Synthesis and Properties of Morpholyl Substituted Naphthophosphacyclophanes

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Phosphorylation of dihydroxynaphthalenes with trimorpholylphosphite has been studied. The peculiarities of behavior and chemical activity of acyclic and “homogeneous” cyclic systems are considered. The oxidation reactions of the phosphorus center and the substitution of the morpholine fragment are carried out.

Keywords: Dihydroxynaphthalenes, naphthophosphacyclophanes, morpholine, phosphorylation, substitution reactions.

Introduction

Chemistry of macrocyclic compounds is an actual and demanded field of science. The use of naphthalene fragments as building blocks for macrocycles is widely used in synthetic practice,[1] since naphthalene derivatives are used in the synthesis of polymers, fluorescent dyes, and drugs.[2]

Introduction of the phosphorus center containing the morpholine substituent into the molecule of the macrocycle significantly expands the range of functional possibilities of the cavity system. Morpholine and its derivatives are widely used in various branches of modern science and technology: for corrosion control, synthesis of antibiotics and enamines, plasticizers for synthetic rubbers, etc.[3]

In recent years, morpholine-modified oligonucleotides – the so called “morpholino” gained wide application to control gene expression. These molecules are synthetic DNA analogues containing morpholine rings and phosphorus-diamide bonds, were first synthesized in 1997.[4] Antisense oligomeric morpholines are used to block the access of other molecules to specific sequences of nucleic acids; they block small single-chain areas on the surface of RNA molecules. Gene expression can be therefore switched off, which is used to study the function of specific proteins, to create pharmacological drugs for the treatment of bacterial and viral diseases, and to reduce the intensity of genetic disorders.[5]
Results and Discussion

Dihydroxynaphthalenes 1–3 with remote hydroxy-groups were used as phosphorylation objects: they have shown high activity in the processes of cyclophosphorylation by full amides of phosphoric acid, these reactions were characterized by the best reaction times and yields of products in comparison with other diatomic phenols. In the present work trimorpholylphosphite (TMP) was used as a phosphorylating reagent.

Synthesis of naphthophosphacyclophanes 8–10 was performed using either the method of molecular assembly, or direct synthesis (Scheme 1). Bisphosphorylation time varied from 5.5 h for asymmetrical 1,6-dihydroxynaphthalene 1 to 4.5 h for symmetrical dihydroxynaphthalenes 2 and 3. The reaction course was controlled by $^3$P NMR method – by disappearance of TMP signal ($\delta_P = 115.3$ ppm) and accumulation of acyclic diamidophosphite 5–7 signal ($\delta_P = 126–129$ ppm).

According to the $^3$P NMR spectroscopy, there was no significant difference in the rate of phosphorylation of $\alpha$- and $\beta$-hydroxy groups of asymmetric 1,6-dihydroxynaphthalene by TMP, as well as in the 1,3-dihydroxynaphthalene studied earlier.

Dismutation of bisphosphorylated derivatives 5–7 took a fairly long time – about 1 month when acetonitrile and methylene chloride were used as solvents. This observation is comparable to the same results for piperidyl derivatives. In dioxane, benzene and diethyl ether, there was virtually no dissimulation.

The second stage of molecular assembly (Scheme 1), as in the case of other full amides, was comparable in time with the cyclization process in the direct synthesis method, i.e., at the ratio of initial reagents (1–3):4 = 1:1. In this case, these processes proceeded for 2 days. Naphthophosphacyclophanes 8–10 were isolated from the acetonitrile solution in the form of viscous oils and did not solidify even after long drying in vacuum. The peculiarity of cycloamidophosphites 8–10 in comparison with other similar systems was the decrease of solubility after drying.

In $^1$H NMR spectra of naphthophosphacyclophanes 8–10, there were signals from all proton groups with respective ratios of integral intensities. The signals of morpholine fragments in all cases were broadened, and in the aromatic part the broadening was observed only in the case of derivative 10. In $^1$H NMR spectra of derivatives 8 and 9, unlike derivative 10, in addition to the signals of the target product there were signals of morpholine, which was produced in the process of phosphorylation and could not be removed even in the process of vacuum drying and heating. The latter fact was noted earlier, it was explained by the formation of stable complexes of naphthalene fragments with amines.

Noteworthy, asymmetrical 1,6-dihydroxynaphthalene 1 in principle can from two isomeric cyclophanes with different sequence of $\text{P}−\text{O}$ bonds, namely (1,1′:6,6′) and (1,6′:1,6′)-isomers (Figure 1). According to the obtained physical-chemical data (one singlet in $^3$P NMR spectrum and one set of signals in the $^1$H and $^{13}$C NMR spectra), the reactions given in Scheme 1 produce (1,6′:1,6′)-cyclophane 8 as a sole isomer.

Its formation was also confirmed by T1-thermochemical calculations in SPARTAN’14 package (www.wavefun.com). This recipe reproduces heats of formation obtained from the highly accurate but time-consuming G3(MP2) model, which in turn closely reproduces experimental heats. T1 recipe was designed to deal with conformationally flexible molecules and it affords 2–3 orders of magnitude less computation time in comparison with G3(MP2). Due to these benefits this method was widely used previously for prediction and interpretation of reactivity of various organic compounds. Herein, application of T1 to isomers of cyclophane 8 based on asymmetric naphthalene units suggest that the isomer (1,6′:1,6′) is by 15 kJ/mol more stable than its (1,1′:6,6′) counterpart. Conformational analysis sug-

![Scheme 1](image-url)
gests notable overlap between the stacked naphthalene rings in this cyclophane (Figure 2).

Oxidation of the phosphorus atom was carried out in CH₂Cl₂ at room temperature by adding sulphur or urea peroxide (Scheme 2), and it took about 2 days. The formation of thionamidophosphates 11–13 was detected in the solution by ³¹P NMR method (δₓ = 64–65 ppm), but it was not possible to isolate the obtained compounds in their pure form: they underwent complete degradation during chromatographic isolation.

Amidophosphates 14–16 were isolated by the precipitation method as oil-like substances well soluble in chlorinated solvents.

Transamidification of the phosphorus atom with the preservation of the macrocyclic structure is not always possible and it is often accompanied by ring-opening reaction. However, in the studied systems, the morpholine fragments could be substituted using diethylamine (pKₐ = 8.3) which is more basic in comparison with morpholine (pKₐ = 11.1). The proceeded in dioxane upon heating to 75 °C. After sulfurisation of the reaction mass products 17–19 were isolated column chromatography, which were analogous in their physical and chemical characteristics to those obtained earlier.

Thus, as a result of the work done, naphthophosphacyclophanes with morpholine substituents at phosphorus atoms were obtained and their physicochemical properties were studied. The synthesized compounds are supposed to be tested for biological activity.

**Experimental**

All syntheses were conducted in dry solvents under an argon atmosphere. ¹H, ¹³C and ³¹P NMR spectra were recorded on a JEOL ECX-400 spectrometer operating at 400, 100.5 and 161.8 MHz respectively; chemical shifts (δ, ppm) were referenced to TMS (¹H and ¹³C) or to 85 % H₃PO₄ (³¹P). Spin-spin coupling constants (J) are given in hertz (Hz). Mass spectra were measured on a Bruker Ultraflex MALDI-TOF spectrometer using a nitrogen laser (λ = 337 nm) and trihydroxyanthracene as a matrix. TLC was performed on Silufol plates (UV-254) using benzene:dioxane (5:1). Detection was achieved using iodine vapor treatment and calcination.

Trimorpholylphosphite 4 were synthesized by the previously reported method. 3,7-Dimorpholinol-1,5-dinaphthalina-2,4,6,8-tetraoxa-3,7-diphosphacylooctaphane. General procedure of molecular...
using. A solution containing 0.145 g (0.5 mmol) of TMP 4 in 3 ml of benzene was mixed with solution of 0.04 g (0.25 mmol) of dihydronaphthalenes 1−3 in 3 ml of acetonitrile, at room temperature and continuous stirring. After 30 min, all solvent was completely removed in vacuum (12 mmHg), the reaction mass was dissolved in 5 ml of acetonitrile, and the resulting solution was stirred for another 5 h. Then, another 0.04 g (0.25 mmol) of dihydronaphthalenes 1−3 in 2 ml of acetonitrile was introduced into the reaction mixture, stirred for 2 h, and left for 2 days. The remaining oil precipitated was washed twice with acetonitrile and dried in vacuum for 2 h (1 mmHg, 60 °C).

General procedure of direct synthesis. A solution containing 0.145 g (0.5 mmol) of TMP 4 in 3 ml of benzene was mixed with solution of 0.08 g (0.5 mmol) of dihydroxynaphthalenes 1−3 in 3 ml of acetonitrile, at room temperature and continuous stirring. After 30 min, all solvent was completely removed in vacuum (12 mmHg), the reaction mass was dissolved in 5 ml of acetonitrile, and the resulting solution was stirred for another 5 h and left for 2 days. The remaining oil precipitated was washed twice with acetonitrile and dried in vacuum for 2 h (1 mmHg, 60 °C).

3,7-Diphosphacyclooctaphane (8): Yield: 0.159 g (58 %). Oil substance. 1H NMR (d-DMSO) δ ppm: 3.32 (8H, brd, CH2−N), 3.63 (8H, brd, CH2−O), 7.06−8.11 (12H, brm, CH). 13C NMR (d-DMSO) δ ppm: 43.8 (d, 2JCH = 8.7), 7.45 (4H, s, CH2−N), 7.68 (4H, d, CH3−O), 8.70 (4H, d, CH2−O). 13P NMR (CH3Cl) δ ppm: 136.9. Found: C, 61.0; H, 5.13; N, 5.09 %.

3,7-Dimorpholino-1,5(2,7)-dinaphthalina-2,4,6,8-tetraoxa-3,7-diphosphacyclooctaphane (8). Yield: 0.168 g (61 %). Oil substance. 1H NMR (d-DMSO) δ ppm: 3.36 (8H, brd, CH2−N, 1JCH = 5.5, 6.0), 3.65 (8H, brd, CH2−O), 7.24 (4H, d, CH3−O), 7.45 (4H, s, CH2−N), 7.68 (4H, d, CH3−O), 8.70 (4H, d, CH2−O). 13P NMR (CH3Cl) δ ppm: 136.6. Calculated: C, 60.61; H, 5.13; N, 5.09 %.

3,7-Dimorpholino-1,5(2,7)-dinaphthalina-2,4,6,8-tetraoxa-3,7-diphosphacyclooctaphane (9). Yield: 0.182 g (66 %). Oil substance. 1H NMR (d-DMSO) δ ppm: 3.34 (8H, brm, CH2−N, 1JCH = 6.1, 6.9), 3.69 (8H, brd, CH2−O), 7.18 (4H, d, CH3−O), 7.37 (4H, s, CH2−N), 7.80 (4H, d, CH2−O). 13P NMR (CH3Cl) δ ppm: 136.6. Calculated: C, 60.61; H, 5.13; N, 5.09 %.

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