

Synthesis and Properties of a Twistophane Ion Sensor: A New Conjugated Macrocyclic Ligand for the Spectroscopic Detection of Metal Ions

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The synthesis of a structurally new type of conjugated macrocyclic ligand (**1**) is reported that comprises a dehydroannulene framework incorporating two 2,2'-bipyridine units. Modeling studies showed the ligand to possess an unusual chirally twisted and relatively rigid architecture capable of binding metal ions in an enforced tetrahedral coordination geometry. The macrocycle was prepared in seven steps from (2-bromophenylethynyl)-trimethylsilane (**2**) and characterized by spectroscopic techniques. The pyridine H3 protons in the ¹H NMR spectrum of **1** showed a marked temperature dependency that may be related to conformational opening and closing motions of the macrocyclic ring. Ligand **1** was found to spectroscopically detect the presence of Co²⁺, Ni²⁺, Cu²⁺, and Zn²⁺ and, in particular, to function as a multiple readout sensor, giving different sequences of signal output depending upon the type of metal ion analyte with which the system was addressed. Macrocycle **1** also gave a highly characteristic and specific visual output response in the presence of Zn²⁺ consisting of a bright turquoise fluorescence and in this respect may find applications in the sensing of this biologically important metal ion.

Introduction

After a period of quiescence spanning almost 20 years, acetylene chemistry has again become the focus of intense activity and interest within the chemical community.¹ Many factors have contributed to this era of renaissance, the principle of which being the following: (1) the recent availability of a suite of transition metal-catalyzed carbon–carbon coupling protocols,^{2a,b} (2) the discovery of naturally occurring enediyne antibiotics,³ (3) the theoretical prediction of ethynyl-expanded all-carbon networks with novel materials properties,^{4a–c} and perhaps most importantly, (4) the discovery of fullerenes and carbon nanotubes.⁵

In particular, the latter two developments have inspired the creation of a wealth of unsaturated hydrocarbon architectures incorporating multiple numbers of ethynyl subunits such as conjugated molecular polymers and wires,^{6a,b} hyperbranched dendritic structures,^{7a–c}

carbon network components,^{8a–e} macrocyclic structures,^{7c,9a–b} hinged molecular cages^{7c,10a,b} and fullerene precursors.¹¹ Many of these constructs have served as model systems for the study of fundamental issues such as electron and energy transfer,^{12a,b} donor–acceptor conjugation circuitry,^{13a,b} and foldamer dynamics and molecular helicity.^{14a–c} They have also recently been demonstrated to exhibit properties such as host–guest inclusion,^{14c,15a–c} NLO behavior,¹⁶ liquid crystallinity,¹⁷ sensing,¹⁸ and porosity^{19a–b} and may thus play an im-

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portant role in the emerging fields of molecular electronics and nanotechnology.

Interestingly, some of the earliest types of multiethynyl hydrocarbons to be described in the literature were macrocycles.¹ In recent years, the number of reports on macrocyclic structures have rapidly increased such that they currently represent one of the largest classes of polyethynyl hydrocarbon scaffolds comprising a great diversity of species such as, for example, annulenes,²⁰ dehydroannulenes,^{1,21a-c} expanded radialenes,²² cyclines, [*n*]pericyclines, expanded [*n*]pericyclines,^{1,23a,b} [*n*]rotanes, exploded [*n*]rotanes,^{1,24} and many varied types of ethynyl-incorporated cyclophanes.^{25a-d} As well as addressing basic questions on aromaticity and cyclic conjugation, a number of these macrocycles have been shown to function as high energy materials and as precursors to carbon nanotubes.^{1,24,26}

To establish new properties and further potential applications of these fascinating compounds, one avenue of especial interest would be to create macrocyclic hydrocarbon architectures of the types described above, which additionally incorporate sites for the purpose of binding metal ions.^{23a,27} The combined structural features comprising rigid preorganization, spatially well-defined shape, extensive conjugation, and electronically linked metal ions would yield a new class of hybrid organic/inorganic molecular materials that would be expected to display a range of physicochemical properties in addition to those of the parent hydrocarbon. Compounds of this type may thus exhibit multiple redox, photochemical, optical, catalytic, substrate inclusion, and sensing ability as well as bulk properties such as magnetic and unusual mechanical behavior.

In earlier work, it was demonstrated that the linear conjugated rigid-rod ligand, 1,4-bis[5-ethynyl-(5'-methyl-2, 2'-bipyridyl)]benzene was able to function as an optical

sensor for the detection of specific types of metal ions.²⁸ It was concluded from the latter study that a further improvement in selectivity toward particular metal ions may be achieved by designing a macrocyclic analogue that combines the necessary structural requirements of enhanced conjugation with a spatially enforced coordination pocket upon binding to a metal ion of complementary size. As a first step toward this goal, it was decided to prepare cyclophane **1** (Scheme 1), which comprises a dehydroannulene-type hydrocarbon framework incorporating two 5,5'-disubstituted 2,2'-bipyridine ligand units positioned on opposite sides of the macrocyclic ring.^{29a-g} Cyclophane **1** is an ortho-cyclically conjugated structure and should in principle undergo significant electron distribution perturbations upon coordination to metal ions. Macrocycle **1** may, therefore, represent an optimized scaffold for the optical sensing of metal ions of preferred tetrahedral coordination geometry.

The following account describes the successful synthesis of **1**, its structural characterization by spectroscopic techniques, its physicochemical properties and a detailed investigation into its metal ion coordination behavior. The metal ion-binding studies in particular, amply demonstrated the validity of the above expectations and showed **1** to be a specific chromogenic fluorescent sensor for Zn²⁺ ions.

Synthesis of 1. Macrocycle **1** was synthesized in reasonable overall yield via a seven-step reaction sequence starting from the commercially available (2-bromophenylethynyl)trimethylsilane (**2**) and 2-chloro-5-iodopyridine (**3**) (Scheme 1). Initially, **3** was converted to 2-chloro-5-trimethylsilylethynylpyridine (**4**) via a Sonogashira reaction^{30a,b} with trimethylsilylethyne, and **4** subsequently deprotected with aqueous NaOH to give 2-chloro-5-ethynylpyridine (**5**) as reported previously.²⁸ However, the reaction between **2** and **5** in triethylamine at 80–100 °C in the presence of CuI and PdCl₂(PPh₃)₂ catalysts resulted in the formation of 2-chloro, 5-[(2-trimethylsilylethynylphenyl)ethynyl]pyridine (**7**) in only low and irreproducible yields. Varying the relative quantities of CuI and PdCl₂(PPh₃)₂ also failed to provide any yield enhancements. The reason for this may in part originate from the thermal instability of **4** under the Sonogashira reaction conditions. It was therefore decided to proceed using the more reactive (2-iodophenylethynyl)trimethylsilane (**6**) in place of **2**.

Thus treatment of **2** in diethyl ether solution at –78 °C with 1 equiv of *n*-butyllithium resulted in quantitative

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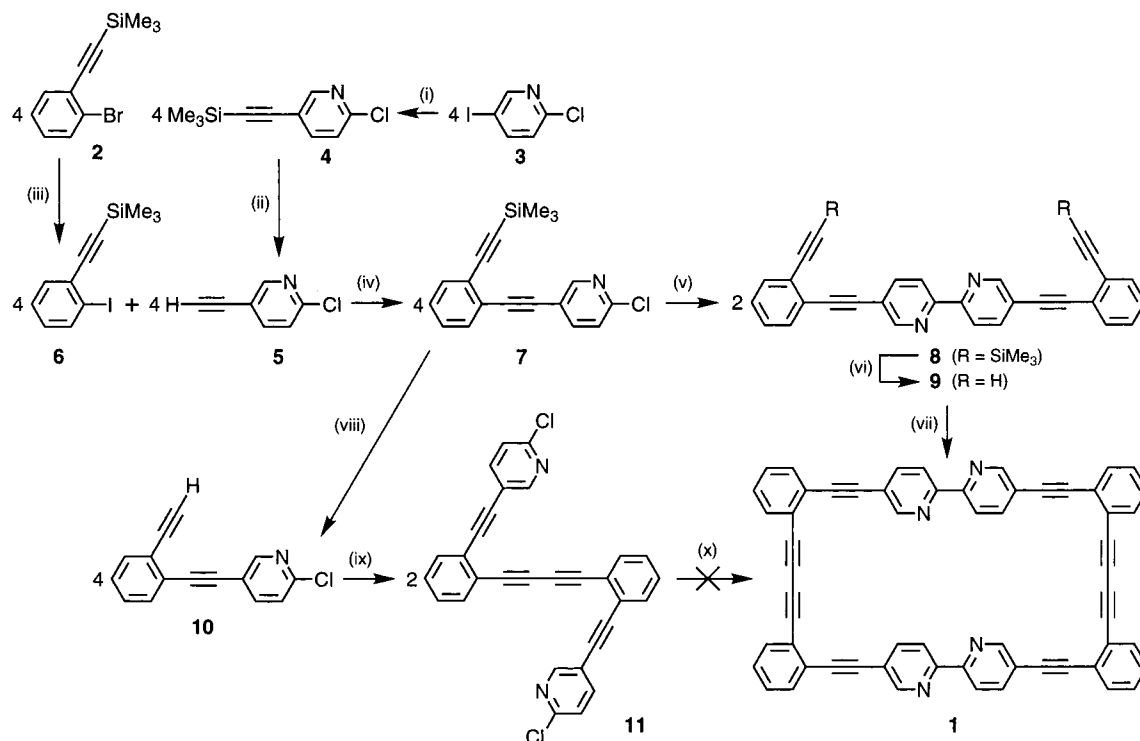
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Scheme 1. Synthesis of Macrocycle **1**^a

^a Reaction conditions and yields: (i) $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI cat., Et_3N , TMS(ethyne), 20°C , 48 h (94%); (ii) aqueous NaOH , THF, MeOH, 20°C , ≤ 24 h (82–95%); (iii) *n*-BuLi, Et_2O , -78°C , 3 h, then $\text{ICH}_2\text{CH}_2\text{I}$ quench (95%); (iv) $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI cat., Et_3N , 20°C , 48 h (80%); (v) Sn_2Me_6 , $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ cat., toluene, 120°C , 20 h, (73%); (vi) 1 M (*n*-Bu) $_4\text{NF}$, THF, H_2O , 20°C , 20 h (96%); (vii) CuCl cat., O_2 , pyridine, 20°C (34%); (viii) as in (ii) (95%); (ix) as in (vii) (86%); (x) as in (v), zero yield.

lithium–halogen exchange to give (2-lithiophenylethynyl)trimethylsilane, which was subsequently quenched with excess 1,2-diiodoethane to furnish **6** in 95% yield after workup. This lithiation/iodination protocol was found to be more efficient than that of the reported statistical preparation of **6** via a transition metal-catalyzed reaction between 1,2-diiodobenzene and trimethylsilylethyne.³¹ The latter approach necessitated the additional laborious chromatographic separation of the product from unreacted 1,2-diiodobenzene and 1,2-bis(trimethylsilylethynyl)benzene. The Sonogashira reaction of **6** with **5** at ambient temperature under conditions similar to those employed for the reaction with **2** in place of **6** resulted in the formation of **7** in 80% yield after chromatography.

Although surprisingly little used, a mild and efficient method for the palladium-catalyzed homocoupling of aryl halides has been reported using hexamethylditin as an in situ stannylating agent.^{32a–c} The documented ability of 2-chloropyridines to undergo Stille cross-coupling reactions^{33a,b} therefore suggested that the former methodology may be applicable to the homocoupling of **7**. However, refluxing **7** together with 0.6 equiv of Sn_2Me_6 and a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ in toluene solution

resulted only in the isolation of unreacted **7**. Subsequent experimental investigations revealed that a dramatic effect on the reaction occurred when the $\text{Pd}(\text{PPh}_3)_4$ was replaced by $\text{PdCl}_2(\text{dppf})$. Using the latter catalyst, the desired product 5,5'-bis[(2-trimethylsilylethynyl)phenyl]-2,2'-bipyridine (**8**) was isolated in 73% yield under identical reaction conditions. This effect may be related to the 96° P–Pd–P bite angle of $\text{PdCl}_2(\text{dppf})$, which lies at an optimal value for electronically facilitating the oxidative addition and reductive elimination steps of the catalytic cycle, and responsible for the enhanced activity of this complex.³⁴ The trimethylsilyl protecting groups of **8** were best removed with an aqueous THF solution of (*n*-Bu) $_4\text{NF}$ to give 5,5'-bis[(2-ethynyl)phenyl]-2,2'-bipyridine (**9**) in 96% isolated yield as an air-stable white solid. The alternative procedure using 1–5 equiv of aqueous NaOH per TMS group of **8** required extended reaction times and resulted in the formation of a crude product of inferior purity.

Finally, the CuCl -catalyzed oxidative Hay coupling³⁵ of **9** in pyridine solution at ambient temperature furnished the desired cyclophane **1** in 34% yield as an amorphous white, light-sensitive solid after workup. Prior to purification, the crude yield of **1** also contained a pale yellow byproduct that was completely insoluble in the conventional laboratory organic solvents and probably comprised uncyclized oligomeric and polymeric derivatives of **9**. Interestingly, the column chromatographic purification of **1** using toluene as the eluant failed to yield any trace of higher oligomeric cyclized homologues.

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However, the existence of such cyclic byproducts cannot be ruled out, as it may be that their solubility in toluene was also too low to allow isolation by chromatography. It must be noted that **1** was soluble in only a relatively restricted number of solvents such as hot 1,1,2,2-tetrachloroethane, toluene, pyridine, and very dilute, hot CHCl_3 .

In parallel to the above-described synthesis of macrocycle **1**, an alternative reaction pathway via the intermediate products **10** and **11** was also investigated (Scheme 1). Thus, aqueous NaOH-promoted deprotection of the trimethylsilyl group of **7** provided 2-chloro-5-[(2-ethynylphenyl)ethynyl]pyridine (**10**) in 95% yield after chromatography. Subsequent oxidative dimerization of **10** in pyridine solution at ambient temperature with a catalytic amount of CuCl furnished [1,3-butadiyne-1,4-diylbis(2,1-phenylene-2,1-ethynediyl)]-bis[5-(2-chloropyridine)] (**11**) in 86% isolated yield as light-sensitive crystals. Refluxing **11** together with 1.2 equiv of Sn_2Me_6 and a catalytic amount of $\text{PdCl}_2(\text{dppf})$ in toluene solution under medium dilution conditions resulted in complete reaction and consumption of the starting **11**. However no trace of **1** was detected in the reaction mixture, a result that is consistent with the instability of **11** toward thermally induced polymerizations under Stille coupling conditions.

Characterization of 1. The structure of the product isolated from the Hay coupling of **9** was established to be that of the macrocyclic architecture **1** (Scheme 1) on the basis of mass spectroscopic, infrared spectroscopic, ^1H NMR, and ^{13}C NMR studies.

The FAB mass spectrum of the coupling product recorded in CF_3COOH solution displayed only a single cluster of isotopic peaks, the most intense of which occurring at $m/z = 805$. The intensity and distribution pattern of the latter isotope cluster corresponded exactly to that calculated for the $M + 1$ isotopic envelope of the structure depicted for **1**. The high-resolution FAB mass spectrum of the latter $M + 1$ isotopic cluster also confirmed the exact elemental composition of the product to be $\text{C}_{60}\text{H}_{29}\text{N}_4$, i.e., that expected for the macrocyclic structural assignment for **1** plus a hydrogen atom.

The infrared spectrum of the Hay coupling product of **9** also reinforced the above structural assignment to that of **1**. The IR spectrum was surprisingly simple, displaying only five strong bands, and indicative of a highly symmetric structure such as **1**. In addition, the normally very intense peak originating from the $\nu(\text{C}-\text{H})$ stretch of a terminal ethyne was completely absent in the IR spectrum of the coupling product of **9**. This observation rules out the possibility of the product being a linear oligomer with terminal unreacted ethyne groups and establishes that it is a macrocyclic entity.

The ^{13}C NMR spectrum of the product from the coupling of **9** was also consistent with that of a macrocyclic structural identity and displayed the expected fifteen peaks, four of which corresponded to the carbons of two chemically and magnetically inequivalent difunctionalized ethynes at 78.1 to 92.0 ppm. The proton NMR spectrum of the coupling product of **9**, recorded at 100 °C in $\text{CDCl}_2\text{CDCl}_2$ was additionally supportive of the cyclic structure illustrated for **1** in Scheme 1, displaying the expected five peaks (two sets overlapping), and with a complete absence of any bands originating from the protons of terminal ethynes. The doublet at 7.88 ppm and the doublet of doublets at 7.80 ppm were assigned on the

basis of $^1\text{H}-^1\text{H}$ COSY connectivities and spectral comparisons with the proton NMRs of **7**, **8** and **9** to the respective H3 and H4 protons of the pyridine rings. The narrow doublet at 8.71 ppm was also thus assigned to the characteristically deshielded pyridine H6 proton. The pair of multiplets centered at 7.70 and 7.44 ppm on the other hand corresponded to those of the four chemically and magnetically inequivalent protons of the 1, 2-disubstituted phenyl rings. The former group of overlapping bands of simpler multiplicity were assigned to the H3 and H6 phenyl ring protons ortho to the alkynes. These would be expected to occur further downfield due to the electron-withdrawing effect of the pyridine rings transmitted through the intervening ethyne bonds. The latter higher field and more complex multiplet was therefore assigned to the overlapping signals of the phenyl ring H4 and H5 protons in meta and para positions with respect to the ethyne groups.

Interestingly, the chemical shifts of some of the protons in the ^1H NMR spectrum of **1** showed a marked temperature dependence (Figure 1). In particular, the 2,2'-bipyridine H3 protons experienced a significant and continual downfield shift from 7.68 to 7.91 ppm in $\text{CDCl}_2\text{-CDCl}_2$ solution upon increasing the temperature from zero to 120 °C. The phenomenon was completely reversible, as re-cooling resulted in regeneration of the original ambient temperature spectrum and reheating gave spectra identical to those previously obtained at high temperature. Comparison of the ambient temperature (25 °C) proton NMR spectrum of **1** with those of **8** and **9** revealed that the pyridine H3 protons of **1** occurred at an abnormally upfield position at 7.71 ppm. In **8** and **9**, the pyridine H3 protons were situated at 8.46 and 8.45 ppm, respectively, in CHCl_3 solution. Heating the solution of **1** therefore causes the surrounding chemical and magnetic environment of the pyridine H3 protons to become more similar to that of the corresponding protons of uncyclized **8** and **9**. Furthermore, heating a CHCl_3 solution of **8** from 25 to 60 °C resulted in only a small change in the chemical shift of the pyridine H3 protons from 8.46 to 8.47 ppm, showing that the temperature-dependent effect in **1** originates from the presence of a specific structural feature within the latter compound.

A possible explanation for the unusually shielded environment of the pyridine H3 protons of **1** and their progressive deshielding upon increasing the temperature may lie in the conformational properties of the macrocyclic architecture. Molecular modeling performed upon the cyclic architectural assignment of **1** (Figure 2) showed the minimum energy conformation to be highly twisted with the 2,2'-bipyridine units in very close proximity. The pyridine H3 protons in particular lie closest of all to each adjacent 2,2'-bipyridine unit. They must therefore spend a significant period of time on the NMR time scale lying against the surface of the partner 2,2'-bipyridine unit and pointing toward the interior of the cavity of **1** as the two 2,2'-bipyridines rotate alongside each other. As a result, the pyridine H3 protons would be expected to be shielded to a greater extent than normal. Furthermore, the twisted conformation of **1** is chiral and possibly flexible enough to allow facile enantiomer interconversion via a flattened and open macrocyclic transition state. Increasing the temperature of the system would induce an increased degree of enantiomer interconversion and thus an increased opening of the macrocyclic ring. The pyridine H3 protons would therefore experience a greater

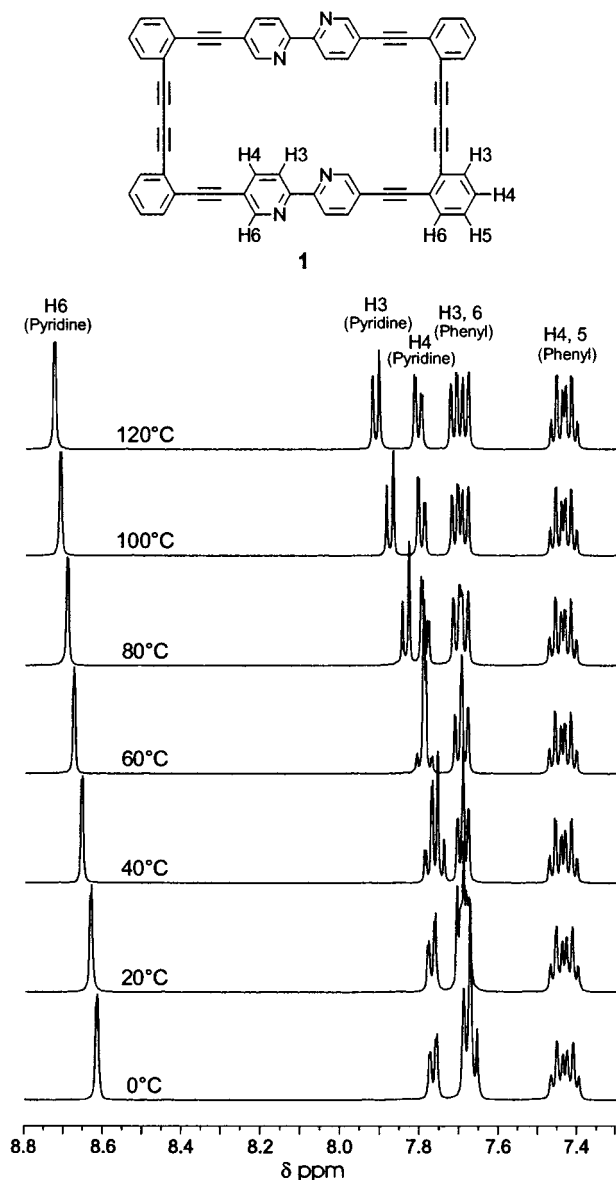


Figure 1. Variation in the chemical shifts of the protons of **1** with temperature. Note the maximum relative deshielding experienced by the pyridine H3 protons upon increasing temperature (the ^1H NMR spectra were recorded at 500 MHz in $\text{CDCl}_2\text{CDCl}_2$ solution).

degree of exposure to the surrounding medium at successively higher temperatures and thus a progressively increasing degree of deshielding.

Spectroscopic Sensing of Metal Ions by 1. The relatively rigid and twisted structure of cyclophane **1** comprises a mutually crossed arrangement of two 2,2'-bipyridine ligands in its lowest energy conformation (Figure 2), held in position by two bridging diphenyl-1,4-butadienyl subunits on opposite sides of the macrocycle. Product **1** may therefore be described as a "twistophane", the distinctive and specific structural features of which constitute a rare but slowly expanding class of cyclophane scaffolds.^{26,36a-f} Molecular modeling studies on **1** also revealed that when the 2,2'-bipyridine rings are in a cisoid conformation with all nitrogen lone pairs directed toward the interior of the cavity of the macrocycle, small flexures in the ligand framework can open up a small central void. The cavity possesses an enforced tetrahedral arrangement of nitrogen lone pair electrons that would

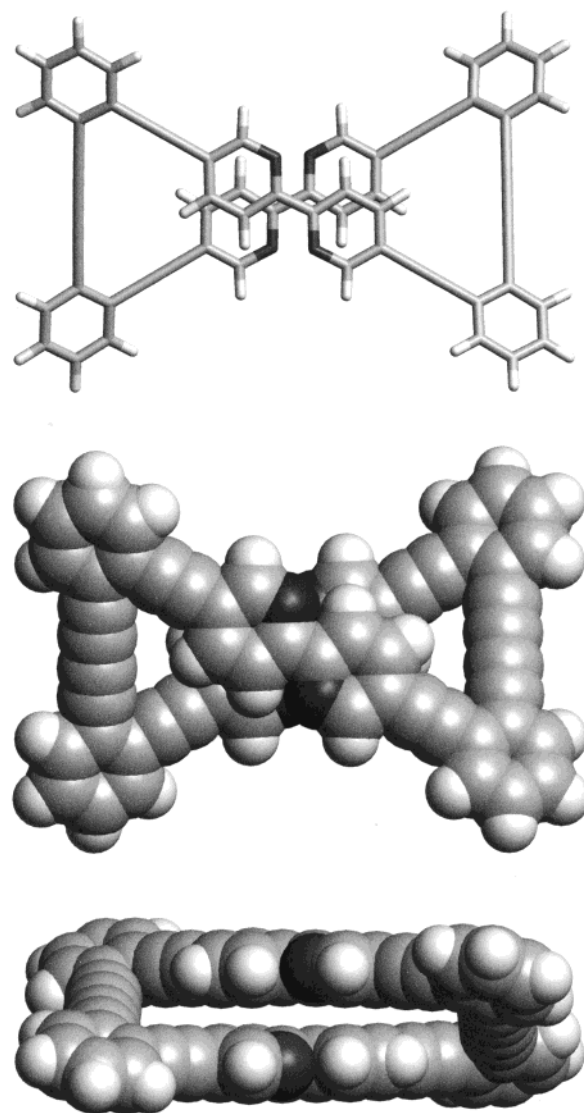


Figure 2. Energy-minimized structure of macrocycle **1** showing the chirally twisted cyclophane framework: plan view stick representation (top), CPK representation (center), and side view through ring (bottom), CPK representation. (The minimization was performed using the MMFF force field with MacroModel version 5.5 (Columbia University, NY).)

be expected to be able to bind metal ions of complementary size. This possibility coupled with the enhanced cyclic conjugation resulting from the intervening ethynyl and butadienyl bridges suggested that **1** may display very selective binding characteristics toward particular metal ions and that it would also undergo spectroscopic changes upon coordination. Subsequent experimental investigations confirmed that this was indeed the case.

UV/Vis Absorption Spectra. To obtain a detailed picture of the coordination properties of **1**, UV/vis spectra

(36) For reports on the preparation of structurally related, twisted macrocyclic hydrocarbons, see: (a) Baldwin, K. P.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J. *Synlett*, **1993**, 853. (b) Guo, L.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J. *J. Chem. Soc., Chem. Commun.* **1994**, 243. (c) Baldwin, K. P.; Simons, R. S.; Rose, J.; Zimmerman, P.; Hercules, D. M.; Tessier, C. A.; Youngs, W. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1257. (d) Haley, M. M.; Bell, M. L.; English, J. J.; Johnson, C. A.; Weakley, T. J. R. *J. Am. Chem. Soc.* **1997**, *119*, 2956. (e) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 385. (f) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 3189.

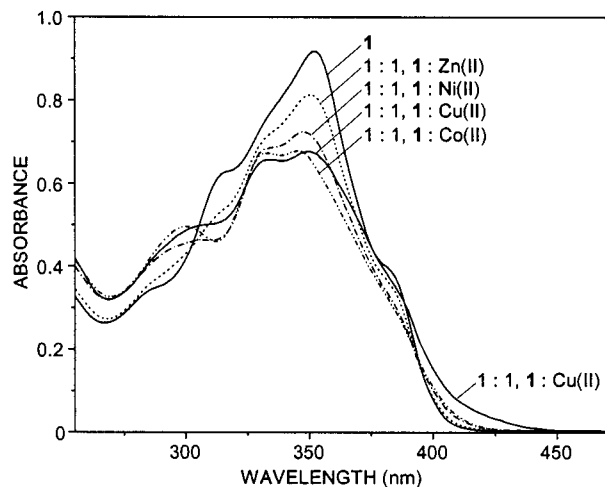


Figure 3. UV/vis absorption spectra of 1:1 stoichiometric mixtures of **1** with M^{2+} in 1:2, $\text{CHCl}_3/\text{MeOH}$, where $M^{2+} = \text{Co}^{2+}$, Ni^{2+} , Cu^{2+} and Zn^{2+} and at a [**1**] of $6.56 \times 10^{-6} \text{ mol L}^{-1}$.

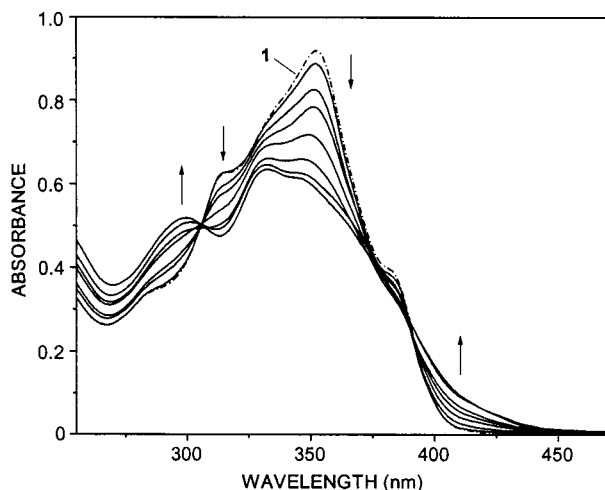


Figure 4. UV/vis spectra of the titration of Cu^{2+} into **1** at a [**1**] of $6.56 \times 10^{-6} \text{ mol L}^{-1}$ in 1:2 $\text{CHCl}_3/\text{MeOH}$ and 1/ Cu^{2+} ratios of, respectively, 1:0.2, 1:0.4, 1:0.6, 1:0.8, 1:1, 1:1.5, and 1:3.

of 1:1 stoichiometric mixtures of $1:M^{n+}$ in 1:2 $\text{CHCl}_3/\text{MeOH}$ were recorded at a [**1**] of $6.56 \times 10^{-6} \text{ mol L}^{-1}$. The UV/vis spectra of free uncoordinated **1** in 1:2 $\text{CHCl}_3/\text{MeOH}$ and pure CHCl_3 display a series of intense absorption maxima at 316, 356, and 384 nm, characteristic of conjugated oligophenylethynyl structures. The energies and shape of these bands remained invariant over the concentration range of 8.7×10^{-7} – $1.1 \times 10^{-5} \text{ mol L}^{-1}$ in CHCl_3 showing that **1** was not undergoing aggregation in dilute solution. A slight hypsochromic shift in the most intense absorption from 356 to 352 nm did, however, occur upon changing the solvent from pure CHCl_3 to 1:2 $\text{CHCl}_3/\text{MeOH}$. Stoichiometric 1:1 solutions of **1** with Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} in 1:2 $\text{CHCl}_3/\text{MeOH}$ gave spectra that were significantly different from that of the free ligand and indicative of coordination of these metal ions to **1** (Figures 3–5). In all four cases, the presence of the metal ion caused a significant reduction in the extinction coefficient of the most intensely absorbing band of the free ligand at 352 nm and an accompanying slight shift to higher energy. The maxima at 316 and 384 nm in the spectrum of **1** also completely disappeared in the presence of \geq stoichiometric ratios of the above

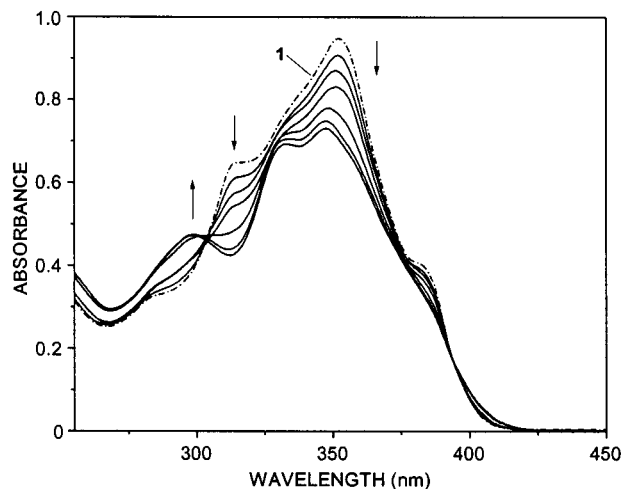


Figure 5. UV/vis spectra of the titration of Zn^{2+} into **1** at a [**1**] of $6.56 \times 10^{-6} \text{ mol L}^{-1}$ in 1:2 $\text{CHCl}_3/\text{MeOH}$ and 1/ Zn^{2+} ratios of, respectively, 1:0.5, 1:0.75, 1:1, 1:1.5, 1:2, and 1:2.5.

metal ions and were instead replaced by two new bands at 299 and 332 nm, respectively. The relative magnitudes of the metal ion-induced perturbations of the absorption envelopes of 1:1 solutions of $1:M^{n+}$ in 1:2 $\text{CHCl}_3/\text{MeOH}$ were found to lie in the following order $\text{Cu}^{2+} \approx \text{Co}^{2+} > \text{Ni}^{2+} > \text{Zn}^{2+}$ (Figure 3).³⁷

The addition of Co^{2+} and Cu^{2+} (Figures 3 and 4) therefore provokes the greatest and most dramatic changes in the UV/vis spectrum of **1**, and Zn^{2+} gives the smallest perturbation within the series (Figures 3 and 5). In addition, Cu^{2+} causes a further bathochromic shift in the edge of the lowest energy absorption envelope of **1** (Figure 4). This effect is signaled by the development of a yellow coloration at 1/ Cu^{2+} ratios of 1: \geq 2. On the other hand, either negligible or zero changes were observed in the UV/Visible spectrum of **1** upon 1:1 stoichiometric combination with M^{n+} in 1:2 $\text{CHCl}_3/\text{MeOH}$ at a [**1**] of $6.56 \times 10^{-6} \text{ mol L}^{-1}$, where $M^{n+} = \text{Li}^+$, Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Sc^{3+} , Cr^{3+} , Mn^{2+} , Fe^{2+} , Ag^+ , Cd^{2+} , Hg^{2+} , Pb^{2+} , Tl^+ , In^{3+} , La^{3+} , Eu^{3+} , and Tb^{3+} .³⁸ Macrocycle **1** therefore exhibits preferential binding to late first row transition metals, i.e., metal cations which satisfy the following criteria: (1) high surface charge density, (2) ionic radii $\leq 0.96 \text{ \AA}$ (i.e., the radius of Cu^+ , which was the largest cation found to interact with **1**),³⁷ (3) adaptable coordination polyhedra, and (4) an electronic preference for nitrogen donor ligands.

To evaluate the ability of **1** to discriminate and signal specific metal ions in the presence of other metal cations, competitive binding experiments were performed. Thus,

(37) The metal ion salts used in the study were $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, ZnCl_2 , and $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ and were all $\geq 99.9\%$ purity. They were each dissolved into one drop of distilled water prior to the preparation of standard solutions in methanol in order to ensure complete solubility. Copper(I) in the form of $[\text{Cu}(\text{MeCN})_4](\text{CF}_3\text{SO}_3)$, also bound to **1** as evidenced by coordination induced perturbations in the UV/vis spectrum of the ligand. This was not investigated further at this stage as a greater number of sensory applications are to be found for copper(II) which is both more stable and of greater abundance in nature.

(38) Chromium(III) and iron(II) were used as the respective $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and anhydrous FeCl_2 salts, and were also dissolved into a drop of distilled water prior to solution preparation in MeOH . All remaining metal ions investigated were in the form of the anhydrous triflate salts. A 1:1 mixture of $\text{NH}_4(\text{CF}_3\text{SO}_3)$ and **1** in 1:2 $\text{CHCl}_3/\text{MeOH}$ at the same concentration as that used for the metal ion-binding studies produced no change in the UV/vis spectrum of the ligand, indicating a weak or negligible interaction between the latter two species.

UV/vis spectra of **1** at 6.56×10^{-6} mol L⁻¹ with stoichiometric mixtures of ions taken from the series Co²⁺, Ni²⁺, Cu²⁺, and Zn²⁺ were recorded in 1:2 CHCl₃/MeOH and compared to those of the corresponding 1:1 **1**/Mⁿ⁺ solutions. A 1:1:1 mixture of **1**/Zn²⁺/Cu²⁺ yielded a spectrum intermediate in intensity and shape between those of the 1:1 **1**/Zn²⁺ and **1**/Cu²⁺ spectra, suggesting that **1** has a similar binding propensity toward both Zn²⁺ and Cu²⁺. Mixtures of 1:1:1 **1**/Zn²⁺/Co²⁺ and **1**/Zn²⁺/Ni²⁺, on the other hand, gave spectra identical to those of the 1:1 **1**/Co²⁺ and **1**/Ni²⁺ spectra, showing that Zn²⁺ is displaced from **1** by Co²⁺ and Ni²⁺. A 1:1:1 mixture of **1**/Co²⁺/Ni²⁺ gave a spectrum intermediate between those of the 1:1 **1**/Co²⁺ and **1**/Ni²⁺ spectra, indicating that these two metal ions have similar binding preferences toward **1**. These results therefore demonstrate that the metal ion binding strengths to **1** follow the qualitative order Co²⁺ ≈ Ni²⁺ > Cu²⁺ ≈ Zn²⁺. Interestingly, a 1:1:1:1 mixture of **1**/Zn²⁺/Cd²⁺/Hg²⁺ was identical to that of the 1:1 **1**/Zn²⁺ solution at the same [1]. This remarkably strong selectivity for Zn²⁺ in the presence of Cd²⁺ and Hg²⁺ ions must reflect the importance of complementarity in size between the Zn²⁺ ion and the ligating cavity of **1**. Cd²⁺ and Hg²⁺ are presumably too large to coordinate both 2,2'-bipyridine binding sites of **1** in a strain-free conformation.

The metal ion-complexation studies thus revealed that macrocycle **1** functions as a UV/vis spectroscopic sensor for Co²⁺, Ni²⁺, Cu²⁺, and Zn²⁺. Of all metal ions investigated, Cu²⁺ was found to induce the greatest bathochromic shift in the lower energy absorption edge of **1** (Figure 4). The detection limit for Cu²⁺ was estimated to be at a [Cu²⁺] of 2.63×10^{-6} mol L⁻¹ in the latter spectral window of 390–435 nm. Macrocycle **1** may therefore potentially function as a chromogenic spectroscopic sensor for Cu²⁺ providing that the interfering Co²⁺, Ni²⁺, and Zn²⁺ cations that compete for binding to **1** are absent.³⁹

Fluorescence Emission Spectra. The fluorescence emission spectrum of free uncoordinated **1** in CHCl₃ solution at 6.56×10^{-7} mol L⁻¹ comprised two emission maxima at 406 and 431 nm when excited at the wavelength of the absorption peaks at 316, 356 and 384 nm respectively. Emission spectra of **1** recorded over the concentration range of 6.56×10^{-8} – 6.56×10^{-6} mol L⁻¹ showed negligible shifts in the energy of the maxima indicating that aggregation of the excited state of **1** was not a dominant process. Emission spectra were then recorded of 1:1 stoichiometric combinations of **1**/Mⁿ⁺ in 1:2 CHCl₃/MeOH at a [1] of 6.56×10^{-7} mol L⁻¹, and where Mⁿ⁺ = Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Sc³⁺, Cr³⁺, Mn²⁺, Fe²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺, Ag⁺, Cd²⁺, Hg²⁺, Pb²⁺, Tl⁺, In³⁺, La³⁺, Eu³⁺, and Tb³⁺.³⁸ Of all metal ions investigated, only Co²⁺, Ni²⁺, Cu²⁺, and Zn²⁺ induced changes in the fluorescence emission of **1**.³⁷ The presence of Ni²⁺ caused only a minor reduction in the fluorescence intensity of **1**, and with no change in emission energy. However with Co²⁺ and Cu²⁺ a significant drop in the fluorescence intensity of **1** occurred. This latter effect was dramatically signaled visually by an almost total extinction of the characteristic strong purple-blue colored emission of free **1** at a 1:1 **1**/M²⁺ ratio.

Zinc ions on the other hand produced an entirely different effect upon the fluorescence emission of **1**. Thus

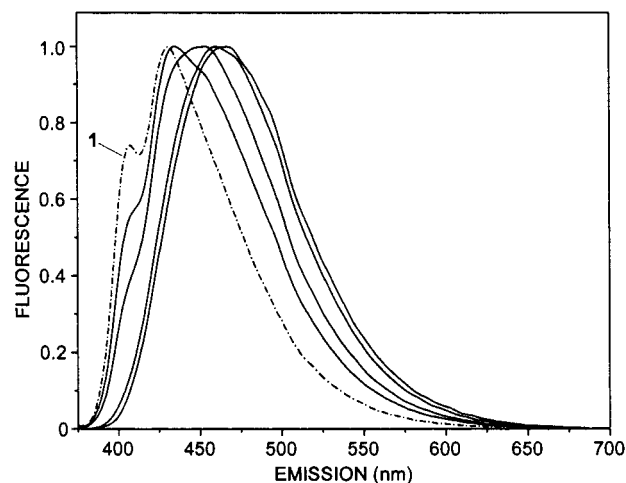


Figure 6. Normalized fluorescence emission spectra (from left to right) of uncomplexed **1** and mixtures comprising **1**/Zn²⁺ ratios of, respectively, 1:5, 1:10, 1:100, and 1:1000 in 1:2 CHCl₃/MeOH and at a [1] of 6.56×10^{-7} mol L⁻¹.

increasing the **1**/Zn²⁺ ratio from 1:1 to 1:100 caused the initial disappearance of the higher energy, lower intensity emission maximum of **1** at 406 nm and a concomitant broadening and shifting of the remaining higher intensity emission envelope at 431 nm to lower energy. Further incremental additions of Zn²⁺ resulted in only minor movements of the emission maximum to lower energy. The emission maximum eventually reached a limiting value of 466 nm at a **1**/Zn²⁺ ratio of 1:1000 (Figure 6). This process could be clearly visualized as a progressive change in color from the purple-blue fluorescence of pure **1** to a bright turquoise fluorescence characteristic of the Zn²⁺ complex of **1**. The concentration limit for the detection of Zn²⁺ ions as indicated by the onset of the turquoise fluorescence was estimated to be at a **1**/Zn²⁺ ratio of 1:5 corresponding to a [Zn²⁺] of 3.3×10^{-6} mol L⁻¹. Significantly, a 6.56×10^{-6} mol L⁻¹ solution of **1** in CHCl₃ was able to extract ZnCl₂ from aqueous solution in the presence of MeOH at **1**/Zn²⁺ ratios of 1:≥100. This latter phenomenon was again signaled by the appearance of a turquoise fluorescence in the organic layer, and is particularly noteworthy considering the fact that **1** is totally insoluble in water. The fact that **1** is able to extract Zn²⁺ out of aqueous solution highlights the potential practical utility of this type of ligand for metal ion sensing, as further synthetic incorporation of water solubilizing groups may not be a prerequisite for the sensory detection of aqueous analytes.

Macrocycle **1** therefore functions as a multisubstrate, multiple readout sensor that is able to generate different sequences of output responses depending upon the way the system is externally addressed. For example, the presence of Co²⁺ is signaled by both a decrease in the UV/vis absorption and fluorescence emission intensities of **1**. The output response for Cu²⁺ consists of a reduction in the intensity of the fluorescence emission and absorption maxima of **1**, but with an accompanying bathochromic shift of the lower energy absorption edge. However, in the case of Zn²⁺ as the input, a reduction in the intensity of the absorption maxima of **1** occurs, but the fluorescence emission undergoes a pronounced bathochromic shift which is visually signaled by the development of a turquoise fluorescence.^{40a-c}

(39) This limitation may potentially be overcome by the selective precipitation of interfering cations within the sample prior to the introduction of the sensor.

Conclusion

In summary, the above work describes the successful preparation of macrocycle **1**, which is the first representative member of a new class of "bow-tie" shaped, geometrically twisted metal ion-coordinating cyclophane or "twistophane" ligands. The synthesis was readily accomplished using standard organometallic coupling protocols in a relatively short number of steps starting from the commercially available (2-bromophenylethynyl)trimethylsilane (**2**) and 2-chloro-5-iodopyridine (**3**). Thus, **3** was converted to **5** by a reported procedure and the latter reacted with **6**, the lithiation/iodination product of **2**, to give intermediate **7**. Product **7** was then coupled to give **8** in the presence of Sn_2Me_6 via a palladium-catalyzed Stille reaction. The type of palladium catalyst used for the homocoupling of **7** was found to be of crucial importance. Highest yields of the coupled product **8** were obtained with $\text{PdCl}_2(\text{dppf})$. Bipyridine **8** was then smoothly deprotected to give the bis-terminal ethyne **9** and the latter cyclodimerized to give the final product **1**, via the CuCl -catalyzed oxidative Hay coupling procedure. The convenience and economy of the above synthetic pathway to **1** makes this approach very attractive for the generation of larger quantities of **1**, and as a potentially general method for the preparation of structurally related twistophane ligands.

The macrocyclic structural assignment of **1** was established on the basis of mass spectrometry and IR and NMR spectroscopy. Interestingly, the ^1H NMR of **1** displayed temperature-dependent dynamic phenomena between zero and 120 °C. In particular, the 2,2'-bipyridine H3 protons moved downfield upon heating and upfield upon cooling. This may be attributed to temperature-dependent opening and closing motions of the macrocycle as it interconverts between the two enantiomeric forms of **1**. Molecular modeling of the macrocyclic structure of **1** confirmed the overall chirally twisted framework of the lowest energy conformation. The latter study also revealed the close proximity of the H3 protons of the two 2,2'-bipyridine units as they reside alongside each other, lending further support for the explanation of the marked temperature dependence of the ^1H NMR chemical shift of these protons.

Macrocycle **1** possesses specific structural features such as (1) a relatively rigid hydrocarbon framework comprising ethynyl and phenyl subunits which is (2) cyclically conjugated when the 2,2'-bipyridine moieties are in planar conformations and (3) an enforced tetrahedral coordination pocket when bound to a metal ion of appropriate size. The summed effect of these characteristics suggested that **1** might experience electron cloud perturbations upon coordination, and may function as a spectroscopic sensor for specific types of metal ions. Investigations into the metal ion coordination behavior of **1** showed that it responded spectroscopically to a surprisingly narrow range of cations comprising Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} . Of particular significance is the fact that **1** displays differing sequences of signal output depending on the identity of the metal ion with which

the system is addressed. In this respect, twistophane **1** operates as a multisubstrate, multiple readout sensor for multiple types of metal ion analyte. The specific fluorescence chromogenic sensing of Zn^{2+} by **1** is especially interesting in the light of the biological importance of this metal ion.⁴¹ Macrocycle **1** and related structures may therefore find potential applications in the detection and monitoring of Zn^{2+} in biological media.

Many structural modifications of the conjugated framework of **1** may be envisioned in order to further refine and optimize its sensory properties and selectivity toward particular metal ions.^{42a-d} The structural and physicochemical properties of twistophane **1** therefore suggest that this fascinating new type of metal ion-binding cyclophane may potentially discover a rich variety of future applications in fields such as molecular sensorics, catalysis and materials science, and for obtaining fundamental insights into unusual metal ion-ligand coordination processes.

Experimental Section

Methods and Materials. Standard inert atmosphere and Schlenk techniques were employed for reactions conducted under argon. The reagents 1,2-diiodoethane, (2-bromophenylethynyl)trimethylsilane (**2**),⁴³ trimethylsilylethyne, and catalysts $\text{PdCl}_2(\text{PPh}_3)_2$,^{44a-c} $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$,^{45a,b} CuI , and CuCl were purchased from Aldrich and used as received. Hexamethylditin was prepared according to a published procedure.⁴⁶ The Et_2O was freshly distilled off sodium/benzophenone under argon and the toluene used in the preparation of **8**, was degassed by bubbling with argon directly before use. Intramolecular proton connectivities were unambiguously determined

(41) More than 200 zinc proteins are currently known and perform a spectacular range of biological functions. For example synthase, ligase and polymerase enzymes that catalyze the metabolic conversion of proteins, nucleic acids, lipids and porphyrin precursors, etc. Zinc also plays a structural role in the conformational stabilisation of, for example insulin, hormone receptor complexes and transcription regulating factors for the transfer of genetic information. Zinc is thus ubiquitous in life, and new methods for the selective detection and monitoring of this important metal ion will therefore continue to be of paramount interest. Kaim, W.; Schwederski, B. *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*; John Wiley & Sons Ltd.: New York, 1998; Chapter 12, p 242.

(42) For example, increasing the degree of conjugation and incorporation of organic donor/acceptor dyes to enhance the chromogenic response, and variations in the geometry, denticity and donor ability of the binding sites to induce greater metal ion specificity and discrimination. Furthermore, under particular conditions, it may be possible to isolate $[\text{M1}]^{n+}$ complexes with metal ions that do not normally occur with a tetrahedral coordination polyhedron of nitrogen donor ligands. Compounds such as these would for example enable the physicochemical properties of entatic state models to be measured as well as functioning as a new class of redox catalysts. For reports on the syntheses of ligands which enforce tetrahedral coordination geometries around metal ions upon binding, and the properties of their metal complexes, see: (a) Knapp, S.; Keenan, T. P.; Zhang, X.; Fikar, R.; Potenza, J. A.; Schugar, H. J. *J. Am. Chem. Soc.* **1987**, *109*, 1882. (b) Müller, E.; Piguët, C.; Bernardinelli, G.; Williams, A. F. *Inorg. Chem.* **1988**, *27*, 849. (c) Judice, J. K.; Keipert, S. J.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1323. (d) Frydendahl, H.; Toftlund, H.; Becher, J.; Dutton, J. C.; Murray, K. S.; Taylor, L. F.; Anderson, O. P.; Tiekink, E. R. T. *Inorg. Chem.* **1995**, *34*, 4467. An additional possibility for **1** is that of exo-coordination in the case where all the 2,2'-bipyridine nitrogens point outwardly and in an opposite direction to the centroid of the macrocyclic ring. This latter mode of binding would give rise to $[\text{M}_2\text{1}]^{2m+}$ complexes from which intriguing types of metallocyclophane polymer materials could be constructed.

(43) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637.

(44) (a) Chatt, J.; Mann, F. G. *J. Chem. Soc.* **1939**, p1631. (b) Tayim, H. A.; Bouldoukian, A.; Awad, F. *J. Inorg. Nucl. Chem.* **1970**, *32*, 3799. (c) Brumbaugh, J. S.; Sen, A. *J. Am. Chem. Soc.* **1988**, *110*, 803.

(45) (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158. (b) Corain, B.; Longato, B.; Favero, G.; Ajò, D.; Pilloni, G.; Russo, U.; Kreissl, F. R. *Inorg. Chim. Acta*, **1989**, *157*, 259.

(40) For a detailed review on sensory optodes for metal ions, see: (a) Bühlmann, P.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593. For an earlier approach to the fluorescence sensing of zinc(II) using modified zinc fingers, see: (b) Walkup, G. K.; Imperiali, B. *J. Am. Chem. Soc.* **1997**, *119*, 3443. For a recent review on the fluorescence sensing of zinc(II) ions with polyamine macrocycles, see: (c) Pina, F.; Bernardo, M. A.; Garcia-España, E. *Eur. J. Inorg. Chem.* **2000**, 2143.

by ^1H – ^1H COSY measurements. The fluorescence spectra were recorded at 25 °C on a Aminco, Bowman Series 2 luminescence spectrophotometer (SLM Instruments, Inc.) and were corrected for the instrumental response.⁴⁷ Melting point measurements were performed on an Electrothermal Digital Melting Point apparatus calibrated with standards of known melting points. Elemental analyses were performed by the Service de Microanalyse, Institut de Chimie, Université Louis Pasteur.

(2-Iodophenylethynyl)trimethylsilane (6). Dry Et₂O (55 mL) was added via syringe to 5.173 g (2.04×10^{-2} mol) of **2** in a dried argon-filled flask equipped with an alcohol thermometer, septum, and argon/vacuum inlet adaptor. The stirred solution was then cooled to –78 °C, and 13.2 mL (2.11×10^{-2} mol) of 1.6 M *n*-butyllithium was added dropwise via syringe. The colorless reaction solution was stirred at –70 to –78 °C for 0.5 h, allowed to warm to 0 °C over 2.5 h, and finally recooled to –78 °C with continued stirring. Dry Et₂O (23 mL) was syringed into a separate dried argon-filled Schlenk containing 6.66 g (2.36×10^{-2} mol) of 1,2-diiodoethane, and this solution was subsequently added dropwise via syringe to the previously prepared (2-lithiophenylethynyl)trimethylsilane solution at a rate that maintained the reaction temperature between –60 and –78 °C. Toward the end of the addition, a suspended white solid formed. The mixture was stirred at –70 °C for 1 h, allowed to warm to 0 °C with stirring, and quenched by the addition of 5 mL of water. The solution was extracted with water (2 × 50 mL), the organic layer dried (MgSO₄) and filtered, and the solvent distilled off on a waterbath at atmospheric pressure. The crude product oil was finally purified by flash chromatography on silica with hexane eluant followed by drying under vacuum (0.01 mmHg) for 48 h to remove residual diiodoethane, to yield 5.826 g (95%) **6** as a pungent smelling oil. The spectral properties of the product **6** were as reported.^{31, 48}

2-Chloro-5-[(2-trimethylsilylethynylphenyl)ethynyl]pyridine (7). Triethylamine (15 mL) was added via syringe to a mixture of 0.829 g (6.03×10^{-3} mol) of **5**,²⁸ 1.824 g (6.08×10^{-3} mol) of **6**, and 0.086 g (1.23×10^{-4} mol) of PdCl₂·(PPh₃)₂ under an atmosphere of argon and the suspension stirred for 0.2 h. A solution of 0.084 g (4.41×10^{-4} mol) of CuI in 5 mL of triethylamine was then added via syringe, and stirring was continued for 48 h at ambient temperature. During this time, the initially formed khaki precipitate became dark brown in color. After 48 h, all solvent was removed under reduced pressure and the residue extracted with boiling hexane (4 × 20 mL). The combined hexane extracts were filtered, the solvent distilled off under reduced pressure, and the residue flash chromatographed on silica eluting with 1:1 CH₂Cl₂/hexane. The product thus obtained was finally boiled in 50 mL of MeOH with 0.1 g of Norit A decolorizing charcoal, the mixture filtered, and the solvent removed under reduced pressure. Further drying under vacuum (0.01 mmHg) yielded 1.492 g (80%) of **7** as a pale yellow oil that slowly crystallized to a cream solid (mp 47.0–49.6 °C) upon standing for several days.

¹H NMR (CDCl₃, 500 MHz, 25 °C) δ: 8.56 (d, ⁴J_{6,4} = 1.7 Hz, 1H; pyridine H6), 7.77 (dd, ³J_{4,3} = 8.3 Hz, ⁴J_{4,6} = 2.4 Hz, 1H; pyridine H4), 7.52 (m, 2H; phenyl H3, 6), 7.34 (dd, ³J_{3,4} = 8.2 Hz, ⁵J_{3,6} = 0.6 Hz, 1H; pyridine H3), 7.31 (m, 2H; phenyl H4,

5), 0.26 (s, 9H; Si(CH₃)₃). ¹³C NMR (CDCl₃, 125.8 MHz, 25 °C) δ: ppm: 152.1, 150.6, 140.8, 132.4, 131.8, 128.6, 128.3, 125.8, 124.9, 123.9, 119.4, 103.0 (C≡C), 99.2 (C≡C), 92.5 (C≡C), 88.4 (C≡C), 0.0 (Si(CH₃)₃). EIMS *m/z*: 309 (M⁺, 60), 294 ([M – Me]⁺, 100), 258 ([M – Me – Cl]⁺, 20). Anal. Calcd for C₁₈H₁₆ClN₃: C, 69.77; H, 5.20; N, 4.52. Found: C, 69.51; H, 4.98; N, 4.44.

5,5'-Bis[(2-trimethylsilylethynylphenyl)ethynyl]-2,2'-bipyridine (8). Toluene (25 mL) was added via syringe to a mixture of 1.007 g (3.25×10^{-3} mol) of **7** and 0.069 g (8.45×10^{-5} mol) of PdCl₂(dppf)·CH₂Cl₂ under an atmosphere of argon. Hexamethylditin (0.584 g, 1.78×10^{-3} mol) was then added via microsyringe and the reaction stirred and heated in a bath at 120 °C for 20 h. The reaction darkened considerably during reflux. After heating, all solvent was removed under reduced pressure, CH₂Cl₂ added, and the solution flash column chromatographed on silica eluting with 1% MeOH/CH₂Cl₂. The product thus obtained was then recrystallized from boiling ethanol and dried under vacuum (0.01 mmHg) to give 0.649 g (73%) of **8** as pale yellow needles (mp 199.0–200.1 °C).

¹H NMR (CDCl₃, 500 MHz, 24 °C) δ: 8.84 (d, ⁴J_{6,4} = 1.4 Hz, 2H; pyridine H6), 8.46 (d, ³J_{3,4} = 8.2 Hz, 2H; pyridine H3), 7.97 (dd, ³J_{4,3} = 8.2 Hz, ⁴J_{4,6} = 2.2 Hz, 2H; pyridine H4), 7.55 (m, 4H; phenyl H3, 6), 7.32 (m, 4H; phenyl H4, 5), 0.29 (s, 18H; Si(CH₃)₃). ¹³C NMR (CDCl₃, 125.8 MHz, 24 °C) δ: 154.2, 151.7, 139.5, 132.4, 131.9, 128.5, 128.3, 125.8, 125.3, 120.7, 120.5, 103.2 (C≡C), 99.1 (C≡C), 92.6 (C≡C), 90.2 (C≡C), 0.0 (Si(CH₃)₃). UV/vis (CHCl₃) λ (nm) (ε, M⁻¹ cm⁻¹): 353 (82300). Fluor. emission (CHCl₃, 350 nm excitation) λ (nm): 388, 410. IR cm⁻¹: 2958s, 2159s ν(C≡C), 1481s, 1249s, 873s, 841s, 755s. EIMS *m/z*: 548 (M⁺, 100), 533 ([M – Me]⁺, 29). Anal. Calcd for C₃₆H₃₂N₂Si₂: C, 78.78; H, 5.88; N, 5.10. Found: C, 78.70; H, 5.92; N, 5.10.

5,5'-Bis[(2-ethynylphenyl)ethynyl]-2,2'-bipyridine (9). To a stirred solution of 0.250 g (4.56×10^{-4} mol) of **8** in 15 mL of THF and 0.5 mL of distilled water was added 1.10 mL (1.10×10^{-3} mol) of a 1.0 M solution of (*n*-Bu)₄NF in THF and the reaction stirred at ambient temperature for 20 h. All solvent was then removed under reduced pressure on a waterbath, and 20 mL of distilled water was added to the residue. The mixture was briefly ultrasonicated and the suspended solid isolated by filtration under vacuum, washed with excess distilled water, and air dried. The crude product was purified by flash chromatography on silica eluting with 1% MeOH/CH₂Cl₂ and then washed with Et₂O and air dried to give 0.177 g (96%) of **9** as white flakes (mp 201.0–201.5 °C dec).

¹H NMR (CDCl₃, 500 MHz, 25 °C) δ: 8.85 (s, 2H; pyridine H6), 8.45 (d, ³J_{3,4} = 8.3 Hz, 2H; pyridine H3), 7.97 (dd, ³J_{4,3} = 8.2 Hz, ⁴J_{4,6} = 2.1 Hz, 2H; pyridine H4), 7.58 (m, 4H; phenyl H3, 6), 7.35 (m, 4H; phenyl H4, 5), 3.41 (s, 2H; ethyne H). ¹³C NMR (CDCl₃, 125.8 MHz, 25 °C) δ: 154.2, 151.9, 139.4, 132.7, 131.9, 128.6, 128.5, 125.6, 124.8, 120.6, 120.4, 92.2 (C≡C), 90.4 (C≡C), 82.0 (C≡C), 81.5 (C≡C). UV/vis (CHCl₃) λ (nm) (ε, M⁻¹ cm⁻¹): 351 (65870), 373sh (41220). Fluor. emission (CHCl₃, 350 nm excitation) λ (nm): 385, 406. IR cm⁻¹: 3294s ν(C≡C–H), 3285s ν(C≡C–H), 1480s, 846s, 761s, 652s. EIMS *m/z*: 404 (M⁺, 100). Anal. Calcd for C₃₀H₁₆N₂: C, 89.09; H, 3.99; N, 6.93. Found: C, 89.26; H, 3.90; N, 7.13.

Macrocycle (1). A solution of 0.022 g of CuCl (2.22×10^{-4} mol) in 3 mL of pyridine was added to 0.135 g (3.34×10^{-4} mol) of **9** dissolved in 230 mL of pyridine and the olive green reaction solution bubbled with oxygen and vigorously stirred for 120 h. After 5 days, the solvent had evaporated to about 150 mL and was rediluted to 230 mL. During this time, the solution also became cloudy due to the formation of a small amount of a suspended insoluble solid. The solvent was then distilled off under reduced pressure on a waterbath until about 4 mL remained, then 20 mL of saturated aqueous KCN was added and the suspension stirred for 24 h at ambient temperature. The solid was then isolated by filtration under vacuum, washed with excess distilled water, and air dried. After this, the crude yield was suspended in 200 mL of CHCl₃, the mixture boiled and filtered to remove the insoluble byproducts, and the solvent distilled off under reduced pressure on a water

(46) Kraus, C. A.; Sessions, W. V. *J. Am. Chem. Soc.* **1925**, *47*, 2361. After evaporation of the ammonia, the product was best worked up by addition of pentane and extraction with water. The pentane extract was dried (MgSO₄) and filtered, the solvent removed under reduced pressure at ambient temperature, and the colorless Sn₂Me₆ product oil stored under argon.

(47) The fluorescence emission spectra of **1**, **8**, and **9** recorded, respectively, in deoxygenated (argon bubbled) and undegassed CHCl₃ were found to be identical, demonstrating that the excited states were insensitive to quenching by oxygen. The fluorescence emission spectra of the metal ion complexes with macrocycle **1**, on the other hand, were recorded in solvents which had not been previously deoxygenated, to reveal the optical responses of this system under the normal environmental and atmospheric conditions encountered in sensory applications.

(48) Lavastre, O.; Cabioch, S.; Dixneuf, P. H.; Vohlidal, J. *Tetrahedron* **1997**, *53*, 7595.

bath. The remaining solid was dissolved in 10–15 mL of boiling toluene and chromatographed on a column of alumina (Basic, activity III) with toluene as the eluant. The product thus obtained was finally purified by extraction with boiling acetone (2 × 150 mL) and air-dried to give 0.045 g (34%) of **1** as a light-sensitive amorphous white solid (mp >340 °C with a gradual color change over 200–300 °C to dark brown).⁴⁹

¹H NMR (CDCl₂CDCl₂, 500 MHz, 100 °C) δ: 8.71 (d, ⁴J_{6,4} = 1.4 Hz, 4H; pyridine H6), 7.88 (d, ³J_{3,4} = 8.3 Hz, 4H; pyridine H3), 7.80 (dd, ³J_{4,3} = 8.2 Hz, ⁴J_{4,6} = 2.2 Hz, 4H; pyridine H4), 7.70 (m, 8H; phenyl H3, 6), 7.44 (m, 8H; phenyl H4, 5). ¹³C NMR (CDCl₂CDCl₂, 125.8 MHz, 60 °C) δ: 153.5, 151.4, 139.0, 133.3, 132.2, 129.2, 128.7, 126.3, 124.5, 120.3, 119.7, 92.0 (C≡C), 91.6 (C≡C), 81.5 (C≡C), 78.1 (C≡C). UV/vis (CHCl₃) λ (nm) (ε, M⁻¹ cm⁻¹): 316 (88670), 356 (127930), 384 (54680). Fluor. emission (CHCl₃, 350 nm excitation) λ (nm): 406, 431. IR cm⁻¹: 2208w ν(C≡C), 1487s, 1480s, 1463s, 840s, 754s. FABMS (CF₃COOH) *m/z*: 805 ([M + 1]⁺, 100). HRMS (FAB, CF₃COOH, [M + 1]⁺): calcd for C₆₀H₂₉N₄ 805.2392, found 805.2389. Anal. Calcd for C₆₀H₂₈N₄: C, 89.53; H, 3.51; N, 6.96. Found: C, 89.72; H, 3.81; N, 6.91.

2-Chloro-5-[(2-ethynylphenyl)ethynyl]pyridine (10). A solution of 0.045 g (1.13 × 10⁻³ mol) of NaOH in 0.5 mL of water and 1 mL of MeOH was added to a stirred solution of 0.160 g (5.16 × 10⁻⁴ mol) of **7** in 8 mL of THF and stirring maintained for 5 h at ambient temperature. By this time, all the starting **7** had disappeared as judged by TLC (1:1 CH₂-Cl₂/hexane, silica). The reaction solution was poured onto brine and extracted with 40 mL of Et₂O. The organic layer was re-extracted with distilled water (2 × 20 mL), dried (MgSO₄), and filtered and the solvent evaporated off at ambient temperature under reduced pressure. The remaining oil crystallized upon drying under vacuum to give 0.116 g (95%) of **10** of sufficient purity for the subsequent preparation of **11**. Further purification could however be achieved upon flash column chromatography on silica with 1:3 hexane/CH₂Cl₂ as eluant, followed by washing the product with a small portion of hexane and drying under vacuum at 0.01 mmHg. The melting point of the chromatographed **10** was 76.8–77.5 °C. Compound **10** underwent partial decomposition upon attempted purification by sublimation.

(49) It must be noted that the oxidative macrocyclisation is not optimised and that further variation in concentration, solvent type, **9**:CuCl ratio, copper catalyst, and temperature may result in the formation of higher yields of **1** as well as higher molecular mass cyclic oligomers and possibly catenated structures.

¹H NMR (CDCl₃, 500 MHz, 25 °C) δ: 8.56 (d, ⁴J_{6,4} = 2.0 Hz, 1H; pyridine H6), 7.78 (dd, ³J_{4,3} = 8.2 Hz, ⁴J_{4,6} = 2.4 Hz, 1H; pyridine H4), 7.55 (m, 2H; phenyl H3, 6), 7.35 (m, 2H; phenyl H4, 5), 7.33 (d, ³J_{3,4} = 8.0 Hz, 1H; pyridine H3), 3.37 (s, 1H; ethyne H). ¹³C NMR (CDCl₃, 125.8 MHz, 25 °C) δ: 152.2, 150.7, 141.0, 132.7, 131.8, 128.70, 128.67, 125.2, 124.8, 123.9, 119.2, 92.1 (C≡C), 88.6 (C≡C), 81.8 (C≡C), 81.5 (C≡C). IR cm⁻¹: 3216s ν(≡C–H), 2098m ν(C≡C), 1547s, 1479s, 1454s, 1106s, 834s, 760s. EIMS *m/z*: 237 (M⁺, 100), 201 ([M – Cl]⁺, 48). Anal. Calcd for C₁₅H₈ClN: C, 75.80; H, 3.39; N, 5.89. Found: C, 76.03; H, 3.28; N, 5.99.

[1,3-Butadiyne-1,4-diylbis(2,1-phenylene-2,1-ethynediyl)]-bis[5-(2-chloropyridine)] (11). A solution of 0.010 g (1.01 × 10⁻⁴ mol) of CuCl in 2 mL of pyridine was added to 0.116 g (4.88 × 10⁻⁴ mol) of **10** dissolved in 15 mL of pyridine and the reaction bubbled with oxygen and vigorously stirred for 1 h. After this, the reaction was stirred under an oxygen atmosphere for 24 h. All solvent was then removed under reduced pressure on a waterbath and the residue flash column chromatographed on silica eluting with CH₂Cl₂. The product thus obtained was further purified by brief ultrasonication in 2 mL of cold MeOH, filtering under vacuum, washing the collected solid with 1 mL of cold MeOH and air-drying to furnish 0.099 g (86%) of **11** as a light sensitive white solid (mp 157.0–159.5 °C).

¹H NMR (CDCl₃, 500 MHz, 25 °C) δ: 8.545 (d, ⁴J_{6,4} = 1.9 Hz, 2H; pyridine H6), 7.77 (dd, ³J_{4,3} = 8.2 Hz, ⁴J_{4,6} = 2.3 Hz, 2H; pyridine H4), 7.58 (m, 4H; phenyl H3, 6), 7.38 (m, 4H; phenyl H4, 5), 7.25 (d, ³J_{3,4} = 8.5 Hz, 2H; pyridine H3). ¹³C NMR (CDCl₃, 125.8 MHz, 25 °C) δ: 152.1, 150.6, 141.0, 132.9, 131.8, 129.2, 128.8, 126.1, 124.5, 123.9, 119.0, 92.0 (C≡C), 89.4 (C≡C), 81.3 (C≡C), 77.9 (C≡C). IR cm⁻¹: 3057m, 2219w ν(C≡C), 1475s, 1106s, 1020s, 829s, 750s. EIMS *m/z*: 472 (M⁺, 100), 437 ([M – Cl]⁺, 90). Anal. Calcd for C₃₀H₁₄Cl₂N₂: C, 76.12; H, 2.98; N, 5.92. Found: C, 75.99; H, 2.69; N, 5.81.

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Supporting Information Available: Complete ¹H and ¹³C NMR spectra of macrocycle **1**. This material is available free of charge via the Internet at <http://pubs/acs/org>.

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