Studies on nucleoside H-phosphonoselenoate chemistry and chalcogen exchange reaction between P(V) and P(III) compounds

Martin Kullberg

Stockholm University
2005
Abstract

In this thesis, the chemistry of compounds containing P-Se bonds has been studied. As a new addition to this class of compounds, H-phosphonoselenoate monoesters, have been introduced and two synthetic pathways for their preparation have been developed.

The reactivity of H-phosphonoselenoate monoesters towards a variety of condensing agents has been studied. From these, efficient conditions for the synthesis of H-phosphonoselenoate diesters have been developed. The produced diesters have subsequently been used in oxidative transformations, which gave access to the corresponding P(V) compounds, e.g. dinucleoside phosphoroselenoates or dinucleoside phosphoroselenothioates.

Furthermore, a new selenizing agent, triphenyl phosphoroselenoate, has been developed for selenization of P(III) compounds. This reagent has high solubility in organic solvents and was found to convert phosphite triesters and H-phosphonate diesters efficiently into the corresponding phosphoroselenoate derivatives.

The selenization of P(III) compounds with triphenyl phosphoroselenoate proceeds through a selenium transfer reaction. A computational study was performed to gain insight into a mechanism for this reaction. The results indicate that the transfer of selenium or sulfur from P(V) to P(III) compounds proceeds most likely via an X-philic attack of the P(III) nucleophile on the chalcogen of the P(V) species. For the transfer of oxygen, the reaction may also proceed via an edge attack on the P=O bond.
# Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Papers</td>
<td>III</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>IV</td>
</tr>
<tr>
<td><strong>1. Introduction</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 Oligonucleotides as therapeutics</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Oligonucleotides with a phosphoroselenoate modification</td>
<td>2</td>
</tr>
<tr>
<td>1.3 Selenophosphorus chemistry</td>
<td>3</td>
</tr>
<tr>
<td><strong>2. Nucleoside H-phosphonoselenoates</strong></td>
<td>4</td>
</tr>
<tr>
<td>2.1 Nucleoside H-phosphonoselenoate monoesters (Paper I, II &amp; III)</td>
<td>4</td>
</tr>
<tr>
<td>2.1.1 Synthesis of nucleoside H-phosphonoselenoate monoesters via the</td>
<td>5</td>
</tr>
<tr>
<td>phosphinate approach</td>
<td></td>
</tr>
<tr>
<td>2.1.2 Synthesis of nucleoside H-phosphonoselenoate monoesters using</td>
<td>7</td>
</tr>
<tr>
<td>9-fluorenemethyl H-phosphonoselenoate monoester as an H-phosphonoselenoate group transferring reagent</td>
<td>7</td>
</tr>
<tr>
<td>2.2 Nucleoside H-phosphonoselenoate diesters (Paper IV)</td>
<td>10</td>
</tr>
<tr>
<td>2.2.1 Condensation of nucleoside H-phosphonoselenoate monoesters with</td>
<td>11</td>
</tr>
<tr>
<td>hydroxylic components</td>
<td></td>
</tr>
<tr>
<td>2.2.2 Oxidative transformations of dinucleoside H-phosphonoselenoate</td>
<td>15</td>
</tr>
<tr>
<td>diesters</td>
<td></td>
</tr>
<tr>
<td>2.3 Conclusions</td>
<td>18</td>
</tr>
<tr>
<td><strong>3. Selenium transfer reactions</strong></td>
<td>19</td>
</tr>
<tr>
<td>3.1 Triphenyl phosphoroselenoate as a selenium-transferring reagent</td>
<td>19</td>
</tr>
<tr>
<td>(Paper V)</td>
<td></td>
</tr>
<tr>
<td>3.2 Investigation of mechanisms of chalcogens transfer (Paper VI)</td>
<td>22</td>
</tr>
<tr>
<td>3.2.1 Computational methods</td>
<td>23</td>
</tr>
<tr>
<td>3.2.2 Geometries of the starting structures</td>
<td>23</td>
</tr>
<tr>
<td>3.2.3 Transition state geometries of chalcogen transfer</td>
<td>26</td>
</tr>
<tr>
<td>3.2.4 Activation energies of the chalcogen transfer reactions</td>
<td>29</td>
</tr>
<tr>
<td>3.3 Conclusions</td>
<td>32</td>
</tr>
<tr>
<td>Closing remarks</td>
<td>33</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>34</td>
</tr>
<tr>
<td>References</td>
<td>35</td>
</tr>
</tbody>
</table>
List of Papers

This thesis is based on the following articles and manuscripts, which will be referred to by their Roman numerals:


IV. “Synthetic and $^{31}$P NMR studies on the preparation and oxidation of dinucleoside H-phosphonoselenoates”. Kullberg, M.; Stawinski, J. *Manuscript*

V. “Triphenyl phosphoroselenoate - a new selenizing agent for P(III) compounds”. Kullberg, M; Bollmark, M; Stawinski, J. *Collection Symposium ser.*, 2002, 5, 290-294

## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>B</td>
<td>Nucleobase</td>
</tr>
<tr>
<td>B3LYP</td>
<td>Becke exchange/Lee-Yang-Parr correlation functional</td>
</tr>
<tr>
<td>BSA</td>
<td>O, N-bis(trimethylsilyl)acetamide</td>
</tr>
<tr>
<td>BTSe</td>
<td>3H-1,2-benzothiaselenol-3-one</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DECP</td>
<td>Diethyl phosphorochloridate</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMT</td>
<td>4,4’-dimethoxytrityl</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DPCP</td>
<td>Diphenyl phosphorochloridate</td>
</tr>
<tr>
<td>EDC</td>
<td>1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>H</td>
<td>Hartree (627.5095 kcal/mol)</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
<tr>
<td>NEP-Cl</td>
<td>2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphinane</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>OXP</td>
<td>N,N-bis(2-oxazolidinyl)phosphorodiamic chloride</td>
</tr>
<tr>
<td>Pv-Cl</td>
<td>Pivaloyl chloride</td>
</tr>
<tr>
<td>RDS</td>
<td>Rate determining step</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets</td>
</tr>
<tr>
<td>TMS-Cl</td>
<td>Trimethylsilyl chloride</td>
</tr>
<tr>
<td>TPOPSe</td>
<td>Triphenyl phosphoroselenoate</td>
</tr>
<tr>
<td>TPPSe</td>
<td>Triphenylphosphine selenide</td>
</tr>
<tr>
<td>TPS-Cl</td>
<td>2,4,6-trisopropylbenzenesulfonyl chloride</td>
</tr>
<tr>
<td>TS</td>
<td>Transition state</td>
</tr>
</tbody>
</table>
1. Introduction

Phosphorus was first discovered by Henning Brand in 1669. By distilling urine he obtained a new substance, which glowed in the dark and which combusted spontaneously when exposed to air. Since then phosphorus compounds have found many applications in human activity, for instance as detergents, fertilizers, pesticides, herbicides, warfare agents and therapeutic agents, to mention just a few. Phosphorus is also an essential element of all living organisms. In animals, phosphorus is found as inorganic phosphate in blood and urine but is mainly present as calcium salts in bones and teeth. The rest of the phosphorus is found as organic phosphate mono- and diesters. These organic phosphates play many fundamental roles, e.g. as components of cell membranes in form of phospholipids, as energy carriers (ATP), but by far the most famous biomolecules containing phosphorus are nucleic acids (DNA and RNA).

![Figure 1. Examples of important biomolecules containing phosphorus](image)

1.1 Oligonucleotides as therapeutics

In 1978 Zamecnik and Stephenson demonstrated that the growth of Rous sarcoma virus in cell culture could be suppressed by addition of a synthetic 13-nucleotide long DNA fragment complementary to the viral mRNA, and thus the antisense approach to regulation of gene expression was born. For an oligonucleotide to work as an antisense drug it has to fulfill a number of basic criteria, e.g. it must be able to penetrate the cell membrane and reach its target, and once inside the cell it must be resistant to the nucleolytic enzymes present in the cytoplasm. Also it has to bind specifically to a target mRNA sequence. The latter criteria is by far the simplest one to fulfill, as a 17-base pair long sequence statistically occurs only once in the human genome.

There are many strategies on how to stabilize an oligonucleotide against degradation in the cytoplasm, and the most conservative approach (from a structural point of view) to achieve this is to exchange one of the nonbridging oxygens in the internucleotide phosphodiester linkage by a sulfur atom. In fact, it was this type of modification of oligonucleotides that reached clinical trials first, under the name Vitravene. Although oligonucleotide phosphorothioates
are polyanions, *in vitro* and *in vivo* studies showed that such oligonucleotides penetrate cell membranes much more effectively than one should have expected for a passive diffusion process. This demonstrates that even a very slight structure alteration of natural oligonucleotides is sufficient to get a functional drug.

The phosphorothioates or “first generation” antisense drugs are relatively stable in the bloodstream, but have to be given intravenously. To increase stability, potency, and to possibly make them orally active, ISIS Pharmaceuticals and others developed a “second generation” of modified phosphorothioates (Figure 2), with a backbone containing 2′-O-methoxyethyl RNA moieties or a mixture of DNA- and modified RNA-units. If oral availability of an antisense drug could be achieved, this would provide a major advantage over other bio-tech therapeutics.

Figure 2. Examples of oligonucleotide analogues in clinical trials

1.2 Oligonucleotides with a phosphoroselenoate modification

Oligonucleotides containing a phosphoroselenoate modification have received much less attention than phosphorothioates as possible therapeutic agents. This is most likely due to phosphoroselenoates cellular toxicity and the fact that they are also less hydrolytically stable. However, phosphoroselenoates can be useful as synthetic intermediates, since it may be possible to replace selenium with other functionalities.

Also, selenium is finding applications in structural studies of oligonucleotides as means of getting X-ray crystal structures of high resolution. Heavy elements are commonly introduced to macromolecules in order to enhance the resolution of the crystal structure received. There are several approaches to do this, *e.g.*, heavy atom soaking, cocrystallization and halogen derivatization. However, introducing selenium either as a modification on the sugar backbone or by replacing one of the nonbridging oxygens in the phosphodiester linkage, has advantages over the other methods.
1.3 Selenophosphorus chemistry

In 1957 it was found that selenium is an essential trace nutrient for mammals. Experiments showed that rats who were fed with a selenium deficient diet suffered from fatal liver necrosis.\textsuperscript{12} Since that time it has been demonstrated, that depleted amounts of selenium in the diet is associated with earlier mortality in HIV-positive patients,\textsuperscript{13} and that there is a higher mortality from cardiovascular diseases in selenium-deficient areas of the US.\textsuperscript{14} Also poor selenium intake leads to increased cancer incidences and cancer mortality.\textsuperscript{15}

The best understood role of selenium is its incorporation into proteins and so far approximately 22 selenoproteins have been identified.\textsuperscript{16} The selenium is believed to be incorporated into proteins via selenophosphates as an intermediate.\textsuperscript{17} In the quest for finding biologically interesting compounds, selenium has been incorporated into several important biomolecules \textit{e. g.} carbohydrates,\textsuperscript{18} lipids,\textsuperscript{19,20} nucleosides\textsuperscript{21,22} and oligonucleotides.\textsuperscript{23}

The first synthetic compound containing a P-Se bond was probably trimethylphosphine selenide and its preparation, reported in 1857,\textsuperscript{24} was achieved by oxidation of trimethylphosphine with elemental selenium. Oxidation of P(III) compounds into their P(V) derivatives using elemental selenium is still the most common way to introduce this heteroatom into phosphorus compounds.

In this thesis new synthetic pathways to selenophosphorus compounds and a new selenium-transferring reagent soluble in organic solvents, will be discussed.
2. Nucleoside H-phosphonoselenoates

H-Phosphonoselenoates are a largely unexplored class of phosphorus compounds. Until recently there were only two methods available to synthesize H-phosphonoselenoates and these were limited to H-phosphonoselenoate diesters.

The first of these methods (Scheme 1) consists of treating dialkyl phosphorochloridites with hydrogen selenide. This method can, in principle, give access to a variety of H-phosphonoselenoate diesters but it suffers from some fundamental drawbacks. Although, it is relatively simple to make the intermediate dialkyl phosphorochloridites, these species are extremely reactive so low temperature and anhydrous conditions are necessary. Another inconvenience of this approach is the use of hydrogen selenide. Hydrogen selenide is a gas at room temperature and it is several times more toxic than hydrogen sulfide. Also it smells much worse than hydrogen sulfide and is a powerful reducing agent.

The other method reported for the preparation of H-phosphonoselenoate diesters involves reduction of 2-chloro-4-methyl-1,3,2-dioxaphosphinane with tri-n-butyltin hydride to produce the corresponding phosphonite, which is then oxidized with elemental selenium to produce a H-phosphonoselenoate diester (Scheme 1).

![Scheme 1. Reported procedures for the synthesis of H-phosphonoselenoate diesters](image)

These methods do not appear to be generally applicable to natural product synthesis, therefore we set out to develop new synthetic protocols which would be both general and convenient to use.

In this chapter a new and efficient approach to produce H-phosphonoselenoate mono- and diesters and some basic reactivity of these compounds, will be presented.

2.1 Nucleoside H-phosphonoselenoate monoesters (Paper I, II & III)

Oligonucleotide synthesis using H-phosphonate chemistry utilizes H-phosphonate or H-phosphonothioate monoesters as starting materials for
the formation of oligonucleotides and their analogues. In order to expand the H-phosphonate methodology to include H-phosphonoselenoate derivatives it was crucial to have easy access to nucleoside H-phosphonoselenoate monoesters. In this section two simple and effective procedures for the synthesis of H-phosphonoselenoate monoesters are presented.

### 2.1.1 Synthesis of nucleoside H-phosphonoselenoate monoesters via the phosphinate approach

Previously in this laboratory, synthesis of nucleoside H-phosphonate\(^{27,28}\) and H-phosphonothioate monoesters\(^{29-35}\) have been developed and their chemistry extensively studied. Thus, it was a logical step to continue the homologous series by investigating H-phosphonoselenoate monoesters.

An effective and simple approach to synthesize H-phosphonothioate monoesters is via the sulfurization of phosphinate ester intermediates with elemental sulfur.\(^{35}\) It seemed likely, that this reaction could be adapted to provide a convenient access to H-phosphonoselenoate monoesters (Scheme 2).

![Scheme 2. Synthesis of H-phosphonoselenoates via the phosphinate approach](image)

Preliminary experiments indicated that treating 2 equiv. of simple alcohols and triethylammonium phosphinate (1 equiv.) with pivaloyl chloride (1.5 equiv.) in pyridine, generated the phosphinate intermediate 1 quantitatively as assessed by \(^{31}\)P-NMR spectroscopy. Selenization of the produced phosphinate with elemental selenium (3 equiv.) was clean but much slower than the analogous reaction with sulfur (typically 3 h, compared to 15 minutes for the reaction with sulfur). When a nucleoside was used as a hydroxylic component, formation of the corresponding nucleoside phosphinate 1 (\(\delta_p = 14.22\) ppm, \(^1J_{PH} = 572\) Hz, \(^3J_{PH} = 9.8\) Hz, td) was uneventful and proceeded virtually quantitatively as revealed by \(^{31}\)P-NMR spectroscopy (Scheme 2). However, in contrast to simple alkyl phosphinates, the intermediate 1 bearing a nucleoside moiety proved to be much more difficult to convert into the corresponding H-phosphonoselenoate monoester 2. In pyridine, the selenization with elemental selenium proceeded very slowly (3-4 h) and the amount of H-phosphonoselenoate 2 produced (\(\delta_p = 48.2\) and 47.2 ppm, \(^1J_{PH} = 564\) and 569 Hz, \(^1J_{PSe} = 713\) and 713 Hz) did not exceed 30-40 %. \(^{31}\)P-NMR spectroscopy revealed formation of various side products that made up 60-70% of the reaction mixtures. Sonication shortened the reaction time to approximately 30 minutes but with no
effect on the product distribution. Decreasing the amount of pyridine in the reaction mixture suppressed formation of some side products, but the reaction became very slow and competing side reactions became significant over time. Eventually, a reaction in chloroform containing of pyridine (2 equiv.) and triethylamine (2 equiv.) led to a reasonably fast (4 h) and clean (ca. 80%, \(^{31}\)P-NMR) formation of nucleoside H-phosphonoselenoate 3, that could be isolated in 45-60% yield.

In order to improve the selenization step, \(3H\)-1,2-benzothiaselenol-3-one (BTSe)\(^{36}\) or potassium selenocyanate\(^{37}\) were tried. With these selenizing agents the only observed products were mixtures of symmetrical phosphoroselenoates and H-phosphonate monoesters. With triphenylphosphine selenide (TPPSe)\(^{38}\) as a selenizing agent the initial results were also rather disappointing. With pyridine as the only base present in the reaction we could not observe any selenization of the phosphinate intermediate 1 at all, however, the addition of triethylamine (3 equiv.) led to ca. 50% conversion within 15 minutes. The reaction, was unfortunately not clean. Using DBU as base gave full conversion within a few minutes, but with the same products distribution as with triethylamine. Thus, it seemed that using

![Scheme 3](image)

**Scheme 3.** Synthesis of H-phosphonate monoesters using TPPSe as a selenizing agent

To remedy these problems, a silylation step was included into the synthetic protocol (Scheme 3). Thus, treating the intermediate phosphinate ester 4a with a silylating reagent, e.g. trimethylsilyl chloride (TMS-Cl, 3 equiv.) resulted in the formation of the phosphonite intermediate 5a (\(\delta_p = 149.9\) and 147.2 ppm, \(^{1}J_{PH} = 356\) and 349 Hz) which should be more susceptible to selenization than phosphinate ester 4a. This strategy proved to be fruitful indeed. Treatment of suitably protected nucleosides 3a-d and triethylammonium phosphinate (1 equiv.) with pivaloyl chloride (1.5 equiv.) in chloroform-pyridine (3:1 v/v) generated the phosphinate esters 4a-d. These, upon reaction with TMS-Cl (3 equiv.) in the presence of TPPSe (2 equiv), produced within 15 minutes nucleoside trimethylsilyl H-phosphonoselenoate diesters, which afforded the desired nucleoside H-phosphonoselenoates 6a-d during aqueous work-up.

Replacing TPPSe with a less reactive selenium-transferring reagent, triphenyl phosphoroselenoate\(^{38}\) (TPOPSe, see also Chapter 3.1), did not result in the
formation of the desired product 6a. Instead, a decomposition of the phosphonite intermediate 5a and a subsequent disproportionation of the phosphinate ester 4a was observed by $^{31}$P-NMR spectroscopy.

However, in our attempts to produce phosphonite intermediate 5a using different silylating agents, it was observed that in the absence of chloride-containing silylating agents, the silyl phosphonite 5a was significantly more stable. For example, when BSA was used to generate 5a it was possible to observe this silyl intermediate for at least 30 minutes using $^{31}$P-NMR spectroscopy, and it was possible to selenize it efficiently with TPOPSe under such conditions.

The main advantage of using TPOPSe as a selenizing agent is that it has more favorable solubility than TPPSe, which makes it possible to synthesize H-phosphonoselenoate monoesters using acetonitrile (MeCN) as a solvent. On a preparative run, phosphinate intermediate 4 was treated with TPOPSe (3 equiv.) in the presence of BSA (3 equiv.) in MeCN/pyridine (3:1 v/v). This protocol afforded nucleoside H-phosphonoselenoates 6 in comparable yields to those obtained using TPPSe/TMS-Cl for the selenization step.

Although the above approach to H-phosphonoselenoate monoesters requires an excess of the hydroxylic component, it is simple, reproducible and very easy to work with. After extraction with water the only salt present in the reaction mixture is usually the triethylammonium salt of the H-phosphonoselenoate monoester. When loaded on a silica gel column, all nonpolar components are washed away with ethyl acetate, and the product is rapidly eluated with CH$_2$Cl$_2$ containing 5% methanol and 0.5% triethylamine. This gives nucleoside H-phosphonoselenoates 6 of purity > 98% ($^1$H-NMR), typically in 80-90% yield.

### 2.1.2 Synthesis of nucleoside H-phosphonoselenoate monoesters using 9-fluorenemethyl H-phosphonoselenoate monoester as an H-phosphonoselenoate group transferring reagent

All methods for the synthesis of H-phosphonoselenoate monoesters mentioned above rely on phosphinate intermediates 4, which are known to be prone to disproportionation unless an excess hydroxylic component is present in the reaction mixture. In the case when an alcohol is expensive or due to solubility problems cannot be used in excess, it would be convenient to have an alternative method for the preparation of H-phosphonoselenoate monoesters.

9-Fluorenemethyl H-phosphonate monoester and 9-fluorenemethyl H-phosphonothioate monoester have previously been reported as facile reagents for transferring an H-phosphonate or H-phosphonothioate group to hydroxylic components. Inspired by these reports we set out to develop the analogous reagent for the synthesis of H-phosphonoselenoate monoesters.

As it was mentioned above, simple alkyl phosphinate derivatives undergo smooth selenization to the corresponding H-phosphonoselenoate monoesters, and thus we chose this method for the preparation of reagent 9 (Scheme 4). Treating 9-fluorenemethanol 7 (1.5 equiv.) with triethylammonium
phosphinate (1 equiv.) in the presence of pivaloyl chloride (1.5 equiv.) gave quantitative conversion into the 9-fluorenemethyl phosphinate intermediate 8, which upon addition of selenium (3 equiv.) was slowly (2 h) converted into 9-fluorenemethyl H-phosphonoselenoate monoester 9 ($\delta_p = 50.56$ ppm, $^{1}J_{PH} = 567$ Hz, $^{3}J_{PH} = 9.7$ Hz, $^{1}J_{PSe} = 732$ Hz). $^{31}$P-NMR spectroscopy revealed that the amount of the desired product 9 exceeded 90% of all phosphorus-containing material present in the reaction mixture.

![Scheme 4. Synthesis of 9-fluorenemethyl H-phosphonoselenoate monoester](image)

As it was mentioned above, simple alkyl phosphinate derivatives undergo smooth selenization to the corresponding H-phosphonoselenoate monoesters, and thus we chose this method for the preparation of reagent 9 (Scheme 4). Treating 9-fluorenemethanol 7 (1.5 equiv.) with triethylammonium phosphinate (1 equiv.) in the presence of pivaloyl chloride (1.5 equiv.) gave quantitative conversion into the 9-fluorenemethyl phosphinate intermediate 8, which upon addition of selenium (3 equiv.) was slowly (2 h) converted into 9-fluorenemethyl H-phosphonoselenoate monoester 9 ($\delta_p = 50.56$ ppm, $^{1}J_{PH} = 567$ Hz, $^{3}J_{PH} = 9.7$ Hz, $^{1}J_{PSe} = 732$ Hz). $^{31}$P-NMR spectroscopy revealed that the amount of the desired product 9 exceeded 90% of all phosphorus-containing material present in the reaction mixture.

The produced triethylammonium salt of 9 was isolated as a sticky oil in typically 90% yield, but it turned out to be rather unstable and deposited selenium upon storage. The selenium wash-out was most likely due to protonation of the selenium, followed by attack of spurious water on the phosphorus centre. This hypothesis was substantiated by synthesis of the N-methyl morpholinium salt. This salt, which contained a more acidic cation, decomposed with release of selenium at a substantially higher rate than the triethylammonium salt.

In order for 9-fluorenemethyl H-phosphonoselenoate monoester 9, to be a useful agent for transferring the H-phosphonoselenoate group, it must be easy to handle and it has to be stable upon storage. To achieve this, 9 was converted into salts bearing various counter ions. Metal cations, e.g. sodium and potassium, gave solid and stable products, but these salts were tedious to prepare; the DBU salt was simple to make, but it was somewhat hygroscopic and turned into a gum upon storage. Eventually, the 4-chlorobenzyl isothiuronium salt was tested, since it has been reported to give crystalline salts with simple H-phosphonate monoesters. Using isothiuronium derivatives as a counter cation for
9-fluorenemethyl H-phosphonoselenoate monoester 9 resulted in a stable white solid, which could be easily prepared by partitioning the triethylammonium salt of 9 between water and diethyl ether containing 4-chlorobenzyl isothiuronium chloride (1.1 equiv.) (the overall yield of 9 was 80-90 %). Attempts of using 4-chlorobenzyl isothiuronium salt of phosphinic acid as a starting material, gave inferior results, both in terms of yield and purity of the produced

\[
\text{H-phosphonoselenoate } \overset{\text{9-fluorenemethyl H-phosphonoselenoate monoester}}{\rightarrow} \text{stable white solid, which could be easily prepared by partitioning the triethylammonium salt of 9 between water and diethyl ether containing 4-chlorobenzyl isothiuronium chloride (1.1 equiv.) (the overall yield of 9 was 80-90 %). Attempts of using 4-chlorobenzyl isothiuronium salt of phosphinic acid as a starting material, gave inferior results, both in terms of yield and purity of the produced }
\]

\[
\begin{align*}
\text{DMT} &= 4,4'-\text{dimethoxytrityl; DPCP = diphenyl phosphorochloridate; TEA = triethylamine} \\
3a, 10a, 6a, B &= \text{thymin-1-yl} \\
3b, 10b, 6b, B &= \text{N4-benzylocytosin-1-yl} \\
3c, 10c, 6c, B &= \text{N6-benzoyladenin-9-yl} \\
3d, 10d, 6d, B &= \text{N2-isobutyrylguanin-9-yl}
\end{align*}
\]

\[\text{Scheme 5. Synthesis of H-phosphonoselenoate monoesters using 9-fluorenemethyl H-phosphonoselenoate monoester}\]

In order to transfer the H-phosphonoselenoate group, H-phosphonoselenoate 9 must be condensed with a hydroxylic component 3 to produce 9-fluorenemethyl derivatives 10 (Scheme 5). The condensation using diphenyl phosphorochloridate (DPCP, 2.5 equiv.) in MeCN-pyridine (4:1 v/v) was rapid and quantitative (\(^{31}\text{P-NMR})\), but in this solvent system the product was sensitive to hydrolysis and decomposed partly via a ligand exchange reaction.\(^{41}\) This was circumvented by reducing the amount of pyridine to 5 equiv. in the solvent system. These condensation conditions were then used for studying different coupling agents.

Pivaloyl chloride (1.5 equiv.) gave rise to significant amounts of by-products, the major ones being H-phosphonate diesters and also P-acylated H-phosphonoselenoate diesters. This was not unexpected since it was previously observed for condensations of H-phosphonothioates.\(^{41}\) When 2-chloro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphinane (NEP-Cl) was used as a coupling agent, the chemoselectivity was excellent, but the reaction was very slow and required over 1 h to completion.

The best condensing agent in terms of chemoselectivity and the reaction time, turned out to be DPCP. Treating nucleoside 3a and H-phosphonoselenoate 9 with DPCP (2.5 equiv.) in MeCN containing pyridine (5 equiv.), gave within 10 min, a complete conversion into the expected H-phosphonoselenoate 10a as the sole nucleotidic material (\(\delta_P = 77.29\) and 76.43 ppm, \(\text{J}_{\text{PSe}} = 870\) Hz and 871 Hz). These reaction conditions worked well for all nucleosides 3 investigated. The coupling reactions can also be performed in CH\(_2\)Cl\(_2\) as solvent but then a longer
reaction time is required (ca. 2 h).

Due to some instability of nucleoside H-phosphonoselenoate diesters 10 in aqueous basic media, the work-up of the reaction mixtures after condensations was critical. Quenching the reaction with water and pyridine (20 equiv.) for 10 min, followed by dilution with toluene-ethyl acetate (1:1 v/v) and passing the reaction mixture through a silica gel pad using the dry column chromatography procedure, worked well and provided 9-fluorenemethyl nucleoside H-phosphonoselenoate diesters 10 in high yields. Too short quenching time could cause the product to be contaminated by small amounts of DPCP, diphenyl phosphate and tetraphenyl pyrophosphate. However, if 10 are intended for the preparation of the corresponding monoesters, these impurities can be tolerated as they do not affect the purity of the final H-phosphonoselenoate monoesters 6.

Removal of the 9-fluorenemethyl group from H-phosphonoselenoate diesters 10 proceeded quantitatively by treatment with TEA (10 equiv.) in CH$_2$Cl$_2$ for 1 h. The products were isolated by precipitation from pentane-ether (2:1 v/v), to produce H-phosphonoselenoate monoesters 6a-d as white powders in 74-98% yield with purity > 98% (1H NMR spectroscopy). It is worth noting that this reaction does not work well in MeCN. When H-phosphonoselenoate 10 was treated with TEA in MeCN, significant amounts of an unidentified by-product (δ$_p$ = 90.55 ppm) were formed together with the desired product (ca. 50%).

Since nucleoside H-phosphonoselenoate monoesters 6 are chiral at the phosphorus centre, it was of interest to have access to their separate R$_p$ and S$_p$ diastereoisomers. These compounds are very difficult to separate into diastereoisomers by silica gel chromatography since the presence of a negative charge overshadows any chromatographic differences between the diastereoisomers. However, this problem can be circumvented by making separation into diastereoisomers at the level of H-phosphonoselenoate diesters. Since, 9-fluorenemethyl nucleoside H-phosphonoselenoate 10 are neutral and lipophilic compounds, they could be separated into diastereoisomers using silica gel chromatography. The separate diastereoisomers of H-phosphonoselenoate diesters 10 were then deprotected using standard protocol to give diastereomerically pure H-phosphonoselenoate monoesters 6. Since the removal of a fluorenemethyl group proceeds via a β-elimination mechanism, its deprotection from 10 does not affect the stereochemical integrity of the phosphorus center.

### 2.2 Nucleoside H-phosphonoselenoate diesters (Paper IV)

By far the most important reaction in oligonucleotide synthesis is the condensation of a nucleotide component with a nucleoside to form the basic skeleton of an oligonucleotide chain. The requirement for this reaction is that it must be essentially quantitative, consistently fast, robust and, in the case of H-phosphonothioates and H-phosphonoselenoates, it must proceed with complete chemoselectivity. Another important step in oligonucleotide synthesis is oxidation of H-phosphonate, H-phosphonothioate or H-phosphonoselenoate diester intermediates, which converts this rather labile P(III) derivatives into stable P(V)
compounds. At this stage of a synthesis it is also possible to control what kind of derivatives can be obtained from a common P(III) precursor.

In this section coupling reactions of H-phosphonoselenoate monoesters with a nucleosidic component, and oxidation of the produced H-phosphonoselenoate diesters into the corresponding P(V) derivative, will be discussed.

2.2.1 Condensation of nucleoside H-phosphonoselenoate monoesters with hydroxylic components

Synthesis of esters from acid derivatives and alcohols is a fundamental transformation in organic synthesis and there is a large number of reagents available to effect this transformation. We used different classes of condensing agents i.e., acyl chlorides, phosphorochloridates, arylsulfonyl chlorides and carbodiimides to evaluate; (i) their efficiency to promote formation of H-phosphonoselenoate diesters, (ii) their chemoselectivity during the activation of H-phosphonoselenoate monoesters, and (iii) the reactivity toward the P-H bond in H-phosphonoselenoate diesters (Figure 3 and Schemes 6 & 7). The condensing agents studied for the synthesis of H-phosphonoselenoate diesters are summarized in Figure 3.

![Condensing agents](image)

**Figure 3.** Condensing agents evaluated for the activation of H-phosphonoselenoate monoesters

Pv-Cl is commonly used in as a coupling reagent in the automated synthesis of oligonucleotides via the H-phosphonate approach.\(^{43}\) Phosphorochloridates, e.g. DPCP,\(^{44}\) DECP,\(^{45}\) NEP-Cl\(^{45}\) and OXP\(^{46}\) have all been evaluated for their ability to promote clean formation of H-phosphonate\(^{45}\) and H-phosphonothioate diesters.\(^{41}\) Arylsulfonyl derivatives, e.g. TPS-Cl,\(^{47}\) have been introduced as coupling reagents in phosphodiester chemistry, but proved to be particularly useful in phosphotriester methodology.\(^{48}\) An activation of H-phosphonate monoester with these reagents has been studied in detail.\(^{49}\) Carbodiimides, standard condensing agents for phosphodiesters, have been
studied in the activation of H-phosphonothioates and are known to preferentially activate the sulfur atom in phosphorus compounds.

In this study we explore reactivity of dicyclocarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) towards H-phosphonoselenoate monoesters.

**Pivaloyl chloride as a condensing agent.** Since pivaloyl chloride is the most commonly used condensing agent in H-phosphonate chemistry it was worth investigating its utility in the synthesis of H-phosphonoselenoate diesters 12 (Scheme 6). Unfortunately, when H-phosphonoselenoate 6a (1.1 equiv.) and a protected nucleoside 11 (1 equiv.) in pyridine were treated with Pv-Cl (3 equiv.), the reaction was fast (< 5 min), but no desired product was formed. Instead, the major components of the reaction mixture were phosphate triester 14a (δ_p = 140.04 ppm, J_PH = 6.23 Hz), P-acylated H-phosphonoselenoate diester 15 (δ_p = 72.59 and 72.26 ppm), and dinucleoside H-phosphonate 13 (δ_p = 9.56 and 7.97 ppm, J_PH = 714 and 717 Hz) (Figure 4). Other by-products gave rise to two signals at 133.76 and 132.94 ppm and at 53.63 and 53.42 ppm, these were tentatively assigned to dinucleoside acyl phosphite 14b and a P-acylated mixed anhydride 16, respectively.

Lowering the amount of Pv-Cl to 1.5 equiv. had a beneficial effect on the outcome of this reaction. In this case, the desired dinucleoside H-phosphonoselenoate 12 (δ_p = 76.29 and 74.84 ppm, J_PH = 653 and 650 Hz, J_PSe = 876 and 877 Hz) was the major product, but small amounts of dinucleoside H-phosphonate 13, phosphites 14 and mixed anhydride 16, were still present. It also became apparent that H-phosphonoselenoate diesters in pyridine, undergo a ligand exchange to form symmetrical H-phosphonoselenoate diester 17 and 18 (δ_p = 77.30 and 73.82 ppm, J_PH = 644 and 644 Hz), analogously to H-phosphonothioate diesters.

In order to suppress the ligand exchange reaction it was necessary to reduce the amount of pyridine by the addition of a cosolvent. When the coupling
reaction was run in MeCN-pyridine (4:1 v/v) the ligand exchange phenomenon was significantly suppressed but the amount of other by-products remained unaffected. Reducing the amount of pyridine to 5 equiv. completely eliminated formation of the ligand exchange products, and also suppressed the formation of H-phosphonate diester 13 and mixed anhydrides 16.

![Chemical structures](image)

**Figure 4.** By-products formed during condensation of H-phosphoselenoate monoester promoted by pivaloyl chloride

This trend was continued when pyridine was replaced by a non-nucleophilic base. In 2,6-lutidine as solvent, treatment of H-phosphonoselenoate 6a (1.1 equiv.) and nucleoside 11 (1 equiv.) with Pv-Cl (1.5 equiv.) gave a rapid and fairly clean reaction. Only traces of H-phosphonate 13 and mixed anhydride 16 could be detected, but unfortunately there was a significant increase in the formation of P-acylated H-phosphonoselenoate diester 15. It appears that although it is possible to achieve acceptable chemoselectivity (O vs. Se activation) with Pv-Cl, the high reactivity towards the P-H bond prohibits its use as a condensing agent for H-phosphonoselenoate monoesters.

**Phosphorochloridates as condensing agents.** Since various phosphorochloridates have displayed excellent chemoselectivity in coupling reactions of H-phosphonothioate monoesters, we expected that this should also
be the case for H-phosphonoselenoate monoesters.

Indeed, when nucleoside H-phosphonoselenoate 6a (1.1 equiv.) and nucleoside 11 (1 equiv.) were treated with DPCP (3 equiv.) in pyridine, the reaction was fast (< 5 min) and proceeded with complete chemoselectivity. Signals from products of a ligand exchange (compounds 17 & 18) were already visible in the first spectrum and they grew stronger over time. However, no by-products associated with the use of DPCP could be detected.

Using MeCN as a solvent with a limited amount of pyridine (5 equiv.) gave quantitative and fast (< 5 min) formation of the desired product 12, without any traces of the ligand exchange products. When these conditions were applied on a preparative scale, the desired H-phosphonoselenoate 12 could be isolated in 80% yield. It was also possible to separate the product into diastereoisomers on a silica gel column.

Replacing DPCP with DECP (3 equiv.) gave identical results, so DECP can function as a substitute for DPCP. The only drawback of DECP compared to DPCP is that it generates tetraethyl pyrophosphate and this is known to be a potent neurotoxic agent.

A sterically hindered phosphorochloridate, NEP-Cl (3 equiv.) in pyridine, gave fast and quantitative formation of dinucleoside H-phosphonoselenoate 12. Unfortunately, the reaction becomes significantly slower when the amount of pyridine was diminished to suppress the ligand exchange process. For example, when nucleoside H-phosphonoselenoate monoester 6a (1.1 equiv.) and nucleoside 11 (1 equiv.) in MeCN containing pyridine (5 equiv.) were treated with NEP-Cl (3 equiv.) the reaction required 1 hour for completion. The reaction proceeded with complete chemoselectivity but after 1 hour traces of the ligand exchange products became visible in the $^{31}$P-NMR spectrum. Thus, it was apparent that NEP-Cl promoted condensations are probably too slow to be useful in the synthesis of H-phosphonoselenoate diesters.

Coupling of H-phosphonoselenoate monoester 6a (1.1 equiv.) and nucleoside 11 in the presence of OXP (3 equiv.) in MeCN containing pyridine (5 equiv.) resulted in quantitative conversion into H-phosphonoselenoate diester 12 in 30 minutes. The reaction was very clean, and although it constitutes a good alternative for the solution phase synthesis, it is probably too slow to be useful in a solid-phase oligonucleotide synthesis.

Other condensing agents. The reaction of nucleoside H-phosphonoselenoate 6a (1.1 equiv.) with nucleoside 11 (1 equiv.) in the presence of TPS-Cl (3 equiv.), resulted in a very complex reaction mixture with no signals in the $^{31}$P-NMR spectrum that could be assigned to the desired products or other derivatives containing a P-H bond. It has previously been documented that H-phosphonothioates and H-phosphonates undergo oxidative degradation in the presence of TPS-Cl and since H-phosphonoselenoates are more reactive than the corresponding H-phosphonothioates and H-phosphonates, it was not surprising that H-phosphonoselenoates were incompatible with TPS-Cl as a condensing agent.
Since carbodiimides are known to preferentially activate the sulfur atom of H-phosphonothioate monoesters to form the corresponding H-phosphonate diesters, it was expected that in the case of H-phosphonoselenoates activation of selenium would also occur. When H-phosphonoselenoate 6a (1.1 equiv.) and nucleoside 11 (1 equiv.) were treated with DCC (3 equiv) in pyridine containing pyridine hydrochloride (3 equiv.) as a catalyst, the reaction was very fast and gave the expected H-phosphonate diester 13 as the major product, together with trace amounts of nucleoside H-phosphonate monoester and H-phosphonoselenoate diester 12 (typically ca. 1-2 %) (Scheme 7). Changing solvent to MeCN-pyridine (4:1 v/v) had no effect on the outcome of the reaction. Using EDC (3 equiv.) instead of DCC in MeCN-pyridine (4:1 v/v) gave essentially identical results, but in this case there was more nucleoside H-phosphonate monoester formed.

It seems that the chemoselectivity was not affected by the nature of the carbodiimide to any appreciable extent. Since EDC was used as its hydrochloride salt, it could in principle function without external acid catalyst. Indeed, when the reaction was run without pyridinium hydrochloride, it proceeded slowly to completion (30 min) with complete chemoselectivity. Unfortunately, there was a significant amount of H-phosphonate monoester formed during this reaction, probably due to traces of water present in the reaction mixture. Since H-phosphonate monoesters react very slowly under these reaction conditions to form H-phosphonate diesters, hydrolytic decomposition of H-phosphonoselenoate 6 do not necessarily pose a problem in this reaction.

2.2.2 Oxidative transformations of dinucleoside H-phosphonoselenoate diesters

Dinucleoside H-phosphonoselenoate diesters are usually considered as intermediates in organic synthesis of nucleotide analogues rather than the final products. Therefore, it was of high importance to be able to perform efficient
oxidative transformation on H-phosphonoselenoate diesters to convert them into various P(V) derivatives.

The most fundamental of these transformations is oxidation of H-phosphonoselenoate 12 into the corresponding dinucleoside phosphoroselenoates 19 (Scheme 8). This transformation is usually performed with an oxidant (iodine, NIS or carbon tetrachloride) in the presence of water. By replacing water by other nucleophiles, one can gain access to a variety of nucleotide analogues containing selenium.

\[
\text{DMTO} \quad \text{B} \quad \text{H-P=Se} \quad \text{Pyridine/water} \quad \text{[Ox]} \quad \text{DMTO} \quad \text{B} \quad \text{Se-P=O} \\
\text{ODMT} \quad \text{B} \quad \text{ODMT}
\]

\[\text{DMT} = \text{4,4'-dimethoxytrityl}; \ [\text{Ox}] = \text{oxidant}\]

\[\text{12, 19, B = thymin-1-yl}\]

**Scheme 8.** Oxidation of dinucleoside H-phosphonoselenoate diester

The standard conditions used for oxidation of H-phosphonate diesters consist of iodine (2 equiv.) in pyridine containing 2% water. When these were applied to dinucleoside H-phosphonoselenoate 12, a rapid and quantitative conversion into the corresponding dinucleoside phosphate, with no desired product 19, was observed. This indicated that selenium in phosphoroselenoate 19 is apparently highly prone to oxidative activation by iodine. To suppress this reaction, the amount of iodine was reduced to 1 equiv. (added as 0.5 M solution in benzene), but still a significant amount of dinucleoside phosphate was formed. Since it is known that phosphoroselenoates loose selenium rapidly in water \(^7,8\) it could be beneficial to limit the amount of water during oxidation. To this end H-phosphonoselenoate 12 (1 equiv.) was treated with iodine (1 equiv.) in MeCN containing pyridine (20 equiv.) and water (50 equiv.). Unfortunately there was no visible improvement in the composition of the reaction mixture.

At this point it became apparent that iodine is not a suitable oxidant for H-phosphonoselenoate diesters. Therefore, we set out to test other potential oxidants. We thought that N-iodosuccinimide (NIS) might have a more favourable oxidation potential. When NIS (2 equiv.) was used with pyridine containing 2% water for the oxidation of H-phosphonoselenoate 12, the results were rather disappointing as only the corresponding dinucleoside phosphate could be observed in the reaction mixture. Lowering the amount of NIS to 1 equiv. still gave rise to selenium wash-out from the expected product. Changing the solvent to MeCN containing water (50 equiv.) and pyridine (20 equiv.) did not improve...
the reaction either. On this basis we excluded NIS as a viable oxidant for H-phosphonoselenoate diesters.

Carbon tetrachloride (CCl₄), which has been known as an oxidant for H-phosphonates, was tried. After complete failure with other oxidizing agents, it was a pleasure to observe that when H-phosphonoselenoate 12 was treated with CCl₄ (10 equiv.) in pyridine containing 2% water, a rapid and quantitative formation of dinucleoside phosphoroselenoate 19 (δₚ = 53.81 ppm, Jₚ,ₚₚ₈ = 830 Hz, diastereoisomers coincide). When TEA (5 equiv.) was added to the reaction mixture, signals from both diastereoisomers became visible (δₚ = 51.93 and 51.69 ppm, Jₚ,ₚ₈ = 824 and 823 Hz) in the 31P-NMR spectrum.

Even though the reaction was rapid, there was some concern about hydrolysis and possibly ligand exchange of the starting H-phosphonoselenoate 12 in pyridine. Therefore this reaction was studied using limited amount of pyridine and water. To this end H-phosphonoselenoate 12 (1 equiv.) was treated with CCl₄ (10 equiv.) in MeCN containing pyridine (20 equiv.) and water (50 equiv.). This resulted in quantitative conversion into the desired product 19 within 10 min. When these reaction conditions were applied on a preparative scale, dinucleoside phosphoroselenoate 19 could be isolated in 95% yield.

Another oxidative transformation commonly performed on H-phosphonates and H-phosphonothioates is sulfurisation using elemental sulfur. This is usually a straightforward and reliable reaction and its efficiency for H-phosphonoselenoate diesters was demonstrated by treating 12 with sulfur (3 equiv.) in MeCN containing pyridine (20 equiv.). The reaction was, as expected, uneventful and produced the desired phosphoroselenothioate 20 quantitatively within 10 minutes (Scheme 9).

Since it is well documented that sulfurization of P(III) compounds with elemental sulfur proceeds stereospecifically with retention of configuration at the phosphorus center, it was therefore of interest to sulfurize separate diastereoisomers of H-phosphonoselenoate 12. These reactions, as expected, were completely stereospecific (31P-NMR spectroscopy), and the separate diastereoisomers of phosphoroselenothioate 20 could be isolated in 95% yield.

![Scheme 9. Sulfurization of dinucleoside H-phosphonoselenoate diester](image-url)
2.3 Conclusions

Developing new methods to gain access to nucleoside H-phosphonoselenoate monoesters was a crucial step in exploration of H-phosphonoselenoate chemistry. For this purpose, two general and efficient methods for the synthesis of H-phosphonoselenoate monoesters have been proposed. One of them is based on a direct selenization of phosphinate esters, and the other one is making use of an H-phosphonoselenoate group transferring reagent, 9-fluorenemethyl H-phosphonoselenoate monoester. With these methods at hand it became possible to synthesize various nucleoside H-phosphonoselenoate monoesters and to separate them into diastereoisomers.

Taking H-phosphonoselenoate monoesters as a starting material in the synthesis of more complex derivatives, condensations with hydroxylic components were studied. Efficient coupling conditions have been developed which permit synthesis of H-phosphonoselenoate diesters in high yield.

Nucleoside H-phosphonoselenoates obtained have been subjected to various oxidative transformations. It was demonstrated that it is possible to get access to nucleotide analogues containing selenium, e.g. dinucleoside phosphoroselenoates, dinucleoside phosphoroselenothioates, using the H-phosphonoselenoate approach.

To conclude, it seems that H-phosphonoselenoate derivatives explored in this thesis can be considered as potentially useful synthetic intermediates in the preparation of biologically important selenium-containing phosphorus compounds.
3. Selenium transfer reactions

A classical way of preparing phosphoroselenoate derivatives consists of selenization of the corresponding P(III) precursors, e.g. phosphite triesters, and H-phosphonate and H-phosphonothioate diesters. The most common reagent used for this purpose is elemental selenium or, to a lesser extent, potassium selenocyanate. These reagents have, however, poor solubility in organic solvents and react very slowly, which make them incompatible with solid phase synthesis. This led to the development of various new selenium-transferring reagents such as 3H-1,2-benzothiaselenol-3-one (BTSe) and bis(di-O,O-isopropylphosphinot hionyl) diselenide, that are soluble in organic solvents and efficiently transfer selenium to P(III) compounds.

Recently, in this laboratory a new type of selenizing agent, triphenylphosphine selenide (TPPSe, $\delta_P = 36.5$ ppm, $^1\!J_{PSe} = 640$ Hz), which mode of action is based on a selenium exchange process between P(III) and P(V) compounds (Scheme 10), was developed.

This reaction is not unique for selenium derivatives, and it was first reported by Gottlieb in 1932, for the transfer of sulfur between thiophosphoryl trichloride and different phosphites. The reaction has been used sporadically for the preparation of various P(V) derivatives containing either sulfur or selenium, or to reduce P(V) compounds into the corresponding P(III) derivatives. The transformations involving transfer of sulfur and selenium are relatively common, but there are only a few reports in the literature on the transfer of oxygen between P(V) and P(III) derivatives, and these involve exclusively phosphine oxides with at least one good leaving group in the donor molecule.

Since it is apparent that this process is not an isolated phenomenon and can be performed on a variety of substrates, it was therefore interesting to gain more insight into a possible mechanism of this reaction.

3.1 Triphenyl phosphoroselenoate as a selenium-transferring reagent (Paper V)

Although the previously developed selenizing agent in our lab, TPPSe, transfers selenium efficiently to phosphites, and H-phosphonate diesters and phosphinate esters, we have noticed that with triphenyl phosphate in dichloromethane, the reaction occurred only to 10% after 24 h. This indicated that apparently the equilibrium in this reaction was shifted towards TPPSe, i.e. that...
triphenyl phosphoroselenoate 21 (TPOPSe, δ_P = 60.1 ppm, ^1J_PSe = 1023 Hz) was a more potent selenizing agent than TPPSe itself.

![Figure 5: Solubility of TPOPSe and TPPSe in various solvents](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>TPOPSe, 21</th>
<th>TPPSe, 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetonitrile</td>
<td>313</td>
<td>6</td>
</tr>
<tr>
<td>tetrahydrofuran</td>
<td>1520</td>
<td>80</td>
</tr>
<tr>
<td>chloroform</td>
<td>1220</td>
<td>100</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>1780</td>
<td>130</td>
</tr>
<tr>
<td>pyridine</td>
<td>1420</td>
<td>230</td>
</tr>
</tbody>
</table>

In order to investigate this phenomenon equimolar amounts of TPOPSe 21 and triphenyl phosphine were kept at room temperature for 24 h in dichloromethane. ^31P-NMR spectroscopy revealed that triphenylphosphine selenide was formed in 90%, an indication that the outcome of the reaction was controlled by the equilibrium. From these experiments it seemed apparent that TPOPSe 21 was a more potent selenizing agent than TPPSe, although it exhibited less favorable kinetics of selenium transfer. For example, selenization of triethyl phosphite in dichloromethane using TPOPSe (1.5 equiv.) required 2 h for completion, while an analogous reaction with TPPSe was over within 3 minutes. The lower reactivity of TPOPSe compared to TPPSe, can be compensated by using a larger excess of TPOPSe, and this is possible due to its much higher solubility in organic solvents than that of TPPSe (Figure 5).

Another way to speed up selenization with TPOPSe is to utilize better kinetics of selenium transfer of TPPSe, and to use a small amount of triphenylphosphine as a catalyst for the reaction (Scheme 11). Indeed, we found that the time for selenization of triethyl phosphite with TPOPSe (1.5
equiv.) in dichloromethane was shortened from 2 h to 20 min, in the presence of triphenylphosphine (0.2 equiv.). It was possible to increase the reaction rate further by the addition of more triphenylphosphine.

**Scheme 12.** Selenization of dinucleoside phosphite

The fact that more basic P(III) compounds react faster indicates a nucleophilic attack on the selenizing agent in RDS. For example, strongly nucleophilic N,N,N-hexamethyltriaminophosphine is completely selenized within 5 minutes upon treatment with TPOPSe (1.5 equiv.; $^3$P-NMR spectroscopy). The time for 50% conversion of triethyl phosphite into the corresponding phosphoroselenoate using TPOPSe (1.5 equiv.) was measured in various solvents, but no pronounced solvent effect was found.

**Scheme 13.** Selenization of dinucleoside H-phosphonate with TPOPSe

The efficiency of TPOPSe as selenium transferring reagent was demonstrated by converting various P(III) compounds into the corresponding phosphoroselenoate derivatives (Scheme 12 and 13).

Selenization of dinucleoside phosphite (δ_p = 141.3 and 140.3 ppm)
with TPOPSe (4 equiv.) in dichloromethane yielded triester 24 \((\delta_p = 74.7\) and \(74.1\) ppm) in 80% isolated yield after 1.5 h. This reaction was very sensitive to the amount of TPOPSe used and with 1.1 equiv. of the selenizing agent, it required 7 h for the completion in this instance. The reaction time could be reduced to 40 min by the addition of 10% triphenyl phosphine as a catalyst.

The rate of selenization of dinucleoside H-phosphonate 13 \((\delta_p = 9.4\) and \(8.4\) ppm, \({}^1\text{J}_{\text{PH}} = 716\) and 719 Hz) with TPOPSe (Scheme 13) could be modulated in several ways. Treating 13 with TMS-Cl (6 equiv.) and TPOPSe (1.1 equiv.) in MeCN/pyridine (3:1, v/v) resulted in very slow \((ca 18\) h) selenization, but increasing the amount of TPOPSe to 4 equiv., shortened the reaction time to 1 h. By changing to TEA (10 equiv.) as a base, the amount of TMS-Cl could be reduced to 3 equiv. and the reaction was complete within 30 min. Using these reaction conditions for selenization, dinucleoside phosphoroselenoate 19 \((\delta_p = 56.9\) and \(56.6\) ppm) could be isolated in 88% yield. In the instance of using strong bases \(e.g.\) DBU (5 equiv.), this reaction was finished within 10 minutes.

### 3.2 Investigation of mechanisms of chalcogens transfer (Paper VI)

One can envisage two likely mechanisms for a chalcogen transfer reaction as depicted in Scheme 14. Mechanism 1, proceeds \(via\) a nucleophilic attack of a P(III) species on the phosphorus centre of a P(V) compound with a three-membered cyclic transition state, and Mechanism 2, which is an X-philic attack of a P(III) compound on the chalcogen of the P(V) species and involves a linear transition state.

![Mechanism 1 and 2](image)

**Scheme 14.** Two possible mechanisms of chalcogen transfer

The former mechanism, postulated for the selenium exchange reaction,\(^{38}\) could explain the fact that oxygen transfer is facilitated by the presence of strong electron-withdrawing groups,\(^{77,78}\) while the later one, was claimed to be...
consistent with the observed second order kinetics for the sulfur transfer process.\textsuperscript{74} This mechanism was also proposed for the oxygen transfer from phosphorus oxychloride to trialkylphosphine.\textsuperscript{80}

In order to get a detailed knowledge about the chalcogen transfer process and to determine through which mechanism these reactions most likely proceed, we undertook a theoretical study using density functional theory calculation on the model reactions showed in Scheme 15. The insight gained from this study could be helpful in rational design of new, effective chalcogen transferring and reducing reagents for phosphorus compounds.

\[
\begin{align*}
\text{R}_1 \cdot \cdot \cdot \text{R}_1 \cdot & \cdot \cdot \text{P} \cdot \cdot \cdot \text{X} \cdot \cdot \cdot \text{R}_2 \cdot \cdot \cdot \text{R}_2 \quad \rightarrow \quad \text{X} \cdot \cdot \cdot \text{R}_1 \cdot \cdot \cdot \text{P} \cdot \cdot \cdot \text{R}_1 \cdot \cdot \cdot \text{R}_2 \cdot \cdot \cdot \text{X} \\
\text{R}_1 & = \text{H, Me} \\
\text{R}_2 & = \text{H, OMe}
\end{align*}
\]

\textbf{Scheme 15.} The model reactions studied by DFT calculations

\subsection*{3.2.1 Computational methods}

All DFT calculations were performed with GAUSSIAN 98 package\textsuperscript{81} using the B3LYP\textsuperscript{82-84} method of density functional theory at the 6-31G* level of theory. All transition states were found by relaxed potential energy surface scanning along the reaction coordinate and then optimized by TS optimization. The stationary points were characterized as minima or transition states by analytical frequency calculations. Visualization of the orbitals was carried out with GaussView 3.0.

\subsection*{3.2.2 Geometries of the starting structures}

The optimized geometries of the starting materials showed reasonable to good agreement with the experimentally determined structures reported in the literature.\textsuperscript{85} Selected structural data and energies are summarized in Table 1. Available experimentally determined data (in parenthesis) have been included for comparison.

It was found that in vacuum the reactants gain stabilization by forming contact complexes, probably through electrostatic interactions of the dipoles of the molecules. In order to make meaningful comparisons between the reactions investigated, the contact complexes of all the reactants and products were calculated and used as starting structures for the reactions. The energy data for these complexes are summarized in Table 2.
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Energy, H</th>
<th>0-point E, kcal/mol</th>
<th>P=X, Å</th>
<th>P-Y, Å</th>
<th>Z-Y, Å</th>
<th>∠XPY, deg</th>
<th>∠YPY, deg</th>
<th>∠PYZ, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3P</td>
<td>-343.1403</td>
<td>15.2024</td>
<td>1.424 (1.412)</td>
<td>93.37 (93.36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3PO</td>
<td>-418.3577</td>
<td>19.5875</td>
<td>1.494</td>
<td>1.420</td>
<td>117.61</td>
<td>100.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3PS</td>
<td>-741.3326</td>
<td>18.2595</td>
<td>1.9603</td>
<td>1.4184</td>
<td>118.10</td>
<td>99.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3PSe</td>
<td>-2742.5239</td>
<td>17.8801</td>
<td>2.0999</td>
<td>1.4178</td>
<td>118.30</td>
<td>99.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me3P</td>
<td>-461.0984</td>
<td>71.1797</td>
<td>1.8673 (1.847)</td>
<td>99.35 (98.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me3PO</td>
<td>-536.3530</td>
<td>74.1125</td>
<td>1.5013 (1.489)</td>
<td>1.8350 (1.771)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me3PS</td>
<td>-859.3223</td>
<td>73.0894</td>
<td>1.9718 (1.959)</td>
<td>1.8405 (1.798)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me3PSe</td>
<td>-2860.5123</td>
<td>72.6053</td>
<td>2.1103 (2.111)</td>
<td>2.0999 (2.111)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO3P</td>
<td>-686.1764</td>
<td>80.6503</td>
<td>1.6540</td>
<td>1.4264</td>
<td>105.18</td>
<td>132.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO3PO</td>
<td>-762.0471</td>
<td>84.8259</td>
<td>1.4789</td>
<td>1.6076</td>
<td>1.4401</td>
<td>115.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO3PS</td>
<td>-1085.0046</td>
<td>83.4280</td>
<td>1.9334</td>
<td>1.6160</td>
<td>1.4412</td>
<td>116.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO3PSe</td>
<td>-3086.1646</td>
<td>81.9194</td>
<td>2.0578</td>
<td>1.6228</td>
<td>1.4305</td>
<td>111.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3PO</td>
<td>-3086.1646</td>
<td>81.9194</td>
<td>2.0578</td>
<td>1.6228</td>
<td>1.4305</td>
<td>111.42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean values are quoted when available.*
Inspection of the frontier molecular orbitals of our model systems may give a qualitative insight into possible interactions between the P(V) and P(III) substrates during the chalcogen transfer reaction. Since Mechanism 1 and Mechanism 2 (Scheme 13) involve an attack of a phosphorus nucleophile, geometry of HOMO of a P(III) species and LUMO of the chalcogenides (Figure 6), may provide a qualitative way to determine if the proposed mechanisms are reasonable.

Figure 6 shows that phosphine sulfide and phosphine selenide have LUMOs that are very similar in shape and both have a strong lobe pointing straight out from the chalcogen, which may invite a nucleophilic attack on this centre. The part of the orbitals centered on the phosphorus seems to be buried inside the occupied orbitals, and may be less accessible to nucleophilic attack.

**Table 2. Energies of contact complexes**

<table>
<thead>
<tr>
<th>Contact complex</th>
<th>Energy, H</th>
<th>0-point E, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{H}_3\text{PO H}_3\text{P} )</td>
<td>-761.5005</td>
<td>35.2935</td>
</tr>
<tr>
<td>( \text{H}_3\text{PS H}_3\text{P} )</td>
<td>-1084.4728</td>
<td>33.5494</td>
</tr>
<tr>
<td>( \text{H}_3\text{PSe H}_3\text{P} )</td>
<td>-3085.6654</td>
<td>33.2494</td>
</tr>
<tr>
<td>( \text{Me}_3\text{PO MeO}_3\text{P} )</td>
<td>-1223.1313</td>
<td>155.6822</td>
</tr>
<tr>
<td>( \text{Me}_3\text{PS MeO}_3\text{P} )</td>
<td>-1546.0977</td>
<td>154.3262</td>
</tr>
<tr>
<td>( \text{Me}_3\text{PSe MeO}_3\text{P} )</td>
<td>-3547.2991</td>
<td>154.5506</td>
</tr>
<tr>
<td>( \text{MeO}_3\text{PO Me}_3\text{P} )</td>
<td>-1223.1519</td>
<td>156.6844</td>
</tr>
<tr>
<td>( \text{MeO}_3\text{PS Me}_3\text{P} )</td>
<td>-1546.1078</td>
<td>155.1035</td>
</tr>
<tr>
<td>( \text{MeO}_3\text{PSe Me}_3\text{P} )</td>
<td>-3547.3038</td>
<td>155.2194</td>
</tr>
</tbody>
</table>

**Figure 6.** Frontier molecular orbitals for phosphine and phosphine chalcogenides
LUMO of phosphine oxide differs significantly from those of phosphine sulfide and phosphine selenide. It is more diffuse and has a different geometry from the LUMOs of the other chalcogenides. To find any orbital on phosphine oxide that resembles the LUMOs of phosphine sulfide and phosphine selenide one has to turn to LUMO + 1. This orbital of phosphine oxide bears a close resemblance to that of LUMO of the sulfide and the selenide, although it is more centered on the phosphorus. Taking this into account, one may expect that for phosphine oxide, both the phosphorus (Mechanism 1) and the oxygen centres (Mechanism 2) may be available for attack by a phosphorus nucleophile.

3.2.3 Transition state geometries of chalcogen transfer

The transition state structures for the investigated reactions were localized by incremental scanning of the potential energy surface along the reaction coordinate. For Mechanism 2, which involves an X-philic attack at the chalcogen, this was done by varying the distance between the attacking phosphorus nucleophile and the corresponding chalcogen, and in the instance of Mechanism 1, by varying the distance between the nucleophile and the phosphorus centre in the chalcogenide. This strategy worked well for Mechanism 2, for which we could pinpoint roughly the whereabouts of the transition state and then perform TS optimization.

In the case of Mechanism 1, this protocol was more troublesome as the curvature could not be mapped well enough to get an idea of the whereabouts of the TS. Instead, exhausting frequency calculations were performed along the reaction coordinate and when negative frequencies corresponding to movement along the reaction coordinate were found, these structures were used as starting points for TS optimization.

Study of the transition state structures for X-philic attack on the chalcogen (Mechanism 2) revealed a striking difference between the transfer of sulfur and selenium, on one hand, and the transfer of oxygen, on the other (Figure 7). For the reactions involving transfer of sulfur and selenium the transition states were nearly completely linear, while that for the oxygen transfer, was bent and resembles more the transition states for Mechanism 2 (Figure 8). All the localized transition state structures were identified as true TS by analytical frequency calculations that revealed only one negative frequency corresponding to the movements along the reaction coordinates. The energies and the selected geometrical data of these transition states are summarized in Table 3.

Examples of TS structures for chalcogen transfer reactions proceeding through Mechanism 1 are summarized in Figure 8.
Figure 7. Localized TS of the chalcogen exchange reactions via Mechanism 2. (a) $\text{H}_3\text{PO} + \text{H}_3\text{P}$; (b) $\text{H}_3\text{PS} + \text{H}_3\text{P}$; (c) $\text{H}_3\text{PSe} + \text{H}_3\text{P}$; (d) $\text{(MeO)}_3\text{PO} + \text{Me}_3\text{P}$; (e) $\text{(MeO)}_3\text{PS} + \text{Me}_3\text{P}$; (f) $\text{(MeO)}_3\text{PSe} + \text{Me}_3\text{P}$

Figure 8. Localized TS of the chalcogen exchange reactions via Mechanism 1. (a) $\text{H}_3\text{PO} + \text{H}_3\text{P}$; (b) $\text{H}_3\text{PS} + \text{H}_3\text{P}$; (c) $\text{H}_3\text{PSe} + \text{H}_3\text{P}$
Table 3. Geometries and energy of transition states for Mechanism 2

<table>
<thead>
<tr>
<th>Transition state</th>
<th>Energy, H</th>
<th>0-point E, kcal/mol</th>
<th>P&lt;sub&gt;1&lt;/sub&gt;-X, Å</th>
<th>P&lt;sub&gt;2&lt;/sub&gt;-X, Å</th>
<th>P&lt;sub&gt;1&lt;/sub&gt;-Y , Å</th>
<th>P&lt;sub&gt;2&lt;/sub&gt;-Y , Å</th>
<th>Π&lt;sub&gt;PXP&lt;/sub&gt;, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;P-O-PH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-761.4129</td>
<td>34.2360</td>
<td>1.8057</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;P-S-PH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-1084.3732</td>
<td>348.956</td>
<td>2.3402</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;P-Se-PH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-3085.6505</td>
<td>33.22939</td>
<td>2.4734</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeO&lt;sub&gt;3&lt;/sub&gt;P-O-PMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-1223.0451</td>
<td>154.3283</td>
<td>1.7196</td>
<td>1.9298</td>
<td>1.6803</td>
<td>1.8521</td>
<td>134.93</td>
</tr>
<tr>
<td>MeO&lt;sub&gt;3&lt;/sub&gt;P-S-PMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-1546.0640</td>
<td>154.3262</td>
<td>2.3524</td>
<td>2.4027</td>
<td>1.6422</td>
<td>1.8513</td>
<td>177.14</td>
</tr>
<tr>
<td>MeO&lt;sub&gt;3&lt;/sub&gt;P-Se-PMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-3547.2781</td>
<td>154.0133</td>
<td>2.4376</td>
<td>2.5155</td>
<td>1.6398</td>
<td>1.8518</td>
<td>173.72</td>
</tr>
</tbody>
</table>

*Mean values are quoted*
For the reaction between \( \text{H}_3\text{P} = \text{X} \) and \( \text{H}_3\text{P} \), no transition states could be localized along the reaction coordinate for the initial nucleophilic attack at the phosphorus centre. Instead, only three-membered cyclic TS corresponding to the edge attack of the phosphorus nucleophile on the \( \text{P} = \text{X} \) bond were found, which indicate that in vacuum these are essentially cycloaddition reactions (Figure 8). These transition states were confirmed to be connected to the products, by performing IRC calculations.\(^{86,87}\)

The transition states found for Mechanism 1 were characterized by frequency calculations, and their geometry and energy data are summarized in Table 4.

### 3.2.4 Activation energies of the chalcogen transfer reactions

To facilitate comparison of the activation energies of different reactions, the energies of all contact complexes were set to 0 regardless of their initial values, and all energies were compensated for the zero point vibrational energy.

The energy diagrams for edge attack of the phosphorus nucleophile on the \( \text{P} = \text{X} \) bond (Mechanism 1) are shown in Figure 9. It is apparent that activation energies for all investigated reactions are very high (above 50 kcal/mol) and contrary to the experimental data, the energy barriers are similar for all the chalcogens. This is a strong indication that Mechanism 1 cannot be a general mechanism for chalcogen transfer reactions.

![Activation energies diagram](image)

**Figure 9.** Activation energies (in kcal/mol) of chalcogen transfer via Mechanism 1
In contrast to these, the activation energies for the X-philic attack (Mechanism 2) showed the expected trend for the investigated chalcogenides (Figure 10). Thus, the reactions involving transfer of oxygen had very high activation energy (*ca.* 56-69 kcal/mol), while those for sulfur and selenium transfer, were significantly lower (for sulfur, *ca.* 20-29 kcal/mol and for selenium, *ca.* 9-17 kcal/mol). This trend is in agreement with the observed reactivity of phosphine chalcogenides in the chalcogen exchange reactions between P(V) and P(III) compounds. The activation energy for the sulfur transfer reaction was of the same order of magnitude as the activation energy for the reaction of triphenylphosphine sulfide and tributylphosphine reported in the literature (~22.3 kcal/mol).

The data for the nine transition states that have been localized and characterized, strongly indicate that transfer of sulfur and selenium, from P(V) compounds to P(III) proceed most likely through a linear transition state via a direct attack of the phosphorus nucleophile on the chalcogen. The data are, however, inconclusive for the oxygen transfer reaction, since attack on the oxygen and attack on the phosphorus of the P(V) compound, both have similar activation energy (*ca.* 55.9 and 54.4 kcal/mol, respectively). For the oxygen transfer reaction, Mechanism 1 is only marginally favoured.
Figure 10. Activation energies (in kcal/mol) of chalcogen transfer via Mechanism 2
3.3 Conclusions

Selenization of P(III) compounds to produce the corresponding selenium-containing P(V) derivatives, is by far the most important way to get access to phosphoroselenoates. A new selenizing agent, triphenyl phosphoroselenoate, have been developed for this purpose. This new reagent has favourable solubility in organic solvents compared to other selenizing reagents and is effective in selenization of various P(III) compounds.

The selenizing reagents, triphenylphosphine selenide and triphenyl phosphoroselenoate, which have been developed in this laboratory, are both based on a chalcogen transfer reaction. In order to get a better understanding of this reaction a computational study of a mechanism of chalcogen exchange was undertaken. From this study we can conclude that the transfer of selenium proceeds most likely via an X-philic attack of the P(III) nucleophile on the chalcogen of the P(V) compound, while for the oxygen transfer, X-philic attack and the edge attack at the P=O bond, is equally likely.
Closing remarks

Through the work presented in this thesis nucleoside H-phosphonoselenoates evolved from an obscure class of phosphorus compounds useful synthetic intermediates in nucleotide chemistry.

H-Phosphonoselenoates are selenium bearing P(III) species and this may provide access to selenium derivatives which might have been difficult to obtain by traditional synthetic methodologies. In order for H-phosphonoselenoate monoesters to be useful in H-phosphonate chemistry, it must be possible to couple these compounds with hydroxylic components chemoselectively to form the corresponding H-phosphonoselenoate diesters. For this purpose several coupling agents have been evaluated for their reactivity towards H-phosphonoselenoate monoesters, and efficient conditions for the synthesis of H-phosphonoselenoate diesters were developed.

In the synthesis of nucleotide analogues the target compounds are usually P(V) derivatives, therefore various oxidation conditions have been evaluated for dinucleoside H-phosphonoselenoate diesters. These resulted in development of efficient protocols for dinucleoside phosphoroselenoate and dinucleoside phosphoroselenothioate in good yields.

Furthermore, a new reagent, triphenyl phosphoroselenoate, for the selenization of P(III) compounds has been developed. This reagent, which has good solubility in organic solvents and high selenium transfer potential, was used to produce phosphoroselenoate derivatives from H-phosphonates and phosphite triesters in high yields.

Since selenization of P(III) compounds using triphenylphosphine selenide and triphenyl phosphoroselenoate proceed via a selenium transfer reaction, we carried out a computational study on a mechanism of chalcogens transfer reaction. The DFT calculations implied that the transfer of selenium and sulfur proceeds most likely via X-philic attack on the chalcogen. For the transfer of oxygen, the results were inconclusive as both mechanisms, a nucleophilic attack of the P(III) species on the oxygen atom and the edge attack on the P=O bond, are equally likely.
Acknowledgements

I would like to thank...

- My supervisor, Professor Jacek Stawinski for granting me the privilege to work with him and learn from him.

- Professor Jan-Erling Bäckvall for his kind interest in this work.

- Doctor Martin Bollmark for his contribution to this work and for always taking time to answer my questions.

- The present members of the nucleotide group, Renáta Híresová and Gaston Lavén for fun in and outside the lab.

- Former members of the nucleotide group, especially Dr. Tommy Johansson and Dr. Johan Nilsson for all the crazy fun we’ve been up to during my time here, but others are also worth mentioning: Dr. Helena Almér, Dr. Martin Bollmark, Dr. Tomas Szabo and Prof. Stephan Stamatov.

- All former members of the office, once you learned to work in our office you can work anywhere. Even though you abandoned us, I thank you, Ann-Britt Runmo, for the time you did brighten up our office.

- My good, good friend Doctor Auri Lindén for always staying with me until last orders and for, almost without fail, keeping me out of trouble.

- Former and present members of the Department of Organic Chemistry for making the department a fun and creative place to work.

- My friends outside the department, Henrik Rundgren, Adam Closson and the gang from my time at Luleå Institute of Technology.

- Charlotte Stoltz for making me live in interesting times.

- My mother, Ragna Kullberg, for maintaining faith in my abilities despite all the evidence to the contrary.

- My family and my relatives.
References


(64) Pistschimuka, P. J. Prakt. Chem. 1911, 84, 746-760.
(79) In separate experiments carried out in various solvents we found that the time for 50% conversion of triethyl phosphite ($\delta_p = 131.0$ ppm) into the corresponding phosphoroselenoate ($\delta_p = 72.0$ ppm, $^{1}J_{PS} = 938$ Hz) using TPOPSe 22 (1.5 equiv.) was: MeCN 7 min, pyridine 9 min, DMF 10 min, dichloromethane 11 min, toluene 14 min, tetrahydrofurane 25 min, isopropanol 58 min ($^{31}$P NMR experiments).
Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc. Pittsburgh PA 1998


