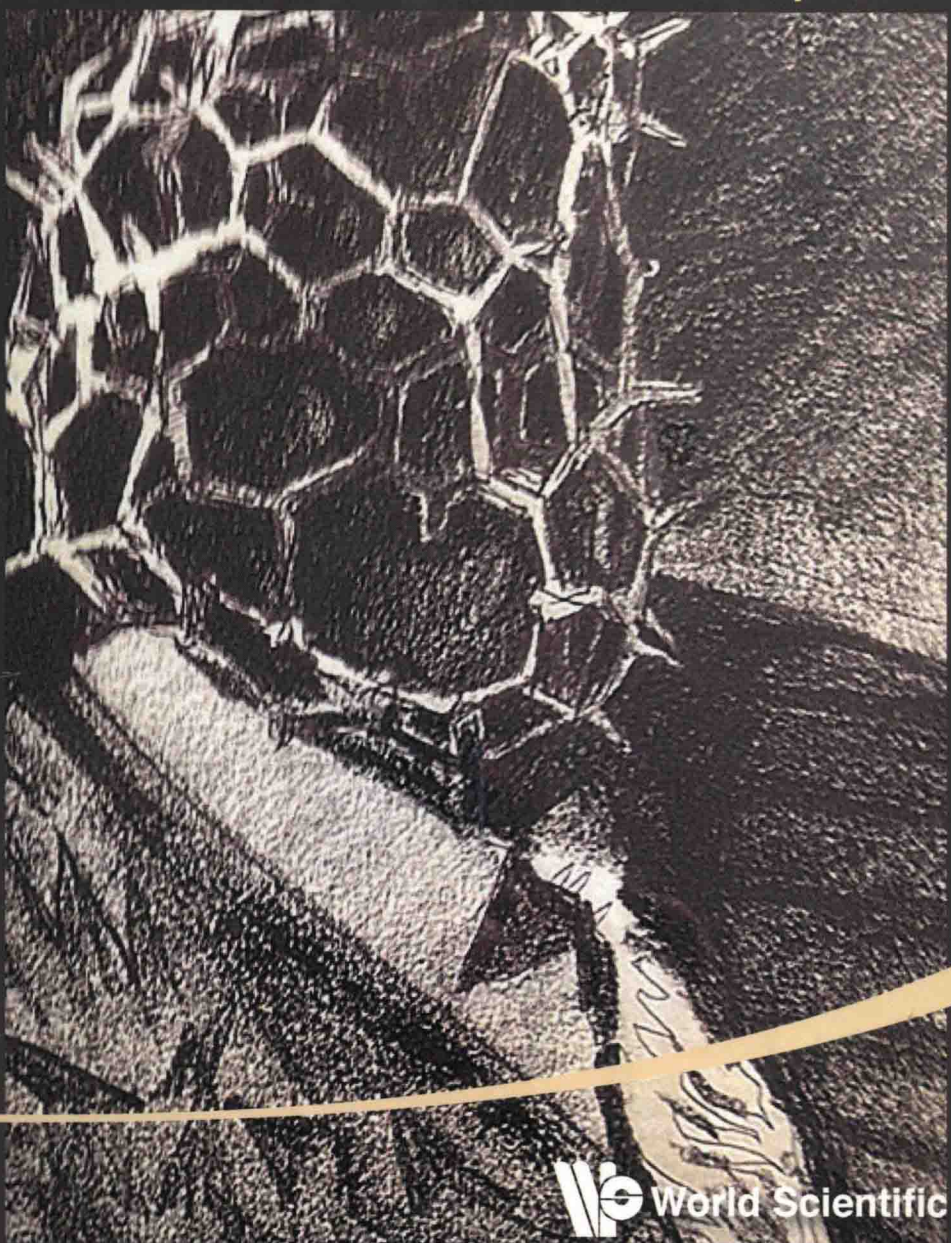
Julius Rebek, Jr.

Hydrogen-bonded Capsules

Molecular Behavior in Small Spaces



World Scientific

Hydrogen-bonded Capsules

Molecular Behavior in Small Spaces

Julius Rebek, Jr.
Fudan University, China & The Scripps Research Institute, USA

World Scientific

NEW JERSEY · LONDON · SINGAPORE · BEIJING · SHANGHAI · HONG KONG · TAIPEI · CHENNAI · TOKYO

Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

Library of Congress Cataloging-in-Publication Data

Rebek, Julius, Jr.

Hydrogen-bonded capsules : molecular behavior in small spaces / Julius Rebek, Jr., Fudan University, China & The Scripps Research Institute, USA.

pages cm

Includes bibliographical references and index.

ISBN 978-9814678353 (hardcover : alk. paper) -- ISBN 981467835X (hardcover : alk. paper)

1. Nanochemistry. 2. Microencapsulation. 3. Hydrogen bonding. 4. Chemistry, Organic. I. Title.

QC176.8.N35R42 2015

541'.2--dc23

2015023647

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Printed in Singapore

For

Stephen L. Buchwald and Jin-Quan Yu

Architects of chemical catalysis

Contents

Prologue

Research on molecular recognition became a fashionable topic for physical organic chemists in the 1980s. At the time there was growing disenchantment with the nonclassical ion controversy, and orbital symmetry fatigue was taking hold in the community. But the discovery of crown ethers by Pedersen in 1962 ignited the study of their complexes with ions, and macrocyclic polyethers dominated the scene for decades. The weak intermolecular interactions of these complexes gave rise to the concepts of molecular recognition: complementarity of sizes, shapes and chemical surfaces. The culmination of this activity was the award of the Nobel Prize in Chemistry to Pedersen, Cram and Lehn in 1987 for establishing host–guest chemistry and, on a grander scale, supramolecular chemistry.

While most practitioners favored macrocyclic compounds for the recognition of ions, there were several groups who pursued receptors of different shapes for other molecular targets. The shapes included a number of concave surfaces and — in our case — clefts, optimized for the study of reversible interactions. Along with many others, we became proficient in sculpting molecular surfaces to complement the convex surfaces of the small molecular targets. This activity was a departure from targeting spherical ions with circular receptors — the low-hanging fruit — since neutral molecule targets come in all manner of sizes and shapes. The application of hydrogen bonding for recognition purposes offered much appeal and became suspiciously close to the base-pairing of DNA. Purines, pyrimidines and other heterocyclic bases, rich in hydrogen-bonding possibilities, became popular targets. We pursued synthetic receptors that contacted incresingly large fractions of surfaces of the target molecules, and it became a reasonable

goal to engineer a system that completely surrounded the (convex) target molecule by the (concave) synthetic receptor. After all, enzymes and other biological receptors are capable of doing just that: folding around their targets, isolating them from the medium, surrounding them with a hydrophobic environment and presenting them with functional groups for signaling and catalysis. The present synthetic constructs are similar; interactions between the container and contained molecules are constant and encounters are not left to chance — they are prearranged, private and prolonged.

At that time we collaborated with Javier de Mendoza, and our most advanced receptor chelated adenosine phosphate, in such a way that most of the target molecule's surface was in contact with the synthetic receptor. We discussed the possibility of completely surrounding and isolating a target molecule — encapsulating it — through the assembly of self-complementary receptor pieces. This notion eventually became the "tennis ball," and started our journey on the road to hydrogen-bonded capsules and their open-ended cousins, the cavitands. Only recently have we been able to combine the two types of containers in that special solvent — water. Now, a little more than 20 years after we started, we explore our experiences with capsules in this monograph. Despite admonishments to the contrary, we will strive to tell the story chronologically, as far as a given container is concerned. We will also emphasize how we developed methods and interpreted our data at the time, and we make apologies in advance to other researchers who may feel left out. After all, this is a narrative of our own work.

CHAPTER 1

Spherical and Similar Capsules

A Drop Shot with a Tennis Ball

The ungainly shapes of nucleotides require unsymmetrical complements,[1] but for structures that are intended to completely surround a smaller, convex molecule, a sphere is not a bad starting point. The initial design[2] is shown in Figure 1.1; the compound **1** was intended to dimerize on account of its self-complementarity. The hydrogen bond donors of the glycolurils at the ends of the structure were to find their complements in the carbonyl acceptors of the imides at the center. The roughly spherical dimer **1.1** evokes a baseball or tennis ball, with the hydrogen bonds acting as the seams that hold it together. Rene Wyler set out to synthesize the compound but made an ingenious abbreviation of the original design. He realized that the *glycoluril carbonyls* could also act as acceptors in a self-complementary sense if a shorter spacer separated the molecule's ends. He hit a drop shot and produced the appropriate module **2** in a single chemical step from durene tetrabromide and the notoriously insoluble diphenyl glycoluril shown.[3] The condensation occurred in hot DMSO with KOH as the base, a recipe that the reader will recognize will also lead to polymerization, and it did. Fortunately, however, the polymer is insoluble while the module remains in solution. The yield was low (20%) but the isolation was easy. Much later, a variant of the procedure suitable for undergraduate laboratories was developed by Fraser Hof and Liam Palmer.[4] However, in 1993, we still intended to go for the baseline shot and synthesize the longer **1.1**. So we promoted its stature to the larger "softball" and referred to the smaller **2a.2a** as the "tennis ball."

The compound showed the expected NMR earmarks of a hydrogen-bonded dimer **2a.2a**, but it was not until a guest could be

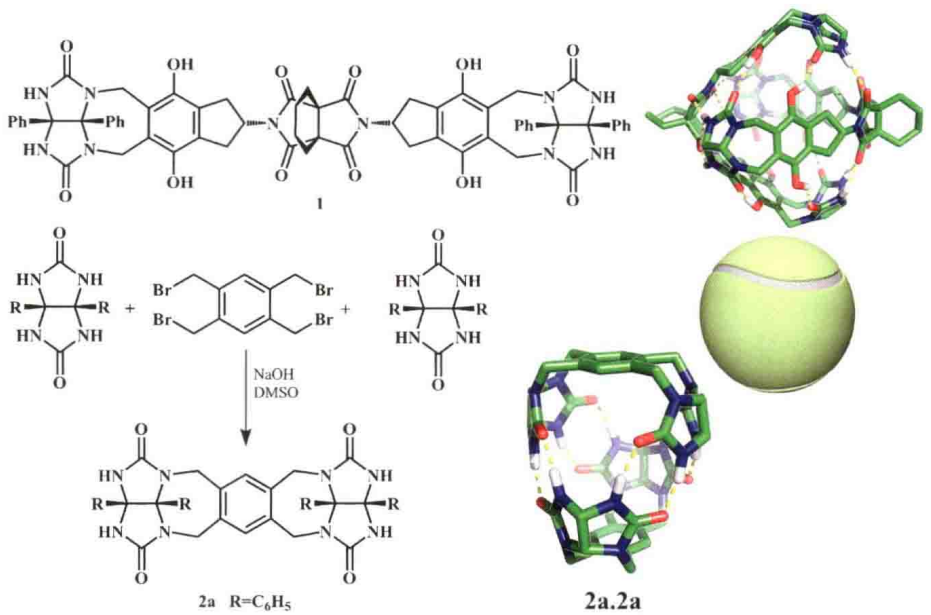


Figure 1.1 *Top*: The original sportsball design and its intended dimerization into a notional tennis ball. *Bottom*: The actual synthesis of the module **2a** and the corresponding hydrogen-bonded capsule with peripheral phenyl groups removed.

observed inside that we were sure of a capsular structure. Our source of methane in the laboratories at MIT showed the presence of considerable ethane and even some propane, but when Neil Branda and Rene Wyler bubbled this gas through a solution of **2a** in $CDCl_3$, encapsulation of the gases occurred (Figure 1.3).[5] The signals for the bound gases at −0.4 and −0.9 represent encapsulated CH_3–CH_3 and CH_4, respectively. The upfield shifts are a result of the anisotropy imparted by the two aromatic spacers of the capsule. The shifts would be even larger but the four peripheral phenyl groups are arranged edge-on to the guest and impart a *downfield* shift. Notice that these signals are sharp and widely separated from those of free ethane and methane, a feature that speaks for a large energy barrier between inside and outside the capsule. In other words, the rate of in–out exchange is slow on the NMR timescale. But exchange is fast on the human timescale, since equilibrium is established upon merely mixing the components. Integration of the spectra gives access to easily calculated

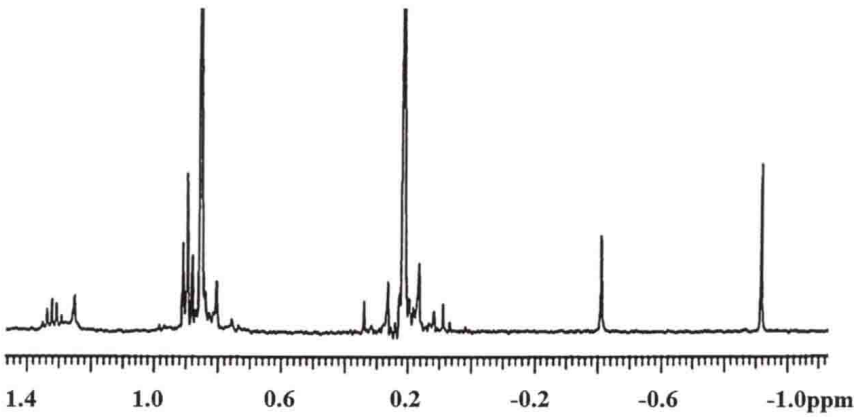


Figure 1.2 NMR spectrum of the tennis ball **2a.2a** in $CDCl_3$ saturated with commercial methane gas. [From *Science* (1994) **263**(5151): 1267–1268. Reprinted with permission from AAAS.]

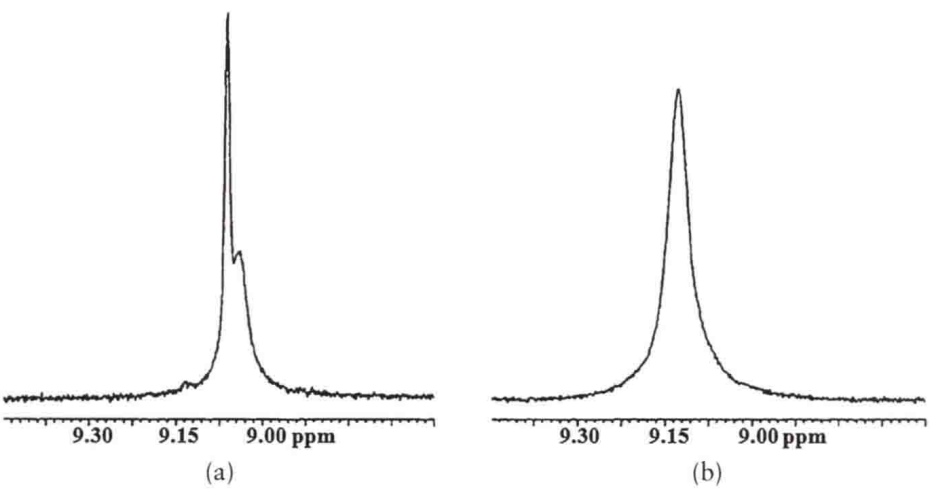


Figure 1.3 Downfield region of the 500 MHz NMR spectrum of **2a.2a** in $CDCl_3$ at −20°C. a) With ambient atmospheric gases; b) after degassing with helium. Reprinted with permission from *JACS* **117**(51): 12733–12745. [Copyright 1995 American Chemical Society.]

equilibrium constants, and changes of temperature give data from which thermodynamic parameters are readily obtained. *We emphasize these features since they are generally observed in hydrogen-bonded encapsulation complexes.*

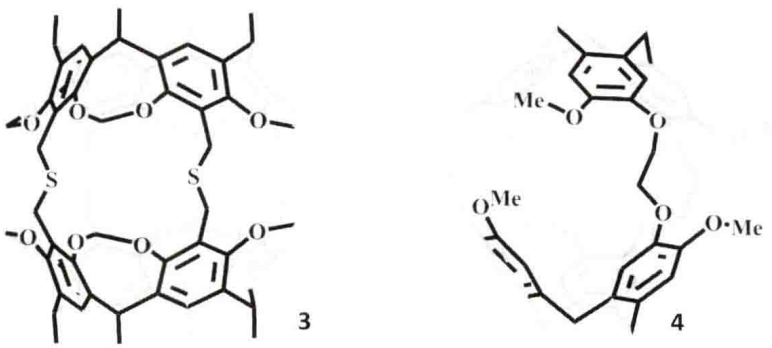


Figure 1.4 Cram's carcerand 3 and Collet's cryptophane 4, the original covalent container molecules.

The original studies of gas binding in the tennis ball assumed a solvent-filled capsule in $CDCl_3$, but that solvent is much too large to fit inside. Instead, the atmospheric gases dissolved in the solvent are the occupants in the resting state. An example is shown in Figure 1.4, where the N–H NMR signal of the resting state of the tennis ball in $CDCl_3$ shows at least three capsular species present. After flushing with helium, only one species is present.[6] These (NMR-silent) gases are easily displaced by the intended guests, which are presented in higher concentrations.

This should have been a valuable lesson — namely, that encapsulation is best performed in a solvent that cannot compete with the solute for the space inside — but the lesson did not sink in until much later. We will return to this subject, but the importance of solvent size was introduced by Clark Still,[7] who noticed that binding to an open-ended synthetic receptor resulted in very high association constants when a solvent too large to fit was used. Also, and apparently independently, Cram used large solvents that could not be accommodated (incarcerated) by his covalent capsules.[8] The solvent size issue now seems self-evident but was momentous to us then; molecular modeling has vastly improved since then, and solvents of different sizes can quickly be screened for fit. Also, there is the obvious requirement that the solvent be capable of *dissolving* the components, but this has to be done empirically. Finally (for NMR purposes), the desired solvent needs to be available in deuterated form — a requirement that is not always met.

At the time, we were confronted with our first encapsulation complex and needed to place it into some historical perspective. As mentioned earlier, various receptor shapes with concave surfaces, such as clefts,[9] armatures,[10] tweezers,[11] bowls[12] and other vehicles,[13] were under study for recognition. But something special occurs when a guest is completely surrounded by a host. These situations had been encountered with covalent compounds by Cram at UCLA, and Collet in Lyon in the mid-1980s (Figure 1.4). In Cram's case, structures such as **3** became known as carcerands,[14] because in the final step the covalent assembly could capture any nearby, appropriately positioned chemical debris and seal it off — more or less forever, as is characteristic of covalent bonds. In Collet's case there was also a covalent capsule **4**, but reversible guest capture was possible.[15] The tennis ball that we had in hand, having had experience with hydrogen bonds and their dynamics of rapid formation and dissipation, was expected to have lifetimes of milliseconds to hours. But determining the lifetimes had to wait for the right expertise to appear in the group. In the meantime, we took a brute force approach to getting things in and out of the tennis ball.

Neil Branda, Robert Grotzfeld and Carlos Valdes prepared more soluble versions of the glycoluril, bearing *p*-dimethyaminophenyl or carboethoxy groups,[16] and incorporated them into the corresponding tennis ball modules **2b,c** (Figure 1.5). In deuterated DMF as a solvent, the compounds remained as monomers since the solvent could not be encapsulated. Moreover, DMF competes well for the hydrogen bond donors of the module. But adding gases such as methane, ethylene or even xenon nucleated the assembly of the capsular complex. The

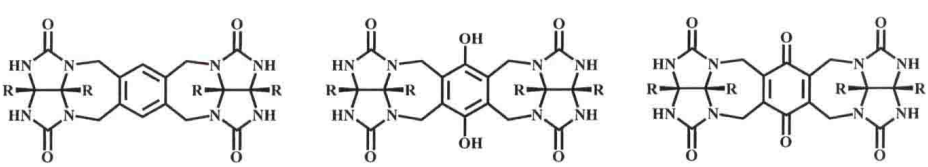


Figure 1.5 Tennis balls with varied peripheral groups for solubility and proximal groups for recognition of guests.

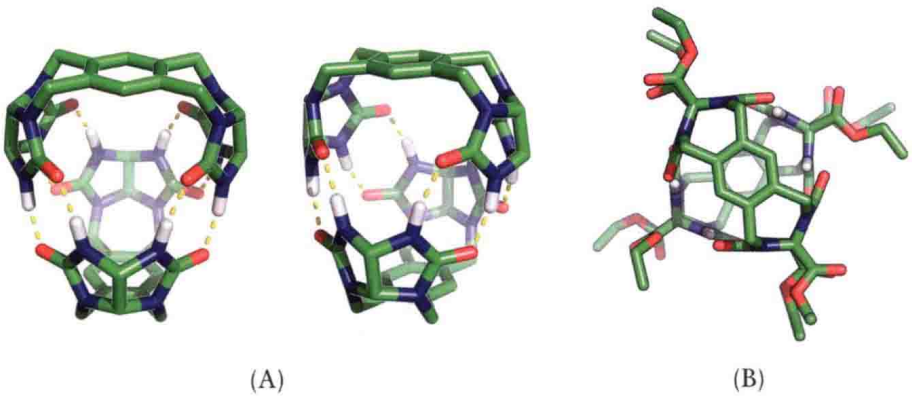
Table 1.1 Association constants K_a (M^{-1}, 298°K) for the encapsulation of guests in the tennis ball dimers (K_a = [2-guest-2]/[2-2] x [free guest]).

Guest	Host 2c-2c	2d-2d	2e-2e
CH_4	33	70	10
C_2H_6	51	51	13
CH_3F	10	17	<0.3
CF_4	0.7	0.6	<0.2

peripheral basic groups of **2b** were expected to provide sites for protonation and it seemed reasonable that multiple charges on the capsule would force the two halves apart and liberate the guest. The state of the system could be conveniently monitored by both ^1H and ^{129}Xe NMR spectroscopy. Control of guest binding and release turned out to be possible in this system: protonation with p-TsOH gave the protonated monomers and free gas, then neutralization with Na_2CO_3 regenerated the capsular assembly **2b.2b**.

The slow exchange of guests allowed the determination of equilibrium constants by simple integration of the NMR signals for free and bound species. These are shown in Table 1.1.

The availability of a variety of peripheral groups on the tennis ball through synthesis paid a great dividend: it eventually led to a crystalline sample, and its X-ray structure was solved by Leticia Toledo. The carboethoxy compound **2c.2c** showed the expected, nearly spherical space inside occupied by a guest.[17] Although disorder prevented the identification of the guest with certainty, it fit the parameters for CH_3OH, one of the solvents of crystallization. A stereoview of the capsule with deleted ester groups is shown in Figure 1.6(A), while the disorder of the esters can be seen in Figure 1.6(B). This was the first direct observation of a solvent molecule inside, albeit in the solid state. The dimeric structure showed signs of binding CH_2Cl_2 but was reluctant to take up the larger $CHCl_3$. The use of $^{13}CH_2Cl_2$ permitted the direct observation of this guest inside and in solution for the first time.



(A) (B)

Figure 1.6 (A): Stereoview of the solid state structure of the tennis ball **2c.2c** with the carbethoxy groups removed. (B): A view of the dimer showing the disorder of the ester groups.

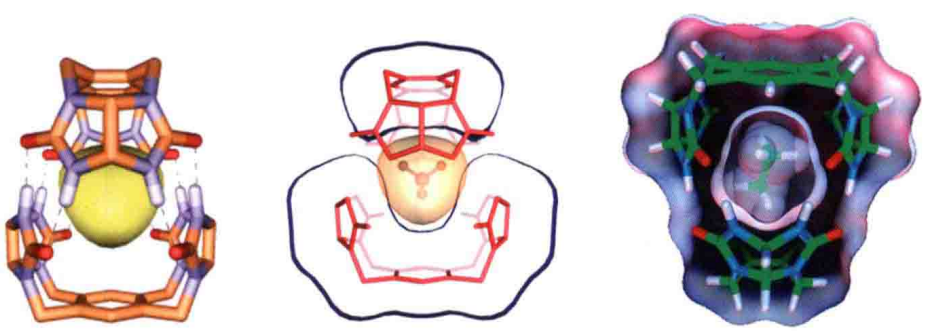


Figure 1.7 Views of the tennis ball. *Left*: Hydrogen bonds. *Center*: solvent accessible surfaces of capsule and CH_4 guest. *Right*: Modeled complex with C_2H_6.

What are the relative sizes of the guests and the cavity of the tennis ball? It is easy to be misled by software in answering this question. What you see depends on the software you use, as illustrated by Figure 1.7. Simple modeling packages are accurate in finding the eight hydrogen bonds but rolling a standard H_2O-size probe around to find the solvent-accessible surface of the tennis ball and methane leads to the central figure. The surfaces overlap and one could conclude that methane is too big to fit inside. More sophisticated software gives the rendering on the right, which shows that even ethane leaves plenty of

empty space inside. Other professional computations of the capacity followed.[18]

The self-complementary hydrogen bond patterns of glycoluril demanded incorporation into related architectures with different spacers. A shorter one, ethylene (as in **5**, Figure 1.8 (top)), was clearly a good candidate for assembly into a dimeric capsule, as its O-to-O dimensions were close to those of the tennis balls. The longer spacers, such as naphthalene **6** and bridged anthracene **7**, showed less promise, but these were all eventually synthesized by Carlos Valdes, Uri Spitz and Stefan Kubik. The ethylene-spaced module **5** (R = CO_2Et) formed

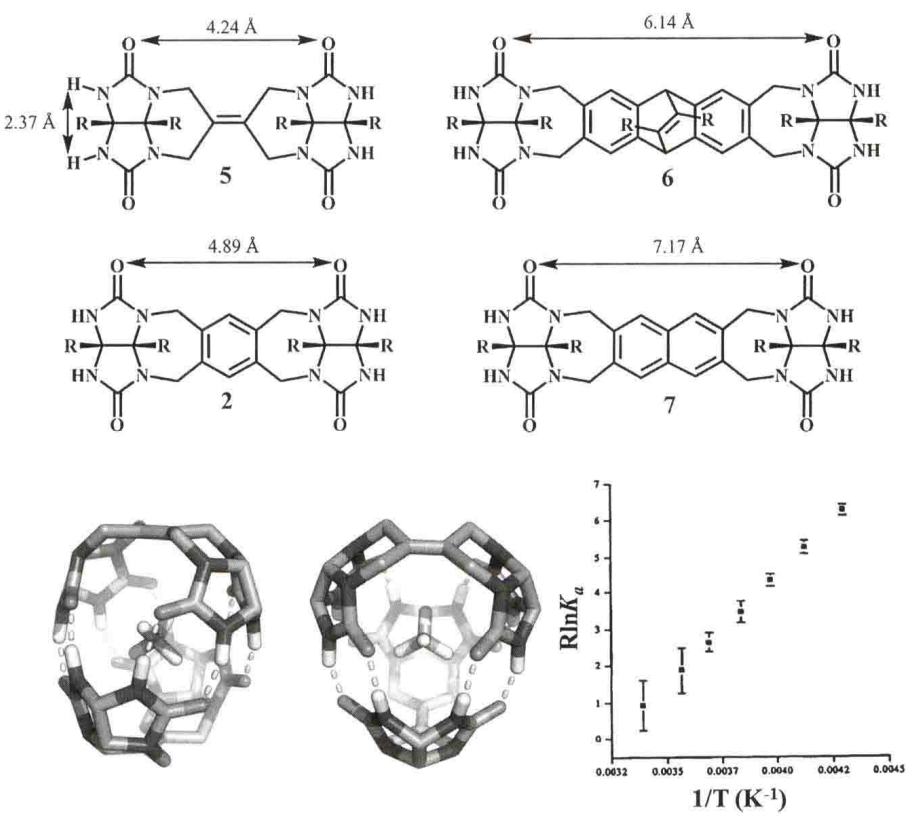


Figure 1.8 *Top*: Glycolurils separated by different spacers also dimerize. *Bottom*: X-ray stereoview of dimer **5**.5 without esters and the van 't Hoff plot for its binding of CH_4 in $CDCl_3$. [Reprinted with permission from *Chemistry — A European Journal* 2(8):989–991. Copyright 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.]