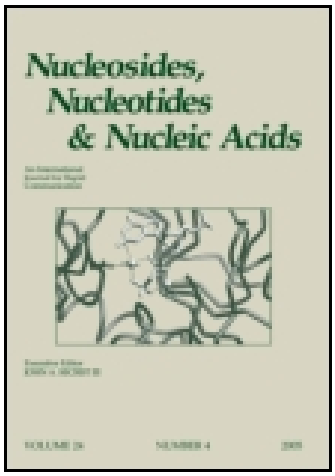

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ARYL NUCLEOSIDE H-PHOSPHONATES AS A TOOL FOR INVESTIGATION OF STEREOSPECIFICITY DURING COUPLING

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▫ *It was found that in stereoselective condensations of ribonucleoside 3′-H-phosphonates with alcohols, the major diastereomer of the produced H-phosphonate diesters is formed from the minor diastereomer of the intermediate phosphonic-pivalic anhydride.*

Keywords *H*-phosphonates, Stereospecific Coupling, ^{31}P NMR Spectroscopy

INTRODUCTION

During condensations of ribonucleoside *H*-phosphonate monoesters with nucleosides the formation of S_P diastereomers is favored, and thus the reaction is noticeably stereoselective.[1,2] This stereoselectivity was found to be dependent mainly on the nature of reacting *H*-phosphonate (e.g., kind of a nucleobase and base and sugar protecting groups), and on the solvent composition.[1,2]

To find possible sources of the observed stereoselectivity, we investigated the stereochemical aspects of the activation of *H*-phosphonate monoesters and reactivity of the produced intermediates.

RESULTS AND DISCUSSION

The reaction of nucleoside *H*-phosphonates with pivaloyl chloride yields mixed anhydrides,[3,4] which, due to chirality at the phosphorus center, exist as a mixture

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of two diastereoisomers. Since mixed anhydrides are extremely reactive species, it is not possible to isolate them or to assign their configuration at the phosphorus centre directly.

In the case of activation of 5′-*O*-dimethoxytrityl-2′-*O*-*t*-butyldimethylsilyl-uridin-3′-yl *H*-phosphonate **1** (abbreviated as $dmtU_{PH}$ throughout the text) the ratio of diastereomers of mixed anhydride **2** is usually ca. 2:1. Upon the reaction with ethanol, these afforded two diastereomeric *H*-phosphonate diesters **3** in the 4:1 ratio. The configuration of the major diastereomer of **3** (resonating in ^{31}P NMR at lower field) was assigned as S_P,[1,2] however, it was not known from which diastereomer of the mixed anhydride **2**, **A** (major) or **B** (minor), it was formed (Figure 1).

Since the ratio of the formed *H*-phosphonate diesters **3** was different from that of the mixed anhydride **2**, one diastereomer of this compound, **A** or **B**, evidently reacted faster than the other one. In addition, **A** and **B** diastereomers have to exist in a rapid equilibrium to regenerate the more reactive species. For mixed anhydride **2** this equilibrium was apparently significantly faster than the reaction with ethanol, and thus it was difficult to find out from which diastereomer of **2**, the major diastereomer of **3** was formed and, in consequence, to assign the absolute configuration to **A** and **B**. However, our earlier work on the less-reactive aryl nucleoside *H*-phosphonates[5,6] suggested that these *H*-phosphonate derivatives could be helpful in the present studies.

To this end, phenyl (**4a**), *p*-chlorophenyl (**4b**), and *p*-nitrophenyl (**4c**) uridine *H*-phosphonates were reacted with ethanol and progress of these reactions was followed by ^{31}P NMR spectroscopy (Figure 2).

The reaction of phenyl derivative **4a** (Figure 2, panel A) was very slow and required a few days to reach completion. During this period the product **3a** partly

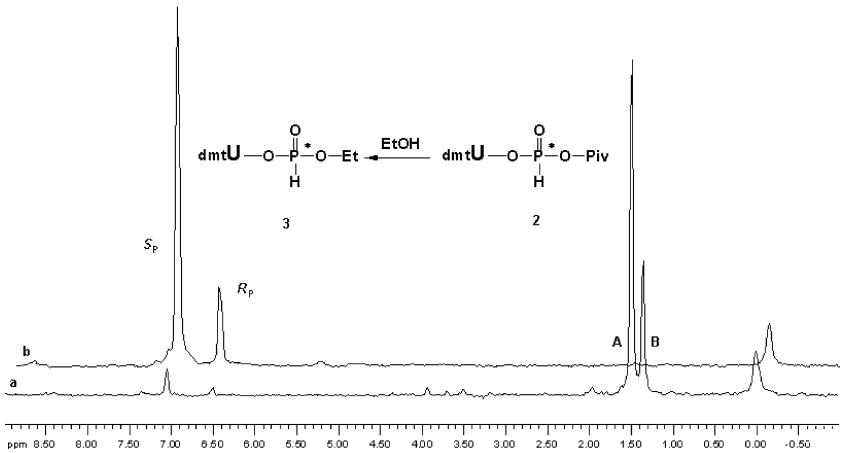

FIGURE 1 ^{31}P NMR spectra of the reaction of mixed anhydride **2** with ethanol in methylene chloride containing 3 equiv. of pyridine; (a) after addition of 0.1 equiv. of ethanol (b) after addition of another 2 equiv. of ethanol.

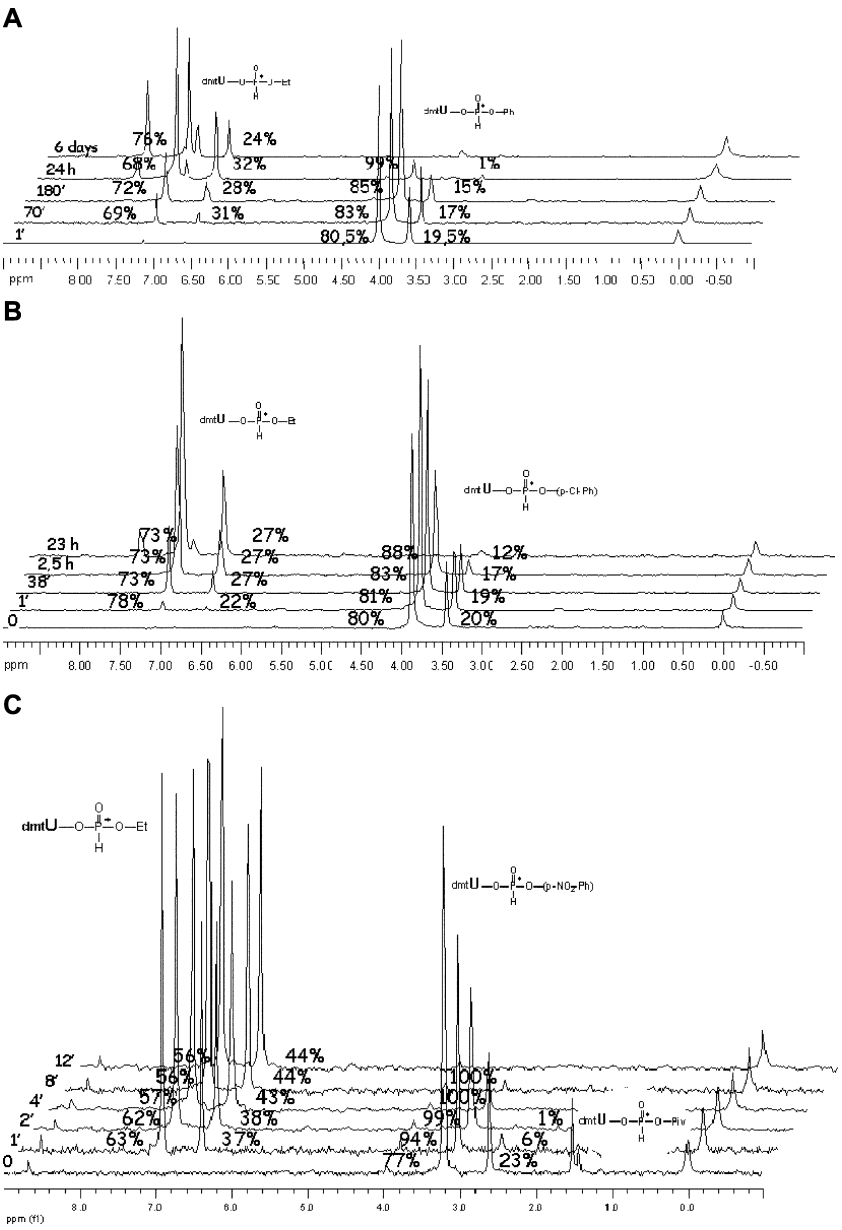

FIGURE 2 ^{31}P NMR spectra of the reactions of aryl nucleoside *H*-phosphonates **4a–4c** with ethanol; (A) reaction of **4a**, (B) reaction of **4b**, (C) reaction of **4c**.

decomposed, making integration of the signals difficult. However, investigation of this reaction at the earlier stages indicated that there was no significant changes in the ratios of diastereomers of the starting material **4a** and that of the produced *H*-phosphonate **3**. This was also true for the more reactive *p*-chlorophenyl *H*-phosphonate **4b** (Figure 2, panel B), and indicated that under the reaction

conditions the equilibria between diastereomers of aryl *H*-phosphonates **4a** and **4b** were faster than the reactions with ethanol, although the minor diastereomers of these compounds seemed to react slightly faster.

Clear-cut results were obtained, however, for the most reactive *p*-nitrophenyl *H*-phosphonate **4c**. For this compound, the minor diastereomer disappeared within a few minutes upon addition of ethanol, and the ratio of diastereomers of the product **3** underwent gradual changes during the course of the reaction from the initial value of ca. 2:1, to 1:1 at the end of the reaction (Figure 2, panel C).

On the basis of these experiments, we could conclude that in these reactions the major diastereomer of product **3** was formed from the minor diastereomer of the starting materials **4a–4c**. Thus, assuming the S_P configuration of the major diastereomer of the product **3**, one can assign S_P configuration* to the minor, more reactive diastereomer of **4** (high-field signal in the ^{31}P NMR spectra) and R_P configuration to the main diastereomers of nucleoside aryl *H*-phosphonates **4** (low-field signal in the ^{31}P NMR spectra). Considering a similar type of reactivity and a similar product distribution in condensations promoted by acyl chlorides, we believe that this assignment can be extended to the mixed phosphonic-carboxylic anhydrides. Thus, for phosphonic-pivalic mixed anhydride **2**, we tentatively assigned R_P configuration to the diastereomer **A** (resonating at lower field in the ^{31}P NMR) and S_P configuration to the isomer **B**[7] (resonating at higher field in ^{31}P NMR) (Figure 1).

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*This esterification reaction is assumed to proceed with inversion of configuration [$S_N2(P)$], however according to CIP rules, the priority of substituents simultaneously changes, so the substrate for the main product diastereomer should also have the configuration noted S_P.