cl2	107.8	108.6	109.3	106.9
O12-P1-O11	107.4	110.4	104.3	103.9	O22-P2-O21	112.0	110.4	113.4	103.9
O13-P1-O11	111.3	106.9	112.3	115.9	O23-P2-O21	104.2	107.1	113.2	115.9
O13-P1-O12	119.0	119.7	119.4	118.4	O23-P2-O22	120.0	119.8	112.8	118.4
C11-O11-P1	126.8	122.8	126.3	123.1					

EXPERIMENTAL

General. - All solvents and reagents were high-purity reagent-grade materials and used without further purification. ^{31}P NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 101.3 MHz using 85% H_3PO_4 as an external standard. ^{13}C and ^{1}H spectra were recorded on a Bruker AM 400 WB operating at 100.6 MHz and 400.1 MHz, respectively, using TMS or TSP (for D_2O solutions) as a reference. Normal $^{3}J_{HH}$ couplings are marked by letter "J" and all the J_{HP} couplings are calculated from coupled ^{31}P spectra. Carbon signals are assigned using Greek letters indicating the relative position of the carbon atom (α, α', β, β',...) and on which (P or P') side of the molecule corresponding shift is. For some representative compounds, elemental analyses were determined in the Department of Chemistry of the University of Joensuu. The purity of products were ≥95% unless stated otherwise. Yields are not optimised. Synthesis and characterization of the bisphosphonate starting materials have been reported earlier.[7,13] P,P-dimethyl (**5a**) and P,P-diisopropyl (**5b**) Cl_2MDP PEs as their dipiperidinium salts were purchased from the Leiras Oy.

Dealkylation of XYMBD tetraesters 4 to triesters 1. General produce (I) for methyl containing esters. - Equimolar amounts of XYMBD tetraester **4** and tributylamine in acetonitrile were heated as described in Table 1 followed by evaporation to constant weight under reduced pressure.

[(Dimethoxyphosphino)dichloromethyl]phosphonic acid monomethyl ester N,N,N-tributyl-N-methyl ammonium salt (**1a**). - NMR ($CDCl_3$): δ_H 3.99 (6H, d, J=10.6), 3.82 (3H, d, J=10.3), 3.40 (6H, m), 3.27 (3H, s),

1.65 (6H, m), 1.44 (6H, m), 1.00 (9H, t, J=7.3). δ_P 15.3 d ($^2J_{PP}$=16.6), 4.3 d. δ_C 76.32 d+d ($^1J_{CP}$=146.6, $^1J_{CP'}$=118.9), 61.16 t ($^+$N<u>C</u>H$_2$), 55.84$^{\alpha}$ q+d ($^2J_{CP}$=6.9), 54.98$^{\alpha'}$ q+d ($^2J_{CP'}$=7.0), 48.84 q ($^+$N<u>C</u>H$_3$), 24.40 t, 19.73 t, 13.73 q. Anal. Calcd for $C_{17}H_{39}Cl_2NO_6P_2$: C, 41.98; H, 8.08; N, 2.88. Found: C, 41.36; H, 8.14; N, 2.86.

[(Dimethoxyphosphino)dibromomethyl]phosphonic acid monomethyl ester N,N,N-tributyl-N-methyl ammonium salt (**1b**). - NMR ($CDCl_3$): δ_H 3.99 (6H, d, J=10.7), 3.84 (3H, d, J=10.3), 3.40 (6H, m), 3.27 (3H, bs), 1.65 (6H, m), 1.45 (6H, m), 1.00 (9H, t, J=7.3). δ_P 15.6 d ($^2J_{PP}$=13.4), 4.0 d. δ_C 61.19 t ($^+$N<u>C</u>H$_2$), 56.09$^{\alpha}$ q+d ($^2J_{CP}$=7.0), 55.34$^{\alpha'}$ q+d ($^2J_{CP'}$=7.1), 52.70 d+d ($^1J_{CP}$=135.2, $^1J_{CP'}$=109.8), 48.89 q ($^+$N<u>C</u>H$_3$), 24.36 t, 19.72 t, 13.74 q.

[[Bis(1-methylethoxy)phosphino]dichloromethyl]phosphonic acid monomethyl ester N,N,N-tributyl-N-methyl ammonium salt (**1c**). - NMR ($CDCl_3$): δ_H 4.99 (2H, m, $^3J_{HP}$=6.6), 3.82 (3H, d, J=10.3), 3.41 (6H, m), 3.29 (3H, bs), 1.63 (6H, m), 1.50-1.40 (18H, m), 0.99 (9H, t, J=7.4). δ_P 11.1 d ($^2J_{PP}$=17.3), 4.9 d. δ_C 76.96 d+d ($^1J_{CP}$=147.4, $^1J_{CP'}$=119.7), 73.70$^{\alpha}$ d+d ($^2J_{CP}$=7.2), 61.04 t ($^+$N<u>C</u>H$_2$), 54.72$^{\alpha'}$ q+d ($^3J_{CP}$=7.0), 48.78 q ($^+$N<u>C</u>H$_3$), 24.38 t, 23.60$^{\beta}$ q+d ($^3J_{CP}$=6.6), 19.67 t, 13.71 q.

General procedure (II) for other esters. - XYMBD tetraester **4** and a 20 fold excess of tertiary amine were heated as described in Table 1. Excess amine was evaporated under reduced pressure at 40°C, the oily residue was washed several times with a small amount of cold n-hexane and evaporated to constant weight.

[(Diethoxyphosphino)dichloromethyl]phosphonic acid monoethyl ester N-ethyl pyridinium salt (**1d**). - NMR ($CDCl_3$): δ_H 9.46 (2H, m), 8.15 (1H, m), 7.85 (2H, m), 4.66 (2H, q, J=7.2), 4.04 (4H, m, $^3J_{HP}$=7.8), 3.86 (2H, m, $^3J_{HP}$=7.1), 1.34 (3H, t, J=7.2), 1.02 (6H, t+d, J=6.9 and 1.0), 0.90 (3H, J=7.2). δ_P 12.5 d ($^2J_{PP}$=17.5), 1.3 d. δ_C 145.4 d, 143.8 d, 127.9 d, 75.95 ($^1J_{CP}$=145.4, $^1J_{CP'}$=118.5), 64.59$^{\alpha}$ t+d ($^2J_{CP}$=7.2), 62.82$^{\alpha'}$ t+d ($^2J_{CP}$=7.0), 56.2 t ($^+$N<u>C</u>H$_2$), 24.7 q, 16.62$^{\beta'}$ q+d ($^3J_{CP}$=6.1), 15.64$^{\beta}$ q+d ($^3J_{CP}$=5.7).

[[Bis(1-methylethoxy)phosphino]dichloromethyl]phosphonic acid mono(1-methylethyl) ester N-ethyl pyridinium salt (**1e**). - NMR ($CDCl_3$): δ_H 9.69 (2H, m), 8.39 (1H, m), 8.28 (2H, m), 5.52 (1H, sep, J=6.7), 4.98 (2H, m, $^3J_{HP}$=6.6), 4.83 (1H, m, $^3J_{HP}$=7.3), 1.72 (6H, d, J=6.7), 1.39 (6H, d, J=6.2), 1.38 (6H, d, J=6.2), 1.30 (6H, d, J=6.2). δ_P 11.1 d ($^2J_{PP}$=19.9), 3.3 d. δ_C 144.6 d, 144.5 d, 129.1 d, 77.14 d+d ($^1J_{CP}$=147.3, $^1J_{CP'}$=120.9), 73.94$^{\alpha}$ d+d ($^2J_{CP}$=7.4), 70.87$^{\alpha'}$ d+d ($^2J_{CP'}$=7.0), 64.5 d ($^+$N<u>C</u>H), 24.79$^{\beta'}$ q+d ($^3J_{CP'}$=4.3), 24.36$^{\beta}$ q+d ($^3J_{CP}$=2.9), 23.77$^{\beta}$ q+d ($^3J_{CP}$=6.3), 23.3 q. Anal. Calcd for $C_{18}H_{33}Cl_2NO_6P_2$: C, 43.91; H, 6.76; N, 2.85. Found: C, 43.40; H, 6.82; N, 2.74.

[(Dihexoxyphosphino)dichloromethyl]phosphonic acid monohexyl ester N-hexyl pyridinium salt (**1f**). - NMR ($CDCl_3$): δ_H 9.48 (2H, d+d, J=6.7 and 1.2), 8.37 (1H, t+t, J=7.8), 8.13 (2H, d+d), 4.86 (2H, t, J=7.4), 4.31 (4H, d+m, $^3J_{HP}$=7.2), 4.17 (2H, t+d, J=7.0, $^3J_{HP}$=6.8). 1.98 (2H, m), 1.76-1.58 (6H, m), 1.43-1.20 (24H, m), 0.91-0.83 (12H, m). δ_P 12.4 d ($^2J_{PP}$=18.1), 3.7 d. δ_C 146.04 d, 144.35 d, 128.54 d, 76.59 d+d ($^1J_{CP}$=145.3, $^1J_{CP'}$=120.1), 69.42$^{\alpha}$ t+d ($^2J_{CP}$=7.5), 68.17$^{\alpha'}$ t+d ($^2J_{CP'}$=7.2), 61.87 t ($^+$N<u>C</u>H$_2$), 31.98 t, 31.73$^{\delta'}$ t, 31.52$^{\beta'}$ t+d ($^3J_{CP'}$=5.9), 31.44$^{\delta}$ t, 30.73$^{\beta}$ t+d ($^3J_{CP}$=5.5), 30.72 t, 25.81 t, 25.50$^{\gamma'}$ t, 25.18$^{\gamma}$ t, 22.67$^{\varepsilon'}$ t, 22.56$^{\varepsilon}$ t, 22.43 t, 14.08$^{\varphi'}$ t, 14.00$^{\varphi}$ t, 13.93 t.

Dealkylation of XYMBD tetraesters 4 to P,P'-diesters 2. General procedure. - XYMBD tetraester **4** and a ten fold excess of secondary amine were heated as described in Table 1. The mixture was cooled to 0°C, the solids were filtered, washed several times with cold ether and dried to constant weight.

(Dichloromethylene)bisphosphonic acid P,P'-dimethyl ester dipiperidinium salt (**2a**). - NMR (D_2O): δ_H 3.77 (6H, m), 3.14 (8H, m), 1.77 (8H, m), 1.67 (4H, m). δ_P 9.7. δ_C 79.39 t ($^1J_{CP}$=138.1), 57.65 q+qv (ΣJ_{CP}=6.7, see text), 47.45 t ($^+$N<u>C</u>H$_2$), 25.26 t, 24.49 t.

(Dibromomethylene)bisphosphonic acid P,P'-dimethyl ester dimorpholinium salt (**2b**). - NMR (D_2O): δ_H 3.96 (8H, m), 3.78 (6H, m), 3.30 (8H, m). δ_P 9.7. δ_C 62.71 t ($O\underline{C}H_2$), 54.09 q+qv (ΣJ_{CP}=7.0), 53.06 t ($^1J_{CP}$=128.1), 42.22 t ($^+N\underline{C}H_2$).

(Dichloromethylene)bisphosphonic acid P,P'-diethyl ester dimorpholinium salt (**2c**). - NMR (D_2O): δ_H 4.05 (4H, m), 3.87 (8H, m), 3.21 (8H, m), 1.18 (6H, t, J=7.1). δ_P 8.58. δ_C 80.07 t ($^1J_{CP}$=137.7), 67.50 t+qv (ΣJ_{CP}=7.0), 66.7 t ($O\underline{C}H_2$), 46.2 t ($^+N\underline{C}H_2$), 19.46 q+qv (ΣJ_{CP}=5.2).

(Dichloromethylene)bisphosphonic acid P,P'-diethyl ester dipiperidinium salt (**2c'**). - NMR (D_2O): δ_H 4.14 (4H, m), 3.16 (8H, m), 1.78 (8H, m), 1.68 (4H, m), 1.28 (6H, t, J=7.0). δ_P 8.86. δ_C 80.03 t ($^1J_{CP}$=136.7), 67.15 t+qv (ΣJ_{CP}=6.9), 47.4 t ($^+N\underline{C}H_2$), 25.0 t, 24.3 t, 19.19 q+qv (ΣJ_{CP}=5.2).

(Dichloromethylene)bisphosphonic acid P,P'-bis(1-methylethyl) ester dimorpholinium salt (**2d**). - NMR (D_2O): δ_H 4.70 (2H, m), 3.97 (8H, m), 3.31 (8H, m), 1.32 (12H, d, J=6.2). δ_P 7.86. δ_C 80.47 t ($^1J_{CP}$=137.3), 75.17 d+qv (ΣJ_{CP}=6.9), 66.4 t ($O\underline{C}H_2$), 46.0 t ($^+N\underline{C}H_2$), 26.48 q+qv (ΣJ_{CP}=4.3). Crystallized for x-ray analysis from H_2O. Anal. Calcd for $C_{15}H_{34}Cl_2N_2O_8P_2$: C, 35.80; H, 6.81; N, 5.57. Found: C, 36.01; H, 6.74; N, 5.41.

(Dichloromethylene)bisphosphonic acid P,P'-bis(1-methylbutyl) ester dimorpholinium salt (**2e**). - NMR (D_2O): δ_H 4.45 (2H, m), 3.72 (8H, m), 2.92 (8H, m), 1.7-1.2 (8H, m), 1.20 (6H, d, J=6.3), 0.81 (6H, t, J=7.2). δ_P 8.24. δ_C 80.80 t ($^1J_{CP}$=137.6), 78.65 d+qv (ΣJ_{CP}=7.4), 68.9 t ($O\underline{C}H_2$), 47.1 t ($^+N\underline{C}H_2$), 42.85 t+qv (ΣJ_{CP}=4.5), 24.42 q+qv (ΣJ_{CP}=3.8), 21.20 t, 16.49 q. Anal. Calcd for $C_{19}H_{42}Cl_2N_2O_8P_2$: C, 40.80; H, 7.57; N, 5.01. Found: C, 40.84; H, 7.58; N, 4.87

(Dichloromethylene)bisphosphonic acid P,P'-bis(cyclopentyl) ester dimorpholinium salt (**2f**). - NMR (D_2O): δ_H 4.82 (2H, m), 3.85 (8H, m), 3.19 (8H, m), 1.8-1.3 (16H, m). δ_P 8.38. δ_C 84.37 d+qv (ΣJ_{CP}=7.3), 80.68 t ($^1J_{CP}$=137.9), 66.8 t ($O\underline{C}H_2$), 46.2 t ($^+N\underline{C}H_2$), 37.16 t+qv (ΣJ_{CP}=4.4), 25.98 t. Anal. Calcd for $C_{19}H_{38}Cl_2N_2O_8P_2$: C, 41.09; H, 6.90; N 5.04. Found: C, 41.49; H, 6.93; N, 4.93.

(Dichloromethylene)bisphosphonic acid P,P'-dihexyl ester dimorpholinium salt (**2g**). - NMR (D_2O): δ_H 4.01 (4H, m), 3.86 (8H, m), 3.18 (8H, m), 1.56 (4H, m), 1.38-1.17 (12H, m), 0.80 (6H, m). δ_P 8.81. δ_C 80.25 t ($^1J_{CP}$=136.2), 71.32$^\alpha$ t+qv (ΣJ_{CP}=7.2), 66.48 ($O\underline{C}H_2$) t, 45.98 t ($^+N\underline{C}H_2$), 33.91$^\delta$, 33.51$^\beta$ t+qv (ΣJ_{CP}=5.3), 27.68$^\gamma$ t, 24.97$^\varepsilon$ t, 16.32$^\varphi$ q. Anal. Calcd for $C_{21}H_{46}Cl_2N_2O_8P_2$: C, 42.94; H, 7.89; N, 4.77. Found: C, 43.26; H, 8.01; N, 4.74.

(Dichloromethylene)bisphosphonic acid P,P'-bis(2-propene) ester dipiperidinium salt (**2i**). - NMR (D_2O): δ_H 6.00 (2H, m), 5.37 (2H, d+m, J=17.2), 5.21 (2H, d+m, J=10.6), 4.58 (4H, m), 3.14 (8H, m), 1.77 (8H, m), 1.66 (4H, m). δ_P 8.84. δ_C 137.59$^\beta$ d+qv (ΣJ_{CP}=5.1), 119.15$^\gamma$ t, 79.84 t ($^1J_{CP}$=137.5), 71.40$^\alpha$ t+qv (ΣJ_{CP}=6.9), 47.37 t ($^+N\underline{C}H_2$), 25.04 t, 24.29 t. Anal. Calcd for $C_{17}H_{34}Cl_2N_2O_6P_2$: C, 41.22; H, 6.92; N, 5.66. Found: C, 40.90; H, 6.95; N, 5.71.

(Dichloromethylene)bisphosphonic acid P-butyl-P'-(1-methylethyl) ester dipiperidinium salt (**2j**). - NMR (D_2O): δ_H 4.61 (1H, m, $^3J_{HP}$=6.6), 4.01 (2H, m, $^3J_{HP}$=8.0), 3.07 (8H, m), 1.77-1.49 (14H, m), 1.30 (2H, m), 1.22 (6H, d, J=6.1), 0.83 (3H, t , J=7.4). δ_P 8.98 d ($^2J_{PP}$=16.0), 8.27 d. δ_C 80.25 d+d ($^1J_{CP}$=137.2, $^1J_{CP}$=137.4), 75.15$^{\alpha'}$ d+d ($^2J_{CP}$=7.0), 70.84$^\alpha$ t+d ($^2J_{CP}$=7.1), 47.30 t ($^+N\underline{C}H_2$), 35.45$^\beta$ t+d ($^3J_{CP}$=4.7), 26.39$^{\beta'}$ q+d ($^3J_{CP}$=4.3), 24.99 t, 24.26 t, 21.03$^\gamma$ t, 15.83$^\delta$ q.

{[Hydroxy(methoxy)phosphino]dichloromethyl}phosphonic acid dipiperidinium monomorpholinium salt (**3a**). Equimolar amounts of P,P-diester **5a** and morpholine in acetonitrile were heated as described in Table 1 followed by evaporation to constant weight under reduced pressure. NMR (D_2O): δ_H 3.76 (3H, d, $^3J_{HP}$=10.3),

3.68 (4H, m), 3.26 (4H, m), 3.16 (8H, m),1.79 (8H, m), 1.68 (4H, m). δ_P 12.97 d ($^2J_{PP}$=15.1), 9.17 d. δ_C 82.97 d+d ($^1J_{CP}$=138.4, ($^1J_{CP'}$=118.7), 70.62 t ($O\underline{C}H_2$), 57.41 q+d ($^2J_{CP}$=6.9), 49.12 t ($N\underline{C}H_2$), 47.39 t (4C, $^+N\underline{C}H_2$), 25.06 t, 24.33 t.

Some of the amine salts **1-2** were converted to sodium salts **6** *via* free acids using H^+-form Dowex resin followed by addition of NaOH to pH 10 and crystallisation from water/alcohol solution (typical yield 85 - 90%).

[(Dimethoxyphosphino)dichloromethyl]phosphonic acid monomethyl ester (**6a**). - NMR ($CDCl_3$): δ_P 16.5 d ($^2J_{PP}$=19.6), 3.4 d.

[(Dimethoxyphosphino)dichloromethyl]phosphonic acid monomethyl ester monosodium salt (**6a'**). - NMR (D_2O): δ_P 15.6 d ($^2J_{PP}$=19.6), 6.6 d.

[(Diethoxyphosphino)dichloromethyl]phosphonic acid monoethyl ester monosodium salt (**6b**). - NMR (D_2O): δ_P 13.5 d ($^2J_{PP}$=17.0), 5.6 d.

[[Bis(1-methylethoxy)phosphino]dichloromethyl]phosphonic acid mono(1-methylethyl) ester monosodium salt (**6c**). - NMR (D_2O): δ_P 11.9 ($^2J_{PP}$=17.3 Hz), 5.2.

[(Dihexoxyphosphino)dichloromethyl]phosphonic acid monohexyl ester monosodium salt (**6d**). - NMR (D_2O/CD_3CD_2OD): δ_H 4.18 (4H, m, $^3J_{HP}$=7.8), 3.99 (2H, t+d, $^3J_{HP}$=7.4), 1.68-1.48 (6H, m), 1.40-1.15 (18H, m), 0.79 (12H, m). δ_P 13.06 d ($^2J_{PP}$=18.0), 5.18 d. δ_C 77.09 d+d ($^1J_{CP}$=152.7, $^1J_{CP'}$=132.3), 72.40 t+d ($^2J_{CP}$=7.7), 70.82 t+d ($^2J_{CP'}$=7.1), 34.08$^{\delta'}$ t, 33.80$^{\delta}$ t, 33.48$^{\beta'}$ t+d ($^3J_{CP'}$=6.3), 32.96$^{\beta}$ t+d ($^3J_{CP}$=5.4), 27.79$^{\gamma}$ t, 27.60$^{\gamma}$ t, 24.98$^{\varepsilon'}$ t, 24.92$^{\varepsilon}$ t, 16.04$^{\varphi'}$ q, 15.98$^{\varphi'}$ q.

(Dichloromethylene)bisphosphonic acid P,P'-bis(1-methylethyl) ester disodium salt (**6e**). - NMR (D_2O): δ_P 8.3. Crystallized for x-ray analysis using the gel technique.[9]

(Dichloromethylene)bisphosphonic acid P,P'-dihexyl ester disodium salt (**6f**). - NMR (D_2O/CD_3CD_2OD): δ_H 4.1 (4H, m), 1.6-1.2 (16H, m), 0.8 (6H, m). δ_P 9.0. Only slightly soluble in organic and inorganic solvents.

[(Hydroxyethoxyphosphino)dichloromethyl]phosphonic acid trisodium salt (**6g**). - NMR (D_2O): δ_P 11.9 ($^2J_{PP}$=15.4 Hz), 9.4.

[[Hydroxy(1-methylethoxy)phosphino]dichloromethyl]phosphonic acid trisodium salt (**6h**). - Prepared as in ref. 3b. NMR (D_2O): δ_P 11.0 ($^2J_{PP}$=16.6 Hz), 9.5. Crystallised for x-ray analysis using the gel technique.[9]

X-ray structure analysis. - Details of crystal parameters, data collection parameters and refined data for compounds **6e**, **2d** and **6h** are summarized in Table 3. Intensity measurements were made on an Enraf-Nonius CAD-4 diffractometer (ω-2θ mode, scan width 0.40+0.14 tanθ for 96 and 0.47+0.35 tanθ for 98, and scan speed 0.7-6.7°min^{-1}) using DIFABS[14] absorption correction or on a Nicolet R3m diffractometer (ω mode with 1.2° scan width and scan speed 2.44-29.3°min^{-1}) using Ψ-scan[15] data (max/min transmission factors 0.3627/0.3211). Intensity data were corrected for Lorentz and polarisation effects. For compound **6e** a loss in intensity (29.6%) was observed and corrected (correction factors max/min: 1.433/0.997). The crystal structures were solved by direct methods using the SHELXS86[16] program and were refined by full matrix least squares, with all non-H atoms anisotropic. The program CRYSTALS[17] was used to refine the structures **6e** and **6h** while the SHELXTL-Plus[18] package was used to refine **2d**. The positions of the H atoms bonded to C were calculated (C-H distance for **6e** and **6h** 1.00 Å, and for 97 0.96 Å) whereas the H atoms in crystal water molecules were located from the $\Delta\rho$ map. All H-atoms were treated as riding atoms with fixed thermal

parameters (U=0.08 Å^2). The Chebychev[19] weighting scheme was used for **6e** (with correction factors 12.6, 3.75, 8.93) and **6h** (with correction factors 5.78, -1.97, 4.29, -0.724).

Table 3. Crystal data and details of the crystallographic analyses for compounds **6e**, **2d** and **6h.**

	6e	**2d**	**6h**
Formula	$C_7H_{14}Cl_2Na_2O_6P_2$ *4 H_2O	$C_7H_{14}Cl_2O_6P_2^{2-}$	$C_4H_7Cl_2Na_2O_6P_2$ *5 H_2O
M_r	445.08	503.30	442.99
Crystal system	Monoclinic	Monoclinic	Rhombohedral
Space group	$P2_1/C$	$P2_1$	R-3
a/Å	13.936(1)	9.201(1)	32.026(4)
b/Å	6.282(2)	22.883(3)	32.026(4)
c/Å	21.957(1)	12.422(2)	8.907(2)
β/°	95.78(1)	109.56(1)	
V/Å^3	1912.3(6)	2464.5(6)	7912(3)
Z	4	4	18
D_c/g cm^{-3}	1.55	1.36	1.67
Crystal size/mm	0.25*0.25*0.40	0.20*0.35*0.50	0.15*0.30*0.50
Radiation	Cu-K_α	Mo-K_α	Mo-K_α
μ/mm^{-1}	5.58	0.43	0.66
Θ min. - max/°	2-75	2-27.5	2-25
Collected data	4097	5819	5045
Obs. data (I>nσ(I))	3271 (1.5 σ)	4600 (2 σ)	2666 (3.0 σ)
Diff. abs., max/min	1.972/0.797		1.079/0.914
Residual density:			
Max./min. (e Å^{-3})	0.42/-0.44	0.25/-0.23	0.46/-0.55
Number of parameters	209	522	199
Extinction parameter	71	-	-
Final R (%)	4.8	3.4	2.9
R_w (%)	6.2	3.9	3.1
Goodness of fit	1.10	1.08	0.75

The full listing of the crystallographic data collection details, data reduction and refinement procedures, bond lengths, bond angles, positional parameters, thermal parameters, tables of calculated and observed structure factors have been deposited at the Cambridge Crystallographic Data Centre.

Table 4. Fractional atomic coordinates with standard deviations (in parentheses) and equivalent isotropic temperature factors U(iso), for symmetrical disodium salt **6e**.

Atom	x	y	z	U(iso)	Atom	x	y	z	U(iso)
Cl(1)	0.13042(5)	-0.2006(1)	0.88341(3)	0.0609	Cl(2)	0.17865(5)	0.1925(1)	0.82134(3)	0.0538
P(1)	0.29791(4)	-0.1947(1)	0.80981(3)	0.0397	P(2)	0.30150(4)	0.0553(1)	0.93157(2)	0.0377
Na(1)	0.37878(8)	-0.4659(2)	0.95132(4)	0.0483	Na(2)	0.39214(8)	0.3161(2)	0.80647(4)	0.0493
O(11)	0.2191(2)	-0.3049(3)	0.76359(8)	0.0558	O(12)	0.3474(1)	-0.3649(3)	0.84769(8)	0.0491
O(13)	0.3569(1)	-0.0413(3)	0.77785(7)	0.0469	O(21)	0.2389(1)	0.2354(3)	0.95976(8)	0.0482
O(22)	0.3199(1)	-0.1274(3)	0.97377(7)	0.0452	O(23)	0.3841(1)	0.1734(3)	0.90921(7)	0.0432
O(101)	0.5529(2)	-0.4229(4)	0.94739(8)	0.0577	O(102)	0.4302(1)	-0.0127(4)	1.07951(8)	0.0562
O(103)	0.5633(2)	0.3792(4)	0.83312(9)	0.0667	O(104)	0.4391(2)	0.3836(5)	0.70711(9)	0.0692
C(1)	0.2270(2)	-0.0377(4)	0.8618(1)	0.0425	C(111)	0.1786(2)	-0.2227(7)	0.7047(1)	0.0628
C(112)	0.1951(4)	-0.385(1)	0.6575(2)	0.0971	C(113)	0.0750(3)	-0.176(1)	0.7062(2)	0.1007
C(211)	0.1667(2)	0.2018(5)	1.0026(1)	0.0592	C(212)	0.1929(4)	0.3426(9)	1.0564(2)	0.0849
C(213)	0.0690(3)	0.2576(8)	0.9704(2)	0.0848					

Table 5. Fractional atomic coordinates with standard deviations (in parentheses) and equivalent isotropic temperature factors U(iso), for symmetrical dimorpholinium salt **2d**.

Atom	x	y	z	U(iso)	Atom	x	y	z	U(iso)
Cl(1)	0.2043(1)	0.1780(2)	-0.1880(1)	0.046(1)	Cl(2)	0.4219(1)	0.1621(2)	-0.3098(1)	0.048(1)
Cl(1')	0.147(1)	0.2707(2)	0.1445(1)	0.046(1)	Cl(2')	0.2274(1)	0.2847(2)	0.0188(1)	0.048(1)
P(2)	0.4614(1)	0.0926(2)	-0.0987(1)	0.030(1)	P(1)	0.1864(1)	0.0700(2)	-0.3253(1)	0.029(1)
P(1')	-0.0036(1)	0.3779(2)	0.0039(1)	0.030(1)	P(2')	0.2737(1)	0.3551(2)	0.2299(1)	0.029(1)
O(23)	0.5469(3)	0.0469(2)	-0.1388(2)	0.042(1)	O(21)	0.5792(3)	0.1444(2)	-0.0467(2)	0.039(1)
O(22)	0.3776(3)	0.0765(2)	-0.0190(2)	0.037(1)	O(12)	0.1120(3)	0.0373(2)	-0.2531(2)	0.041(1)
O(11)	0.0557(3)	0.1088(2)	-0.4116(3)	0.042(1)	O(13)	0.2741(3)	0.0375(2)	-0.3873(2)	0.038(1)
O(11')	-0.1300(3)	0.3385(2)	-0.0861(2)	0.041(1)	O(13')	0.0858(3)	0.4121(2)	-0.0552(2)	0.038(1)
O(12')	-0.0809(3)	0.4096(2)	0.0744(2)	0.041(1)	O(23')	0.3651(3)	0.3990(2)	0.1906(2)	0.039(1)
O(21')	0.3849(3)	0.3019(2)	0.2842(2)	0.039(1)	O(22')	0.1912(3)	0.3743(2)	0.3085(2)	0.039(1)
N(2)	0.1185(4)	0.0263(2)	-0.0112(3)	0.039(1)	N(2')	-0.0718(4)	0.4216(2)	0.3171(3)	0.038(1)
N(1')	0.3617(4)	0.4603(2)	-0.0264(3)	0.036(1)	O(1)	0.6257(5)	0.0309(3)	-0.5437(3)	0.070(2)
O(2)	0.0374(5)	0.1076(3)	0.1326(3)	0.065(2)	O(2')	-0.1643(4)	0.3390(3)	0.4532(3)	0.065(2)
O(1')	0.4225(5)	0.4238(3)	-0.2255(3)	0.072(2)	N(1)	0.5535(4)	-0.0106(2)	-0.3510(3)	0.038(1)
C(1)	0.3188(4)	0.1250	-0.2305(3)	0.030(1)	C(1')	0.1283(4)	0.3233(2)	0.1000(3)	0.028(1)
C(21)	0.5590(5)	0.1864(3)	0.0362(4)	0.040(2)	C(22)	0.6710(6)	0.1709(3)	0.1524(4)	0.060(2)
C(23)	0.5880(6)	0.2463(3)	-0.0034(5)	0.059(2)	C(11)	0.0613(6)	0.1268(3)	-0.5225(4)	0.054(2)
C(13)	0.0042(10)	0.1891(3)	-0.5418(6)	0.100(3)	C(12)	-0.0359(7)	0.0861(4)	-0.6122(4)	0.068(2)
C(11')	-0.1238(5)	0.3234(3)	-0.1986(4)	0.048(2)	C(13')	-0.1745(8)	0.2613(3)	-0.2235(6)	0.080(3)
C(12')	-0.2214(6)	0.3664(3)	-0.2844(4)	0.066(2)	C(21')	0.3638(6)	0.2637(3)	0.3726(4)	0.047(2)
C(22')	0.4725(9)	0.2828(4)	0.4855(5)	0.094(3)	C(23')	0.3892(10)	0.2028(3)	0.3445(7)	0.094(3)
C(64)	-0.0246(5)	0.0610(3)	-0.534(4)	0.051(2)	C(63)	-0.0094(8)	0.1173(3)	0.0114(5)	0.068(2)
C(62)	0.1809(6)	0.0797(3)	0.1681(4)	0.056(2)	C(61)	0.1726(6)	0.0205(3)	0.1147(4)	0.048(2)
C(64')	-0.2243(5)	0.3910(3)	0.2738(4)	0.049(2)	C(63')	-0.2159(6)	0.3335(3)	0.3320(4)	0.058(2)
C(62')	-0.0124(7)	0.3631(3)	0.4923(5)	0.061(2)	C(61')	-0.0131(6)	0.4246(3)	0.4442(4)	0.047(2)
C(51')	0.3165(5)	0.4961(3)	-0.1330(4)	0.045(2)	C(52')	0.2878(6)	0.4575(3)	-0.2360(4)	0.054(2)
C(53')	0.4580(8)	0.3864(3)	-0.1290(5)	0.071(3)	C(54')	0.4916(6)	0.4207(3)	-0.0204(4)	0.053(2)
C(52)	0.4893(6)	-0.0016(3)	-0.5578(4)	0.060(2)	C(51)	0.5102(5)	-0.0431(3)	-0.4605(4)	0.045(2)
C(54)	0.6887(6)	0.0285(3)	-0.3369(4)	0.052(2)	C(53)	0.6593(7)	0.0655(3)	-0.4426(5)	0.070(3)

Table 6. Fractional atomic coordinates with standard deviations (in parentheses) and equivalent isotropic temperature factors U(iso), for monoester **6h**.

Atom	x	y	z	U(iso)	Atom	x	y	z	U(iso)
Cl(1)	0.56378(1)	0.12168(2)	0.73695(5)	0.0333	Cl(2)	0.49530(2)	0.15550(2)	0.77094(6)	0.0354
P(1)	0.50822(1)	0.10067(2)	1.01793(4)	0.0219	P(2)	0.45909(1)	0.05115(1)	0.71357(4)	0.0180
Na(1)	0.53859(2)	0.01718(3)	0.86754(7)	0.0289	Na(2)	0.58535(3)	0.08094(3)	1.19075(8)	0.0378
Na(3)	0.38455(2)	0.05890(3)	1.00859(8)	0.0313	O(11)	0.55678(5)	0.14688(5)	1.0698(2)	0.0344
O(12)	0.51707(5)	0.05966(5)	1.0438(1)	0.0298	O(13)	0.46489(4)	0.09900(5)	1.0846(1)	0.0306
O(21)	0.46449(4)	0.06297(4)	0.5475(1)	0.0267	O(22)	0.47026(4)	0.01215(4)	0.7541(1)	0.0253
O(23)	0.41113(4)	0.04213(4)	0.7781(1)	0.0246	O(101)	0.60874(4)	0.03790(5)	1.0122(1)	0.0337
O(102)	0.65992(5)	0.11199(5)	1.2952(1)	0.0378	O(103)	0.54355(5)	0.06212(5)	1.4188(1)	0.0382
O(104)	0.30326(5)	-0.00167(5)	0.9371(1)	0.0344	O(105)	0.35484(5)	0.11213(4)	1.0333(1)	0.0321
C(1)	0.50558(6)	0.10668(6)	0.8116(2)	0.0211	C(111)	0.56123(9)	0.19067(8)	1.1340(3)	0.0493
C(112)	0.5753(1)	0.1923(1)	1.2950(4)	0.0727	C(113)	0.5981(2)	0.2319(1)	1.0445(6)	0.0962

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