investigations can be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-406847.
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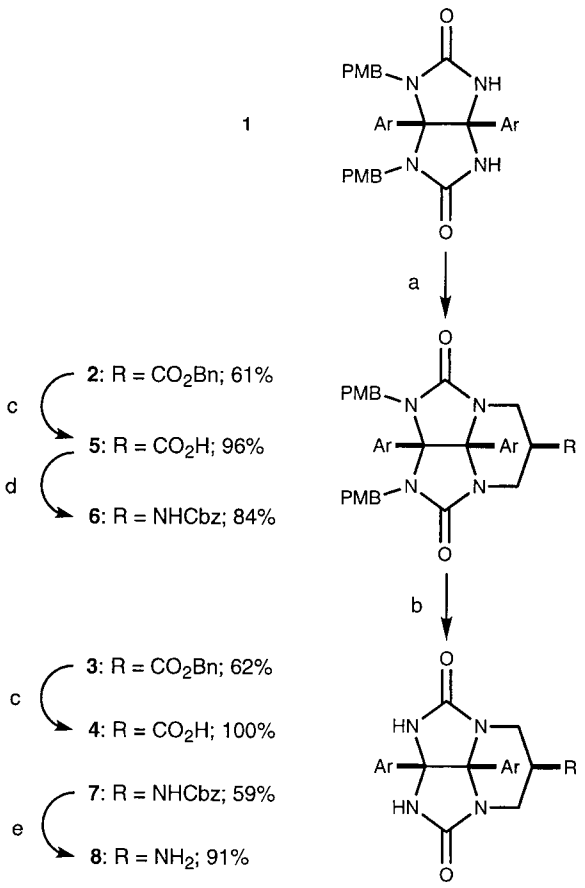
Self-Assembling Sieves**

Tomas Szabo, Brendan M. O'Leary, and Julius Rebek, Jr.*

"Molecule within molecule"[1] complexes have been useful in stabilizing reactive intermediates,[2] defining new forms of stereoisomerism,[3] and accelerating Diels–Alder reactions.[4] Other applications await the availability of diverse sizes and shapes for selective and reversible encapsulation. We describe here a modular approach that gives access to some of the largest hydrogen-bonded capsules ($\approx 0.5\ nm^3$) reported to date. These modules promise versatility in the assembly of many new structures using diverse molecular scaffolds.

The modules are based on the glycoluril system, a structure that provides both molecular curvature and a richness of hydrogen-bonding sites (Scheme 1). Alkylation of the unprotected face of **1**[5] with benzyl 2-(bromomethyl)acrylate[6] gives



Scheme 1. Synthesis of glycoluril building blocks **4** and **8**. a) Benzyl 2-(bromomethyl)acrylate, Cs_2CO_3, MeCN, reflux, 3 h; b) CAN, MeCN/H_2O (5/1), RT, 24 h; c) H_2, Pd/C, EtOH, 3 h; d) DPPA, PhMe, RT, 30 min; then BnOH, reflux, 2 h; e) H_2, Pd/C, EtOH/EtOAc/AcOH (49/49/2), 3 h. Ar = 4-*n*-heptylphenyl, PMB = 4-methoxybenzyl, Cbz = phenylmethoxycarbonyl; CAN = ceric ammonium nitrate, DPPA = diphenylphosphoryl azide.

the tricyclic structure **2** featuring the equatorial ester as the major product. The fused six-membered ring contributes to the overall rigidity of the glycoluril unit and offers an attachment point for coupling to appropriate spacer units. Two deprotection steps then yield acid module **4**, suitable for condensation with amine- or alcohol-bearing spacers. Alternatively, subjecting acid **5** to a modified Curtius rearrangement[7] followed by deprotection affords amine module **8** for use with spacers containing carboxylic or sulfonic acids.

Our initial efforts focused on D_{3d}-symmetric capsules assembled through a seam of twelve hydrogen bonds. The hexa-substituted spacers **9**[8] and **10**[9] (Scheme 2) were expected to provide a geared arrangement[10] of substituents around the benzene ring and present all three modules on one side of the spacer. Condensation of triamine **9** with acid module **4** gave monomer **11** in 68% yield, while coupling triacid **10** with amine module **8** gave a 49% yield of monomer **12**, differing from **11** only by the "direction" of the amide linkage.[11]

Both systems gave tell-tale signs of exclusive dimerization as indicated by far downfield shifts for the glycoluril N–H resonances and sharp, first-order signals for the remaining

[*] Prof. J. Rebek, Jr., Dr. T. Szabo
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 619-7842876
E-mail: jrebek@scripps.edu
B. M. O'Leary
Department of Chemistry
Massachusetts Institute of Technology (USA)

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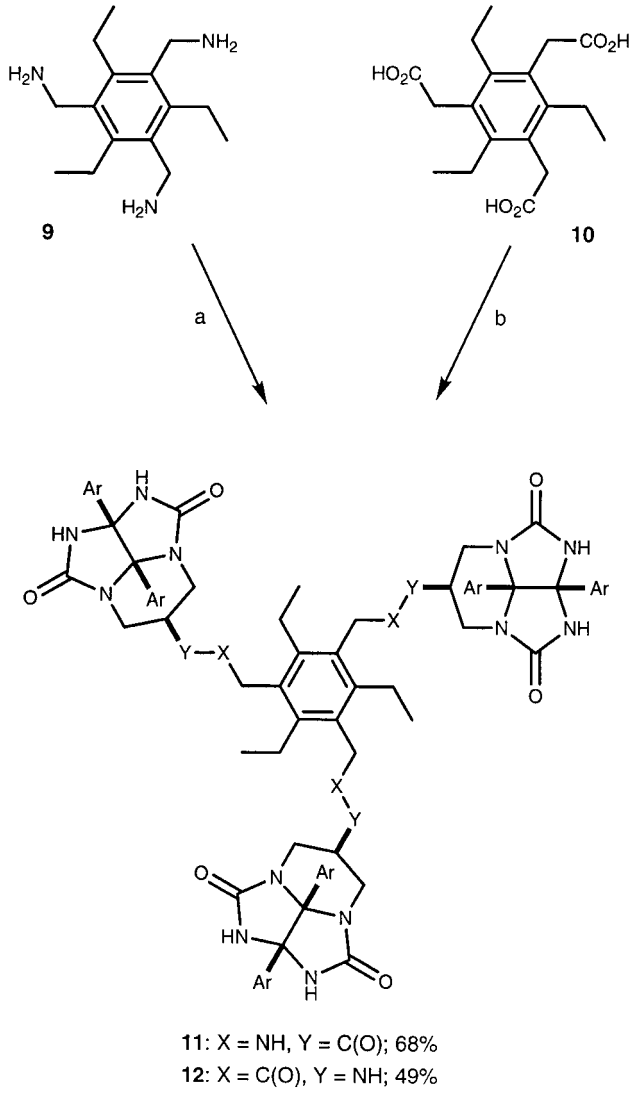

Scheme 2. Synthesis of **11** and **12**. a) **4**, EDC, HOBt, Et_3N, DMF, RT, 6 h; b) **8**, EDC, HOBt, Et_3N, DMF, RT, 6 h. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole.

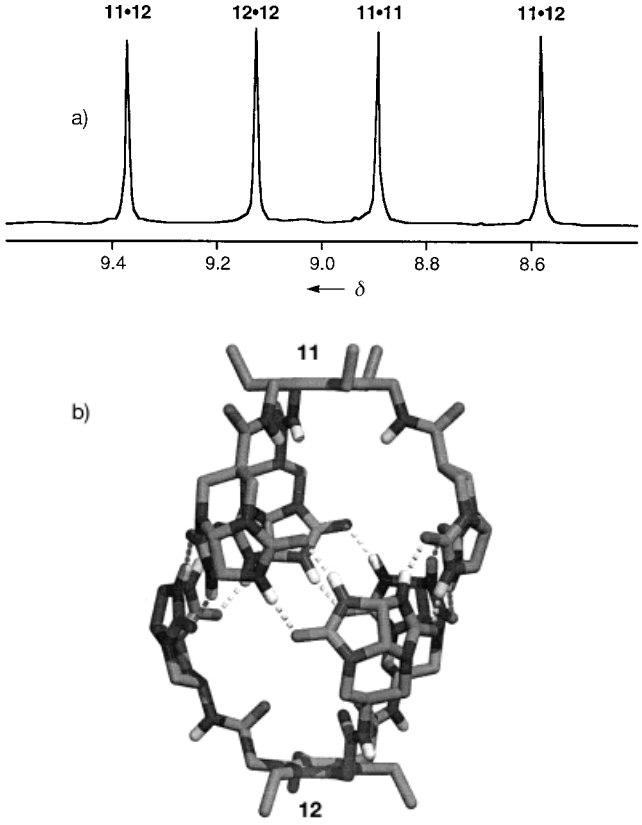

Figure 1. a) ^{1}H NMR spectrum showing glycoluril N–H resonances for a 1:1 mixture of **11** and **12**. The heterodimer **11**·**12** has two different glycoluril N–H resonances. b) Energy-minimized structure of **11**·**12** (some groups omitted).

protons in ^{1}H NMR spectra in $CDCl_3$.[12] Furthermore, no concentration dependence was observed for any shifts in solvents used for this study.[12] These indicators of large dimerization constants were supported by mass spectrometric (MALDI) detection of dimer **11**·**11**. Other proof of dimeric assemblies came from heterodimer formation upon mixing **11** and **12** (Figure 1 a), whose close structural resemblance led to a nearly statistical distribution of dimeric species. Finally, as described below, the dimers were found to encapsulate a variety of guests.

In contrast to the above indications of dimerization, mixtures of deuterated solvents failed to show the expected formation of at least two distinct complexes for hosts **11**·**11** and **12**·**12**.[13] This suggests that those solvent molecules rapidly move between the capsule interior and exterior resulting in an averaging of complexes on the NMR time scale. The mechanism of this exchange probably depends upon the breathing dynamics of these flexible capsules. Too fast to measure by NMR spectroscopy, these motions might increase the pore sizes enough to permit easy passage of solvent molecules through the dimer, akin to the flow of water through a sieve.

Previous studies identified solvent release as a significant driving force for encapsulation,[14] but the large holes in these sieve-like molecules led us to doubt their utility as hosts. If solvents could enter and depart at will, entropic gains from guest encapsulation might be too small to make the process favorable. Indeed, this idea was supported by the fact that **11**·**11** had little or no affinity for a variety of guests while dissolved in $CDCl_3$. However, dimer **12**·**12** showed remarkable binding affinity [Eqs. (1) and (2)] for several guests in this solvent (Table 1).

$$\text{host}\cdot(\text{solvent})_n + \text{guest} \rightleftharpoons \text{host}\cdot\text{guest} + n\,\text{solvent} \quad (1)$$

$$K_a = \frac{[\text{host}\cdot\text{guest}]}{[\text{host}\cdot(\text{solvent})_n]\,[\text{guest}]} \quad (2)$$

How can this discrepancy be explained? One possible answer rests with size and shape differences between the two cavities. In a recent report from our lab discussing size complementarity in liquid state host–guest systems, an ideal packing coefficient (PC) was proposed.[15] For the dimers described here, binding affinities can be understood through evaluating ideal PCs (0.59 ± 0.09) and shape congruence between cavity and guest.

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Table 1. Apparent binding constants K_a in M^{-1} for **11**·**11** and **12**·**12** in the solvents $CDCl_3$ (71 Å^3) and [D_{12}]mesitylene (124 Å).

Guest (volume, Å^3)	**11**·**11**	**12**·**12**
$CDCl_3$		
[2.2]paracyclophane (195)	0	0.51
ferrocene (146)	0	2.7
1,1′-dimethylferrocene (178)	0	5.8
ferrocenemethanol (170)	[a]	$\gg 25$[b]
1,1′-ferrocenedimethanol (191)	[d]	24
ferrocenecarboxylic acid (170)	0	8.6
(1*S*)-(−)-camphor (159)	0	0.55
1-adamantaneethanol (184)	1.4×10^{-3}	1.5
[D_{12}]mesitylene		
[2.2]paracyclophane (195)	2.0×10^{-3}	[c]
ferrocene (146)	0	[c]
1,1′-ferrocenedimethanol (191)	$\gg 25$[b]	[c]
(1*S*)-(−)-camphor (159)	9.2×10^{-2}	[c]
1-adamantaneethanol (184)	4.6×10^{-3}	[c]

[a] Not evaluated. [b] Too large to measure accurately. [c] Insoluble host. [d] This guest appeared to break up the dimer **11**·**11** in this solvent.

Computer modeling of complex **11**·**11**, with pores blocked, reveals a rugby-ball shaped cavity measuring approximately 490 Å^3.[16] All six of the amide carbonyls point outward, while the amide NH groups point into the cavity. Dimer **12**·**12** has a related structure, but features a smaller, more spherical cavity (434 Å^3) because the six carbonyls point into the cavity. Figure 1b shows the calculated representation of the heterodimer **11**·**12** whose halves allude to the structures of the respective homodimers.

Dimer **12**·**12** readily encapsulates ferrocene as indicated by a ^{1}H NMR spectrum showing a new set of host peaks and a new peak for encapsulated ferrocene downfield of the "free" guest.[17] These characteristics indicate that ferrocene is too large to move freely through the dimer and is trapped in the sieve (slow exchange). Integration of these peaks reveals one ferrocene molecule per new host molecule corresponding to a PC of only 0.34.[18] This small PC suggests an unfavorable complex due to insufficient "solvation" of the cavity. However, co-inclusion of one or two chloroform molecules on average (fast exchange) with each ferrocene would increase the PC to a more comfortable 0.50 or 0.66, respectively. While still speculative, this scenario appears feasible by molecular modeling.

In contrast, dimer **11**·**11** does not encapsulate ferrocene even at large exterior concentrations of this compound. Encapsulation of two chloroform molecules and one ferrocene molecule produces a favorable PC of 0.59, but an ideal PC does not automatically translate into a good fit. Shape is a major consideration, that is a square peg may have the same volume as a round hole, but the different shapes preclude a good fit. The rugby-ball shaped cavity of **11**·**11** is presumably filled on average with four molecules of chloroform (PC = 0.58). These solvent molecules can be thought of as small spheres. Replacing two of these with a larger sphere (like free-tumbling ferrocene) may not be favorable because this new guest may not be able to "solvate" the tapered ends of the cavity as well as chloroform.

While almost every prospective guest shunned the cavity of **11**·**11** in $CDCl_3$, the story changed upon switching to the largest deuterated solvent available, [D_{12}]mesitylene (Table 1).[19] Calculation of PCs showed that the included guests plus one mesitylene gave values in the upper end of the ideal range. Unsurprisingly, the better binders tended to be more complementary in shape and possessed functionality capable of hydrogen bonding to polar surfaces within the cavity. In short, **11**·**11** preferred these guests to the poorer solvation offered by large, disc-shaped mesitylenes.[20] However, as indicated in Table 1, none of these guests could compete as well against chloroform solvation of the interior.

What is the mechanism of encapsulation? A clue is given by the heterodimerization of the two capsules. The disproportionation of **11**·**11** and **12**·**12** to the heterodimer requires the complete dissociation of a dimeric capsule by the eventual disruption of 12 hydrogen bonds. This process reaches equilibrium in chloroform over the course of hours. The common finding that encapsulation equilibrium is reached within minutes for all viable guests suggests a mechanism of guest uptake not dependent upon complete dissociation. Instead, modeling shows that opening one glycoluril "flap" by breaking four hydrogen bonds creates a pore large enough to accommodate the passage of most guests.[21]

In summary, large capsular assemblies are made readily available by modular syntheses. Studies with these porous capsules suggest that the encapsulation of large guests is not dependent on entropically favorable release of trapped solvent molecules and, instead, appears to be an enthalpy-driven process. Further reports detailing the unique host properties of these and other large systems will be forthcoming.

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[15] S. Mecozzi, J. Rebek, Jr., *Chem. Eur. J.* **1998**, *4*, 1016 – 1022. Cavity volumes likely are underestimated due to the necessary hole-blocking method used in calculations. Therefore, PCs will appear larger than the reported ideal. The best binders in this study gave an apparent average PC = 0.59 ± 0.09. [PC = volume of guest(s)/volume of cavity].
[16] Modeling was performed by using a Macromodel v5.5, Amber* forcefield. Pore blocking was necessary to define a cavity. This involved replacing the equatorial hydrogen atoms on each module's six-membered ring with a cyclopropyl group. Volumes are based upon a static structure and calculated as described in reference [15].
[17] The twelve phenyl groups of the glycolurils present their edges to the cavity which accounts for the downfield shifts of guests' signals from their "free" positions.
[18] Ferrocene derivatives were modeled by using MacSpartan Plus and their volumes were calculated by using MacroModel.
[19] Dimer **12**·**12** displayed poor solubility and dimer **11**·**11** was only moderately soluble in $[D_{12}]$mesitylene. This probably results from the poor shape complementarity of two encapsulated mesitylenes (PCs = 0.57 and 0.51, respectively) with the cavities.
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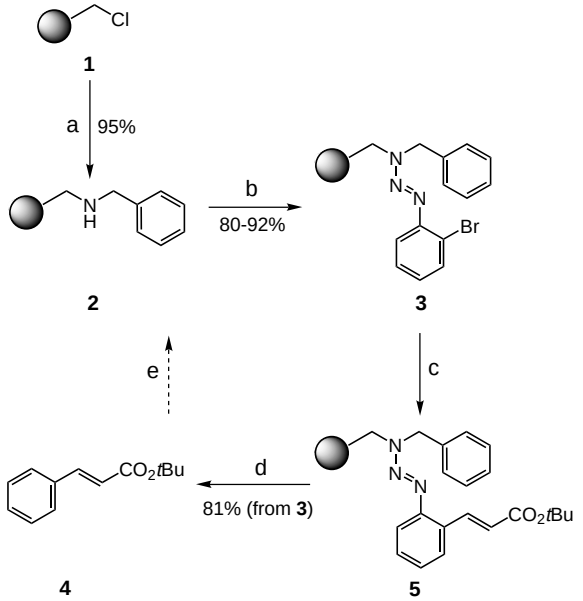
A Surprising Solid-Phase Effect: Development of a Recyclable "Traceless" Linker System for Reactions on Solid Support**

Stefan Bräse,* Dieter Enders, Johannes Köbberling, and Frank Avemaria

The development of high-throughput screening (HTS) processes and the associated demand for large substance libraries has recently led to an expansion of new synthetic strategies, often described as "combinatorial chemistry".[1] In connection with these developments was a renaissance in solid-phase synthesis. While mixtures of substances were synthesized initially, more recently parallel solid-phase synthesis of single compounds has been given a great deal of attention, because of the advantages of its ease of automation and unambiguous test results in HTS. The associated strategies for the construction of organic molecules and their functionalization are often limited by the nature of the linker.[2] Since most linkers are derived from protecting groups linked to the solid support the seceding molecules generated upon cleavage always contain a functional group that has to be present at the beginning of the synthesis and on which transformations cannot be carried out. To overcome this disadvantage the attached synthetic building block has to be connected to the resin in such a manner that only a C – H bond remains on the target molecule after cleavage ("traceless" cleavage). Only a few solutions exist for this particular problem, none of which are general.[3–5] During our work towards the synthesis of functionalized arenes by organometallic methods we were challenged by the problem of attachment and traceless removal of functionalized arenes. The published strategies of Ellman et al., Veber et al. and others.[3] that use the recently commercialized "silyl linker" suffer from the length of the synthesis and the sensitivity. Herein we report a new "traceless linker" system without these disadvantages, which in contrast, possesses the advantage that the resin can be regenerated.

One possible method by which functionalized arenes can be converted into the corresponding hydrocarbons is the reduction of diazonium compounds. Since they react with amines to yield triazenes,[6] which can be transformed under mildly acidic conditions back to diazonium compounds, the use of triazenes as "linkers" seemed to be very promising. The attachment of triazenes to a solid support is an immobilization method that is rarely used.[7]

Commercially available Merrifield resin (**1**; 1% divinylbenzene, 200 – 400 mesh, 0.72 mmol g^{-1} Cl) could be treated with benzylamine to yield **2** (Scheme 1) or with piperazine to give the corresponding resin (90 – 97%).[8] Coupling was



Scheme 1. Synthesis of **3** and Heck reaction. a) $BnNH_2$, DMF, 48 h, 60 °C; b) ArN_2^+, THF, 0 → 25 °C; c) $H_2C{=}CHCO_2tBu$, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 24 h, 80 °C, ultrasound; d) HCl/THF or H_3PO_2/Cl_2HCCO_2H; e) regeneration.

[*] Dr. S. Bräse, Prof. Dr. D. Enders, Dipl.-Chem. J. Köbberling, F. Avemaria
Institut für Organische Chemie der Technischen Hochschule
Professor-Pirlet-Strasse 1, D-52074 Aachen (Germany)
Fax: (+49) 241-8888127
E-mail: braese@oc.rwth-aachen.de

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