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Syntheses of phosphorus containing hydrolytically stable multisite receptors

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Abstract: Facile condensation reactions between 4'-formylbenzo-15-crown-5 and tris and hexa-hydrazino substituted phosphorus compounds lead quantitatively to three new polymacrocyclic compounds **3a,b** and **5**.

Since the pioneering work of Pedersen[1], extensive research has been devoted to the preparation and study of the properties of macrocyclic polyethers.

Several types of ligands have been synthesized to enhance the stability of the cation-ligand complex and to achieve a better selectivity[2]. The observation that many crown ethers form sandwich-complexes with two crown moieties per cation exceeding slightly the size of the cavity, induced the synthesis of bis(crown ether) or multisite receptors containing more than two macrocyclic cavities[3]. These compounds are of very high interest since they may allow new insights into ion channel transfer, ion conduction[4], and be useful as new catalysts.

In 1994, we have reported the easy and quantitative preparation of two new polymacrocyclic systems[5], where three or six crown ethers were linked to a $X{=}PO_3$ with (X = O, S) or $N{=}P(O_2)N$ core, by the reaction between a triarylphosphane or the hexa(phenoxy-4-carboxaldehyde) and three or six equivalents of 4-aminobenzo-15-crown-5. The two types of polymacrocyclic compounds were obtained easily by a condensation reaction between the amino groups of the crown ether and the aldehyde groups of the phosphorus core. Unfortunately, these compounds hydrolyzed rapidly, which excludes alkali-metal extraction from an aqueous phase.

This observation led us to prepare new compounds based on the same design but stable against hydrolysis by treatment of 4'-formylbenzo-15-crown-5 **1** (3 or 6 equiv. respectively) with phosphotrihydrazide **2a,b** (1 equiv.) or the hexahydrazide[6] **4** (1 equiv.) in tetrahydrofuran (Scheme 1). After stirring for 48 h at room temperature, compounds **3a,b** and **5** are obtained in good yield (~80%) after washing in a mixture of diethyloxyde-chloroform (3:1). Reactions are monitored by ^{31}P NMR. The condensation reaction is evidenced by a distinct shielding of ^{31}P NMR signals compared with the starting materials ($\Delta\delta$ = 9.8 for **3a**, 9.5 for **3b** and 10.2 for **5**) and by the disappearance of resonances in ^{1}H NMR attributed to aldehyde groups (δ 9.8) and NH_2 groups (δ 3.5). ^{13}C NMR and infrared spectroscopy confirm the proposed structures, which are also corroborated by mass spectrometry (**3a** *m/z* 1033 [M+1]; **3b** *m/z* 1017 [M+1]; **5** *m/z* 2076 [M+1])[7].

Because of the very strong hydrazone bond, these polymacrocycles are stable against hydrolysis. In order to investigate the ability of these compounds to form specific stable complexes, preliminary studies of their

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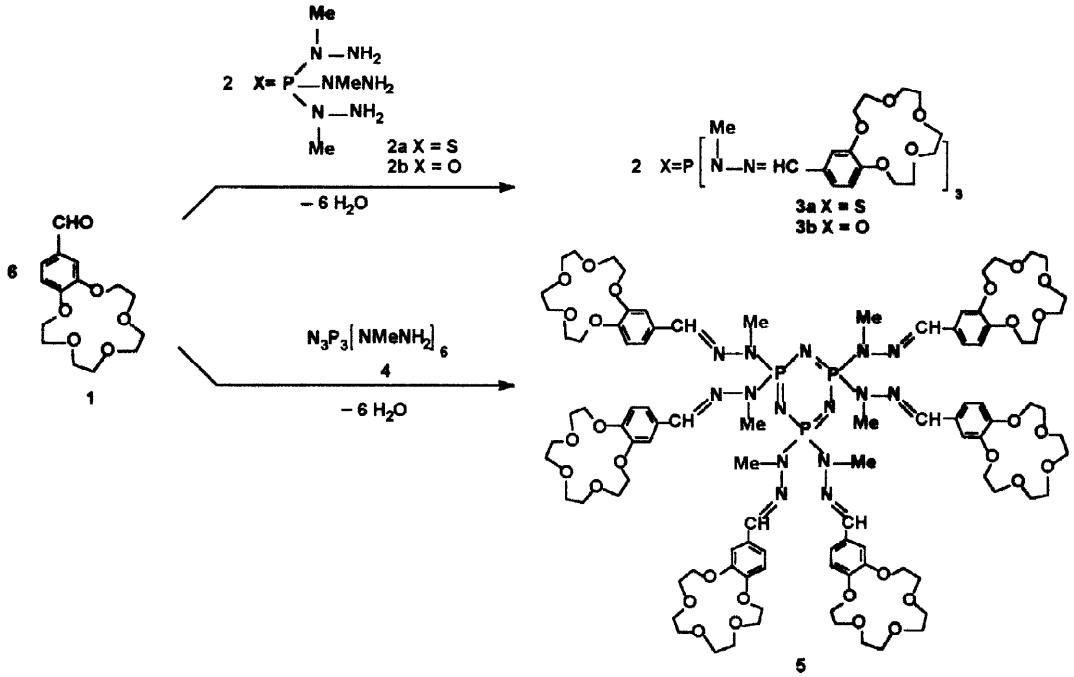
complexation behavior have been performed with an acetonitrile solution of **5**. Up to six equivalents, successively added by one equivalent at a time, of different metal triflates (Na^+, Mg^{2+}) and hexafluorophosphate (K^+) were added. Complexation was evidenced mainly by ^1H, ^{13}C and ^{19}F NMR.



Scheme 1

In case of the addition of sodium ions to ligand **5**, complexation leads to a significant and characteristic change of the chemical shift of the aromatic, imine, and methylene carbon nuclei. However, rapid dynamic exchange between complexed and uncomplexed sites on the ^{13}C NMR time scale at room temperature leads to the observation of averaged resonance signals. After addition of about six equivalents, no further change of the chemical shifts is observed which is explained by the saturation of the binding capability of the ligand (Figure 1).

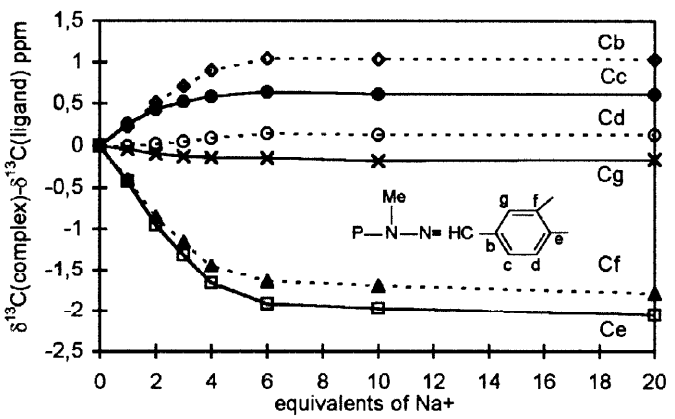


Figure 1 : Variation of the ^{13}C chemical shift of compound **5** as a function of the number of equivalents of Na^+ in acetonitrile solution.

In order to clarify this figure, only the aromatic carbons are represented. The carbons of the crown ether present a similar evolution as Cf and Ce. Interestingly, in case of addition of $Mg(OSO_2CF_3)_2$, rather complex ^{13}C and ^1H NMR spectra are obtained as long as the ratio of Mg^{2+} to ligand is smaller than 6:1. Moreover, in the ^{19}F

NMR spectrum, distinct resonances for two chemically different triflate moieties are detected of which one corresponds to a metal unbounded triflate anion. These observations may be explained by a strong complexation of the highly charged magnesium ions by the ligand. Obviously, each magnesium ion binds tightly to one crown ether moiety of the ligand and completes its coordination sphere by additional binding to one $CF_3SO_3^-$ group while the other one remains uncomplexed. Since many different isomers are possible which seemingly do not undergo rapid interconversions on the NMR time scale as long as the ratio Mg^{2+}/ligand is smaller than 6:1, very complex spectra are observed.

On the other hand, addition of a bigger cation (K^+) to hexamacrocycle **5** and 4'-formylbenzo-15-crown-5 **1** shows that saturation is obtained after 3 equivalents added, pointing out that these two compounds are inclined to form sandwich complexes (2:1) instead of 1:1 complexes. The RMNSTAB[8] program which can provide us with a plot of percentages of the different complexes formed against the number of equivalents added for the two hosts (Figure 2) let us know that in both cases, after 3 equivalents of K^+ added, 2:1 complexes are formed.

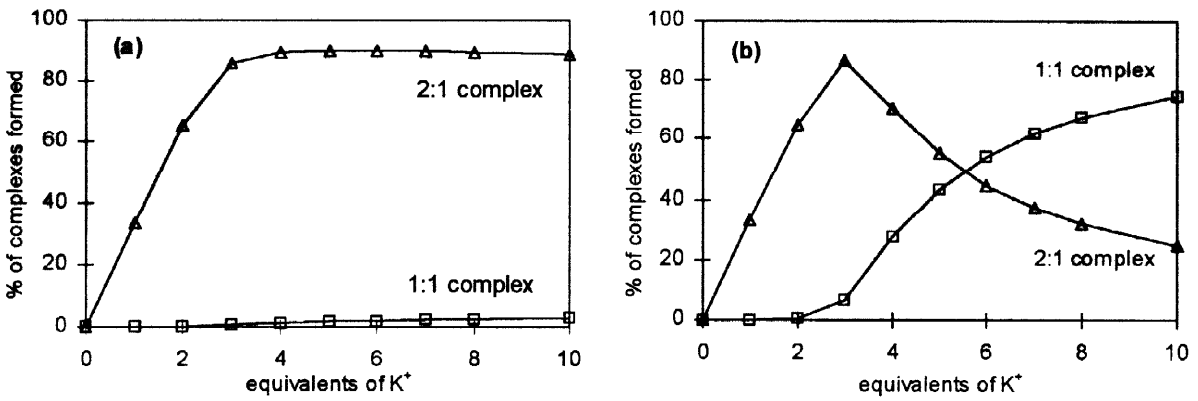


Figure 2 : Percentages of complexes formed as a function of the number of equivalents of K^+ in acetonitrile solution. (a) Hexamacrocycle - (b) 4'formylbenzo15-crown-5

By further addition of the cation, 2:1 complex changes into 1:1 complex for the 4'-formylbenzo-15-crown-5 **1** when 2:1 complex remains for the hexamacrocycle **5**. This first study shows the cooperative effect of the crown ethers of compound **5** due to their proximity which afford a better stability of the sandwich complex. More detailed studies of the complexation selectivity of this host **5** as well as compounds **3a,b** are undergoing.

References and notes :

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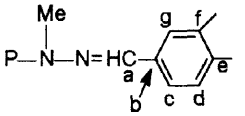
7. Selected spectral data for **3a,b** and **5**.

Assignments made as follows:



3a: White powder; yield: 77%; mp: 68°C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 75.0; ^1H NMR ($CDCl_3$): δ 3.3 (d, $^3J_{HP}$ = 9 Hz, 9H, P-N-Me), 3.5-4.2 (m, 48H, CH_2), 6.7 (d, $^3J_{HH}$ = 8 Hz, 3H, C_6H_3), 6.9 (dd, $^3J_{HH}$ = 8 Hz, $^4J_{HH}$ = 1.5 Hz, 3H, C_6H_3), 7.1 (d, $^4J_{HH}$ = 1.5 Hz, 3H, C_6H_3), 7.5 (s, 3H, CH=N); $^{13}C\{^1H\}$ NMR [$CDCl_3$, 75.46 MHz; the carbon nuclei could be partially assigned on basis of a heteronuclear multibond correlation (HMBC) experiment[9]]: δ 32.24 (d, $^2J_{CP}$ = 9.6 Hz, CH_3], 68.13 (s, CH_2), 68.93 (s, CH_2), 69.17 (s, CH_2), 69.39 (s, CH_2), 70.28 (s, CH_2), 70.34 (s, CH_2), 70.84 (s, CH_2), 71.05 (s, CH_2), 109.47 (s, Cg, C_6H_3), 113.18 (s, Cd, C_6H_3), 121.00 (s, Cc, C_6H_3), 129.62 (s, Cb, C_6H_3), 135.90 (d, $^3J_{CP}$ 14.4 Hz, CaH=N), 149.33 (s, Cf, C_6H_3), 149.64 (s, Ce, C_6H_3); IR (KBr): 1599 ($\nu_{C=N}$); mass spectra: *m/z* 1033[M + 1]$^+$; Anal. Calcd for $C_{48}H_{69}N_6O_{15}PS$: C, 55.80; H, 6.75; N, 8.13. Found C, 55.42; H, 6.72, N, 8.01 %. **3b**: White powder; yield: 75%; mp: 75°C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 16.5; ^1H NMR ($CDCl_3$): δ 3.2 (d, $^3J_{HP}$ = 7.2 Hz, 9H, P-N-Me), 3.5-4.0 (m, 48H, CH_2), 6.6 (d, $^3J_{HH}$ = 8.1 Hz, 3H, C_6H_3), 6.9 (d, $^3J_{HH}$ = 8.1 Hz, 3H, C_6H_3), 7.1 (s, 3H, C_6H_3), 7.5 (s, 3H, CH=N); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 31.90 (d, $^2J_{CP}$ = 7.8 Hz, CH_3], 68.15 (s, CH_2), 69.01 (s, CH_2), 69.20 (s, CH_2), 69.44 (s, CH_2), 70.33 (s, CH_2), 70.40 (s, CH_2), 70.90 (s, CH_2), 71.13 (s, CH_2), 109.40 (s, Cg, C_6H_3), 113.21 (s, Cd, C_6H_3), 120.97 (s, Cc, C_6H_3), 129.49 (s, Cb, C_6H_3), 136.05 (d, $^3J_{CP}$ 15.5 Hz, CaH=N), 149.40 (s, Cf, C_6H_3), 149.73 (s, Ce, C_6H_3); IR (KBr): 1602 ($\nu_{C=N}$), 1271 ($\nu_{P=O}$); mass spectra: *m/z* 1017[M + 1]$^+$; Anal. Calcd for $C_{48}H_{69}N_6O_{16}P$: C, 56.68; H, 6.84; N, 8.26. Found C, 56.33; H, 6.82, N, 8.13 %. **5**: White powder; yield: 82%; mp: 128°C; $^{31}P\{^1H\}$ NMR (CD_3CN): δ 17.8; ^1H NMR ($CDCl_3$): δ 3.3 (brs, 18H, P-N-Me), 3.6-4.0 (m, 96H, CH_2), 6.8 (d, $^3J_{HH}$ = 8.3 Hz, 6H, C_6H_3), 7.1 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.6 Hz, 6H, C_6H_3), 7.2 (d, $^4J_{HH}$ = 1.6 Hz, 6H, C_6H_3), 7.6 (s, 6H, CH=N); $^{13}C\{^1H\}$ NMR [CD_3CN, 125.76 MHz]: δ 32.28 [m, (br) AXX'$_2$ system, $^2J_{CP}$ + $^4J_{CP}$ = 8.4Hz, CH_3], 68.72 (s, CH_2), 68.89 (s, CH_2), 69.34 (s, CH_2), 69.37 (s, CH_2), 70.28 (s, CH_2), 70.30 (s, CH_2), 70.96 (s, CH_2), 70.98 (s, CH_2), 110.35 (s, Cg, C_6H_3), 113.54 (s, Cd, C_6H_3), 120.83 (s, Cc, C_6H_3), 130.13 (s, Cb, C_6H_3), 137.03 [m, (br) AXX'$_2$ system, $^3J_{CP}$ + $^5J_{CP}$ = 16.0Hz, CaH=N], 149.41 (s, Cf, C_6H_3), 149.76 (s, Ce, C_6H_3); IR (KBr): 1614 ($\nu_{C=N}$); mass spectra: *m/z* 2076 [M+1]$^+$; Anal. Calcd for $C_{96}H_{138}N_{15}O_{30}P_3$: C, 55.56; H, 6.70; N, 10.13. Found C, 54.95; H, 6.72, N, 9.95%.

8. This program has been created by Marcel Perry (Université Paul Sabatier - Laboratoire de Synthèse et Physicochimie Organique - UPR ESA 5068 - 31062 Toulouse Cedex).
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