Control of Self-Assembly and Reversible Encapsulation of Xenon in a Self-Assembling Dimer by Acid−Base Chemistry

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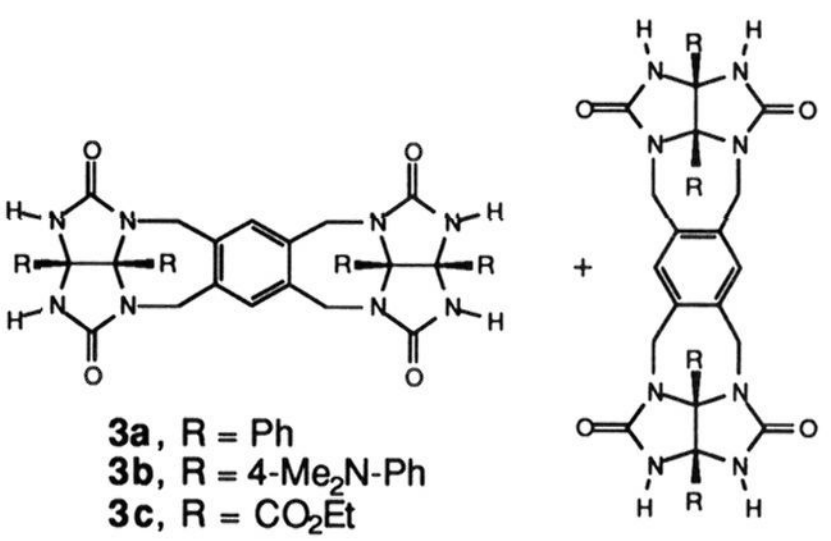
Abstract: Two new self-complementary molecules are described which are capable of assembling into dimeric capsules. The size and shape of the cavity follow previous designs, but peripheral functional groups permit enhanced solubility. Binding of CH_4, $H_2C{=}CH_2$, and xenon within the capsules is demonstrated. Peripheral basic sites on one of the capsules permit the control of assembly by protonation/deprotonation reactions. The encapsulation of xenon is demonstrated for the more organic soluble capsule by proton and xenon nuclear magnetic resonance spectroscopy.

The generation of intermolecular assemblies continues to be a dominant theme of molecular recognition in this decade. Many multicomponent systems have been characterized,[1] with the nucleation of the assemblies being initiated by weak intermolecular forces between complementary components. We recently introduced a minimalist, self-complementary structure which dimerizes to form a roughly spherical capsule.[2] Here we elaborate the behavior of two related systems. In one, a monomeric structure can be induced to dimerize by small molecules or even atoms, and its assembly can be controlled by changes in the acidity of the medium. In the second, a more soluble version, the subunit can be fully transformed into a xenon-inclusion complex as evidenced by ^1H and ^{129}Xe NMR studies.

The notional and practical aspects of self-complementary structures for assembly have been described in detail for the case at hand (Figure 1, structure **3a**).[3] The hydrogen-bonding information needed for the correct assembly is built into the edges of the monomeric subunit and its skeletal curvature. Versions of the structure bearing peripheral *p*-dimethylanilino and carbethoxy groups have now been prepared (Figure 1, structures **3b** and **3c**). The appropriate glycolurils[4] were synthesized from 4,4′-bis(dimethylamino)benzil[5] or dihydroxytartaric acid disodium salt by condensation with urea[6] (Scheme 1). Alkylation of the glycolurils with durene tetrabromide gave the new self-complementary molecules, having good organic solubility. In particular, compound **3c** exhibited high solubility



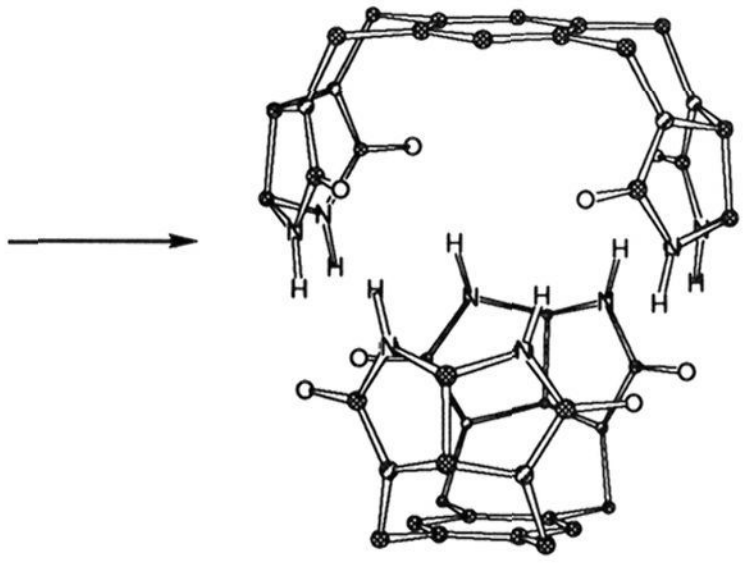


Figure 1. Dimerization of self-complementary subunits to form a capsule. The aromatic and ester groups and carbon-bound protons have been removed from the computer-aided[7] rendering for clarity.

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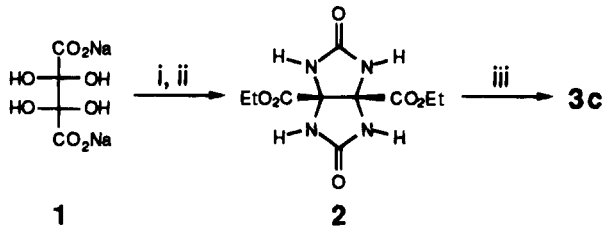
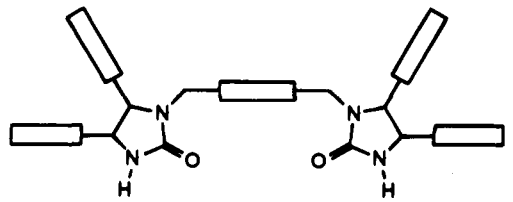
Scheme 1



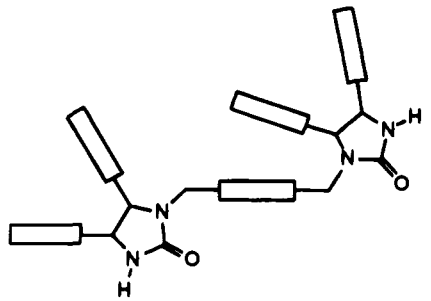
[a] Reagents: (i) EtOH, HCl; (ii) urea, benzene, CF_3CO_2H; (iii) *t*-BuOK, DMSO, tetrabromodurene.

in organic solvents such as chloroform, tetrahydrofuran, and *N,N*-dimethylformamide (in $CHCl_3$, the solubility is greater than 0.1 M).

In DMF-d_7, the ^1H NMR spectrum of structure **3b** shows broadened signals corresponding to an exchange process. It is unlikely that this process is intermolecular as the spectra are concentration independent. Rather, it is likely that this process involves interconversion between two conformational forms, **A** and **B** (Figure 2a). Modeling[7] indicates that the terminal



A



B

dimethylanilino groups raise the barrier to this interconversion versus the unsubstituted phenyl derivative **3a** or the ester derivative **3c**. Trace amounts of a dimeric complex are also observed as evidenced by the small signal at ~9.2 ppm. Perhaps dissolved gases occupy the cavity in the dimer, as it is unlikely to be empty. Stochastic dynamics simulations[8] indicate that

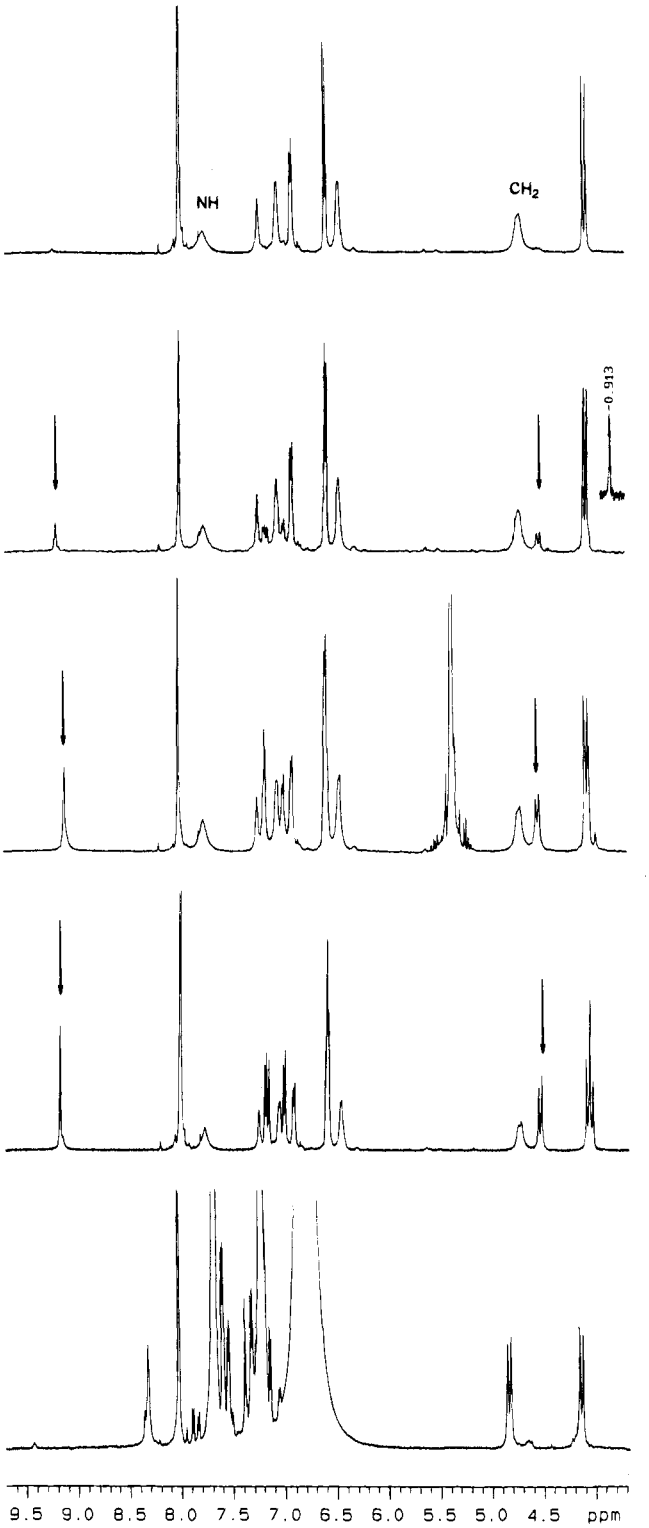


Figure 2. ^1H NMR spectra of **3b** in DMF-d_7 at ~2 mM (a) and of **3b** in DMF-d_7 at ~2 mM treated with (b) methane (the inset shows the peak for encapsulated methane at −0.913 ppm), (c) ethylene, (d) xenon, and (e) xenon and excess *p*-toluenesulfonic acid. The arrows highlight the signals for the amides (NH) and one of the benzyl resonances (CH_2) of the inclusion complexes. Spectra a−e are the spectra from top to bottom.

the hydrogen bonds of the dimer must be considerably lengthened to accomodate the solvent (DMF).

Although the monomer of **3b** predominates in DMF, the dimerization can be nucleated by small, complementary convex structures.[9] For example, when methane is added to the DMF-d_7 solution, the appearance of the new CH_4-occupied dimer can

(7) Molecular modeling was performed on Silicon Graphics Personal Iris workstations (4D25 or 4D30) using MacroModel 3.5X. Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467. The inner van der Waals volume of the capsule was estimated to be ~55 Å^3 (see ref 3); the volume of DMF is ~75 Å^3 (calculated from modeling).

(8) Stochastic dynamics simulations were run in the MacroModel version of the AMBER force field at 300 K with GB/SA chloroform solvation, extended nonbonded distance cutoffs, and constrained bond lengths (SHAKE). After a 15-ps induction period, structures were sampled every 1.5 fs using the minimized conformation of the structure as the starting point. In general, each run was over a 240-ps time period. (a) van Gunsteren, M. F.; Berendsen, H. J. C. *Mol. Simul.* **1988**, *1*, 173. (b) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S., Jr.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765−784. (c) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127−6129.

be monitored by ^{1}H NMR (Figure 2b). The signals for the N−H resonance (~9.2 ppm) and one of the benzyls (~4.6 ppm) of the assembled capsule emerge, while the encapsulated methane can also be directly observed (~−0.92 ppm). Similar changes in spectra result on the introduction of ethylene (Figure 2c). The characteristic signals of the capsule permit inclusion of other guests to be monitored indirectly. For example, molecular hydrogen, helium, or neon fails to alter the ^{1}H NMR spectrum, but argon and xenon[10] induce the formation of the dimer (Figure 2d).

The basicity of the peripheral amino groups of **3b** permits the control of the assembly by changes in the acidity. For example, as acid (*p*-toluenesulfonic acid) is added to the DMF-d_7 solution saturated with xenon in Figure 2d, the inclusion capsule begins to disappear (Figure 2e) and a new species, the protonated monomer, emerges. With a large excess of acid (~80 equiv) the spectrum shows that the equilibria can be driven to the dissociated and, presumably, multiprotonated monomer. The site of protonation, while not unequivocally established, is likely to be the dimethylamino group. The alternatives—the urea oxygen atoms—are expected to show enhanced basicity due to the same dimethylamino groups, but the comparable bases represented by the sea of DMF would consume most of the added acid. Protonation on the urea oxygens would have the same effect on the capsule; as the hydrogen bonds along the seam would be replaced by protons, the dimer would dissociate. The process is fully reversible; the addition of bases (Na_2CO_3) neutralizes the medium, and the spectrum of the capsule containing xenon is regenerated. This behavior is likely caused by the buildup of positive charge on the periphery of the capsule. Eventually, sufficient amino groups are protonated and electrostatic repulsion forces the two components of the dimer apart. A further possibility is that protonation could also cause conformational changes that destabilize the capsule.[11] The addition of base returns the components to their neutral state, which then nucleate around the xenon atoms.

In $CDCl_3$, the ^{1}H NMR spectrum of **3c** shows a sharp signal at ~9 ppm characteristic of the amide resonance of the hydrogen-bonded dimer (Figure 3a). Saturation of the chloroform solution with xenon gave a new signal at ~8.9 ppm corresponding to the amides of the xenon-inclusion complex (Figure 3b). Virtually all of the dimer can be occupied by xenon since only trace signals for the "empty" capsule are observed. The high solubility of structure **3c** in $CDCl_3$ allows for the encapsulated xenon to be observed directly by broad band ^{129}Xe NMR.[12] The spectrum at 138.3 MHz shows a signal for encapsulted xenon at ~19 ppm upfield from the solvated xenon signal (Figure 3c).

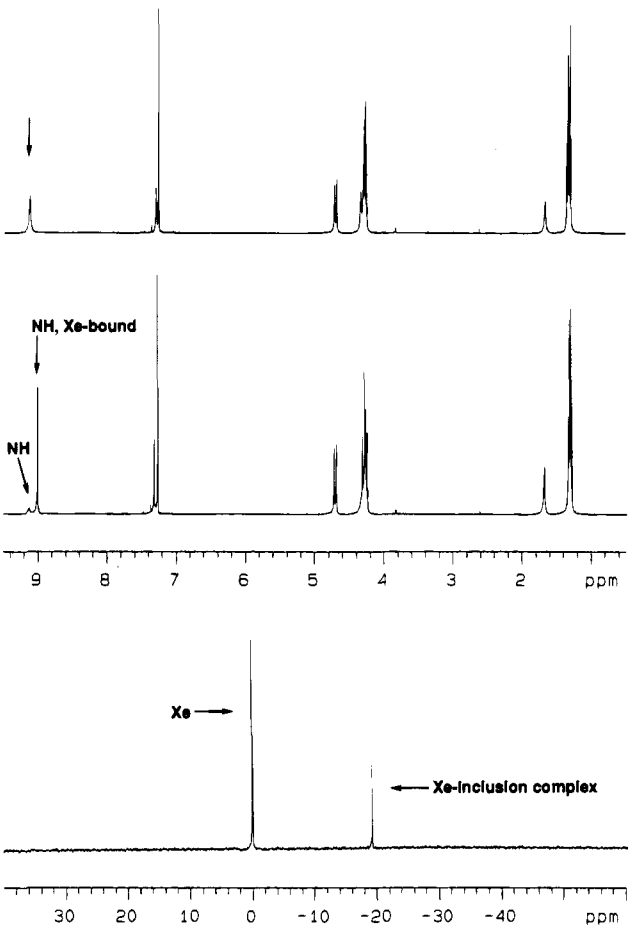


Figure 3. ^{1}H NMR spectra at 500 MHz of (a) **3b** in $CDCl_3$ and (b) **3b** in $CDCl_3$ saturated with xenon. The signals for the amides (NH) and bound xenon are highlighted. (c) ^{129}Xe NMR spectrum at 138.3 MHz in $CDCl_3$.In the ^{129}Xe NMR spectrum the signal for solvated xenon is used as the reference. Spectra a−c are the spectra from top to bottom.

The experiments above reveal a delicate balance between the entropic cost of a termolecular complex and the enthalpic gains provided by the weak intermolecular forces in the nucleated assembly. Even relatively competitive solvents (such as DMF) can be released from the hydrogen-bonding sites along the edge of the relatively rigid monomer by the satisfaction of the complementarity of size, shape, and chemical linings in the cavity of the dimer. The balance can be manipulated by environmental effects. Specifically, the encapsulation and the release of xenon can be reversibly controlled by changes in the acidity of the medium. The control of macromolecule assembly by such charge effects has been recently observed in transferrin iron release,[13] while a lot of literature exists on these effects in hemoglobin's binding of oxygen.[14]

Experimental Section

Dihydroxytartaric acid disodium salt (**1**) was obtained as the dihydrate from ICN Biomedicals, anhydrous DMSO was from Aldrich, and deuterated solvents were from Cambridge Isotope Labs. NMR spectra were recorded on Bruker AC250, Varian XL300, and Varian VXR 500 spectrometers with the solvents as the internal lock and internal reference (^{1}H NMR: $CDCl_3$, 7.26 ppm; DMF-d_7, 2.91 ppm;

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^{13}C NMR: $CDCl_3$, 77.0 ppm). Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected.

3a,6a-Bis(diethoxycarbonyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (2). A suspension of dihydroxytartaric acid disodium salt (**1**) (50 g, 0.19 mol) in 500 mL of ethanol was cooled in an ice bath and saturated with HCl gas. After stirring at room temperature for 16 h, the solids were filtered off and washed with ethanol. Upon concentration of the filtrate the crude diester was obtained as a viscous orange liquid which was used without further purification. A mixture of the crude diester, urea (27 g, 0.45 mol), trifluoroacetic acid (35 mL), and 300 mL of benzene was heated to reflux for 20 h using a Dean-Stark trap. After cooling to room temperature (rt), the supernatant was decanted and the semisolid was shaken with ethanol (200 mL) on a vibrator until complete separation of solid material. The colorless product was collected by filtration, washed with ethanol, and dried under vacuum. Yield: 25.7 g (51%). Mp 299 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 8.02 (s, 4H, NH), 4.07 (q, 4H, CH_2), 1.62 (t, 6H, CH_3) ppm. HRMS: calcd for $[M + H]^+$ $C_{10}H_{15}N_4O_6$ 287.099 2, found 287.098 6.

3a,6a-Bis(4-(dimethylamino)phenyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione. A mixture of 4,4′-bis(dimethylamino)benzil[5] (20.75 g, 0.07 mol), urea (9.0 g, 0.15 mol), trifluoroacetic acid (15 mL), and 250 mL of benzene was heated to reflux for 20 h using a Dean-Stark trap. Benzene and trifluoroacetic acid were removed by rotary evaporation, and the residue was stirred in methanol overnight. The precipitate was collected by filtration, washed with methanol and acetone, and dried. Yield: 21.8 g (82%, lit.[4a] 67%). ^1H NMR (300 MHz, DMSO-d_6): δ 7.44 (s, 4H, NH), 6.88 (d, 4H, J = 8.7 Hz, CH ar), 6.43 (d, 4H, J = 8.7 Hz, CH ar), 2.76 (s, 12H, N-CH_3) ppm.

Compound 3b. 3a,6a-Bis(4-(dimethylamino)phenyl)tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (16.89 g, 44.4 mmol) was suspended in 250 mL of DMSO at 100 °C. Finely ground KOH (4.98 g, 88.8 mmol) was added. After stirring for 15 min, tetrabromodurene (1.0 g, 2.22 mmol) was added. Stirring was continued for 60 min at 100 °C. After cooling to rt, the mixture was poured into 2500 mL of water and the precipitate was collected by filtration. The filter cake was thoroughly washed with water and after drying at 100 °C was extracted with 300 mL of boiling CH_2Cl_2. After evaporation of CH_2Cl_2 the residue was washed with boiling THF and acetone. The crude material was dissolved in CH_2Cl_2, stirred with charcoal, filtered, and evaporated. The evaporation residue was taken up in 25 mL of methanol/CH_2Cl_2 (4:1), sonicated, filtered, washed with 1 mL of CH_2Cl_2, and dried under vacuum. Yield: 180 mg (9%). ^1H NMR (500 MHz, DMF-d_7) δ 7.7−7.9 (br, 4H, NH), 7.25 (s, 2H, CH ar), 7.07 (br, 4H, CH ar), 6.93 (d, 4H, CH ar), 6.60 (d, 4H, CH ar.), 6.48 (br, 4H, CH ar), 4.65−4.70 (br, 4H, CH_2), 4.09 (d, 4H, CH_2), 2.83 (s, 12H, NCH_3), 2.81 (s, 12H, NCH_3) ppm. HRMS: calcd for $[M + H]^+$ $C_{50}H_{55}N_{12}O_4$ 887.446 9, found 887.447 6.

Compound 3c. Glycoluril **2** (4.58 g, 15.1 mmol) was dissolved at rt in 50 mL of anhydrous DMSO under argon. *t*-BuOK (3.3 g, 30.2 mmol) was added in one portion. After stirring for 15 min, tetrabromodurene (564 mg, 1.22 mmol) was added and stirring was continued for 75 min at room temperature. The mixture was poured into 0.1 N HCl (1000 mL) and extracted with ethyl acetate (3 × 400 mL). The organic layer was washed with brine (3 × 300 mL), dried over Na_2SO_4, and concentrated, affording a white solid in which both isomers of **3c** could be identified by ^1H NMR. The solid was stirred with chloroform (150 mL) for 30 min. The insoluble material—containing the *S*-shaped isomer—was separated by filtration. Upon evaporation of the filtrate a solid was obtained which was dissolved in boiling benzene. After cooling to rt, a precipitate was collected, affording 130 mg of a colorless solid. Yield: 130 mg (15%). Mp 360 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 9.08 (s, 4H, NH), 7.30 (s, 2H, CH ar), 4.68 (d, 4H, J = 15.5 Hz, CH benz), 4.4−4.2 (m, 12 H, CH benz + CH_2O), 1.31 (m, 12 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 158.6, 135.6, 131.2, 82.2, 74.9, 62.8, 43.5, 13.8 ppm. HRMS: calcd for $[M + H]^+$ $C_{30}H_{35}N_8O_{12}$ 699.237 4, found 699.241 5.

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