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Stereoselective synthesis of the $R_PS_PS_PR_P$ isomer of 22-membered P_4N_2 macrocycles

Elvira I. Musina,*[a] Tatiana I. Wittmann,[a] Alena S. Shpagina,[a] Andrey A. Karasik,[a] Peter Lönnecke[b] and Evamarie Hey-Hawkins[b]

[a] *A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 843 273 9365; e-mail: elli@iopc.ru*

[b] *Faculty of Chemistry and Mineralogy, Institute of Inorganic Chemistry, Leipzig University, D-04103 Leipzig, Germany*

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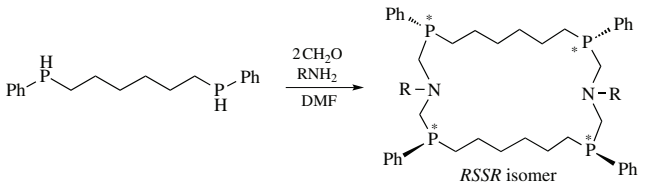
Stereoselective synthesis of the first representatives of 1,12-diaza-3,10,14,21-tetraphosphacyclodocosanes was achieved *via* the Mannich-type condensation of 1,6-bis-(phenylphosphino)hexane, formaldehyde and primary amines. Due to covalent self-assembly, individual $R_PS_PS_PR_P$ isomer was isolated from a dynamic system containing all possible stereoisomers and a number of by-products.



Keywords: dynamic covalent chemistry, self-assembly, macrocycles, tetrakis-phosphines, 1,12-diaza-3,10,14,21-tetraphosphacyclodocosanes, Mannich-type condensation, stereoselectivity.

Convenient syntheses of macrocylic oligophosphines are of particular interest due to their potential application in coordination and supramolecular chemistry, as well as in catalysis.[1] The main problem arising in the synthesis of macrocyclic oligophosphines is the formation of stereoisomeric mixtures due to the high inversion barrier of phosphines (137–153 kJ mol^{-1}).[2] Numerous synthetic methodologies have been developed for the rational design of macrocyclic phosphines, namely, high dilution methods, template synthesis and a relatively novel covalent self-assembly of macrocycles.[1–3] The last two approaches solve the problem of stereoselectivity. The stereoselectivity of template synthesis is the result of the preorganization of interacting subunits coordinated at a template (usually a transition metal ion), while the second approach is based on the principles of dynamic covalent chemistry (DCvC) dealing with a sequence of reversible reactions leading to a dynamic system of interconverting products. When a dynamic system reaches equilibrium, the thermodynamically most stable species would predominate[4–7] and can usually be separated by crystallization. The yield of the isolated product often exceeds its percentage in the reaction mixture due to interconversion of dynamic system members.

Condensation reactions are dynamic covalent ones because they result in dynamic covalent bonds. For example, the condensation of bis-aldehydes containing one or two phosphine groups with bis-amines gave 22-membered P_2N_4-macrocycles,[8] and 14- and 15-membered P_2N_2 macrocycles,[9–11] respectively. In these cases, the phosphine groups were included in the starting material and did not participate in the new bond formation. The synthesis of phosphorus macrocycles by self-assembly which is accompanied by P–C bond formation is quite rare. Examples include the synthesis of metacyclophane *via* condensation of isophthaloyl chloride and (methyl)bis(trimethylsilyl)phosphane,[12] and formation of tetrakis-phosphonium macrocycle by the tetramerization of 3-(diphenylphosphino)-propanal under acidic conditions.[13] Recently, we developed the stereoselective synthesis of various macrocyclic aminomethylphosphines, namely $(P_2N_2)_2$-cyclophanes, P_2N_4-cyclophanes, P_4N_2-cryptands and 14-, 16-, 18- and 20-membered P_4N_2-corands[1,14] *via* the Mannich-type condensation of P–H-functionalized phosphines or bis-phosphines, formaldehyde and N–H-functionalized amines or diamines. The covalent self-assembly of P_4N_2-corands ensures the isolation of only one stereoisomer from a dynamic system containing at least five stereoisomers of P_4N_2-corands (Figure 1) and two isomers of P_2N-corands as products of [1+1] condensation.

The 16- and 20-membered macrocycles were usually isolated as $R_PS_PS_PR_P$ isomers,[1,14] while their 14- and 18-membered homologues were predominantly $R_PR_PR_PR_P/S_PS_PS_PS_P$ isomers.[15–17] An empirical rule predicting the preferred configuration of P_4N_2-macrocycles depending on an even or odd number of methylene fragments between the phosphorus atoms was established.[17] However, we recently noticed that an extension of the hydrocarbon chain between the phosphorus atoms of the 18-membered macrocycle resulted in formation of both $R_PS_PS_PR_P$ isomers and $R_PR_PR_PR_P/S_PS_PS_PS_P$ isomers.[18] In order to verify the application of this synthetic approach to larger $[P_4N_2]$ macrocycles and to confirm the validity of the established empirical rule, we herein report the synthesis of first

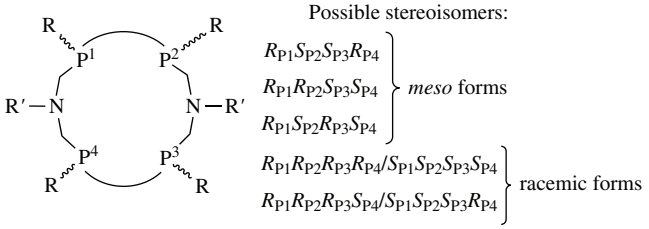
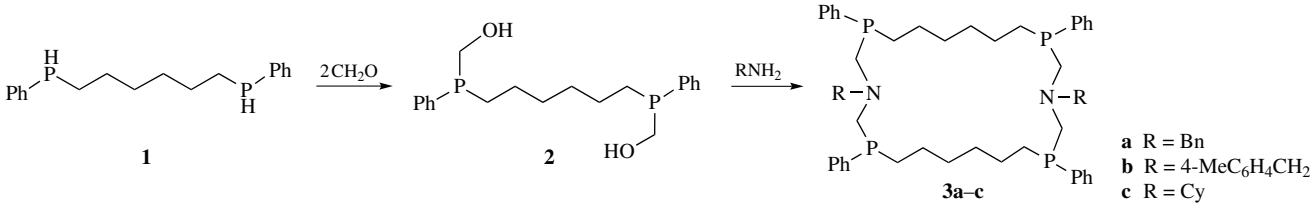


Figure 1 Possible stereoisomers of P_4N_2 corands: three achiral *meso* forms and enantiomeric pairs of two racemic forms.



Scheme 1

representatives of 22-membered macrocyclic (aminomethyl)-phosphines.

The treatment of 1,6-bis(phenylphosphino)hexane **1** with paraformaldehyde gave intermediate 1,6-bis[(hydroxymethyl)-phenyphosphino]hexane **2** as a diastereoisomeric *rac/meso* mixture (Scheme 1). Its further *in situ* condensation with benzyl-, 4-methylbenzyl- or cyclohexylamines in DMF at 80 °C afforded 22-membered 1,12-diaza-3,10,14,21-tetraphospha-cyclodocosanes **3a–c** as $R_PS_PS_PR_P$ isomers in moderate (32–35%) yields.[†]

According to the $^{31}P\{^1H\}$ NMR spectroscopy, the reactions proceed through the formation of a large number of products. The $^{31}P\{^1H\}$ NMR spectra of the final reaction mixtures show several intensive signals, one prevailing, in the range of –30 to –40 ppm, which is typical of macrocyclic (aminomethyl)-phosphines.[15–19] Compounds **3a–c** could be obtained by recrystallization (for details, see Online Supplementary Materials) as air-stable solids easily soluble in chloroform, dichloromethane and benzene. Elemental analysis, mass spectrometry and NMR spectroscopy confirmed the structures of the 22-membered macrocyclic compounds. In the $^{31}P\{^1H\}$ NMR spectra of **3a–c**, one narrow signal at –35.8 to –36.7 ppm is present indicating that only one symmetric diastereoisomer of five possible ones was isolated. In the ^1H NMR spectra, the protons for the $P(CH_2)_6P$ fragment are observed as five multiplets in the ranges of 1.4 to 2.2 ppm, the methylene protons of the PCH_2N fragments as two multiplets [a doublet of doublets at 2.64 to 2.80 ppm ($^2J_{HH}$ = 12.2–12.6 Hz, $^2J_{PH}$ = 11.2–15.0 Hz) and a doublet or a doublet of doublets at 3.57 to 3.83 ppm ($^2J_{HH}$ = 12.2–12.6 Hz, $^2J_{PH}$ = 0–4.7 Hz)]. The patterns indicate similar configurations and conformations of the obtained diastereomers of macrocycles **3a–c** and the previously reported $R_PS_PS_PR_P$ isomer of 14-membered[19] and 18-membered corands.[18] Ultimately, their $R_PS_PS_PR_P$ configuration was established by X-ray study of the representative compound **3a** (Figure 2).[‡]

The molecule is located on a crystallographic center of inversion; accordingly, the lone pairs of electrons at the phosphorus atoms have *syn–anti–syn* orientation and the phenyl substituents on the phosphorus atoms occupy equatorial positions (see Figure 2). The geometry of the 22-membered ring can be described as a parallelogram with long [N(1)···C(8) 10.560(3) Å]

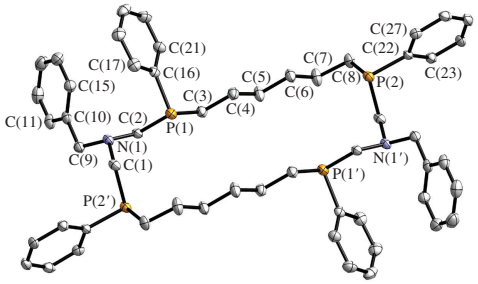


Figure 2 Molecular structure of the $R_PS_PS_PR_P$ isomer of macrocycle **3a**. Hydrogen atoms are omitted for clarity. Displacement ellipsoids are drawn at the 50% probability level.

and short [N(1′)···C(8) 4.172(3) Å] edges. The atoms of the long edge [C(8), C(7), C(6), C(5), C(4), C(3), P(1), C(2), N(1)] lie in one plane and form a *zigzag* chain. The fragments P(1)–C(2)–N(1)–C(1)–P(2′) are twisted, and the lone pairs of electrons of the nitrogen atoms have *anti* orientation. The conformation of the macrocycle is similar to those of the $R_PS_PS_PR_P$ isomers of 14- and 18-membered macrocycles[18,19] and differs mainly in the longer edge of the parallelogram (5.444 Å) whereas the lengths of the short edges are similar (4.159 Å) for 14-membered macrocycles.[19]

In summary, we have successfully employed the main principles of DCvC (reversibility of reaction, dynamic system formation, self-assembly) for the stereoselective synthesis of three 22-membered P_4N_2 macrocycles by the Mannich-type condensation of 1,6-bis(phenylphosphino)hexane, formaldehyde and primary amines. The $R_PS_PS_PR_P$ isomers were isolated instead of expected $R_PR_PR_PR_P/S_PS_PS_PS_P$ ones which were predicted by the 'even/odd' rule for P_4N_2 macrocycles. We assume that increasing the number of methylene fragments in the hydrocarbon chain between the phosphorus atoms in the macrocycle leads to an increase in the number of stable ring conformations. This supposition requires detailed DFT calculations which will be presented in the future.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.002.

[†] *General procedure for the synthesis of macrocycles* **3a–c**. A solution of 1,6-bis[(hydroxymethyl)phenylphosphino]hexane **2** (3 mmol) (obtained *in situ* by heating a mixture of 1,6-bis(phenylphosphino)hexane **1** (3 mmol) and paraformaldehyde (6 mmol) at 100–110 °C until homogenization) and the corresponding primary amine (3 mmol) in DMF (10 ml) was stirred at 80 °C for 24 h. The mixture was cooled and concentrated *in vacuo* up to 1/4 or 1/6 of the initial volume. The residue was crystallized from a 4 : 1 : 4 acetone/benzene/ethanol mixture (for compound **3a**), diethyl ether/benzene (10 : 1) (for compound **3b**), while compound **3c** was crystallized from diethyl ether which was employed for the extraction of the residue. The crystalline precipitate was filtered off, washed with ethanol or diethyl ether and dried for 4–5 h at 0.01 Torr.

[‡] *Crystal data for* **3a**. Crystals of $C_{54}H_{66}N_2P_4{\cdot}O(C_2H_5)_2$ (M = 941.08) are triclinic, space group $P\bar{1}$: a = 5.5934(3), b = 12.5104(9) and c = 19.487(1) Å, α = 90.037(5)°, β = 97.683(4)°, γ = 100.199(5)°, V = 1329.6(1) Å^3, Z = 1, d_{calc} = 1.175 g cm^{-3}, $\mu_{(MoKa)}$ = 0.182 mm^{-1}, $F(000)$ = 506. The data were collected on a CCD Gemini diffractometer (Rigaku Oxford Diffraction) at 130 K, [$\lambda_{(MoK\alpha)}$ = 0.71073 Å] using ω scan mode and semi-empirical absorption corrections from equivalents with SCALE3 ABSPACK.[20] The structure was solved with SHELXT-2018 (dual-space methods).[21(a)] Structure refinement was carried out with SHELXL-2018.[21(b)] All hydrogen atoms could be located with a difference-density Fourier map. Attempts to localize solvent molecules within a reasonable accuracy failed. The electron density of one highly disordered diethyl ether molecule had been removed with the SQUEEZE routine implemented in PLATON.[22] 13834 measured (6126 independent) reflections (R_{int} = 0.0549) were used for the refinement. The final structure parameters are R_1 = 0.0554, wR_2 = 0.1129 [for $I > 2\sigma(I)$] and R_1 = 0.1019, wR_2 = 0.1326 (for all data).

CCDC 2016579 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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