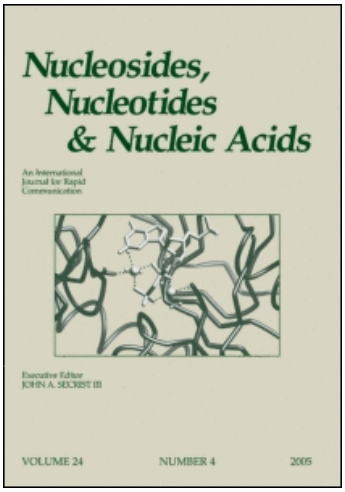


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

KINETIC STUDIES OF THE DEGRADATION OF OXYCARBONYLOXYMETHYL PRODRUG OF ADEFOVIR AND TENOFOVIR IN SOLUTION

Reza Oliyai[a]; Lung-Chi Yuan[a]; Terry Dahl[a]
[a] Gilead Sciences Inc., Foster City, California, U.S.A.

Online publication date: 31 March 2001

To cite this Article Oliyai, Reza , Yuan, Lung-Chi and Dahl, Terry(2001) 'KINETIC STUDIES OF THE DEGRADATION OF OXYCARBONYLOXYMETHYL PRODRUG OF ADEFOVIR AND TENOFOVIR IN SOLUTION', Nucleosides, Nucleotides and Nucleic Acids, 20: 4, 1295 — 1298
To link to this Article: DOI: 10.1081/NCN-100002540
URL: http://dx.doi.org/10.1081/NCN-100002540

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 1295–1298 (2001)

KINETIC STUDIES OF THE DEGRADATION OF OXYCARBONYLOXYMETHYL PRODRUG OF ADEFOVIR AND TENOFOVIR IN SOLUTION

Reza Oliyai,* Lung-Chi Yuan, and Terry Dahl

Gilead Sciences Inc., 335 Lakeside Drive, Foster City, California 94404

ABSTRACT

The decomposition kinetics of bis-POC PMEA and bis-POC PMPA followed pseudo-first order kinetics with the corresponding mono-POC ester detected as the only observable degradation product for all the pH values studied. The rates of hydrolysis of bis-POC PMEA over the pH range studied was described by

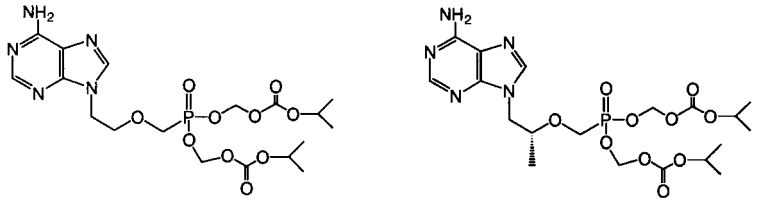
$$k_o = k_H f_{AH}[H^+] + k_{H2O} f_{AH} + k'_{H2O} f_A + k_{OH} f_A [OH^-].$$

The ^{18}O incorporation studies revealed that hydrolysis of bis-POC PMEA at pH 7.0 primarily proceeds via P-O cleavage with an additional minor pathway involving C–O bond cleavage. Hydrolysis of bis-POC PMPA was found to be about 2 fold slower than bis-POC PMEA at pH values above 6.0.

INTRODUCTION

Phosphonate analogs of nucleotides have received considerable attention as potential antiviral agents. The ionic character of these agents limits their permeability across the human intestinal mucosa, resulting in low bioavailability after oral administration [1–2]. We have previously demonstrated the utility of the bis-isopropyloxycarbonylmethyl (bis-POC) moiety in improving the oral bioavailability of phosphonate nucleotides [3–5]. The bis-POC promoiety utilizes the oxycarbonyloxymethyl spacer group. In the present study, we have applied the bis-POC promoiety to 9-[(R)-2-(phosphonomethoxy)ethyl] adenine (Adefovir,

*Corresponding author.



Bis-POC PMEA **Bis-POC PMPA**

Figure 1. Chemical structures of bis-POC PMEA and bis-POC PMPA.

PMEA, Fig. 1) and to 9-[(R)-2-(phosphonomethoxy)propyl] adenine (Tenofovir, PMPA, Fig. 1).

MATERIALS AND METHODS

The pseudo-first order rate constant, kobs, was obtained by following the disappearance of the peak area of the prodrugs as a function of time for at least two half-lives. All prodrugs and their degradation products were analyzed by a reverse phase HPLC method using the modular system described in the instrumentation section. The site of nucleophilic attack was determined by hydrolyzing bis-POC PMEA in $H_2{}^{18}O$ and $H_2{}^{16}O$ and then performing mass spectral analysis of the hydrolytic product, mono-POC PMEA. The mass spectra samples were analyzed using the liquid secondary ion mass spectrometry technique (LSIMS, Negative FAB-MS). The incorporation of ^{18}O to the phosphorous for bis-POC PMEA was determined based on the ratio of $(M+1)/(M-1)$ of the corresponding mono-POC PMEA by negative FAB-MS, corrected for the final content of ^{18}O in water.

RESULTS AND DISCUSSIONS

Mono-POC PMEA was the only degradation product observable by HPLC. The pH-dependency of the buffer-independent rate constants, ko, for bis-POC PMEA is shown in Figure 2. Over the pH range studied, the rates of hydrolysis of bis-POC PMEA were described by the following equation, $k_o = k_H f_{AH}[H^+] + k_{H2O} f_{AH} + k'_{H2O} f_A + k_{OH} f_A\,[OH\text{-}]$. Eq (1) where, f_{AH} is the fraction of conjugate acid and fA is the fraction of free base, k_H is the microscopic second-order rate constant for the hydronium ion catalyzed hydrolysis, k_{H2O} is the first-order rate constant for water catalyzed or spontaneous hydrolysis of the conjugate acid, k'_{H2O} is the first-order rate constant for water catalyzed or spontaneous hydrolysis of the free base, and k_{OH} is the microscopic second-order rate constant for hydroxide ion catalyzed hydrolysis.

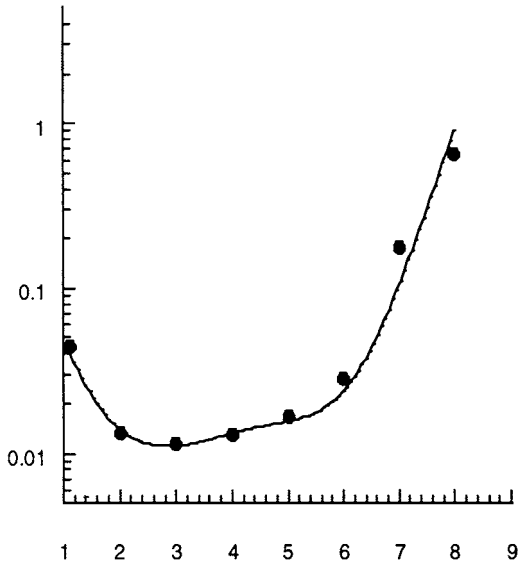
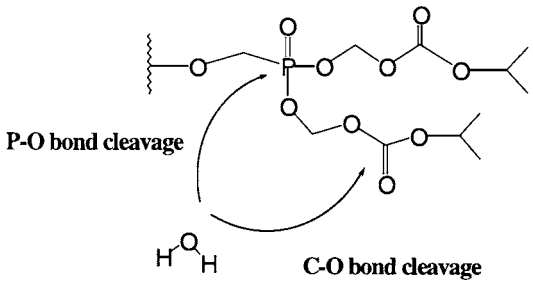


Figure 2. The pH-rate profiles for the degradation of bis-POC PMEA at 50°C.



Scheme I.

Hydrolysis of bis-POC PMEA may proceed via two distinct pathways as shown in Scheme I. The first involves the nucleophilic attack of water at the carbonyl center to form the tetrahedral intermediate (C–O bond cleavage) and the second involves the nucleophilic attack of water on the phosphorus atom (P–O bond cleavage). Both pathways lead to the formation of the mono-POC PMEA. The extent of P–O bond cleavage was estimated to be 85% ± 5% for bis-POC PMEA at pH 7.0, 37°C. These observations suggest that hydrolysis of bis-POC PMEA primarily proceeds via P–O bond cleavage with an additional minor pathway involving C–O bond cleavage.

Bis-POC PMPA demonstrated better chemical stability than bis-POC PMEA at pH values above 6.0. The rate of hydrolysis of bio-POC PMEA was about two times higher than bis-POC PMPA.

REFERENCES

1. M. Wachsman, B. G. Petty, K. C. Cundy, H. S. Jaffe, P. E. Fisher, A. Pastelak, P. S. Lietman. Antiviral Res., **1996**, 29:153–161.
2. M. J. M. Hitchcock, H. S. Jaffe, J. C. Martin, R. J. Stagg. Antiviral Chem. and Chemother., **1996**, 7:115–127.
3. M. N. Arimilli, C. U. Kim, J. Dougherty, A. Mulato, R. Oliyai, J. P. Shaw, K. C. Cundy, N. Bischofberger. Antiviral Chemistry & Chemotherapy **1997**, 8:557–564.
4. J.-P. Shaw, C. M. Sueoka, R. Oliyai, W. A. Lee, M. N. Arimilli, C. U. Kim, K. C. Cundy. Pharm. Res. **1997**, 14:1824–1829.
5. M. N. Armilli, K. C. Cundy, J. P. Dougherty, C. U. Kim, R. Oliyai, V. J. Stella. U. S. Patent 5,977,089.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Request Permission or Order Reprints Instantly!