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Bisphosphonic Compounds V. Selective Preparation of (Dichloromethylene)bisphosphonate Partial Esters.

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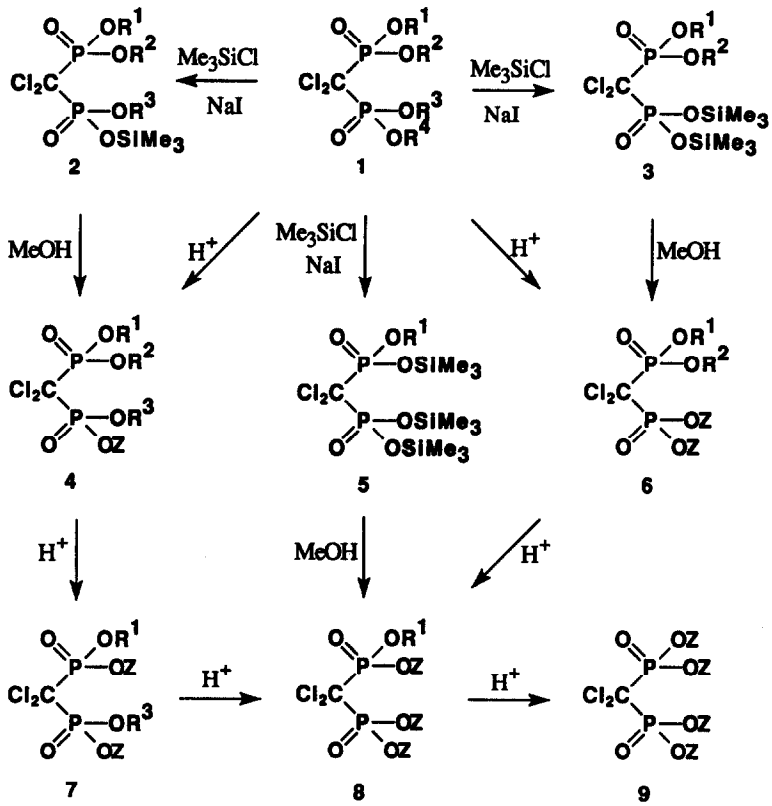
Abstract: The preparations of tri-, P,P'-di-, P,P-di- and mono partial esters of (dichloromethylene)bisphosphonic acid with good selectivity and purity have been described.

Methylenebisphosphonate (MBP) compounds, containing a stable P-C-P bridge, are widely used for the treatment of bone formation and resorption disorders. Their physicochemical interaction with bone differs greatly from one MBP tetraacid to another and no clear structure-activity correlation has been found. The known MBP compounds are very polar lowering their bioavailability and binding tightly to bone.[1] Several MBP tetraacids have been prepared[2], but a little is known about the preparation of pure partial esters (PE) of MBPs[3] and Cl_2MBP[4]. The main difficulties in preparing PEs are the selective reactions at specific positions with desired chain shape and length. Here, we descibe two selective methods to produce Cl_2MBP PEs: *via* silyl derivatives and *via* hydrolysis of branched alkyl groups over n-alkyl groups.

All the tetraalkyl Cl_2MBP starting materials were prepared using the methods described earlier.[5] Several low-selective methods were tested like hydrolysis of symmetric MBP tetraesters **1** with either acids[6], bases[3a,c] or silyl intermediates[3b,3e,7], but all these methods produced mixtures of PEs requiring chromatographic methods or efficient fractional crystallization for separation. *E.g.* hydrolysis of **1j** with water taking place stepwise mainly *via* path **1-4-7-8-9** (Scheme 1), but this was effective only in producing the symmetric P,P'-diester **7a**[8] with sufficient yield, partially succesful for **4a**, **8a** and **8c**, but failed totally with P,P-diester **6** (see Table 1). Moreover, only branched PE derivatives were stable enough to undergo repeated alkaline conditions during separation. The other alkyl and aromatic derivatives tended to decompose gradually into mono-phosphorus species.

A more convenient approach to PEs is based on silylation of methyl containing mixed tetraesters since the order of silylation depends on the ester as follows: Me > 1°-alkyl > 2°-alkyl.[9] On the other hand, the hydrolysis rate of silyl and alkyl esters of Cl_2MDP is as follows: $SiMe_3$ > 3°-alkyl > 2°-alkyl > 1°-alkyl ≈ arom.

Combining these trends provides a potential path to produce numerous PEs of Cl_2MDP. The silylation was easily accomplished by reacting the mixed tetraesters and the silyl reagent in a dry solvent for a controlled time, followed by filtration, evaporation, pH adjustiment and crystallization. The selective silylation of the methyl group resulted in even when the mixed tetraester contained ethyl groups. The main difficulties in this method were the tedious preparation of starting materials from toxic monophosphorus compounds, and the unselectivity of silylation in some cases. In contrast to the hydrolysis method, synthesis of P,P-diesters **6** was accomplished using **1b, d** or **e** as a starting-point. The preparation of **6b** from **1d** via **3b** was without any by-products, **6a** from **1a** via **3a** yielded some and **6c** from **1e** via **3c** gave many side products. In general, the more the alkyls resembled each other the more unselective is the silylation. Several potential silyl reagents were tested, but the best combination was Me_3SiCl in CH_3CN with NaI as a catalyst.



Scheme 1. Preparation of tri-, P,P'-di-, P,P-di- and mono PEs of (dichloromethylene)bisphosphonic acid.

An alternative approach was also developed to produce n-alkyl PEs. Three mixed esters **1g, h** and **i** were prepared in order to test different hydrolysis properties of branched alkyls over n-alkyls with acids. We also attempted synthesis of Bu^t analogues instead of the Pr^i esters, but these esters tended to decompose during preparation. We found that acid hydrolysis of Pr^i groups from mixed esters was a practical method to produce PEs containing long n-alkyls. **1g** was easily converted in to **6d**, but the shorter n-alkyls resulted in complicated

mixtures. This is explained by the phase transfer conditions at the event of hydrolysis. Cleavage of one Pr^i group from **1g** leading to a distribution of the dihexyl and mono-Pr^i moieties of the bisphosphonate between the organic and acid phases, respectively. If the n-alkyls are enough long, the dialkyl part stays in the organic phase without tending to hydrolyse significantly. This method was applied as a synthetic route for longer (> C_5) tri-n-alkyls PEs, but preparation of desired starting mixed tetraester, containing *e.g.* three hexyl and one Pr^i group, resulted in severe problems.[5b] This method was also less favourable for the synthesis of any mono-n-alkyl or short (< C_5) di-n-alkyl PEs, since the separation of products from reagents and side products was troublesome.

^{31}P NMR spectroscopy was used to follow the progress of the reactions and to analysize the purity of the products. The multiplicity of the ^{31}P signals offered an unambiguous method to assign the amounts and the types of alkyls in each phosphorus atom. Also the $^1J_{CP}$ couplings for the middle carbon were sensitive to the number of ester groups on the phosphorus it was coupled to; being approximately 155 Hz for $P(O)(OR)_2$, 135 Hz for P(O)(OR)(OZ) and 110 Hz for $P(O)(OZ)_2$ fragments. For the 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 rapid walk of the cation between the two anionic oxygens.

Table 1. Preparation of Cl_2MBP PEs from Mixed and Symmetric Cl_2MBP Tetraesters.

	Starting material				Reaction			Product				
Comp.	R^1	R^2	R^3	R^4	method	time	Comp.	R^1	R^2	R^3	Z	Yield %
1a	Pr^i	Pr^i	Pr^i	Me	A	15 min	**4a**	Pr^i	Pr^i	Pr^i	Na	87
1b	Pr^i	Pr^i	Me	Me	A	15 min	**6a**	Pr^i	Pr^i	Na	Na	88
1c	Pr^i	Me	Me	Me	A	25 min	**8a**	Pr^i	Na	Na	Na	80
1d	Ph	Ph	Me	Me	A	20 min	**6b**	Ph	Ph	Na	Na	95
1e	Et	Et	Me	Me	A	5 min	**6c**	Et	Et	Na	Na	41
1f	Et	Et	Et	Et	A	5h	**8c**	Et	Na	Na	Na	27
1g	Hex	Hex	Pr^i	Pr^i	B	130 min	**6d**	Hex	Hex	Na	Na	44
1h	Bu	Bu	Pr^i	Pr^i	B	130 min	**6e**	Bu	Bu	Na	Na	15[a]
1i	Et	Et	Pr^i	Pr^i	B	130 min	**6c**	Et	Et	Na	Na	trace
1j	Pr^i	Pr^i	Pr^i	Pr^i	C	4h	**4a**	Pr^i	Pr^i	Pr^i	Na	22
1j	Pr^i	Pr^i	Pr^i	Pr^i	C	8h	**7a**	Pr^i	Na	Pr^i	Na	44
1j	Pr^i	Pr^i	Pr^i	Pr^i	C	10h	**8a**	Pr^i	Na	Na	Na	15

Methods: A) NaI, dry CH_3CN and Me_3SiCl were refluxed, the residue was dissolved in methanol, evaporated, adding NaOH and crystallized using Pr^iOH/H_2O. B) $MeSO_3H$ in toluene were heated at 50°C, the toluene layer separated, washed with water, dried and evaporated and isolated as A. C) Refluxed in water and isolated as A. [a] Contained several impurities.

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10. Product analyses. NMR: Bruker AM 400 WB, ^{31}P, ^{13}C and ^{1}H at 161, 101 and 400 MHz. Elemental analyses: Univ. of Joensuu, Dept. Chem. The purity of products were ≥95%.
    Silyl intermediates. NMR ($CDCl_3$): **2a** (R^1=R^2=R^3=Pr^i): δ_P 11.62, 0.63 ($^2J_{PP}$=24.6 Hz). **3a** (R^1=R^2=Pr^i): δ_P 7.50, -9.67 ($^2J_{PP}$=24.3 Hz). **3b** (R^1=R^2=Ph): δ_P 2.03, -11.26 ($^2J_{PP}$=26.6 Hz). **3c** (R^1=R^2=Et): δ_P 9.36,-9.81 ($^2J_{PP}$=23.7 Hz). **5a** (R^1=Pr^i): δ_P -1.18, -9.71 ($^2J_{PP}$=27.1 Hz).
    Partial Cl_2MBP esters. **6b**: NMR (D_2O): δ_H 7.43 (4H, m), 7.31 (2H, m), 7.27 (4H, m); δ_C 152.81 ($^2J_{CP}$=10.3 Hz), 132.86, 129.00, 123.94, 78.04 (d+d, $^1J_{CP}$=154.6 and 107.1 Hz); δ_P 11.0 ($^2J_{PP}$=14.7 Hz), 6.5. Calcd for $C_{13}H_{10}Cl_2Na_2O_6P_2$: H, 2.29; C, 35.40. Found: H, 2.33; C, 35.31.
    6c: NMR (D_2O): δ_H 4.16 (4H, m), 1.29 (t, 6H); δ_C 78.96 ($^1J_{CP}$=148.6 and 110.5 Hz), 69.38 ($^2J_{CP}$=7.6 Hz), 18.8 ($^3J_{CP}$=5.2 Hz); δ_P 16.67 ($^2J_{PP}$=15.5 Hz), 7.2. Calcd for $C_5H_{10}Cl_2Na_2O_6P_2$: H, 2.92; C, 17.41. Found: H, 2.89; C, 17.62.
    6d: (Z=H): NMR ($CDCl_3/CD_3CD_2OD$): δ_P 11.89 ($^2J_{PP}$=21.0), 5.27. (Z=Na, DMSO-D_6): δ_C 74.38 (d+d, $^1J_{CP}$=147.9 and 132.9 Hz), 69.18 ($^2J_{CP}$=7.3 Hz), 30.98, 30.20 ($^3J_{CP}$=5.5 Hz), 24.79, 22.24, 14.1; δ_P 15.04 ($^2J_{PP}$=17.3 Hz), 7.3. Calcd for $C_{13}H_{26}Cl_2Na_2O_6P_2$: H, 5.73; C, 34.15. Found: H, 5.83; C, 34.60.
    8c: NMR (D_2O): δ_H 4.16 (4H, m), 1.28 (t, 6H); δ_C 83.13 ($^1J_{CP}$=135.6 and 117.6 Hz), 67.07 ($^2J_{CP}$=6.9 Hz), 19.27 ($^3J_{CP}$=5.0 Hz); δ_P 11.9 ($^2J_{PP}$=15.4 Hz), 9.4. Calcd for $C_3H_5Cl_2Na_3O_6P_2$: H, 1.49; C, 10.63. Found: 1.53; C, 10.54.

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