Supramolecular Chemistry

[2]Pseudorotaxanes through Second-Sphere Coordination**

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Interlocked compounds such as rotaxanes and catenanes have become increasingly common as synthetically accessible targets over the past two decades owing to the emergence of a number of highly effective template methods for their synthesis.[1] Some of these strategies have employed the direct coordination of organic ligands to transition metals to achieve an interlocked geometry. The use of a metal center in this

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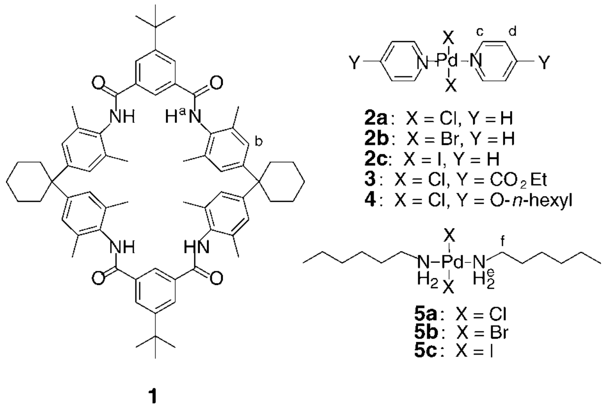
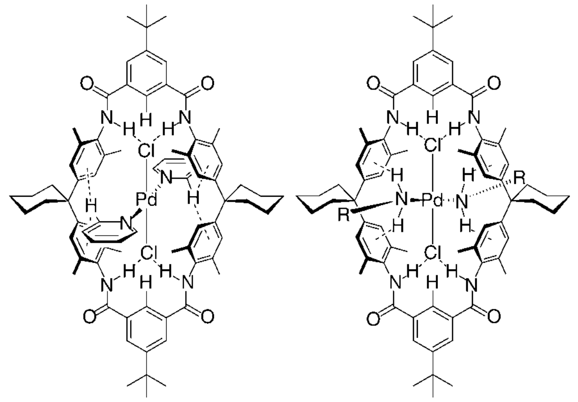
context varies widely. Metals have been applied as an organizational template to arrange organic ligands into the appropriate topology for further covalent reaction,[1d,f,2] coordinated to a terminal ligation point on a prethreaded axle to "stopper" a pseudorotaxane complex,[3] or as a reversible link in the backbone of wheel-shaped components to permit their thermodynamic macrocyclization.[4] These designs are attractive owing to the desirable properties that transition-metal complexes can impart to the interlocked structure, such as redox and photophysical activity.[5]

The common theme in all of these approaches is an exploitation of direct, or first-sphere, coordination of a metal atom by organic ligands. A natural extension of these strategies is the application of two or more of them in a single synthetic step. This type of integration is difficult to rationalize using first-sphere coordination alone, given the common ambiguity of multiple ligand exchanges in metal complexes of sufficient lability to be useful for thermodynamic self-assembly. However, this uncertainty may be avoided by separating the coordination spheres within which each function of the metal template is exploited. Thus, by utilizing first-sphere coordination of a metal atom to form an axle-shaped molecule and subsequent second-sphere coordination of the resulting complex by a macrocycle, the metal center may fulfill two template roles within the same supramolecular assembly. Here we demonstrate how a new template, which involves a well-known macrocyclic isophthalamide-based tetralactam system and simple preassembled *trans*-palladium dihalide complexes, produces [2]pseudorotaxanes through second-sphere coordination. Given the wide literature precedent for the thermodynamic palladium-based self-assembly of supramolecular architectures,[6] this template should provide the foundation for the generation of a considerable range of complex interlocked compounds in a single synthetic step.



Scheme 1. Structures of the macrocyclic and axle-shaped components of the [2]pseudorotaxanes.

The template was based on the potential interaction of an isophthalamide subunit through hydrogen bonding to a metal-bound chloride ligand. Isophthalamide-based compounds have been shown to form complexes with chloride anions preferentially over other halides because of shape complementarity with their hydrogen-bond-donating clefts.[7] This complexation has also been shown to template the formation of interpenetrated and interlocked compounds in an appropriately designed system.[8] Ligation of the chloride anion to a transition metal was expected to reduce its hydrogen-bond-acceptor character significantly. However, it was anticipated that enough residual electron density would remain on the chloride ligands such that they might still interact with isophthalamide-containing compounds in a similar manner to the free anions, although less strongly. To increase the magnitude of a possible template effect, we wished to incorporate two pairs of potential chloride–isophthalamide conjugates within the design.[9] These considerations led to the use of *trans*-palladium dihalide complexes as the axle-shaped molecules and a macrocycle with two opposing isophthalamide moieties incorporated in the ring (Scheme 1). An analysis of several spacers between the isophthalamide subunits using molecular models resulted in the choice of macrocycle **1**, which has been used in the synthesis of pseudorotaxanes, rotaxanes, and catenanes for a number of years.[10] The spacing of the isophthalamide clefts within the macrocycle was calculated by using molecular models to be a near-identical match to the spacing of the chloride ligands in the palladium complexes. Another advantage was the further possibility of attractive $\mathrm{C{-}H\cdots\pi}$ and $\mathrm{N{-}H\cdots\pi}$ interactions between the aromatic diphenylcyclohexyl sidewalls of **1** and acidic protons of the pyridine or hexylamine ligands of **2**–**5** upon interpenetration (Scheme 2).[11]



Scheme 2. Proposed [2]pseudorotaxane structures with potential stabilizing noncovalent interactions highlighted (dashed lines).

Titrations of **1** with each of the potential axles **2**–**5** were carried out in solution in $CDCl_3$, and the resulting proton shifts were monitored by NMR spectroscopy.[12] This allowed the evaluation of the strength of any potential complexation as well as providing diagnostic information as to the nature of the complexes formed (Table 1). In all of the cases examined, except that of **2c**, there exists both a 1:1 equilibrium and a generally much weaker 2:1 (macrocycle:axle) equilibrium.[13] The two series of axles **2a**–**c** and **5a**–**c** exhibit the same overall trends with respect to the extent of complex formation under the conditions studied. As the size of the halide ligand increases from $\mathrm{Cl} < \mathrm{Br} < \mathrm{I}$, both the magnitude of the association constants and the proton shifts at equivalent concentrations diminish substantially. The amide protons of **1** (H^a) in all of the complexes shift downfield with respect to

Table 1: Association constants ($K_{1:1}$ and $K_{2:1}$), free energies of complexation (ΔG), and selected ^{1}H NMR shifts of **2–5** with **1** in $CDCl_3$ at 298 K.

Complex	$K_{1:1}$ [M^{-1}]	$-\Delta G_{1:1}$ [kJ mol^{-1}]	$K_{2:1}$ [M^{-1}]	$-\Delta G_{2:1}$ [kJ mol^{-1}]	Change in chemical shift ($\Delta\delta$)[a]					
					H^a	H^b	H^c	H^d	H^e	H^f
1·2a	5.0×10^3	19.3	2.0×10^2	12.0	0.63	0.15	−0.63	−0.10	–	–
1·2b	7.5×10^2	15.0	1.1×10^2	10.6	0.18	0.05	−0.14	−0.04	–	–
1·2c	4.0×10^1	8.4	–	–	0.02	0.01	−0.01	−0.01	–	–
1·3	2.4×10^3	17.7	4.5×10^2	13.9	0.47	0.13	−0.49	−0.09	–	–
1·4	5.5×10^3	19.5	1.8×10^2	11.8	0.91	0.22	−0.34	−0.29	–	–
1·5a	5.0×10^4	24.6	2.0×10^1	6.8	1.21	0.16	–	–	−0.50	−0.21
1·5b	4.2×10^3	18.9	1.2×10^2	10.8	0.56	0.08	–	–	−0.47	−0.15
1·5c	4.2×10^2	13.7	1.1×10^2	10.7	0.03	0.01	–	–	−0.02	−0.06

[a] Shifts determined from 1:1 mixtures at a concentration of 5×10^{-4} M.

their free components and this is consistent with hydrogen bonding to the halide ligands, which are the only hydrogen-bond acceptors present in these axles. These results are mirrored by previous observations involving halide anions and isophthalamide receptors which display similar selectivity owing to both the hydrogen-bond-acceptor ability of the halides and a reduction in size-complementarity between the larger anions and the hydrogen-bond-donating clefts of the receptor.[7]

Axles **3** and **4** were investigated to determine the effect of modifying the donating ability of the pyridine ligands on the strength of complexation. An electron-withdrawing substituent at the 4-position of the pyridine rings in **3** decreases its association constant with **1** by roughly half. We interpreted this as a result of a decrease in electron density on the palladium metal center, which in turn decreases electron density on the chloride co-ligands and renders them less-effective hydrogen-bond acceptors. However, axle **4**, which incorporates an electron-donating 4-hexyloxy substituent on the pyridine rings, only increases the association constant with **1** by 10 %, an amount that lies within the error margins of the values determined. While this result does not invalidate our hypothesis, it is clear that this relationship warrants a more detailed analysis to fully elicit its basis.

Upfield shifts of acidic protons H^c–H^f in both types of neutral ligands were observed which are indicative of C–H···π and N–H···π interactions with the aryl sidewalls of **1**. This is concomitant with a downfield shift of protons H^b in the macrocycle. However, the shifts of protons on the aryl sidewalls of the cavity may be a result of both interactions with the neutral ligands, as well as inductive effects from the amide N–H···Cl hydrogen bonds. In any case, the evidence from the NMR spectra fully supports the anticipated interpenetrated geometry of the complexes.

Confirmation of the [2]pseudorotaxane geometry of the 1:1 complexes in the solid state was obtained by single-crystal X-ray diffraction studies. Slow diffusion of isopropyl ether into solutions of **1·2a** and **1·5a** in chloroform yielded pale yellow crystals which were suitable for crystallographic analysis.[14,15] Complex **1·2a** crystallized in space group $P\bar{1}$ to yield two conformationally different centrosymmetric pseudorotaxanes per unit cell. The two complexes have very similar interpenetrated geometries and only differ significantly in the disposition of the neutral ligands of **2a** with respect to the aryl sidewalls of **1**. In both cases, the Cl-Pd-Cl axes are canted in relation to the least-squares planes of the macrocyclic rings by an angle of 25° and diverge from the planes that bisect the isophthalamide rings by 5–6°.[16] This arrangement results in short contacts between the hydrogen atoms of the amide groups and the chloride ligands (N–Cl = 3.30–3.40 Å, N-H-Cl = 154–159°) and reveals the hydrogen-bonding interactions anticipated in the original design. Apparently the Cl–Cl distance of the axle is slightly too long to allow the halide ligands to completely reside within the isophthalamide clefts of **1**. Thus, the amide groups of the isophthalamide subunits deviate from coplanarity with the attached *tert*-butylphenyl rings by 10–25° to maintain the hydrogen-bonding contacts observed. The aryl C–H groups that further define the isophthalamide clefts also have contacts with the halide ligands (C–Cl = 3.54 and 3.56 Å, C-H-Cl = 143 and 144°).

The two complexes present different relationships between the pyridine ligands of the axles and the aryl sidewalls of the macrocycle. In the first case (Figure 1), the pyridine ligands are tilted into the cleft, which is defined by the sidewalls, and engage in C–H···π interactions that involve the protons at the 2-positions of the pyridine rings. The distances between the hydrogen atoms of the pyridine rings to the least-squares planes of the aryl rings are 3.03 and 2.97 Å, and their respective C–H···plane angles are 152 and 150° (C···π(least-squares plane) = 3.47 and 3.43 Å, respectively). In contrast, the faces of the pyridine ligands of the second complex (Figure 2) point towards the opening of the iso-

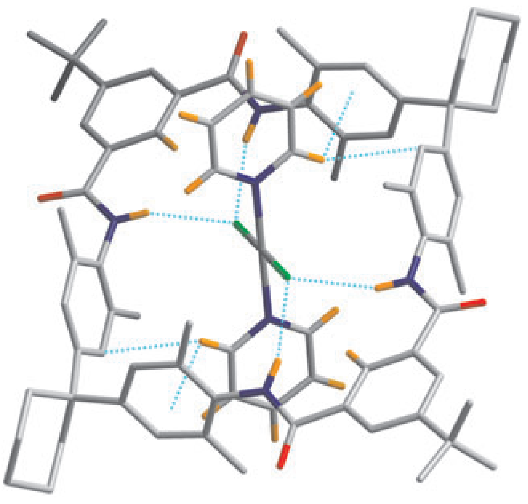


Figure 1. Stick representation of the solid-state structure of **1·2a** (conformer 1). For clarity, all hydrogen atoms have been removed from the macrocycle except those engaged in noncovalent interactions (light-blue dashed lines).

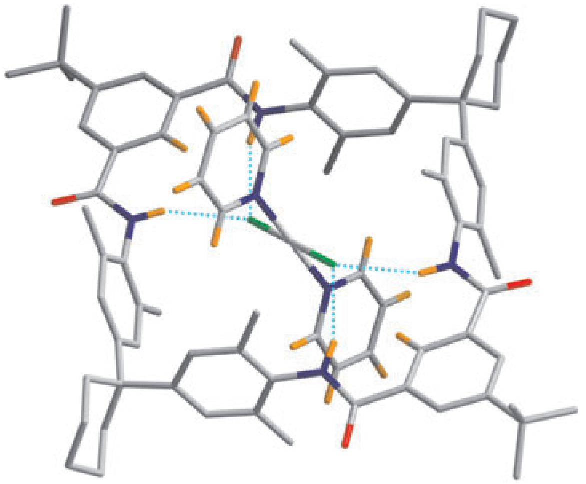


Figure 2. Stick representation of the solid-state structure of **1·2a** (conformer 2). For clarity, all hydrogen atoms have been removed from the macrocycle except those engaged in noncovalent interactions (light-blue dashed lines).

phthalamide clefts of the macrocycle. However, the protons at the 2- and 6-positions of the pyridine rings do not interact significantly with the aryl rings of **1**.

Complex **1·5a** also crystallized in space group $P\bar{1}$, but was modeled as a single centrosymmetric pseudorotaxane in the unit cell (Figure 3). The geometry is similar to **1·2a** in that the chloride ligands of the axle do not fully reside within the isophthalamide cavities. In this example, the Cl-Pd-Cl axis forms an angle with both the mean plane of the macrocyclic ring and in relation to the plane that bisects the isophthalamide ring of 14°.[16] Only one amide hydrogen atom per isophthalamide subunit is hydrogen-bonded to the chloride ligands (N–Cl = 3.38 Å, N-H-Cl = 154°) and remains coplanar with its attached *tert*-butylphenyl ring to within 1°. The other amide group deviates from coplanarity by 26° and, although it has a short contact with the chloride ligands (N–Cl = 3.40 Å), the N-H-Cl angle is too acute to provide an effective hydrogen bond (N-H-Cl = 119°). The C–H groups which complete the isophthalamide clefts of the macrocycle also display contacts with the chloride ligands (C–Cl = 3.62 Å, C-H-Cl = 172°).

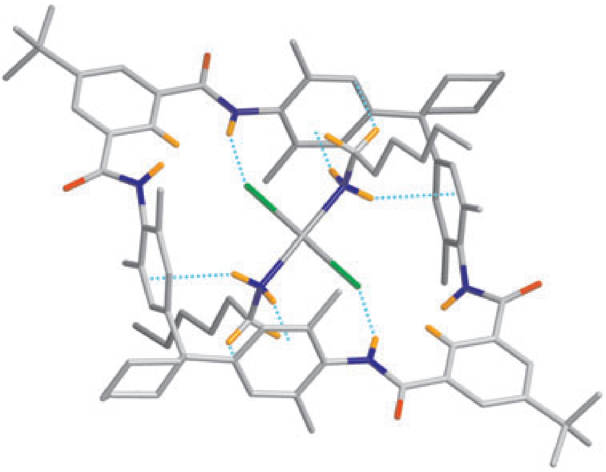


Figure 3. Stick representation of the solid-state structure of **1·5a**. All hydrogen atoms have been removed from the structure except those that define the isophthalamide cleft and the amine protons of the neutral ligands and their corresponding α protons. Noncovalent interactions between the two components have been indicated by light-blue dashed lines.

The neutral hexylamine ligands engage the aryl sidewalls of **1** through four N–H⋯π interactions (N⋯π(least-squares plane) = 3.25 and 3.51 Å; NH⋯π = 2.36 and 2.73 Å, and N–H⋯plane = 167 and 148°, respectively), which are augmented by two more stabilizing C–H⋯π interactions that involve the α protons of the hexyl chains (C⋯π(least-squares plane) = 3.60 Å; CH⋯π = 3.05 Å, C–H⋯plane = 146°). The hexyl chains attached to the amines extend through opposite faces of the macrocycle in an extended all-*anti* conformation to give an interpenetrated complex geometry.

In summary, the results discussed here demonstrate the viability of a new template route to [2]pseudorotaxanes using second-sphere coordination to form the complexes. We are currently developing the synthesis of interlocked molecules such as rotaxanes and catenanes by this method with more-complex ligand systems.[17] Furthermore, we believe that this approach will be amenable to other metal centers and anionic ligands, a goal we are actively pursuing.

Experimental Section

Compounds **1**,[18a] **2a–b**,[18b] **2c**,[18c] **3**,[18d] **4**,[18e] and **5**[18f] were prepared according to reported procedures and were characterized by ^{1}H and ^{13}C NMR spectroscopy as well as by high resolution ESI-MS. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz Varian Mercury and 600 MHz Varian Inova spectrometers, respectively, with the residual solvent peak used as reference. $CDCl_3$ used in the NMR titration experiments was purchased from Cambridge Isotope Laboratories and dried over 4 Å molecular sieves before use.

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[12] Titrations were performed with a constant concentration of the host of $5\times10^{-4}\,\mathrm{M}$ and the addition of appropriate aliquots of a solution of guest at $5\times10^{-3}\,\mathrm{M}$ (with background host concentration) using Hamilton Gastight microliter syringes. All titrations were performed three times, and the average value of the association constants obtained are reported. In all cases, the results had an estimated error of $\leq 10\,\%$ for $K_a > 100\,\mathrm{M}^{-1}$ and $\leq 20\,\%$ for $K_a < 100\,\mathrm{M}^{-1}$. Titrations were performed with both **1** and **2**–**5** as host species to verify the presence of 2:1 (with **1** as host) and 1:2 (with **2a**, **2b**, and **3**–**5** as hosts) equilibria where necessary. Titration data from the observation of the appropriate protons H_a–H_f were analyzed with the program EQNMR (M. J. Hynes, *J. Chem. Soc. Dalton Trans.* **1993**, 311–312) and fit 1:1, 1:2, and 2:1 binding models with excellent agreement ($R_f = 0.05\,\%$).

[13] While the geometries of the 2:1 complexes have not been explicitly determined, they are likely a partially interpenetrated arrangement spanning two macrocycles, similar to that of the 1:1 complex from similar ^{1}H NMR chemical shift behavior. Regardless, they are a minor component in the equilibria when compared to the stabilities of the prevailing 1:1 complexes.

[14] Crystal structure data for **1·2a**: triclinic, space group $P\bar{1}$, $a = 14.9144(6)$, $b = 17.24338(6)$, $c = 19.9135(6)$ Å, $\alpha = 105.773(2)$, $\beta = 109.268(2)$, $\gamma = 104.509(2)°$, $V = 4361.4(3)$ Å^3, $Z = 2$, $\rho_{\mathrm{calcd}} = 1.394\,\mathrm{g\,cm^{-3}}$, $2\theta_{\max} = 50.00°$, $\mathrm{Mo}_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 150$ K. A pale yellow crystal with dimensions $0.43\times0.38\times0.16\,\mathrm{mm}^3$ was grown by vapor diffusion of isopropyl ether into a solution of **1·2a** in $CHCl_3$ and mounted on a glass fiber. The 44888 unique reflections ($R_{int} = 0.060$) were integrated from frame data obtained from programmed hemisphere scan routine on a Nonius Kappa-CCD diffractometer. Lorentz and polarization corrections followed by a multiscan (HKL SCALEPACK; Otwinowski, Minor, **1997**) absorption correction were applied to the data ($\mu = 0.692\,\mathrm{mm}^{-1}$, min./max. transmission $= 0.8973/0.7550$). The structure was solved by Patterson methods, followed by difference Fourier syntheses to find the remaining atoms. Refinement was performed with full-matrix least-squares methods against $|F^2|$ data using SHELXTL-NT

6.1 (G. M. Sheldrick, Madison, WI, **2000**) to give final R values of $R_1 = 0.0568$, $wR_2 = 0.1329$, GOF = 1.008, $N_o/N_v = 15\,321/967$ with $I > 2\sigma(I)$. All of the non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atom positions were calculated geometrically and were included as riding on their respective carbon atoms. CCDC 253083 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] Crystal structure data for **1·5a**: triclinic, space group $P\bar{1}$, $a = 11.9303(6)$, $b = 12.0968(9)$, $c = 15.9729(14)$ Å, $\alpha = 112.045(3)$, $\beta = 90.375(4)$, $\gamma = 105.800(5)°$, $V = 2040.6(3)$ Å^3, $Z = 1$, $\rho_{\text{calcd}} = 1.331\,\text{g cm}^{-3}$, $2\theta_{\max} = 50.04°$, $\text{Mo}_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 150$ K. A pale yellow crystal with dimensions 0.38 × 0.13 × 0.05 mm^3 was grown by vapor diffusion of isopropyl ether into a solution of **1·5a** in $CHCl_3$ and mounted on a glass fiber. The 14 996 unique reflections ($R_{\text{int}} = 0.059$) were integrated from frame data obtained from programmed hemisphere scan routine on a Nonius Kappa-CCD diffractometer. Lorentz and polarization correction followed by a multiscan (HKL SCALEPACK, Otwinowski, Minor, **1997**) absorption correction were applied to the data ($\mu = 0.541\,\text{mm}^{-1}$, min./max. transmission = 0.9734/0.8228). The structure was solved by Patterson methods followed by difference Fourier syntheses to find the remaining atoms. Refinement was performed with full-matrix least-squares methods against $|F^2|$ data using SHELXTL-NT 6.1 (G. M., Sheldrick, Madison, WI, **2000**) to give final R values of $R_1 = 0.0565$, $wR_2 = 0.1162$, GOF = 1.030, $N_o/N_v = 7071/457$ with $I > 2\sigma(I)$. All of the non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atom positions were calculated geometrically and were included as riding on their respective carbon atoms. CCDC 253084 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] The least-squares plane of the macrocycle was calculated using the four carbonyl carbon atoms. Calculation of the angle between the Cl-Pd-Cl axis and the plane that bisects the isophthalamide aryl ring was performed by calculating the angle between the planes perpendicular to the lines defined by a) the Cl-Pd-Cl axis and b) the line described by the two carbonyl-substituted carbon atoms of the isophthalamide ring. The value obtained had 90° subtracted from it to arrive at the final figure.

[17] We very recently confirmed the synthesis of a [2]rotaxane by this method in our laboratories, the results of which will be reported in due course.

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