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Direct Synthesis of Hollow Polymeric Nanocapsules of Variable Shell Thickness and Rigidity

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The thiol-ene photopolymerization of resorcinarene cavitand thiol with various alkene building blocks led to the formation of hollow nanocapsules of varying thickness and rigidity, depending on the valency of the alkenes.

There is currently a lot of interest in controlling the size, shape and composition of polymeric materials for diverse applications from material science to nanomedicine.^{1–3} In the context of nanomedicine, recently it has been shown that the rigidity of polymeric materials plays a crucial role in determining their internalization, biodistribution and circulation.^{4,5} Polymeric capsules are hollow container molecules or molecular assemblies of nanometer to micrometer dimensions with a liquid core and a polymeric shell.^{6,7} They have attracted a lot of attention in recent years due to their intrinsic ability to encapsulate a variety of guest molecules for wide-ranging applications.^{8–11} Among various physical parameters, the thickness of the capsules plays a crucial role in controlling properties such as mechanical strength, permeability, rigidity, degradation kinetics *etc.*^{10–12} For example, when compared to liposomes, polymersomes with thicker membranes have enhanced mechanical stability, higher encapsulation capability and lower permeability.^{13,14} The shell thickness of capsules can also be controlled by layer-by-layer assembly based methods.¹¹ Despite the recent advances in capsule synthesis, the methods to control the thickness are still in their infancy.¹² A variety of methods have been developed for the preparation of capsules, and they typically involve self-assembly, sacrificial templates, surfactant emulsions or combinations thereof.^{6–14} Furthermore, the current methods for capsule formation have certain intrinsic limitations such as viability and stability of self-assembled systems, incomplete or difficult removal of template and surfactant, capsule porosity, multistep assembly processes, reproducibility *etc.*^{6–14} Hence there is a need to develop newer,

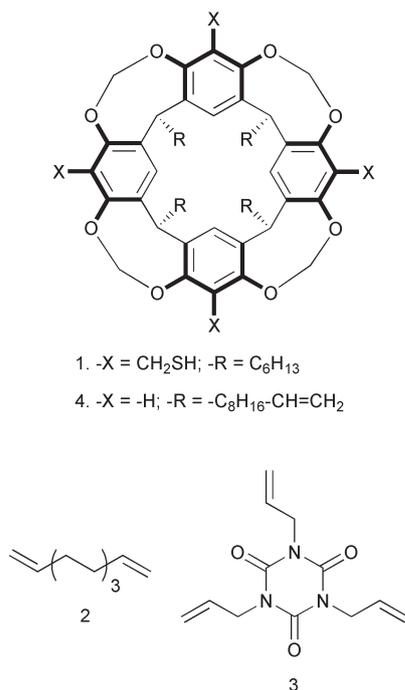
direct methods for the fabrication of hollow polymeric capsules with tunable physical characteristics.

Research from our group^{15,16} and others¹⁷ has shown that thiol-ene photopolymerization^{18–20} can lead to the formation of covalently assembled nanocapsules in the absence of any template or surfactants. We have recently shown that resorcinarene tetraalkene tetrathiol, a single-component multi-thiol and multi-alkene monomer, can lead to the direct formation of hollow polymeric nanocapsules.¹⁵ Further we have extended this method for the synthesis and *in situ* functionalization of resorcinarene nanocapsules.¹⁶ We hypothesized that by having the thiol and ene functional groups in different monomers the mechanical properties of the polymer could be controlled by independently varying the valency and directionality of the monomers. In the past, Kim and coworkers have shown that the two-component photopolymerization of a macrocyclic cucurbituril-alkene monomer with linear dithiol linkers can directly yield nanocapsules with a very thin shell.¹⁷ In this communication, we show that the photopolymerization of resorcinarene cavitand thiol **1** (Scheme 1) with readily available alkene building blocks **2–4** led to the formation of hollow polymeric nanocapsules. Further we show that the thickness and rigidity of the resulting nanocapsules can be varied substantially by varying the valency of the alkene building blocks.

The photopolymerization of resorcinarene cavitand thiol **1** and alkenes **2–4** was carried out in chloroform as described elsewhere.^{15,16} In all these experiments the equivalents of thiol and alkene were kept at a 1 : 1 ratio. Briefly, a filtered and degassed solution of resorcinarene cavitand thiol **1** (1.5 mM), and alkene (**2** (3 mM) or **3** (2 mM) or **4** (1.5 mM)) in chloroform was irradiated in a Srinivasan–Griffin photoreactor equipped with 4 × 254 nm and 4 × 300 nm lamps for 3 h. Aliquots of the photoproducts thus obtained were transferred into a spectra por membrane (6000–8000 molecular weight cut off) and dialyzed against a 3 : 1 mixture of chloroform : methanol. Volatiles of such dialyzed samples were removed by rotary evaporation and the residue obtained was used to calculate the mass recovery. The yields of these photopolymerization reactions varied somewhat depending on the monomer. While the reaction of resorcinarene cavitand thiol **1** with triene monomer **3** gave a yield of 79%, the polymer formed with diene **2**

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Scheme 1 Thiol- and ene-building blocks for resorcinarene nanocapsules.

was obtained in 51% yield. All analysis reported in this communication were carried out on as-prepared photopolymer samples.

Note that the benzylic thiol group present in resorcinarene cavitand **1** is more reactive²⁰ than the thiophenol based monomers employed in our earlier studies.^{15,16,21} Among the alkenes, the reactivity of diene **2** and tetraene **4** is slightly higher than triene **3**.¹⁹ The FTIR analysis of the photoproducts obtained after 3 h of UV irradiation revealed the complete disappearance of the thiol stretch in all three photoproducts (Fig. S1, ESI†), unlike the photoproducts obtained from resorcinarene thiophenol under similar reaction conditions.¹⁵

Due to inherent low contrast, the photopolymers were stained with OsO₄ or uranyl acetate for transmission electron microscopic (TEM) analysis. TEM analysis revealed the presence of spherical structures with a lighter core and darker rim in all three cases examined (Fig. 1), indicating the formation of hollow polymeric nanocapsules. The TEM analysis gave average dimensions of 130 ± 40 nm, 100 ± 50 nm, and 120 ± 50 nm for nanocapsules obtained from alkenes **2–4** respectively (Table 1). Noticeably the nanocapsules obtained from triene **3** and tetraene **4** showed a bimodal size distribution.

It is worth noting that these nanocapsules are formed from a rigid multi-thiol resorcinarene monomer and flexible alkene building blocks, unlike Kim and coworkers¹⁷ who used rigid multi-alkene cucurbituril monomer and flexible di-thiol linkers for the preparation of hollow nanocapsules. These studies suggest that at least one of the functional groups (thiol or ene) must be present in a somewhat rigid environment for the formation of nanocapsules by thiol-ene photopolymerization.

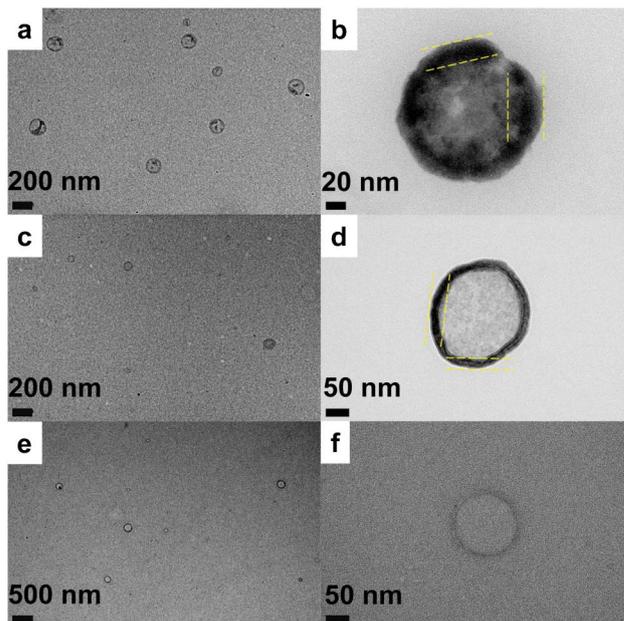


Fig. 1 TEM images of photopolymers obtained from resorcinarene cavitand thiol **1** and diene **2** (a–b), triene **3** (c–d), and tetraene **4** (e–f). Except Fig. 1a (which was obtained from a uranyl acetate stained sample), all other images were obtained with OsO₄ stained samples. The yellow lines were added to highlight the thickness of the nanocapsule shell wall.

Interestingly, the higher magnification images revealed dramatic differences in the thickness of the nanocapsules obtained. The nanocapsules formed in the presence of diene **2** showed a typical thickness of ~24–34 nm (Fig. 1b). In fact with OsO₄ staining at lower magnifications, these nanocapsules with thicker shells looked more like dark spherical objects (Fig. S2, ESI†). On the other hand, the nanocapsules obtained from triene **3** (Fig. 1d) were less thick (~18–29 nm) than those obtained from diene **2**, while the nanocapsules obtained from tetraene **4** (Fig. 1f) had the thinnest shell (~3 nm). Note that there were some variations in the shell thickness between and within nanocapsules prepared in the same batch (Fig. S3, ESI†).

We investigated the dimensions (Table 1, Fig. 2, S4 and S5, ESI†) of these nanocapsules by atomic force microscopy (AFM). Consistent with the TEM analysis, AFM showed that the nanocapsules prepared from triene **3** and tetraene **4** had a bimodal size distribution with a relatively higher percentage of smaller nanocapsules (Fig. S5, ESI†). Histograms of nanocapsules obtained from resorcinarene cavitand thiol **1** and triene **3** (Fig. S5b, ESI†) showed two distinct sets of nanocapsule population centered around 75 nm (72%) and 125 nm (28%). Similarly nanocapsules obtained from the tetraene monomer (Fig. S5c, ESI†) showed two distinct sets of nanocapsule population centered around 65 nm (68%) and 105 nm (32%). Unlike much larger capsules with micron dimensions,²² these nanocapsules did not collapse upon drying. The average height of various nanocapsules obtained from alkene monomers **2–4** are summarized in Table 1. The nanocapsules obtained from diene **2** showed a typical height of 60 ± 10 nm, higher when compared to those obtained from

Table 1 Summary of the average dimensions of various nanocapsules obtained from thiol **1** and various alkenes **2–4** by TEM^a and AFM^b

1 +	Diameter ^a (in nm)	Height ^b (in nm)	Diameter ^b (in nm)	Height ^b /Diameter ^b
2	130 ± 40	60 ± 10	150 ± 30	0.41 ± 0.05
3	100 ± 50	30 ± 10	90 ± 30	0.35 ± 0.05
4	120 ± 50	30 ± 10	80 ± 20	0.33 ± 0.04

triene (30 ± 10 nm) and tetraene (30 ± 10 nm). Given the vast differences in height, we calculated the ratio^{23,24} of height/diameter for several individual nanocapsules and the average ratio is provided in Table 1. Such a height/diameter ratio (Table 1) decreased systematically upon increasing the valency of the alkene building block. Note that a higher ratio is expected for more rigid nanocapsules and a lower ratio is expected for more flexible nanocapsules.^{23,24} Our studies indicate that the nanocapsules with thicker shells (*i.e.*, those obtained from diene **2**) are also more rigid than those with thinner shells (*i.e.*, those obtained from triene **3** and tetraene **4**). It is worth noting that Zimmerman and coworkers²⁴ have shown that dendrimers show reduced flattening, *i.e.*, an increased height in AFM analysis in air, upon crosslinking. It is possible that these thicker shells could also be highly crosslinked leading to the formation of more rigid nanocapsules. However, a thicker shell does not always translate to a rigid nanocapsule, as despite the differences in shell thickness for nanocapsules obtained from triene **3** and tetraene **4** there was only

a minor difference in the height/diameter ratio for these nanocapsules.

From a mechanistic stand point, Kim and coworkers¹⁷ have proposed the initial formation of a disk-shaped 2D oligomeric patch and its eventual bending leading to the formation of hollow polymeric nanocapsules. Our studies^{15,16} showed that the reaction medium too plays a crucial role in the morphological development of thiol-ene photopolymers. We believe¹⁵ that the formation of morphologically distinct polymeric structures such as nanocapsules, fibrous network structures, nanoparticles and lattices in various solvents upon photopolymerization of the same single-component thiol-ene monomer under otherwise identical conditions could be a function of two antagonistic effects: thiol-ene polymerization rate (or reaction extent) and phase separation effects.^{25,26} While the specific details of the formation of the nanocapsules with varying thickness under two-component thiol-ene photopolymerization is still unclear, it appears that reactivity of the alkene monomers¹⁹ alone does not dictate the thickness of the nanocapsules and that the orientation and valency of the alkene monomers may also play a crucial role in the morphological development of these photopolymers. It is possible that the observed results could be due to the formation of 2D oligomeric patches of varying thickness during the early stages of photopolymerization.¹⁷ Currently, this observation is under detailed investigation in our laboratory.

In conclusion, we have shown that resorcinarene cavitand thiol can form hollow polymeric nanocapsules with a variety of alkenes. TEM analysis revealed that the thickness of the resulting nanocapsules varied substantially depending on the valency of the alkene building blocks. Further, AFM analysis showed that the nanocapsules with thicker shells were also more rigid than those with a thinner shell. In principle, the rigidity of the nanocapsules can be further varied by varying the duration of photopolymerization. This facile, one-step, template- and surfactant-free, direct synthesis of nanocapsules with varying thickness and rigidity is expected to play a crucial role in their applications as nanoreactors and in nanomedicine.²¹

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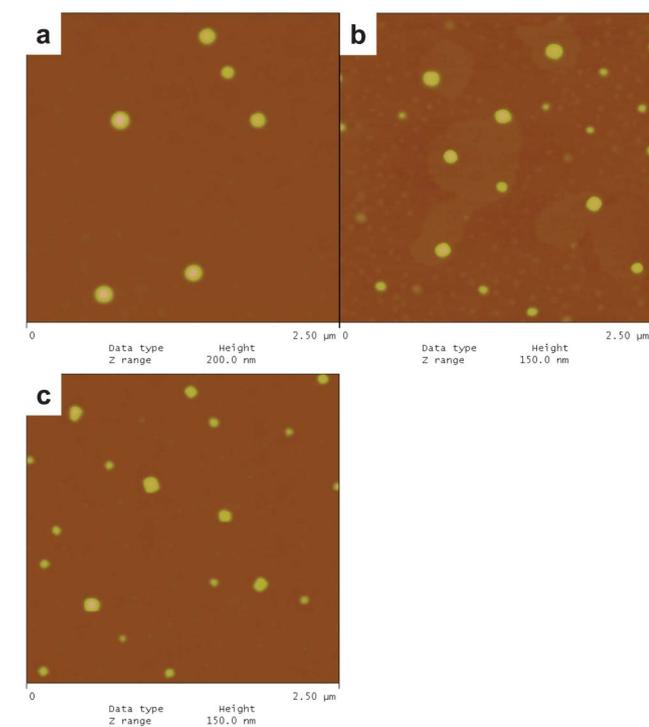


Fig. 2 AFM analysis of photopolymers obtained from resorcinarene cavitand thiol **1** and alkenes **2** (a), **3** (b) and **4** (c).

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