[1]Rotaxanes based on phosphorylated pillar[5]arenes

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[1]Rotaxanes based on monosubstituted phosphorus-containing pillar[5]arenes have been synthesized for the first time by the Kabachnik-Fields reaction with good yields. The introduction of bulky phosphoryl function stopper led to formation of the [1]rotaxane core. Structures and compositions of the synthesized compounds were fully confirmed by one- and two-dimensional ^{1}H, ^{13}C, ^{1}H-^{1}H NOESY NMR spectroscopy, IR spectroscopy, mass spectrometry and elemental analysis. It was found that the [1]rotaxanes were robust and unaffected by changes in temperature or solvent.

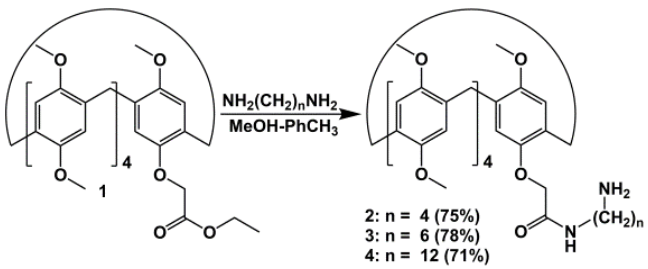
In recent years, supramolecular chemistry has focused on systems capable of self-organization [1]. This process makes it possible to create molecular machines, catalysts, biomimetic systems and effective and selective synthetic receptors [2]. The synthesis of supramolecular assemblies occurs due to various non-covalent interactions (Van der Waals forces, hydrogen and halogen bonding, hydrophobic, π-π / CH-π and Coulombic interactions). Among the variety of supramolecular assemblies, rotaxanes are of particular interest for chemists and nanotechnologists. This is due to the potential use of rotaxanes as molecular switches and machines including "molecular muscles" capable to quasi-mechanical movements aimed at performing useful work [3]. It should be noted that lasso peptides, analogs of rotaxanes, exist in nature. They exhibit antimicrobial activity, anticancer properties and inhibit enzymes [4]. The discovery of natural rotaxane analogs confirms the continued relevance of the study and development of this topic. Today, rotaxanes are described as complexes consisting of cyclic molecules threaded onto linear molecules. Bulky fragments (stoppers) covalently attached to the ends of linear molecules prevent the dissociation of a rotaxane into its constituent parts.

The "host-guest" interaction is one of main considerations in the design of rotaxane and pseudorotaxane structures. With the discovery of pillararenes in 2008, it became possible to create new rotaxanes and pseudorotaxanes with interesting and practically useful properties [5]. This class of macrocycles has many advantages over other macrocycles, such as synthetic accessibility, the ability to introduce both hydrophilic and hydrophobic fragments on both rims and the control of complexation by external stimuli [6]. The relative ease of synthesis and presence of an electron-donor cavity make it possible to create various mechanically blocked molecules based on monosubstituted pillar[5]arenes. The aminoalkylamide derivatives are the most common parent compounds for the creation of rotaxane structures on the pillar[5]arene platform [7]. The terminal primary proton-donating NH group and the nitrogen lone electron pair provide an easy route to introduce bulky stoppers such as ferrocene [7c], terpyridine [7d], 3,5-dimethoxybenzene [7e], triphenylamine [7f, 7g], mono- and di(hydroxyalkoxy) benzoic acid [7h].

Mechanically interlocked molecules, including rotaxanes, open up endless prospects for the creation of molecular machines, as clearly demonstrated by the 2016 Nobel Prize, including those with biomimetic properties [8]. One approache to the creation of such structures is the simultaneous introduction of fragments containing carbon, oxygen, nitrogen and phosphorus atoms. This work presents the preparation of pillar[5]arenes containing an aminophosphonate fragment, which served as a prototype for the creation of oligophosphates. Stoppering by phosphorus-containing fragments of pillar[5]arenes containing the *N*-(aminoalkyl)amide substituent was carried out by the Kabachnik-Fields reaction. The possibility of using an aminophosphonate fragment as stopper for the preparation of [1]rotaxanes on monosubstituted pillar[5]arenes is reported for the first time.

The five most common ways to obtain rotaxanes are: stoppering (I), snapping (II), clipping (III), slipping (IV) and the active metal template approach (V) [9]. Method (I) is most often used for the synthesis of pillar[5]arene [1]rotaxanes. In this regard, we have chosen this method to obtain [1]rotaxanes from the monosubstituted phosphorus-containing pillar[5]arene platform. Monosubstituted pillar[5]arenes containing alkylamide fragment were earlier synthesized and studied in our research group [10]. The synthesized compounds are prone to the formation of self-inclusion complexes. It was found that four methylene fragments of the alkyl substituent are located in the macrocyclic cavity of the pillar[5]arene regardless of the substituent's length. The next stage of the investigation involved preparation of the monosubstituted pillar[5]arenes containing *N*-(aminoalkyl)amide group from which to prepare [1]rotaxanes.

Monosubstituted pillar[5]arene **1**, containing an ester fragment, was synthesized according to the literature [11]. Compound **1** was reacted with 1,4-diaminobutane, 1,6-diaminohexane and 1,12-diaminododecane. Analysis of the literature [12] showed that aminolysis of the monosubstituted pillar[5]arene derivatives occurs in polar solvents with a large excess of the amine. However, the use of a large excess of amine seems inconvenient as it reduces the yield of target products. Thus, the reaction was carried out in methanol with a threefold excess of amine. Unfortunately, these conditions proved unsuitable for the synthesis of (aminoalkyl)amides based on pillar[5]arene. Methanol was replaced by the methanol-toluene solvent mixture whereupon target compounds **2**-**4** were obtained in 71-78% yields (Scheme 1).



Scheme 1. Synthetic route for the preparation of pillar[5]arenes **2-4**.

There are significant upfield shifts (-1.99 and -1.80 ppm respectively) of the methylene proton (H^6 and H^7) signals of the

alkyl fragment of **3** in the ^{1}H NMR spectrum. This fact unambiguously indicates inclusion of the alkyl substituent in the pillar[5]arene cavity (Fig. 1).

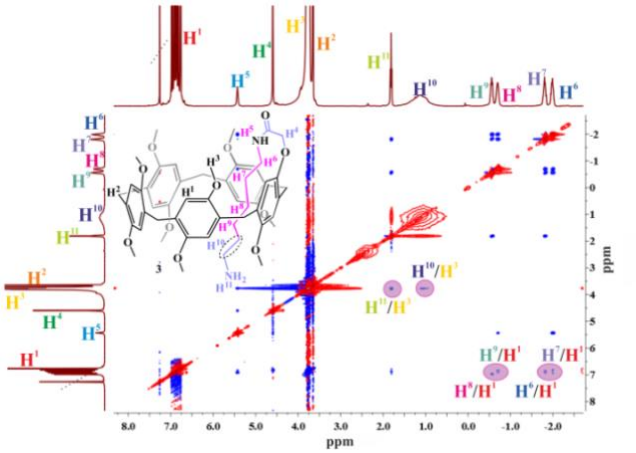


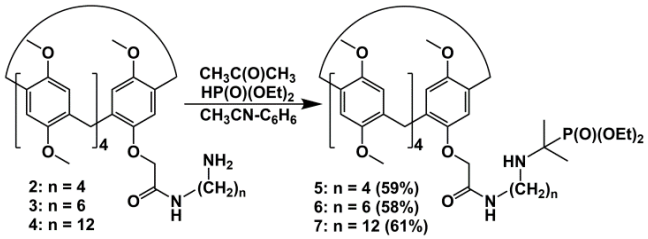
Fig. 1. 2D ^{1}H–^{1}H NOESY NMR spectrum of the compound **3** ($CDCl_3$, 298 K, 400 MHz).

The interactions between the methylene groups of (6'-amino)hexamethyleneamide fragment were established by 1D and 2D NMR spectroscopy (Fig. 1). The proton signals of the amide group served as the reference point to establish the relative position of methylene protons by analogy with our previous work [9]. The signal of amide proton (H^5) resonated as a broadened triplet at 5.43 ppm.

It was found by ^{1}H and ^{1}H-^{1}H NOESY NMR spectroscopy that the (6'-amino)hexamethyleneamide fragment was included in the macrocyclic cavity up to the 4th carbon atom while the amino group remained outside the macrocyclic cavity. The same behavior was observed for the compounds **2** and **4**. Upfield shifts of the methylene protons from the alkyl fragments in the ^{1}H NMR spectra indicatedthe inclusion of (4'-amino)tetramethyleneamide (**2**) and (12'-amino)dodecamethyleneamide (**4**) fragments were included in an identical manner. It should also be noted that the replacement of $CDCl_3$ by DMSO-d_6 did not lead to changes in the chemical shifts of the methylene proton signals for **2**-**4** (Fig. S2, S4, S6). Thus, it can be asserted on the basis of the 1D and 2D NMR spectra recorded in two solvents differing in their solvating ability ($CDCl_3$ and DMSO-d_6) that the alkyl substituents are self-included into the macrocycle cavity.

Earlier, Wang *et al.* [13] showed the formation of an intramolecular hydrogen bond NH···OCH_2 and inclusion of an alkylamide fragment into the macrocyclic cavity by X-ray diffraction for compounds with a similar structure. Self-inclusion of the *N*-(aminoalkyl)amide fragments into the macrocyclic cavity in the case of pillar[5]arenes **2**-**4** is also confirmed by IR spectroscopy data. There is a narrow intense band at 3400 cm^{-1} indicating the formation of a strong hydrogen bond between the NH-protons and oxygen of methoxyl fragment (Fig. S28-S30) leading to the formation of stable self-inclusion complexes by *N*-(aminoalkyl)amide substituents. It also was found by analogy with our previous work [10] that macrocycles **2**-**4** tend to form supramolecular polymers in chloroform and the formation of nanosized particles in DMSO despite the formation of self-inclusion complexes.

Introduction of phosphonate fragments into macrocycles **2**-**4** to stopper the [1]rotaxanes was the final stage. The Kabachnik-Fields reaction with **2**-**4** was studied for this purpose (Scheme 2).



Scheme 2. Synthetic route for the preparation of pillar[5]arenes **5**-**7**.

Optimization of the reaction conditions was carried out using the pillar[5]arene **2**, acetone, and diethyl phosphite in a mixture of benzene-acetonitrile in a 1:1 ratio. Its progress was monitored by ^{31}P NMR spectroscopy (Fig. 2b, 2c).

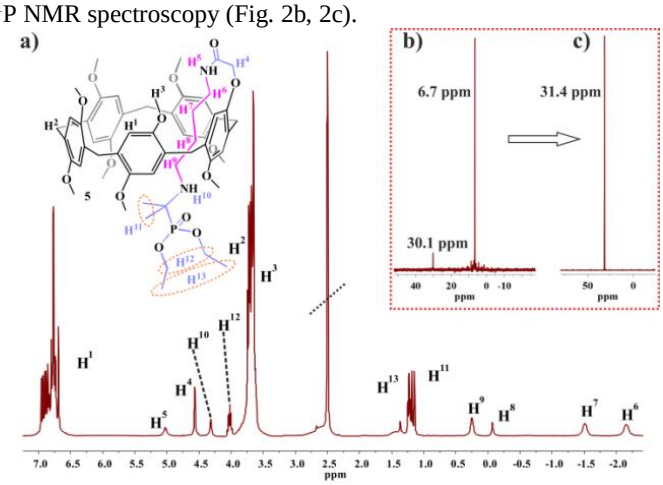


Fig. 2. a) ^{1}H NMR spectrum of **5** (DMSO-d_6, 298 K, 400 MHz); b) ^{31}P{^{1}H} NMR spectrum of the reaction mixture during the synthesis of **5** (298 K, 162 MHz); c) ^{31}P{^{1}H} NMR spectrum of **5** (DMSO-d_6, 298 K, 162 MHz).

A signal with a chemical shift of 30.1 ppm, in addition to that of the starting diethyl phosphite at 6.7 ppm, was observed in the ^{31}P{^{1}H} NMR spectrum of the reaction mixture recorded after 10 hours of reflux.

Target compound **5** was isolated in a yield of 59%. Its ^{31}P{^{1}H} NMR spectrum showed a single signal with δ_P at 31.4 ppm (Fig. 2c). Its ^{1}H NMR spectrum confirmed the proposed structure of target compound **5** (Fig. 2a). The signals of aromatic protons as well as of the amide proton (H^5) were observed as a multiplets from 6.69 ppm to 6.96 ppm and in the 5.02 ppm region, respectively. The proton signals of the oxymethylene fragment (H^4) appeared as a singlet at 4.57 ppm. The signals of the amino group (H^{10}) protons, oxymethylene protons (H^{12}) of the ethoxyl group at the phosphorus atom were observed as multiplets at 4.32 ppm and 4.02 ppm, respectively. The proton signals of the methylene group of amide substituent resonated as multiplets at -2.16, -1.51, -0.07 and 0.25 ppm. The signals of the H^{11} methyl protons formed a doublet at 1.16 ppm ($^3J_{PH}$ = 15.6 Hz), and the methyl protons of the ethoxyl group at the phosphorus atom appeared as a triplet at 1.23 ppm ($^3J_{HH}$ = 7.0 Hz).

Chemical shifts (-2.16, -1.51, -0.07 and 0.25 ppm) of H^6-H^9 proton signals in the upfield indicated that the tetramethylene fragment was shielded by the aromatic groups of pillar[5]arene **5** and that the substituent remained included in the macrocyclic cavity throughout the reaction. Moreover, we have previously established [14] that a bulky phosphonate fragment was not incorporated into the macrocyclic cavity of the pillar[5]arene.

Therefore, it can be affirmed that the introduction of the phosphonate fragment into the structure of the aminoamide **2** does not lead displace the (4'-amino)tetramethyleneamide fragment from the macrocyclic cavity but promotes the formation of a [1]rotaxane based on monosubstituted pillar[5]arene (Fig. 3). The same formation of [1]rotaxanes was observed for the macrocycles **6** and **7**.

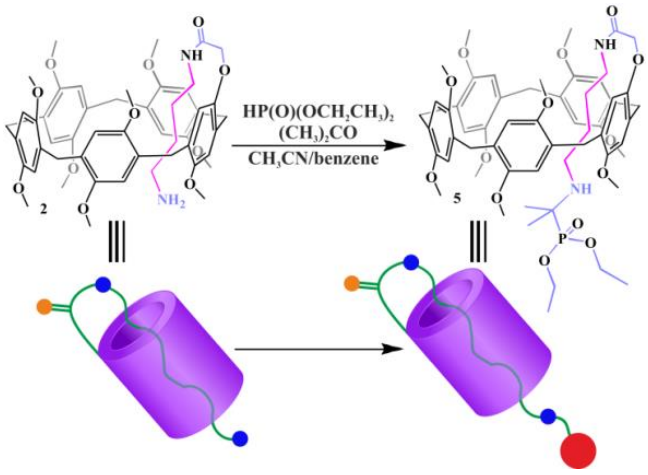


Fig. 3. Schematic representation of [1]rotaxane formation in the synthesis of compound **5**.

The formation of pseudo[1]rotaxanes **2-4** and [1]rotaxanes **5-7** was investigated by DFT using the EDF2 functional which has been shown to be appropriate for systems involving hydrogen bonding [15]. The results corroborate the ^{1}H NMR data as all hydrogen atoms exhibiting upfield shifts (H^{6}-H^{9}) are predicted to lie within the macrocyclic cavity and those unaffected (e.g. H^{4}, H^{5}, H^{10} and H^{11}) are outside the cavity as shown in Fig. 4 and Fig. S43 (ESI†).

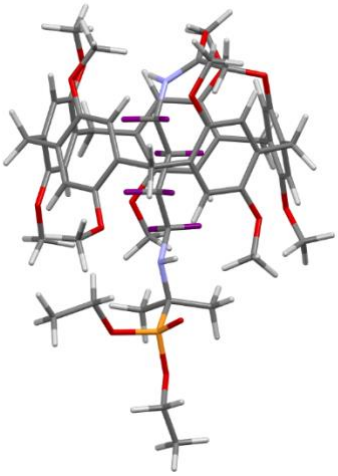


Fig. 4. Computer model of [1]rotaxane **5** (shielded protons shown in purple).

Macrocycles **5-7** were also investigated by variable temperature ^{1}H NMR measurements in DMSO at 298 K and 353 K. Thus, it was shown that there were no significant changes in the ^{1}H NMR spectrum of the compound **6** (Fig. S40). This confirmed the formation of the [1]rotaxanes and suggests that strong hydrogen bonds between NH-protons and oxygen of methoxyl fragment played a key role in the [1]rotaxane formation.

In summary, novel monosubstituted pillar[5]arenes containing *N*-(aminoalkyl)amide and 1-aminophosphonate fragments were synthesized. Phosphoryl group stoppers were used for the first time in the synthesis of pillar[5]arene-based [1]rotaxanes containing *N*-(aminoalkyl)amide fragments. The formation of stable [1]rotaxanes is possible due to the presence of a strong hydrogen bond between the NH-protons and the oxygen of methoxyl fragment. The synthetic developed is based on the tendency of *N*-(aminoalkyl)amide moieties to form self-inclusion complexes with pillar[5]arenes and on the use of the phosphoryl group as a stopper. This opens up the opportunity to create new molecular machines.

Author contributions

Conceptualization, writing—review and editing, and supervi- sion, I. S.; investigation, writing—original draft and visualiza- tion, A. N.; formal analysis, data curation and supervision P. P.; software, P. J. C. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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