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Dynamics of Assembly and Guest Exchange in the Tennis Ball

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Molecules within molecules provide physical organic chemistry with a way to stabilize reactive intermediates,[1] accelerate reactions,[2] and create new forms of stereoisomerism.[3] Hydrogen-bonded capsules are especially promising in this regard, as guest exchange is reversible and the energetics of the encapsulation process can be obtained from equilibrium measurements. We describe here the rates of the dissociation−association process and the mechanism of guest exchange for the parent compound—the "tennis ball"[4] (**1**) (Figure 1).

The tennis ball in apolar organic solvents is held together by a seam of eight hydrogen bonds. In $CDCl_3$ it is likely that the dimeric assembly is empty or occupied only by dissolved atmospheric gases, since a solvent molecule of about 70 $Å^3$ is too large for an internal volume of about 60 $Å^3$. When guests such as methane or ethane are added, reversible encapsulation occurs, rapidly on the human time scale but slowly on the NMR time scale at ambient temperatures.[5]

The use of two differently substituted glycoluril functions on the durene spacer as in structure **2** reduces the symmetry of the corresponding dimer, and the assembly exists as a pair of enantiomers (Scheme 1). These can interconvert (racemize) by dissociation and recombination of the two subunits; this process results in the exchange of the nonequivalent N−H resonances at each glycoluril. At the same time, the exchange of guests can be studied by monitoring the resonances of the free and encapsulated species.

Upon dimerization to **2·2**,[6] four, well-separated N−H signals are observed in the downfield region (at δ 8.7−9.7) of the NMR spectrum. A series of 2D EXSY experiments showed exchange cross-peaks between pairs of the N−H signals. A corresponding ROESY experiment ruled out the possibility that these cross-peaks arise from NOE contacts. Rates for the exchange processes were deduced from cross- and diagonal-peak intensities.[7] The N−H exchange rate constant was determined to be $k_{\mathrm{rac}} = 0.31 \pm 0.02$ s^{-1}. Since the two halves can either recombine to the same enantiomer, without exchange, or form the other enantiomer, giving rise to exchange cross-peaks in the EXSY spectra, and both pathways are equally likely, the dissociation process for **2·2** in $CDCl_3$ at 295 K has a rate constant k_{diss} of 0.62 ± 0.03 s^{-1} (i.e., $2k_{\mathrm{rac}}$). This rate constant corresponds to an activation energy $\Delta G^{\ddagger}$ of 17.5 ± 0.1 kcal mol^{-1} at 295 K. If the dimerization rate constant is assumed to be 2×10^9 M^{-1} s^{-1}, a typical value for diffusion-controlled hydrogen bond formation in $CHCl_3$,[8] an estimate of the dimerization constant K_a for **2·2** in $CDCl_3$ of 3.2×10^9 M^{-1} ($\Delta G° = 12.6$ kcal mol^{-1}) can be made.

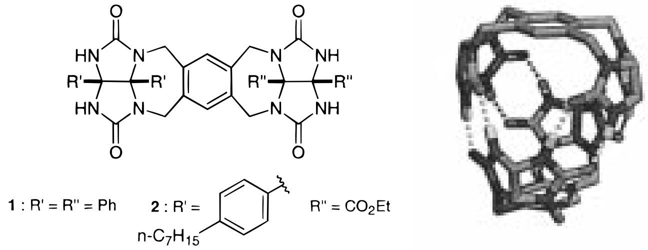
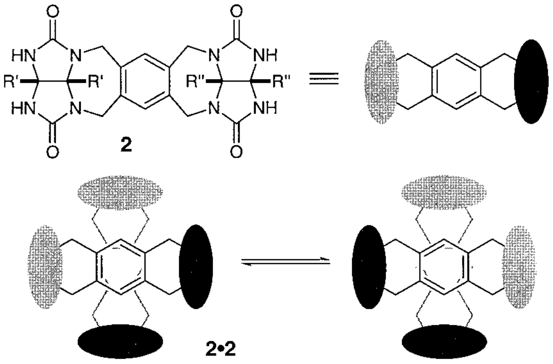


Figure 1. Left: The original tennis ball subunit **1** and the desymmetrized version **2**. Right: Energy-minimized[14] (AMBER* force-field used) structure of an assembled tennis ball. Glycoluril substituents omitted for clarity.

Scheme 1. Interconversion of Dimeric Assemblies



The cyclic array of eight hydrogen bonds involves both repulsive and attractive secondary interactions.[9] An empirical treatment of hydrogen-bonded complexes in $CDCl_3$ assigned 1.9 kcal mol^{-1} to the primary interaction and 0.7 kcal mol^{-1} to the secondary interactions.[10] Accordingly, a lower limit of 9.6 kcal mol^{-1} is predicted for the binding in **2·2** if one views the seam of hydrogen bonds as four isolated acceptor−donor/donor−acceptor pairs. If the 8 hydrogen bonds are viewed as a single entity with 16 secondary interactions, an upper limit of 15.1 kcal mol^{-1} for dimerization is calculated. The binding energy obtained from the kinetic data falls gracefully between these estimates.

The dynamics of both methane and ethane exchange were examined. These guests fill most of the capsules present and allow a simplified kinetic treatment that neglects empty hosts for the exchange process. The remaining processes that contribute to the observed cross-peaks can be described by eqs 1−3 (Scheme 2). Since it is unlikely that a guest molecule stays encapsulated in one of the subunits after the dissociation, process 1 can be neglected as contributing to cross-peak buildup. This additional simplification reduces the rate for host racemization and guest exchange to k_{rac} [process 2 alone] and k_{ex} [sum of processes 2 and 3], respectively. Table 1 summarizes the rate constants extracted from the series of 2D EXSY experiments.

From the data it is evident that encapsulation of methane or ethane stabilizes the capsule by ~1 kcal mol^{-1}, ethane being the slightly better guest.[11] Since $k_{\mathrm{ex}} > k_{\mathrm{diss}}$ for the guests studied, a mechanism exists for exchange of guests without complete

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[6] Spectroscopic data for **2·2**: ^1H NMR (600 MHz, $CDCl_3$) δ 9.66 (s, 2H, NH), 9.27 (s, 2H, NH), 8.98 (s, 2H, NH), 8.70 (s, 2H, NH), 7.35 (s, 2H, ArH), 7.13 (d, 4H, ArH), 6.98 (d, 2H, ArH), 6.94 (d, 2H, ArH), 6.88 (m, 6H, ArH), 6.83 (d, 4H, ArH), 4.60−4.74 (m, 8H, CH_2), 4.25−4.35 (m, 12H, CH_2), 3.98 (dd, 4H CH_2), 2.38−2.41 (m, 8H, CH_2), 1.15−1.50 (m, 52H alkyl groups), 0.86−0.91 (m, 12H, CH_3); HRMS(FAB) calcd for $C_{50}H_{62}N_8O_8Cs^+$ 1035.3745, found 1035.3794.

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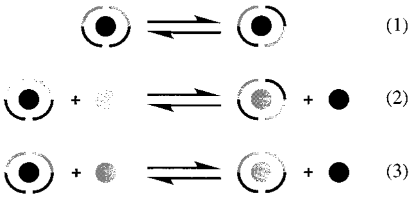
S0002-7863(98)00161-9 CCC: $15.00

Scheme 2. Processes Contributing to Cross-Peaks in the EXSY Experiments[a]



[a] Arcs represent tennis ball subunits, and circles represents guest molecules. A change in shading indicates racemization of the dimeric assembly and guest exchange, respectively.

Table 1. Kinetic Data[a] for the Dissociation/Reassociation Rates [$k_{diss} = 2k_{rac}$] of **2·2** and Exchange Rates [k_{ex} and k_{ex}'] for Guests Encapsulated by **2·2**

guest	k/s^{-1}	$\Delta G^{\ddagger}_{295}$/(kcal mol^{-1})
empty[b]		
k_{diss}	0.62 ± 0.03	17.5 ± 0.1
methane		
k_{diss}	0.14 ± 0.06	18.5 ± 0.3
k_{ex}	1.14 ± 0.06	17.2 ± 0.1
k_{ex}'	1.0 ± 0.1	17.3 ± 0.1
ethane		
k_{diss}	0.10 ± 0.02	18.6 ± 0.1
k_{ex}	0.56 ± 0.06	17.6 ± 0.1
k_{ex}'	0.46 ± 0.08	17.7 ± 0.1

[a] Reported values are the average from three different sets of measurements. [b] Empty or occupied by dissolved atmospheric gases.

dissociation of the host. We define the rate for this pathway as $k_{ex}' = k_{ex} - k_{diss}$. The data in Table 1 identify this pathway as the predominant mechanism for guest exchange, accounting for 80−90% of all guest exchange.

How can guest exchange occur in the hydrogen-bonded dimer? Two mechanisms are possible, and both involve ring inversion of the seven-membered ring connecting the glycoluril to the aromatic spacer. The inversion breaks four hydrogen bonds, and the ring undergoing inversion may be either proximal or distal to the hydrogen bonds being broken (Figure 2). The remaining four hydrogen bonds hold the two halves of the tennis ball together. Either motion provides an opening large enough to allow guest exchange to occur through an S_N2-like process: displacement of the outgoing guest by an incoming one.[12] A crude estimate for the barrier to inversion of a seven-membered ring fused to a benzene spacer, obtained using molecular mechanics, is ~10 kcal mol^{-1}. The additional energy required to break the four hydrogen bonds should fall between 4.8 and 6.2 kcal mol^{-1}.[10] The sum approaches the experimental barrier, especially since guest exchange need not take place every time ring inversion occurs. More refined calculations and experiments with model compounds for the ring inversion are in progress.[13]

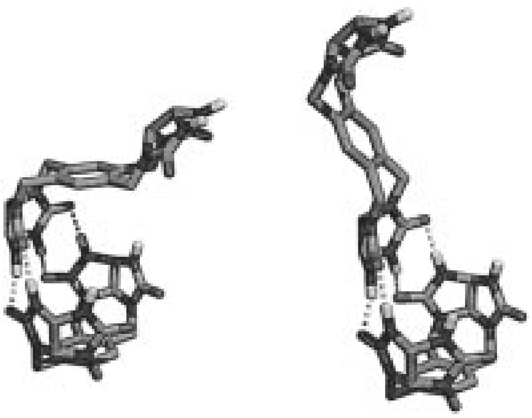


Figure 2. Energy-minimized[14] (AMBER* force-field used) structures of postulated openings. Glycoluril substituents omitted for clarity.

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(11) The same guest preference ($\Delta\Delta G \sim 0.3$ kcal mol^{-1}) was found for a symmetrically substituted tennis ball; see: Garcias, X.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1225−1228.

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