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Synthesis of phosphocyclic 2,2′,7,7′-tetrahydroxydinaphthylmethane derivatives

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Abstract—Two types of phosphocyclic derivatives were synthesized by phosphorylation of 2,2′,7,7′-tetrahydroxydinaphthylmethane with triamidophosphites: triphosphorus containing compounds with a phosphocine ring and two acyclic diamidophosphite fragments, and tetraphosphorus-containing macrocycles with a 24-membered ring and two eight-membered phosphorus rings. It was shown that interaction of triphosphorus compounds with resorcinarene gives tetraphosphorus macrocycles.

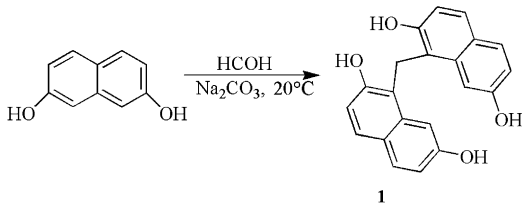
Triamidophosphites are efficient reagents used for the synthesis of different phosphocyclic compounds.[1] This is due to the presence of three cleavable P–N bonds. The structure of the phosphorylation products depends on the reactivity and mutual orientation of nucleophilic groups in the substrate.

This letter considers approaches to the design of previously unknown macrophosphocyclic systems based on 2,2′,7,7′-tetrahydroxydinaphthylmethane **1**. The latter is a conformationally mobile system containing two pairs of hydroxyl groups with different reactivities. These features of the molecule allow the regulation of its phosphorylation regioselectivity.

Compound **1** was first synthesized by the condensation of 2,7-dihydroxynaphthalene with 40% formaldehyde in an acid solution as performed by Wolff[2] in 1893. During the next hundred years, the chemistry of **1** was not widely studied. In 1998, Kallmayer and Schröeder-Mann[3] performed a thorough study of the above reaction and found that it resulted in a mixture of products. Replacement of acid catalysis by basic catalysis (saturated Na_2CO_3 solution) allowed us to decrease the reaction time to 30 min and to implement the process regioselectively (Scheme 1).

In the MALDI spectrum of the reaction mixture, only a single peak corresponding to the calculated molecular weight of **1** was observed. The ^1H NMR spectrum of the isolated product completely coincided with that of compound **1** obtained by the Wolff procedure.[3]

The simplest triamidophosphites **2a**,**b**, which are readily available, easy to handle, and have high phosphorylating activity, were used as phosphorylating agents. The reactions were carried out in dioxane in the temperature range 20–90 °C.



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Scheme 1. Reaction of 2,7-dihydroxynaphthalene with formaldehyde resulting in the formation of 2,2′,7,7′-tetrahydroxydinaphthylmethane **1**.

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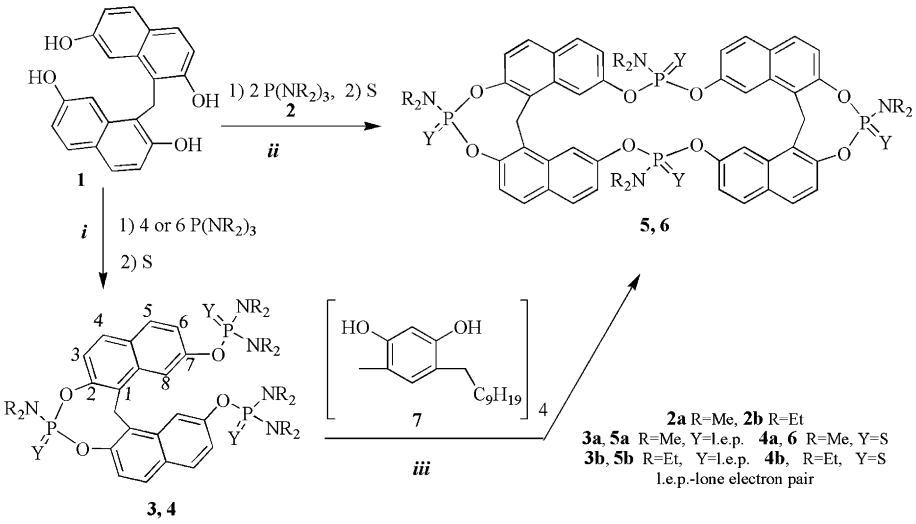
The study of reaction mixtures using MALDI and ^{31}P NMR spectroscopy showed that the main reaction products are the phosphocyclic compounds **3** and **5**, the product ratio depending on the initial reagent ratio (Scheme 2). Increasing the temperature had no significant effect on the regioselectivity of this process; it only increases the reaction rate.

The use of an excess of triamidophosphite (**1**:**2** = 1:4–6) mainly resulted in the formation of compounds **3** containing a phosphocine ring and two acyclic diamidophosphite fragments in the molecule (Scheme 2, i). For example, when **2b** was used at the initial reagent ratio **1**:**2** = 1:4, the ^{31}P NMR spectrum of reaction mixture recorded 9 days (20–25 °C) or 27 h (80–85 °C) after the beginning of the reaction showed three singlets with chemical shifts of 139.3, 132.1 (**3b**), and 118.1 ppm (**2b**). The ratio of the integrated intensities of the signals was 1:2:1, respectively. Further exposure of the reaction mixture at room or elevated temperature did not affect the spectrum. Compounds **3** were sulfurized without isolation from the reaction mixture.[†] The ^{31}P NMR spectra of the isolated thione derivatives **4** displayed two singlets with chemical shifts typical for acyclic diamidothionophosphates and cyclic monoamidothionophosphates (downfield and upfield signals, respectively). The ratio of the integrated intensities of the signals was 2:1. In the upfield range of the ^1H NMR spectrum of **4a**, three doublets were observed for the methyl protons of the phosphamide groups with integrated intensities of 1:2:2; the ^1H NMR spectrum of **4b** contained two multiplets for the methylene protons and three triplets for the methyl protons of the diethylamide groups with integrated intensities of 1:4 and 1:2:2, respectively. In the downfield range of the ^1H NMR spectra of both compounds, two doublets (C_6D_6) or a singlet ($CDCl_3$) were observed for the methylene bridge protons, as well as a singlet (H^8) and four doublets ($H^{3–6}$) for the aromatic protons. The integrated intensities of these signals corresponded with theoretical values. The MALDI spectrum of **4b** showed a single peak corresponding to its calculated molecular weight.

A decrease in the content of triamidophosphite in the reaction mixture resulted in a reduction in the percentage of compound **3** in the reaction products. At a reagent ratio of **1**:**2** = 1:2, the major reaction product was the macrocyclic compound **5** consisting of three phosphorus-containing rings, namely, two eight-membered rings and one 24-membered ring (Scheme 2, ii). Compound **5a** precipitated from the reaction mixture as a complex with two dioxane molecules, and was isolated in a 50% yield.[‡] We could not isolate pure **5b** even by preparative column or thin-layer chromatography. The elemental analysis and the molecular weight of **5a** determined by the MALDI method corresponded with calculated values. The ^{31}P NMR spectrum of **5a** contained two pairs of singlets with very close chemical shifts and of equal intensities. Its ^1H NMR spectrum displayed four doublets for the methyl protons of the phosphamide groups, four H^8 singlets, and doubled signals for the other aromatic protons and methylene bridge protons. A similar situation was observed in

[†] Compound **4a**. A solution of **1** (0.09 g, 0.27 mmol) and **2a** (0.27 g, 1.62 mmol) in dioxane (4 ml) was maintained at 20 °C for 48 h. Dioxane and excess **2a** were removed under vacuum. The residue was dissolved in a solvent mixture (benzene/chloroform = 1:1, 2 ml), and sulfur (0.025 g, 0.81 mmol) was added. The reaction mixture was stirred for 3 h at 20 °C. The solvents were evaporated under vacuum. The reaction product was isolated by column chromatography (silica gel, benzene/dioxane = 5:1, R_f = 0.61). Compound **4a** (0.076 g, 38%) is a yellow film. Mp 137–138 °C. ^{31}P NMR (32.4 MHz, $CDCl_3$): δ 69.57 (s, 1P), 80.91 (s, 2P). ^1H NMR (200 MHz, C_6D_6): δ 2.39 (d, $^3J_{HP}$ = 12.1 Hz, 12H, N–CH_3), 2.50 (d, $^3J_{HP}$ = 12.4 Hz, 12H, N–CH_3), 2.64 (d, $^3J_{HP}$ = 13.2 Hz, 6H, N–CH_3), 4.89 (d, $^2J_{HH}$ = 16.1 Hz, 1H, CH_2), 5.12 (d, $^2J_{HH}$ = 16.1 Hz, 1H, CH_2), 7.00 (d, $^3J_{HH}$ = 9.1 Hz, 2H, H^4 or H^5), 7.30 (d, $^3J_{HH}$ = 9.1 Hz, 2H, H^3 or H^6), 7.44 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^4 or H^5), 7.52 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H^3 or H^6), 8.07 (s, 2H, H^8). Anal. Calcd for $C_{31}H_{42}N_5O_4P_3S_3$: C, 50.46%; H, 5.74%; N, 9.49%, P, 12.59%. Found: C, 50.22%; H, 5.35%; N, 9.40%, P, 12.75%. Compound **4b**. A solution of **1** (0.24 g, 0.73 mmol) and **2b** (0.71 g, 2.9 mmol) in dioxane (4 ml) was heated at 80–85 °C for 27 h. Then, a solution of sulfur (0.27 mg, 8.7 mmol) in benzene (1 ml) was added, and the reaction mixture was stirred for 3 h at 60 °C. After cooling, hexane (4 ml) was added; the resulting precipitate of hexaethyltriamidothionophosphate was filtered off, and the solvents were evaporated under vacuum. The product was isolated by column chromatography (benzene/dioxane = 5:2, silica gel, R_f = 0.68). Compound **4b** (0.21 g, 32%) is a yellow film. Mp 77–78 °C. ^{31}P NMR (32.4 MHz, $CDCl_3$): δ 67.29 (s, 1P), 76.64 (s, 2P). ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, $^3J_{HH}$ = 7.3 Hz, 12H, N–CH_2–CH_3), 1.13 (t, $^3J_{HH}$ = 7.0 Hz, 12H, N–CH_2–CH_3), 1.26 (t, $^3J_{HH}$ = 6.9 Hz, 6H, N–CH_2–CH_3), 3.02–3.21 (m, $^3J_{HP}$ = 13.9 and 12.4 Hz, 16H, N–CH_2–CH_3), 3.36 (m, $^3J_{HP}$ = 14.6 Hz, 4H, N–CH_2–CH_3), 4.85 (s, 2H, CH_2), 7.12 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^4 or H^5), 7.40 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^4 or H^5), 7.72 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 7.80 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 7.83 (s, 1H, H^8). MALDI-TOF-MS *m*/*z*: 878 [M^+]. Anal. Calcd for $C_{41}H_{62}N_5O_4P_3S_3$: C, 56.08%; H, 7.12%; N, 7.98%, P, 10.58%. Found: C, 56.28%; H, 7.15%; N, 7.74%, P, 10.40%.

[‡] Macrocycle **5a**. A solution of **1** (0.31 g, 0.93 mmol) and **2a** (0.31 g, 1.86 mmol) in dioxane (2 ml) was maintained at 20 °C for 48 h. The resulting precipitate was filtered off, washed with dioxane, and dried under vacuum (1 mmHg, 110–115 °C). Compound **5a** (0.24 g, 54%) is a white powder. Mp 298–300 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 138.17 (s, 1P), 138.2 (s, 1P), 139.60 (s, 1P), 139.95 (s, 1P). ^1H NMR (300.1 MHz, $CDCl_3$): δ 2.43 (d, $^3J_{HP}$ = 6.1 Hz, 6H, N–CH_3), 2.78 (d, $^3J_{HP}$ = 9.2 Hz, 6H, N–CH_3), 2.82 (d, $^3J_{HP}$ = 9.8 Hz, 6H, N–CH_3), 2.83 (d, $^3J_{HP}$ = 9.9 Hz, 6H, N–CH_3), 4.51 (dd, $^2J_{HH}$ = 16.2 Hz, $^5J_{HP}$ = 4.0 Hz, 1H, CH_2), 4.55 (dd, $^2J_{HH}$ = 15.9 Hz, $^5J_{HP}$ = 3.4 Hz, 1H, CH_2), 4.89 (d, $^2J_{HH}$ = 16.4 Hz, 1H, CH_2), 4.91 (d, $^2J_{HH}$ = 15.9 Hz, 1H, CH_2), 7.05 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^4 or H^5), 7.10 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^4 or H^5), 7.13 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H^4 or H^5), 7.18 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H^4 or H^5), 7.57 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 7.62 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 7.64 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 7.71 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HP}$ = 2.4 Hz, 2H, H^3 or H^6), 7.79 (s, 1H, H^8), 7.84 (s, 1H, H^8), 7.85 (s, 1H, H^8), 7.90 (s, 1H, H^8). MALDI-TOF-MS *m*/*z*: 958 [M^+]. Anal. Calcd for $C_{50}H_{48}N_4O_8P_4{\cdot}2C_4H_8O_2$: C, 60.48%; H, 6.16%; N, 4.28%. Found: C, 60.00%; H, 6.05%; N, 4.43%.



Scheme 2. Reactions resulting in the formation of phosphocyclic derivatives of 2,2′,7,7′-tetrahydroxydinaphthylmethane **1**.

the NMR spectra of thione derivative **6** obtained by addition of sulfur to **5a**.[§]

To study the potential of compounds **3** as phosphorylating agents in the design of complex polyphosphocyclic systems, we introduced **3a** into the reaction with resorcinarene **7** (Scheme 2, iii). The reaction was carried out in dioxane at 70 °C and was monitored by ^{31}P NMR spectroscopy. A decrease in the signal intensity of diamidophosphite fragments (δ_P 135.4 ppm) was observed during the reaction, as well as the appearance of signals in the region (δ_P 140 ppm) typical for phosphocyclic derivatives. The process was considered complete when the signals of the diamidophosphite fragments completely disappeared from the spectra of the reaction mixture. Analysis of the precipitate resulting from the reaction showed that its physicochemical parameters completely coincided with those of the dimer **5a**.[‡] Oligomeric compounds with higher molecular weights were found in the filtrate, and could not be separated. Thus, the resorcinarene **7** acts in this process as a catalyst for the oligomerization of monophosphocyclic compound **3a** resulting in the formation of polyphosphocyclic systems.

Acknowledgements

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References and notes

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[§] Macrocycle **6**. A suspension of **5a** (0.245 g, 0.26 mmol) and sulfur (0.032 g, 1.02 mmol) in 2 ml of mixed solvent (benzene/chloroform = 1:1) was stirred for 4 h at 70 °C. The resulting precipitate was filtered off, washed with benzene, and dried under vacuum (1 mmHg, 110–115 °C). Compound **6** (0.18 g, 63%) is a white powder. Mp 240–241 °C. ^{31}P NMR (32.4 MHz, $CDCl_3$): δ 69.91 (s, 1P), 68.34 (s, 1P). ^1H NMR (200 MHz, $CDCl_3$): δ 2.75 (d, $^3J_{HP}$ = 11,6 Hz, 6H, N–CH_3), 2.78 (d, $^3J_{HP}$ = 11.6 Hz, 6H, N–CH_3), 2.98 (d, $^3J_{HP}$ = 13.2 Hz, 6H, N–CH_3), 3.00 (d, $^3J_{HP}$ = 13.2 Hz, 6H, N–CH_3), 4.94 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 7.16 (d, $^3J_{HH}$ = 8.6 Hz, 2H, H^4 or H^5), 7.21 (d, $^3J_{HH}$ = 7.8 Hz, 2H, H^4 or H^5), 7.30 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^4 or H^5), 7.43 (d, $^3J_{HH}$ = 9.5 Hz, 2H, H^4 or H^5), 7.65 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 7.74 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H^3 or H^6), 7.78 (d, $^3J_{HH}$ = 9.5 Hz, 2H, H^3 or H^6), 7.82 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H^3 or H^6), 8.02 (s, 1H, H^8), 8.11 (s, 1H, H^8), 8.20 (s, 1H, H^8), 8.28 (s, 1H, H^8). Anal. Calcd for $C_{50}H_{48}N_4O_8P_4S_4$: C, 55.34%; H, 4.46%; N, 5.16%. Found: C, 55.23%; H, 4.59%; N, 5.48%.