Diels−Alder Reactions through Reversible Encapsulation

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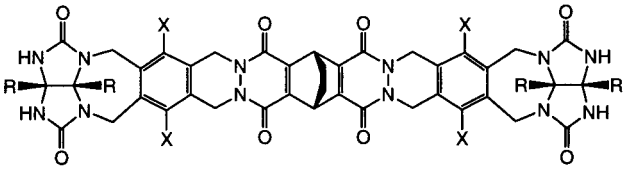
Abstract: Experimental details are given for the preparation of large self-complementary molecules capable of assembly into pseudospherical capsules. These structures exist as hydrogen bonded dimers in organic solvents, and they form and dissipate on a time scale that permits direct NMR observation of the reversible encapsulation of smaller molecules. The cavity is roomy enough to accommodate more than one molecule, and two solvent molecules such as benzene appear to occupy the resting state of the capsules. Liberation of these solvent molecules is responsible for the unexpected thermodynamic parameters of the encapsulation process. A bimolecular reaction—the Diels−Alder reaction—is shown to be accelerated by the capsule as both reactants can occupy the capsule concurrently. Size selectivity, saturation kinetics, and product inhibition studies point to a reaction that takes place within the capsule.

Molecules **1a** and **1b** were recently shown to be capable of self-assembly in organic solvents.[1] These compounds dimerize through a self-complementary system of hydrogen bonds: the hydrogen bond donors at the glycoluril ends of the structure find their complements in the carbonyl acceptors of the bridged bicyclic centerpiece. The dimerization gives a closed-shell capsule of roughly spherical shape—a notional "softball"—when the concave surfaces of two molecules of **1** are brought together (Figure 1). The structure's 13 fused and one bridged ring system provide rigidity, and the stereochemistry shown imparts the curvature necessary for a three-dimensional assembly.

The capsule can bind smaller molecules of complementary size and shape. Accordingly, these "molecules within molecules"[2] resemble the carcerands and cryptophanes of Cram[3] and Collet,[4] but because they are formed reversibly, their dynamic qualities permit observation of new intermolecular interactions—even reactions—to occur within them. We report on these developments here.

Because higher order aggregates were evident in solutions of **1**, and even gellike phases were encountered under some conditions, it seemed likely that the self-complementary nature of the structure could be expressed in ways other than simple dimerization. For example, the same number of hydrogen bonds can be formed if the concave surface of one molecule faces the convex surface of another, thereby leading to the polymeric structure shown in Figure 2. Structure **2**, on the other hand, is less likely to engage in a polymeric assembly: the additional hydrogen bonds provided by the phenolic hydroxyl groups can stabilize the capsular dimer but offer nothing to the stability of the polymeric chain.



1a R = phenyl, X = H
1b R = CO_2-i-pentyl, X = H
2 R = 4-n-heptylphenyl, X = OH

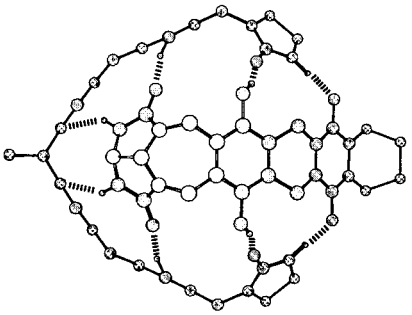


Figure 1. Self-complementary molecules **1** and **2** (top). The hydrogen bonding network of dimeric **2**, the hydroxy "softball", as calculated using MacroModel 5.5[5] with the AMBER force field and GB/SA chloroform solvation (bottom). The dimer is presented in cross-section and the interaction of the two phenolic donors with the glycoluril carbonyl acceptors is highlighted. Peripheral atoms have been deleted for viewing clarity.

Synthesis

The synthesis of **2** began with the reductive coupling of 4-*n*-heptylbenzoic acid **3** to give 4-*n*-heptylphenyldiketone **4**,[6] which was condensed with urea to give di-(4-*n*-heptylphenyl)glycoluril **5** (Figure 3). The synthesis of compound **10** from hydroquinone **6** is also outlined in the figure.[7] Condensation of modules **5** and **10**, followed by deprotection, gave the hydrazine salt **12**. The synthesis of centerpiece **13** and its acylation reactions with

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(1) Meissner, R. S.; Rebek, J., Jr.; Mendoza, J. D. *Science* **1995**, *270*, 1485−1488.

(2) This phrase first appears as the title of a lecture by D. J. Cram at the C. David Gutsche Symposium, Washington University, St. Louis, Missouri, May 5, 1990. For examples, see: Cram, D. J. *Nature* **1992**, *356*, 29−36.

(3) Cram, D. J.; Choi, H.-J.; Bryant, J. A.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7748−7765. Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7765−7773.

(4) Collet, A. *Tetrahedron* **1987**,*43*, 5725; Canceill, J.; Cesario, M.; Collet, A.; Guilhem, J.; Lacombe, L.; Lozach, B.; Pascard, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1246−1248.

(5) Mohamadi, F.; Richards, N. G. J.; Guidia, W. C.; Liskamp, R.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(6) Karaman, R.; Fry, J. L. *Tetrahedron Lett.* **1989**, *30*, 6267−6270.

(7) Suzuki, H. *Bull. Chem. Soc. Jpn.* **1979**, *43*, 3299−3301.

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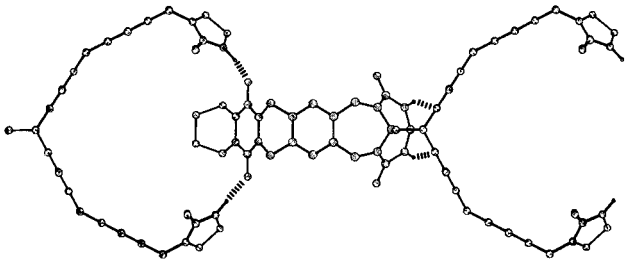


Figure 2. The chain structure proposed for the assembly in $CDCl_3$, using three subunits of **1**. The peripheral atoms have been deleted.

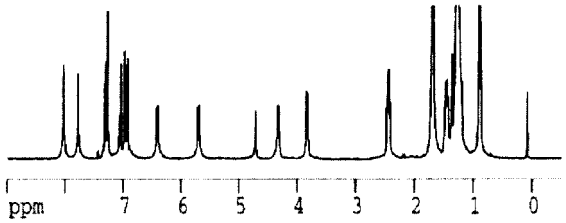


Figure 3. ^{1}H NMR spectra of **2** in $CDCl_3$.

structures related to **12** has been described previously.[8] Compound **12** was coupled with half of 1 equiv of tetraacid chloride **13** and afforded all three possible stereoisomers in the expected statistical ratios. In accord with recent observations concerning the role of solvent in such reactions,[9] we found that the yield of the C-shaped isomer could be increased to 50% of the product mixture by starting from the tetra(pentafluorophenyl) ester **14** and using benzene as solvent. Presumably, the initial reaction of **12** with **14** gives equal quantities of cis and trans isomers. While the cis can give rise to the C-shaped **15** and its S-shaped isomer, the trans is doomed to give only the undesired S- and W-shaped isomers. That such a high yield of C-shaped **15** is obtained suggests that the solvent might act as a template around which the C-shaped isomer forms almost exclusively from the cis intermediate. Isolation of the desired isomer **15** was achieved using column chromatography on silica gel. Finally, the deprotection of the phenolic functions to give **2** was accomplished by treatment of **15** with $AlCl_3$ in CH_2Cl_2 (Scheme 1).

Solution Characteristics

Molecule **2** dissolves in $CDCl_3$, and its ^{1}H NMR spectrum shows the sharp signals characteristic of an ordered, well-defined assembly (Figure 3). Both the N−H and O−H chemical shifts are concentration independent. In contrast, **1a** showed a broadened NMR spectrum in this solvent and produced a gellike phase.[1] The downfield shifts observed for the glycoluril N−H (7.74 ppm) and O−H (8.00 ppm) resonances in the spectrum indicate extensive hydrogen bonding. The N−H resonances of **2** are not as far downfield as those of other dimeric capsules (∼9 ppm), and it is likely that the hydrogen bonds to this group in **2** are somewhat lengthened. The constant chemical shift of the O−H peak of **2** indicates consistent hydrogen bonding at these sites. While intramolecular hydrogen bonding of the O−H functions would also result in such consistency, we propose that the intermolecular hydrogen bonding of this group, which reinforces the dimeric capsular form, is responsible for the chemical shift observed. Ultimately, the shape and volume of the cavity is determined by the average geometries of all the hydrogen bonds involved in its maintenance.

(8) Meissner, R.; Garcias, X.; Mecozzi, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 77−85.

(9) Tokunaga, Y.; Rudkevich, D. M.; Rebek, J. Jr. *Angew Chem., Int. Ed. Engl.* **1997**, *36*, 2656−2659. Tokunaga, Y.; Rudkevich, D. M.; Santamaría, J.; Hilmersson, G.; Rebek, J., Jr. *Chem. Eur. J.*, in press.

Scheme 1

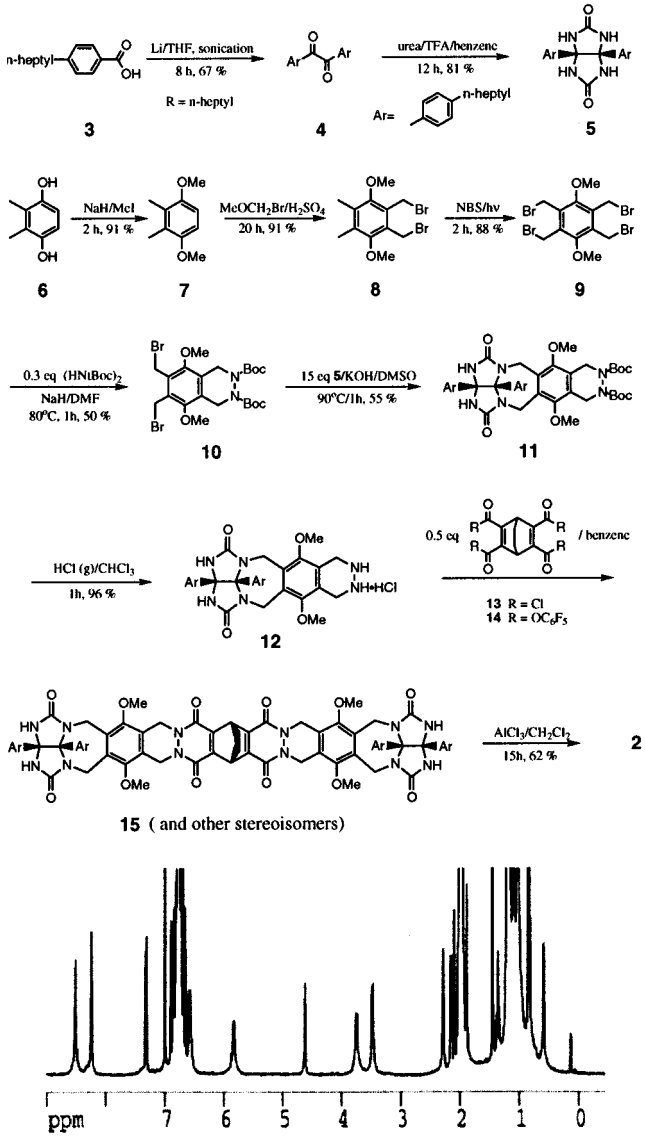


Figure 4. ^{1}H NMR spectra of **2** in *p*-xylene-d_{10}.

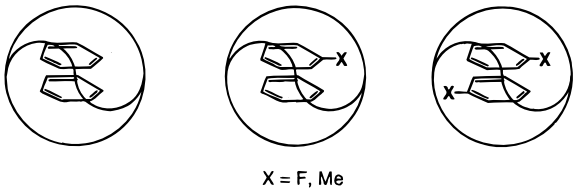


Figure 5. The three capsular species possible with two solvent molecules inside.

The spectrum of **2** in *p*-xylene-d_{10} solution likewise shows sharp signals (Figure 4). Spectra taken in mixtures of two solvents ($CDCl_3$ / CD_2Cl_2, *p*-xylene-d_{10}/CD_2Cl_2, or toluene-d_8/*p*-xylene-d_{10}) showed only a single capsular species, rather than two or three.[10] However, spectra taken in a mixture of deuterated benzene and deuterated monofluorobenzene or deuterated benzene and deuterated toluene both showed **three** capsular species. This is the expected result if two solvent molecules occupy the resting state of the capsule (Figure 5).[10]

This is also a reasonable consequence of how the capsule itself might form: two solvated hemispheres come together to afford a well-filled capsule. The separation of the fully solvated

(10) Kang, J.; Rebek, J., Jr. *Nature* **1996**, *382*, 239−241.

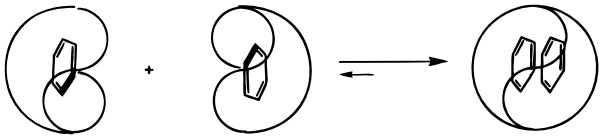


Figure 6. Dimerization of solvated monomers and the reverse.

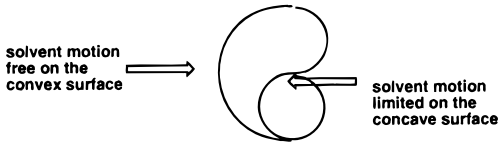


Figure 7. Entropies of solvent molecules can be related to their microenvironments.

capsule into its halves—the microscopic reverse of the dimerization process—is likewise easy to interpret: the two solvents are positioned in a way that one solvent remains in the concavity of each subunit (Figure 6) as the seam of hydrogen bonds is pulled apart. Accomplished in this way, the dissociation process minimizes the creation of empty of space and vacuums are avoided.[8] As simple as it seems, this mechanism for "solvation" of the interior is energetically the most costly as 16 hydrogen bonds must be broken. It is not without precedent: a recent study[11] of capsules based on a calixarene platform concludes that breaking 16 hydrogen bonds is required to exchange guest species. Elsewhere[12] we have discussed an alternative, the possibility of ring inversion of the seven-membered ring. This process breaks only four hydrogen bonds but creates a large enough opening to permit solvents to enter and exit the cavity in an orderly displacement mechanism—the supramolecular equivalent of an SN2 reaction. Ongoing experiments are directed at resolving the mechanics of the exchange process.

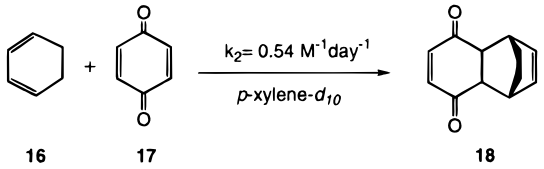
The consequences of having two guest solvents inside the capsule have been discussed at length for the original softball[8] and are only summarized here. The role of solvent is generally regarded as passive except in the specific case of hydrophobic effects. This is a puzzling distinction since release of solvent is a universal feature of association processes; it occurs whenever two molecular surfaces come together in solution. Solvent *environment* may provide a means of estimating the degree to which entropy plays a role in the recognition process: a solvent molecule on a concave surface is much more limited in its freedom than a solvent molecule on a convex surface (Figure 7). Accordingly, a solvent in the latter environment will contribute less to the entropy term than one in the former.

Consider then an encapsulated solvent molecule, one in the ultimate concave microenvironment; its liberation will contribute a large and positive entropy term. If two *p*-xylene-d_{10} solvent molecules are held in the capsule's interior, and a single new guest of approximately the size of two *p*-xylene-d_{10} solvent molecules enters, two solvent molecules are released. The encapsulation of ferrocene by **2** increases entropy in this manner. Alternatively stated, there are three freely moving particles on the right side of the equation but only two on the left.

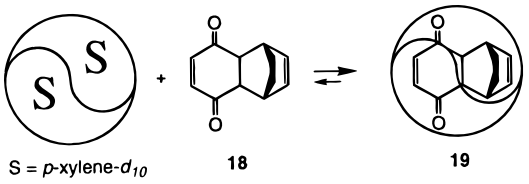
Encapsulating Transition States

Ferrocene is chosen in the example above because its size and shape resembles the transition state for the dimerization of cyclopentadiene. Since more than one solvent molecule is accommodated by **2**, its cavity appears roomy enough to act as chamber for a Diels–Alder reaction. The specific Diels–Alder reaction initially examined was that of cyclohexadiene **16** with *p*-benzoquinone **17** (Scheme 2) which leads to the endo product **18**. The reaction is conveniently slow at room temperature: in *p*-xylene-d_{10} at *molar* concentrations a half-life of about 2 days can be observed ($k_2 = 0.54$ M^{-1} day^{-1}). Studies reported earlier[13] indicated a value of 0.41 M^{-1} day^{-1} for this rate, but the results reported here are based on multiple determinations, different analytical techniques, and tighter controls. The quantitative aspects vary in the present study, but the conclusions remain as reported earlier. At *millimolar* concentrations no product is detected by NMR in a week and the half-life at 4 mM for each of **16** and **17** is calculated to be 460 days.

Scheme 2



Scheme 3



In dilute solution, (e.g., 1 mM) the Diels–Alder adduct **18** is nicely encapsulated by the dimer **2** (Scheme 3), and NMR signals unique to the encapsulated species **19** can be observed (Figure 8b). The widely separated and relatively sharp signals for the free and bound species indicate slow exchange of the guest into and out of the host capsule. The adduct is an excellent guest; the binding affinity is too large for accurate NMR titrations, and only an estimate ($K_a \approx 10^4$ M^{-1}) can be made for the association constant, through competition experiments between **18** and other guests.

At millimolar concentrations *p*-benzoquinone alone forms a well-defined complex with the dimer. A new signal for encapsulated *p*-benzoquinone can be observed in the spectrum and integration of this signal *gives direct evidence that 2 equiv of p-benzoquinone are inside each capsule* (Figure 8c). The broadening of the spectrum may be due to intermediate rates of exchange of this guest into and out of the capsules. Lowering the temperature to 0 °C (the freezing point of the solution) failed to sharpen the spectra; heating gave somewhat improved resolution of the capsule's signals, while the signal for the free *p*-benzoquinone broadened in accord with a classical exchange process. The chemical shift differences between the new species and those capsules filled with solvent are small, and broadening may result from the superimposition of the somewhat overlapped spectra.

Free *p*-benzoquinone has the right size, shape, and functionality to complement the hydrogen bond donors at the ends of **2** and could compete with the assembly of the dimeric form. At the same concentrations cyclohexadiene alone has little effect on the spectrum of **2**; a slight broadening is observed, but no signals attributable to encapsulated cyclohexadiene can be distinguished.

(11) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706–5712.

(12) Rebek, J., Jr. *Acc. Chem. Res.* in press. Szabo, T.; Hilmersson, G. Rebek, J., Jr. *J. Am. Chem. Soc.* submitted.

(13) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50–52.

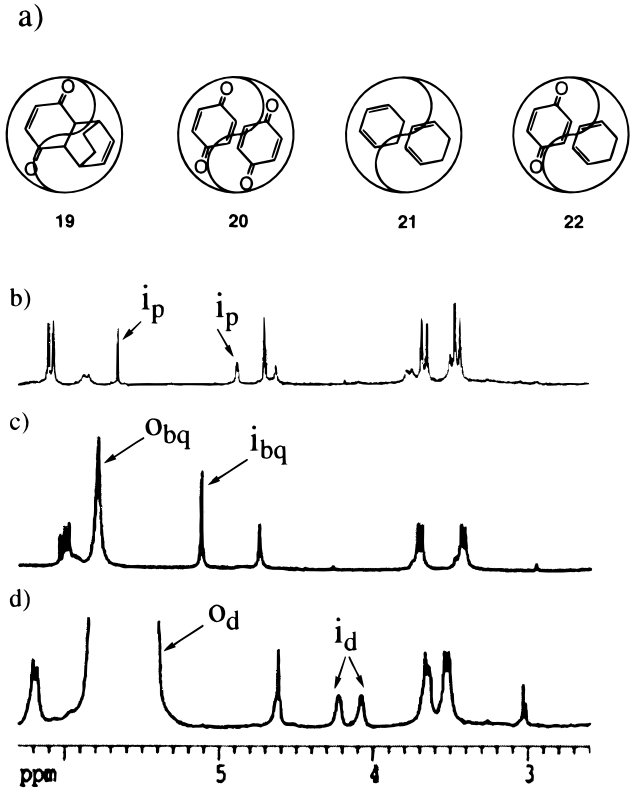


Figure 8. (a) The different hydroxy "softball" complexes with *p*-benzoquinone and cyclohexadiene and the adduct **19**. (b) NMR signals unique to the encapsulated species **19** (i_p) can be observed. (c) ^{1}H NMR spectra of **2** with two molecules of *p*-benzoquinone (i_{bq}) encapsulated and free *p*-benzoquinone (o_{bq}). (d) ^{1}H NMR spectra of **2** with two molecules of cyclohexadiene (i_d) encapsulated and free cyclohexadiene (o_d).

Apparently cyclohexadiene alone is unable to compete with solvent to form complexes with the dimeric form. However, at very high concentrations of cyclohexadiene (>200 mM) it can compete enough to allow observation by NMR (Figure 8d). The spectrum allows the calculation of the encapsulation constant (K) for the (tetramolecular!) complexes as 22 M^{-2} for cyclohexadiene and 1.9×10^5 M^{-2} for *p*-benzoquinone. No resonances from hydroxy "softball" with only one cyclohexadiene or only one *p*-benzoquinone were detected. Accordingly, a equimolar mixture of the diene and dienophile cannot give rise to observable amounts of a capsule containing one of each reaction component as in **22**, because of the favorable conversion to **20**.

In the experiment, when **both** *p*-benzoquinone and cyclohexadiene (4 mM each) are dissolved with the dimeric capsule (1 mM) in *p*-xylene-d_{10} at room temperature, the spectra again show the characteristics of *p*-benzoquinone encapsulation (Figure 9a). This appears to be the dominant species, and no signals unique to encapsulated cyclohexadiene can be assigned. Nonetheless, there must be a fully loaded (reactive) capsule *since the signal for the encapsulated adduct emerges within 1 day* and continues to grow at the expense of the encapsulated *p*-benzoquinone (Figure 9 (parts b and c)). At 60 °C the corresponding changes take place within 1 h.

The half-life calculated from the initial rate (0.26 day^{-1}) is 2.7 days. Accordingly, the reaction—under these conditions and at 22 °C—is accelerated roughly 170-fold in the presence of **2**.

A number of factors including heat, pressure, medium,[14,15] template effects,[16] the presence of acids, antibodies,[17] micelles,[18−21] and possible inclusion in a cyclodextrin cavity[15] can accelerate Diels−Alder reactions. Before reversible encapsulation in self-assembled capsules is added to this list some assurance is required that the rate accelerations provided by **2** are due to just that condition of the components, rather than some of the other effects noted above. For example, carefully designed biphenylenediols[22] that can provide convergent hydrogen bonds to the carbonyl oxygens of some dienophiles are known to be catalysts for this reaction, and as numerous hydrogen bonding sites are featured on the edges of **2**, control experiments were set up to test this possibility. Molecule **2s** presents the same functionalities as does **2**, but it differs in shape: it is S-shaped (Figure 10). Its ends are too far apart to grasp a *p*-benzoquinone at both oxygen atoms with its glycoluril hydrogens. Molecule **15a** has the same shape and the grasping

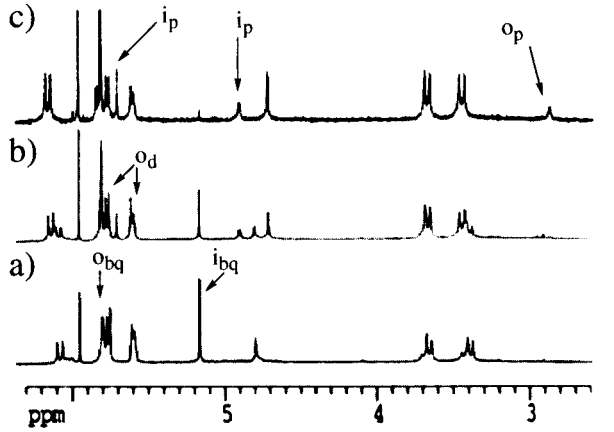


Figure 9. (a) The reaction mixture shortly after mixing the reactants. (b) After 2 days. (c) After 19 days.

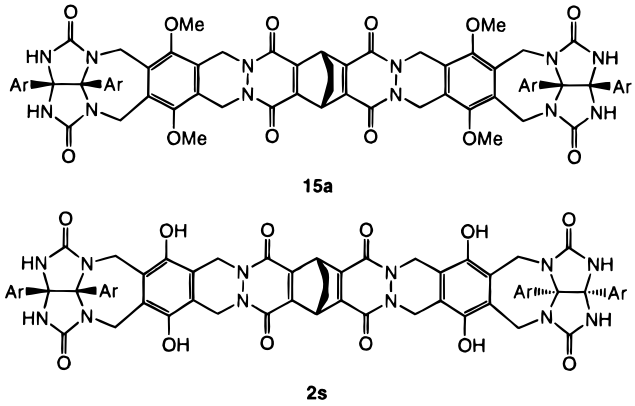


Figure 10. Phenol alkylation in **15a** or change to an S-shape **2s** abrogates acceleration of the Diels−Alder reaction.

(14) Grieco, P. A.; Kaufman, M. D.; Daeuble, J. F.; Saito, N. *J. Am. Chem. Soc.* **1996**, *118*, 2095−2095.

(15) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613−5617.

(16) Walter, C. J.; Anderson, H. L.; Sanders, J. K. M. *J. Chem. Soc. Chem. Commun.* **1993**, 458−460. For catalysis by zeolites see Dessau, R. M. *J. Chem. Soc. Chem. Commun.* **1986**, 1167−1168. For catalysis by RNA, see: Tarasow, T. M.; Tarasow, S. L.; Eaton, B. E. *Nature* **1997**, 389, 54−57.

(17) Hilvert, D.; Hill, K. W.; Auditor, M. T. M. *J. Am. Chem. Soc.* **1989**, *111*, 9261−9263.

(18) Grieco, P. A.; Garner, P.; He, Z.-M. *Tetrahedron Lett.* **1983**, *24*, 1897−1900.

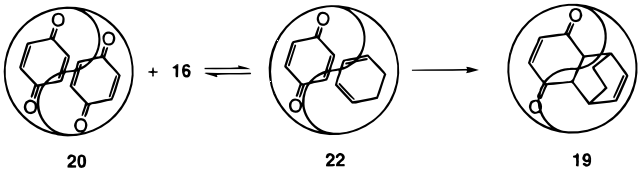
(19) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901−1904.

(20) Braun, R.; Schuster, F.; Sauer, J. *Tetrahedron Lett*. **1986**, *27*, 1285−1288.

(21) Singh, V. K.; Raju, B. N. S.; Deota, P. T. *Synthetic Commun.* **1988**, *18*, 567−574.

(22) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381−3384.

Scheme 4



capability of **2** but differs in that the phenols are alkylated. This results in a structure which is prevented from dimerizing into a capsule. Neither **2s** nor **15a** had any effect on the rate of the Diels−Alder reaction, but **15a** had very low solubility. Catalysis through hydrogen bonding to the phenols or the glycoluril functions of a single molecule of **2** therefore cannot be the source of rate acceleration. If this form of acid catalysis is available only within the capsule, then there are no obvious controls that are likely to expose it.

The reaction of 1,4-naphthoquinone with cyclohexadiene was also studied. The Diels−Alder adduct forms at a background rate about half of that seen with *p*-benzoquinone, as might be expected on statistical grounds. There were no spectroscopic changes when 1,4-naphthoquinone was added to a solution of **2**, and no acceleration of the reaction was observed in the presence of **2**. Naphthoquinone is too large a molecule to fit into the capsule but could have been grasped by the monomeric form of **2**. Based on this admittedly limited sampling, we conclude that there is a size selectivity inherent in reactions accelerated by **2**. This may seem self-evident but is meant to distinguish the effects of **2** from the more general effects of other catalysts such as micelles or bovine serum albumin.[23]

Kinetic Studies

The putative precursor to **19** under the reaction conditions is the equivalent of a "Michaelis complex" in enzymology, the fully loaded enzyme−substrate complex. This is the (unobserved) tetramolecular complex **22** (Scheme 4), and its conversion to **19** is regarded as a first-order process. The dominant (observed) species under these conditions is the capsule doubly occupied with *p*-benzoquinone **20**. The formation of **22** should show some saturation effects if it is involved in the Diels−Alder reaction. The rate of the reaction, as followed by the appearance of encapsulated adduct **19** at cyclohexadiene concentrations from 1 to 7 mM, shows the expected saturation effects and was reported earlier,[13] but we were unable to examine a wider range of concentrations for this case. The similarities between enzymology and encapsulation are notional rather than precise because exact solutions to the complete kinetic description of the present system are elusive.

After several days at ambient temperature some of the adduct appears outside the capsule, and in the longest run of 19 days some turnover was evident. Specifically, about 1 equiv of free adduct and 1 equiv of encapsulated adduct were present (starting with 4 equiv each of diene and dienophile and 1 equiv capsule) as the reaction ground to a halt. It is clear that product inhibition is the cause of this effect. Indeed, the addition of adduct **18** or other good guests (benzene, [2,2]paracyclophane) effectively shuts down the reaction. From the considerations of entropy, the replacement of two reactants by one well-accommodated product is more reasonable than the reverse, and this prevents the system from turning over and offering true catalysis. This process only follows first-order kinetics up to approximately 10% conversion. Thus, product inhibition, size selectivity, and saturation kinetics all support a reaction mechanism that takes place within the capsule.

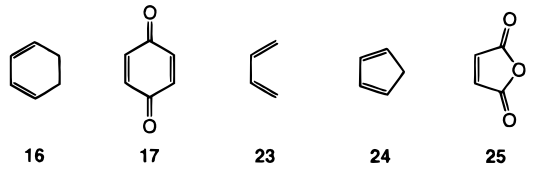


Figure 11. Cyclohexadiene **16**, *p*-benzoquinone **17**, butadiene **23**, cyclopentadiene **24**, and maleic anhydride **25**.

Other diene-dienophile pairs were screened for their suitability as guests in the system (Figure 11). *p*-Benzoquinone **17** consistently showed itself a willing reaction partner, a result that further reinforces the probability that its interactions with the interior of the capsule and the observed rate accelerations are inextricably entwined. The effective molarities (EM's)[24] and the methods for their calculations are given in Table 1.

Maleic anhydride is also a relatively good reaction partner for cyclohexadiene in the capsule. Although maleic anhydride is in fast exchange between encapsulated and free forms, the encapsulation constant (K) for the tetramolecular complex is approximated to be 2×10^5 M^{-2} based on analysis of chemical shift data. However, none of the Diels−Alder reactions of cyclopentadiene were found to be accelerated in the presence of the capsule. The smaller size of this guest compared to the already unfavorably small cyclohexadiene may be the cause.

The reaction between cyclohexadiene **16** and *p*-benzoquinone **17** shows strong product inhibition. Furthemore, the high affinity of **17** for the capsule keeps the concentration of the complex **22** low. A system that shows less severe product inhibition is the reaction of cyclohexadiene **16** with maleic anhydride **25**, and we investigated the kinetic parameters of this reaction. This process follows first-order kinetics in the capsule up to approximately 30% conversion (Figure 12).

The plot shown in Figure 13 supports the claim that the Diels−Alder reactions are indeed accelerated by the increased concentration of the reactants inside the capsule—the pseudo-first-order rate constant (k') approaches saturation when the concentration of cyclohexadiene is increased.

Another line of reasoning, albeit indirect, is also consistent with the proposed acceleration simply through encapsulation rather than some special stabilization of the transition state. This involves estimating the effective molarity (EM)[24] of the encapsulated reactants. When the first-order rate within the capsule (k') is compared to the background bimolecular rate (k) an EM value of up to 0.48 M is obtained.[25] In other words, the "concentration" of the reagents provided by the capsule when they are trapped inside for some time is more than 100 times larger than that of the bulk solution (4 mM). Notwithstanding the above, we are still uncomfortable with the use of EM's in this context. This treatment has been applied in the past to compare rates of bimolecular reactions with those of their unimolecular counterparts. However, reaching the transition state of a bimolecular reaction can be more difficult—and involve a different geometry—than reaching the same point for a (reasonable) unimolecular model. Inside the softball the two components are likely to find the same geometry, orientation, and transition state that characterizes the reaction outside.

True catalysis via encapsulation can result if the size and shape selectivity can be extended to preferential recognition of

(23) Hollfelder, F.; Kirby, A. J.; Tawfik, D. S. *Nature* **1996**, *383*, 60−63.

(24) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(25) This number is roughly 5 times smaller than that we previously reported. After repeating the Diels−Alder reaction between **17** and **18** at 22 °C a number of times we found a low accuracy in determining this rate constant for only 10% conversion using NMR ^{1}H integrals.

Table 1. Concentration of the Diene and the Dienophile in the Control Reactions Was Chosen Such as More than 50% Conversion Was Obtained over 12 h[b]

diene	dienophile	temp (°C)	k for control reaction	k' inside reaction	E.M. (M^{-1})	acceleration[a]
16	**17**	22	0.54 M^{-1} day^{-1}	0.26 day^{-1}	0.48	174
16	**25**	22	5.9 M^{-1} day^{-1}	2.1 day^{-1}	0.36	128
23	**17**	70	5.5 M^{-1} day^{-1}	1.9 day^{-1}	0.35	125
24	**17**	22	0.35 M^{-1} min^{-1}	0.0031 min^{-1}	0.0089	3
24	**25**	22	3.9 M^{-1} min^{-1}	0.012 min^{-1}	0.0031	1

[a] Ratio of the half-life time for the control reaction versus that of the capsule accelerated reaction. [b] For the kinetic experiments with the capsule the concentration of the hydroxy "softball" was 1 mM, while the substrates had an initial concentration of 4 mM each.

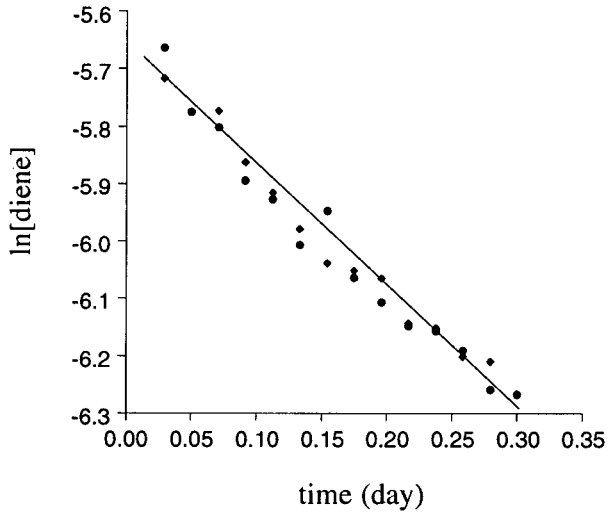


Figure 12. Logarithmic plot of the variation of the cyclohexadiene concentration, in its reaction with maleic anhydride, in the presencie of hydroxy "softball", to obtain the rate constant.

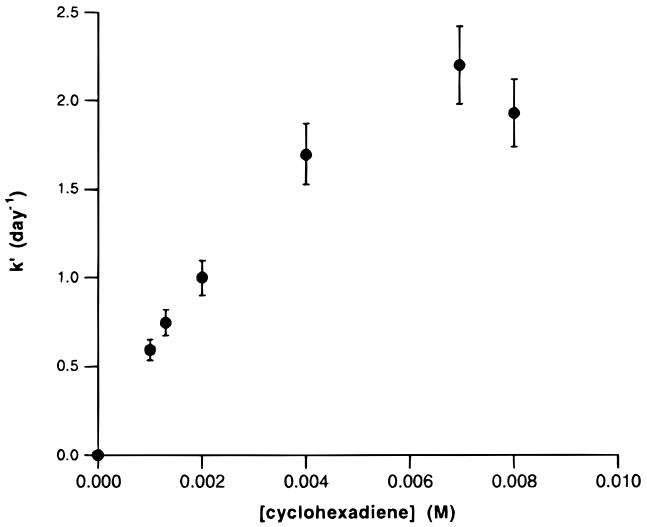


Figure 13. Plot made with the values of the pseudo-first-order rate constants (k') using a constant concentration of 4 mM for the maleic anhydride and 0.9 mM for the hydroxy "softball", while the concentration of cyclohexadiene was varied from 1 to 8 mM. Error bars represent 10% error.

transition states[26,27] or even high-energy intermediates. Dealing with product inhibition will generally be a problem for associative processes, unless the product is bound less well than the reactants. Alternatively, dissociative processes, i.e., reactions that result in an increased number of encapsulated species, could result in turnover since product release would then be entropically favored.[28] We have recent evidence that catalysis is possible with these capsules, even in the Diels−Alder context, and these results augur well for the continued application of reversibly formed molecular capsules as reaction chambers. We will report on these developments in due course.

Experimental Section

General Methods. *p*-Xylene-d_{10} was purchased from Aldrich and used as the solvent for all Diels−Alder reactions. *p*-Benzoquinone and maleic anhydride were purified by sublimation under reduced pressure. Cyclohexadiene and cyclopentadiene were distilled at atmospheric pressure. Standard solutions (25−50 mM) of the dienes and the dienophiles were prepared and subsequently used for the kinetic experiments. All Diels−Alder reactions were performed in *p*-xylene-d_{10} at a constant temperature of 295 ± 1 K except for those involving butadiene which were performed at 343 K. The progress of the reactions were monitored by NMR spectroscopy. The reactions for the Diels−Alder reactions without capsule **2** followed second-order kinetics. The corresponding reactions in the presence of the hydroxy "softball" initially followed first-order kinetics. Only traces (<10%) of the kinetically less favored exo-isomer of the Diels−Alder reactions were found.

1,2-Di(4-heptylphenyl)-1,2-ethanedione (4). To a suspension of 0.710 g (0.100 mol) of lithium metal (high sodium) in 120 mL of dry THF was added 5.00 g (22.7 mmol) of 4-heptylbenzoic acid. This mixture was sonicated for 8 h. After this period, the reaction mixture was carefully added to 300 mL of 1 N HCl. The resulting mixture was extracted with hexane and dried over $MgSO_4$. Evaporation of the solvent and chromatography on silica gel (5% ethyl acetate in hexane) gave 3.27 g (71%) of 4-heptylbenzil. ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87 (d, 4H, J = 8.25 Hz, arom), 7.29 (d, 4H, J = 8.25, arom), 2.67 (t, 4H, J = 7.7 Hz, CH_2-arom), 1.6 (m, 4H, alkyl), 1.28 (m, 16H, alkyl), 0.87 (t, 6H, J = 6.6 Hz, CH_2); HRMS (EI, M^+) calculated for $C_{28}H_{38}O_2$, 406.2871; found 406.2869.

3a,6a-Di(4-heptylphenyl)perhydroimidazo[4,5-*d*]imidazol-2,5-dione. (4-Heptylphenyl Glycoluril) (5). To 2.50 g (6.00 mmol) of **4** was added 0.730 g (12.0 mmol) of urea and 2 mL of trifluoroacetic acid. The resulting mixture was refluxed in 100 mL of benzene under a Dean−Stark trap. After 12 h, the solvent was evaporated, and the residue was filtered and washed with methylene chloride and methanol to give 2.37 g (81%) of a white solid: mp > 300 °C; IR (film) 3231, 2925, 2853, 1718, 1686, 1490, 1229, 1142, 1115, 778 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 7.64 (s, 4H, NH), 6.90 (d, 4H, J = 8.3 Hz, arom), 6.82 (d, 4H, J = 8.3 Hz, arom), 2.35 (t, 4H, J = 7.25 Hz, CH_2-arom), 1.39−1.09 (m, 20H, alkyl), 0.84 (t, 6H, J = 6.9 Hz, CH_3); HRMS (FAB, M + H^+) calculated for $C_{30}H_{43}N_4O_2$, 491.3386; found 491.3377.

1,4-Dimethoxy-2,3-dimethylbenzene (7). To a suspension of 108 mmol of sodium hydride in 100 mL of DMF was added 5.00 g (36.2 mmol) of commercially available 2,3-dimethylhydro-*p*-benzoquinone. The mixture was stirred for 10 min and then cooled to 0 °C. A solution of 11.8 g (83.0 mmol) of methyl iodide in 50 mL of DMF was added dropwise at 0 °C. After 5 h at 0 °C and 2 h at room temperature, the reaction mixture was poured into 1 L of water and filtered. Recrystallization of the residue from methanol gave 5.47 g (91%) of product **7**: mp 74−75 °C; IR (film) 2922, 1481, 1257, 1117, 1099, 800 cm^{-1};

(26) Mock, W. L.; Irra, T. A.; Wepsiec, J. P.; Adhya, M. *J. Org. Chem.* **1989**, *54*, 5302−5308.

(27) McCurdy, A.; Jimenez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc*. **1992**, *114*, 10314−10321.

(28) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024−1027.

^{1}H NMR (300 MHz; $CDCl_3$) δ 6.61 (s, 2H, arom), 3.72 (s, 6H, OCH_3), 2.11 (s, 6H, CH_3); HRMS (EI, M^+) calculated for $C_{10}H_{14}O_2$, 166.0994; found 166.0990.

1,4-Dimethoxy-2,3-dibromomethyl-5,6-dimethylbenzene (8). To a solution of 6.75 g (40.7 mmol) of 1,4-dimethoxy-2,3-dimethylbenzene in bromomethyl methyl ether (25.0 g) was added 60% sulfuric acid (25.0 mL). The two-phase reaction mixture was stirred at 40 °C for 24 h and subsequently poured into 100 mL of water and extracted with CH_2Cl_2 (5 × 50 mL). The organic layer was washed with 10% sodium bicarbonate solution (3 × 50 mL) and water (2 × 50 mL). The resulting solution was dried over $MgSO_4$. Chromatography of the residue on silica gel (5% ethyl acetate in hexane) gave 13.0 g (91%) of compound **8**: mp 88−89 °C; IR (film) 2924, 2853, 1459, 1430, 1267, 1086, 1012, 962 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 4.80 (s, 4H, CH_2Br), 3.83 (s, 6H, OMe), 2.21 (s, 6H, CH_3); HRMS (FAB, M − Br^+) calculated for $C_{12}H_{16}O_2Br$ 271.0334; found 271.0341.

1,4-Dimethoxy-2,3,5,6-tetrabromomethylbenzene (9). A solution of 6.34 g (18.0 mmol) of **8** and 6.42 g (36.0 mmol) of N-bromosuccinimide in 150 mL of CCl_4 was irradiated with a sun lamp for 1 h. The CCl_4 was evaporated, and the residue was stirred in 20 mL of MeOH for 5 min. Filtration gave 8.08 g (88%) of compound **9**: mp 218−219 °C; IR (film) 2940, 1459, 1410, 1277, 1198, 1025, 928, 831, 753, 623 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 4.76 (s, 8H, CH_2Br), 4.06 (s, 6H, OMe); HRMS (EI, M^+) calculated for $C_{12}H_{14}Br_4O_2$, 509.8574; found 509.8538

1,4-Dimethoxy-5,6-dibromomethyl-2,3-(di-*tert*-butyl-1,2,3,4-tetrahydrophthalazine-2,3-dicarboxylate) (10). A mixture of 50 mL of THF and 50 mL of DMF at 70−80 °C was used to dissolve 6.58 g (12.9 mmol) of compound **8**. After complete dissolution, 1.00 g (4.10 mmol) of di-Boc-hydrazide was added, followed by 0.200 g (8.20 mmol) of NaH with stirring. After 20 min, the DMF was evaporated, and the residue was diluted with ether. Excess tetrabromide (**9**) was removed by filtration. The dilution was repeated, and the excess tetrabromide was filtered again. Chromatography of the residue on silica gel (20% ethyl acetate in hexane) gave 1.19 g (50%) of **10**: mp 210−211 °C; IR (film) 2975, 1706, 1456, 1393, 1367, 1266, 1151, 1023, 754, 665 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$, mixture of rotamers) δ 5.15 (br, CH_2N), 4.73 (br, 4H, CH_2Br), 3.89 (s, 6H, OMe), 1.49 (s, 18H, $C(CH_3)_3$); HRMS (EI, M^+) calculated for $C_{22}H_{32}Br_2N_2O_6$, 580.3126; found for 580.3214.

Glycoluril Coupled Compound (11). A mixture of 7.35 g (15.0 mmol) of 4-heptylphenylglycoluril (**5**) and 350 mL of 20% THF in DMSO was heated at 90 °C for 1 h or until dissolution of the glycoluril, then 2.40 g (34.5 mmol) of potassium hydroxide was added, and the reaction mixture was stirred for 1 h at 90 °C. Following this period, 0.580 g (1.00 mmol) of dibromide **10** in 25 mL of DMSO was added via syringe. After 1 h, the heat was removed, and the reaction mixture was allowed to cool to room temperature. The mixture was poured into 400 mL of water (0 °C). The white-beige precipitate was filtered and washed with ethyl acetate until no further product was detected by TLC. Evaporation and chromatography on silica gel (50% ethyl acetate/hexane) gave 0.500 g (55%) of product **11**: mp 250−251 °C; ^{1}H NMR (300 MHz; $CDCl_3$, mixture of rotamers) δ 6.8 (br, 8H, arom), 6.15 (br, 2H, NH), 5.42 (br, 2H, CH_2N), 5.09 (br, 2H, CH_2N), 4.15 (br, 2H, CH_2N), 3.80 (br, 8H, OMe, CH_2N); HRMS (FAB, M + H^+) calculated for $C_{52}H_{78}N_6O_8$, 909.5411; found 909.5475.

Phthalazine Hydrochloride Salt (12). To a solution of 0.700 g (0.770 mmol) of **11** in $CHCl_3$, HCl (g) was bubbled for 1 h. The reaction mixture was purged with Ar for 10 min and then evaporated to give 0.621 g (96%) of **11**: mp 268−270 °C; IR (film) 3233, 2925, 2853, 1702, 1460, 1345, 1045, 933, 800, 747 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.14 (s, 2H, NH), 6.87 (m, 8H, arom), 5.23 (d, 2H, CH_2N), 4.13 (s, 4H, CH_2NH·HCl), 3.79 (s+d, 8H, OMe, CH_2N), 2.78 (m, 4H, CH_2-arom), 1.25 (m, 20H, alkyl), 0.84 (m, 6H, CH_3); HRMS (FAB, M + Cs^+) calculated for $C_{42}H_{58}N_6O_4ClCs$, 841.3417; found 841.3432.

Coupled Methoxy Compounds (15 and Stereoisomers). To a solution of 294 mg (0.350 mmol) of **12** and a catalytic amount of DMAP in 20 mL of benzene was added 0.200 mL (3.00 mmol) of Et_3N and 170 mg (0.180 mmol) of tetraester (**14**). The reaction mixture was stirred for 30 min under argon. The solvents were evaporated, and the residue was purified by chromatography on silica gel ($CHCl_3$: ethyl acetate:methanol (6.5:2.5:1)) to give 140 mg (49%) of C-shaped isomer **15a**, 94 mg (33%) of S-shaped isomer (**15b**), and 25 mg (8.7%) of a mixture of C-shaped **(15a)** and W-shaped isomers (**15c**). This mixture was used directly in the next demethylation step. IR (film) 3250, 2925, 2853, 1711, 1638, 1462, 1343, 1250, 1115, 1034, 960 cm^{-1}; C-shaped isomer (**15a**): mp 191−192 °C (dec); ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.12 (s, 4H, NH), 6.90 (m, 16H, arom), 5.54 (d, 4H, J = 15.6 Hz, CH_2N), 5.27 (d, 4H, J = 15.7, CH_2N), 4.93 (s+d, 6H, CH, CH_2N), 3.89 (s, 6H, OMe), 3.74 (d, 4H, J = 15.7 Hz, CH_2N), 2.36 (m, 8H, CH_2-arom), 1.14 (m, 44H, CH_2), 0.84 (m, 12H, CH_3). S-shaped isomer (**15b**): mp 195−196 °C (dec): ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.12 (s, 2H, NH), 8.09 (s, 2H, NH), 6.90 (m, 16H, arom), 5.54 (d, 4H, J = 15.6 Hz, CH_2N), 5.31−5.12 (m, 4H, CH_2N), 4.94 (s+d, 6H, CH, CH_2N), 3.90 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.72 (m, 4H, CH_2N), 2.36 (m, 8H, CH_2-arom), 1.14 (m, 44H, CH_2), 0.84 (m, 12H, CH_3); HRMS (FAB, M + H^+) calculated for $C_{96}H_{115}N_{12}O_{12}$, 1627.8678; found for 1627.8654.

Hydroxy "Softball" (2). To a solution of 50.0 mg (0.0307 mmol) of C-shaped isomer **15a** in 25 mL of methylene dichloride was added 100 mg (0.74 mmol) of $AlCl_3$ at 0 °C. The mixture was stirred overnight. The reaction mixture was treated with methanol and then chromatographed on silica gel (7% methanol in chloroform) to give 29.9 mg (62%) of C-shaped compound **2**: mp 170−172 °C (dec); IR (film) 3265, 2925, 2854, 1692, 1626, 1467, 1251, 1017 cm^{-1}; ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.69 (s, 4H, OH), 8.10 (s, 4H, NH), 6.89 (m, 16H, arom), 5.52 (d, 4H, J = 15.6 Hz, CH_2N), 5.32 (d, 4H, J = 15.6 Hz, CH_2N), 4.97 (s, 2H, bridgehead CH), 4.78 (d, 4H, J = 15.6 Hz, CH_2N), 2.36 (m, 8H, CH_2-arom), 1.14 (m, 44H, CH), 0.84 (m, 12H, CH_3); ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.02 (s, 8H, OH), 7.77 (s, 8H, NH), 6.84 (m, 32H, arom), 6.40 (d, 8H, J = 16.5 Hz, CH_2N), 5.69 (d, 8H, J = 16.0 Hz, CH_2N), 4.71 (s, 4H, bridgehead CH), 4.32 (d, 8H, J = 16.5, CH_2N), 3.82 (d, 8H, J = 16.0 Hz, CH_2N), 2.44 (m, 16H, CH_2-arom), 1.15 (m, 88H, alkyl, bridge CH_2), 0.88 (m, 24H, CH_3); For **2w**: mp 194−196 °C (dec); ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.66 (s, 4H, OH), 8.11 (s, 4H, NH), 6.89 (m, 16H, arom), 5.36 (d, 4H, J = 15, N−CH_2), 5.28 (d, 4H, J = 15, N−CH_2), 4.97 (s, 2H, bridgehead CH), 4.94 (d, 4H, J = 15,N−CH_2), 3.62 (d, 4H, J = 15,N−CH_2), 2.44 (m, 16H, CH_2-arom), 1.15 (m, 88H, alkyl, bridge CH_2), 0.88 (m, 24H, CH_3); For **2s** mp 180−182 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ 8.69 (s, 2H, OH), 8.68 (s, 2H, OH), 8.12 (s, 2H, NH), 8.08 (s, 2H, NH), 6.80 (m, 16H, arom), 5.37 (m, 8H, N−CH_2), 4.97 (s, 2H, bridgehead CH), 4.87 (m, 4H, N−CH_2), 3.63 (m, 4H, N−CH_2), 2.44 (m, 16H, CH_2-arom), 1.15 (m, 88H, alkyl, bridge CH_2), 0.88 (m, 24H, CH_3); HRMS (FAB, M + H^+) calculated for $C_{92}H_{107}N_{12}O_{12}$, 1571.8052; found for 1571.8038.

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