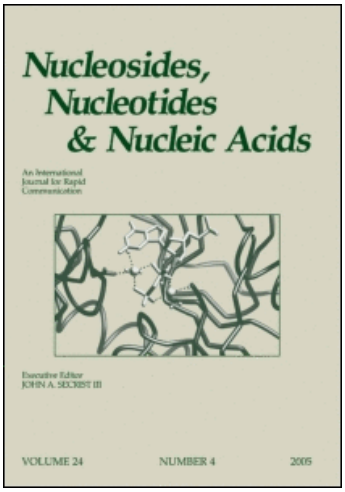

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A Simple Multi-Gram Synthesis of 5'-Hydrogenphosphonates and 5'-Phosphorofluoridates of Sugar Modified Nucleosides

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A SIMPLE MULTI-GRAM SYNTHESIS OF 5'-HYDROGENPHOSPHONATES AND 5'-PHOSPHOROFLUORIDATES OF SUGAR MODIFIED NUCLEOSIDES[1]

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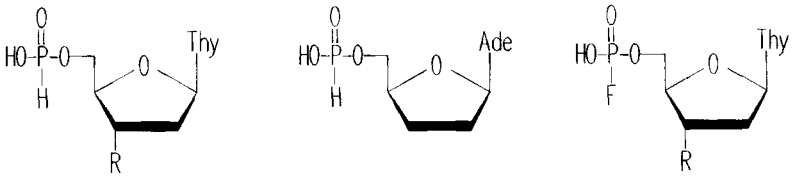
ABSTRACT: Treatment of 3'-fluoro-3'-deoxythymidine (FLT), 3'-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxyadenosine (ddA) with tris(1,1,1,3,3,3-hexafluoro-2-propyl)phosphite or phosphorous acid and N,N'-dicyclohexylcarbodiimide produced the corresponding nucleoside 5'-hydrogenphosphonates. Reaction of FLT, AZT and 3'-deoxythymidine (ddT) with fluorophosphoric acid and 2,4,6-triisopropylbenzenesulfonyl chloride lead to the corresponding nucleoside 5'-phosphorofluoridates also on a multi-gram scale. All the compounds were isolated in high pure state by chromatographic technique.

Nucleoside hydrogenphosphonates (H-phosphonates), which are the tautomeric forms of nucleoside 5'-phosphites (Figure 1), have been prepared by treatment of nucleosides with phosphorous acid in the presence of carbodiimides[2,3] or arylsulfonylimidazoles[4]. Transesterification of triphenylphosphite with alcohols followed by an alkaline work-up yields H-phosphonates[5]. Reaction of a nucleoside with tris(1,2,4-triazolyl)phosphite, generated *in situ* from phosphorous trichloride, 1,2,4-triazole and N-methylmorpholine, followed by hydrolysis yielded nucleoside H-phosphonates[6].

Recently we reported the synthesis of a series of sugar modified pyrimidine nucleoside 5'-H-phosphonates that were investigated for their anti-HIV-1 activity *in vitro*,[7] in the hope that such H-phosphonates may penetrate HIV-1 infected cell membrane, and eventually be converted into their corresponding nucleoside triphosphates (the active inhibitors of HIV reverse transcriptase) in metabolic transformations. These H-



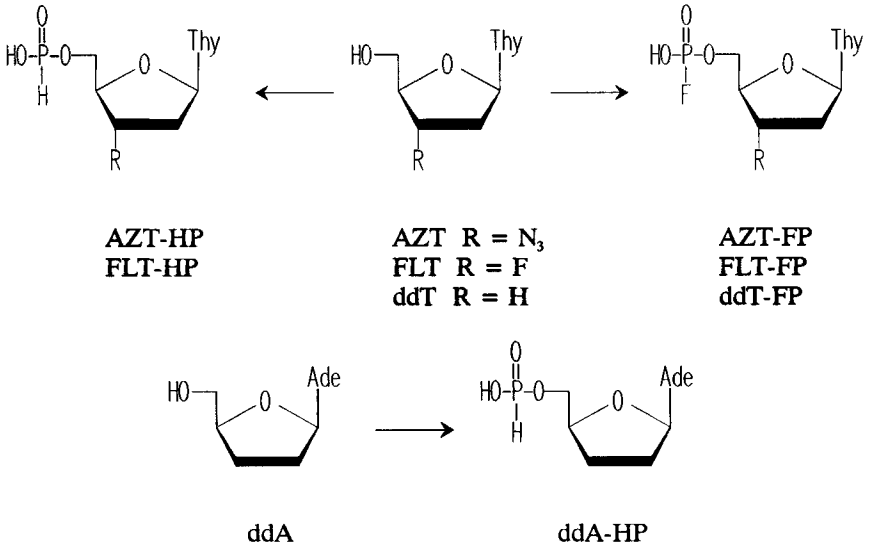
AZT-HP, R = N_3 ddA-HP FLT-HP, R = F
AZT-FP, R = N_3
ddT-FP, R = H

Figure 1

phosphonates were synthesized on a 0.2-0.3 mmol scale by the modified method of Chen and Benkovic[3] in yields ranging from 36 to 84%. Purification of the phosphonates was performed on preparative TLC plates using *i*-PrOH/NH_4OH/H_2O (7:1:2) for development, followed by purification by reverse phase (RP) HPLC on a C18 column. Two compounds, the 5'-H-phosphonates of 3'-azido-3'-deoxythymidine (AZT-HP) and of 3'-fluoro-3'-deoxythymidine (FLT-HP), exhibited potent anti-HIV-1 activity with selectivity indexes similar to or better than those of their parent nucleosides. We, therefore, extended the H-phosphonate approach to purine nucleoside area. We, thus, synthesized H-phosphonates of the anti-HIV-1 purine nucleosides, 2',3'-dideoxyadenosine (ddA) and 2',3'-dideoxyinosine (ddI). It was found that ddA-HP exhibited significantly potent anti-HIV-1 activity *in vitro* (MT4 cells) (IC_{50} = 0.24 mM, CD_{50} >1000 mM, selectivity index (SI) >4160; IC_{50} for ddA = 5.04 mM, CD_{50} = 1490, SI = 330), but ddI-HP was found to be inactive[7,8].

These findings prompted us to search for a method for simpler synthesis of nucleoside 5'-H-phosphonates amenable to multi-gram scale for more comprehensive biological evaluation (including *in vivo* toxicology) of these nucleoside H-phosphonates. We reported[7] the preparation of FLT-HP in high yields using a new phosphonylating agent, tris(1,1,1,3,3,3-hexafluoro-2-propyl)phosphite[9]. Purification was carried out on a DEAE Sephadex A-25 (HCO_3^- form) column with linear gradient (0-->0.3 M) of triethylammonium hydrogen carbonate (TEAB) buffer (pH 7.5). It was found that the product purified in this way was always contaminated with a small amount of phosphorous acid which was detected by ^{31}P NMR spectrometry. The final purification, therefore, had to be carried out by RP HPLC on a C18 column.

We report herein a simple procedure for multi-gram synthesis of pure FLT-HP and ddA-HP that should also be applicable to other deoxynucleoside 5'-H-phosphonates (Scheme



Scheme 1

1). After treatment of FLT with (1,1,1,3,3,3-hexafluoro-2-propyl)phosphite, the crude reaction mixture was subjected to flash chromatography on a silica gel column, followed by conversion into sodium salt, yielded the product that was 99.0% pure by HPLC. In a similar manner the sodium salt of ddA-HP was synthesized.

The above described preparation and purification represent a convenient means to prepare large quantities of nucleoside 5'-H-phosphonates for *in vivo* studies.

5'-Phosphorofluoridates of 3'-azido-3'-deoxythymidine, 3'-fluoro-3'-deoxythymidine and 3'-deoxythymidine (AZT-FP, FLT-FP, and ddT-FP) belong to another chemical group. Several methods have been available for the preparation of nucleoside phosphorofluoridate.

The first synthesis is involved in fluorination of nucleotides with 2,4-dinitrofluorobenzene.[10-12] The second method utilizes condensation of nucleosides with phosphorofluoridate in the presence of N,N'-dicyclohexylcarbodiimide.[13] The third procedure includes interaction of nucleoside 5'-phosphoroester azolides with benzoyl fluoride resulting in the corresponding 5'-phosphoroalkylfluoridates.[14] Nucleoside 3'- and 5'-phosphorofluoridates were recently synthesized by action of sulfuryl chloride fluoride upon trimethylsilyl derivatives of nucleoside 3'- and 5'-phosphites, respectively.[15,16]

In this paper, we describe a simple synthesis of nucleoside 5'-phosphorofluoridates based on direct acylation of nucleosides with an activated phosphorofluoridate, *i.e.*,

phosphorofluoridate is activated *in situ* by means of 2,4,6-triisopropylbenzenesulfonyl chloride or 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole and then subjected to condensation with the corresponding nucleosides (Scheme **1**). Gram quantities of AZT-FP, FLT-FP and ddT-FP were prepared by this procedure. Isolation of the pure nucleoside phosphorofluoridates was performed by ion exchange and RP chromatography.

Although nucleoside 5'-H-phosphonates described in this paper exhibit activity against HIV-1 *in vitro*, there is no animal model for this virus to test their *in vivo* activity. Toxicity of FLT-HP in uninfected mice, however, was determined in the following manner:[17] BD_2F_1 female mice ranging from 20 to 24 grams are given FLT-HP daily for 5 days (QDx1) through inter-peritoneal injection at 200 mg/kg, 1 gm/kg, and 2 gm/kg. There is no sign of intoxification and the body weight is not decreased during the test period. FLT-HP is dissolved in phosphate buffered saline. Vehicle injected mice served as the control. In a similar experiment it was showed that CD_{50} for AZT-HP was 12.8 g/kg.[18]

Phosphorofluoridates AZT-FP, FLT-FP, and ddT-FP were found to be highly active with respect to HIV-1 and these data will be published elsewhere.

EXPERIMENTAL

General. 3'-Deoxy-3'-fluorothymidine (FLT),[19,20] 2',3'-dideoxyadenosine (ddA),[21] 3'-azido-3'-deoxythymidine (AZT)[22] and 3'-deoxythymidine (ddT)[23] were prepared by the literature procedures. Dry pyridine and DMF were purchased from Aldrich. Tris(1,1,1,3,3,3-hexafluoro-2-propyl)phosphite was prepared by the published procedure.[9] Silica gel TLC was performed on Analtech Uniplates using *i*-PrOH/conc. NH_4OH/H_2O (7:2:1) for development, and short-wavelength UV for visualization. Column chromatography was carried out on flash grade silica gel (Merck 9385-9, 40-63 μm). Elemental analyses were performed by M.H.W.Laboratories, Phoenix, AZ. ^1H and ^{31}P NMR spectra were recorded on a JEOL FX90Q spectrometer in D_2O with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard for ^1H NMR and 85% H_3PO_4 as external standard for ^{31}P NMR.

Preparation of FLT-HP (Na^+ salt). FLT (5 g, 20.47 mmol) was dissolved in dry pyridine (200 mL) and Et_3N (0.29 mL). The solution was cooled to O° C, and tris(1,1,1,3,3,3-hexafluoro-2-propyl)phosphite (10.25 mL, 34 mmol) was added dropwise under N_2. The mixture was warmed to room temperature, and kept standing overnight. It was then cooled to 0^0 C, and quenched with 2M TEAB (60 mL). The mixture was stirred for 1 h, and evaporated to a syrup which was coevaporated with toluene (2 x 50 mL). The residue was

dissolved in EtOAc (20 mL), and chromatographed on a silica gel column (5 x40 cm) using EtOAc/Me_2CO/EtOH/H_2O (4:1:1:1) as the eluent (2 L). Traces of unreacted FLT were eluted first, followed by FLT-HP (Et_3NH^+ salt). Fractions containing the phosphonate were combined and concentrated to 20 mL, and then applied on a column of Dowex 50 x 8 (Na^+ form, 3.5 x20 cm). Elution with H_2O, evaporation, and several coevaporations of the residue with EtOH yielded FLT-HP (Na^+ salt) as a white powder (6.6 g, 93%), Rf 0.63. *Anal.* Calcd for $C_{10}H_{13}FN_2NaO_6P.H_2O$ (348.20): C, 34.49; H, 4.34; N, 8.05; P, 8.89. Found: C, 34.86; H, 4.32; N, 7.98; P, 9.06.

Preparation of AZT-HP (Na^+ salt). A solution of phosphorous acid (4.26 g, 52 mmol) and tri-n-butylamine (12.4 mL, 52 mmol) in dry pyridine (70 mL) was evaporated to dryness and coevaporated with pyridine (50 mL). The residue was dissolved in dry pyridine (80 mL) and AZT (10.6 g, 40 mmol) and N,N'-dicyclohexylcarbodiimide (13 g, 60 mmol) were added. The mixture was stirred for 12 h at 4°C (TLC control) and then acetic acid (2 mL) was added. The mixture was stirred for 15 min at room temperature and filtered. The filtrate was evaporated, quenched with water (500 mL) and applied on a Dowex 1x4 (HCO_3^- form) column. Elution with linear gradient (0-->0.6 M) of ammonium bicarbonate buffer (pH 7.5) (total volume 4 L) , evaporation and coevaporation with water (3 x 200 mL) yielded the crude product. The residual syrup was dissolved in water (500 mL) and applied on a Dowex 50x4 (H^+ form) column. The phosphonate was eluted with 80% ethanol (total volume 600 mL) and collected in a vessel with a stoichiometric amount of powdered $NaHCO_3$ (5 g, 60 mmol). The resulting solution was evaporated to dryness, coevaporated with ethanol (300 mL) and dried. The yield of AZT-HP as a white powder was 11 g (78%), R_f 0.65. ^{1}H-NMR (D_2O, δ, ppm): 7.52d (0.5 Hz, 1H, H6), 6.64d ($J_{H,P}$ = 629 Hz , 1H, H-P), 6.52t ($J_{1',2'}$ = 6.0 Hz, 1H, H1'), 4.42-3.90m (4H, H3', H4', H5',5"), 2.45m (2H, H2'), 1.92d ($J_{Me,6}$ = 0.5 Hz, 1H, CH_3). *Anal.* Calcd for $C_{10}H_{13}N_5NaO_6P$ H_2O (353.21) C, 34.00; H, 3.71; N, 19.83; P, 8.77. Found: C, 34.32; H, 3.60; N, 19.66; P, 8.77.

Preparation of AZT-FP and FLT-FP, NH_4^+ salts. AZT or FLT (10 mmol, 2.67g or 2.44 g, respectively) was dissolved in dry pyridine (100 mL) and the solution of bis(tri-n-butylammonium)fluorophosphate (15 mmol, from 2.14 g 70% fluorophosphoric acid) in DMF (30 mL) and then 2,4,6-triisopropylbenzenesulfonyl chloride (7.57 g, 25 mmol) were added. The reaction mixture was stirred at room temperature for 20 and 50 min respectively (TLC control) and diluted with water (750 mL). After 2 h stirring the residue was separated and supernatant was put on a Toyopearl DEAE (HCO_3^- form) column (5 x40 cm). The main

compound was eluted with linear gradient of ammonium bicarbonate buffer (0-->0.2 M, pH 7.5), total volume 4 L. Fractions containing the product were combined and evaporated to dryness. The residue was dissolved in water (20 mL) and applied onto a LiChroprep RP-18 column (2.5 x 35 cm). Elution with water and freeze-drying yielded 2.16 g of AZT-FP (62%) and 1.67 g of FLT-FP (49%). **AZT-FP**: Rf 0.60. ^{1}H NMR (D_2O, δ, ppm): 7.75d (1.0 Hz, 1H, H6), 6.50t ($J_{1',2'a} = J_{1',2'b} = 6.0$ Hz, 1H, H1'), 5.53m (1H, H3'), 4.80m (1H, H4'), 4.20-4.15m (2H, H5',5"), 2.50-2.40m (2H, H2'), 1.95d ($J_{Me,6}$ = 1.0 Hz, 3H, CH_3). *Anal.* Calcd. for $C_{10}H_{16}FN_6O_6P$ (366.25): C 32.77; H 4.40; N 22.95; P 8.46. Found: C 32.61; H 4.71; N 22.31; P 8.49.

FLT-FP: Rf 0.61. ^{1}H NMR (D_2O, δ, ppm): 7.80d (1.0 Hz, 1H, H6), 6.48dd (J 5,0 Hz, $J_{1',2'b}$ 9,0 Hz, 1H, H1'), 5.48dd ($J_{2'a,3'}$ = 0 Hz, $J_{2'b,3'}$ = 5,0 Hz, $J_{3',F}$ = 52.5 Hz, 1H, H3'), 4.60m ($J_{4',F}$ 25.0 Hz, 1H, H4'), 4.18-4.12m (2H, H5',5"), 2.74 m ($J_{2'a,F}$ = 21.0 Hz, 1H, H2'a), 2.48 m ($J_{2'b,F}$ 41.0 Hz, $J_{2'a,2'b}$ = 15.0 Hz, 1H, H2'b), 1.98d ($J_{Me,6}$ = 1.0 Hz, 3H, CH_3). *Anal.* Calcd. for $C_{10}H_{16}F_2N_3O_6P$ (343.23): C 32.77; H 4.40; N 22.95; P 8,46. Found: C 32.92; H 4.12; N 22.56; P 8.72.

ddT-FP, NH_4^+ salt (0.89 g, 62%) was prepared from ddT (2.26 g, 10 mmol), bis(tri-n-butylammonium)fluorophosphate (15 mmol, from 2.14 g 70% fluorophosphoric acid) and 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole (7.4 g, 25 mmol) as condensing agent under the similar conditions. The reaction time was 50 min. Rf 0.62. ^{1}H NMR (D_2O, δ, ppm): 7.78d (0.5 Hz, 1H, H6), 5.04m (1H, H1'), 4.25m (1H, H4'), 4.08-3.92m (2H, H5',5"), 2.40-1.90m (4H, 2H2', 2H3'), 1.93d .($J_{Me,6}$ = 0.5 Hz, 1H, CH_3). *Anal.* Calcd. for $C_{10}H_{17}FN_3O_6P$ (325.23): C 36.93; H 5.27; N 12.92; P 9.52. Found: C 36.72; H 5.62; N 12.67; P 9.31.

Preparation of ddA-HP (Na^+ salt). A solution of ddA (3g, 12.75 mmol) in dry pyridine was evaporated, and residue was re-dissolved in dry pyridine (45 mL). N,N-Di-n-butylformamide dimethylacetal (3.9 mL, 16.7 mmol) was added, and the mixture was stirred for 24 h at room temperature under N_2. The mixture, after cooling to 0°C, was diluted with water (30 mL), and the solution was stirred for 20 min. The solution was evaporated to dryness, and the residual syrup, after coevaporation with pyridine, was dissolved in dry pyridine (120 mL) and Et_3N (0.18 mL, 1.30 mmol). After cooling the mixture to 0°C, tris-(1,1,1,3,3,3-hexafluoro-2-propyl)phosphonate (8.13 g, 15.3 mL) was added dropwise under N_2, cooling to 0°C, and then quenched with 1.6 M TEAB (30 mL) for 30 min. The mixture was evaporated to

dryness, and the residue, after coevaporation with toluene (2 x 15 mL), dissolved in a mixture of 1.6 M TEAB and $CHCl_3$ (100 mL, 1:1). The aqueous layer was separated and extracted by $CHCl_3$ (3 x 50 mL), the organic solutions were combined, dried (Na_2SO_4), evaporated to dryness, and residue was dissolved in conc. NH_4OH (50 ml). The solution was kept overnight at 50-55°C, and then evaporated to dryness. The residue was dissolved in mixture of water and $CHCl_3$ (200 mL, 1:1 v/v). The aqueous portion was separated and applied on a Sephadex DEAE A-25 (HCO_3^-) column (3 x 50 cm) and eluted using linear gradient (0-->0.2 M) of TEAB, pH 7.5 (total volume 4 L). The fractions containing the phosphonates were concentrated to ca. 20 mL and then purified as described above for FLT-HP. After drying *in vacuo* the Na salt of ddA-HP was obtained as a white powder (3.2 g, 78%). Rf 0.57. ^1H NMR (D_2O, δ, ppm): 8.39s (1H, H2); 8,16s (1H, H8); 6.50d ($J_{H,P}$ = 638.3 Hz, 1H, H-P); 6.34q ($J_{1',2'ab}$ = 7.0 Hz, 1H, H1'); 4.46-3.88m (1H, H4'); 3.56m (2H, H5',5"), 2.91-2.41m (2H, H3'); 2.21-2.05m (2H, H2'). *Anal.* Calcd for $C_{10}H_{13}N_5O_4NaP.H_2O$ (339.25): C 35.40; H 4.46; N 20.60; P.9.13. Found: C 35.06; H 4.62, N 20.36; P 8.87.

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