CHAPTER 6

6. CONCLUSION

The chemical reactivities of the different analogues were expected to be comparable however, it proved to be very different. Most of the phosphoryl derivatives in the series were relatively easy to prepare and isolate (R=Ar), others were more difficult (R=aliphatic) to prepare and some of the thiophosphoryl could not be synthesized successfully. The exact reaction conditions could not be found to prepare any of the phosphine derivatives.

Both the substrates for the phosphoryl and thiophosphoryl series were prepared, via the same synthetic route, under the same experimental conditions, except for the starting materials of $P(O)Cl_3$ and $P(S)Cl_3$ respectively. The phosphoryl derivatives with *N*-Phenyl substituents were also prepared and no stumbling blocks were anticipated in the preparation of the thiophosphoryl analogues. The thiophosphoryl substrate proved to be resistant to reaction with aniline however, the substrate reacted relatively easy with benzylamine. The second and third nitrogen atoms with a phenyl substituent could be introduced by another route. This result indicated that the thiophosphoryl center with one nitrogen attached to phosphorus is not completely resistant to nucleophilic attack.

The alcoholysis of the *N*-alkyl bicyclic substrates progressed differently from the *N*-aryl derivatives. In the case of the *N*-aryl substrates, the acidic alcoholysis resulted in the eight-membered ring product **5a** and the basic alcoholysis in the five-membered ring isomer **6a**. Both the acidic and basic alcoholysis of the *N*-alkyl substrates resulted in the same product namely the eight-membered ring compound **15**. The alcoholysis products were isolated and characterized. The hydrochloric salts were not suitable for X-ray determination. The free base of the alcoholysis product, the eight-membered ring, in both cases could not be isolated. The reaction kinetics of the alkyl derivative were studied. The free amine of the P(S)*N*-Phenyl derivative was very unstable and resulted in a mixture of unidentified phosphorus compounds. For this reason it was not possible to perform any kinetic studies on this compound.

A difference between the *N*-aryl and *N*-alkyl substrates was also observed for their reactivity in the related eight-membered to five-membered ring rearrangement.

From the crystal structures it was clear that the two halves (two five membered rings) of **3a** and **11a** had remarkably different dihedral angles. The NMR data represented an average of the two rings; therefore they appear identical on the NMR-scale.

Comparing the dihedral angles as determined from NMR data, by utilization of the Karplus equation, with the dihedral angles obtained from X-ray diffraction data was only approximate. There was very little correlation between the experimental and the calculated dihedral angles for compounds **3a** and **11a**. An average value of the dihedral angles, resulting from NMR data, was not in agreement with the crystal structures.

The analysis of the crystal structures did not reveal any significant differences in the geometries of the phosphoryl and thiophosphoryl analogues. The geometries around phosphorus and nitrogen were comparable. The thiophosphoryl substrate had a P=S bond distance of 1.889 Å, which is shorter than the average P=S bond length of 1.926 Å in similar compounds, The P-N bond distance (1.732 Å) was longer than the average P-N bond length of 1.65 Å. The nitrogen atoms in both substrates were planar i.e. the sum of the bond angles around nitrogen is 359.61° and 358.81° respectively. The two bicyclic analogues **3a** and **11a** also had comparable geometries and revealed no deviations from the normal bond angles or bond distances of this class of compound[1].

The reason for their different chemical reactivity must lie in the differences between the phosphoryl and thiophosphoryl centers.

Molecular mechanical calculations were used to optimize the geometries of all the phosphotriamidates discussed in this work. The Hyperchem MM+ force field in its original form, was not suitable for the type of compounds discussed in this manuscript. Parameters were added to prepare an improved force field to represent the compounds, under question. There were however a few limitations. There was no clear information on how to treat the lone pairs in Hyperchem. Hyperchem only adds lone pairs on sp^3 oxygen and sp^3 nitrogen. Hyperchem treated the sp^3 nitrogen, without the lone pair, as a sp^2 nitrogen and therefore an out-of-plane bending term were added to the total energy calculation. The reason for this selective use of the lone pairs might be to cancel the out-of-plane bending. The absence of the lone pairs did not influence the geometry, however it did add to the calculated electrostatic energy as well as the bond stretch energy. In the case of sp^3 oxygen and sp^3 sulphur, the addition of the lone pairs also did not influence the geometry but an out-of-plane bending term is involved. This out-of-plane bending for the sp^2 oxygen contributes significantly to the total energy.

The new force field was employed to optimize the geometries of the series of compounds listed in **Table 5.1**. The results indicated that it was a reliable model to use for similar compounds, for which no experimental data exists.

The molecular mechanical calculation results clearly confirmed the experimental result for the eight-membered to five-membered ring rearrangement. The five-membered ring is thermodynamically more favoured than the eight-membered ring. Similar results were obtained for the thiophosphoryl analogues of both the *N*-phenyl and *N*-benzyl derivatives, i.e. the calculated energy for the five-membered ring compound was lower in each case.

The structures in the thiono-thiolo rearrangement had comparable energies, with that of the thiono isomer of the *N*-Benzyl derivative slightly lower than that of the thiolo isomer. It can be argued that in the case of the *N*-Benzyl derivative the thiono isomer is thermodynamically more favourable in energy than the thiolo isomer.

To perform a more thorough and complete study of the chemical behaviour of the phosphotriamidates and the differences between the phosphoryl and thiophosphoryl analogues, it will be required to perform quantum mechanical calculations. This will yield more information on the thermodynamics, reaction kinetics, as well as the activation energies of these compounds.

The mechanism of the eight-membered to five-membered ring rearrangement is also a matter that is worth a thorough investigation. Molecular mechanical methods are not sufficient to study this mechanism since MM+ was not developed to accommodate atomic charges. The postulated mechanism for the rearrangement, as discussed in the introductory chapter, progressed via a trigonal bipyramidal intermediate[2,3]. No experimental data were available for the trigonal bipyramidal structures of the phosphotriamidates to test any calculation results.

The thiono-thiolo rearrangement is a temperature dependent reaction and proceeds via a bimolecular reaction mechanism. Quantum mechanical calculations could be utilised to get more information on this process.

6.1 References

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Publications originated from this work:

1. Z. He, S. Laurens, X.Y. Mbianda, A.M. Modro, T.A. Modro, *J. Chem. Soc. Perkin Trans. II,* 2589, (1999).

2. S. Laurens, V.V.H. Ichharam, T.A. Modro, *Heteroatom Chem.,* **12 (5)**, 327 (2001).