

From Dendrimers to Knedel-like Structures**

Karen L. Wooley*

Abstract: Shell-crosslinked knedels are nanometer-sized (5–200 nm diameters), amphiphilic core–shell spheres that are prepared by the self-assembly of amphiphilic block copolymers into polymer micelles, followed by crosslinking of side chain functionalities along the block composing the shell of the polymer micelles. Such structures resemble dendrimers in the basic structural components, and have the advantages of a rapid synthetic approach and the production of larger and broader size ranges.

Keywords: dendrimers · polymers · micelles · nanospheres · supramolecular chemistry

In the quest for the creation of organic materials possessing new properties, the construction of unique macromolecular architectures and assemblies are actively investigated areas of research. Dendritic macromolecules have received a great deal of attention,^[1] due to the combination of unusual physical properties resulting from their highly branched architecture and seemingly unlimited control over the chemical composition at any location within their structure. Modification of the numbers and types of chain-end functionalities has led to dendrimers with potential applicability in broad areas including catalysis, imaging, DNA transfection and molecular machines, whereas the incorporation of functionality at internal sites has been mainly driven by the proposed similarities between dendrimers and enzymes. Coordination of the functions of the chain ends and the core has allowed for the creation of sophisticated energy transfer systems, or structures that are capable of selective encapsulation and release.

Considering the growing exploration of applications for dendrimers and the promise that they have shown, some attention has shifted toward the development of less costly, higher-yielding and less time-consuming syntheses. A double-stage convergent growth approach,^[2] a branched monomer approach,^[3] double-exponential dendrimer growth^[4] and orthogonal coupling strategies^[5] are several methods that have been used to

accelerate the preparation of dendritic macromolecules. The direct polymerization of A_xB monomers gives hyperbranched polymers^[6] of high molecular weight in a single step, but unlike dendrimers, the structures are imperfect, with polydisperse molecular weights and undefined branching sequences. In addition, compositional control at different locations within the structures is lost, for the hyperbranched materials. Arborescent graft copolymers^[7] are highly-branched, spherical structures that possess a core–shell morphology, and thus resemble dendrimers. However, a multistep synthesis is still involved.

If one considers only the basic components of the dendrimer structure, then dendrimers can be thought of as small particles with globular or spherical shape of 5–15 nm diameters and narrow size distribution, bearing peripheral functionalities and a unique core environment. It seems that a self-assembly process would be a powerful tool for the generation of dendritic-like structures. For example, when surfactant molecules are placed within the appropriate environment, micellar aggregates are formed, which are spherical core–shell structures. In fact, several examples of dendritic, covalently bound micelles have been reported,^[8] and the micellar core–shell dendrimers successfully encapsulate small molecules. Again, the syntheses of these structures are not trivial. The linking together of individual surfactant molecules, through covalent bonds, would stabilize micelles and produce materials similar in shape and composition to the dendritic micelles. However, attempts to do so have proved difficult,^[9] due to intramicellar reactions. Furthermore, a large core volume is desired to optimize loading for encapsulation or delivery applications.

Amphiphilic block copolymers, composed of blocks of hydrophilic and hydrophobic nature, self-assemble into micellar aggregates much like classical surfactants when placed into a solvent selective for one of the blocks.^[10] Although polymer micelles have greater stability than those formed from small-molecule surfactants, their existence remains environment specific; the polymer micelles can be distorted or destroyed by concentration changes, shear forces, etc. Therefore, reactions to bind the preformed polymer micelles is a practical method to stabilize the structures. Reaction at only one site of the polymer chains has been used to prepare star polymers.^[11] However, if one takes advantage of the numerous functional sites along the backbone of the polymer chains, then particles are possible with either the core^[12] or the shell^[13] crosslinked (Figure 1).

The shell-crosslinked polymer micelles are termed shell-crosslinked knedels (SCK's), and they resemble dendrimers in having a spherical shape, a large number of peripheral function-

[*] K. L. Wooley
Department of Chemistry
Washington University
St. Louis, Missouri 63130-4899 (USA)

[**] Knedel is a Polish word to describe a food of meat surrounded by a dough layer.

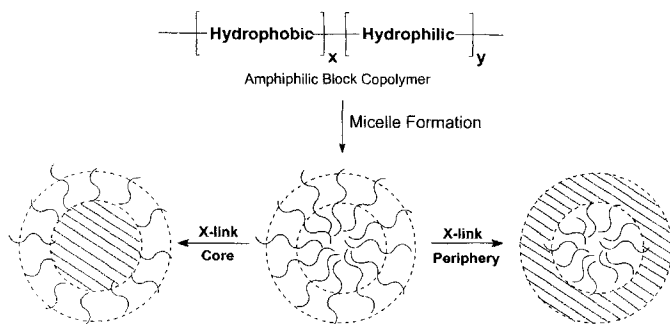


Figure 1. Schematic drawing of the self-assembly of amphiphilic block copolymers into polymer micelles, followed by crosslinking of the polymer chains through functionalities along the polymer block located either in the core or the shell.

alities with limited mobility, and a core-shell structure (Figure 2). Therefore, the objectives for the SCK synthesis were the preparation of spherical nanometer-sized particles possessing a core-shell morphology and reactive peripheral groups. The

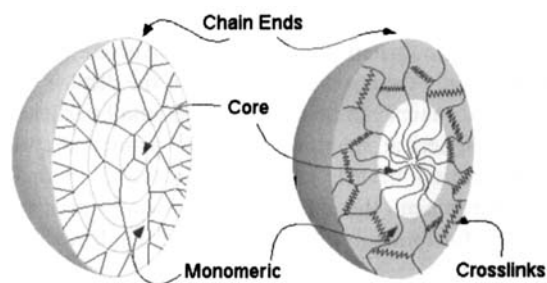
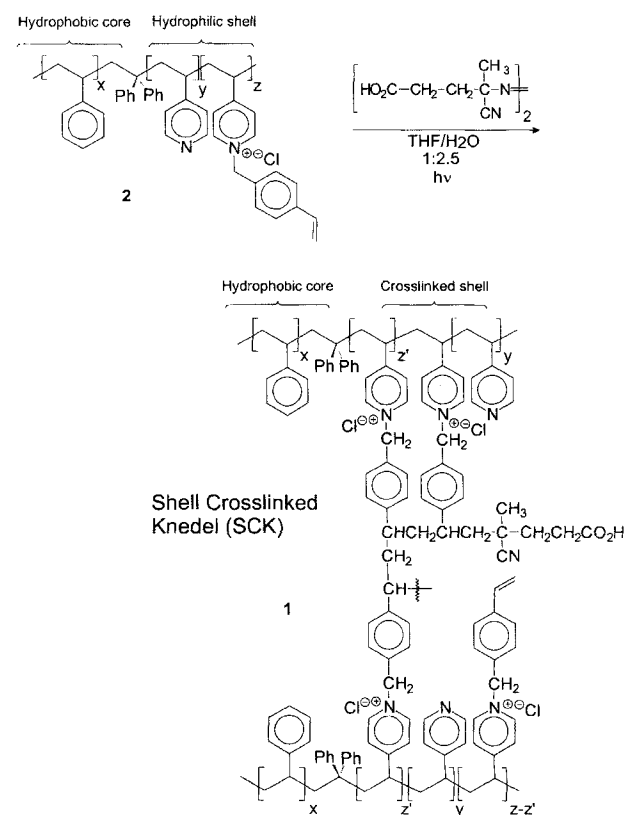


Figure 2. Cross-sectional drawings of the basic structural components of dendrimers and SCK's.

ability to easily produce such structures with narrow size distribution and with control and variability over the dimensions of the entire particle, the shell thickness and the core diameter was also of high importance. As shown in Scheme 1, each of these goals was met by using standard chemistry, however, applied in a new manner to prepare a polystyrene/poly(4-vinylpyridine) SCK, **1**. Anionic polymerization was first used to synthesize a block copolymer of polystyrene (PS) and poly(4-vinylpyridine) (PVP). The PVP pyridyl nitrogen atoms were then quaternized by reaction with *p*-chloromethylstyrene. This quaternization step imparted the amphiphilic nature over the block copolymer and also incorporated a polymerizable styrenyl double bond to be used for crosslinking. Organization of **2** into micelles segregated the PS and PVP into different domains composing a spherical macromolecular core-shell assembly. Addition of a water-soluble radical initiator to the micellar solution and irradiation facilitated polymerization of the styrenyl side groups, which formed crosslinks between the PVP chains in the shells of the polymer micelles. The final product was an SCK, **1**, whose composition is shown in Scheme 1. A schematic drawing of this SCK structure is given in Figure 3 a.

Since the first report of SCK's, control over their dimensions has been accomplished through variation in the compositions and ratios of hydrophobic and hydrophilic block lengths.^[14] Thus, SCK's having diameters ranging from 5 to 200 nm (how-

Spherical micelles composed of:



Scheme 1. Reaction sequence for the preparation of polystyrene/poly(4-vinylpyridine) SCK's, by crosslinking of PS-b-PVP micelles through styrenyl moieties along the PVP backbone within the PVP shell layer, with the PS composing the core.

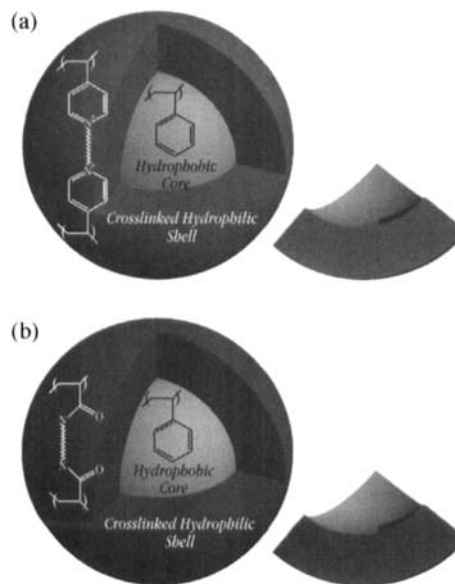


Figure 3. Three-dimensional representation of two SCK's of differing chemical composition. Both SCK's contain a noncrosslinked hydrophobic PS core, surrounded by and covalently bound to a crosslinked hydrophilic shell. The crosslinked shell is composed of either polystyrene-quaternized PVP (a) or a polyamide containing water-soluble crosslinkers (b).

ever, each sample is of narrow dispersity) have been prepared. Although the shell is crosslinked and several nanometers thick, it is penetrable to even medium-sized hydrophobic organic molecules, for example, pyrene and BDPA.

The versatility of the formation of SCK's has been further demonstrated by the preparation of a second series of SCK's, composed of the chemistry shown in Figure 3b.^[15] In this case, a block copolymer of PS and poly(acrylic acid) (PAA) is organized into spherical micelles, followed by crosslinking of the PAA shell through amidation reactions involving a water-soluble diamino linker, for example, diaminotriethylene glycol, using a water-soluble carbodiimide as the coupling agent.

Atomic force microscopy (AFM) has proven to be an invaluable tool in the characterization of the sizes and shapes of the SCK's. Dynamic light scattering is also being applied, to determine the sizes of the SCK's in aqueous solution. Solution-state NMR reveals information regarding the core mobility, and solid-state NMR is being used for characterization of the entire SCK structure, as well as the location and interaction of small molecules encapsulated within their cores. DSC shows glass transition temperatures for both of the components, indicating phase separation between the cores and shells.

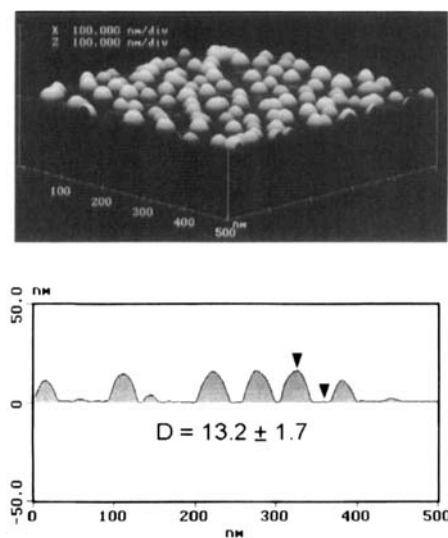


Figure 4. Atomic force microscopy (AFM) image (tapping mode) and height profile for a PS/PVP SCK, 1, demonstrating the solid-state diameter and narrow size distribution.

A broad range of experiments are currently in progress to evaluate the performance of SCK's in a number of applications. Importantly, the SCK's are prepared in aqueous solution and many of their applications will therefore involve an aqueous environment. The formation of SCK's bearing the opposite core-shell arrangement, with an organic, hydrophobic shell are also in progress.

The SCK's are of unique size—larger than most dendrimers and smaller than particles prepared by emulsion polymerization. Therefore, they are expected to perform well in applications targeted for dendrimers, technologies employing latex particles, as well as unique areas, where the stability of SCK's will make them superior to noncrosslinked polymer micelles.

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