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New Efficient Procedure for the Use of Diethoxyphosphoryl as a Protecting Group in the Synthesis of Polyazamacrocycles. Preparation of Polyazacyclophanes Derived from Resorcinol

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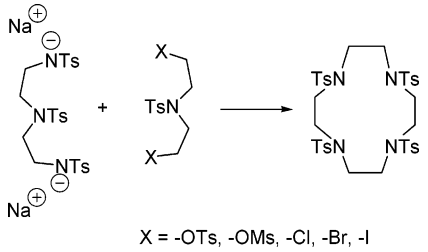
Abstract: The synthesis of polyazamacrocycles containing an electron-rich aromatic subunit derived from resorcinol is described. The reported synthetic procedure is based on the use of diethoxyphosphoryl (Dep) as an amine protecting group. The new conditions employed for the cyclization reaction allow for a generalized use of Dep in the synthesis of polyazamacrocycles.

Polyazamacrocycles have received much attention due to their different applications which are related to their interesting properties as ligands.[1] This type of compounds forms complex species with metal cations and anions which are very useful in fields such as NMR imaging,[1g] medicinal chemistry,[1i] or analytical chemistry.[1f] Therefore, the optimization or the development of new synthetic procedures for the preparation of polyazamacrocycles is an important challenge.

Several strategies have been described for the preparation of polyazamacrocycles in order to overcome successfully the entropically unfavorable macrocyclization reaction.[1c,f] These include the use of high dilution conditions, templates, or conformationally preorganized macrocycle precursors. Associated with the latter strategy, reactions involving Richman−Atkins cyclization or related procedures are used to prepare polyazamacrocycles. In this approach, as shown in Scheme 1, an *N*-protected

SCHEME 1. Richman−Atkins Cyclization



polyamine is reacted with a bis-electrophile to yield the macrocyclic product. The protecting group is required both to provide enough acidity to the protected primary amine groups so that they can be deprotonated under mild conditions and to avoid reaction at the secondary nitrogen atoms.

The original Richman−Atkins procedure uses tosyl as a protecting group but several alternatives have been described during the last years. This is mainly due to the rather harsh conditions required for the transformation of tosylamides into amines, which can be incompatible with some functional groups present in the structure of the macrocycle. Recently reported examples of substitutes for the tosyl groups include nitrobenzenesulfonyl (nosyl),[3b,c,e] β-trimethylsilylethanesulfonyl (SES),[3f] *tert*-butoxyoxycarbonyl (*t*-BOC),[3g] and diethoxyphosphoryl (Dep).[3a,d]

The use of Dep as a protecting group in the synthesis of polyaazamacrocyles is appealing for several reasons. Dep-protected polyamines are easy to prepare in multigram quantities, and the cyclization products are in general very soluble in common organic solvents, a property that facilitates their purification if required. Especially interesting is the fact that this protecting group can be removed quantitatively under mild conditions (HCl/dioxane, for example). However, the use of Dep in the synthesis of polyazamacrocycles is not generalized. Mertes and co-workers reported the cyclization of Dep-protected polyamines using DMSO as solvent and sodium hydride as the base.[3a] According to later work by Giovenzana, Palmisano, and co-workers with this protecting group, those conditions are not of general applicability, and in any case, the use of a solvent of such a high boiling point as DMSO is a serious drawback from a practical point of view. The alternative proposed by these authors is exemplified with the efficient preparation of polyazacyclophanes employing a biphasic toluene/water system as the solvent, sodium hydroxide as a base, and a phase-transfer catalyst for the cyclization reaction.[3d]

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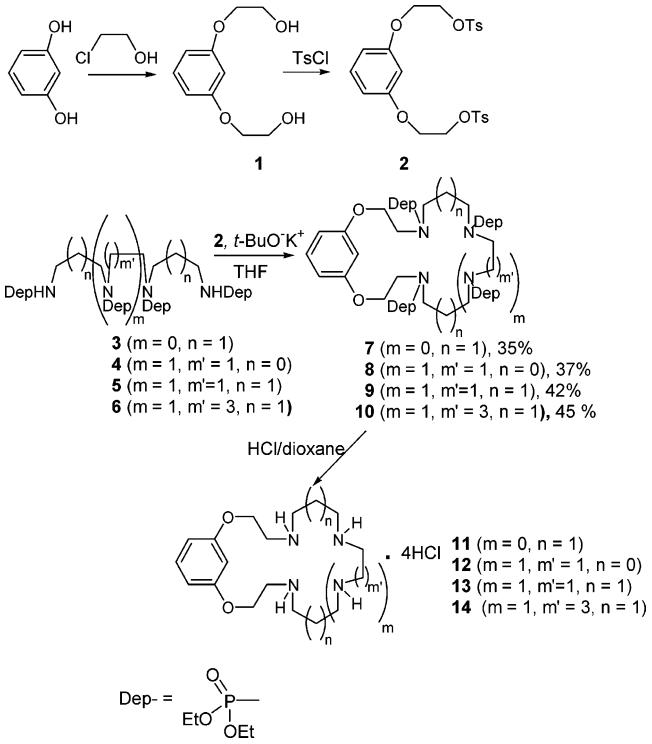
SCHEME 2



Keeping in mind all this information and following our ongoing research in polyazamacrocycles and their use in supramolecular chemistry, we targeted the preparation of polyazacyclophanes containing electron-rich aromatic subunits such as those shown in Scheme 2. Accordingly, a bis-electrophile derived from resorcinol was prepared by reaction of this aromatic compound with 2-chloroethanol followed by tosylation under standard conditions. Dep-protected polyamines were easily prepared in multigram quantities from commercially available polyamines using the Atherton−Openshaw−Todd procedure as reported recently.[3d] The cyclization reaction shown in Scheme 2 was attempted according to the procedure described by Giovenzana, Palmisano, and co-workers using a biphasic toluene/water system. Regrettably, it was found that the bistosylate hydrolysis was the main reaction yielding the corresponding dialcohol. Since in the original procedure the hydrolysis of bis-halide electrophiles is not an important side reaction, it seems that the nature of the electrophile used in the cyclization (probably its hydrophobicity) plays an important role in the success of the reaction, and therefore, the method is not of general applicability.

Here we report on new improved conditions for the cyclization of polyamines protected with Dep. We have found that the cyclization reaction can be performed using a common organic solvent such as THF and potassium *tert*-butoxide as the base. In the experimental procedure, the base dissolved in THF is added to a solution of the Dep-protected polyamine, which results in partial precipitation of the dianion formed upon polyamine deprotonation. Fortunately, for all the studied polyamines this dianion is partially soluble in THF and upon addition of the corresponding bis-electrophile all the starting material was reacted after a few hours. The use of different reaction conditions such as NaH/THF or K_2CO_3/CH_3CN was found to be ineffective. After chromatographic purification of the cyclic products, the deprotection reaction was performed quantitatively (yield > 95%) to afford the corresponding hydrochlorides using 3 M HCl in dioxane. The yield of the cyclization reactions after chromatographic purification was 35−45% (see Scheme 2). These values are moderate compared, for example, to other related cyclizations described by us using tosyl or nosyl as protecting groups [4a,b,e] (70−90%) and comparable to those reported previously using this protecting group.[3d] However, the overall methodology compares favorably with the use of other protecting groups. The mild and quantitative deprotection reaction extends the attainable structural diversity of the polyazamacrocycles when compared to tosyl. In the case of nosyl, the low solubility of the pernosylated macrocyclic compounds in common organic solvents can be a serious drawback if purification of the protected polyamines is required. The method compares well with the use of β-trimethylsilylethanesulfonyl if the easy and cheap preparation of multigram quantities of protected polyamine is considered. It has also to be noted that the deprotection under acidic conditions affords hydrochlorides that are easy to handle and stable solids, while the methods based on nosyl and β-trimethylsilylethanesulfonyl yield polyamines in their basic form that can be rather unstable and difficult to handle.

In summary, the new cyclization conditions reported here for a particular case allow for a generalized use of Dep-protected polyamines for the preparation of polyazamacrocycles. The new methodology constitutes an important improvement over the previous procedures that have not achieved a broad applicability.

Experimental Section

Dep-protected polyamines **5** and **6** were obtained following the procedure reported in the literature for the preparation of compounds **3** and **4**.[3d]

***N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-1,5,8,12-tetraazadodecane (5).** Compound **5** (11.4 g, 69%) was prepared from commercially available *N*,*N*′-bis(aminopropyl)ethylenediamine (4.00 g, 23 mmol). ^{1}H NMR ($CDCl_3$, δ ppm): 1.31 (m, 24H), 1.66 (m, 4H), 2.95 (m, 12H), 3.56 (m, 2H), 4.01 (m, 16H). ^{13}C NMR ($CDCl_3$, δ ppm): 16.5, 30.6, 38.3, 43.7, 44.8, 62.4, 62.7. MS(ES) (*m*/*z*): M + H = 719. IR (cm^{-1}): 3425, 3238, 2983, 2940, 2906, 2800, 1641, 1444. Anal. Calcd for $C_{24}H_{58}N_4O_{12}P_4$: C, 40.11; H, 8.13; N, 7.80. Found: C, 40.24; H, 8.02; N, 7.77.

***N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-1,5,10,14-tetraazatetradecane (6).** Compound **6** (12.0 g, 81%) was prepared from commercially available spermine (4.00 g, 19.8 mmol). ^{1}H NMR ($CDCl_3$, δ ppm): 1.28 (m, 24H), 1.40 (m, 4H), 1.63 (m, 4H), 3.05 (m, 12H), 3.45 (m, 2H), 4.01 (m, 16H). ^{13}C NMR ($CDCl_3$, δ ppm): 16.6, 26.1, 30.6, 38.4, 42.7, 45.6, 62.5. MS (ES) (*m*/*z*): M + H = 747. IR (cm^{-1}): 3235, 2981, 2936, 2906, 1648, 1444. Anal. Calcd for $C_{26}H_{62}N_4O_{12}P_4$: C, 41.82; H, 8.37; N, 7.50. Found: C, 41.71; H, 8.49; N, 7.38.

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General Procedure for the Cyclization Reaction. A solution of potassium *tert*-butoxide (0.021 mol) in 30 mL of dry THF was added dropwise under nitrogen and with stirring to a solution of Dep-protected polyamine (0.01 mol) in 150 mL of dry THF cooled in an ice bath. At that moment, a yellowish precipitate appeared. Then, ditosylate **2** (0.01 mol) dissolved in 150 mL of THF was added dropwise (30−60 min) and the mixture was refluxed overnight. The reaction was cooled to room temperature, the solvent was removed under vacuum, and the solid residue was added to a mixture of CH_2Cl_2 (100 mL) and water (10 mL). The aqueous solution was extracted with additional CH_2Cl_2 (2 × 30 mL), and the organic extracts were dried (Na_2SO_4). After filtration, the solvent was removed under vaccum and the residue purified by flash chromatography (silica gel, EtOAc/MeOH 9:1).

***N,N′,N″*-Tris(diethoxyphosphoryl)-4,8,12-triaza-1,5-dioxa[15]metacyclophane (7).** Macrocycle **7** (2.28 g, 35%) was prepared as indicated in the general procedure from **3** (5.00 g, 9.3 mmol). ^{1}H NMR ($CDCl_3$, δ ppm): 1.24 (m, 18H), 1.75 (m, 4H), 2.95 (m, 8H), 3.34 (m, 4H), 4.0−3.86 (m, 12H), 4.08 (t, J = 5.4 Hz, 4H), 6.40 (m, 3H), 7.12 (t, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 16.3, 28.3, 43.5, 45.1, 45.2 45.6, 62.3, 67.9, 101.3, 107.3, 130.7, 159.5. MS (ES) (*m*/*z*): M + H = 702. IR (cm^{-1}): 3406, 2979, 2928, 2862, 1602, 1440. Anal. Calcd for $C_{28}H_{54}N_3O_{11}P_3$: C, 47.93; H, 7.76; N, 5.99. Found: C, 48.36; H, 7.73; N, 5.66.

***N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-4,7,10,13-tetraaza-1,16-dioxa[16]metacyclophane (8).** Macrocycle **8** (1.83 g, 37%) was prepared as indicated in the general procedure from **4** (4.00 g, 5.8 mmol). ^{1}H NMR ($CDCl_3$, δ ppm): 1.25 (m, 24H), 3.20 (m, 12H), 3.35 (m, 4H), 4.01 (m, 16H), 4.16 (t, 4H), 6.46 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 2H), 6.5 (t, J = 1.4 Hz, 1H), 7.15 (t, J = 7.8 Hz,1H). ^{13}C NMR ($CDCl_3$, δ ppm): 16.5, 16.6, 47.0, 47.4, 62.6, 68.2, 101.3, 107.7, 130.7, 159.6. MS (ES) (*m*/*z*): M + H = 853. IR (cm^{-1}): 3448, 2981, 2929, 2899, 1596, 1444. Anal. Calcd for $C_{32}H_{64}N_4O_{14}P_4$: C, 45.07; H, 7.56; N, 6.57; Found: C, 44.69; H, 7.61; N, 6.52.

***N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-4,8,11,15-tetraaza-1,18-dioxa[18]metacyclophane (9).** Macrocycle **9** (2.06 g, 42%) was prepared as indicated in the general procedure from **5** (4.00 g, 5.6 mmol). ^{1}H NMR ($CDCl_3$, δ ppm): 1.20 (m, 24H), 1.88 (m, 4H), 3.20 (m, 12H), 3.45 (m, 4H), 4.01 (m, 16H), 4.08 (m, 4H), 6.45 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 2H), 6.48 (t, J = 1.4 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), ^{13}C NMR ($CDCl_3$, δ ppm): 16.5, 29.7, 45.4, 46.5, 46.7, 47.1, 62.4, 68.7, 103.2, 105.9, 130.5, 159.8. MS (ES) (*m*/*z*): M + H = 881. IR (cm^{-1}): 3445, 2983, 2927, 2897, 1603, 1445. Anal. Calcd for $C_{34}H_{68}N_4O_{14}P_4$: C, 46.36; H, 7.78; N, 6.36. Found: C, 45.99, H, 7.89; N, 6.31.

***N,N′,N″,N‴*-Tetrakis(diethoxyphosphoryl)-4,8,13,17-tetraaza-1,20-dioxa[20]metacyclophane (10).** Macrocycle **10** (2.19 g, 45%) was prepared as indicated in the general procedure from **6** (4.00 g, 5.4 mmol). ^{1}H NMR ($CDCl_3$, δ ppm) 1.28 (m, 24H), 1.44 (m, 4H), 1.81 (q, 4H), 3.02 (m, 16H), 3.45 (m, 4H), 4.02 (m, 20H), 6.37 (t, J = 7.8 Hz, 1H), 6.48 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 2H), 7.18 (t, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 16.5, 16.6, 26.6, 28.6, 44.0, 45.9, 46.1, 46.6, 62.4, 69.0, 103.0 106.2, 130.5, 159.8. MS (ES) (*m*/*z*): M + H = 909. IR (cm^{-1}): 3445, 2983, 2927, 2897, 1603, 1445. Anal. Calcd for $C_{36}H_{72}N_4O_{14}P_4$: C, 47.57; H, 7.98; N, 6.16. Found: C, 47.49; H, 7.87; N, 6.25.

General Procedure for Dep Removal. Dep-protected polyazamacrocyle (2 mmol) was dissolved at room temperature in 15 mL of 3 M HCl/dioxane and stirred overnight. The solvent was removed, and the residue refluxed in 5 mL of absolute ethanol for 2 h to obtain the compound as a solid that was filtered.

4,8,12-Triaza-1,5-dioxa[15]metacyclophane trihydrochloride (11). Macrocycle **11** (0.81 g, 95%) was prepared as indicated in the general procedure from **7** (1.50 g, 2.1 mmol). Mp: 234 °C. ^{1}H NMR (D_2O, δ ppm): 1.85 (m, 4H), 2.91 (t, J = 7.8 Hz,4H), 3.04 (t, J = 7.8 Hz, 4H), 3.34 (t, J = 5.1 Hz, 4H), 4.31 (t, J = 5.1 Hz, 4H), 6.60 (dd, J_1 = 2.4, J_2 = 8.3 Hz, 2H), 6.64 (t, J = 2.4 Hz,1H), 7.2 (t, J = 8.3 Hz,1H). ^{13}C NMR (D_2O, δ ppm): 21.9, 42.9, 43.8, 44.6, 62.7, 105.5, 107.6, 131.6, 158.1. MS (ES) (*m*/*z*): M + H = 294. Anal. Calcd for $C_{16}H_{36}Cl_3N_3O_2$: C, 47.00; H, 8.88; N, 10.28. Found: C, 46.61; H, 8.80; N, 10.14.

4,7,10,13-Tetraaza-1,16-dioxa[16]metacyclophane Tetrahydrochloride (12). Macrocycle **12** (0.75 g, 93%) was prepared as indicated in the general procedure from **8** (1.5 g, 1.8 mmol). Mp: 177 °C. ^{1}H NMR (D_2O, δ ppm): 2.92 (s, 4H), 3.21 (t, J = 7.3 Hz, 4H), 3.29 (t, J = 7.3 Hz, 4H), 3.38 (t, J = 5.1 Hz, 4H), 4.28 (t, J = 5.1 Hz, 4H), 6.56 (dd, J_1 = 2.4 Hz, J_2 =8.3 Hz, 2H), 6.61 (t, J = 2.4 Hz,1H), 7.23 (t, J = 8.3 Hz, 1H). ^{13}C NMR (D_2O, δ ppm): 43.1, 43.3, 43.7, 46.3, 63.3, 105.3, 107.8, 131.5, 158.2. MS (ES) (*m*/*z*): M + H = 309. Anal. Calcd for $C_{16}H_{44}Cl_4N_4O_2$: C, 41.21; H, 9.51; N, 12.01. Found: C, 40.81; H, 9.55; N, 11.90.

4,8,11,15-Tetraaza-1,18-dioxa[18]metacyclophane Tetrahydrochloride (13). Macrocycle **13** (0.81 g, 96%) was prepared as indicated in the general procedure from **9** (1.5 g, 1.7 mmol). Mp: 243 °C. ^{1}H NMR (D_2O, δ ppm): 1.1 (q, J = 7.3 Hz, 4H), 3.35 (t, J = 7.3 Hz, 4H), 3.45 (s, 4H), 3.52 (t, J = 5.1 Hz, 4H), 4.35 (t, J = 5.1 Hz, 2H), 6.69 (dd,J_1 = 2.4 Hz, J_2 = 8.3 Hz, 2H), 6.79 (t, J = 2.4 Hz, 1H), 7.31 (t, J = 8.3 Hz, 1H). ^{13}C NMR (D_2O, δ ppm): 29.4, 48.4, 48.5, 48.9, 49.6, 68.0, 103.9, 107.8, 130.2, 160.3. MS (ES) (*m*/*z*): M + H = 337. Anal. Calcd for $C_{18}H_{48}Cl_4N_4$: C, 43.73; H, 9.79; N, 11.33. Found: C, 43.65; H, 9.83; N, 11.25.

4,8,13,17-Tetraaza-1,20-dioxa[20]metacyclophane Tetrahydrochloride (14). Macrocycle **14** (0.83 g, 96%) was prepared as indicated in the general procedure from **10** (1.5 g, 1.7 mmol). Mp: 145 °C. ^{1}H NMR (D_2O, δ ppm): 1.62 (m, 4H), 1.98 (m, 4H), 2.93 (m, 4H), 3.02 (t, J = 7.3 Hz, 4H), 3.11 (t, J = 7.3 Hz, 4H), 3.36 (t, J = 5.3 Hz, 4H), 4.22 (t, J = 5.3 Hz, 4H), 6.56 (dd, J_1 = 2.4 Hz, J_2 = 8.3 Hz, 2H), 6.61 (t, J = 2.4 Hz, 1H), 7.18 (t, J = 8.3 Hz, 1H). ^{13}C NMR (D_2O, δ ppm): 22.1, 22.5, 43.8, 43.9, 46.3, 62.7, 103.9, 107.4, 130.9, 158.5. MS (ES) (*m*/*z*): M + H = 365. Anal. Calcd for $C_{20}H_{52}Cl_4N_4O_2$: C, 45.98; H, 10.03; N, 10.72. Found: C, 45.51; H, 10.08; N, 10.62.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **4**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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