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Heptakis-6-(5-methylene-ureido-5′-methyl-2,2′-bithiazolyl)-cyclomaltoheptaose as a new fluorescent polydentate ligand

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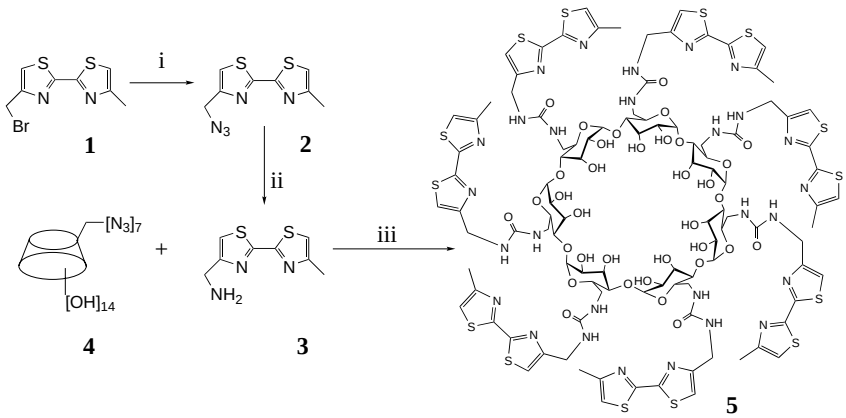
Abstract—The present work describes the one-pot synthesis of the new intrinsically fluorescent heptakis-(bithiazolyl-ureido)-β-cyclodextrin podand in a 29% global yield, by the direct 'phosphinimide' approach. Preliminary results on fluorescence properties are reported. © 2001 Elsevier Science Ltd. All rights reserved.

Little attention has been given to the organising properties of cyclodextrins towards bi-heterocyclic chelating systems.[1,2] In order to develop a new kind of multichromophoric cyclodextrin podand able to complex lanthanide ions and to express an absorption–energy transfer–emission [A–ET–E] light conversion process, we have recently prepared, via the 'phosphinimide' approach,[3] a new upper rim (5,5′-dimethyl-2,2′-bipyridinyl)-β-cyclodextrin host which showed interesting antennae effect.[4]

Among the different chelating heterocyclic systems we have studied, the 2,2′-bithiazole was chosen for its potent N and S chelating sites and for its specific intrinsic blue fluorescence, which could be modulated by metal complexation.[5] The present work describes a convenient one-step synthesis (Scheme 1) of the full-substituted upper ring bithiazolyl-β-cyclodextrin **5** and some of its photo-physical properties.

The 4-aminomethyl-4′-methyl-2,2′-bithiazole **3** was synthesised from 4,4′-dimethyl-2,2′-bithiazole via a three-step process involving a preliminary selective mono-functionalisation by radical bromination with NBS in CCl_4.[6] The mono-bromide **1** was treated with an excess of NaN_3 in DMSO at 70°C to give the mono-azido analogue **2**, which was obtained pure after chromatography (Al_2O_3; hexane/CH_2Cl_2; 50:50 then 40:60) with a yield of 92%. Catalytic hydrogenation of **2** over 10% Pd/C was performed in a 1:3 mixture of CH_2Cl_2 and C_2H_5OH at rt, affording the corresponding amine which was immediately salified with HCl to give



Scheme 1. (i) NaN_3, DMSO, 92%; (ii) a. H_2, Pd/C 10%, EtOH, CH_2Cl_2, HCl, 76%; b. Dowex® 1×8-100; (iii) PPh_3, CO_2, DMF, 29%.

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the hydrochloride **3-HCl** with a yield of 76%. The free amine **3** was obtained prior to use by elution of an aqueous solution of **3-HCl** over a column of Dowex® 1X8-100 anion exchange resin.

The heptapode **5** was prepared by a one-pot condensation process involving the heptakis-[6-azido]-β-cyclodextrin **4**,[7] a slight excess (8 equiv.) of the free base **3**, a 70-fold excess of triphenylphosphane and a continuous bubbling of anhydrous CO_2, over a period of 24 h, at rt in dry DMF. **5** was isolated with a yield of 29% (ca. 84% by one step) as a solid material by a simple workup procedure, nevertheless involving several washing steps with CH_2Cl_2 and MeOH to remove residual triphenylphosphine oxide.[8]

Elemental analysis was consistent with the presence of $2CH_2Cl_2$ and $6H_2O$. The IR spectrum of **5** exhibited the characteristic $\nu(CO\text{-NH})$ carbonyl frequency of the urea functions at 1640 cm^{-1} and the strong $\nu(C{=}N)$ aromatic frequency corresponding to the bithiazole units at 1565 cm^{-1}. Positive mode FAB-MS showed the presence of the desired compound with a base peak at 2789.2 a.m.u. $[\mathbf{5}+H]^+$, accompanied by a fragmentation signal at 2552.0 a.m.u. $[M-CH_3btzCH_2NHC(O)]^+$ (80%).

The ^1H NMR spectrum exhibited broad resonance signals in the regions expected for cyclodextrins, with, in addition, the presence of bithiazolyl signals in the aromatic part. The integration ratio of 2:1 observed between the aromatic part and the broad singlet at 4.90 ppm, attributed to $H(1)$ of the cyclodextrin, was consistent with the desired *per*-substitution. Structural investigation of **5** was completed with the help of ^{13}C NMR. Except for the resonance signals of the cyclodextrin-CH_2-N and btz-CH_2-N methylene groups, which were hidden by DMSO-d_6 between 39.00 and 41.50 ppm, the spectrum exhibited the expected cyclodextrin, bithiazole and carbonyl signals.

The electronic spectrum of **5**, recorded in degassed DMF, showed an intense absorption band at a maximum of 330 nm, due to the bithiazole arms, with a molar extinction coefficient value of 75600 $mol^{-1}\cdot L\cdot cm^{-1}$. The average extinction per bithiazole unit was thus estimated to be ca. 11000 $mol^{-1}\cdot L\cdot cm^{-1}$, in the range of values measured with 2,2′-bithiazole and other 2,2′-bithiazole-containing compounds.[6,9]

As expected,[5,10] the presence of the bithiazole units resulted in a strong intrinsic blue fluorescence of **5** (Fig. 1). When excited at 338 nm in degassed DMF at rt, **5** fluoresces at 400 nm with a quantum yield of 0.5 versus anthracene ($C = 5.8\times10^{-7}$ M). Knowing that the fluorescence quantum yield of the free 4,4′-dimethyl-2,2′-bithiazole is close to 1 ($\Phi = 0.92$),[11] the loss of fluorescence observed for **5** can be related to previous results concerning similar calixarene podands.[5,6,11] The functionalisation of the 2,2′-bithiazole moiety, as well as the probable close contacts imposed between fluorescent units by their spatial organisation on the calixarene backbone, were used to explain the loss of fluorescence in these podands, and can also be retained for **5**.

Attempts to evaluate by UV–vis spectroscopy the complexation properties of **5** towards the copper(I) cation were unsuccessful. The absence of the expected MLCT (metal to ligand charge transfer) at ca. 450 nm was explained by the use of DMF as solvent, imposed for the solubilisation of **5**, and which may strongly compete with bithiazole, with regards to Cu(I), as already observed in acetonitrile with other bithiazole-containing systems.[5]

In the same way, the fluorescence spectra of **5** in the presence of Eu(III) and Tb(III) were recorded in carefully degassed DMF. Unfortunately, attempts to observe the structured emission of lanthanide ions via the A–TE–E light conversion process failed in this system. As mentioned above for Cu(I), this result reveals the strong competition of the solvent in the chelation process, which inactivates the lanthanide complexation and, consequently, the expected light transfer process previously observed in the equivalent bipyridinyl system.[4]

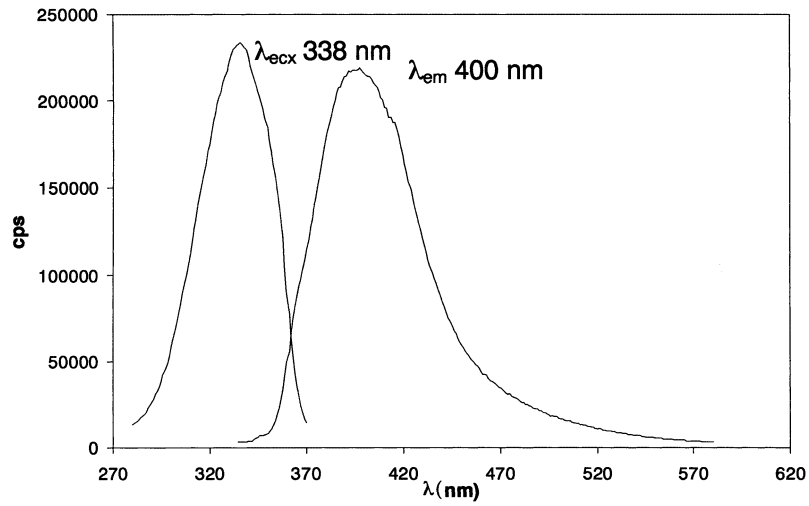

Figure 1. Excitation and emission spectra of **5**. ($C = 1.015\times10^{-6}$ mol L^{-1} in DMF).

In the near future the use of a single sugar urea bithiazole derivative and regioselectively bithiazolyl functionalised cyclodextrin analogues should allow a better understanding of the fluorescence process in such structures. In addition the ligand/solvent competition observed with cations, should be resolved with the corresponding permethylated Cds derivatives for which a good solubility in non-coordinating solvents is expected.

Overall, such an oligomeric bithiazolyl system remains intrinsically attractive, as it may be used as a highly fluorescent probe displaying further preorganised reactive sites, allowing the building of more elaborated structures; this aspect is actually under investigation through the selective functionnalisation of the lower rim of **5**.

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References

1. Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1994**, *116*, 7893–7894.
2. Brüger, N.; Deschenaux, R.; Ruch, T.; Ziessel, R. *Tetrahedron Lett.* **1992**, *33*, 3871–3874.
3. Charbonnier, F.; Marsura, A.; Roussel, K.; Kovacs, J.; Pinter, I. *Helv. Chim. Acta* **2001**, *84*, 535–551.
4. Charbonnier, F.; Humbert, T.; Marsura, A. *Tetrahedron Lett.* **1999**, *40*, 4047–4050.
5. Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R.; Meallier, P.; Guittonneau, S.; Fenet, B. *Helv. Chim. Acta* **1997**, *80*, 1229–1243.
6. Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R. *Tetrahedron Lett.* **1996**, *37*, 5889–5892.
7. Parrot-Lopez, H.; Ling, C.-C.; Zhang, P.; Baskin, A.; Albrecht, G.; De Rango, C.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, *118*, 5432–5442.
8. **Azide 2**. A solution of 4-bromomethyl-4′-methyl-2,2′-bithiazole (3.0 g;10.9×10^{-3} mol) and NaN_3 (2.6 g; 40.0×10^{-3} mol) in DMSO (30 mL) was stirred under N_2 at 70°C during 2 h. After cooling at rt, H_2O (30 mL) was added, affording a cloudy suspension which was washed with toluene (4×75 mL). The organic phases were combined, washed with H_2O (75 mL), dried over $MgSO_4$, then evaporated to dryness. The resulting solid was finally chromatographed (Al_2O_3; hexane/CH_2Cl_2; 50:50 then 40:60) to give an oil which slowly crystallised (2.37 g; 92%). White solid. Mp: 37–38°C. IR: 2200–2000 cm^{-1} (s, N_3). UV–vis (CH_3OH): 340 nm (17300 $mol^{-1}\cdot L\cdot cm^{-1}$). ^1H NMR ($CDCl_3$, 400 MHz; ppm): 2.549 (d, $J=0.76$ Hz, 3H, CH_3); 4.548 (s, 2H, CH_2); 7.025 (q, $J=0.76$ Hz, 1H, *H* btz); 7.322 (s, 1 H, *H* btz). ^{13}C NMR ($CDCl_3$, 400 MHz): 17.537 (CH_3); 50.545 (CH_2); 116.549 ($C(5')$); 118.412 ($C(5)$); 152.683 ($C(4)$); 154.792 ($C(4)$); 160.555 (C (2)); 162.769 ($C(2)$). EI-MS: 273 $[M]^+$. Anal. calcd for $C_8H_7N_5S_2$ (237.29): C, 40.49; H, 2.97; N, 29.51; found: C, 40.48; H, 3.06; N, 29.46. **Amine 3-HCl**. To a solution of 4-azidomethyl-4′-methyl-2,2′-bithiazole (0.8 g; 3.371×10^{-3} mol) in 60 mL of a 1:3 mixture of CH_2Cl_2 and C_2H_5OH, was added 10% Pd on charcoal (0.250 g) and H_2 was bubbled during 1 min. The mixture was vigorously stirred under H_2 at rt overnight then the catalyst was filtered off over a Celite pad. The solid was rinsed with CH_2Cl_2 and CH_3OH, then the filtrates were combined and evaporated to dryness. The solid residue was dissolved in H_2O (250 mL) and 1 M HCl was added up to neutrality. The resulting solution was washed with CH_2Cl_2 (3×50 mL) then evaporated to dryness under vacuum. The solid was dissolved with MeOH (50 mL) and the addition of Et_2O (200 mL) resulted in the precipitation of the hydrochloride which was collected by filtration. (0.642 g; 76%). White solid. Mp: 229–230°C. IR: 3100–2800 cm^{-1} (s, NH_3^+). UV–vis (CH_3OH): 328 nm (17300 $mol^{-1}\cdot L\cdot cm^{-1}$). ^1H NMR (D_2O, 400 MHz): 2.295 (s, 3H, CH_3); 4.221 (s, 2H, CH_2); 7.169 (s, 1H, *H* btz); 7.627 (s, 1H, *H* btz). ^{13}C NMR (D_2O, 400 MHz): 16.010 (CH_3); 38.679 (CH_2); 117.935 ($C(5')$); 121.698 ($C(5)$); 148.668 ($C(4')$); 154.460 ($C(4)$); 160.255 ($C(2')$); 162.368 ($C(2)$). EI-MS: 211 $[M]^+$. Anal. calcd for $C_8H_{10}N_3S_2Cl$, $0.1H_2O$ (249.575): C, 38.50; H,4.12; N, 16.83; found: C, 38.69; H, 4.05; N, 16.51. **Heptapode 5**. To a solution of **4** (0.165 g; 0.126×10^{-3} mol) and PPh_3 (2.312 g; 8.82×10^{-3} mol) in anhydrous DMF (20 mL) was added the base **3** (0.213 g; 1.0×10^{-3} mol, from 0. 26 g of **3-HCl**). The mixture was stirred at rt during 24 h, while anhydrous CO_2 was bubbled in. The solvent was then evaporated to dryness, and the residue was triturated in Et_2O and CH_2Cl_2 to give **5** as a cream-white precipitate (0.11 g; 29%). IR: 1640 cm^{-1} (CONH); 1565 cm^{-1} (CN-btz). UV–vis (DMF): 330 nm (75600 $mol^{-1}\cdot L\cdot cm^{-1}$). ^1H NMR (DMSO-d_6, 400 MHz): 2.32 (CH_3-btz); 3.70 (H(4), H(6) of β-CD); 4.17 (H(5) of β-CD); 4.37 (H(2), H(3) of β-CD); 4.90 (H(1) of β-CD); 7.23 (H(5′) or H(5) of btz); 7.26 (H(5) or H(5′) of btz). ^{13}C NMR (DMSO-d_6): 17.5 (CH_3-btz); 39.49–41.07 (DMSO, CH_2-btz, C(6) of β-CD); 71.31–73.22 (C(2), C(3), C(5) of β-CD); 84.69 (C(4) of β-CD); 103.09 (C(1) of β-CD); 117.52 (C(5), C(5′) of btz); 154.15, 157.19, 159.58, 160.36, 161.38 (C(4′), C(4), C(2′), C(2) of btz; CO). FAB$^+$-MS: 2983.7 $[M+CH_3btzCH_2]^+$; 2789.2 $[M+H]^+$; 2552.0 $[M-CH_3btzCH_2NHC(O)]^+$. Anal. calcd for $C_{105}H_{126}N_{28}O_{35}S_{14}$, $6H_2O$, $2CH_2Cl_2$ (3067.17): C, 41.90; H, 4.67; N, 12.79; found: C, 42.24; H, 4.64; N, 12.25.
9. For example: (a) Baudrion, C.; Thèse d'Université, Aix-Marseille III, 1991; (b) Lehn, J.-M.; Regnouf-de-Vains, J.-B. *Helv. Chim. Acta* **1992**, *75*, 1221–1236; (c) Nussbaumer, T.; Neidlein, R. *Helv. Chim. Acta* **2000**, *83*, 1161–1167.
10. See for example: (a) Vitachrome: Stämpfli, R. *Helv. Physiol. Acta* **1943**, *1*, 265–273; (b) Karrer, P.; Sanz, M. C. *Helv. Chim. Acta* **1943**, *26*, 1778–1784; (c) Karrer, P.; Sanz, M. C. *Helv. Chim. Acta* **1944**, *27*, 619–621.
11. Pellet-Rostaing, S., Thèse d'Université, Université Claude Bernard Lyon I, 1997.