Pergamon

Tetrahedron Letters 43 (2002) 5245–5248

TETRAHEDRON LETTERS

Phosphite macrocycles of varying size

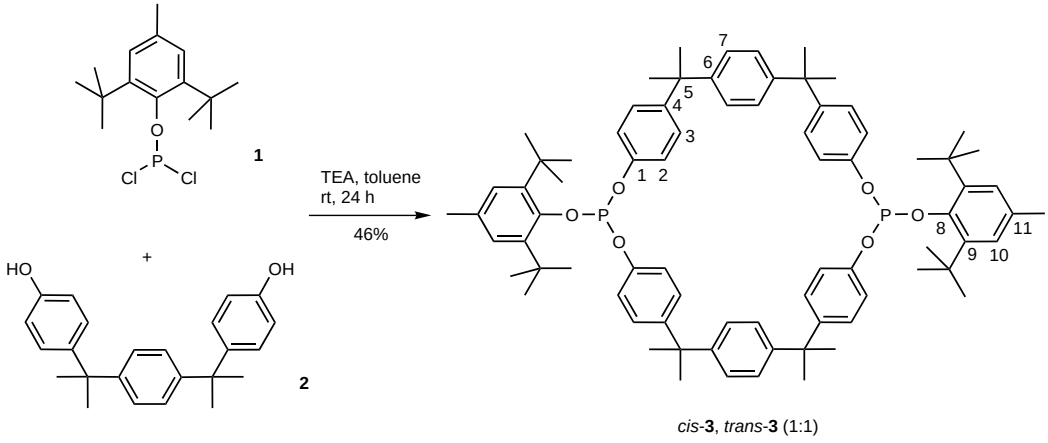
I. Bauer* and W. D. Habicher

Institut für Organische Chemie, Technische Universität Dresden, Mommsenstraße 13, D-01062 Dresden, Germany

Received 31 May 2002; accepted 3 June 2002

Abstract—The condensation reaction of a dichlorophosphite with different bisphenols afforded macrocyclic phosphites of different sizes in dependence on the geometry of the bisphenol applied. A tri-nuclear flexible bisphenol yielded a dimeric macrocycle in moderate yield. Application of a bi-nuclear bisphenol in this reaction resulted in the formation of both dimeric and trimeric macrocycles in almost equal amounts, whereas the linear 1,1′-biphenyl-4,4′-diol led to a tetrameric, square, macrocyclic phosphite. © 2002 Published by Elsevier Science Ltd.

Phosphorus containing macrocycles are attractive molecules with potential applications in supramolecular and synthetic organic chemistry.[1] Cyclocondensation reactions with phosphorous chlorides occupy a large place in the synthesis of such structures. We reported on the [2+2]-cyclocondensation of dichlorophosphites with a bi-nuclear and a tri-nuclear bisphenol.[2] This reaction gives surprisingly good yields especially for the flexible, sterically hindered, tri-nuclear 4,4′-[1,4-phenylenebis(1-methylethylidene)]bis(2,6-dimethylphenol). We were even able to employ this bisphenol in a *double-capping* synthesis of a P-bridgehead macrobicyclic compound showing homeomorphic *in*,*out*-isomerism.[3] Using a non-hindered bisphenol we could isolate all three homeomorphic isomers of a P-cage compound in reasonable yields.[4] The *in*,*out*-P atoms showed a remarkably different reactivity toward cumene hydroperoxide as an oxidizing agent. The cavity of these cryptands encloses solvent molecules like toluene and chloroform. In order to synthesize macrobicyclic phosphorus containing compounds in a more selective and stepwise way we tried to employ the phosphorous amide method[5] for the synthesis of phosphites. It turned out, however that the substitution of the final exocyclic amide group is suppressed in favor of a transesterification of a P–OAr moiety.[6] This was attributed to a ring tension effect even in a macrocyclic system that weakens the intracyclic P–O bond. However, more recently the same phenomenon was also observed for a number of other



Scheme 1. Reaction of bisphenol **2** with dichlorophosphite **1** to form P-macrocycle **3**.

* Corresponding author. Tel.: +49-351-463-32489; fax: +49-351-463-34093; e-mail: ingmar.bauer@chemie.tu-dresden.de

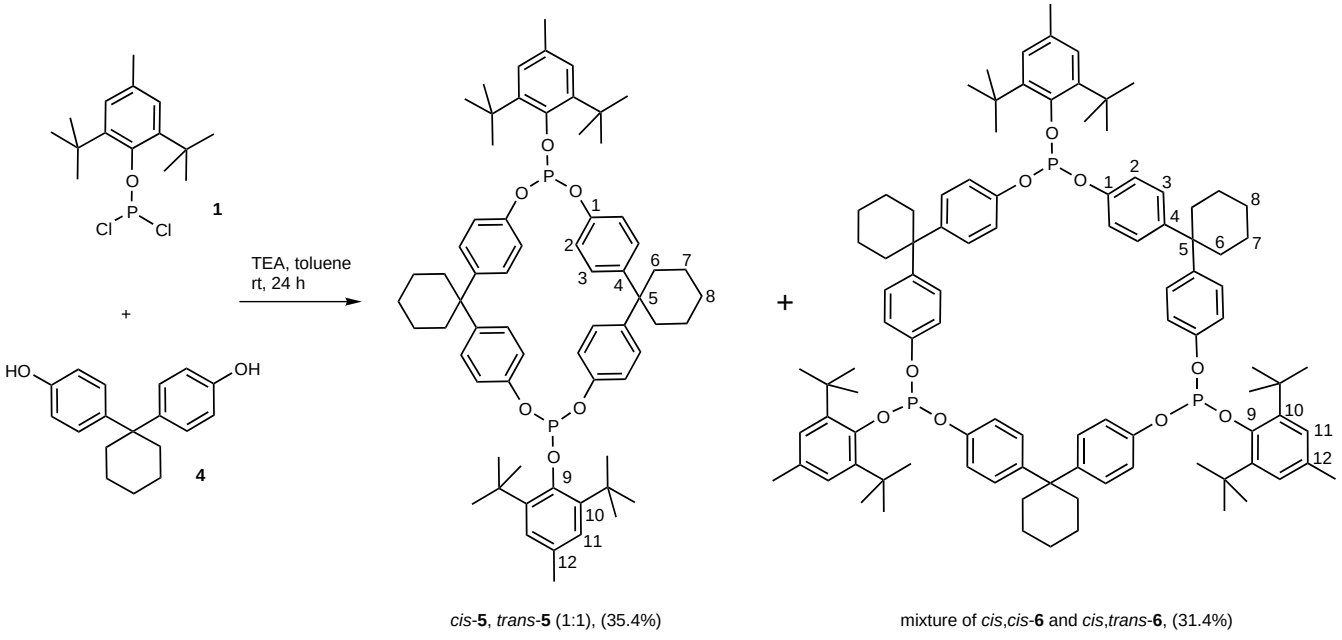
0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)01037-7

phosphorous arylester amides and was rationalized in terms of a preorientation of the attacking aryl moiety with intracyclic aryl groups by π-stacking, forcing the intracyclic aryl group into a leaving position.[7] For this reason, the phosphorous chloride route remains the most widespread method for the synthesis of P-macrocycles up to now.

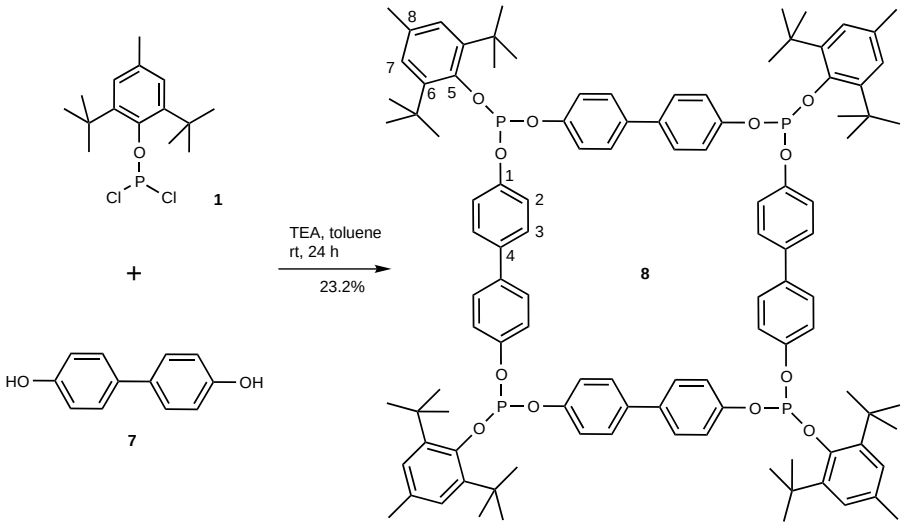
In this paper we report on the comparative synthesis of P-macrocycles starting from phosphorous dichloride **1**[8] and bisphenols of different shape and flexibility under equal conditions. The reaction is carried out in toluene at room temperature for 24 h in the presence of triethylamine (TEA) as a base with a concentration of the starting materials of about 4.5×10^{-3} M.[9] It shows that the intrinsic structural information of the building-blocks leads to macrocycles of different sizes thus amplifying the structural differences of the starting materials. Using the same bisphenol (**2**) as for the synthesis of macrobicyclic compounds[4] we obtained the corresponding P-macrocycle **3** in moderate yield as a mixture of *cis*- and *trans*-isomers (Scheme 1).[10] It demonstrates that bisphenol **2** is very well suited for this type of [2+2]-macrocyclocondensation as only minor amounts of oligomeric side products were observed. The two isomers of **3** are formed in a 1:1 ratio according to the intensity of ^{31}P NMR peaks at 137.2 and 136.9 ppm, respectively.

The large size of the macrocycle is probably responsible for the absence of any substrate induced diastereoselectivity mediated by the first phosphite center formed, even though it bears a very bulky exocyclic substituent. Bisphenol **4** has been repeatedly used for the synthesis of macrocyclic products as its 1,1-cyclohexylene unit forces the molecule into a curved shape which seems to fit extremely well for the formation of macrocycles. In the reaction of **4** with **1** we obtained the corresponding dimeric macrocyclic product **5** as a 1:1 mixture of *cis*- and *trans*-isomers with ^{31}P NMR peaks at 141.4 and 141.2 ppm, respectively (Scheme 2).[11]

However the trimeric product **6** was also isolated in nearly the same quantity.[12] In the case of this macrocycle two isomers (*cis*,*cis* and *cis*,*trans*) can also be formed, giving up to three different peaks in ^{31}P NMR in the reaction mixture. As the peaks at 137.2 and 137.1 ppm always appear in a 1:2 ratio they are tentatively assigned to *cis*,*trans*-**6**. That means *cis*,*cis*-**6** is formed only in minor amounts (*cis*,*cis*-**6**:*cis*,*trans*-**6** ~1:10) as can be concluded from the ^{31}P NMR spectrum of the crude product. The isolation of a pure isomer, however, was unsuccessful due to their very similar chromatographic behavior. 1,1′-Biphenyl-4,4′-diol (**4**) is, according to its geometrical properties, not predestined to form macrocyclic compounds. In fact one would expect the preferred formation of oligomeric compounds. However, even in this case we could isolate the tetrameric macrocycle **8**[13] as a mixture of diastereoisomers (*rccc*, *rcct*, *rctt*, *rtct*, following the nomenclature of resorcincalix[4]arenes) (Scheme 3). These structures are reminiscent of the macrocyclic transition metal complexes of Fujita et al.,[14] using a similar biphenyl linker. The finally isolated product **8** gives only one ^{31}P NMR peak at 138.4 ppm. However, it is assumed that in this case a mixture of isomers with no resolution of different ^{31}P NMR signals was also obtained.



Scheme 2. Reaction of bisphenol **4** with dichlorophosphite **1** to form macrocycles **5** and **6**.



Scheme 3. Reaction of bisphenol **7** with dichloride **1** under formation of the tetrameric macrocyclic product **8**.

Acknowledgements

The authors gratefully acknowledge the financial support of this work by the Deutsche Forschungsgemeinschaft (HA 2133/3).

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9. *General procedure*: The respective bisphenol (**2**, **4** or **7**) and triethylamine (TEA, 10% molar excess) were dissolved in the specified amount of toluene in a flame-dried flask in an argon atmosphere to give an approximately 4.5×10^{-3} M solution. Under vigorous stirring a solution of the stoichiometric amount of **1** in 10–50 mL of toluene was added dropwise by a syringe within 10 min. The solution was stirred for 24 h at 25°C. The hydrochloride formed was removed by filtration and the solvent was evaporated in vacuo. The crude product was again dissolved in a small amount of toluene and filtered through silica gel in order to remove polar by-products.
Identification of the products: Melting points were determined on a Boëtius melting point apparatus. ^{1}H NMR (TMS internal reference), ^{13}C NMR (TMS internal reference) and ^{31}P NMR spectra (85% H_3PO_4 external reference) were recorded on a Bruker AC-300 and a DRX-500 spectrometer. MALDI-TOF mass spectra were obtained on a Kratos Kompact MALDI II (Shimadzu Europa GmbH, Duisburg, Germany) using a N_2-laser source ($\lambda = 337$ nm), a positive polarity and 20 kV acceleration voltage. The microanalyses were recorded on a CHN-S analyzer (Carlo Erba).
10. Macrocycle **3**: Bisphenol **2** (3.00 g, 8.66 mmol) and TEA (1.92 g, 19.0 mmol) dissolved in 2.0 L of toluene were allowed to react with a solution of **1** (2.78 g, 8.66 mmol) in 50 mL of toluene according to the general procedure. After evaporation of the solvent and filtration through silica gel the product crystallized. Chromatography on silica gel with *n*-pentane/toluene (3:1) afforded 2.40 g (46%) of a 1:1 mixture of *cis*-**3** and *trans*-**3** as a crystalline, colorless solid. Mp 267–270°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 137.2, 136.9 (*cis*- and *trans*-isomer); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.02–6.97 (m, 20H, 2-H or 3-H, 7,10-H), 6.71 (d, ^3J(H,H) = 8.6 Hz, 8H, 2-H or 3-H), 2.23 (s, 6H, 11-Me), 1.53 (s, 24H, 5-Me), 1.369, 1.367 (2s, 18H each, 9-*t*Bu, *cis*- and *trans*-isomer or hindered rotation); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 149.6 (d, ^2J(P,C) = 5.5 Hz, C-1), 147.6 (C-4 or C-6), 146.3 (C-4 or C-6), 146.0 (C-8), 142.9 (d, ^3J(P,C) = 3.2 Hz, C-9), 131.9 (C-11), 128.2 (C-3 or C-7), 127.8 (C-10), 127.4 (C-3 or C-7), 120.2 (d, ^3J(P,C) = 6.8 Hz, C-2), 42.1 (C-5), 35.7 (C-*t*Bu), 32.5, 32.45 (Me-*t*Bu, *cis*- and *trans*-isomer or

hindered rotation), 30.9 (5-Me), 21.2 (11-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): m/z: 1188 $[M+H]^+$. Anal calcd for $C_{78}H_{94}O_6P_2$ (1189.47): C, 78.76; H, 7.97. Found: C, 78.33; H, 8.45%.

11. Reaction of **1** with **4**: Bisphenol **4** (0.5 g, 1.86 mmol) was dissolved in 400 ml of toluene together with 0.41 g TEA (4.05 mmol) and treated with 0.60 g (1.86 mmol) of **1** in 10 mL of toluene according to the general procedure. Chromatography of the product mixture on silica gel with toluene/pentane 1:3 yielded 340 mg (35.4%) of a *cis*,*trans*-mixture (1:1) of macrocycle **5** and 302 mg (31.4%) of the trimeric product **6** as a mixture of *cis*,*cis*- and *cis*,*trans*-isomers. Both macrocycles were isolated as white crystalline solids.
Macrocycle **5**: Mp 295–305°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 141.4, 141.2 (*cis*-**5** and *trans*-**5**); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.14 (s, 4H, 11-H), 6.96 (dd, ^3J(H,H) = 8.7 Hz, ^5J(H,H) = 2.2 Hz, 8H, 2-H or 3-H), 6.66 (d, ^3J(H,H) = 8.5 Hz, 8H, 2-H or 3-H), 2.32 (s, 6H, 12-Me), 2.11 (s., br., 8H, 6-H), 1.53 (s, 36H, Me-*t*Bu), 1.50–1.46 (m, 12H, 7,8-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 148.9 (d, ^2J(P,C) = 6.6 Hz, C-1), 146.4 (C-9), 144. 3 (C-4), 142.9 (d, ^3J(P,C) = 2.4 Hz, C-10), 132.2 (C-12), 128.5 (C-3), 127.3 (C-11), 120.8 (d, ^3J(P,C) = 4.1 Hz, C-2), 46.0 (C-5), 37.67, 37.51, 37.38, (C-6, *cis*-**5** and *trans*-**5**), 35.6 (C-*t*Bu), 32.4, 32.3 (Me-*t*Bu, *cis*-**5** and *trans*-**5**, or hindered rotation), 26.3 (C-8), 22.8 (br., C-7), 21.2 (12-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): m/z: 1032 $[M+H]^+$, 1054 $[M+Na]^+$; 1070 $[M+K]^+$. Anal calcd for $C_{66}H_{82}O_6P_2$ (1033.256): C, 76.71; H, 8.00. Found: C, 77.11; H, 7.96%.
12. Macrocycle **6**: Mp 286–294°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 137.2, 137.1, 137.0 (*cis*,*trans*-isomers); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.07 (s, 6H, 11-H), 6.84 (d, ^3J(H,H) = 8.6 Hz, 12H, 2-H or 3-H), 6.55 (d, ^3J(H,H) = 7.9 Hz, 12H, 2-H or 3-H), 2.11 (s, br., 9H, 12-Me), 1.94 (s., br., 12H, 6-H), 1.24 (s, 54H, Me-*t*Bu), 1.40–1.20 (m, 18H, 7,8-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 149.2 (C-1), 146.0 (C-9), 144. 1 (C-4), 142.9 (C-10), 131.9 (C-12), 128.2 (C-3), 127.4 (C-11), 120.4 (d, ^3J(P,C) = 6.5 Hz, C-2), 45.4 (C-5), 37.3 (br., C-6), 35.6 (C-*t*Bu), 32.4, 32.3 (Me-*t*Bu, different *cis*,*trans*-isomers or hindered rotation), 26.3 (C-8), 22.8 (br., C-7), 21.2 (12-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): m/z: 1553 $[M+H]^+$. Anal calcd for $C_{99}H_{123}O_9P_3$ (1549.884): C, 76.71; H, 8.00. Found: C, 77.16; H, 8.24%.
13. Macrocycle **8**: Bisphenol **7** (1.70 g, 9.13 mmol) and 2.02 g of TEA (20 mmol) were dissolved in 2 L of toluene and allowed to react with 2.93 g (9.13 mmol) of **1** in 20 mL of toluene according to the general procedure. After chromatography on silica gel (toluene/pentane 1:3) and recrystallization from toluene/acetonitrile, 920 mg (23.2%) of macrocycle **8** were isolated as a white solid. Mp 156–158°C; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 138.4; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.39 (d, ^3J(H,H) = 8.6 Hz, 16H, 2-H or 3-H), 7.15 (s, 8H, 7-H), 6.96 (d, ^3J(H,H) = 8.5 Hz, 16H, 2-H or 3-H), 2.33 (s, 12H, 8-Me), 1.52 (s, 72H, Me-*t*Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 151.1 (d, ^2J(P,C) = 5.3 Hz, C-1), 146.1 (d, ^2J(P,C) = 4.3 Hz, C-5), 143.0 (d, ^3J(P,C) = 3.4 Hz, C-6), 136.1.9 (C-4), 132.4 (C-8), 127.9 (C-3), 127.5 (C-7), 120.9 (d, ^3J(P,C) = 6.7 Hz, C-2), 35.6 (C-*t*Bu), 32.4, 32.3 (Me-*t*Bu, different *cis*,*trans*-isomers or hindered rotation), 21.2 (8-Me); MALDI-TOF-MS (matrix: 1,8,9-trihydroxyanthracene): m/z: 1738 $[M+H]^+$. Anal calcd for $C_{108}H_{124}O_{12}P_4$ (1737.952): C, 74.63; H, 7.19. Found: C, 77.40; H, 7.25%.
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