Synthesis and Self-Assembly of the "Tennis Ball" Dimer and Subsequent Encapsulation of Methane

An Advanced Organic Chemistry Laboratory Experiment

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We have developed a set of experiments for the senior organic undergraduate laboratory constituting the synthesis of the "tennis ball" and the study of its self-assembling behavior in solution using ^{1}H NMR (*1, 2*). These experiments are intended to give advanced undergraduates an understanding of noncovalent interactions and supramolecular organization. The synthesis of the tennis ball monomer is completed in two elementary steps from readily available materials during two laboratory periods. The ensuing ^{1}H NMR experiments are completed during one laboratory session.

Noncovalent interactions control the supramolecular organization of molecules (*3*). A wide variety of noncovalent interactions (electrostatic interactions, van der Waals forces, hydrogen bonding, metal–ligand interactions, the hydrophobic effect, cation-π forces, and aromatic–aromatic forces) play important roles in biological chemistry, materials science, and information technology. Despite the importance of these interactions and the supramolecular structures that they spawn, it is uncommon for undergraduates to gain laboratory experience with noncovalent interactions. Although articles have been published that describe small-molecule receptors (*4*), to our knowledge no examples of solution-phase self-assembly have been reported for undergraduate instruction.

Background

Compound **1** (Fig. 1) is a curved molecule that displays self-complementary hydrogen bonding sites. In solvents that effectively compete for hydrogen bonds, **1** exists as a free monomer. In noncompetitive solvents and in the presence of a suitable guest molecule, **1** self-associates through hydrogen bonds, forming a dimeric structure that encapsulates the smaller guest molecule within the cavity. The symmetry of this complex has led to it being dubbed the "tennis ball" (*1*) (Fig. 1). Hydrogen-bonding interactions between monomers (aided by van der Waals interactions between guest and capsule walls) drive assembly of the complex.

The guest encapsulated within the capsule interior possesses properties very different from those of the guest free in solution. Because the encapsulated guest exchanges slowly with the free guest, it is possible to observe the encapsulated guest in its highly shielded environment using ^{1}H NMR. Other structural features of the assembly are indicated in the NMR spectrum—most notably the presence of sharp, concentration-independent, downfield shifted signals for protons that participate in hydrogen bonds. Importantly for undergraduates, the key signals for encapsulated guests and hydrogen bonding protons occur in the upfield and downfield regions of the NMR spectrum, respectively. The signals of different complexes are thus easily observed and interpreted.

Hazards

This experiment requires the use of chemicals that are toxic (chloroform-*d*, dichloromethane, methanol, toluene, trifluoroacetic acid), corrosive (trifluoroacetic acid, potassium hydroxide), or flammable (toluene, methanol). Proper laboratory safety guidelines in the handling of these chemicals should be followed.

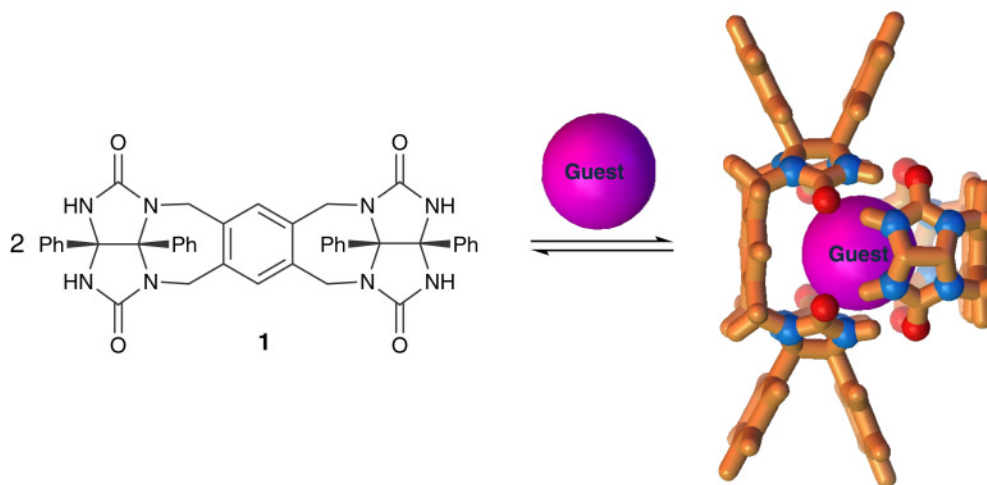Finely ground KOH causes severe chemical burns!

Figure 1. Presence of guest drives dimerization of **1** to form the tennis ball. Phenyl groups on the right-hand monomer are omitted for clarity.

Experiment Part A: Synthesis

Reagents

All reagents and solvents were used as received from Aldrich (Milwaukee, WI). Per student, this laboratory requires benzil (2.00 g); urea (1.14 g); toluene (25 mL); trifluoroacetic acid (1 mL); dichloromethane (100 mL); methanol (50 mL); DMSO (20 mL); potassium hydroxide (85%, 1.04 g); 1,2,4,5-tetrakis(bromomethyl)benzene (0.18 g); magnesium sulfate (5 g).

Equipment

The following equipment is required: Pasteur pipets, spatulas, stir bars, magnetic stirrer, heating mantle, 50- and 100-mL round-bottom flasks, Dean–Stark trap, condenser, drying tube, filter flask, Büchner funnel, filter paper, mortar and pestle, Erlenmeyer flask, rotary evaporator, NMR tubes.

Procedure

Diphenylglycoluril (Scheme I). Benzil (2.00 g), urea (1.14 g), toluene (15 mL), and trifluoroacetic acid (1 mL) were combined in a single-neck 50-mL flask fitted with a Dean–Stark trap, a condenser, and a drying tube. The mixture was brought to reflux for 12–24 hours. After cooling to room temperature, the mixture was filtered and the filter cake washed with dichloromethane (50 mL) and methanol (50 mL) and air-dried to yield diphenylglycoluril as a white powder (2.32 g, 83%).

Tennis ball monomer (1) (Scheme I). Grind some technical grade (85%) KOH using a mortar and pestle. Add the freshly ground KOH (1.04 g) to a suspension of diphenyl glycoluril (2.32 g) and dimethylsulfoxide (DMSO, 20 mL) in a 50-mL round-bottom flask. Fit the flask with a condenser and heat it rapidly to 120 °C using a preheated heating mantle. After 5 minutes add 1,2,4,5-tetrakis(bromomethyl)benzene (0.18 g) as a solid and continue heating for 45 minutes. Cool the reaction mixture to room temperature and pour it into an Erlenmeyer flask containing water (300 mL). Collect the white precipitate by vacuum filtration on a Büchner funnel.

Table 1. Representative Chemical Shifts of Selected Signals for Samples of 1

| Sample	δ (ppm)		
	NH	CH$_2$	Guest (free, bound)
A (DMSO-d_6)	8.22	3.95, 4.71	N/A
B (CDCl$_3$)	9.23	4.68, 3.95	N/A
C (CDCl$_3$ + CH$_4$)	9.23, 9.27	4.68, 3.95	0.22, -0.91

Resuspend the residue in an additional 100 mL of water, stir for 5 minutes, and filter. (The filtration may take up to one hour.) To extract the product from the solid, place the solid filter cake in a single-neck 100-mL flask, add dichloromethane (50 mL), and fit the flask with a condenser. Use a heating mantle to heat the mixture briefly to reflux, cool it to room temperature, and filter it again, washing with more dichloromethane (50 mL). Collect the combined organic filtrates, dry them over magnesium sulfate, and concentrate the resulting solution to dryness on a rotary evaporator to give the crude tennis ball monomer (1) as a pale yellow powder (40–75 mg). This material can be used for the subsequent NMR studies without further purification.

If desired, both steps are easily performed by teaching assistants on a scale large enough to produce material for many students (20× the scale reported above). This eliminates the synthetic component for the student and reduces the total laboratory to a single day of NMR sample preparation and studies as outlined below.

Experiment Part B: NMR Studies

Reagents and Equipment

CDCl$_3$ and DMSO-d_6 were used as purchased from Aldrich. Methane was used directly from in-house gas lines. NMR tubes and an NMR spectrometer are required. In our laboratory, ^{1}H NMR spectra (300 MHz) were recorded on a Brüker AM300 spectrometer.
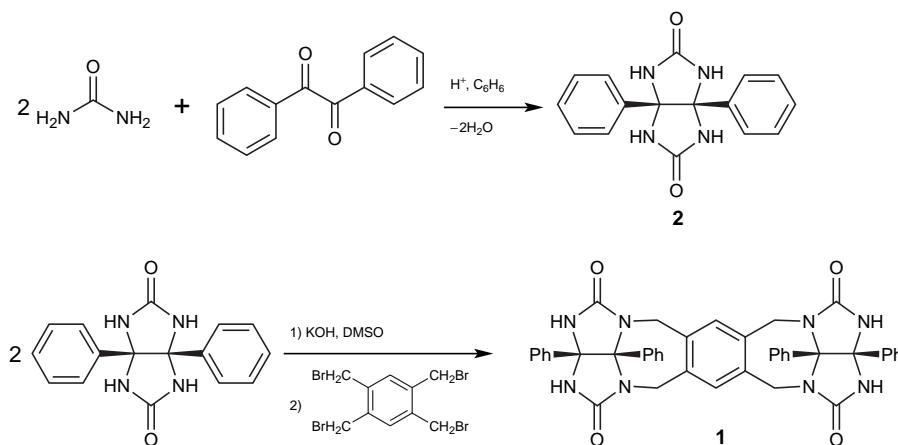
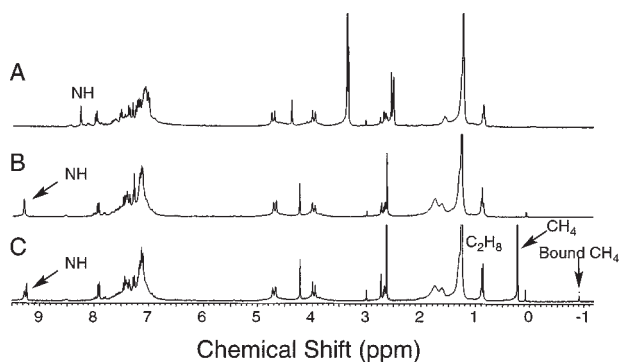Scheme I: Synthesis of compound **1**

Figure 2. ^{1}H NMR (300 MHz) spectra of samples A, B, and C.

Procedure

Three samples were prepared for ^{1}H NMR analysis (see Table 1). Sample A contained 4–6 mg of **1** in 0.6 mL of DMSO-d_6. Sample B contained 4–6 mg of **1** in 0.6 mL of CDCl$_3$. Sample C was prepared by bubbling in-house methane into a solution prepared similarly to B. ^{1}H NMR spectra were collected at 300 MHz, scanning from –2 to 11 ppm.

Results and Discussion

The behavior of **1** in solution can be monitored by observation of a few signals that are clearly visible in all spectra. The methylene protons display two characteristic sets of doublets (J = 15 Hz) in all spectra, whereas the aromatic region is complex and not useful for interpretation of structure. The amide protons give rise to a diagnostic singlet. In cases where amide protons are hydrogen bound, the amide signal shifts *downfield* owing to electrostatic deshielding. In the case of hydrogen bonding within a discrete complex (i.e., the self-assembled tennis ball), the amide signals are also concentration independent (Fig. 2). Also important for characterization of the self-assembled state is the presence of signals for both free and encapsulated guest molecules.

In DMSO solution the solvent molecules effectively solvate the hydrogen bonds of **1**, preventing dimerization. The upfield amide resonances in A confirm the solvent competition for hydrogen bonding sites (see Table 1). In chloroform the amide protons of **1** shift downfield, suggesting self-assembly to a discrete structure. Based on previous reports, the structure in non-hydrogen-bonding solvents is best described as a dimeric capsule held together by eight hydrogen bonds

and containing a single solvent molecule (*1*). When methane gas is bubbled through the chloroform solution (C), the solution is found to contain both free and encapsulated methane (δ 0.22 and –0.91 ppm, respectively), confirming the dynamic nature of the assembly and encapsulation processes. The encapsulated methane peak is shifted upfield by more than 1 ppm (Table 1). Note that the presence of 7 to 10% ethane in commercial-grade methane results in an extraneous peak for free ethane at about 1.8 ppm, but owing to its large size no ethane is encapsulated. Amide peaks for two separate complexes are observed: one containing chloroform (as in B) and another containing methane.

Summary

In nature, noncovalent interactions govern the folding and assembly of proteins and nucleic acids, and nearly every biological recognition event. Noncovalent interactions also govern the supramolecular organization utilized in the creation of liquid crystalline displays (LCDs) and other modern electronic devices. This laboratory demonstrates to undergraduates in a simple and accessible way the use of noncovalent interactions in the creation of supramolecular organization.

ᵂSupplemental Material

Written information for use by students is available in this issue of *JCE Online*.

Literature Cited

1. Wyler, R.; de Mendoza, J.; Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699–1701.
2. Branda, N.; Wyler, R.; Rebek, J. Jr. *Science* **1994**, *263*, 1267–1268.
3. Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley: New York, 1995.
4. Cox, J. R. *J. Chem. Educ.* **2000**, *77*, 1424–1428. Heller, B. A.; Gindt, Yvonne M. *J. Chem. Educ.* **2000**, *77*, 1458–1459. Hessley, R. K. *J. Chem. Educ.* **2000**, *77*, 203–205. Brown, K. C.; Tyson, R. L.; Weil, J. A. *J. Chem. Educ.* **1998**, *75*, 1632–1635. Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375–378. Craik, D. J.; Higgins, K. A.; Kneen, M. M.; Munro, S. L. A.; Waterman, K. J. *J. Chem. Educ.* **1991**, *68*, 258. Seyse, R. J.; Pearce, H. L.; Rose, T. L. *J. Chem. Educ.* **1975**, *52*, 194. These references were selected from articles matching the following keywords: Molecular Recognition, Intermolecular Forces, Organic Synthesis, Organic Chemistry, and NMR Spectrometry.