Dimeric nanocapsule induces conformational change†

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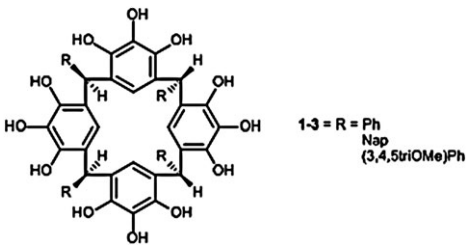
An induced *cis–trans–trans* (*rctt*) chair to cone structural rearrangement is forced by the addition of a pentacoordinate zinc(II) complex, overcoming thermodynamic and kinetic factors to produce the first phenyl-substituted zinc dimeric nanocapsule.

With inherent voids or cavities that allow for encapsulation of a variety of unique guests, molecular capsules have numerous applications ranging from catalysis and molecular-device design to gas storage and pharmaceutical drug delivery.[1] Currently, several research groups are pushing the limits of supramolecular chemistry in an attempt to expand our knowledge of the effect of factors such as size, kinetic control, and solubility on capsule formation.[2] These factors, if balanced, give rise to a simple synthetic procedure with limitless possibilities.

In the past, research groups have implemented sub-unit architecture to allow for easy self-assembly. "Bowl shaped"[3] and flexible linear moieties comprise the majority of these sub-units, which yield large nanocapsules based on hydrogen bonding or metal coordination. Hemispherical alkyl-substituted resorcin[4]arenes have led to, for example, the Atwood hexameric sphere,[4] whereas the Rebek tennis ball[5] was synthesized with flexible diphenylglycoluril and durene tetrabromide moieties.

Acid-catalyzed condensations of a phenol and an aldehyde produce resorcin[4]arenes and pyrogallol[4]arenes in a variety of diastereomers, *rccc*, *rctt*, *rcct* and *rtct*, depending on the reaction conditions.[6] Although the pyrogallol[4]arenes for which R is an aryl group are relatively unexplored (Scheme 1), the main stereoisomeric product for the alkyl-substituted arenes and aryl-substituted resorcin[4]arenes is often the thermodynamically preferred all-*cis* (*rccc*) isomer in the crown conformation, due to cooperative hydrogen bonding between the hydroxyl groups of the aromatic rings.[7] The kinetically preferred *cis–trans–trans* (*rctt*) isomer has also been isolated in good yield, especially when the insolubility of this isomer prevents its interconversion to the *rccc* configuration. Control of the stereoselectivity is still not well understood, but on the basis of their analysis of alkyl and aryl resorcin[4]arenes, Cram and co-workers[8] have concluded that the R group is one of the key factors in determining the preferred stereostructure.



Scheme 1 Preparation of compounds **1–3** was achieved through acid-catalyzed condensation reactions of equimolar concentrations of aldehyde and pyrogallol.

Due to the lack of both conformational control and easy self-assembly associated with the *rctt* isomer, it has attracted less attention in sub-unit architectural design.[9] Although Castellano *et al.*[10] have shown conformational control of tetraurea calix[4]arene *via* intermolecular hydrogen bonding, the possibility of inducing a conformational change during self-assembly has otherwise largely been ignored. We report herein new dimeric metal-seamed nanocapsules formed from phenylpyrogallol[4]arene§ and derivatives¶ (Fig. 1) in a *rctt* chair arrangement converting to a kinetically-locked *rccc* bowl arrangement. The analysis of the ^{1}H NMR spectra,‖ fast HMQC NMR spectra, crystallographic structures, and *ab initio* electronic structure calculations also suggests that the *rctt* chair structure is now favored thermodynamically.

Computational studies were performed with the use of the Gaussian 03 suite of programs[11] to compare experimental, solid-state results with gas-phase calculations. In the absence of solvent, the B3LYP/6-31G(d) calculations indicate that the lowest energy arrangement of phenylpyrogallol[4]arene is the *rccc* cone. Although entropically more favorable, the *rctt* chair conformers with C_1 or C_i symmetry are considerably enthalpically less favorable than the cone conformer at this level of theory (Table 1). The only difference between the former two conformers is that in the C_i system the medial hydroxyl proton on the two pyrogallol sub-units that form the "back" and

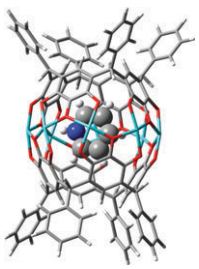


Fig. 1 Schematic representation of [Zn_8(*C*-phenylpyrogallol[4]arene)$_2$-(pyridine)$_8$⊂(pyridine)]. Zn: aqua, O: red, N: blue, C: grey, H: white.

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Table 1 Calculated relative enthalpies and free energies (kJ mol^{-1}) for different conformations of *C*-phenylpyrogallol[4]arene

	B3LYP[a]		MP2[b]	
PgPh (conformation)	ΔH	ΔG	ΔH	ΔG
Cone [C_4]	0	1.1	0	11.0
1,2-Chair [C_1]	25.1	2.6	12.6	0
1,2-Chair [C_i]	70.9	45.3	68.6	52.8

[a] B3LYP/6-31G(d) optimized. [b] MP2/6-31G(d,p)//B3LYP/6-31G(d) single-point energy + B3LYP thermal correction terms.

"legs" of the chair is rotated out-of-plane, disrupting the intramolecular hydrogen-bonded network and destabilizing the molecule by, surprisingly, 40 kJ mol^{-1} with respect to the C_1 system (Table 1). At the higher MP2/6-31G(d,p)//B3LYP/6-31G(d) level of calculation, which accounts for stabilizing π–π interactions, there is a change in relative free energies and the *rctt* chair C_1 structure is now preferred (Table 1). Interestingly enough, the chair with C_i symmetry is destabilized relative to the C_1 form. However, that trend could be reversed in the presence of solvent (see below), and we are currently looking at how interaction with explicit solvent molecules affects the relative stabilities of all of the possible isomers.

That the gas-phase computations suggest *rctt* chair phenylpyrogallol[4]arene is the thermodynamically-favored product of the acid-condensation reactions raises the question of which structure is preferred by this arene and its derivatives in solution and the solid state. To examine the effect of R-group steric bulk on the preferred stereochemistry in the solid, a variety of ligands was used in the macrocyclic synthesis, three of which are given in Scheme 1. Benzene, naphthalene, and various hydroxy, methoxy and nitro derivatives of benzene provided a wide range of symmetric and asymmetric substitution. In each case, the phenyl derivatives of pyrogallol[4]arene show preference toward the *rctt* isomer. To test the thermodynamic stability of the *rctt* configuration, the isolated product was refluxed in DMSO for a period of five days and allowed to recrystallize. Again, only the *rctt* configuration was observed. One explanation for the observed results is that the *rctt* chair arrangement allows for steric decongestion in the lower rim[12] of the macrocycle while increasing its stabilization *via* π–π interactions (Fig. 2).

Solvent interaction also plays a crucial role in the structure of the *rctt* isomer. Oxygenated aprotic solvents such as dimethyl sulfoxide and dimethylformamide are capable of hydrogen bonding motifs, and the crystal structures of the aryl-substituted pyrogallol[4]arenes indicate that O–H···O(solvent) H-bonding causes directional flipping of one or more hydroxyl protons. Thus, intrinsic stability, packing effects and solvent effects[13] appear to control the overall stereostructure of these macrocycles in the solid state.

^{1}H NMR was utilized to study the alkyl- and aryl-substituted pyrogallol[4]arenes in solution, looking specifically at the methine protons. For the alkyl-substituted arenes a singlet appears around 4 ppm, indicative of a uniform chemical environment. Observed in the spectra for the aryl-substituted arenes are four unique singlets, caused by distortion of the macrocycle, grouped into two distinct regions at 6 and 5.75 ppm. Fast HMQC shows a correlation between the four singlets and the bridging carbon. The groupings can be explained by two bridging protons up and two down out of the equatorial plane, confirming the presence of the (distorted) *rctt* chair structure in solution.

Our work in all three phases (solid, solution and gas) points to the *rctt* chair arrangement as the product of the acid-catalyzed condensation reaction. Yet, when macrocycles **1–3** are mixed with a pentacoordinated zinc(II) complex, consisting of two nitrate and three pyridine ligands in the axial and equatorial positions, respectively, a dimerization reaction occurs in which molecular capsules with an estimated internal volume of 141 Å^3 are formed. Displaced metal ligands and solvent molecules are encapsulated during closure, and the disordered nature of the guests leads to two unique chemical environments between the upper and lower hemispheres.[14] Other metal–ligand derivatives of pyridine, such as 3-methylpyridine and 4-ethylpyridine, have also successfully produced zinc-seamed dimers. However, size limitations do apply and must be taken into account when choosing the metal coordination complex.

Since X-ray quality crystals have proven difficult to acquire other methods, such as NMR and MALDI-TOF MS, were used to confirm the formation of the desired product. The MALDI-TOF MS analysis reveals two major peaks, one associated with occupied dimers, the other with unoccupied. Dimeric capsules synthesized *via* macrocycle **3** give peaks at 3024.02 Da and 2946.9 Da. The calculated isotopic masses are 3023.1 Da and 2941.06 Da (Fig. 3).

In conclusion, we have shown through computation and experiment that unlike aryl-substituted resorcin[4]arenes, for aryl-substituted pyrogallol[4]arenes the chair conformation is thermodynamically preferred in all three phases. Moreover, metal insertion induces a chair-to-cone conformational change to form zinc-seamed dimeric capsules. Further studies are needed to understand the intricacies of interconversion and

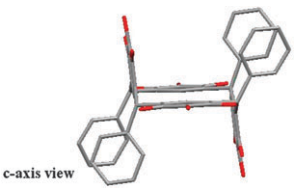

Fig. 2 Crystal structure of **1** viewed along the *c*-axis (side view). Hydrogens omitted for clarity.

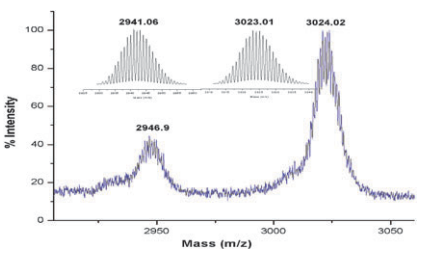

Fig. 3 MALDI-TOF MS spectrum of ionized [Zn_8(*C*-(3,4,5-trimethoxyphenyl)pyrogallol[4]arene)$_2$(3-methylpyridine)$_8$⊂(3-methylpyridine)] using a dithranol matrix.

dimeric nanocapsule formation. However, overcoming thermodynamics to induce a conformational change opens the door to new, diverse groups of capsules that allow for easy functionalization.

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Notes and references

§ *C*-Phenylpyrogallol[4]arene: synthesis was readily achieved following previous methods.[15] Benzaldehyde (2.083 mL, 18.8 mmol) and pyrogallol (2.38 g, 18.8 mmol) were simply added to a flask filled with 40 mL ethanol. The solution was allowed to stir at room temperature for 30 min. 2 mL conc. HCl were then added. The mixture was refluxed at 78 °C for 24 h. The solution was then filtered using a cold methanol wash yielding a white precipitate. Recrystallization in DMSO yielded suitable X-ray crystals. Yield: 3.27 g, 80.9%. ^{1}H NMR (300 MHz, DMSO-d_6, shifts relative to DMSO): δ = 7.70 (12H, m), 6.80 (20H, m), 6.48 (1H, s), 6.19 (1H, s), 6.02 (1H, s), 5.99 (1H, s) 5.78 (1H, s), 5.72 (1H, s), 5.66 (1H, s), 5.19 (1H, s). *Crystallographic data:* $C_{72}H_{100}O_{22}S_{10}$, M = 1091.28 g mol^{-1}, ρ = 0.8892 g cm^{-3}, a = 11.6125(2), b = 11.8904(2), c = 16.1797(3) Å, α = 80.962(1)°, β = 74.912(1)°, γ = 71.909(1)°, U = 2043.31(6) Å^3, triclinic, space group $P\bar{1}$, Z = 1, λ(Mo) = 71 073 Å, T = 173 K, 12 549 reflections, 8205 unique R_1 = 0.1109, wR_2 = 0.3908 (all data), R_{int} = 0.0258, GOF = 1.492 CCDC 752684. Full optimization of crystallographic structures as well as other plausible geometries was done at the B3LYP/6-31G(d) level of theory. Cone, chair, 1,2-alternate, boat, and saddle conformations of the macrocyclic ring, as well as the all-*cis*, *cis–cis–trans*, *cis–trans–trans* and *trans–cis–cis* configurations of the R-groups, were examined. Harmonic vibrational frequencies were also obtained at the B3LYP/6-31G(d) level to determine whether a structure is a minimum or transition state and to evaluate the thermal correction terms. Single-point MP2 energies were computed with the 6-31G(d,p) basis set. The Gaussian 03 program package[11] was used for all calculations.

¶ [Zn_8(*C*-Phenylpyrogallol[4]arene)$_2$(3-methylpyridine)$_8$⊂(3-methylpyridine)]: *C*-phenylpyrogallol[4]arene (100 mg, 116 μmol) was added to a flask with [$Zn^{II}(NO_3)_2$pyridine$_3$·$6H_2O$] (200 mg, 464 μmol) and 5 mL 3 : 1 methanol–acetonitrile solution. The precipitate was then filtered and dried under vacuum. Yield: 0.130 g, 78%. ^{1}H NMR (300 MHz, DMSO-d_6, shifts relative to DMSO): δ = 17.41 (4H, m), 16.97 (4H, m), 8.21 (16H, s), 7.45 (16H, s), 7.31 (8H, s), 7.02 (40H, m), 6.06 (2H, m, ⊂Pyr), 5.71 (2H, m, ⊂Pyr), 5.03 (1H, m, ⊂Pyr), 4.50 (8H, s), −1.91 and −1.92 ppm (2·s, ⊂MeOH). MALDI-TOF MS analysis: spectra were collected on a Voyager DE-PRO. MALDI sample preparation consisted of co-crystallization of product with dithranol (10 mg mL^{-1} in MeOH). All analyses were carried out on a 100 well gold plate. The Voyager DE-PRO was operated in positive ion reflector mode running at 20 kV acceleration, 150 ns delayed extraction, 1000–4000 Da mass range, with low mass filter gate on at 1000 Da. Laser intensity was set to 1708 at 250 shots per acquisition, with the laser randomly positioned per acquisition. Summation of 1500 laser shots was used to acquire better resolution and signal-to-noise ratios, resulting in two separate peaks at 2496.9 and 3204.02 Da associated with unoccupied and occupied species, respectively. The calculated isotopic distributions are 2941.6 and 3023.1 Da, respectively, and coincide with the experimental values *t* taking into account the loss of the 8 pyridine ligands from the ionization process.

‖ NMR spectra for characterization were collected on a Bruker AXR300 and AXR500 (300 MHz and 500 MHz). MALDI-TOF MS was acquired on an ABI Voyager DE-PRO. Crystallographic data were acquired with a Bruker SMART 1000 CCD diffractometer.

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