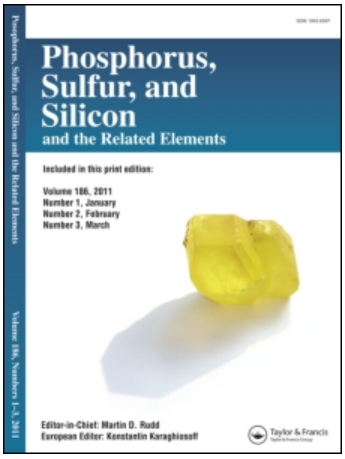

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BISPHOSPHONATES. VI. METHYLENEBISPHOSPHONIC ACID PARTIAL ESTERS AND AMIDES

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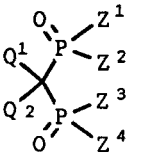
Abstract Syntheses and properties of various partial esters and amides **2-5** of some established methylenebisphosphonic acids **1** have been examined.

INTRODUCTION

Methylenebisphosphonates (MBP), characterized by a stabile P-C-P moiety (Table 1), are synthetic analogues of natural pyrophosphate. MBP tetraacids **1** (MBPA) bind strongly to hydroxyapatite (HA) and inhibit effectively the formation and dissolution of crystals of HA. Up to 50 % of a given dose of MBPA is taken up by the skeleton. The rest is excreted within hours in the urine. The half-life in bone is very long, one year or more.[1]

TABLE 1 MBPA and partial derivatives

	MBPA	Q^1	Q^2	Structures		Type	≠ OH,	= OH
A	Clodronate	Cl	Cl		1	-		Z^{1-4}
B	Etidronate	OH	CH_3		2	Mono	Z^1	Z^{2-4}
C	Tiludronate	H	4-ClPhS		3	Asym.Di	$Z^{1,2}$	$Z^{3,4}$
D	Pamidronate	OH	$(CH_2)_2NH_2$		4	Sym Di	$Z^{1,3}$	$Z^{2,4}$
E	Alendronate	OH	$(CH_2)_3NH_2$		5	Tri	Z^{1-3}	Z^4
F	Risedronate	OH	3-PyCH_2		6	Tetra	Z^{1-4}	

Z^n = NRR' or OR; R,R' = H, C_nH_m

MBPA inhibit the osteoclastic bone resorption via physicochemical interaction with bone mineral and via biochemical effects on cellular metabolism. Their properties

vary greatly from one MBPA to another. No clear structure-activity correlation has been found. Known MBPA (**1**) bind merely too tightly to bone. Some of them block mineralization causing dose-dependent side-effects. As very polar compounds they also suffer from a low bioavailability. Many MBPA are well tolerated with relatively few adverse events, specific for each. The clinical conditions of malignancy treated with MBPA include, e.g. osteolytic bone metastases, hypercalcemia, Paget's disease and ectopic calcification. MBPA are further investigated for benign diseases, especially osteoporosis and arthritis. In general they reduce the pain, lesions and fractures associated and improve the quality of life of patients.[1]

RESULTS AND DISCUSSION

The P-C-P backbone of MBP allows variations either by changing the two groups (Q^1 and Q^2) on the central carbon and/or those (Z^1, Z^2, Z^3 and Z^4) on two phosphorus atoms. According to the literature about 3000 MBP have sofar been reported. A part of them have been biologically tested. Nearly all are MBPA carrying different groups Q while only few partial derivatives (**2-5**) (Z ≠ OH) of MBPA are known.

SCHEME Stepwise cleavage of tetraesters of **A**

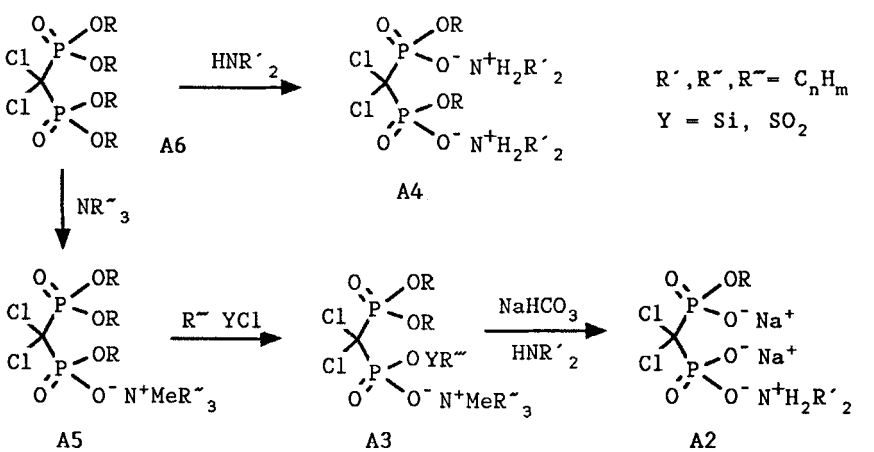


TABLE 2 Partial derivatives of MBPA

	Z^1	Z^2	Z^3	Z^4	Yield[a]	^{31}P NMR		
A Clodronate Esters					%	δ(ppm)		$^2J_{PP}$(Hz)
2a	OH_2B^1	ONa	ONa	OMe	55	12.95	9.17	15.1
2b	ONa	ONa	ONa	OiPr	80	10.95	9.54	16.6
3a	ONa	ONa	OEt	OEt	41	16.27	7.20	16.0
3b	ONa	ONa	OHex	OHex	95	11.01	6.48	14.7
4a	OH_2B^1	OMe	OH_2B^1	OMe	95	9.70		
4b	OH_2B^2	OEt	OH_2B^2	OMe	84	10.03	8.74	15.5
4c	ONa	OEt	ONa	OEt	81	9.20		
4d	OH_2B^3	OiPr	OH_2B^3	OiPr	83	7.86		
5a	ONa	OMe	OMe	OMe	≈90	16.46	3.42	19.6
5b	$ONMeBu_3$	OMe	OMe	OMe	≈100	15.50	4.25	16.6
5c	ONa	OEt	OEt	OEt	≈80	13.47	5.58	17.0
5d	OMePy	OMe	OiPr	OiPr	≈80	11.12	4.85	17.3
A' Clodronate Amides					%	δ(ppm)		$^2J_{PP}$(Hz)
2a	ONa	ONa	ONa	NHBu	≈80	9.49	7.11	21.0
2b	ONa	ONa	ONa	NEt_2	86	15.72	10.23	15.2
3a	OH	OH	B^3	OEt	68	13.39	8.29	22.6
3b	ONa	ONa	NEt_2	NEt_2	63	32.16	8.60	15.6
4a	OH_2B^3	OMe	OH_2B^3	B^3	97	9.70	0.82	15.4
5a	$ONMeBu_3$	OMe	NMeBn	OEt	≈100	18.77	4.94	17.9
5b	$ONMeBu_3$	OMe	NEt_2	NEt_2	98	27.88	6.17	17.2
5c	OH_2B^1	NEt_2	NEt_2	NEt_2	85	30.19	12.26	16.5
B^1= Piperidine, B^2= 4-Me-Piperazine, B^3= Morpholine								
B Etidronate Esters					%	δ(ppm)		$^2J_{PP}$(Hz)
2a	ONa	ONa	ONa	OMe	[b]	24.86	17.25	27.3
2b	OH	OH	OH	OiPr	[b]	22.76	17.72	27.1
3a	ONa	ONa	OiPr	OiPr	[b]	23.24	16.80	37.6
4a	ONa	OMe	ONa	OMe	72	21.19		
5a	ONa	OMe	OMe	OMe	[b]	28.41	16.89	34.8
C Tiludronate Esters					%	δ(ppm)		$^2J_{PP}$(Hz)
2a	ONa	ONa	ONa	OiPr	[b]	18.25	12.21	9.8
3a	OH	OH	OiPr	OiPr	[b]	22.79	10.84	15.2
4a	OH	OiPr	OH	OiPr	[b]	14.00		

[a] Isolated, or from ^{31}P NMR spectra. Based on **6**
[b] Several chromatographic or crystallization steps

Compounds

In order to explore the biological properties of some new partial derivatives of MPBA the esters and amides **2-5** with desired better absorption and controlled affinity for bone with preserved resorption inhibition were prepared. Thus the selective cleavage of tetraesters, -amides and -amide esters **6** their P-C-P backbone being constructed from suitable monophosphonic parts gave, e.g. partial esters (**A2-A5**) of clodronate (**A**) as depicted in Scheme. Reactions from tetraacid **A1** or -acid chloride and further transformations of **A2-A5** were also exploited. Partial amides and amide esters (**A'2-A'5**) of **A** were analogously obtained.

Other partial alkyl esters **2-5** synthesized in this study were those of other MBPA already clinically applied (**B, D**) or in advanced research phase (**C, E, F**), as well as partial esters of a series of MBPA with related $Q^1$and Q^2. Representative structures, yields and ^{31}P NMR data for partial derivatives of **A, A', B** and **C** are shown (Table 2).

Properties

Hydrolytic cleavage aptitudes of tetra compounds **6** and each subsequent partial derivative (**2-5**) were surprisingly greatly depending on differences in substituents Q and Z, the best method for each group and combination varying.

Phosphorus-31 NMR at 101 MHz provided a powerful means to follow the progress of reactions and to check the final purity of the products. The structures, substitution pattern and nature were obtained from coupled spectra.

Mono derivatives **2** complex still with calcium but this being reduced towards the higher derivatives (**3-5**). Binding to HA and inhibition of precipitation were not essential to resorption inhibition in vitro or in vivo.

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