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LETTERS

Novel Cryptand Analogs Incorporating a Chiral Spiran Moiety

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Abstract : Macrobicyclic polyethers based on the cryptand model displaying a chirality due to a spiran junction were synthesized from diamines **7** and **8**. Results of attempted direct macrobicyclisation varied with the length the α,ω–oligoethyleneglycol ditosylates chain used as reagent. The expected structure was obtained only for triethyleneglycol ditosylate. The complexing properties of the diaza-octaoxa ligand **11**, with alkaline and ammonium cations, were measured in THF by UV-Visible spectrophotometry. © 1999 Elsevier Science Ltd. All rights reserved.

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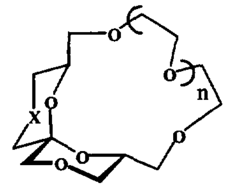
Many supporting skeletons have been studied for the design of macrocyclic polyether receptors with specific properties such as the ability to complex ionic species[1a] and /or recognize enantiomeric forms.[1b] In this context, we recently described the synthesis of new enantiopure crown compounds incorporating a spiroacetal moiety in the polyether chain. Associations formed with alkaline and alkaline-earth cations were studied by spectrophotometry in THF for three representative ligands (Scheme 1, X = O; n = 1, 2, 3).[2]



(+)

X = -O- or >N-R ; n = 1,2,3

Scheme 1

Complexing properties were measurable only for n = 3, with the following determined selectivity order: $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$. We concluded that distortions induced by the spiran junction adversely affected the spatial distribution of the donor oxygens in the coordinating sphere.

We therefore focused on a bicyclic system to improve the stability of association with spheric positively-charged species, and also to study the effect of the strain due to the helically oriented 2- and 8-substitution on the branched diaza-polyether cycle. The structural model chosen was closely related to the cryptands[3] an important family in supramolecular chemistry.[4]

The chiral diamines **7** and **8** were the final precursors for the planned macrobicyclisation (Scheme 2). Their preparation required respectively seven and nine steps from the commercially available synthon D-α,β-isopropylidene glycerol, and proceeded *via* diols **1**[5] (2*R*, 6*S*, 8*R*) or **2**[6] (2*R*, 6*S*, 8*S*) described elsewhere.

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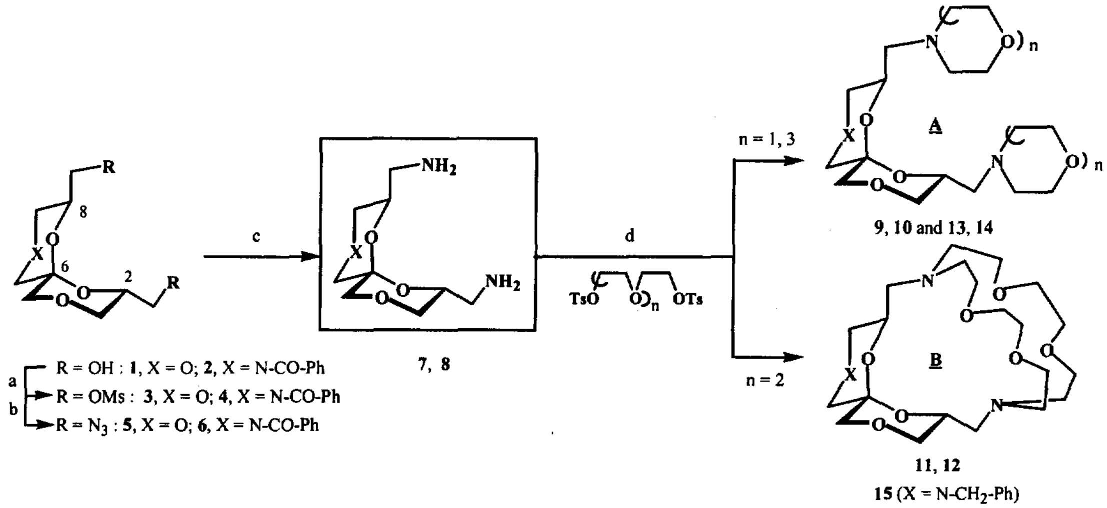
To achieve the synthesis in one step we tested a straightforward method proposed by Pietraskiewicz et al.[7] and developed by Krakowiak et al.[8] for similar cryptand formation from α,ω-diamines.

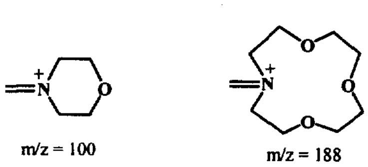


Scheme 2

Reagents and conditions : a) MsCl (2.4 eq), NEt_3 (2.4 eq), CH_2Cl_2, 0°C, 2 h, argon; **3** [96%, $[\alpha]_D^{25}$ -3 (c = 0.01, DMSO)]; **4** [84%, $[\alpha]_D^{25}$ +38 (c = 0.08, $CHCl_3$)] b) NaN_3 (3.5 eq), DMF, 80°C, 6 h, argon; **5** [97%, $[\alpha]_D^{25}$ -25 (c = 0.04, $CHCl_3$)]; **6** [80%, $[\alpha]_D^{25}$ +28 (c = 0.06, $CHCl_3$)] c) H_2, 5%Pd/C (0.05 eq), 3 atm., rt, 1 h; **7** [100%, $[\alpha]_D^{25}$ +27 (c = 0.04, MeOH)]; **8** [100%, $[\alpha]_D^{25}$ +68 (c = 0.03, $CHCl_3$)] d) TsO-$(CH_2CH_2\text{-}O)_n$-CH_2CH_2-OTs (2.2 eq), M_2CO_3 (20 eq), dry CH_3CN (c = 0.032M), reflux, 48 to 120 h; **9** [73%, $[\alpha]_D^{25}$ +7 (c = 0.04, $CHCl_3$)]; **10** [50%, $[\alpha]_D^{25}$ +50 (c = 0.09, $CHCl_3$)]; **11** [34%, $[\alpha]_D^{25}$ +53 (c = 0.04, $CHCl_3$)]; **12** [50%, $[\alpha]_D^{25}$ +46 (c = 0.07, $CHCl_3$)]; **13** [30%, $[\alpha]_D^{25}$ -3 (c = 0.04, acetone)]; **14** [18%, $[\alpha]_D^{25}$ +45 (c = 0.035, THF)]; **15** [63%, $[\alpha]_D^{25}$ +85 (c = 0.075, $CHCl_3$)]

Steps a, b and c gave very high yields. The final macrobicyclisation was carried out in experimental conditions described elsewhere:[8] a solution of the oligoethyleneglycol ditosylate (2.1 eq) was added under reflux to a solution of the diamine in dry acetonitrile in the presence of an excess of metal carbonate, without high dilution conditions. The best results were obtained with Na_2CO_3 for **9** - **12** and K_2CO_3 for **13**, **14**.

Analysis of the ^1H, ^{13}C NMR and MS spectra indicated that for compounds **9**, **10** (n = 1) and **13**, **14** (n = 3) a normally minor[8] internal cyclisation <u>**A**</u> took place on each nitrogen giving exclusively either bis(morpholine) (n = 1) or bis(aza-12-crown-4) (n = 3) branched systems. Evidences were found in ^{13}C spectra which presented seven resonances for **9** and nine for **13** (whereas for a cryptand with C_2 symmetry, nine and thirteen resonances would respectively be required). The simplifications observed on the spectra were consistent with the structures proposed. Analysis of ^1H spectra also supported these structures. Another interesting observation was the presence in the MS spectra of a strong fragmentation (base peak) at m/z = 100 (for **9**, **10**) and 188 (for **13**, **14**) corresponding to a cleavage to the nitrogen, affording the ion fragments depicted in scheme 3.



Scheme 3

In contrast, for n = 2, the expected bridged structures **B** were obtained in fair yields. In this case the base peak was the parent peak in the MS spectra. Reduction of **12** with $LiAlH_4$ (4eq) gave N-benzyl compound **15** [X = N-CH_2-Ph, n = 2, 63%, $[\alpha]_D^{25}$ +85 (c = 0.07, $CHCl_3$)], which was useful for structural confirmations. Spectral data for compounds **11**, **12**, **15** were consistent with a cryptand structure.[9]

The reaction pathway giving **A** or **B** isomers appeared to be linked to the polyethylenoxy chain length which determined the stability of the resulting rings, and possibly to the template effect which governed (or not) the final cyclisation of the bis(N-monosubstituted) intermediate.

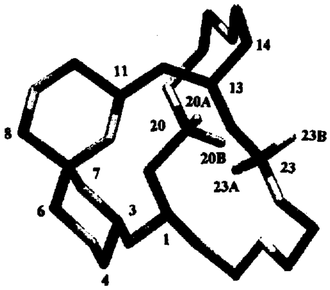
We explored the complexing ability of the new cryptand model. Measurements were performed by UV-Visible spectrophotometry with ligand **11** (X = O, n = 2), available in sufficient quantity, using a method described in details for crown analogs.[2] Complexes ML between ligand (L) and metal (M) were considered according to the equilibrium : M + L ↔ ML (log β_{11}).

Table 1: Association constants (log $\beta_{11} \pm 0.01$) for ligand **11** (THF, 20°C, metal picrates)

	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+
log β_{11}	3.38	4.33	4.80	3.72	2.31	3.73

A discrimination of Cs^+ was observed and a noticeable complexation with NH_4^+ took place. Also, the stability constants were drastically reduced compared with [2.2.2] cryptand for which log K = 10.4 (K^+, in acetonitrile)[1a], for instance. The values recorded were in the range of those obtained for [2.2.C8] cryptand,[1a] suggesting that the diaza-18C6 part of the skeleton was predominantly implicated in the complexing process.

Inclusion complex formation with M^+ cations and preponderant participation of the diaza-18-C6 moiety, were confirmed by 2D ^1H-^1H NMR investigations in $CDCl_3$ for **11**, which was studied as a free ligand and as metal (Li, Na, K) complexes.[10]



Scheme 4

For the free ligand, a remarkable difference in chemical shifts (δ) for protons H-20A, H-23A: 4.36 ppm (ddd) and protons H-20B, H-23B: 3.41 to 3.63 (m) was noted which may be explained by a preferential conformation of the diaza-18C6 ring where H-20A, H-23A are oriented into the cavity, in which case the O-19 and O-24 doublets will point out of the cavity as shown in Scheme 4 (computer simulated structure from ^1H ^3J-coupling constants). In the presence of Li^+, Na^+ or K^+, ^1H NMR spectra were strongly modified mainly for polyethylenoxy chain protons: H-20A, H-23A and H-20B, H23B resonated in the same δ domain (3.59 - 3.82 ppm). This suggested a conformational change with doublets of O-16, O-19, O-24, O-27 all oriented for a better coordination towards the cation. Further works is necessary to confirm this mechanism.

In conclusion, we report the synthesis of a new model of chiral macrobicycles that offer interesting possibilities as receptors for various species; in particular they appear good candidates for chiral recognition studies. This point will be the subject of a forthcoming paper.

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References and notes

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9. Selected spectral data for cryptands **11**, **12**, **15**.

   11: ^{1}H NMR (CDCl$_3$, 400 MHz) 2.38 (d, 2H, *J* = 14.8, 7.2 Hz, H-2B, H-12B), 2.58 (dd, 2H, *J* = 14.8, 1.3 Hz, H-2A, H-12A), 2.67-2.82 (m, 8H, 2H-14, 2H-21, 2H-22, 2H-29), 3.12 (t, 2H, *J* = 11.0 Hz, H-4ax, H-10ax), 3.21 (d, 2H, *J* = 11.3 Hz, H-6ax, H-8ax), 3.57 (d, 2H, *J* = 11.3 Hz, H-6eq, H-8eq), 3.41-3.63 (m, 8H, H-15B, H-17B, H-18B, H-20B, H-23B, H-25B, H-26B, H-28B), 3.69-3.82 (m, 6H, H-15A, H-17A, H-18A, H-25A, H-26A, H-28A), 3.78 (dd, 2H, *J* = 11.0, 2.6 Hz, H-4eq, H-10eq), 4.36 (ddd, 2H, *J* = 9.9, 8.8, 2.6 Hz, H-20A, H-23A), 4.39 (dddd, 2H, *J* = 11.0, 7.2, 2.6, 1.3 Hz, H-3, H-11); ^{13}C NMR (CDCl$_3$, 100 MHz) 59.3 (C-2, C-12), 59.8 (C-14, C-29), 60.1 (C-21, C-22), 68.5 (C-4, C-10), 68.7 (C-6, C-8), 70.7 (C-18, C-25), 70.8 (C-15, C-28), 71.1 (C-3, C-11), 72.4 (C-17, C-26), 73.8 (C-20, C-23), 91.8 (C-7); MS (EI) *m/z* (%) 446 (100, $M^{+\cdot}$), 416 (14), 385 (88), 371 (68), 355 (23), 341 (27), 325 (10), 315 (11), 301 (13), 283 (15), 228 (13), 214 (16), 186 (23), 179 (23), 170 (11), 158 (20), 144 (50), 140 (10), 132 (11), 114 (40), 100 (34), 84 (14), 70 (24), 56 (44). Exact mass found 446.2628, $C_{21}H_{38}N_2O_8$ requires 446.2628.

   12: Two rotamers; ^{1}H NMR (CDCl$_3$, 400 MHz) 2.30-2.90 (m, 16H, 2H-2, 2H-9, 2H-11, 2H-12, 2H-14, 2H-21, 2H-22, 2H-29), 3.30-4.25 (m, 18H, unassigned protons), 4.25-4.66 (m, 4H, H-3, H-11, two unassigned protons), 7.30-7.50 (m, 5H, 5 Ar-H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 44.2 and 45.3 (C-10), 49.5 and 51.2 (C-8), 58.3-61.2 (C-2, C-12, C-14, C-21, C-22, C-29), 68.3-73.8 (C-3, C-4, C-6, C-11, C-15, C-17, C-18, C-20, C-23, C-25, C-26, C-28), 92.1 (C-7), 127.5-129.7 (5 Ar-CH), 135.7 (Ar-C), 170.6 (C=O); MS (EI) *m/z* (%) 549 (100, $M^{+\cdot}$), 519 (19), 488 (80), 474 (66), 462 (14), 458 (21), 444 (27), 386 (12), 301 (15), 289 (14), 237 (19), 230 (21), 170 (10), 158 (20), 144 (50), 114 (40), 105 (98), 100 (43), 84 (17), 77 (40), 56 (52); Exact mass found 549.3022, $C_{28}H_{43}N_3O_8$ requires 549.3050.

   15: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.64 (t, 1H, *J* = 11.0 Hz, H-10ax), 1.83 (d, 1H, *J* = 11.0 Hz, H-8ax), 2.36 (dd, 1H, *J* = 14.7, 7.2 Hz, H-2B), 2.41 (dd, 1H, *J* = 14.7, 7.5 Hz, H-12B), 2.62 (dd, 1H, *J* = 14.7, 6.7 Hz, H-2A), 2.63 (dd, 1H, *J* = 14.7, 6.7 Hz, H-12A,), 2.64-2.80 (m, 10H, H-8eq, H-10eq, 2H-14, 2H-21, 2H-22, 2H-29), 3.11 (t, 1H, *J* = 11.0 Hz, H-4ax), 3.26 (d, 1H, *J* = 11.3 Hz, H-6a), 3.40 (AB spectrum, *J* = 12.9 Hz, Δν = 87.0 Hz, NC*H*$_2$Ph), 3.32-3.65 (m, 9H, H-15B, H-17B, H-18B, H-20B, H-23B, 2H-25, H-26B, H-28B), 3.57 (d, 1H, *J* = 11.3 Hz, H-6eq), 3.70-3.82 (m, 6H, H-4eq, H-15A, H-17A, H-18A, H-26A, H-28A), 4.24 (m, 1H, H-11), 4.38 (m, 3H, H-3, H-20A, H-23A), 7.19-7.35 (m, 5H, 5 Ar-H); ^{13}C NMR (CDCl$_3$, 100 MHz) 55.0 (C-10), 57.3 (C-8), 59.5 (C-2), 59.9 (C-14), 60.0 (C-21), 60.3 (C-22), 60.6 (C-29), 61.7 (C-12), 63.3 (NCH$_2$Ph), 68.5 (C-4), 70.4 (C-25), 70.6 (C-6, C-26), 70.9 (C-15), 71.0 (C-28), 71.1 (C-3), 72.1 (C-11), 72.4 (C-17), 72.9 (C-18), 73.9 (C-23), 74.1 (C-20), 93.0 (C-7), 127.1-129.4 (5 Ar-CH), 138.0 (Ar-C); MS (EI) *m/z* (%) 535 (93, $M^{+\cdot}$), 474 (43), 460 (25), 444 (26), 289 (13), 275 (15), 223 (17), 159 (86), 144 (25), 132 (10), 114 (23), 100 (24), 91 (100), 56 (31); Exact mass found 535.3254, $C_{28}H_{45}N_3O_7$ requires 535.3257.
10. The Li^+, Na^+ or K^+ complexes were generated by addition of respectively LiBr, NaSCN or KBr salt (1.5 eq) to a solution of ligand **11** (10 mg, 0.022 mmol) in CDCl$_3$ (0.4 mL).