Derivatives of cis-NPCl₂(NSOCl)₂ and (NPCl₂)₂NSOCl, Part IX [1]
Substitution Reactions of cis-NPCl₂(NSOCl)₂ with Piperidine

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Aminolysis, Reaction Pattern, Structure Assignment

Aminolysis of cis-NPCl₂(NSOCl)₂ by piperidine in acetonitrile at room temperature proceeds via a non-geminal substitution pattern. During the first substitution step the reactivity of a SOCl-centre appears to be greater than that of a PCl₂-centre. The second and third substitution step successively take place at the PCl₂- and remaining SOCl-centre.

The different isomeric forms of the mono-, bis-, tris-, and tetrakis(piperidino) derivatives are characterized by means of ³¹P NMR data. Application of ¹³C NMR leads in two cases to a structure assignment.

Introduction

Recently we discussed the behaviour of cis-NPCl₂(NSOCl)₂ in reactions with some primary and secondary amines [1, 2]. We demonstrated that the place of nucleophilic attack strongly depends both on the bulk of the incoming group and on the solvent used. In this paper we describe an investigation of the substitution pattern in reactions of cis-NPCl₂(NSOCl)₂ with the cyclic secondary amine NPCl₂(NSOCl)₂ and NPCl₂(NSOPip)₂ with piperidine, using acetonitrile as a solvent. The mono P(pip= piperidino) derivative, NPCl₂NSOCINSOpip, could be isolated in two isomeric forms from the reaction mixture of cis-NPCl₂(NSOCl)₂ and piperidine in molar ratio 1:2. The yield of the two isomers was small, as a consequence of considerable polymerization.

The preparation of the mono morpholino and pyrrolidino derivatives of cis-NPCl₂(NSOCl)₂ shows the same phenomenon [3]. Reactions of the isomers of NPCl₂NSOCINNSOpip with piperidine in molar ratios of 1:2, 1:4 and 1:12 (excess) were investigated and compared with reactions of cis-NPCl₂(NSOCl)₂ with piperidine in a molar ratio of 1:4, 1:6 and 1:14 (excess).

By means of ³¹P NMR measurements it could be derived unambiguously, whether substitution had occurred at phosphorus or at sulphur; as [J₃₁P-H] ≠ 0, while |J₃₁P-H| ≈ 0 and δPCl₂ > δPClp > δpip₂. Additional information about the structures of the isomers of NPClpip(NSOlpip)₂ and NPPip₂(NSOlpip)₂ could be obtained from ¹³C NMR measurements.

Discussion

Aminolysis

From the product mixture obtained by reaction of cis-NPCl₂(NSOCl)₂ (1) with piperidine in a molar ratio of 1:2, using acetonitrile as a solvent, two compounds with formula N₃Ps₉O₄C₁₂Pip were obtained in about equal amounts; they could be isolated by fractional crystallization. Each of the compounds shows in the ³¹P NMR spectrum only one signal: isomer 2 at 28.6 ppm and isomer 3 at 28.1 ppm. Since no ³¹P-H coupling is observed, both isomers can be formulated as

NPCl₂NSOCINNSOpip,
representing a cis- and trans-configuration (Fig. 1).

Fig. 1. Schematic representation of the isomers of NPCl₂NSOCINNSOpip.

A ³¹P NMR spectrum of the crude reaction mixture showed that no compounds, where substitution had occurred at the phosphorus atom, were present.

The reaction of NPCl₂NSOCINNSOpip (2) with piperidine (molar ratio 1:2) yielded a light-yellow oil, mainly consisting of two isomers.
NPClPipNSOClNSOPip with $\delta^{31}P$ values of 21.7 ppm (isomer 4) and 21.1 ppm (isomer 6) respectively.

Like isomer 2, isomer 3 also yielded a yellowish oil in a reaction with piperidine (molar ratio 1:2). In addition to $N_2PS_2O_2Cl_2Pip_2$ small quantities of $N_2PS_2O_2Cl_2Pip$ and $N_2PS_2O_2ClPip_2$ were present (mass spectroscopic evidence). The $^{31}P$ NMR spectrum showed the presence of the four possible isomers of NPClPipNSOClNSOPip with $\delta$ values of 21.7 (4), 21.3 (5), 21.1 (6) and 19.7 (7) ppm in ratio 2:1:1:6 respectively. At lower field three signals of low intensity were present; viz 28.6 (2), 28.1 (3) ppm. The presence of 2 in the reaction mixture indicates some isomerization of product 3 to product 2. However, it is not possible to decide whether the disubstituted products with chemical shifts of 21.7 and 21.1 ppm arise straight from NPClNSOClNSOPip (isomer 2) or by isomerization of the disubstituted products with shifts of 21.3 and 19.7 ppm. The disubstituted compounds formed in the reactions of the isomers of NPClNSOClNSOPip with piperidine (molar ratio 1:2) are also found in the reaction of cis-NPCl$_2$(NSOCl)$_2$ with piperidine in molar ratio 1:4.

Treatment of cis-NPCl$_2$(NSOCl)$_2$ with piperidine (molar ratio 1:6) yielded a yellow oil, consisting of bis-, tris- and tetrakis(piperidino) derivatives (mass spectrum, $^{31}P$ NMR spectrum). Only a very small quantity of a trisubstituted product could be isolated. This product shows in the $^{31}P$ NMR spectrum a resonance signal at 24.3 ppm, which points to a formula NPClPip(NSOPip)$_2$ (8) (PPip$_2$ resonates at higher field, see Table I). In order to obtain a higher yield of 8 (and less polymeric material), a reaction of NPCl$_2$NSOClNSOPip (mixture of the isomers 2 and 3) with piperidine in a molar ratio of 1:4 was carried out. Crystallization of the crude reaction mixture from diethylether yielded 30% of 8.

The fully piperidino substituted derivatives were prepared both from cis-NPCl$_2$(NSOCl)$_2$ and from the isomers of NPCl$_2$NSOClNSOPip. An investigation of the crude reaction mixture of cis-NPCl$_2$(NSOCl)$_2$ and piperidine (molar ratio 1:4) indicated the presence of two isomeric forms of NPPip$_2$(NSOPip)$_2$ with $\delta^{31}P$ values of 14.9 (isomer 11) and 14.1 ppm (isomer 12) in a ratio 5:1. By crystallization from diethylether 9 could be isolated. The reaction of isomer 2 with piperidine (molar ratio 1:12) again led to the formation of both tetrakis(piperidino) derivatives. In contradistinction to the nearly identical results obtained in the two reactions described above, it is surprising that from a reaction mixture of NPClNSOClNSOPip (3) and piperidine (molar ratio 1:12) NPClPip(NSOPip)$_2$ (8) could be isolated in addition to NPPip$_2$(NSOPip)$_2$ (9).

In Table I the $^{31}P$ NMR data of the different piperidino derivatives of NPCl$_2$(NSOCl)$_2$ are listed.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^{31}P$ Chemical shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPCl$_2$(NSOCl)$_2$ (1)</td>
<td>27.6</td>
</tr>
<tr>
<td>NPCl$_2$NSOClNSOPip (2)</td>
<td>28.6</td>
</tr>
<tr>
<td>NPCl$_2$NSOClNSOPip (3)</td>
<td>28.1</td>
</tr>
<tr>
<td>NPClPipNSOClNSOPip (4)</td>
<td>21.7</td>
</tr>
<tr>
<td>NPClPipNSOClNSOPip (5)</td>
<td>21.3</td>
</tr>
<tr>
<td>NPClPipNSOClNSOPip (6)</td>
<td>21.1</td>
</tr>
<tr>
<td>NPClPipNSOClNSOPip (7)</td>
<td>19.7</td>
</tr>
<tr>
<td>trans-NPClPip(NSOPip)$_2$ (8)</td>
<td>24.3</td>
</tr>
<tr>
<td>NPClPip(NSOPip)$_2$ (9)</td>
<td>24.1</td>
</tr>
<tr>
<td>NPClPip(NSOPip)$_2$ (10)</td>
<td>23.7</td>
</tr>
<tr>
<td>trans-NPPip$_2$(NSOPip)$_2$ (11)</td>
<td>14.9</td>
</tr>
<tr>
<td>cis-NPPip$_2$(NSOPip)$_2$ (12)</td>
<td>14.1</td>
</tr>
</tbody>
</table>

**Structure assignment for NPPip$_2$(NSOPip)$_2$ and NPClPip(NSOPip)$_2$**

By means of $^{31}P$ NMR, IR and mass spectroscopy it could be determined to which atom (P or S) the amino ligands are attached; $^{13}C$ NMR was used to get further information on the structures of NPPip$_2$(NSOPip)$_2$ (11) and NPCl(NSOPip)$_2$ (8). Neglecting differences in ring conformation two isomeric forms of NPPip$_2$(NSOPip)$_2$ are possible (Fig. 2).

![Fig. 2. Two isomers of NPPip$_2$(NSOPip)$_2$.](image)

As in the cis-structure the two amino ligands at phosphorus have different chemical environments, it can be expected that in the $^{13}C$ NMR spectrum of this isomer the corresponding C-atoms of the two amino groups attached to phosphorus resonate at somewhat different field strengths.
Table II. \(^{13}\)C NMR data for NPPip\(_2\)(NSOPip)\(_2\) and NPClPip(NSOPip)\(_2\).

<table>
<thead>
<tr>
<th>Compound</th>
<th>(^{13})C Chemical shift(^a)</th>
<th>(^{3})J(_{C-P}) (^b)</th>
<th>(^{3})J(_{C-P}) (^b)</th>
<th>(^{4})J(_{C-P}) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPPip(_2)(NSOPip)(_2) (11)</td>
<td>46.6</td>
<td>45.3</td>
<td>25.1</td>
<td>23.7</td>
</tr>
<tr>
<td>NPClPip(NSOPip)(_2) (8)</td>
<td>46.7</td>
<td>45.0</td>
<td>24.9(^c)</td>
<td>25.1</td>
</tr>
</tbody>
</table>

\(^a\) CDCl\(_3\) is used as a solvent; protons are decoupled.

\(^b\) Numbering of the C atoms: Pip: P-N(...C(6)S-N(...C(5)

In the trans-structure the two amino groups at phosphorus are equivalent. Both in the cis-isomer and the trans-isomers the amino ligands attached to sulphur are equivalent.

The \(^{13}\)C NMR spectrum of NPPip\(_2\)(NSOPip)\(_2\) (11) recorded in CDCl\(_3\) clearly indicate that the amino ligands attached to phosphorus are equivalent; of course, the same holds for the amino ligands at the sulphur atoms (see Table II). In order to exclude that, using CDCl\(_3\) as a solvent, some signals coincide by chance, the spectra were also recorded in CD\(_6\)\(_2\)\(_6\). As the same results were obtained, it is very probably that isomer 11 has a structure with trans-configuration of the two oxygen atoms. It follows, that the configuration of the oxygen atoms is cis in isomer 12. However this compound could not be obtained in a pure state.

The \(^{13}\)C NMR spectrum of NPClPip(NSOPip)\(_2\), recorded in CDCl\(_3\), shows that the C(1) and C(1') atoms of the piperidino groups attached to the two sulphur atoms absorb at different fields (see Table II; the numbering of C-atoms is given in Fig. 3).

This means that the two piperidino ligands at the sulphur atoms have different chemical environments. The difference between the C(3) and C(3') atoms and also between the C(5) and C(5') atoms obviously is too small to give rise to different signals in CDCl\(_3\) as a solvent. However, using CD\(_6\)\(_2\)\(_6\) as a solvent, the chemical inequivalence of both the C(1) and C(1') atoms and of the C(3) and C(3') atoms can be observed. These results indicate that the compound NPClPip(NSOPip)\(_2\) (8) has a structure in which the piperidino ligands attached to the sulphur atoms are in a trans-position (Fig. 4).

**Reaction pattern**

Like the aminolysis of cis-NPCl\(_2\)(NSOCl)\(_2\) by Me\(_2\)NH \([1]\) or t-BuNH\(_2\) \([2]\) in acetonitrile, the aminolysis by piperidine shows that the chlorine atom attached to sulphur is replaced first. As has already been pointed out steric reasons - small intramolecular distances between the chlorine atoms to oxygen, 4.342, 4.893, 3.507 Å \([4]\) in comparison with the sum of the van der Waals radii 3.6 Å \([5]\) – force the reaction to take place at sulphur by an \(S_N^1\) mechanism \([1, 2]\).

The second substitution step takes place at the phosphorus centre. As no structural data of the mono(piperidino) derivatives are available it is not clear whether a suitable configuration or the increased negative charge on the ring now favours an attack at the phosphorus atom.

From the introduction of the third piperidino group at the remaining SOC\(_1\) centre one can conclude that in a nucleophilic substitution reaction an SOC\(_1\) centre is more reactive than a PClPip centre.

**Experimental**

All experiments were carried out under dry nitrogen. Piperidine was purified by distillation over KOH pellets. Solvents were purified and dried...
by conventional methods. The compound cis-NPCl₂(NSOC₁₂) (1) was prepared according to published methods [3, 6]. Element analyses were carried out at the Microanalytical Department of this University under supervision of Mr. A. F. Hamminga. Infrared spectra were recorded on a Hitachi EPI-G spectrophotometer using KBr discs; calibration was performed by means of polystyrene film bands. The mass spectra were taken by Mr. A. Kiewiet (Department of Organic Chemistry of this University) on an AEI/MS 9 mass spectrometer at 70 eV, using an accelerating voltage of 8 kV; the samples were introduced directly by a conventional inlet system. The ³¹P and ¹³C NMR spectra were recorded by Mr. R. H. Fokkens (NMR Department, University of Amsterdam) on a Varian XL-100 FT spectrometer at 40.5 MHz and 25.2 MHz, respectively; chemical shifts were determined relative to the external standards 85% H₃PO₄ (³¹P) and TMS (¹³C) at 37 °C and defined as positive in low-field direction. The deuterium resonance of the solvent CDCl₃ or C₄D₄ was used for field-frequency lock.

1. Reaction of cis-NPCl₂(NSOC₁₂) with piperidine (molar ratio 1 : 2)

A solution of 60.0 mmoles of piperidine in 70 ml of acetonitrile was added dropwise, over a period of about 30 min, to a stirred solution of 30.0 mmoles of cis-NPCl₂(NSOC₁₂) in 600 ml of acetonitrile, cooled at —15 °C. The mixture was allowed to warm slowly to room temperature and was stirred for about 17 h at this temperature. After evaporating the reaction mixture under reduced pressure until dry, the residue was extracted three times with diethyl-ether. Cooling the ether extracts at —20 °C gave 4.0 mmoles of NPCl₂NSOClNSOPip (2) with a melting traject of 129–132.5 °C (uncorr.). After two recrystallizations from diethyl-ether 3.0 mmoles of NPCl₂NSOClNSOPip (2) with a melting traject of 131.8 vs, 1289 s, 1276 vs, 1192 vs, 1157 s, 1130 vs, 1093 m, 1069 s, 1062 s, 1030 s, 940 vs, 864 m, 860 m, 852 m, 830 s, 748 s, 706 s, 702 s, 661 s, 601 vs, 577 vs, 549 s, 535 m, 511 vs, 447 m.

IR (cm⁻¹) NPCl₂NSOClNSOPip (2) m.p. 83–84.5°C. 1318 vs, 1289 s, 1276 vs, 1192 vs, 1157 s, 1130 vs, 1093 m, 1069 s, 1062 s, 1030 s, 940 vs, 864 m, 860 m, 852 m, 830 s, 748 s, 706 s, 702 s, 661 s, 601 vs, 577 vs, 549 s, 535 m, 511 vs, 447 m.

2. 1 with piperidine (molar ratio 1 : 6)

In this reaction considerable amounts of polymeric material were formed. Analysis

NSOClNSOPip dithiatriazaphosphorine NPCl₂ (2)

The composition of the mixtures was determined by mass and ³¹P NMR spectroscopy.

Reactions 2–6 were carried out under analogous experimental conditions as described under 1. Only the method of isolation and purification is given. The composition of the mixtures was determined by mass and ³¹P NMR spectroscopy.

2. 2 with piperidine (molar ratio 1 : 2)

The evaporated reaction mixture was extracted with diethyl-ether. Evaporation of the ether extracts yielded a light-yellow oil, consisting of two isomers of NPCl₂NSOClNSOPip (4 and 5) and a very small amount of trans-NPCl₂NSOClNSOPip (8). Separation of the products by means of crystallization or thin-layer chromatography failed.

3. 3 with piperidine (molar ratio 1 : 2)

See for details experiment 2.

A mixture of isomers of NPCl₂NSOClNSOPip (4, 5, 6 and 7) was obtained in presence of small quantities of trans-NPCl₂NSOClNSOPip (8) and two isomers of NPCl₂NSOClNSOPip (2 and 3). Separation of products failed.

4. 1 with piperidine (molar ratio 1 : 4)

In this reaction considerable amounts of polymeric material were formed. See for further details experiment 2.

A mixture of isomers NPCl₂NSOClNSOPip (4, 5, 6 and 7) together with small amounts of 8 was obtained. Separation of the products failed.

5. 1 with piperidine (molar ratio 1 : 6)

In this reaction considerable amounts of polymeric material were formed.
See for further details experiment 2.

The reaction mixture contained the isomers NPClPipNSOClNSOPip (8, 9 and 10) and small amounts of NPClPipNSOClNSOPip (4, 5, 6 and 7) and of trans-NPPIp(NSOPip)2 (11). By recrystallization from diethyl-ether only isomer 8 could be isolated. Yield 5%.

6. 2 and 3 (mixture of isomers) with piperidine
(molar ratio 1 : 4)

The evaporated reaction mixture was extracted with diethyl-ether. Addition of n-pentane to the extract and cooling at $-20^\circ C$ gave trans-NPClPip(NSOPip)2 (8). Recrystallization from ether yielded white crystals (m.p. 140–141.5°C; yield 30%).

Trans-1,3-dioxo-5-chloro-1,3,5-tris(piperidino)-1,3,2,4,6,5-dithiatriazaphosphorine, trans-NPPIp(NSOPip)2 (8)

**Analysis**

Calcd C39.42 H6.62 N 18.39 S 14.03 C17.76,


IR (cm$^{-1}$) 1280 s, 1270 s, 1245 s, 1236 s, 1208 m, 1182 m, 1065 m, 1049 m, 1025 s, 957 s, 930 s, 918 s, 858 m, 828 s, 715 s, 697 s, 638 m, 697 s, 571 s, 555 s, 541 m, 512 s, 501 s.

m/e 505 M+ 40%, 421 (M-Pip)+ 100%.

7. Reaction of NPCl2(NSOCl)NSOPip (2)
with piperidine (molar ratio 1 : 12)

To a stirred solution of 12.0 mmoles of piperidine in 30 ml of acetonitrile, cooled at $-15^\circ C$, a solution of 1.00 mmoles of NPCl2(NSOCl)NSOPip (2) in 30 ml of acetonitrile was added dropwise over a period of about 30 min. This mixture was allowed to warm slowly to room temperature and stirring was continued for about 17 h at this temperature. Extraction of the evaporated reaction mixture with diethyl-ether and cooling the ether extract at $-20^\circ C$ yielded 8. By recrystallization from diethyl-ether 8 was obtained in a pure state.

Reactions 8-9 were carried out under analogous experimental conditions as described under 7. Only the method of isolation and purification is given. The composition of the reaction mixtures was determined by mass and $^{31}$P NMR spectroscopy.

8. 3 with piperidine (molar ratio 1 : 12)

The evaporated reaction mixture was extracted with diethyl-ether: addition of n-pentane to the extract and cooling at $-20^\circ C$ gave 8. By recrystallization from ether 8 was obtained in a pure state. Yield 38%, m.p. 140–141.5°C.

Partial evaporation of the mother-liquor and cooling at $-20^\circ C$ yielded 11, which was recrystallized from diethyl-ether. Yield 17%, m.p. 115 to 117°C.

9. 1 with piperidine (molar ratio 1 : 14)

Extraction of the evaporated reaction mixture with diethyl-ether and cooling the ether extract at $-20^\circ C$ yielded 11, which was recrystallized from diethyl-ether. Yield 36%, m.p. 115–117°C.

Evaporation of the mother-liquor gave a yellow oil consisting of 11 and 12. Separation of the isomers failed.

The authors wish to thank Prof. F. Jellinek for his stimulating interest during the course of this investigation. H. H. B., R. K. and J. C. v. d. G. are much indebted to the NMR Department of the University of Amsterdam for the fruitful cooperation.

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