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Direct phosphorylation in the synthesis of new bis(phosphorylamino)pyridine ligands

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A simple and efficient synthetic approach to new oligodentate ligands, 2,6-bis(phosphorylamino)pyridine and related compounds, is based on the reaction of diphenylphosphinic chloride Ph_2POCl with various diamines.

Neutral organophosphorus complexing agents and extractants are characterized by higher selectivity in comparison with their organic (carbonyl) analogues.[1] Moreover, the introduction of additional phosphoryl groups in many cases makes it possible to increase considerably (sometimes by dozens of times) the efficiency of extraction of rare-earth metals from liquid radioactive wastes.[2]

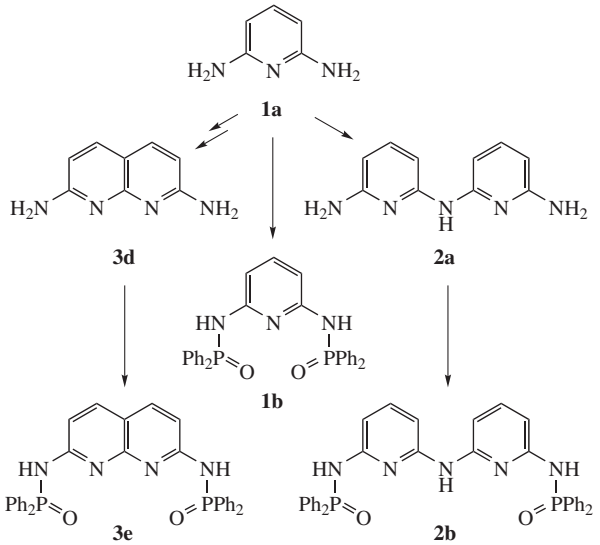
It is well known that poly(diphenylphosphoryl)alkanes and poly(diphenylphosphorylmethyl)arenes are used for extraction of tetra- and hexavalent actinides and lanthanides;[1] at the same time, trivalent transition metals are extracted with them much poorer. However, polydentate nitrogen heterocycles – tripyridyltriazines, terpyridines, bis(benzimidazolyl)pyridines, bis(benzothiazolyl)pyridines and, especially, polyalkyl-substituted 2,6-bis(1,2,4-triazin-3-yl)pyridines – are much more efficient ligands for concentrating trivalent radionuclides.[3,4]

The design of ligand systems containing phosphoryl groups alongside pyridine fragments opens new prospects for the efficient and selective extraction of trivalent lanthanides and actinides. Moreover, interesting luminescent properties of hybrid compounds containing phosphorus and nitrogen (including phosphorus-containing pyridines and naphthyridines) and their complexes with various metals were recently documented.[5–8] Interesting results concerned the synthesis and coordination properties of thiophosphoryl pyridine-type ligands were also obtained.[9]

In this context, we previously reported a highly efficient and regioselective synthesis of 2-phosphorylalkyl- and 2-phosphorylamino-substituted naphthyridines.[10–12] These compounds differ from each other mainly in the structure and the nature of linkers between phosphoryl groups and heteroaromatic fragments. They behave as oligodentate ligands toward lanthanide cations[13] and can be used as selective extractants upon partitioning of radionuclides.[14]

The aim of this study was to develop a facile procedure for the synthesis of bis(phosphorylamino)-substituted molecular architectures that differ in the structure of pyridine-containing bridge between two phosphoryl groups. One can expect that the compounds of this type will be capable to function as multidentate ligands and to form complexes with one or more metal centres.

The direct phosphorylation of amino-substituted pyridines (and related compounds) with chlorides of pentavalent phosphorus acids provides a convenient synthetic route to such systems.[10] We used commercially available 2,6-diaminopyridine **1a** and heterocyclic diamines **2a** and **3d** obtained on its basis as starting materials for constructing target compounds with different sizes of ligand contours. Diphenylphosphinic chloride Ph_2POCl was used as a phosphorylating agent in all cases (Scheme 1).



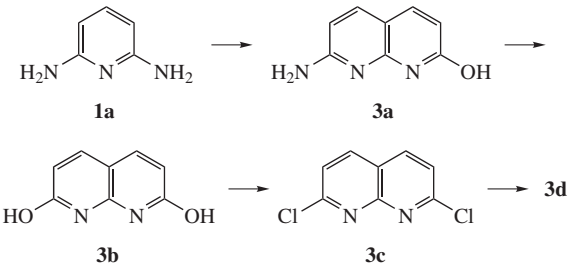
Scheme 1

Initially, we studied a reaction of Ph_2POCl with commercially available diamine **1a**. The stirring of a suspension of the reactants in refluxing chloroform in the presence of triethylamine was a more convenient synthetic procedure than the reaction in benzene[15] or pyridine.[14] The first advantage of this procedure is a possibility to monitor reaction course *via* the dissolution of the starting diamine, and the second one is the simple procedure of isolation of the target bis(phosphorylamino)pyridine. The reaction was complete in 5 h, and product **1b** was isolated in 80% yield.

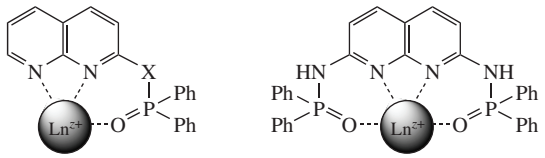
The bisphosphorylation of diamine **2a**, which can be obtained from **1a** in one stage,[16] has been carried out under the same conditions. The reaction was complete in a longer time (18 h) and product **2b** was isolated in 76% yield.

The preparation of ligand **3e** is possible on the basis of 2,7-diamino-1,8-naphthyridine **3d**. The synthesis of this diamine demands a longer chain of transformations.[17,18] Therefore, the first aim was to obtain a sufficient amount of diamine **3d** (Scheme 2).

We improved certain stages leading to 2,7-diamino-1,8-naphthyridine **3d**. In particular, we developed a facile one-pot process for preparing 2,7-dihydroxy-1,8-naphthyridine **3b** in an



Scheme 2



X = NH, CMe_2, CH_2CH_2
Ln = Nd, Eu, Lu

Figure 1 Schematic structures of lanthanide complexes with phosphoryl-substituted naphthyridines.

almost quantitative yield over two initial stages. This process is less time consuming and labour intensive and provides the saving of reagents. The formation of bis(phosphorylamino)-substituted compound **3e** required phosphorylation for 24 h at reflux. Bisphosphorylation product **3e** was obtained in 76% yield.

The bis(phosphorylamino)-substituted ligands obtained in this work are white solids with high melting points. The ^{31}P NMR spectra of the bisphosphorylated diamines show singlets with chemical shifts δ 15–20 ppm typical of the phosphorus atom in the corresponding environment. The ^1H NMR spectra† of all the compounds exhibit expected chemical shifts and multiplicity. The mass spectra of compounds **1b**, **2b** and **3e** display the intense peaks of molecular ions; moreover, peaks related to the main fragmentation directions of these molecules are identified.

Previously we have shown that 2-monophosphoryl-substituted 1,8-naphthyridines reveal highest possible denticity in complexation with lanthanide nitrates. In this case, both nitrogen atoms of pyridine rings and the oxygen atom of the phosphoryl group take part in the formation of coordinative linkages (Figure 1).[13,19,20]

In this work we have obtained a series of new hybrid molecules containing phosphorus and heterocyclic nitrogen that incorporate ligand cavities of various size and type. One can expect the maximal denticity of compounds **1b**, **2b** and **3e** in complexes with relative metals (Figure 1). Investigations of complexation abilities of newly synthesized ligands are in progress now.

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† The NMR spectra were recorded on a Bruker Avance-400 spectrometer operating at 400.13 (^1H) and 161.98 MHz (^{31}P) in [$^2H_6$]DMSO or $CDCl_3$ (for **3e**) solutions using the residual proton signals of the solvent as an internal reference (^1H) and 85% H_3PO_4 (^{31}P) as external reference. The mass spectra were measured on a Finnigan Polaris Q mass spectrometer. 2,6-Diaminopyridine (Acros Organics) was recrystallized from $CHCl_3$ (white plates). Diphenylphosphinylchloride Ph_2POCl (Aldrich) was purified by vacuum distillation. Reactions with Ph_2POCl were carried out in an argon atmosphere. Compounds **3c**[17] and **3d**[18] were synthesized by previously described procedures. Solvents used for syntheses were purified and dried by known procedures.[21]

2,6-Bis(diphenylphosphorylamino)pyridine **1b**. To a suspension of 2,6-diaminopyridine (1.09 g, 10 mmol) in $CHCl_3$ (30 ml), Ph_2POCl (4.97 g, 4 ml, 21 mmol) was added with stirring at 20 °C, and then Et_3N (2.33 g, 3.2 ml, 23 mmol) was added dropwise. The resulting mixture was refluxed for 5 h. After that, the mixture was allowed to cool to 20 °C. White precipitate was filtered off, washed carefully with cold water and dried over $CaCl_2$ in a vacuum. By this procedure 4.07 g (80%) of **1b** was isolated as a white powder, mp 285–286 °C (from $CHCl_3$, decomp.). ^{31}P NMR, δ: 15.9. ^1H NMR, δ: 8.33 (d, 2H, NHP, J_{HP} 11.0 Hz), 7.67–7.74 (m, 8H, *o*-Ph), 7.47–7.56 (m, 12H, *m*-Ph, *p*-Ph), 7.22 (t, 1H, Py-H^4, J_{HH} 8.0 Hz), 6.38 (d, 2H, Py-H^3, Py-H^5, J_{HH} 8.0 Hz). MS, *m/z*: 509 $[M]^+$ (94.9), 508 $[M - H]^+$ (34.1), 432 $[M - Ph]^+$ (22.9), 309 $[C_{17}H_{15}N_3OP]^+$ (50.2), 292 $[C_{17}H_{14}N_2OP]^+$ (35.3), 216 $[C_{12}H_{11}NOP]^+$ (7.3), 201 $[C_{12}H_{10}PO]^+$ (43.3), 185 $[C_{12}H_{10}P]^+$ (100), 77 $[Ph]^+$ (11.8). Found (%): C, 68.40; H, 4.90; N, 8.31; P, 12.08. Calc. for $C_{29}H_{25}N_3O_2P_2$ (%): C, 68.37; H, 4.95; N, 8.25; P, 12.16.

Bis(6-aminopyridin-2-yl)amine **2a**. This compound was synthesized as described elsewhere.[15] Yield, 41% (no indicated yield value in ref. 16). Mp 177–178 °C. ^1H NMR, δ: 8.52 (s, 1H, Py–N*H*–Py), 7.20 (t, 2H, Py-H^4, J_{HH} 7.8 Hz), 6.89 (d, 2H, Py-H^3, J_{HH} 7.8 Hz), 5.91 (d, 2H, Py-H^5, J_{HH} 7.8 Hz), 5.57 (s, 4H, NH_2). Found (%): C, 59.60; H, 5.49; N, 34.86. Calc. for $C_{10}H_{11}N_5$ (%): C, 59.69; H, 5.51; N, 34.80.

Bis[6-(diphenylphosphorylamino)pyridin-2-yl]amine **2b**. To a suspension of diamine **2a** (603 mg, 3 mmol) in $CHCl_3$ (20 ml), Ph_2POCl (1.42 g, 1.2 ml, 6 mmol) was added with stirring at 20 °C, and then Et_3N (0.7 g, 0.97 ml, 6.9 mmol) was added dropwise. The resulting mixture was refluxed for 18 h. After that, the mixture was washed with water (2×10 ml), and combined water layers were washed with $CHCl_3$ (10 ml). Combined organic layers was filtered through Al_2O_3, dried over $MgSO_4$, and then $CHCl_3$ was distilled off under reduced pressure, giving 1.37 g (76%) of yellowish solid, which was washed with hexane. After recrystallization from $CHCl_3$, 0.94 g (52%) of **2b** as a white powder was isolated. Mp 179–180 °C. ^{31}P NMR, δ: 15.0. ^1H NMR, δ: 8.57 (d, 2H, NHP, J_{HP} 11.1 Hz), 8.46 (s, 1H, Py–N*H*–Py), 7.80–7.86 (m, 8H, *o*-Ph), 7.48–7.53 (m, 12H, *m*-Ph, *p*-Ph), 7.27 (t, 2H, Py-H^4, J_{HH} 7.8 Hz), 7.00 (d, 2H, Py-H^3, J_{HH} 8.1 Hz), 6.43 (d, 2H, Py-H^5, J_{HH} 7.5 Hz). MS, *m/z*: 601 $[M]^+$ (42.1), 600 $[M - H]^+$ (11.4), 524 $[M - Ph]^+$ (5.5), 400 $[C_{22}H_{19}N_5OP]^+$ (39.5), 385 $[C_{22}H_{18}N_4OP]^+$ (8.9), 217 $[C_{12}H_{11}NOP]^+$ (100), 201 $[C_{12}H_{10}PO]^+$ (97.1), 77 $[Ph]^+$ (15.6). Found (%): C, 67.75; H, 4.90; N, 11.70; P, 10.41. Calc. for $C_{34}H_{29}N_5O_2P_2$ (%): C, 67.88; H, 4.86; N, 11.64; P, 10.30.

2,7-Dihydroxy-1,8-naphthyridine **3b**. To a conc. H_2SO_4 (40 ml), diamine **1a** (4.4 g, 40 mmol) was added with stirring and cooling in an ice bath (0–5 °C). To the resulting solution carefully grounded DL-malic acid (6.0 g, 44 mmol) was added in small portions. Then, the resulted solution was heated to 110 °C until stopping of gassing. After that, the reaction mixture was kept at this temperature for additional 30 min (2–2.5 h total). Then, $NaNO_2$ (3.3 g, 48 mmol) was carefully added to the resulting mixture with stirring and cooling in an ice bath (0–5 °C). Mixture was stirred for 10 min at 20 °C, poured over crushed ice and allowed to stand for 15 min. The solution was neutralized by Na_2CO_3, acidified by acetic acid (pH 3.5), the resulting precipitate was filtered off and carefully washed with cold water to give 6.35 g (98%) of naphthyridine **3b** as a light-brown powder. Mp 322–323 °C (lit.,[17] 321–323 °C).

2,7-Bis(diphenylphosphorylamino)-1,8-naphthyridine **3e**. To a suspension of diamine **3d** (480 mg, 3 mmol) in $CHCl_3$ (20 ml), Ph_2POCl (1.42 g, 1.2 ml, 6 mmol) was added with stirring at 20 °C, and then Et_3N (0.7 g, 0.97 ml, 6.9 mmol) was added dropwise. The resulting mixture was refluxed for 24 h. After that, the mixture was worked up as it described for **2b**. Yield, 1.28 g (76%) of **3e**, white powder, mp 321–322 °C (from EtOH, decomp.). ^{31}P NMR, δ: 20.4. ^1H-{^{31}P} NMR, δ: 7.87 (d, 8H, *o*-Ph, J_{HH} 7.0 Hz), 7.55 (d, 2H, Napy-H^4, Napy-H^5, J_{HH} 8.6 Hz), 7.48 (t, 4H, *p*-Ph, J_{HH} 7.3 Hz), 7.41 (t, 8H, *o*-Ph, J_{HH} 7.1 Hz), 6.97 (d, 2H, Napy-H^3, Napy-H^3, J_{HH} 8.6 Hz). MS, *m/z*: 560 $[M]^+$ (49.7), 559 $[M - H]^+$ (38.9), 483 $[M - Ph]^+$ (14.6), 359 $[C_{20}H_{16}N_4OP]^+$ (44.3), 343 $[C_{20}H_{15}N_3OP]^+$ (39.8), 219 $[C_{12}H_{11}NOP]^+$ (100), 201 $[C_{12}H_{10}PO]^+$ (68.4), 77 $[Ph]^+$ (13.9). Found (%): C, 68.51; H, 4.69; N, 9.91; P, 10.73. Calc. for $C_{32}H_{26}N_4O_2P_2$ (%): C, 68.57; H, 4.68; N, 10.00; P, 11.05.

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