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Gating and Entropy in Guest Exchange by Rebek’s Sportsballs. Theoretical Studies of One-Door, Side-Door, and Back-Door Gating

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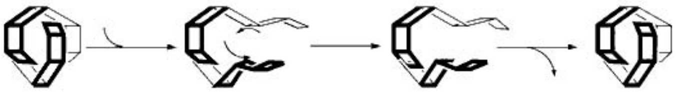
ABSTRACT



“Tennis ball” and “softball” are spherical dimeric molecules held together by hydrogen bonds yet able to exchange guest molecules. Mechanisms of guest exchange were explored with AMBER* force field calculations. The “one-door” S_N1 and the “side-door” S_N2 gating mechanisms are predicted for guest exchanges in the “softball”, while a dissociation mechanism is predicted for the “tennis ball”. Entropy changes have an important influence on the guest exchange mechanisms.

The “tennis ball”[1−7] and “softball”[8−15] molecules, created by Rebek and co-workers,[16] are nearly spherical dimeric container molecules held together by hydrogen bonds (Figure 1). Small guest molecules can be exchanged under mild conditions. Two mechanisms have been considered: a dissociation−recombination mechanism, in which the dimer

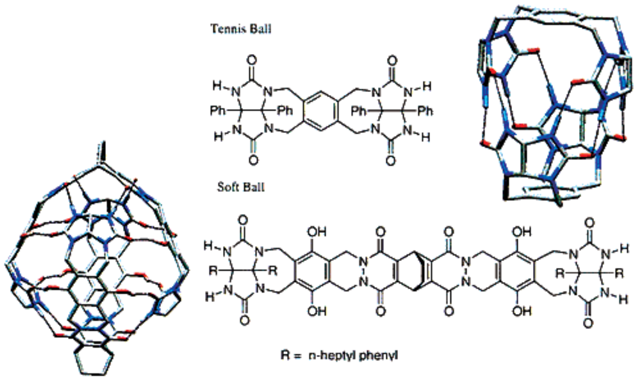


Figure 1. Chemical structures of half of the “tennis ball” and the “soft ball”.

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dissociates, opening the carcerand to form a cavitand, guests are exchanged, and then the ball is reformed; or a gating mechanism such as that predicted for other hemicarceplexes.[17,18] In a gating mechanism, only part of the hemicarcerand host, the gate, opens to create a temporary portal for the possible dissociation of the guest molecule (Figure 2).

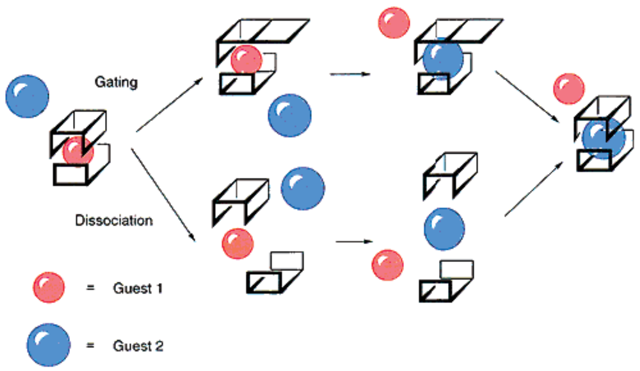

Figure 2. Two mechanisms for guest exchange in the "tennis ball".

To evaluate the energetics of each mechanism, theoretical studies were conducted with AMBER* force field calculations.[19] The GB/SA* solvation model of chloroform was used to evaluate the solvent effect.[20]

The computed structure of the "tennis ball" is shown in Figure 1. The hydrogen bonds that cross-link the two monomers are shown by the pink lines. Up to eight hydrogen bonds can be formed upon dimerization. Computationally, each hydrogen bond contributes 3−4 kcal/mol to the stability of the dimer.[21] A dissociation energy of 29 kcal/mol is needed to break the two monomers apart in chloroform.[22] The free energy for dissociation of the "tennis ball" is only17.5 kcal/mol at room temperature, measured by Rebek's group with ^{1}H NMR EXSY experiments.[1] Since the dissociation is facilitated by a favorable entropy of about 30−40 eu,[23] which amounts to 9−12 kcal/mol at room temperature, the computed and experimental dissociation energies are in good agreement. The energies of complexation of guest molecules inside the "tennis ball" (about 1 kcal/mol, experimentally)[1] are significantly weaker than the association of the two monomers; the dissociation of the capsule must be the rate-determining step in guest exchange.

Is the alternative gating mechanism possible? Two envelope-shaped seven-membered rings are present in each half of the "tennis ball". Inversion of one of these rings results in opening of the "tennis ball" dimer, to give a portal large enough for the passage of guest molecules (Figure 2). Computational studies of the "tennis ball" monomer show that about 15.0 kcal/mol is needed to invert this seven-membered ring.[24] The energy to break four hydrogen bonds costs an additional 15 kcal/mol, and the entropy change here is relatively small. The overall energy needed for the rate-determining step of the gating mechanism, the door-opening step, is about 30 kcal/mol, and there will be little energy lowering from entropic effects. Thus, the exchange of guests by the "tennis ball" goes through the dissociation mechanism.

By contrast, we predict that guest exchange in the "softball" dimer occurs by gating, not dissociation−recombination. The encapsulation of guest molecules in the "softball" dimer is known to be entropy driven.[1] The process is relatively slow and can be monitored by ^{1}H NMR. For example, in chloroform at room temperature, the enthalpy for the encapsulation of adamantane is +5.6 kcal/mol. The free energy, however, is −2.2 kcal/mol, since two solvent molecules escape from the carcerand during the encapsulation, resulting in a favorable entropy.[10] In *p*-xylene and at room temperature, paracyclophane was observed to take the place of adamantane in the "softball" dimers within 4 h.

As shown in Figure 1, 16 hydrogen bonds occur in the dimerization to form the "softball". These are indicated with the pink lines. The dissociation of the "softball" dimer could require as much as 70 kcal/mol to break up these hydrogen bonds.[22]

Gating is a likely alternative mechanism. In the "softball", there are two six-membered rings in each hemisphere. AMBER* force field calculations predict only a 1 kcal/mol activation barrier for inversion of a six-membered ring in a free hemisphere.[24]

Because there is no parameter for *p*-xylene solvent in the GB/SA* solvation model, chloroform was used as solvent model in our calculations. Adamantane and paracyclophane were the guest molecules in the model studies. Computationally, adamantane capture in the "softball" is exothermic by about 18 kcal/mol, while the complexation energy of two chloroform molecules in the "softball" is computed to be −21 kcal/mol. The energy difference is about 3 kcal/mol in favor of two chloroforms, and this is close to the 5.6 kcal/mol binding enthalpy measured experimentally. Our results confirm that the inclusion of guest molecules in the "softball" is most likely entropy driven, resulting from release of two chloroforms.

The encapsulation of paracyclophane in the "softball" is exothermic by about 38 kcal/mol, which is about 20 kcal/mol stronger than the inclusion of adamantane. Due to the favorable van der Waals interactions and π-stacking between the aromatic rings of paracyclophane and the "soft ball", paracyclophane is a better guest. Typically, the better the guest binding, the more negative the entropy, which will

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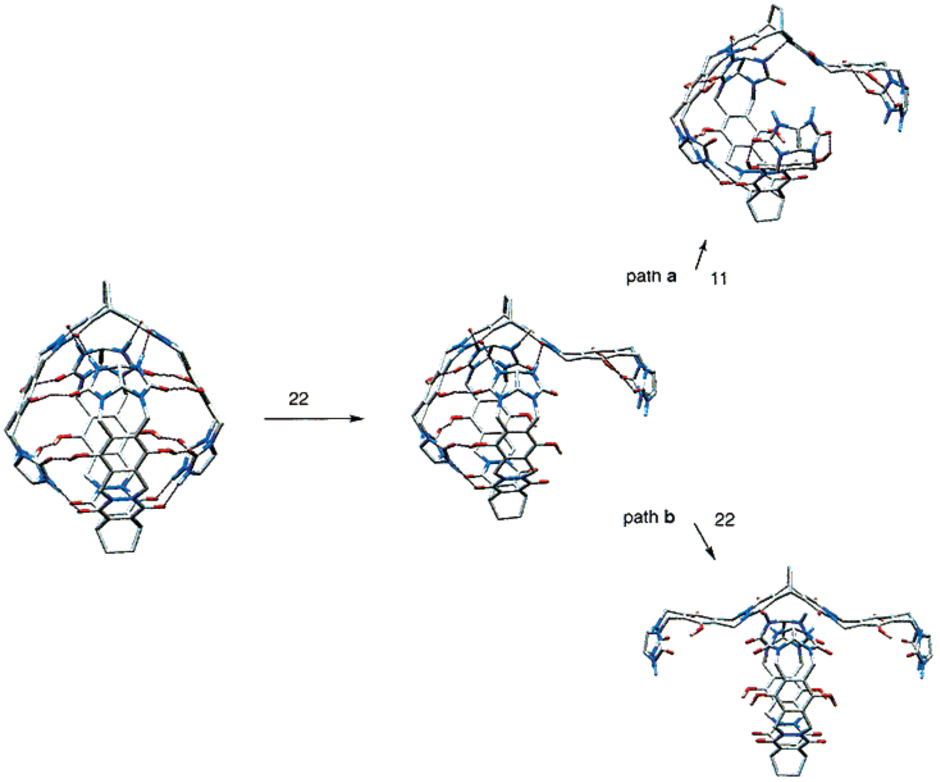

Figure 3. “Side door” and “back door” gating mechanism in the “soft ball”.

counteract the favorable enthalpy of binding.[25] Quite often, only about 10% of the enthalpic gain ($\Delta\Delta H°$) induced by the guest exchange is reflected in the net increase of the complex stability ($\Delta\Delta G°$). Such an entropic effect may account for the small difference in binding energies measured for these guests.

The energetics of three possible exchange pathways in chloroform are shown in Figure 3 and Figure 4. As shown in Figure 3, the gating mechanism starts with the opening of one door, which breaks six hydrogen bonds and costs about 22 kcal/mol. If guest molecules exchange by an S_N1 exchange mechanism, only one door is needed. This is shown as pathway **A** (black arrows) of Figure 4: a door opens up; the host−guest complex dissociates; another guest molecule enters; the gate closes. Opening the door requires about 22 kcal/mol energy, while the cost for the dissociation of the first guest molecule is compensated by the entropy gain of this process. The door-opening step is therefore the rate-determining step and requires a total energy of around 22 kcal/mol, much less than the dissociation mechanism.

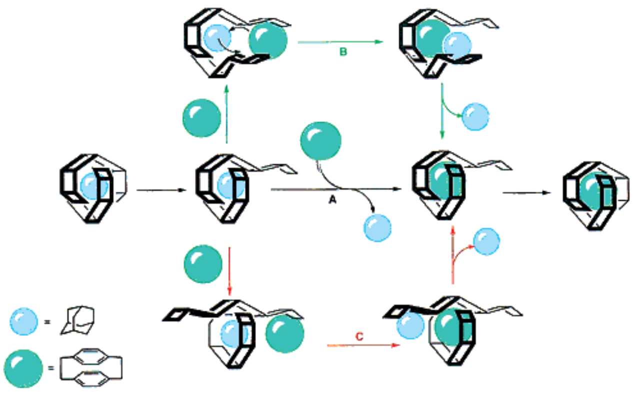

Figure 4. Schematic representation of guest exchange mechanisms. Black arrows: single-door, “S_N1” mechanism (pathway **A**). Green arrows: side double-door mechanism (pathway **B**). Red arrows: back double-door mechanism (pathway **A**).

If the guest molecules exchange by an S_N2 mechanism, a second door must open. There are two ways this can happen. The opening of the “side door” shown as path **a** in Figure 3 breaks four hydrogen bonds and costs about 11 kcal/mol; opening of the “back door” shown as path **b** requires about 22 kcal/mol and breaks six hydrogen bonds. Path **a** is strongly favored. Because opening the second door requires extra energy, this barrier, added to the energy required for the first door-opening step, determines the reaction rates.

Pathways **B** and **C** in Figure 4 are cartoons of the exchange reactions involving the “side door” and the “back door”. The “side door” mechanism (shown as green arrows) involves the following path: when the first door opens, the second guest molecule (shown as a green ball) enters; the side door opens; the second guest molecule gets in and pushes the inside molecule (shown as a blue ball) out the side door;

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the “blue” molecule leaves; finally, the doors close. AMBER* predicts that the “side door” mechanism requires about 24 kcal/mol energy. The “back door” mechanism (shown as red arrows) is very similar to the “side door” mechanism. The only difference is that the back door opens instead of the side door, when the second guest molecule pushes the first guest molecule out. It costs more than 38 kcal/mol of energy to achieve the “back door” mechanism.

Energetically, gating is strongly dominant as a guest exchange mechanism in the “softball”. The side double-door mechanism and one-door mechanism both require about 24 kcal/mol energy and may compete.

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