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Synthesis of Macrobicyclic Cryptates incorporating Bithiazole, Bisimidazole and Bipyrimidine Binding Subunits

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The sodium cryptates of several novel macrobicycles containing 2,2'-bithiazole, 2,2'-bisimidazole and 2,2'-bipyrimidine subunits have been synthesized by a macrobicyclisation procedure; some of their properties are described.

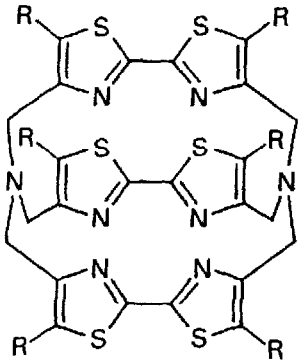
Heterocyclic rings have been extensively used as subunits in a large number of macrocyclic compounds[1]. Because of their varied and pronounced complexation features towards transition metal ions, directly linked bis-heterocyclic groups are of special interest as metal binding sites for macrocyclic ligands. Incorporation of such units into macropolycyclic structures allows to combine within the same ligand the special complexation features of cryptands with the rich photophysical and photochemical properties displayed by the complexes of the bis-heterocycles. Among those, the 2,2'-bipyridine (bpy) unit has been most actively studied and has been introduced into the framework of macrobicyclic ligands forming cryptate type inclusion complexes with various metal ions[2,3]. Of particular interest are the cryptates obtained with the luminescent lanthanide ions such as Eu(III) and Tb(III), which possess a unique combination of structural, photophysical and thermodynamic properties and function as light conversion molecular devices[4,5]. Macrobicyclic cryptands containing 1,10-phenanthroline[2,6] and 2,2'-biisoquinoline[3] groups as well as N,N'-bipyrazole[7] units have also been reported.

In order to further explore the features of such cryptands and take advantage of the variety of properties offered by different heterocyclic subunits, we have investigated several new types of structures. We report here the synthesis of the macrobicyclic cryptands **1-5** incorporating 2,2'-bithiazole (bthaz), 2,2'-bisimidazole (bim) and 2,2'-bipyrimidine (bpym) subunits; functionalized bis-heterocycles have also been obtained, as well as the macrotricyclic cryptand **6**.

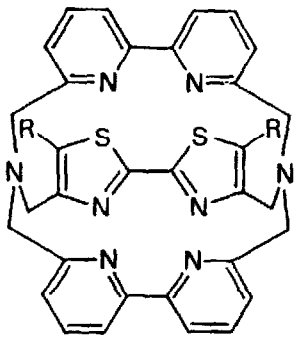
Synthesis of the 2,2'-Bithiazole Cryptands 1, 2, 3 and 6

The bis-bromomethyl-2,2'-bithiazole **7** was obtained in a single step although in low yield (7-14%; m.p. 180-181°) by condensation (refluxing acetone; 6h) of 1,3-dibromoacetone (2 eq.)[8] with dithiooxamide (1 eq.) in the presence of $CaCO_3$ (1 eq.) (see also [9]).

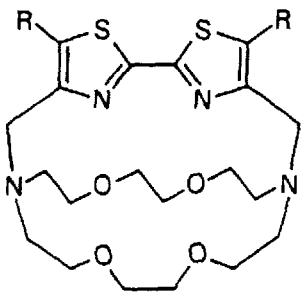
The bis-chloromethyl analogue of **7** was also obtained following the reported procedure[9] (26% yield) and reacted (DMSO, 70°, 2.5h) with NaN_3 (6 eq.) to give the bis-azide **8** (92% yield; m.p. 109-110°). Triphenylphosphine (2 eq.) was added to a solution of **8** in diethylether and the mixture was heated at reflux (2.5h). The resulting bisphosphinimine was directly hydrolyzed ($EtOH/H_2O$/conc. HCl 60/5/2; reflux, 150h) giving after work-up (addition of water; extraction with CH_2Cl_2 to remove phosphine compounds; precipitation with EtOH) a precipitate of the bis-hydrochloride of **9** (70% yield). The free diamine **9** was obtained by passing an aqueous solution of the salt over an anion exchange resin (basic form OH^-) (92% yield; m.p. 146-147°).



1a R=H
1b R=COOEt



2a R=H
2b R=COOEt



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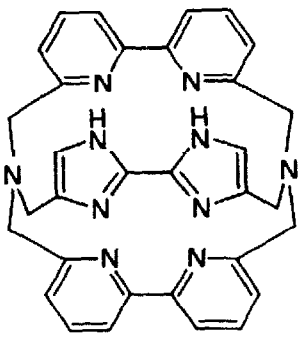
3b R=COOEt



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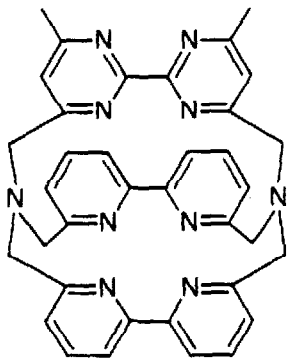

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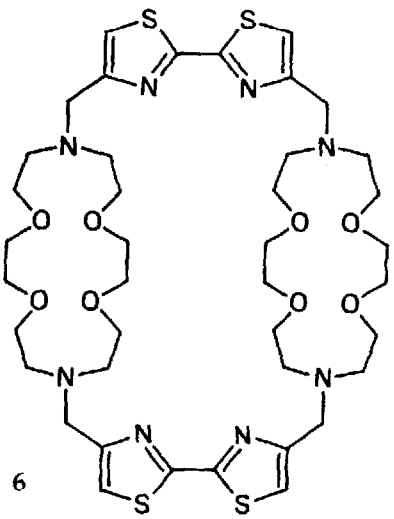

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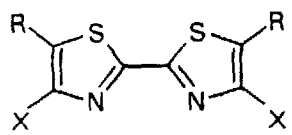
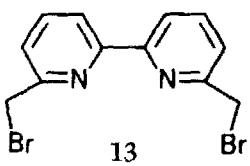


R=H		R=COOEt
7	X=CH_2Br	**10**
8	X=CH_2N_3	**11**
9	X=CH_2NH_2	**12**



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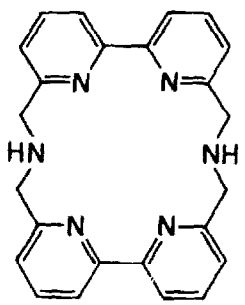

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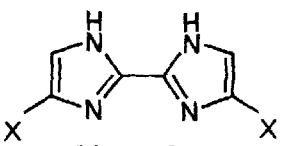
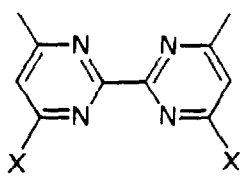


14 X=CN
15 X=CH_2NH_2



16 X=CH_3
17 X=CH_2OCOCF_3
18 X=CH_2Br

The bis-carbethoxy bithiazoles **10-12** were obtained by different procedures. Bromination of 4,4'-dimethyl-5,5'-bis(carbethoxy)-2,2'-bithiazole[10] with N-bromo-succinimide (NBS, 2 eq.; CCl_4, 4h, reflux) in presence of benzoylperoxide (0.05 eq.) under irradiation (tungsten lamp, *100W*) gave the dibromide **10** (40% yield; m.p. 185-186°) together with the related monobromide (20% yield) and the ($CHBr_2$, CH_2Br) tribromide (9% yield). Reaction of **10** with NaN_3 (20 eq.; DMSO, 80°, 20 min.) afforded the bis-azide **11** (87% yield; m.p. 125-126°) which was reduced catalytically with hydrogen (10% Pd/C; CH_2Cl_2/EtOH 1/2; r.t., 3h.) to the diamine **12** (84% yield).

Template synthesis of the sodium cryptates of the macrobicyclic ligands **1**, **2** and **6** was carried out by a direct macrobicyclisation procedure analogous to that reported for the corresponding [bpy.bpy.bpy] cryptand [3]. A solution of the dibromide **7** (2 eq.) and of the diamine **9** (0.61 mmole) in CH_3CN (500 ml) was heated at reflux for 15h in presence of Na_2CO_3 (10 eq.). After filtration, the volume of the solution was reduced to 100 ml. The product deposited in the cold (4°); some more material was recovered from the mother liquors by column chromatography (alumina, CH_2Cl_2/MeOH 4/1) giving the macrobicyclic ligand [bthaz.bthaz.bthaz] **1a** as its sodium cryptate (**1a**, NaBr) in a total yield of 48% (m.p. > 250°). Similar reaction of **9** with 2 eq. of **13** [2] gave the NaBr cryptate of the mixed [bpy.bpy.bthaz] macrobicycle **2a** (21% yield; m.p. > 250°). When the macrocycle [2.2][11] was treated with one eq. of the dibromide **7** the NaBr cryptate of the macrobicycle **3a** (21% yield; m.p. > 250°) was obtained together with the uncomplexed macrotricyclic cryptand **6** (14% yield; m.p. 190-191°); the two compounds were separated by column and preparative thin-layer chromatography (**3a**, R_F ~ *0.5*; **6**, R_F ~ *0.7*; *alumina*, CH_2Cl_2/MeOH 95/5).

The macrobicycles bearing carbethoxy functions **1b**, **2b** and **3b** were synthesized in a similar way from the diamine **12** and the corresponding dibromides **10** and **13** (2 eq.) and from **10** + [2.2][11] and isolated as their NaBr cryptates (yields: **1b**, 4%; **2b**, 18%; **3b**, 12%).

Synthesis of the 2,2'-Bisimidazole Cryptand 4

Reduction of 4,4'-dicyano-bisimidazole[12] **14** with diborane in tetrahydrofurane (BH_3.*THF*, *10* eq.; r.t., 3.5h) followed by acid hydrolysis (6N HCl, 85°, 35 min.) and isolation of the product via precipitation with picric acid and recovery by acid decomposition of the picrate, yielded the bis-aminomethyl bis-imidazole **15** (40-45% yield; kept as the hydrochloride).

Reaction of the diamine **15** (0.78 mmole, obtained from the hydrochloride by treatment with 1N NaOH) with the dibromide **13** [2] (2 eq.) in acetonitrile (600 ml, reflux, 30h) in presence of Na_2CO_3 (1 eq.) gave the NaBr cryptate of the macrobicyclic ligand [bim.bpy.bpy] **4** obtained as needles from CH_2Cl_2/MeOH 8/1 (14%; m.p. > 250°).

Synthesis of the 2,2'-Bipyrimidine Cryptand 5

Reaction of the tetramethyl-bipyrimidine **16** with *m*-chloroperbenzoic acid (2.5 eq., followed by 0.25 eq. after 24h; $CHCl_3$, r.t.) gave the corresponding bis-N-oxide (88% yield) which was rearranged to the bis-trifluoroacetate **17** by treatment with $(CF_3CO)_2O$ (as solvent; r.t., 20h). The crude compound **17** was reacted with NaBr (7 eq.; DMF, r.t., 10h) to give the dibromide **18**, which was purified by column chromatography (alumina, CH_2Cl_2; 25% yield). Condensation of the macrocycle **19** [2,14] (0.67 mmole; 500 ml CH_3CN; Na_2CO_3 10 eq.; r.t.) with **18** (1 eq.; 100 ml CH_3CN; dropwise addition over 3h followed by 30h reflux) gave a crude material from which the NaBr

cryptate of the macrobicycle [bpy.bpy.bpym] **5** was isolated in 14% yield by preparative thin-layer chromatography (silica, eluent CH_2Cl_2/CH_3OH 96/4).

Physico-Chemical Properties of the Cryptates of Macrobicycles 1-5

Macrobicycles **1-5** are novel ligands that should be able to form cryptate type inclusion complexes with a variety of metal ions. The proton NMR spectra of the NaBr complexes isolated agree with inclusion of the Na^+ cation in the central molecular cavity, i.e. with a cryptate structure [$Na^+ \subset$ Ligand]. The CH_2 signals are singlets at 20° indicating accidental equivalence of chemical shifts and/or rapid torsional motion about the N,N-bridgehead axis; signal broadening and splitting was observed in the cases of **2b** and **5** at low temperature (about -60° and -30° respectively) indicating slowing down of the motions (see also[2]).

Eu(III) cryptates of **2a**, **2b**, **4** and **5** have been prepared by refluxing in methanol solution in presence of $EuCl_3\ 6H_2O$(1.1 eq.). They present characteristic proton NMR spectra with strongly shifted signals compared to the Na^+ cryptates, as also observed for the Eu(III) complexes of related cryptands[4]. In particular, for the Eu(III) cryptates of the macrobicycles containing markedly different bridges **2a**, **2b** and **4**, the protons of the CH_2(py) groups give downfield shifted and widely separated AB pattern (J_{AB} = 14-16 Hz) of which one doublet is found at especially low field (at about 14.1, 15.2 and 19.3 ppm with $\Delta\delta AB$ ~ 7.3, 6.5 and 10.5 ppm) for **2a**, **2b** and **4** respectively). In contrast, the Eu(III) cryptate of **5** shows for the same protons an AB system much less spread out and at much higher field (5.90 and 2.85 ppm; J_{AB} = 15 Hz) similar to that found in the Eu(III) cryptate of the symmetrical [bpy.bpy.bpy] ligand[4]. It thus appears that the complexes of sufficiently dissymetric ligands experience Eu(III) induced shifts that are characteristic and markedly different from those found for symmetrical (or almost symmetrical) ligands. The luminescence properties of these new Eu(III) cryptates are being studied.

The $AgNO_3$ cryptates of **2a** and **3a** have been obtained by treating the corresponding sodium cryptates with $AgNO_3$ (4-8 eq., MeOH, reflux, 24-48 h). Cryptands **1-5** should also be able to form complexes with transition metal ions. Of particular interest is the potential ability of the (bthaz), (bim) and (bpym) units to bind cations both inside and ouside the cavity and to allow interaction from the outside with the included cation.

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