Pergamon

Tetrahedron Letters, Vol. 35, No. 39, pp. 7233-7236, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 \$7.00+0.00

0040-4039(94)01529-5

Exoditopic Receptors II: Synthesis and X-ray Crystal Structure of a Disilamacrocycle Bearing Two Bipyridine Units

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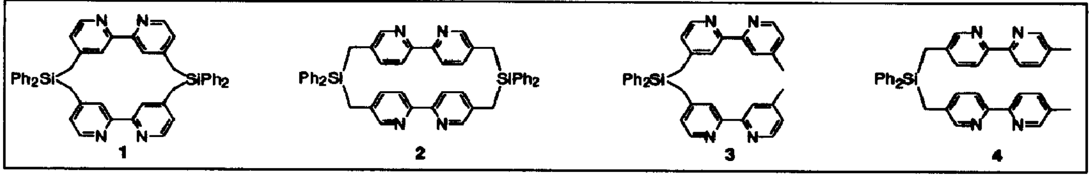
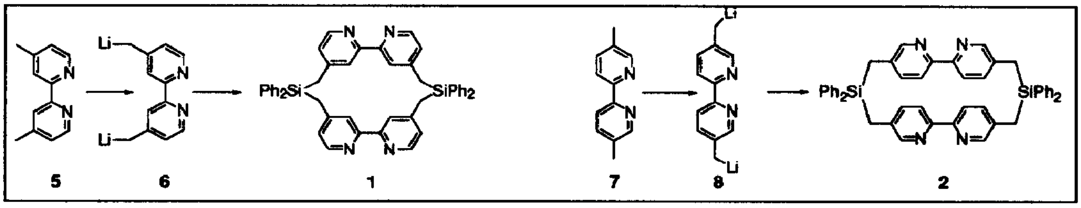
Abstract: The synthesis of a macrocyclic compound composed of two 2,2'-bipyridines interconnected at the 4 and 4' positions by two -CH_2SiCH_2- fragments was achieved and its structure was established in the solid state by X-ray crystallography.

The design and preparation of large size molecules (10^{-6}-10^{-4} m scale) with controlled structures and, thus, properties is currently under active investigation.[1] Whereas the manufacturing of such materials can hardly be attained through stepwise classical synthesis, one may envisage an iterative process based on self-assembly of individual units.[2] In order to allow the iterative process to take place, the individual units must possess connecting points (interaction sites) located in a divergent fashion. We have recently designed and synthesised exo-receptors bearing divergent cavities[3], divergent coordination sites[4], and divergent hydrogen bond donors, forming molecular rods , ribbons and sheets.[5] Divergent bis-tridentate ligands were shown to form molecular wires in the solid state in the presence of transition metal cations.[6] A further step in the manufacturing of new materials consists in the self-assembly of individual large size components such as molecular wires into two and/or three dimensional structures. Our ultimate goal is to assemble large size molecular entities with designed and controlled structures using coordination bonds. The synthesis of large size molecular components bearing coordination sites may be envisaged by the sol-gel process.[7] For this purpose, we designed as a first target the macrocyclic unit **1** in which two 2,2'-bipyridine units, well known for their coordination properties[8], are interconnected at the 4 and 4' positions with two -CH_2SiCH_2- groups. The choice of the 4 and 4' positions was done in order to obtain an exo-receptor. Because of its ability to undergo sol-gel processes, silicon was chosen as the bridging heteroatom interconnecting the two coordinating units. Only few examples of macrocyclic compounds bearing one or two silicon atoms in a endocyclic mode have been reported.[9] The synthesis of a macrocycle composed of two 2,2'-bipyridine interconnected at the 6 and 6' position by -CH_2NCH_2- fragments has been previously published.[10] We report here our first attempt in the synthesis of open chain and macrocyclic mono- and di-silane compounds **1-4**.

For the preparation of macrocycles **1** and **2**, we envisaged two different synthetic strategies. For both cases, the starting reagents were 4,4'-dimethyl-2,2'-bipyridine **5** and 5,5'-dimethyl-2,2'-bipyridine **7**, both prepared by Raney Ni coupling of 4-picoline and 3-picoline respectively.[11] Dealing with the silicon reagent, the commercially available dichlorodiphenylsilane (Ph_2SiCl_2) was used because it has been shown that the phenyl moiety may be substituted by OH group[12] for further use in the sol-gel process. For generating the lithium salts, freshly prepared lithium diisopropylamid (LDA) in THF was used since for 2,2'-bipyridine derivatives, *n*-BuLi has been shown to promote the substitution of an hydrogen atom on the aromatic core.[13]

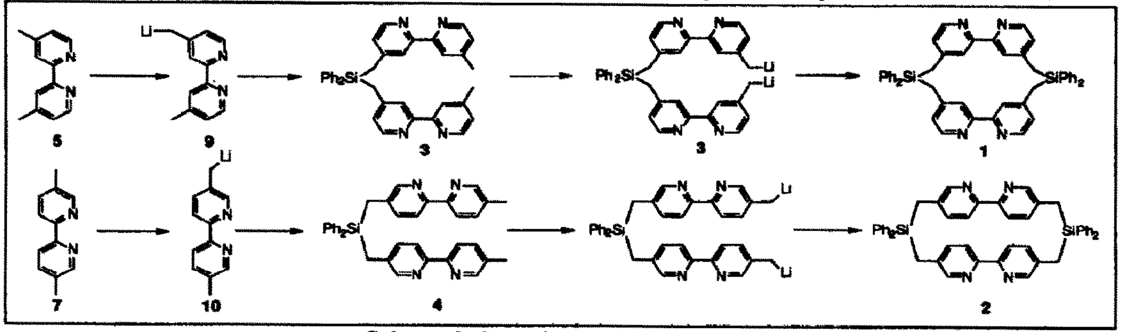


The first strategy attempted (scheme 1), a "one pot" cyclization, was based on the coupling of equimolar amounts of either the dilithium salt **6** of 4,4'-dimethyl-2,2'-bipyridine or the dilithium salt **8** of 5,5'-dimethyl-2,2'-bipyridine with Ph_2SiCl_2 in THF. Both compounds **6** and **8** were prepared by treatment of either **5** or **7** with 2 equivalent of freshly prepared LDA in THF.[14] In the case of the 4,4'-dimethyl-2,2'-bipyridine, the desired macrocycle **1** could be prepared in somewhat poor yield (2.2 %)[15], however, for the 5,5'-dimethyl-2,2'-bipyridine, no trace of the cyclic compound **2** could be observed. Attempts to increase the yield by the following systematic variation of the reaction conditions failed. The best yield of 2.2 % for **1** was obtained when the Ph_2SiCl_2 (1 eq.) was added dropwise at 0 °C to a solution of the dilithium salt **6** (1 eq.) generated at 0 °C by treatment with LDA (2.5 eq.) in THF. The reverse procedure *i. e.* the addition of of **6** to a solution of Ph_2SiCl_2 in THF decreased the yield to 0 %. Simultaneous addition of the dilithium salt **6** and Ph_2SiCl_2 under high dilution condition did not produce any trace of **1**. *In situ* stepwise generation of the monolithium salt **9** at 0 °C by treatment with LDA (1.2 eq.) in THF followed by addition of Ph_2SiCl_2 (0.5 eq.) at 0 °C followed by a second deprotonation with LDA (1.2 eq.) and addition of Ph_2SiCl_2 (0.5 eq.) at 0 °C also failed. Increasing the amount of LDA from 2.5 eq. to 3.5 eq. or the amount of Ph_2SiCl_2 from 1 eq. to 2 eq. resulted in the absence of the desired compound **1** in the mixture. Lowering the temperature from 0 °C to -78 °C or increasing the temperature from 0 °C to 25 °C for the reaction between the dilithium salt **6** (1 eq.), generated at 0 °C by treatment with LDA (2.5 eq.) in THF, and Ph_2SiCl_2 did not enhance the yield. Performing both the generation of the dilithium salt **6** and the reaction with Ph_2SiCl_2 at -78 °C decreased the yield from 2.2 % to 0 %. Replacement of Ph_2SiCl_2 by $Ph_2Si(OEt)_2$ under the same condition did not yield **1**. Addition of HMPA (6 eq.) also decreased the yield. In the same manner, a systematic variation of the reaction conditions did not lead to the isolation of **2**.



Scheme 1: "One pot" synthetic strategy

Since the yield obtained for the "one pot" strategy was very low, we believed that it could be increased by a stepwise strategy avoiding polymer formation reactions (scheme 2). This strategy consisted of preparing the non-cyclic monosila compounds **3** and **4** as isolated intermediates. The cyclization reaction, in this case an obturation, leading to the macrocycles **1** and **2** was planned to take place between the monolithium salts of **3** and **4** and Ph_2SiCl_2. Starting from either **5** or **7**, treatment with 1 equivalent of LDA in THF afforded the monolithium salts **9** or **10** which were condensed with Ph_2SiCl_2 in THF to afford the monosila compounds **3** and 4.[16] In marked contrast with the "one pot" synthesis, the yield (60 %) for 4 in which the two bipyridine units are interconnected at the 5 and 5' positions was substantially higher than for 3 (4 %). An explanation to the rather low yield in the case of 3 may be the following. In 3, the two methyl groups are located at the para position with respect to the nitrogen atoms, in the monolithium salt 9, generated by treatment with LDA, the negative charge may be delocalized over the nitrogen atom. Consequently, compound 9 may undergo both C-silylation and N-silylation in the presence of the electrophile Ph_2SiCl_2. In the case of the monolithio compound 10 however, the undesired N-sililation reaction can not take place. This explanation is also based on experimental facts. Indeed, for the 4,4' substituted bipyridine 5, both the reaction of the monolithium 9 and dilithium 6 salts leads to strongly coloured and insoluble solids, which after addition of water decompose to the starting material 5. The same explanation holds for the poor yield obtained for the "one pot" synthesis of 1. On the other hand, for the 5,5' substituted bipyridine 7 the rather high yield for 4 (60 %) and the absence of any observable trace of 2 during the "one pot" reaction may be due to steric reasons.



Scheme 2: Stepwise synthetic strategy

The structure of 1 was confirmed by X-ray crystallography[17]. In the solid state, compound 1 adopts a centrosymmetric cyclophane type structure in which the two bipyridine units were found to be face to face and almost parallel (Fig. 1). The distances between the two bipyridine units and the two silicon atoms were 3.5 Å and 10.8 Å respectively. The PhSiPh and CH_2SiCH_2 angles were 106.5° and 110.5° respectively. Within each bipyridine unit, the two pyridine moieties adopt a trans configuration.

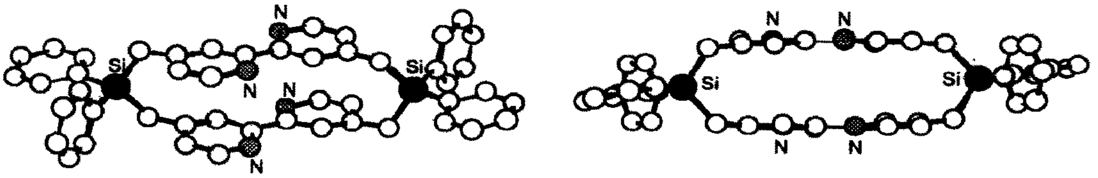


Figure 1: X-ray structure of 1: two different views. Hydrogens were omitted for the sake of clarity. Selected distances: d(Si-Si) = 10.8 Å, d(bipy-bipy) = 3.5 Å and angles: (CH_2SiCH_2) = 110.5 °, (PhSiPh) = 106.5 °

In summary: using a "one pot" strategy based on the reaction of the dilithium salt of 4,4'-dimethyl-2,2'-bipyridine with Ph_2SiCl_2, the synthesis of the macrocyclic compound 1 bearing two 2,2'-bipyridine units interconnected by two CH_2-Si-CH_2 fragments at the 4 and 4' positions was achieved in rather poor yield. Attempts to increase the yield by a systematic variation of the reaction conditions failed. In contrast, using a stepwise route, the acyclic monosila compound 4 in which two 2,2'-bipyridine units were interconnected by a CH_2-Si-CH_2 fragment at the 5 and 5' positions, could be obtained in high yield by coupling of the monolithium salt of 5,5'-dimethyl-2,2'-bipyridine with Ph_2SiCl_2. The structure of the macrocyclic compound 1 was confirmed by X-ray analysis. Formation of binuclear complexes with both **1**, **3** and **4** is under current investigation and will be reported elsewhere.

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15. Compound **1**: In a 100 ml flask, to a stirred solution of freshly prepared LDA (2.5 mmol.) in dry THF (4 ml) a solution of 4,4'-dimethyl-2,2'-bipyridine **5** (0,18 g, 1 mmoles) in dry THF (13 ml) was added dropwise (15 min.) at 0 °C. The red solution thus obtained was further stirred at 0 °C for 1 h. leading to a orange solution. To this mixture, a solution of Ph_2SiCl_2 (0.21 ml, 1 mmol.) in dry THF (15 ml) was added dropwise (15 min) and stirring was further continued for 1 h. at 0 °C leading to a blue-green non homogeneous solution. Addition of H_2O (30 ml) at r. t. afforded a homogeneous solution which was extracted with CH_2Cl_2 (3x 30 ml). The organic layers were combined and further washed with H_2O (50 ml), dried ($MgSO_4$) and evaporated to dryness leaving an orange oil. The pure compound **1** (16 mg, 2.2 %) was obtained as a white solid after chromatography (Al_2O_3, toluene/AcOEt/$CHCl_3$: 60/30/10) and crystallised from $CHCl_3$/Hexane mixture. M. P. : 218-220 °C; ^1H (200 MHz, $CDCl_3$, 25 °C): δ(ppm): 2,82 (s, 8H, CH_2); 6,71 (dd, 4H, 1,1Hz, 5,1Hz); 7,41 (d, 4H, 1,1 Hz); 7,48 (m, 12H, arom.); 7,68 (m, 8H, arom.); 8,45 (d, 4H, 5,1 Hz); ^{13}C (50.32 MHz, $CDCl_3$, 25 °C): δ(ppm): 21,53 (CH_2); 122,35 et 123,24 (C_{pyr} 5,5' and 3,3'); 128,48, 130,16, 134,79, 135,40 (arom.); 148,09 (C_{pyr} 4,4'); 148,50 (C_{pyr} 6,6'); 155,53 (C_{pyr} 2,2'); FAB^+ (*meta*-nitrobenzylalcohol matrix) *m/z* 729.1 (M H^+, 100%).
16. Compound **4**: In a 250 ml flask, to a stirred solution of freshly prepared LDA (5.3 mmol.) in dry THF (10 ml) a solution of 5,5'-dimethyl-2,2'-bipyridine **7** (0,92 g, 5 mmoles) in dry THF (30 ml) was added dropwise (30 min.) at 0 °C. The red solution thus obtained was further stirred at 0 °C for 1 h. before it was allowed to cool to -78 °C. To this mixture, a solution of Ph_2SiCl_2 (0.55 ml, 2.6 mmol.) in dry THF (5 ml) was added dropwise (10 min.) and stirring was further continued for 2 h. at -78 °C. The reaction mixture was allowed to reach the r. t. before H_2O (50 ml) was added. The mixture was extracted with CH_2Cl_2 (3x 50 ml). The organic layers were combined and further washed with H_2O (70 ml), dried ($MgSO_4$) and evaporated to dryness leaving a yellow-orange oil. The pure compound **4** (850 mg, 60 %) was obtained as a white solid after chromatography (Al_2O_3, toluene/AcOEt : 70/30) and crystallised from toluene/AcOEt mixture. M. P. : 147 °C; ^1H (200 MHz, $CDCl_3$, 25 °C): δ(ppm): 2.37 (s, 6H, CH_3); 2.65 (s, 4H, CH_2); 7.13 (dd, 2H, 8.1 Hz, 2.1Hz); 7.39 (m, 10H, arom.); 7.57 (dd, 2H, 8.1 Hz, 2.1 Hz); 8.05 (d, 2H, 8.1 Hz); 8.16 (d, 2H, 8.1 Hz); 8.21 (d, 2H, 2.1 Hz); 8.45 (d, 2H, 2.1 Hz); ^{13}C (50.32 MHz, $CDCl_3$, 25 °C): δ(ppm): 18.17 (CH_3); 19.22 (CH_2); 119.98, 120.09 (C_{pyr} 3,3'); 127.98, 130.01, 133.64, 135.18 ($C_{phényl}$); 132.56, 132.75 (C_{pyr} 5,5'); 136.88, 137.23 (C_{pyr} 4,4'); 149.04, 149.35 (C_{pyr} 6,6'); 152.79, 153,54 (C_{pyr} 2,2').
17. *Crystal structure determination*: crystals suitable for X-ray analysis were obtained by slow liquid-liquid diffusion of hexane into $CHCl_3$ containing **1**. **1**.$CHCl_3$ (T=173 K), monoclinic, space group C2/c, a=26.181(9), b=8.840(3), c=19.129(6) Å, β=106.33(2)°, V=4248.6 $Å^3$, D_{calc}=1.326 gcm^{-3}, Z=4, μ(CuKα)=28.428 cm^{-1} (graphite monochromator). A total of 2551 reflections were collected using a Philips PW1100/16 automatic diffractometer and analysed using the Enraf-Nonius SDP/VAX package. The raw step-scan data were converted to intensities using the Lehmann-Larsen method and corrected for Lorentz, polarization, and absorption factors. The structure was solved using MULTAN and refined to R(F)=0.050 using 1824 reflections with $I > 3\sigma(I)$. Further details of the crystal structure investigations are available on request from Cambridge Crystallographic Data Center.

(*Received in France* 28 *July* 1994; *accepted* 4 *August* 1994)