THE REACTIONS OF ARYL NUCLEOSIDE H-PHOSPHONATES WITH O-, N-, AND S-NUCLEOPHILES

Jacek Cieśliak\textsuperscript{a}, Jadwiga Jankowska\textsuperscript{a}, Michał Sobkowski\textsuperscript{a}, Annika Kers\textsuperscript{b}, Inger Kers\textsuperscript{b}, Jacek Staźniński\textsuperscript{b} and Adam Kraszewski\textsuperscript{a,*}

\textsuperscript{a} Institute of Bioorganic Chemistry, Polish Academy of Sciences, 61-704 Poznań, Poland; e-mail: akad@ibch.poznan.pl
\textsuperscript{b} Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

Aryl nucleoside H-phosphonates, derivatives of controlled reactivity, have been developed as useful synthetic intermediates for the preparation of variety of nucleotide analogues containing P–O, P–N and P–S bonds.

The concept of aryl nucleoside H-phosphonates as reactive intermediates in synthesis of nucleotides, oligonucleotides and their analogues arose from our earlier studies on transesterification reactions of various H-phosphonate diesters\textsuperscript{1}. A synthetic utility of aryl H-phosphonate derivatives has been demonstrated, inter alia, in efficient preparation of various dinucleoside H-phosphonates\textsuperscript{2}, nucleoside H-phosphonamidates\textsuperscript{3}, during functionalization of support-bound oligonucleotides\textsuperscript{4}, and in the synthesis of various auxiliary reagents for nucleotide analogues synthesis\textsuperscript{5}.

Aryl nucleoside H-phosphonates can be regarded as kind of activated nucleoside H-phosphonates which, in contrast to other activated H-phosphonate species, e.g. phosphonate-pivaloyl\textsuperscript{6}, phosphonate-carbonate\textsuperscript{7} or phosphonate-phosphate\textsuperscript{8} mixed anhydrides, have only one electrophilic centre localised on the phosphorus atom. In addition, reactivity of these compounds can be modulated by varying inductive and mesomeric effects of the aryl substituent, what distinguishes this class of compounds from mixed-anhydride type of intermediates, whose reactivity is fixed and determined by the nature of the activator used. It should also be kept in mind that electronic properties of the aryloxy groups may affect the phosphonate ↔ phosphite equilibria in these compounds, and in consequence, the phosphorus center in aryl H-phosphonates can change its character from electrophilic (in the H-phosphonate form) to a nucleophilic one (in the phosphite form), with all chemical implications of this fact.

In this report we wish to present selected examples of reactions of aryl nucleoside H-phosphonates which demonstrate how different aryl substituents influence rates and pathways of the investigated reaction and show how reactivity of aryl H-phosphonates can be modulated by changing electronic properties of the aryl group.
RESULTS AND DISCUSSION

Reactions of Aryl Nucleoside H-Phosphonates with O-Nucleophiles

Aryl nucleoside H-phosphonates 3a-3g are easily accessible from nucleoside H-phosphonate 1 and respective phenol derivatives 2a-2g in a coupling reaction aided by pivaloyl chloride (Pv-Cl) or appropriate chlorophosphates (e.g. NEPCl) (Scheme 1).

Recently, we assessed reactivity of aryl H-phosphonate diesters as a function of the aryl moiety present, by reacting 3a-3g with N4,3'-O-dibenzoyl-deoxycytidine 4a. Progress of the reaction was monitored by oxidising the produced dinucleoside H-phosphonate 5a to a stable dinucleoside phosphate 6a followed by TLC analysis. The most reactive among investigated aryl H-phosphonate derivatives were found those bearing p-nitrophenyl (3f) and 2,4,6-trichlorophenyl (3g) groups, which produced 5a in less than 3 min. The relative order of reactivity in this reaction, 3a : 3b : 3c : 3d : 3e : 3f : 3g was found to be 1 : 4 : 10 : 40 : 350 : 1 100 : 1 100, which parallels that observed for transesterification of 3 with simple alcohols, and reflects an extent of modulation of reactivity available for compounds of type 3.

Reactions of Aryl Nucleoside H-Phosphonates with N-Nucleophiles

Recently, we have shown that direct coupling of nucleoside H-phosphonates with N-nucleophiles (e.g. primary and secondary amines or 5'-amino-5'-deoxynucleosides) is not completely chemoselective and produced N-acylated or N-phosphorylated amines together with the desired nucleoside phosphonamidates. Considering the fact that aryl nucleoside H-phosphonates bear only one electrophilic centre, we investi-
gated these compounds as possible substrates for the formation of nucleoside phosphonamidates.

**Aminolysis of Aryl Nucleoside H-Phosphonates Generated with the Aid of Pivaloyl Chloride**

Aryl nucleoside H-phosphonates 3d or 3g, produced in situ form nucleoside H-phosphonates 1 and appropriate phenol derivative (2d or 2g, 1.2–2.0 molar equivalents) in the presence of Pv-Cl (1.5 molar equivalents) in methylene dichloride–pyridine 9 : 1 (v/v), was treated with amines 7a–7f of rather narrow range of basicity but different steric hindrance at the nitrogen atom (Scheme 2).

All the investigated reactions were rapid (less than 3 min, $^{31}$P NMR) but differed in the distribution of products. For primary amine 7a, the main product of the reaction was the desired nucleoside phosphonamidate 8a (95%) and only small amounts of side-product 9a (<5%; phosphonate-phosphate derivative, giving rise to two groups of resonances centred at $\approx$20 ppm and $\approx$–6 ppm in the $^{31}$P NMR spectrum), was formed. With growing steric hindrance in an amine moiety used for the reaction, the amount of 9a gradually increased and for diisopropylamine, it constituted the sole product of the reaction.

The formation of phosphonate-phosphate 9a as a side-product in these reactions can be explained (Scheme 3) by generation of P-acylation species 11 from substrate 3d and pivaloyl chloride (or phosphono-pivalic mixed anhydride), followed by its reaction (base catalysis) with another molecule of 3d and a spontaneous rearrangement of the produced gem-
diphosphonate 12 to phosphonate-phosphate 9a. This transformation, which seems to be analogous to that reported for simple dialkyl H-phosphonates13, competes with aminolysis of aryl H-phosphonate 3d to produce H-phosphonamidates 8, and explains why the formation of phosphonate-phosphate side-product 9 is most pronounced with sterically hindered amines 7c, 7e and 7f.

We expected that by increasing electrophilicity of the phosphorus centre in 3 we should be able to speed-up the aminolysis and suppress (or eliminates completely) the competing P-acylation that triggered formation of phosphonate-phosphate side-product 9. Indeed, when 2,4,6-trichlorophenyl nucleoside H-phosphonate 3g (prepared in situ as described for 3d) was allowed to react with amines 7a–7e, a quantitative formation of the desired H-phosphonamidates 8a–8e was observed (<3 min, 31P NMR). The only exception was diisopropylamine which also in this reaction produced nearly quantitatively the phosphonate-phosphate 9b.

Aminolysis of Aryl Nucleoside H-Phosphonates Generated by 2-Chloro-5,5-dimethyl-2-oxo-2λ5,1,3,2-dioxaphosphinane (NEPCl)14

The use of chlorophosphates as condensing reagents for the in situ generation of aryl nucleoside H-phosphonates of type 3 should alleviate problems connected with P-acylation of 3 (vide supra) and thus increase efficiency of the aminolysis. We found that using sterically hindered chlorophosphate NEPCl as a condensing agent it was possible to generate 3d and 3g as the only nucleotidic species (31P NMR) from nucleoside H-phosphonate 1 and phenols 2d or 2g (ca 30 min).

As expected, treatment of thus-prepared aryl nucleoside H-phosphonates 3d and 3g with amines 7a–7e resulted in rapid (ca 3 min) and clean formation of the corresponding alkyl nucleoside phosphonamidates 8a–8e, which were purified by silica gel column chromatography and characterised.
by \(^1\)H and \(^31\)P NMR, HRMS and elemental analysis. Thus, due to its simplicity and effectiveness, this approach provides a convenient entry to various alkyl nucleoside H-phosphonamidates.

Also in this case, the course of reaction in the presence of the diisopropylamine \(7f\) was exceptional. As a strong base and a weak nucleophile, it promoted disproportionation of \(3g\) under formation of equimolar amounts of nucleoside diaryl phosphite \(10\) and nucleoside H-phosphonate \(1\) (ref.\(^{15}\)). It is worth noting, however, that diisopropyl H-phosphonamidate \(8f\) can be obtained in high yield in a direct coupling of H-phosphonate \(1\) and diisopropylamine \(7f\) promoted by NEPCl (ref.\(^3\)).

Reactions of Aryl Nucleoside H-Phosphonates with Hydrogen Sulfide

During our recent studies on sulfhydrolysis of aryl nucleoside H-phosphonates, we observed that treatment of nucleoside phenyl H-phosphonate \(3c\) (generated in situ from \(1\) and phenol using 1.1 equivalent of diphenyl chlorophosphate) in pyridine with hydrogen sulfide afforded, instead of the expected nucleoside H-phosphonothioate \(13\), equimolar mixture of nucleoside H-phosphonodithioate \(16\) and nucleoside H-phosphonate \(1\). H-Phosphonates \(3d\), \(3e\) and \(3f\), bearing more electron-withdrawing aryl moieties, reacted faster but with the same product distribution as that during sulfhydrolysis of \(3c\). The reaction was very sensitive to the amount of a condensing agent used for generation of aryl nucleoside H-phosphonates \(3\), and with 3 molar equivalents, instead of usually used 1.1, exclusively H-phosphonodithioate \(16\) was formed during the subsequent sulfhydrolysis.

To explain these findings we propose a plausible mechanism for sulfhydrolysis of aryl H-phosphonate \(3\) in pyridine (Scheme 4). It involves an initial formation of nucleoside H-phosphonothioate \(13\) which reacts
with aryl nucleoside H-phosphonate 3 to produce mixed H-diphosphonate 14, and this in turn, in sulphydrylalysis with H2S affords H-phosphonodithioate 16 and nucleoside H-phosphonate 1. The last step may involve, under the reaction conditions, intermediacy formation of aryl nucleoside H-phosphonothioate 15 (formed from mixed H-diphosphonate 14 and the appropriate phenol), followed by its reaction with hydrogen sulfide to produce 16. This alternative was substantiated by the finding that aryl nucleoside H-phosphonothioates of type 15 readily undergo transformation to H-phosphonodithioates 16, on treatment with H2S in pyridine (31P NMR). The exclusive formation of H-phosphonodithioate 16 in the presence of excess condensing agent during sulphydrylalysis can be explained by generation of various reactive species from the produced H-phosphonate 1 which then collapse to H-phosphonothioate 13 and ultimately, to the final product 16.

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REFERENCES AND NOTES

11. Phosphonate-phosphate derivative 9a was isolated and its structure determined by 1H, 31P NMR spectroscopy and elemental analysis.