

8-2008

High-definition self-assemblies driven by the hydrophobic effect: synthesis and properties of a supramolecular nanocapsule

Bruce C. Gibb

University of New Orleans, bgibb@uno.edu

Follow this and additional works at: https://scholarworks.uno.edu/chem_facpubs

 Part of the [Chemistry Commons](#)

Recommended Citation

Liu, S. and Gibb, B. C. 2008. "High-Definition Self-Assemblies driven by the Hydrophobic Effect: Synthesis and Properties of a Supramolecular Nano-Capsule." *Chemical Communication* 2008: 3709-3716.

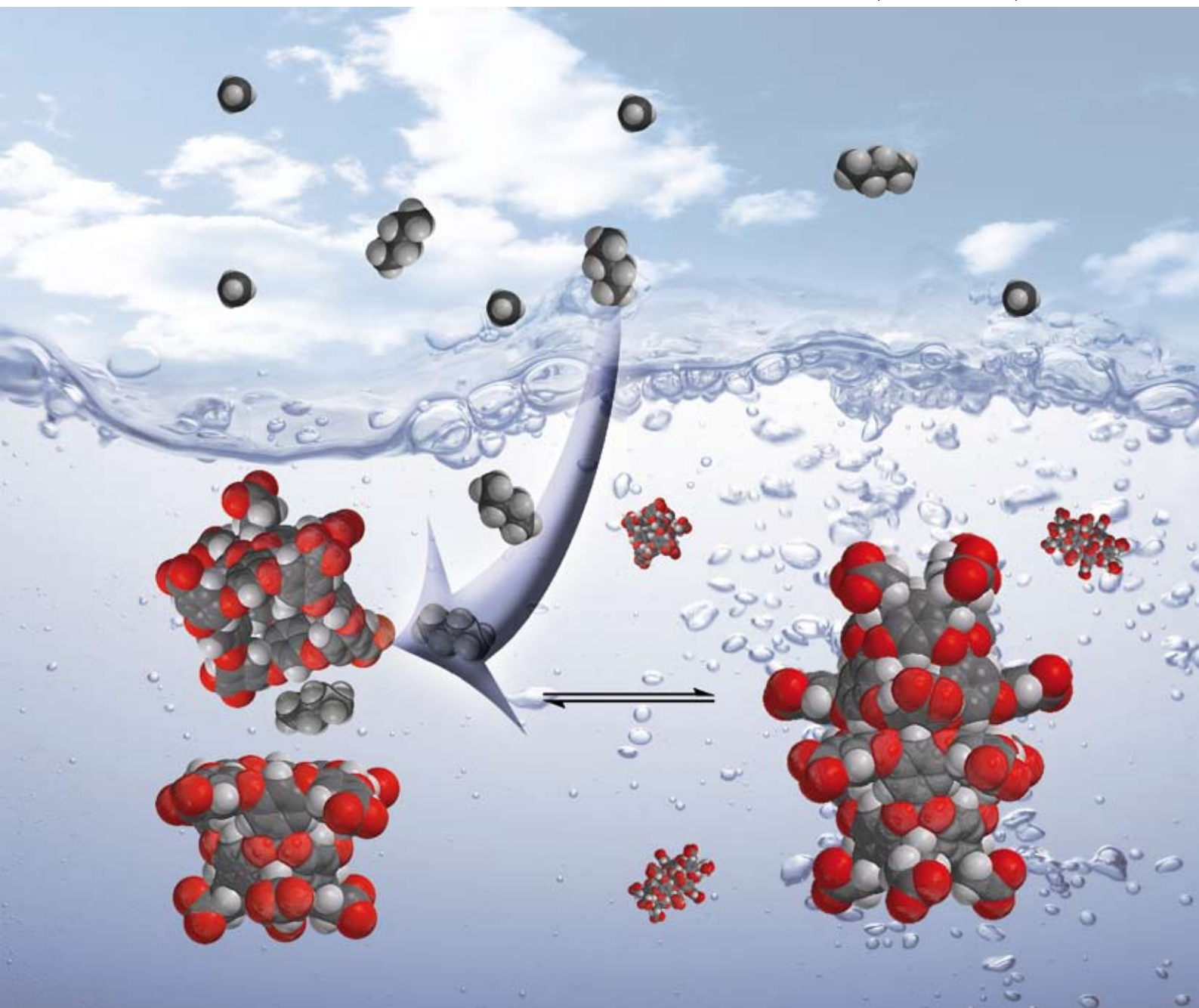
This Article is brought to you for free and open access by the Department of Chemistry at ScholarWorks@UNO. It has been accepted for inclusion in Chemistry Faculty Publications by an authorized administrator of ScholarWorks@UNO. For more information, please contact scholarworks@uno.edu.

ChemComm

Chemical Communications

www.rsc.org/chemcomm

Number 32 | 28 August 2008 | Pages 3693–3808



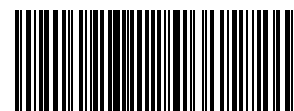
ISSN 1359-7345

FEATURE ARTICLE

Simin Liu and Bruce C. Gibb
High-definition self-assemblies driven
by the hydrophobic effect: synthesis
and properties of a supramolecular
nanocapsule

COMMUNICATION

Jonathan L. Sessler *et al.*
Binuclear organometallic ruthenium
complexes of a Schiff base expanded
porphyrin



1359-7345(2008)32;1-1

RSC Publishing

High-definition self-assemblies driven by the hydrophobic effect: synthesis and properties of a supramolecular nanocapsule

Simin Liu and Bruce C. Gibb*

Received (in Cambridge, UK) 1st April 2008, Accepted 6th May 2008

First published as an Advance Article on the web 6th June 2008

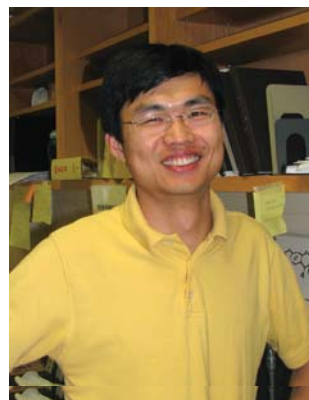
DOI: 10.1039/b805446k

High definition self-assemblies, those that possess order at the molecular level, are most commonly made from subunits possessing metals and metal coordination sites, or groups capable of partaking in hydrogen bonding. In other words, enthalpy is the driving force behind the free energy of assembly. The hydrophobic effect engenders the possibility of (nominally) relying not on enthalpy but entropy to drive assembly. Towards this idea, we describe how template molecules can trigger the dimerization of a cavitand in aqueous solution, and in doing so are encapsulated within the resulting capsule. Although not held together by (enthalpically) strong and directional non-covalent forces, these capsules possess considerable thermodynamic and kinetic stability. As a result, they display unusual and even unique properties. We discuss some of these, including the use of the capsule as a nanoscale reaction chamber and how they can bring about the separation of hydrocarbon gases.

Introduction

In conceiving high definition supramolecular assemblies showing well-defined structure at the molecular level, chemists have traditionally relied upon enthalpy as the means to engender a favorable free energy of assembly (eqn (1)). This is intuitive from the perspective of a written chemical reaction involving only subunits; the bringing together of many chemical entities is not favored by entropy. Consequently, to ensure exothermicity such assemblies are typically driven by functionality—or assembly motifs—capable of partaking in relatively strong and highly directional non-covalent forces, hydrogen bonding^{1–7} and metal coordination^{8–20} being the most common. Indeed, the dominance of enthalpy in high-definition self-assemblies is so great that invoking words such as ‘powerful’ and ‘directional’ can trigger the false assumption that these terms are *necessarily* enthalpically-based. This is of course not the case.

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA. E-mail: bgibb@uno.edu



Simin Liu

Simin Liu received his PhD in 2004 from the Wuhan University, China, under the guidance of Chengtai Wu. From 2005, he worked on cucurbit[*n*]uril chemistry with Lyle Isaacs at the University of Maryland, USA, as a postdoctoral researcher. Subsequently, he joined Bruce Gibb's group in 2007. Currently his research focuses on the synthesis of water-soluble cavitands and the assembly of nanoscale capsules.



Bruce C. Gibb

Bruce Gibb received his BSc and PhD degrees from Robert Gordon's University, UK. In 1992, he took a postdoctoral research post with John Sherman at the University of British Columbia, Canada, and in 1994, a post with James Canary at New York University, USA. His independent career began in 1996. Promoted to University Research Professor in 2007, his interests lie with various aspects of supramolecular chemistry.

$$\Delta G = \Delta H - T\Delta S \quad (1)$$

Nature is very capable of taking the ‘opposite’ approach. Although bringing together two or more species is, from a written chemical equation standpoint, entropically penalized, solution based assemblies do not take place in a vacuum. It is quite possible for the free energy of assembly to be primarily driven by entropy (eqn (1)) if the assembly liberates solvent molecules in the process. The key to such a strategy is of course water and the hydrophobic effect.^{21–25}

Although an abundant molecule (that is made up from the first and third most abundant elements in the universe), many of the properties of water are still poorly understood. If this were not the case, two of the best examples of ‘pathological science’—polywater²⁶ and memory water²⁷—probably wouldn't exist! The complexity of bulk water leads to many (real) emergent phenomena, the most familiar of which is the hydrophobic effect, the tendency for oil and water to segregate.²¹ This phenomenon is manifest in countless ways in Nature,²⁸ including the assembly of phospholipids to form

vesicles, and the folding and assembly of proteins to yield respectively tertiary and quaternary structure. It is also in part responsible for the assembly and structure of duplex DNA, and of course the binding of effectors or substrates to proteins, enzymes, and ribozymes. It is omnipresent.

There are both enthalpic and entropic facets to the hydrophobic effect. Regarding the former, when a hydrophobic solute is expelled from the aqueous phase strong water–water interactions (the cohesive force) are increased at the expense of weaker water–hydrocarbon interactions (a minor enthalpic role can also be played by the polarizability of hydrocarbons *versus* the lack of polarizability of water). Although these factors frequently play a role, often the change in enthalpy as a solute is moved out of the aqueous solution is very small or even positive. In such cases, and indeed in the majority of examples at ambient temperatures, the hydrophobic effect is primarily driven by entropy.^{29,30} Passing over the examples where this is not the case, the hydrophobic effect is commonly viewed in terms of water being ordered around a hydrophobic solute, and if this solute can bind into a hydrophobic environment, then these waters are liberated to the bulk. As has been pointed out,²¹ this notion is correct to a first approximation, but one should take care not to invoke the idea of clathrate structure. Clearly, such an extreme view is incorrect; the dynamics of water structure is on the femtosecond timescale, and so the suggestion of clathrates around hydrophobic solutes is one step towards poly- and memory water. Nevertheless, a corollary of ‘ordered’ water is that self-assemblies in aqueous solution need not rely on enthalpy; entropy can be harnessed if we have a firm understanding of the hydrophobic effect. Herein lies the problem, because as just alluded to, the hydrophobic effect is not fully understood. Our lack of understanding arises in part because what one observes or measures depends on the state of water molecules around a solute, which in turn depends on its hydrophobicity, size and shape. Depending on these and other factors, a solute surface may be wetted (the water density immediately surrounding the hydrophobic solute is greater than the bulk) or dewetted (the water density immediately surrounding the solute is less than the bulk). Consequently, researchers investigating the hydrophobic effect may turn up what *prima facie* appears to be conflicting data, because subtle differences between the systems under study are not fully appreciated. Nevertheless, in mimicry of Nature, the hydrophobic effect has been used to great effect to form host–guest complexes,^{31–37} fold foldamers,^{38–41} and assemble micelles, liposomes and their ilk;^{42,43} entities that are partially ordered in so much as they show structure on scales beyond the molecular, but little or no

structure at the molecular level. However, the synthesis of analogous high definition supramolecular assemblies, those that are well defined at the molecular level, requires an increase in our current understanding of the hydrophobic effect. To take but one example, it is likely that Nature uses many subtle approaches to marshal the hydrophobic effect and bring about protein quaternary structure. Can these be understood and exploited? We know what constitutes a powerful assembly motif in enthalpically driven assemblies; what constitutes a powerful motif in those driven by entropy? What will be the properties of such assemblies? This *feature article* reviews some of our results as we try to answer these and related questions.

A water-soluble, self-assembling, deep-cavity cavitand

The deep-cavity cavitands⁴⁴ developed in our group are resorcinarene-based molecular hosts whose cavities are built up from twelve aromatic rings.^{45–50} We have reported on a number of these hosts, but focus here on the cavitand shown in Fig. 1. Four of the aromatic rings, those that constitute the starting resorcinarene, are termed the first row. Built on this is a second row of rings that deepens the hydrophobic cavity of the resorcinarene considerably, and a third row that both rigidifies the binding pocket whilst providing the host with a wide hydrophobic rim that is essential to its predisposition to assemble in aqueous solution. Water-solubility is by virtue of the external coat of carboxylic acids; the outer edge of the cavity rim is decorated with four, whilst the four ‘feet’ of the cavitand are also each terminated with a carboxylic acid.

The host has limited solubility (tens of micromolar) in neutral solution, presumably because the carboxylic acids have typical pK_a values of between 5–6 and so not all are deprotonated at pH 7. However, in basic solution—most of our studies have been in sodium tetraborate solution (pH = 8.9)—the host is quite soluble. Under these conditions, it is monomeric at millimolar concentrations, but exists as a disordered aggregate at concentrations of ten millimolar and above. In the latter case, the resulting broad signals in the NMR spectrum are not informative, but it is presumably the hydrophobic rim that promotes these kinetically unstable assemblies. Regardless of the host concentration, the addition of a suitable guest molecule triggers dimerization and entrapment of the guest within the resulting capsule (Fig. 2). The range of guests that trigger dimerization is large (*vide infra*); the only prerequisites are that the guest is small enough to fit

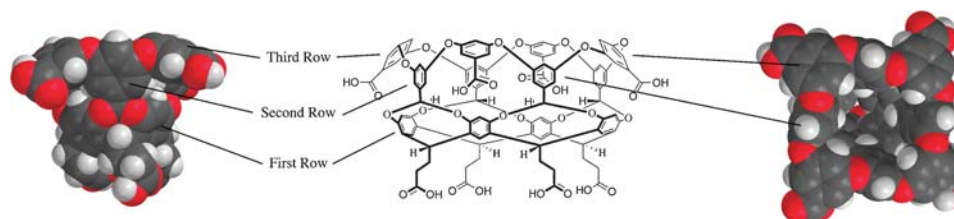


Fig. 1 Left to right: ‘side’ view of space-filling model; chemical structure; and ‘plan’ view of space-filling model of deep-cavity cavitand 1. Highlighted are the three rows of aromatic rings that make up the binding pocket.

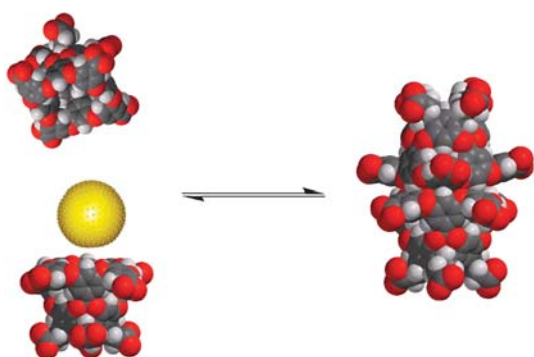


Fig. 2 The dimerization of cavitand **1** around a generic guest (yellow sphere). The capsule is shown in the (orientational) isomer in which all second row rings are edge-to-face stacked with a third row ring in the other hemisphere (D_{4d} symmetry).

within the nanoscale cavity, and is non-polar enough that it is energetically feasible for the guest to partition into the host.

These dimer capsules are not held together by enthalpically strong or directional non-covalent forces. Thus, the interface of the dimer involves only enthalpically weak $\pi \cdots \pi$ interactions.⁵¹ Models suggest that maximal overlap in the interface is achieved in the D_{4d} symmetric capsule (Fig. 2) in which the two hemispheres are out of register by 45° , and the D_{4h} form where the two hemispheres are fully in register. In the former, the interface is composed of edge-to-face stacking between the second row of one hemisphere and the third row of the other, while the latter is composed of slipped stacking between the third rows of each hemisphere. Presumably, ‘free’ rotation of one hemisphere relative to the other is possible without breaking the interface. In part, the complexes are also held together by host–guest interactions. Again however, most of the guests we have examined to date can only partake in enthalpically weak interactions with the host. Nevertheless, both the thermodynamic and kinetic stabilities of these complexes are considerable. Apparent association constants (K_{app} , for empty to filled capsule) can be greater than $1 \times 10^8 \text{ M}^{-1}$, whilst even the encapsulation of small guests that leave considerable empty space result in complexes that are stable on the NMR timescale (greater than millisecond lifetimes). Furthermore, the stability of these complexes can be increased by additives known to enhance the hydrophobic effect, *e.g.*, NaCl, and decreased by common denaturants such as ethanol. These results emphasize that enthalpically strong non-covalent

interactions are not a prerequisite for self-assembly and that careful orchestration of the hydrophobic effect can be a powerful approach to high definition self-assembly. We build on this point using the specific examples below.

Steroid encapsulation

Although we anticipated that cavitand **1** would be able to self-assemble around guest molecules, we were initially concerned that the encapsulation complexes would not possess very high thermodynamic or kinetic stability. Consequently, our first studies “stacked the deck” by examining a range of steroids (Fig. 3, **2–9**).⁵² These rigid molecules were expected to template capsule assembly and enhance its stability by inhibiting lateral slippage of the two cavitands.

In the presence of **1**, all of these guests were shown to dissolve in aqueous solution. Further, NMR spectroscopy revealed that a 2 : 1 ratio of cavitand **1** and steroid gave only encapsulation complexes (*e.g.*, Fig. 4). In each, the signals for the guest all appeared upfield from where they occur in free solution because within the capsule the guests are shielded by the aromatic walls of the host. For the guests dehydroisoandrosterone **2**, progesterone **3**, estradiol **4**, 17α -ethynylestradiol **5**, and estriol **6**, the rate of guest exchange was slow on the NMR timescale and, given an excess of guest, signals for the free and the encapsulated state were visible. To estimate the association constants seen in these complexes we examined the complex formed by estradiol **4** by NMR dilution experiments, and then performed competition experiments between estradiol and the other steroids. Estradiol **4** formed

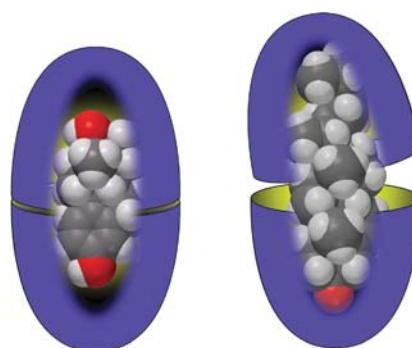


Fig. 4 Representations of the capsule formed by **1** containing estradiol **4** (left) and cholesterol **8** (right).

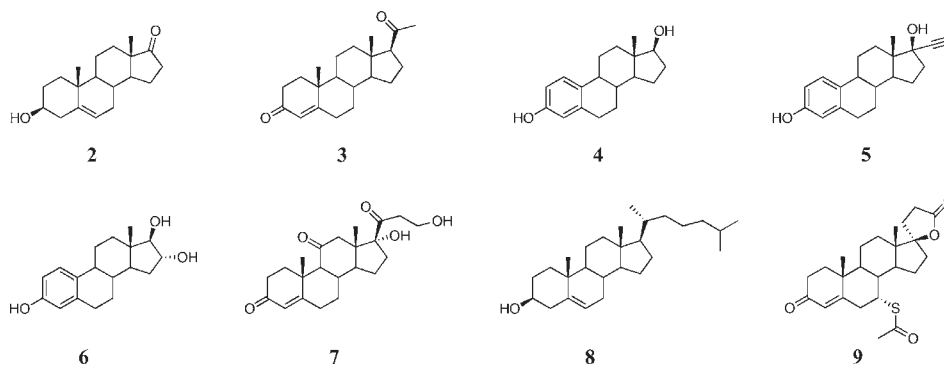


Fig. 3 Guest steroids encapsulated within the dimer of **1**.

a complex with an apparent association constant $K_{\text{app}} > 1 \times 10^8 \text{ M}^{-1}$, however guests with more voluminous A-rings bound more strongly. Thus, for these five guests the strength of binding to the dimer of **1** was: dehydroisoandrosterone **2** > progesterone **3** > estradiol **4** > 17α -ethynylestradiol **5** > estriol **6**. In contrast, with the larger and more water-soluble cortisone **7**, and the larger cholesterol **8** and spironolactone **9**, the corresponding complexes were of much lower kinetic and thermodynamic stability. For example, although solubilized by **1**₂, cholesterol **8** did not form a kinetically stable capsule. NMR signals for this complex were broad. Space-filling models explained these observations; with its C-17 hydrocarbon tail, cholesterol is too long to fit within the cavity (Fig. 4). As a result, the two hydrophobic rims cannot clamp down on one another and so must remain water solvated. We conclude from this that dewetting of the interface at the equator of the capsule is essential to its stability.

Hydrocarbon encapsulation

If steroids can promote the dimerization of the host, can flexible molecules do likewise? That was our next question, and to answer it we turned to the *n*-alkanes from pentane through to octadecane.⁵³ Analogous to cholesterol, the latter proved to be too voluminous for the capsule. The guest was solubilized in aqueous solutions of the host, but the NMR signals of the complex were broad, indicating relatively low kinetic stability. The picture changed dramatically with heptadecane, which was shown to form a more kinetically stable 2 : 1 host–guest complex. Indeed, all guests from nonane through to hexadecane formed similar ternary complexes. In these entities, the methyl ¹H NMR signal of the guest was the most shifted, indicating that each terminal group was anchored deeply into the polar region of a hemisphere. This is a much more efficient packing conformation than U-shaped binding in which two methyls would compete for a polar region, and a turn in the chain would occupy the opposing pole. However, for guests longer than decane, the guest cannot adopt a fully extended conformation. Consequently, the guest must fold up in some manner to be accommodated. For example, NOESY NMR spectroscopy revealed long range interactions down the chain length of dodecane, indicating that it adopts a mainly helical conformation within the capsule. It is interesting to note that such helices have been seen in related, hydrogen bonded capsules.⁵⁴ If the packing of these types of guests within other hosts frequently involves helices, it would parallel the notion that α -helices are the most prevalent of protein secondary structures precisely because they represent such an efficient mode of packing.

Continuing our study of alkane binding to **1**₂, we observed that the guests pentane through to heptane formed not 2 : 1, but 2 : 2 (quaternary) complexes. Furthermore, octane turned out to be the confused guest of the series in so much as it formed both ternary and quaternary complexes. During titration experiments, no free guest was observed until beyond the equivalence point, demonstrating the complexes have considerable thermodynamic stability and that exchange between the free and the bound state was slow on the NMR timescale. Even for pentane, the resulting quaternary complexes had

good kinetic stability. Overall, this family of guests demonstrated packing coefficients (PC, $\rho_{\text{guest}}/\rho_{\text{cav}} \times 100$) of between 48% and 73%, with the best guest dodecane having an occupancy factor of 53%. This latter value is close to the often-quoted ideal occupancy of 55%. However, it ought to be remembered that this value approximates to the height of a bell-curve for a K_{a} versus PC graph and makes no comment regarding its width or shape; it is the width/shape of the bell-curve that defines the range of guests that bind. Although we do not know the precise shape of this bell-curve, the 48–73% PC range for alkane guests suggests a powerful host capable of binding many sizes of guests, and that the hydrophobic effect can be a strong ally to bring about self-assembly and entrapment.

Reactions within the capsule

If many types of molecule trigger dimerization of **1** and in the process are encapsulated, then in theory **1**₂ could be used as a nanoscale reaction vessel.⁵⁵ Taking this thought one-step further, the high kinetic stability of these capsular complexes gives ample opportunity for the reaction performed inside to be templated by the host. With these ideas in mind, we have collaborated with the Ramamurthy group to study photochemical processes within these nanoscale reaction chambers. The nanosecond time frame of these processes means that even complexes at the low end of the range of possible kinetic stabilities remain integral during reaction. Consequently, the capsule can impart considerable (and varied) chemical instruction. For instance, the β -cleavage of naphthyl esters⁵⁶ or the singlet oxidation of olefins⁵⁷ give many different products in solution, but within the capsule these reactions are brought into sharp focus. The latter example is particularly interesting as it demonstrates that capsules containing sensitizers (red in Fig. 5) can chemically communicate, using singlet oxygen, through the aqueous solution with capsules containing substrates (light blue). Once within the substrate-containing capsule, specific orientation of the guest ensures only one of three oxidation pathways can take place (light to dark blue).⁵⁷

The capsule is also capable of templating the formation of products not observed in solution. Thus, the major compound produced from the photolytic cleavage of the α -C–C bond of dibenzyl ketone is not the normally observed decarbonylated product 1,2-diphenylethane, but (*p*-methyl)phenyl benzyl ketone (Fig. 6).⁵⁸ Cleavage of one of the α -C–C bonds initiates

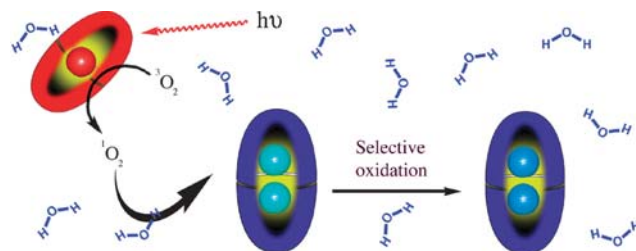


Fig. 5 The selective oxidation of substrates (light to dark blue guests) within a capsule. Singlet oxygen is generated in a sensitizer-containing capsule (red), which must then make its way to a substrate-containing capsule.

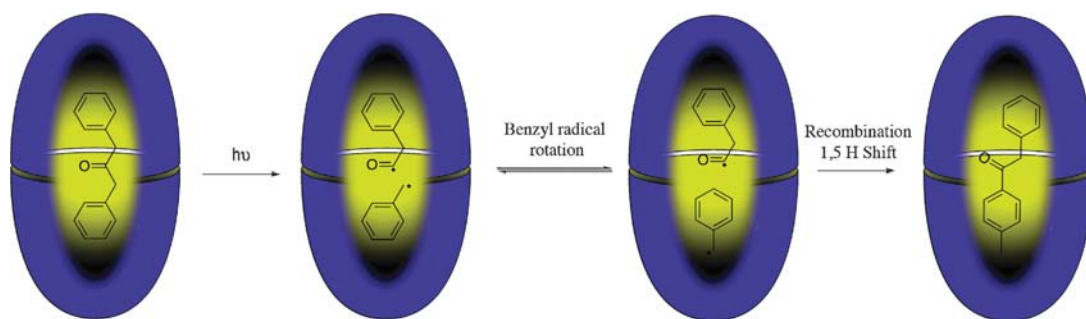


Fig. 6 The capsule-templated rearrangement of dibenzyl ketone to give (*p*-methyl)phenyl benzyl ketone.

this conversion, but the two radicals produced do not optimally fill the cavity and there is a subsequent 180° rotation of the benzyl radical that lowers the overall packing energy. Recombination and a 1,5 hydrogen atom shift leads to the observed rearrangement product.

The flipside of increasing the selectivity of reactions or engendering novel reaction, *i.e.*, bringing normally facile reactions to a halt, can also be induced by encapsulation. By way of example, irradiation of the capsule containing two molecules of anthracene leads to strong excimer emission but no reaction between them. The reason this state of affairs is observed is that the cavity is highly packed (PC = 85%, the highest we have observed) and the essentially immobile guests are held out of register relative to each other and cannot undergo reaction.⁵⁹

Most recently, building on our study of the photochemistry of encapsulated dibenzyl ketones, we turned our attention to a homologous series of flexible guests (**10**, Fig. 7) to examine how guest packing within the capsule influences the multiple chemical channels in their triplet excited-state surface.⁶⁰

NMR experiments reveal that in combination with cavitand **1**, each guest forms 2 : 1 capsular complexes. Furthermore, NMR spectroscopy also reveals that within this series of eight complexes there are three distinct families, each with an identifiable mode of guest packing (Fig. 8). With a small R group such as methyl, the dibenzyl ketone guest (**10a**, R = Me) packs the cavity by inserting its aromatic rings into the hemispheres of the capsule (Fig. 8, left). However, a longer R group is better able to pack the narrowest polar region of a hemisphere and consequently the alkyl chain of the *n*-pentyl derivative (**10b**, R = *n*-pentyl) displaces its nearest neighbor phenyl ring (red) pushing it into an equatorial region of the capsule (Fig. 8, centre). A third method of packing is seen with still longer alkyl chains. Thus, the *n*-octyl case (**10c**, R = *n*-octyl) differs from the *n*-pentyl guest by the two phenyl rings trading positions within the capsule (Fig. 8, right). It is not yet clear why this change occurs, but perhaps the alkyl group is so long the guest tries to decrease its packed length by a

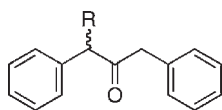


Fig. 7 α -Alkylated dibenzyl ketone guests **10**: R = Me, Et, *n*-Pr, *n*-Bu, *n*-pentyl, *n*-hexyl, *n*-heptyl and *n*-octyl. Guests highlighted in the text are the methyl (**10a**), *n*-pentyl (**10b**) and *n*-octyl (**10c**) compounds.

–CH₂C(O)– unit at the cost of an increase in width by the same amount.

The result of these different packing motifs is that photolysis is highly dependent on the precise length of the alkyl chain, and in all cases, quite different from solution chemistry that produces a preponderance of Norrish type I products, as well as more minor amounts of type II products. Thus, within the capsule the methyl derivative **10a** (R = Me) undergoes a considerable amount of decarbonylation to yield 1,2-diphenylethane, but also yields significant amounts of (*p*-ethyl)phenyl benzyl ketone **11** arising from homolytic cleavage of the alkyl substituted α -C–C bond (Scheme 1). This is the expected rearrangement product arising from formation of the more stable secondary benzyl radical, radical rotation to more optimally fill the cavity, and then recombination.

With a different packing conformation, the *n*-pentyl guest **10b** (R = *n*-pentyl) undergoes relatively little decarbonylation. Instead, the major products are rearrangement products **12** and **13** (Scheme 1), the former through a cleavage mechanism similar to the formation of **11**, the latter arising through cleavage of the alternate (unsubstituted) α -C–C bond and rotation of the benzyl radical before recombination. We believe that cleavage of the unsubstituted α -C–C bond can compete with cleavage of the substituted α -C–C bond because the latter leads to two radicals that pack the cavity efficiently without having to reorientate. The pentyl group is an effective anchor of the secondary benzyl radical and so it and the acyl radical can recombine to regenerate starting material. This biases cleavage of the unsubstituted α -C–C bond, the resulting benzyl radical of which can undergo rotation within the cavity before recombination to form **13**.

Photolysis of guests that pack with the motif shown in Fig. 8 (right), for example **10c** (R = *n*-octyl), give mostly Norrish

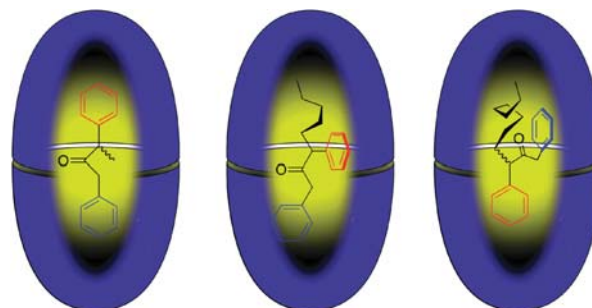
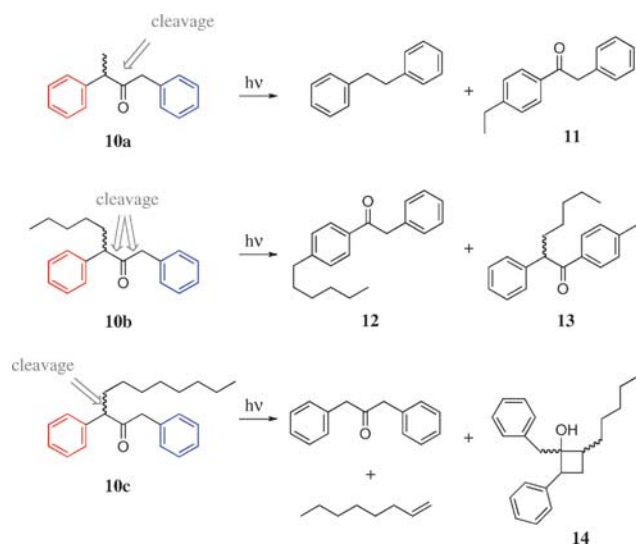


Fig. 8 The three distinct packing motifs observed for guests **10a–c**.



Scheme 1 Representative products arising from the photolysis of the capsular complexes of **10a**, **10b** and **10c**.

type II products. Thus, 90% of encapsulated **10c** forms type II products (Scheme 1); there is an 83% yield of dibenzyl ketone (and 1-octene) and a 7% yield of the cyclobutane **14**. Interestingly, the preponderance of dealkylated product over cyclobutane formation is opposite to that seen in solution. These reactions are initiated by abstraction of a γ -hydrogen in the alkyl chain by the carbonyl oxygen. Consequently, we rationalize the high yields of type II products by assuming the carbonyl group is packed closely to the γ -hydrogens (Fig. 8, right).

These results demonstrate that suitable hosts can harness the hydrophobic effect to influence the outcome of photochemical processes. The capsule **1** forms kinetically stable complexes that allow the redirection of chemical reactions away from that normally seen in solution. At the same time, the capsules are dynamic enough to allow chemical communication between capsules, albeit in a one-way manner. From a slightly different perspective, these results also demonstrate that, like micelles,⁶¹ host **1** can be used to perform reactions that are normally difficult to carry out in aqueous solution.

Electrochemistry within and on the outer surface of the capsule

In collaboration with the Kaifer group, we have examined how the capsule formed by **1** can modify the electrochemistry of redox active guests. In these studies, the necessary presence of a charge carrier (40 mM NaCl) increased the propensity of the cavitand to dimerize and led to some unusual complexes.⁶²

As anticipated, ferrocene readily formed an encapsulation complex. Shielded from the external environment, the cyclic voltammogram recorded for this complex was essentially flat, with very small levels of faradaic currents associated with the oxidation to ferrocenium. In a similar vein, the more sensitive technique square wave voltammetry also showed little or no faradaic response. These results were attributed to slow heterogeneous electron transfer kinetics between the entrapped ferrocene and the electrode surface. The complexation of

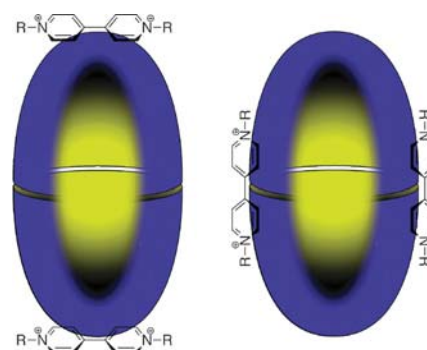


Fig. 9 Cartoon of the possible structures of the quaternary complex formed between cavitand **1** and viologen guests.

methyl, ethyl and butyl viologens was also examined. 1D and PGSE NMR experiments indicated that in these cases two viologen guests were bound to the *outside* of the capsule. Two options seem likely (Fig. 9). Association with the polar-regions of the capsule allows each viologen to closely interact with four carboxylates. Alternatively, in a latitudinal, inter-hemisphere position, the guests could associate with arguably more distal carboxylates, but in doing so would help stitch the capsule together. The two reductions of the dicationic viologen were observed with these complexes using cyclic voltammetry, but the current waves were substantially reduced. Furthermore, the rates of heterogeneous electron transfer were also considerably diminished.

Finally, if the viologens in the aforementioned complexes are not binding to the inside of the capsule then there must be a vacant binding site available. NMR spectroscopy showed this to be the case, with the formation of the corresponding quaternary complexes composed of two cavitands, two viologens, and one (encapsulated) ferrocene.

Hydrocarbon gas separation using the capsule

Our final example of the abilities of supramolecular systems that can harness the hydrophobic effect concerns the separation of hydrocarbon gases. By far the most common approaches to purifying natural gas liquids (NGLs) are: amine absorption (CO₂ removal), glycol absorption (H₂O removal), cryogenic processes (N₂ removal) and subsequent condensation/distillation (hydrocarbon separation). New membrane technologies⁶³ are however becoming increasingly popular, particularly technologies for removing CO₂ from the NGLs, and for crude NGL separation at remote sites. As yet however, there are no practical membrane technologies for separating the hydrocarbon gases themselves.

In studying the binding of *n*-alkanes to the capsule formed by **1**, we had observed that *n*-pentane formed a kinetically stable quaternary complex. With the above thoughts in mind, we consequently sought to determine if the hydrocarbon gases also formed stable complexes.⁶⁴ Our initial attempts involved bubbling pure butane through a solution of the host, a process that resulted in the formation of the corresponding quaternary complex. Exchange between the free and the bound state was slow on the NMR timescale with a stoichiometric amount of host and guest, but at the NMR timescale when there was an

excess of gas. We are still not sure why this change in kinetics is observed, although an intriguing candidate is that in an excess of butane a quaternary complex (three guests within the capsule) can form. Butane did not have to be bubbled through the solution. Its affinity is such that a host solution can extract the gas directly from the gas phase. Similarly, it was shown that propane could also be sequestered directly from the gas phase, and in doing so form a kinetically stable quaternary complex. The limit of capsule templation, at least in the absence of salts known to increase the hydrophobic effect, was ethane. This guest was shown to form a 1 : 1 complex with the cavitand. Regardless, the quaternary complex of propane is a remarkable entity. If viewed in terms of packing coefficient, the cavity is only 28% full. Thus, kinetically stable capsules formed by **1** have so far displayed PC values from 28% to 85%; a wide range which emphasizes the power of the hydrophobic effect. Alternatively, if the conceit is granted to compare the contents of the capsule to an ideal gas, the pressure of propane in the quaternary complex is in excess of 100 atmospheres. Of course, if the packing coefficient is actually larger because the cavity undergoes partial collapse, the pressure within increases!

Although propane binds strongly, it does so one order of magnitude more weakly than butane. This fact can be exploited to effect a unique means of separating the two gases. Thus, when a mixture of propane and butane was placed in the headspace above a solution of host **1**, only butane was extracted from the gas phase into the aqueous phase. As smaller gases are more weakly bound in general, it is theoretically possible to separate any duo of methane, ethane, propane and butane. It is also likely that butane could be separated from a mixture of the four gases, or propane from ethane and methane. It is yet to be determined whether or not the system has the selectivity to separate isobutane from *n*-butane, or if the presence of salting out species such as sodium chloride can promote templation of the capsule by ethane or even methane. These studies are ongoing.

From the above it is apparent that if marshalled correctly, the hydrophobic effect can be used to drive the formation of high definition assemblies. The supramolecular motif in the dimerization of the cavitand does not involve directional functional groups in the traditional (enthalpic) sense envisioned by how the enthalpy of attraction between a hydrogen bond acceptor and donor changes as a function of the angle between them. Instead, the interface is comprised of aromatic rings involved in π - π interactions, groups and interactions that are quite capable of bringing about high definition assembly if the hydrophobic effect is brought to bear. Further studies along these lines are ongoing, and will be reported in due course.

Acknowledgements

SL and BCG gratefully acknowledge the National Institutes of Health for financial support (GM074031).

Notes and references

1 J. Rebek, Jr, *Angew. Chem., Int. Ed.*, 2005, **44**, 2068–2078.

- 2 D. J. Dalgarno, S. A. Tucker, D. B. Bassil and J. L. Atwood, *Science*, 2005, **309**, 2037–2039.
- 3 L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469–472.
- 4 R. P. Sijbesma and E. J. Meijer, *Chem. Commun.*, 2003, 5–16.
- 5 J. L. Sessler and J. Jayawickramarajah, *Chem. Commun.*, 2005, 1939–1949.
- 6 J. T. Davis and G. P. Spada, *Chem. Soc. Rev.*, 2007, **36**, 296–313.
- 7 J. Rebek, Jr, *Acc. Chem. Res.*, 1999, **32**, 278–286.
- 8 M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 369–378.
- 9 M. Fujita, N. Fujita, K. Ogura and K. Yamaguchi, *Nature*, 1999, **400**, 52–55.
- 10 M. Yoshizawa, M. Tamura and M. Fujita, *Science*, 2006, **312**, 251–254.
- 11 S. Sato, J. Iida, K. Suzuki, M. Kawano, T. Ozeki and M. Fujita, *Science*, 2006, **313**, 1273–1276.
- 12 M. D. Pluth, R. G. Bergman and K. N. Raymond, *Science*, 2007, **316**, 85–88.
- 13 D. L. Caulder and K. N. Raymond, *J. Chem. Soc., Dalton Trans.*, 1999, 1185–1200.
- 14 V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2006, **128**, 14464–14465.
- 15 D. H. Leung, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2007, **129**, 2746–2747.
- 16 D. H. Leung, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2008, **130**, 2798–2805.
- 17 J. R. Nitschke, *Acc. Chem. Res.*, 2007, **40**, 103–112.
- 18 N. C. Gianneschi, M. S. Masar III and C. A. Mirkin, *Acc. Chem. Res.*, 2005, **38**, 825–837.
- 19 M. Ruben, J. Rojo, F. J. Romero-Salguero, L. H. Uppadine and J.-L. Lehn, *Angew. Chem., Int. Ed.*, 2004, **43**, 3644–3662.
- 20 S. R. Seidel and P. J. Stang, *Acc. Chem. Res.*, 2002, **35**, 972–983.
- 21 D. Chandler, *Nature*, 2005, **437**, 640–647.
- 22 R. Breslow, *J. Phys. Org. Chem.*, 2006, **19**, 813–822.
- 23 N. T. Southall, K. D. Dill and A. D. J. Haymet, *J. Phys. Chem. B*, 2002, **106**, 521–533.
- 24 L. R. Pratt and A. Pohorille, *Chem. Rev.*, 2002, **102**, 2671–2692.
- 25 C. Tanford, *The hydrophobic effect. Formation of micelles & biological membranes*, John Wiley & Sons, New York, 2nd edn, 1980.
- 26 D. L. Rousseau, *American Scientist*, 1992, **80**, 54–63.
- 27 J. Maddox, J. Randi and W. W. Stewart, *Nature*, 1988, **334**, 287–290.
- 28 Y. Levy and J. N. Onuchic, *Annu. Rev. Biophys. Biomol. Struct.*, 2006, **35**, 389–415.
- 29 A positive change in entropy is a good, but not perfect, indicator of the hydrophobic effect. Rather, a much better indicator is the negative heat capacity change observed when a solute is expelled from the aqueous phase.
- 30 Aqueous-based complexations driven by enthalpy and penalized entropically are often referred to as being driven by non-classical hydrophobic effects. See for example, ref. 31.
- 31 F. Diederich, Molecular recognition studies with cyclophane receptors in aqueous solutions, in *Modern cyclophane chemistry*, ed. R. Gleiter and H. Hopf, Wiley-VCH, Weinheim, 2004.
- 32 S. B. Ferguson, E. M. Sanford, E. M. Seward and F. Diederich, *J. Am. Chem. Soc.*, 1991, **113**, 5410–5419.
- 33 S. B. Ferguson, E. M. Seward, F. Diederich, A. R. Sanford, A. Chou, P. Inocencio-Szweda and C. B. Knobler, *J. Org. Chem.*, 1988, **53**, 5593–5595.
- 34 G. O. Oshovsky, D. N. Reinhoudt and W. Verboom, *Angew. Chem., Int. Ed.*, 2007, **46**, 2366–2393.
- 35 S. M. Biras and J. Rebek, Jr, *Chem. Soc. Rev.*, 2007, **36**, 93–104.
- 36 M. V. Rekharsky and Y. Inoue, *Chem. Rev.*, 1998, **98**, 1875–1917.
- 37 K. Kim, N. Selvapalam, Y. H. Ko, K. M. Park, D. Kim and J. Kim, *Chem. Soc. Rev.*, 2007, **36**, 267–279.
- 38 *Foldamers: structure, properties and applications*, ed. S. Hecht and I. Huc, Wiley-VCH, Weinheim, Germany, 2007.
- 39 A. D. Bautista, C. J. Craig, E. A. Harker and A. Schepartz, *Curr. Opin. Chem. Biol.*, 2007, **11**, 685–692.
- 40 M. S. Cubberley and B. L. Iverson, *Curr. Opin. Chem. Biol.*, 2001, **5**, 650–653.
- 41 S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173–180.
- 42 *Dynamics of surfactant self-assembly: micelles, microemulsions, vesicles and lyotropic phases*, ed. R. Zana, Taylor and Francis, Boca Raton, FL, USA, 2005.

- 43 *Micelles, membranes, microemulsions, and monolayers*, ed. W. M. Gelbart, A. Ben-Shaul and D. Roux, Springer, New York, USA, 1994.
- 44 D. M. Rudkevich and J. Rebek, Jr, *Eur. J. Org. Chem.*, 1999, 1991–2005.
- 45 H. Xi, C. L. D. Gibb, E. D. Stevens and B. C. Gibb, *Chem. Commun.*, 1998, 1743–1744.
- 46 H. Xi, C. L. D. Gibb and B. C. Gibb, *J. Org. Chem.*, 1999, **64**, 9286–9288.
- 47 J. O. Green, J.-H. Baird and B. C. Gibb, *Org. Lett.*, 2000, **2**, 3845–3848.
- 48 C. L. D. Gibb, E. D. Stevens and B. C. Gibb, *J. Am. Chem. Soc.*, 2001, **123**, 5849–5850.
- 49 B. C. Gibb, *Chem.–Eur. J.*, 2003, **9**, 5180–5187.
- 50 Z. R. Laughrey and B. C. Gibb, *J. Org. Chem.*, 2006, **71**, 1289–1294.
- 51 B. C. Gibb, Nano-capsules assembled by the hydrophobic effect, in *Organic nano-structures*, ed. J. L. Atwood and J. W. Steed, John Wiley and Sons, New York, USA, 2007.
- 52 C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.*, 2004, **126**, 11408–11409.
- 53 C. L. D. Gibb and B. C. Gibb, *Chem. Commun.*, 2007, 1635–1637.
- 54 J. Rebek, Jr, *Chem. Commun.*, 2007, 2777–2789.
- 55 D. M. Vriezema, M. C. Aragonès, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan and R. J. M. Nolte, *Chem. Rev.*, 2005, **105**, 1445–1489.
- 56 L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb and V. Ramamurthy, *Org. Biomol. Chem.*, 2007, **5**, 236–238.
- 57 A. Natarajan, L. S. Kaanumalle, S. Jockusch, C. L. D. Gibb, B. C. Gibb, N. J. Turro and V. Ramamurthy, *J. Am. Chem. Soc.*, 2007, **129**, 4132–4133.
- 58 L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb and V. Ramamurthy, *J. Am. Chem. Soc.*, 2004, **126**, 14366–14367.
- 59 L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb and V. Ramamurthy, *J. Am. Chem. Soc.*, 2005, **127**, 3674–3675.
- 60 C. L. D. Gibb, A. K. Sundaresan, V. Ramamurthy and B. C. Gibb, *J. Am. Chem. Soc.*, 2008, **130**, 4069–4080.
- 61 T. Dwars, E. Paetzold and G. Oehme, *Angew. Chem., Int. Ed.*, 2005, **44**, 7174–7199.
- 62 D. Podkoscielny, C. L. D. Gibb, B. C. Gibb and A. E. Kaifer, *Chem.–Eur. J.*, 2008, **14**, 4704–4710.
- 63 *Membrane technologies and applications*, ed. R. Baker, John Wiley & Sons, New York, USA, 2004.
- 64 C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.*, 2006, **128**, 16498–16499.