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Analysis of Molecular Square Size and Purity via Pulsed-Field Gradient NMR Spectroscopy

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The size (volume) of a large tetrametallic molecular square, that has resisted characterization by mass spectrometry, has been determined by pulsed-field gradient NMR spectroscopy, a technique that reports on self-diffusion coefficients. These scale inversely with hydrodynamic radii, which in turn scale approximately as the cube of the assembly's mass. The technique has also been used to determine whether NMR spectral complexities observed for the new compound are due to contamination with chemically related assemblies, or instead reflect the intrinsic structural complexities of the compound itself.

The molecular size and sample purity of a "molecular square" ($[Re^{I}(CO)_3Cl(ligand)]_4$) have been determined by comparison of the molecule's diffusion coefficient (D) relative to the D of several isostructural compounds. Measurements of sample diffusion coefficients and assessment of sample purity were obtained by using pulsed-field gradient (PFG) NMR spectroscopy.[1] Notably, PFG-NMR has been used previously to analyze complex mixtures for environmental applications,[2] characterize dendrimers and metallodendrimers,[3] evaluate gold nanoparticles,[4] monitor small-molecule/soluble-polymer binding,[5] and assess metal complex ion-pairing[3b] and aggregation.[6] It has also been used to characterize labile organic supramolecular assemblies.[7] Additionally, Stang and co-workers report the use of PFG-NMR to estimate the sizes of a pair of platinum-containing dodecahedra. The analyses were single-point experimental comparisons with calculations for spheres (an approach justified for dodecahedra).[8]

As synthetic chemistry in the field of inorganic supramolecular chemistry, including the subfield encompassing discrete metal cyclophane chemistry, becomes more advanced, the resulting structures are often larger and, therefore, more challenging to characterize by traditional methods. For example, characterization of molecular size is typically performed with FAB-mass spectrometry (MS). This methodology becomes unusable, however, if the sample's molecular weight exceeds the instrument's mass limit or, more typically, if the sample simply resists volatilization. Characterization based on X-ray crystallography is often hampered by difficulties in growing high-quality crystals from noninterpenetrating assemblies containing large cavities. Alternative size/mass evaluation methods based on colligative properties, for example, vapor pressure osmometry, require large sample quantities and high solution concentrations, conditions often unachievable with higher molecular weight species because of diminished sample solubility (or availability). Assessment of purity can likewise prove challenging.

Excluding strictly spherical species, evaluation of molecular weights (MWs) via diffusion parameters requires diffusion standards with similar structures because diffusion coefficients are not directly related to MW. Instead, they reflect effective hydrodynamic radii.[1] Therefore, not only the size, but also the shape, of the molecule will determine the value of D. The diffusion standards in this analysis were the well-characterized molecular species comprising series **1**−**4** and ligand **5** of Figure 1, and the complex under question is the molecular square from ligand **5**.[9,10]

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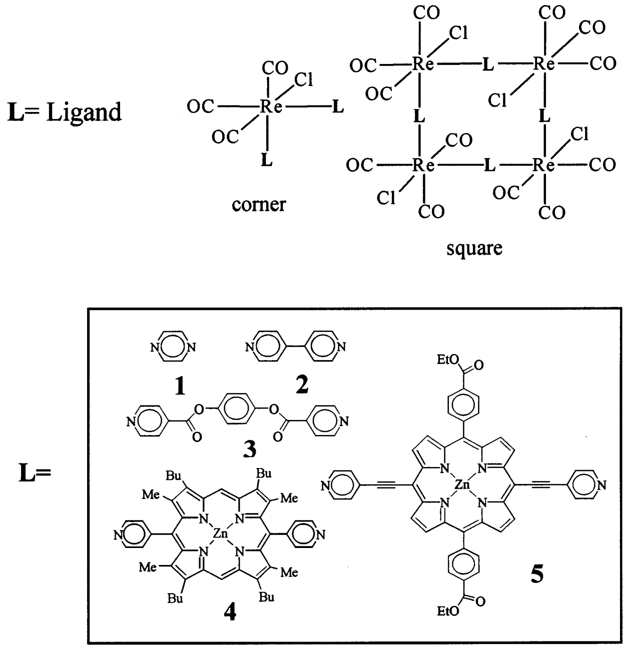

Figure 1. Molecular structures of the diffusion standards (series **1**−**4** and ligand of series **5**) and the presumed structure of the molecule under investigation (molecular square of series **5**).

Table 1. Molecular Diffusion Coefficients[a]

molecule	1	2	3	4	5
ligand	9.68	6.03	3.53	2.24	1.94
	(0.09)	(0.04)	(0.04)	(0.02)	(0.06)
corner	3.62	2.69	na	1.61	na
	(0.08)	(0.02)		(0.03)[b]	
square	2.37	1.42	0.87	1.20	1.04
	(0.11)	(0.05)	(0.02)	(0.04)	(0.03)

[a] Diffusion coefficients reported as ($\times 10^{-10}$ m^2 sec^{-1}) with experimental error reported in parentheses. [b] Modified structure included in the Supporting Information.

Table 1 contains the molecular diffusion coefficients for all of the molecules investigated.[11] As shown in the table, the values become smaller (molecules diffuse more slowly) with increasing size, from ligand to corner to square, within a series. In addition, larger squares diffuse slower than smaller squares. Because *D* values are inversely proportional to hydrodynamic radii, they scale roughly as the inverse of the cube root of the molecular weight.

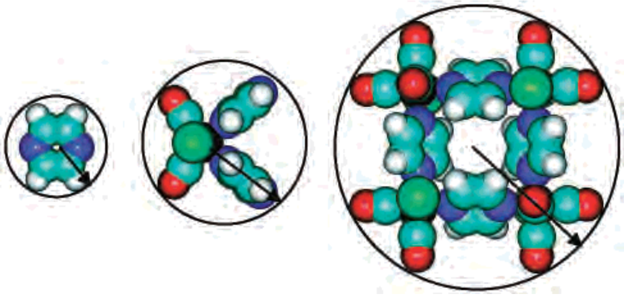

Figure 2. Approximation of molecular radii for square, corner, and ligand members of series **1**.[9b]

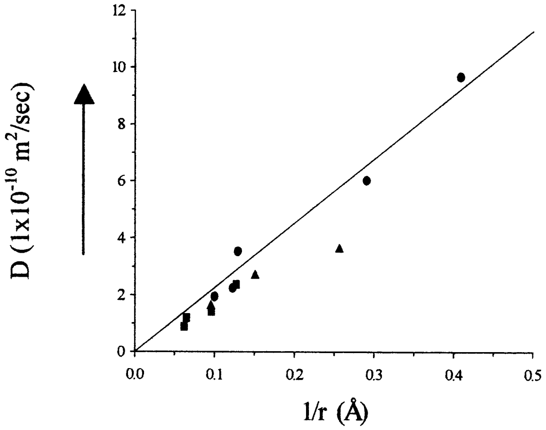

Figure 3. Diffusion coefficients versus the reciprocal of the estimated radii for fully characterized ligand (●), corner (▲), and square (■) members of series **1**−**4** and ligand of **5** in DMSO-d_6.

Generation of a calibration curve from the diffusion standards is necessary to estimate a molecular size for the less fully characterized molecular square **5**. *D* can be related to size via the Stokes−Einstein equation

$$D = k_B T/6\pi\eta r \tag{1}$$

where *T* is absolute temperature, k_B is Boltzmann's constant, *r* is the effective molecular radius, and η is the solvent viscosity. For other geometries, or when the diffusing particle is of similar size to the solvent molecules, more complex theories are available to relate *D* to size.[12]

The molecules studied here (ligands, corners, squares) were first approximated as equivalent encapsulating spheres. Thus, *r* was approximated as the longest axis within the molecule as indicated either by space-filled representations of the crystal structure or by molecular mechanics geometry optimizations from HyperChem 5.1 (Figure 2). A plot of the measured *D* values versus molecular radii, as defined here, is shown in Figure 3. An inverse linear relationship exists indicating that the spherical approximations are both viable and useful. In addition, the slope of the fit (which was forced through zero) corresponds to the known viscosity of the solvent, further validating the fit.

Analysis of the measured *D* value for the newer, less fully characterized molecular square from ligand **5**, using the slope of the best-fit line in Figure 3, gave $r = 22$ Å. In comparison, the HyperChem radii for the uncoordinated ligand and square

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(9) (a) Giordano, P. J.; Wrighton, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 2888. (b) Slone, R. V.; Hupp, J. T.; Stern, C. L.; Albrecht-Schmitt, T. E. *Inorg. Chem.* **1996**, *35*, 4096. (c) Forsyth, T. P.; Nurco, D. J.; Pandey, R. K.; Smith, K. M. *Tetrahedron Lett.* **1995**, *36*, 9093. (d) Slone, R. V.; Hupp, J. T. *Inorg. Chem.* **1997**, *36*, 5422. (e) LeCours, S. M.; Dimagno, S. G.; Therien, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 11854.

(10) All compounds were prepared via literature methods or purchased from Aldrich. Corner **4** was synthesized according to ref 9a, square **5** was synthesized according to the procedure in ref 9d for a closely related square, and ligand **5** was synthesized according to the procedure in ref 9e for closely related porphyrins. Satisfactory elemental analyses were obtained.

(11) Millimolar solutions were prepared by dissolving compounds in 750 μL of DMSO-d_6 (99.9%, Aldrich). A drop of pyridine-d_5 was added to solutions of the ligand and square of **4** to solubilize them fully. The reported *D* values are averages of 3 measurements on the same sample. The reported error is the larger of either the exponential fitting error or the standard deviation of the 3 trials.

(12) (a) Cussler, E. L. *Diffusion; Mass Transfer in Fluid Systems*; Cambridge University Press: Cambridge, 1984. (b) Hansen, J. P.; McDonald, I. R. *Theory of Simple Fluids*; Academic Press: London, 1976.

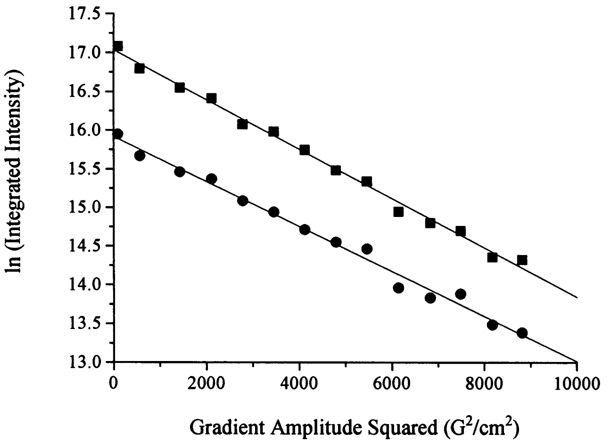

Figure 4. Intensity decay with gradient strength for two proximal resonances (minor resonance (●) and major resonance (■)) in the ^{1}H NMR spectrum of square **5**. From the slopes, D(major) $= 1.07 \pm 0.05 \times 10^{-10}$ m^2/s and D(minor) $= 1.01 \pm 0.05 \times 10^{-10}$ m^2/s. The relatively larger errors obtained for these plots, compared with the values reported in Table 1, reflect the smaller integrated areas (lower intensities) for these resonances.

of **5** are 10 and 19.5 Å, respectively, indicating that the new assembly is in the size range expected for a square structure, but clearly smaller than expected for either a catenated or polymeric structure.[13]

Interestingly, the ^{1}H NMR spectrum of square **5** is more complex than expected from the nominally high symmetry of a simple boxlike structure: numerous poorly resolved "extra" splittings of peaks are observed. The spectrum changes when the temperature is varied and simplifies when a lower viscosity solvent (THF-d_8) is used. These observations are consistent with a structural preference for a lower symmetry square conformation that features tilted porphyrinic walls.[14] In a lower viscosity solvent, rapid interconversion between equivalent tilted conformers could occur, resulting in a simpler averaged spectrum. An alternative interpretation, however, would be that the sample is severely contaminated with related compounds (monomers, corners, nonsquare oligomers, etc.) featuring similar, but slightly shifted, proton resonances.

As illustrated in Figure 4, PFG-NMR measurements offer one way of distinguishing between these two possibilities. Diffusion coefficients are obtained from the slopes of the log of resonance intensity versus the square of the amplitude of the magnetic field gradient. In the figure, responses are plotted for an aromatic proton resonance and for a less intense proximal "extra" resonance due to either symmetry lowering or the presence of a contaminant. The slopes obtained agree within error and, furthermore, match the slope obtained by integrating segments of the broader aromatic region containing the overlapped resonances. The agreement indicates that the resonances are associated with species having identical D values, most likely the same compound. We conclude that low-symmetry conformer stabilization, rather than gross contamination, is responsible for the complexity of the proton spectrum.[15]

In summary, PFG-NMR is a powerful tool for the assessment of the size of well-defined inorganic assemblies,[3,6,8] with shapes other than spheres being amenable to investigation if similarly shaped calibrating compounds are available. A Stokes–Einstein comparison of D values has shown that the new assembly under investigation here is of the size anticipated from the synthetic protocol. Furthermore, PFG-NMR measurements have proven useful for establishing the origin of unexpected NMR spectral complexities. As a tool for characterization of supramolecular assemblies,[6–8] PFG-NMR can prove especially useful when conventional size/mass evaluation methods such as FAB-MS cannot be utilized. Even when MS evaluation is possible, PFG-NMR can provide useful additional or corroborative information. Indeed, conclusive structural analysis of supramolecular systems by MS alone can sometimes be difficult because the observed parent ion may correspond, for example, to a fragment of a polymer, oligomer, or catenated dimer rather than an individual molecule. Furthermore, MS does not readily report on sample purity, in the sense of contamination by component compounds or chemically similar assemblies of other sizes. In comparison, PFG-NMR is an inherently nondestructive technique[1] (ensuring measurement of the intact supramolecular assembly[6–8]) allowing for size and purity assessment.

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Supporting Information Available: NMR parameters for the gradient fits. Structure of "modified corner" **4**. Elemental analysis and other characterization data for corner **4**, square **5**, and ligand **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The fit is insufficiently precise to distinguish a square from a triangle. Studies of rigid multidentate guest binding, however, support the square geometry, as do molecular sieving studies (probe-molecule size cutoff studies) of thin films of **5**.

(14) Fan, J.; Whiteford, J. A.; Olenyuk, B.; Levin, M. D.; Stang, P. J.; Fleischer, E. B. *J. Am. Chem. Soc.* **1999**, *121*, 2741.

(15) In principle, plots of ln intensity versus gradient amplitude squared could also be used to assess the presence of contaminants having resonances identical to those of the parent compound. A straight-line relationship indicates a single unique diffusion coefficient, whereas a nonlinear curve is indicative of multiple species possessing different diffusion coefficients. In practice, experiments using intentionally prepared mixtures of square **2** and either ligand **2** or corner **2**, and integrating over the region containing the overlapped resonances, show that curvature is readily evident only when the "contaminant" comprises a significant percentage (approximately 10–25%) of the sample.