# A cage ligand with three convergent pyridine donors†

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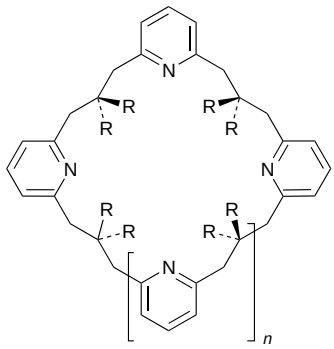
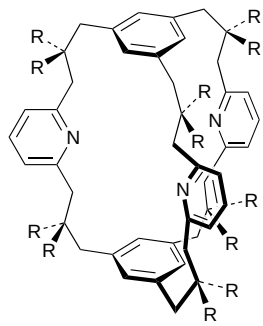
**A macrocyclic malonic ester condensation with pyridine building blocks leads to the new bicyclic host molecule 1 with defined cavity size, the X-ray structure analysis of which reveals three convergent nitrogen donor centres; in radiotracer phase-transfer measurements 1 turns out to be remarkably selective for $Ag^{I}$ cations while discriminating against $Cu^{I}$ and $Cu^{II}$ cations.**

Owing to their interesting complexation behaviour, pyridine subunits play an important role as donor sites for selective complexation of cations.[1,2] In this context Newkome's Cryptanal,[3] the bipyridine cryptands[4] synthesised by Lehn and coworkers, aza-bridged cage ligands[5] and homocalixpyridines[6] are characteristic examples.

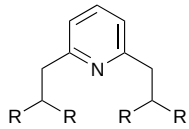
A few years ago we reported about macromonocyclic ligands containing pyridine subunits of the metacyclophane type **I**,



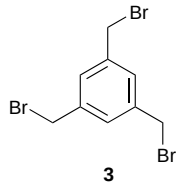
**I** R = $CO_2Et$



**1** R = $CO_2Et$



**2** R = $CO_2Et$



**3**

which could be obtained with different ring sizes by a malonic ester condensation-like pathway.[7] Now we are able to extend this method into the third dimension and to obtain the macrobicyclic tris(pyridine) cage ligand **1**. Because of the convergent (*endo*) orientation of the pyridine nitrogens in **1**, a cooperative binding of guest ions and incorporation in the cavity should be possible. In addition, the overall 12 peripheral ethyl ester groups guarantee good solubility in organic solvents like $CHCl_3$, $CH_2Cl_2$, THF and acetone.

The synthesis of **1** was achieved as follows: the tetraethyl ester[7] **2** and 1,3,5-tris(bromomethyl)benzene[8] **3** were added dropwise and simultaneously under dilution conditions to a stirred suspension of NaH in refluxing 1,4-dioxane, and stirred for 48 h. The reaction mixture was then concentrated *in vacuo*, and the oily residue recovered was dissolved in $CH_2Cl_2$, washed with diluted HCl and water and dried over $Na_2SO_4$ to give a brown oil upon removal of the solvent. After chromatographic separation of the crude product, **1**‡ was isolated as colourless crystals (mp 203 °C, EtOH–$CHCl_3$) in 4% yield.§ The rather poor yield is due to the fact that five components must approach each other to close six σ-bonds and is in accordance with the literature.[1a,9] The optimisation of the yield by stepwise synthesis[1b] or metal ion template strategy (*e.g.* caesium or silver) is currently being investigated.

Indeed, the X-ray structure of **1** shows an *endo* orientation of the pyridine units with a distance of 475 pm between two pyridine nitrogen atoms [N(1), N(2)], while the third pyridine nitrogen N(3) has distances of 771 and 749 pm, respectively, from these two atoms [Fig. 1]. The two benzene rings are not exactly parallel to each other, and the distance between their centres is 454 pm. The deviation from the parallel orientation amounts to 36°. Thus, the cavity of the free ligand is slightly contracted.¶

Molecular modeling calculations revealed almost the same conformation [*cf.* Fig. 1]. The calculated minimum energy conformation of the ligand (PM3) is in very good accordance with the X-ray results (RMS deviation 0.13 Å).

The ligand **1** therefore seems to be suitable for the complex formation with metal ions preferring a linear coordination ($Cu^{I}$, $Ag^{I}$) between the two adjacent pyridine donor atoms. Starting from the minimum energy conformation, a silver complex of **1** was calculated (ZINDO/1). The conformation of the complexed ligand is only a little changed compared to the free ligand. The silver ion is arranged in the middle of N(1) and N(2), both Ag–N bonds being 251 pm long. Additional interaction with N(3) or with benzene rings seems unlikely considering the steric situation.

The complexation behaviour of **1** has been studied experimentally by liquid–liquid extraction[10]‖ measurements: as designed, the pyridine-containing cage ligand **1** shows evidence for $Ag^{I}$ selectivity in extraction. Under experimentally chosen conditions 19.5% of the silver were transferred into the organic phase. In contrast to this, the other metal ions investigated ($Na^{I}$, $Tl^{I}$, $Cu^{I}$, $Ca^{II}$, $Cu^{II}$, $Zn^{II}$, $Hg^{II}$) remained in the aqueous phase (> 99.9%). The high selectivity for $Ag^{I}$ over $Cu^{I}$, $Cu^{II}$ and $Hg^{II}$

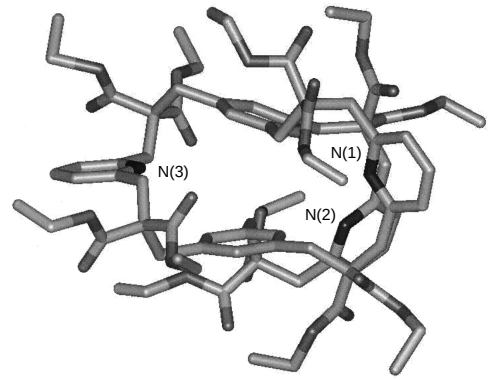
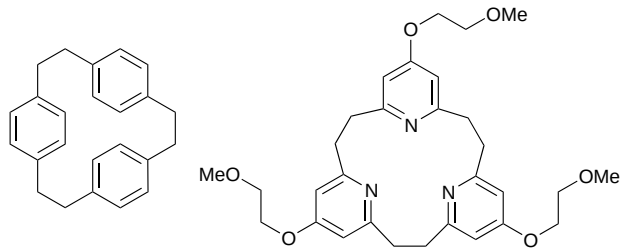



**Fig. 1** X-Ray structure of **1** (side view)

is particularly remarkable. Measuring the distribution ratio $D_{Ag}$ as a function of the ligand concentration in the organic phase, the data obtained with a slope of 1 from the Log $D_{Ag}$ *vs.* Log $c_L$ diagram indicate that 1 : 1 complexes are formed both in picrate (Log $K_{Ex,1}$ = 4.35) and nitrate (Log $K$ = 1.33) containing solution.

Compound **1** turns out to be a more efficient silver extracting reagent than silver-selective concave hydrocarbons[11] and the hydrocarbon [2.2.2]paracyclophane (**4**, picrate system, Log




**4** **5**

$K$ = 3.62) while remaining very selective [Fig. 2]. The interaction of the pyridine nitrogen with the silver ion is apparently stronger than that of π-donors. When a third pyridine nitrogen donor atom is introduced into a ligand molecule (at a suitable distance), the silver affinity is further raised. This is the case for the *all*-homocalix[3](2,6) pyridine (**5**, nitrate system, Log $K_{Ex,1}$ = 5.00)[12,6] with a much more coplanar orientation of the pyridine rings compared to **1**. However, it is at the expense of the separation selectivity; in the case of **5**, mercury(II) and copper(II) ions are extracted as well [Fig. 2].

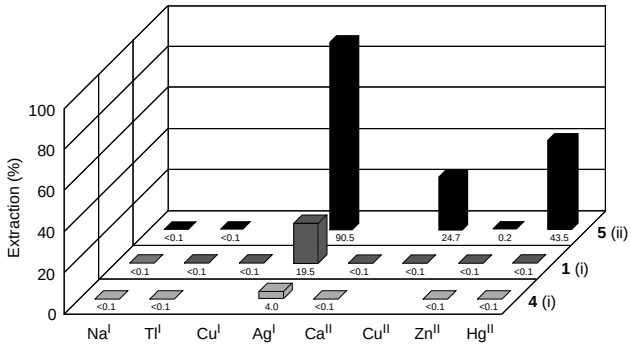



**Fig. 2** Extraction of different metal ions using compounds **1**, **4** and **5**. *Experimental conditions*: (i) [$AgNO_3$] = 1 × $10^{-4}$ M, [picric acid] = 1 × $10^{-2}$ M, [ligand] = 5 × $10^{-4}$ to 5 × $10^{-2}$ M, $CHCl_3$; (ii) [$AgNO_3$] = 1 × $10^{-4}$ M, [$KNO_3$] = 1 × $10^{-1}$ M, pH 6.3 (MES–NaOH buffer, 5 × $10^{-2}$ M), [ligand] = 5 × $10^{-4}$ to 4 × $10^{-3}$ M, $CHCl_3$.

The MALDI-TOF mass spectrum of ligand **1** revealed the molecule peak $[M]^+$ and the species $[Na\cdot\mathbf{1}]^+$ (*m/z* 1519.8) and $[K\cdot\mathbf{1}]^+$ (*m/z* 1535.7). The addition of $CF_3SO_3Ag$ to the sample solution totally suppresses $[Na\cdot\mathbf{1}]^+$ and $[K\cdot\mathbf{1}]^+$ and is accompanied by the formation of $[Ag\cdot\mathbf{1}]^+$ (*m/z* 1607.4).

Because of its ability to form stable complexes due to its novel molecular architecture and its well balanced lipophilicity, **1** is a highly selective phase-transfer host for silver ions. Replacing the ethyl ester groups by long chain aliphatic ones will lead to (ion selective) membrane insertable $Ag^I$ ligands.[13] Similar novel host molecules with larger cavities having more pyridine donor sites should be accessible for the selective complexation of biological relevant guests such as carbohydrates, amino acids, purine and pyrimidine bases.[1b]

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## Footnotes and References

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‡ IUPAC name of **1**: 5,5,13,13,21,21,29,29,34,34,42,42-dodekakis(ethoxycarbonyl)-45,47,48-triazaheptacyclo-[15.15.11.1$^{3,31}$.1$^{7,11}$.1$^{15,19}$.1$^{23,27}$.-1$^{36,40}$]octatetraconta-1,3(44),7(45),8,10,15(46),16,18,23(47),24,26,31,-36(48),37,39-pentadecaene.

§ **1** was fully characterised by $^1$H and $^{13}$C NMR spectroscopy and MALDI-TOF-MS. Elemental analysis: Calc. for $C_{81}H_{99}N_3O_{24}\cdot 2H_2O$: C, 63.35; H, 6.83; N, 2.74; O, 27.09. Found: C, 63.43; H, 6.60; N, 2.76%; sample was recrystallized for X-ray analysis.

¶ *Crystal data* for **1**: $C_{81}H_{99}N_3O_{24}$, $M_r$ = 1498.63, triclinic, space group $P\bar{1}$ (no. 2), $a$ = 13.131(1), $b$ = 13.554(1), $c$ = 22.520(1) Å, $\alpha$ = 88.24(1), $\beta$ = 86.82(1), $\gamma$ = 89.64(1)°, $V$ = 3997.0(5) Å$^3$, $Z$ = 2, $\mu$(Cu-Kα) = 0.759 mm$^{-1}$, $F$(000) = 1596, $T$ = 293(2) K, residual electron density 0.41 and −0.46 e Å$^{-3}$, 12 395 intensity data ($2\Theta_{max}$ = 120°) were collected, 11 809 unique data were used for the structure solution (direct methods) and refinement (full-matrix least-squares on $F^2$, 959 parameters, 16 restraints) to $wR2$ = 0.184 [$R_1$ = 0.062 for $I > 2\sigma(I)$]. CCDC 182/563.

‖ Liquid–liquid extraction investigations were performed according to ref. 11. Screening tests were made in the system metal nitrate (1 × $10^{-4}$ M)–picric acid (1 × $10^{-2}$ M), ligand **1** (1 × $10^{-3}$ M) in $CHCl_3$, without buffer for $Na^I$, $Tl^I$, $Ag^I$, $Ca^{II}$, $Cu^{II}$, $Zn^{II}$, $Hg^{II}$ and copper nitrate (1 × $10^{-4}$ M), and hydroxylammonium sulfate (5 × $10^{-3}$ M)–$KNO_3$ (1 × $10^{-2}$ M) in MES–NaOH buffer (pH 5.3) for $Cu^I$, respectively. After a shaking time of 30 min the equilibrium was reached. Control experiments were performed for each metal ion over a 24 h period.

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