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Cyclophosphazenes Containing Acetyl Salicylic (Aspirin) Substituents

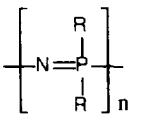
Giancarlo Fantin,*[a] Marco Fogagnolo,[a] Mario Gleria,[b] Alessandro Medici,[a] Francesco Minto,[b] Paola Pedrini[a]

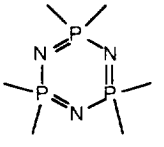
[a] Dipartimento di Chimica, Università di Ferrara, Via L. Borsari 46, I-44100, Ferrara, Italy

[b] Istituto di Fotochimica e Radiazioni d'Alta Energia del Consiglio Nazionale delle Ricerche, Sezione di Legnaro, Via Romea 4, I-35020 Legnaro, Padova, Italy

Abstract: The synthesis of hexakis(4-carboxyl-3-O-acetylphenoxy)cyclophosphazene starting from hexachlorocyclophosphazene is described. Copyright © 1996 Elsevier Science Ltd

Poly(organophosphazenes) (POPs) and their low molecular weight cyclic homologues, the cyclophosphazenes (CP) are reported to possess interesting biomedical properties and promising applications.[1-3]





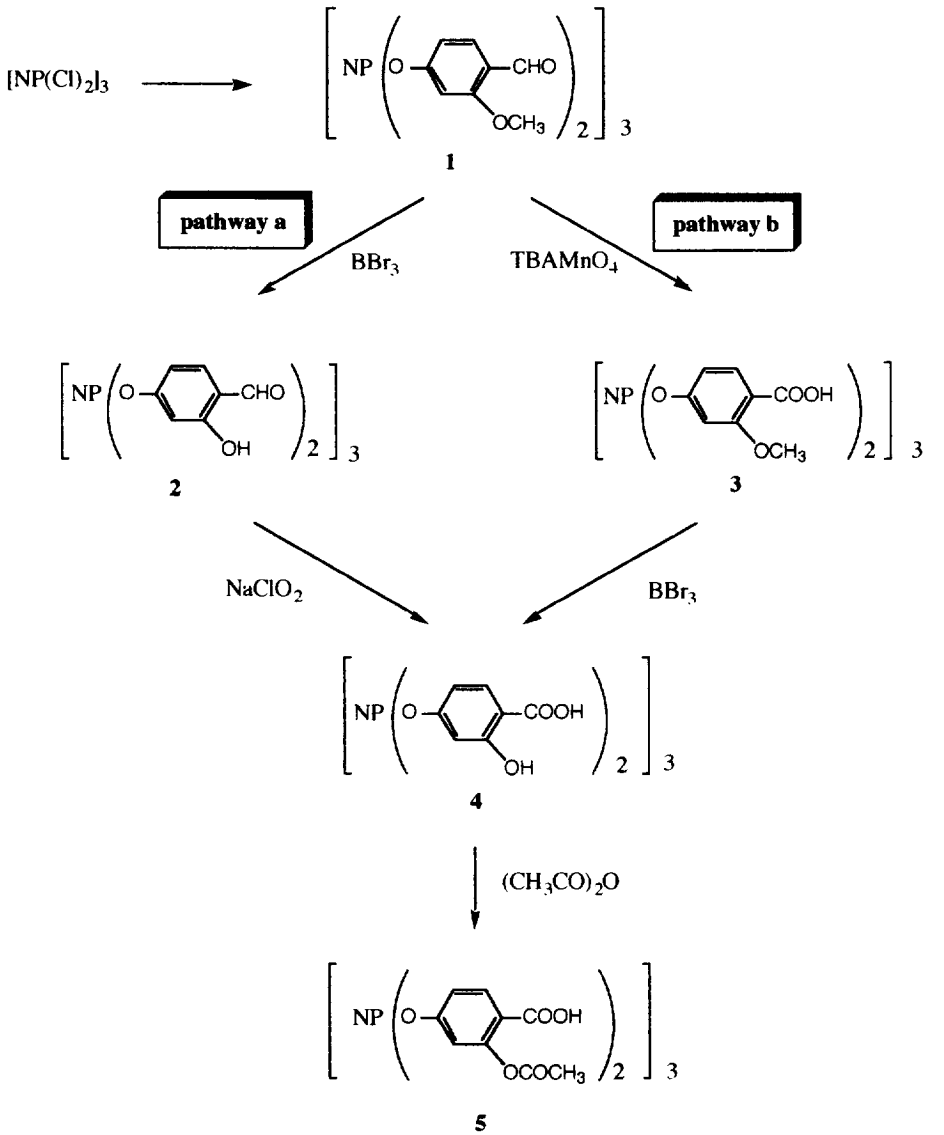
In fact, cyclophosphazene derivatives, substituted with aziridine groups, were extensively investigated over the last fifteen years as biomedical products due to their strong antitumor activity.[4] On the other hand phosphazene polymers bearing fluoroalkoxy or aryloxy groups stimulated considerable interest in the past as biologically-inert, water-insoluble, polymers for blood vessel or heart valve construction;[5] POPs containing quaternized aryloxy substituents ionically bonded to heparin were found to be anticoagulant materials;[6] phosphazene macromolecules having aminoacid ester groups[7-10] or imidazole[9,11] attached to the phosphorus proved to rapidly degrade under hydrolytic conditions to produce phosphates and ammonium salts from the inorganic phosphazene skeleton,[2] and offered interesting applicative perspectives as drug delivery systems.[12]

In the light of these considerations it appears that the biological importance of phosphazene materials is related both to the particular nature of the -P=N- system and to the characteristics of the substituent groups attached to the phosphorus of these substrate.[13]

Many different pharmaceutical products have been attached both to the linear and to the cyclic phosphazene materials, e.g. steroid hormones,[14] dopamine,[15] enzymes,[16] platinum antitumor drugs,[17] anaesthetics,[18] and antibacterial agents.[19]

During our recent work on the chemical modification of phosphazene substrates through functionalization reactions,[20-23] we considered the possibility of attaching on the cyclophosphazene nucleus a novel substituent with biological importance, the acetyl salicylic acid (aspirin), due to the well known therapeutic activity of this product and its world-wide use in medicine.

In this paper we report the synthesis and the characterization of the aspirin containing cyclophosphazene (Scheme).



Scheme

The preparation of hexakis [(4-carboxyl-3-O-acetyl)phenoxy]cyclophosphazene **5** is achieved by the substitution reaction of hexachlorocyclophosphazene with the anion of 4-hydroxy-2-methoxy-benzaldehyde, generated *in situ* by NaH following the general procedure to obtain aryloxy derivatives.[20] The hexakis[(4-formyl-3-methoxy)phenoxy]cyclophosphazene **1** is obtained in good yield (67%), is fully characterized, and the complete substitution of the chlorine atoms is confirmed by elemental analysis and ^{31}P NMR spectroscopy (sharp singlet at δ +6.86 ppm).

As shown in the scheme, the hexakis[(4-carboxyl-3-hydroxy)phenoxy]-cyclophosphazene **4** can be prepared from cyclophosphazene **1** following two pathways: a) deblocking of the methoxy group followed by oxidation of the hydroxyaldehyde **2** (overall yield 89%); b) oxidation of the aldehyde group followed by deblocking of the methoxy carboxylic acid **3** (overall yield 79%).

The 4-formyl-3-hydroxy derivative **2** (pathway a) is produced in almost quantitative yield (98%) by treatment of the cyclophosphazene **1** with BBr_3 in slight excess with respect to the six methoxy groups.[20] The preparation of the same compound by direct reaction of hexachlorocyclophosphazene with 2,4-dihydroxybenzaldehyde under different experimental conditions (e.g. the use of stoichiometric amounts of NaH to react only one hydroxylic group, or the exploitation of pyridine, triethylamine or potassium carbonate as HCl scavengers) failed and led to the formation of insoluble cross-linked materials, probably due to polycondensation reactions of the aldehydic function of the 2,4-dihydroxybenzaldeyde. The subsequent oxidation of the trimer **2** is carried out with $NaClO_2$ and resorcinol in dioxane[24] and the hydroxy acid **4** (91%) is obtained.

Following the pathway b, on the contrary, we first carried out the oxidation of the free formyl function of the cyclophosphazene **1** with tetrabutylammonium permanganate[25] to form 4-carboxyl-3-methoxy derivative **3** in good yield (80%) and subsequently the methoxylic groups are deblocked with BBr_3 to give the hydroxyacid **4** in an excellent yield (99%).

The final step of this synthesis was the acetylation of the free hydroxylic group of **4** with acetic anhydride and dimethylaminopyridine to produce the hexakis [(4-carboxyl-3-O-acetyl)phenoxy]cyclophosphazene **5** (97%), which contains six pendant acetyl salicylic groups.

The extension of the above reported synthetic procedure from the low-molecular weight cyclophosphazene level to phosphazene polymers, together with the investigation of the biological activity of the cyclophosphazene **5** are presently underway and will be reported elsewhere.

EXPERIMENTAL SECTION

General. Hexachlorocyclophosphazene $[(NPCl_2)]_3$ was purchased from Shin Nisso Kako (Japan) and purified by vacuum sublimation until a constant melting point (113°C) was obtained. ^{31}P NMR spectra (in $CDCl_3$) were obtained with a Varian FT 80 NMR spectrometer and ^1H, and ^{13}C NMR spectra (in $CDCl_3$) with a Varian Gemini 300 spectrometer. Infrared spectra were recorded with a Perkin Elmer Model 297 spectrophotometer. All reported syntheses were carried out under a flow of dry nitrogen and with anhydrous solvents. 4-Hydroxy-2-methoxybenzaldehyde was a Lancaster product used as received.

Hexakis[(4-formyl-3-methoxy)phenoxy]cyclophosphazene (1). To a stirred and heated (50°C) suspension of hexachlorocyclophosphazene (5 g, 14.3 mmol), tetrabutylammonium bromide (1 g, 3 mmol)

and NaH, 60% dispersion in mineral oil, (6.89 g, 0.17 mol) in THF (100 mL), a solution of 4-hydroxy-2-methoxybenzaldehyde (21.8 g, 0.14 mol) in the same solvent (100 mL) was added dropwise. When hydrogen was no longer generated, the reaction mixture was refluxed for 24 h. After cooling and centrifusion, the solvent was removed under reduced pressure. The brown-red residue was treated with cold ethanol (100 mL) and frozen for 12 h. A white solid was filtered, washed with water, methanol and diethyl ether and then dried to obtain, without further purification, the pure trimer **1** (10 g, 67%): mp 185-187°C; IR (nujol) 1665, 1600 cm^{-1}; ^1H NMR δ 3.73 (s, 3 H), 6.60 (d, 1 H, J = 2 Hz), 6.79 (dd, 1 H, J = 2 and 8.5 Hz), 7.72 (d, 1 H, J = 8.5 Hz), 10.32 (s, 1 H); ^{13}C NMR δ 55.76, 104.35, 112.53, 122.47, 129.84, 155.75, 162.84, 187.98; ^{31}P δ +6.86 (s).

Anal.Calcd for $C_{48}H_{42}N_3O_{18}P_3$: C, 55.33; H, 4.03; N, 4.03. Found: C, 55.54; H, 4.36; N, 4.13.

Hexakis[(4-formyl-3-hydroxy)phenoxy]cyclophosphazene (2). To a stirred solution of cyclophosphazene **1** (1 g, 0.96 mmol) in CH_2Cl_2 (100 mL) a solution of BBr_3 (1.8 g, 7.18 mmol) in the same solvent (20 mL) was added dropwise (30 min). After stirring overnight, the reaction mixture was evaporated under vacuum. The residue was carefully (exothermic reaction) treated with a mixture of ethanol (100 mL) and water (5 mL). The solution was refluxed for 3 h and then the solvent was removed *in vacuo*. The residue was further treated with water (70 mL) and extracted with ethyl acetate (3 X 50 mL). The organic layer was basified with triethylamine and extracted with water (3 X 50 mL). The aqueous layer, acidified with HCl 20%, was extracted with $CHCl_3$ (3 X 50 mL). All organic extracts were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give 0.9 g (98%) of the pure hydroxy derivative **2**: mp 142-144°C; IR (nujol) 3100, 1660, 1635, 1590, 1500 cm^{-1}; ^1H NMR δ 6.60 (d, 1 H, J = 2.2 Hz), 6.70 (dd, 1 H, J = 2.2 and 8.5 Hz), 7.40 (d, 1 H, J = 8.5 Hz) 9.78 (s, 1 H), 11.18 (s, 1 H); ^{13}C NMR δ 109.63, 113.09, 118.76, 135.56, 156.68, 163.61, 195.90; ^{31}P δ +6.59 (s).

Anal.Calcd for $C_{42}H_{30}N_3O_{18}P_3$: C, 52.68; H, 3.16; N, 4.39. Found: C, 51.47; H, 3.55; N, 4.30.

Hexakis[(4-carboxyl-3-methoxy)phenoxy]cyclophosphazene (3). To a stirred solution of cyclophosphazene **1** (0.5 g, 0.48 mmol) in pyridine (30 mL), tetrabutylammonium permanganate (0.6 g, 1.66 mmol) was added iover about 5 h. The reaction mixture was stirred for a further hour and then was cooled in an ice bath and quenched with HCl 5% and $Na_2S_2O_5$ in order to remove MnO_2. The methoxyacid **3**was filtered off (0.5 g, 80%): mp 220-222°C; IR (nujol) 3500, 1700, 1600 cm^{-1}; ^1H NMR (CD_3OD) δ 3.80 (s, 3 H), 6.75 (dd, 1 H, J = 2.0 and 8.7 Hz), 6.80 (d, 1 H, J = 2.0 Hz), 7.82 (d, 1 H, J = 8.7 Hz); ^{31}P (CD_3OD) δ + 7.39 (s).

Anal.Calcd for $C_{48}H_{42}N_3O_{24}P_3$: C, 50.66; H, 3.72; N, 3.69. Found: C, 50.28; H, 3.52; N, 3.57.

Hexakis[(4-carboxyl-3-hydroxy)phenoxy]cyclophosphazene (4) from formyl derivative 2. To a stirred solution of cyclophosphazene **2** (0.3 g, 0.31 mmol), resorcinol (0.34 g, 3.1 mmol) and acetate buffer at pH 3.9 (7 mL) in 1,4-dioxane (30 mL), $NaClO_2$ (0.32 g, 3.53 mmol), dissolved in the lowest amount of water, was added. After 1 h the reaction mixture was acidified to pH 1 with sulphuric acid 10% and dioxane was evaporated *in vacuo*. The residue was treated with ethyl acetate (50 mL) and the acid **4** was extracted with saturated $NaHCO_3$ (3 X 50 mL). The aqueous extracts were acidified to pH 1 with sulphuric acid 10%. Filtration gave the pure hydroxyacid **4** (0.3 g, 91%): mp > 250°C; IR (nujol) 3200,

1650, 1600 cm^{-1}; ^1H NMR (CD_3OD) δ 6.58 (d, 1 H, J = 2.2 Hz), 6.62 (dd, 1 H, J = 2.2 and 8.8 Hz), 7.80 (d, 1 H, J = 8.8 Hz); ^{13}C NMR (CD_3OD) δ 110.35, 112.09, 113.25, 133.56, 157.14, 165.05, 173.46; ^{31}P (CD_3OD) δ + 7.20 (s).
Anal.Calcd for $C_{42}H_{30}N_3O_{24}P_3$: C, 47.88; H, 3.87; N, 3.99. Found: C, 47.83; H, 3.48; N, 3.48.

Hexakis[(4-carboxyl-3-hydroxy)phenoxy]cyclophosphazene (4) from methoxy derivative 3. To a vigorously stirred suspension of the acid **3** (0.25 g, 0.19 mmol) in CH_2Cl_2 (10 mL), a solution of BBr_3 (0.67 g, 2.67 mmol) in the same solvent (5 mL) was added dropwise and the reaction mixture was stirred overnight. The solvent was removed under vacuum. The residue was carefully (exothermic reaction) treated with a mixture of ethanol (30 mL) and water (3 mL) and then refluxed for about 3 h. The reaction mixture was evaporated under vacuum and, after adding ethyl acetate (50 mL) and water (50 mL), was basified with triethylamine. After acidification of the aqueous layer with HCl 5%, the hydroxyacid **4** was filtered off (0.2 g, 99%). Characterization data as before.

Hexakis[(4-carboxyl-3-O-acetyl)phenoxy]cyclophosphazene (5). To a stirred solution of the hydroxyacid **4** (0.5 g, 0.47 mmol) and catalytic amount of dimethylaminopyridine in pyridine (10 mL) acetic anhydride (0.6 g, 5.87 mmol) was added dropwise. After 3 h stirring, HCl 5% was added until the acetyl derivative **5** precipitated.The reaction mixture was extracted with ethyl acetate (3 X 50 mL). The organic layer was extracted with saturated $NaHCO_3$. The aqueous extracts were acidified with HCl 5% and the pure *O*-acetyl acid **5** was filterd off (0.6 g, 97%): mp 162-165°C; IR (nujol) 3200, 1725, 1690, 1600 cm^{-1}; ^1H NMR (CD_3OD) δ 2.16 (s, 3 H), 6.80-7.10 (m, 2 H), 8.00 (m, 1H); ^{13}C NMR (CD_3OD) δ 20.84, 117.99, 119.75, 123.15, 134.96, 153.87, 155.32, 167.28, 171.70; . ^{31}P (CD_3OD) δ + 7.26 (s).
Anal.Calcd for $C_{54}H_{42}N_3O_{30}P_3$: C, 49.66; H, 3.22; N, 3.22. Found: C, 49.53; H, 3.20; N, 3.03.

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