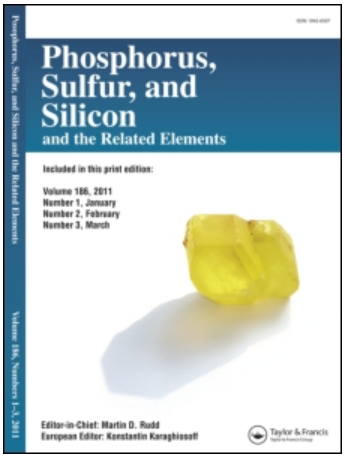

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Dioxazaphosphocanes: Synthesis, Structure and Biological Activity

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Synthesis of dioxazaphosphocanes **2** and podands **3–7** is described. The formation of calcium complexes with compounds **3–7** was studied by UV, IR and NMR spectroscopies. These complexes are able to extract calcium from an aqueous phase to an organic one and were shown to transport this cation across a chloroformic thick membrane. Some of these compounds show a specific antibacterial activity on mycobacteria.

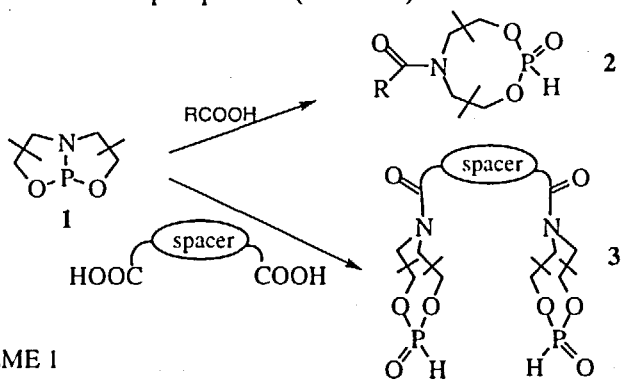
Keywords: Dioxazaphosphocanes; Ca^{2+} complexation; ionophores

INTRODUCTION

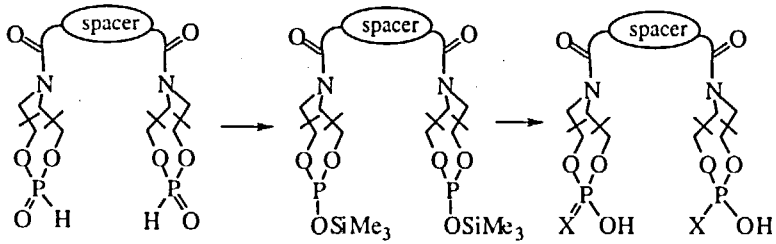
We have shown that eight membered cyclic hydrogenophosphonates-dioxazaphosphocanes- with a lipophilic moiety have phospholipid properties [1] Their reactivity towards calcium dependent systems is related to their ability to complex this cation which was demonstrated in a preliminary work [2]. Going further on, in this paper the study of their ionophoric properties is given.

SYNTHESIS

Synthesis of dioxazaphosphocanes as **2** was performed reacting carboxylic acids with the well known constrained bicyclophosphanes **1** (scheme 1). Extension of this process to diacids leads to podands **3** in which the two dioxazaphosphocane units are linked by a spacer (scheme 1). In order to obtain compounds suitable for calcium complexation various spacers were used including rigid aromatics ($-C_6H_4-$, $-CH_2-C_6H_4-CH_2$, ...), ethers ($-CH_2-O-CH_2-$, $-CH_2-O-CH_2-CH_2-O-CH_2-$) lipophilic spacers ($-CH_2-N(C_{16}H_{33})-CH_2-$). Podands **3** were functionalized into phosphates **6** and thiophosphates **7** (Scheme 2).

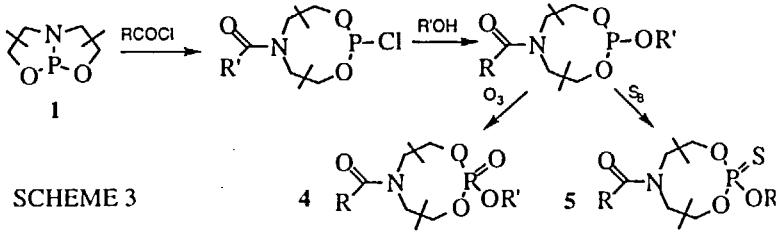


SCHEME 1



SCHEME 2

An original 'one pot ' reaction using acyl chlorides was developed for the obtention of phosphoric **4** and thiophosphoric **5** triesters [3] (Scheme 3).



1

SCHEME 3

4 5

CALCIUM COMPLEXATION

Calcium complexes of podands were obtained from calcium perchlorate in acetonitrile solution. Complexation sites determined by IR and ^{31}P NMR (acetonitrile solution) on the basis of characteristic shifts between the free compounds and their complexes are the two oxygen atoms of the carbonyl and the two oxygen atoms of the phosphoryl group. The perchlorate anion is involved in the complexation.

An example is given on Table 1 for the aromatic spacer -C_6H_4-

TABLE 1 : IR spectral data (KBr, cm^{-1}) and ^{31}P NMR shifts δ (ppm) and coupling constants J (Hz) of the free ligand and of its calcium perchlorate (3, spacer: -C_6H_4-).

vibrator	ligand	complex	Δν	ligand δ ^{31}P (J_{PH})	complex δ ^{31}P (J_{PH})	Δ δ (J)
ν C=O	1647	1627	- 20	– 5,7	– 4,5	1,2
ν P=O	1269	1239	- 30	(706)	(737)	(31)
ν P-H	2436	2463	+ 27			

Stability constants were measured in THF solution by U.V. spectrophotometry for podands/calcium picrate complexes. A computational treatment of the results with the programs STAR/STARFA [4] determined the stoechiometry of the complex formed i.e. one Ca^{2+} for 2 dioxazaphosphocane moieties. The values of the stability constants for ML ranging between 2.6 and 6.2 are function of the nature of the spacer and of the structure of the eight membered ring. Complexes of non substituted eight membered rings are more stable than complexes of gem dimethylated rings. This phenomenon could be explained by molecular modeling, in the last case complexation needs a change in the conformation of the cycle from a boat-boat shape to a boat shape with higher energy.

IONOPHORE PROPERTIES

Liquid-liquid extraction of calcium picrate from an aqueous layer to an organic layer by the podands showed that the percentage of extraction is a function of : - the stability of the complex formed between the podand and Ca^{2+} - and its solubility in the organic layer directly related to the lipophilicity of the podand.

The calcium migration through a liquid membrane system was performed in an original cell which will be described in a later paper. Transport phenomenon needing decomplexation at the organic/aqueous interface is limited by the stability of the complexes. Table 2 summarizes the complexation constants and the ionophoric properties of podands **3**, **6** and **7** with the lipophilic spacer - $CH_2N(C_{16}H_{33})CH_2$-

TABLE 2 : [a] gem-dimethylated eight membered ring, [b] unsubstituted eight membered ring, [c] stability constants in THF at 25 °C for the complex ML, [d] extraction percentages, [e] transport percentages, [f] minimal inhibition concentration towards *Mycobacterium smegmatis*

compound	log β_{ML} [c]	% E [d]	% T [e]	CMI (µM) [f]
3A [a]		3	0.8	7.8
3B [b]	3.7	12	8.6	46.9
6A	5.3	8	3	15.6
6B	6			23.4
7A	ND	36	1.4	23.4
7B	5.5			7.8

Activity tests of the podands revealed that the compounds with aromatic or oxygenated spacers are inactive on all bacteria. On the other hand the podands with a lipophile spacer show a weak but selective activity on mycobacteria (Table 2)

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