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# Synthesis and Properties of Water-Soluble Asterisk Molecules

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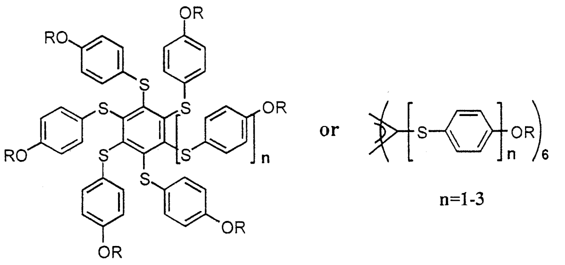
***Abstract:*** An asterisk is comprised of six semirigid arms projecting from a benzene nucleus. In the case at hand, asterisks were synthesized with one, two, or three aromatic rings (connected by sulfur atoms) in each of the six arms. A phosphomonoester at the termini of each arm solubilized the asterisks in water. The colloidal properties of these amphiphilic molecules were investigated by UV−vis and fluorescence spectroscopy, calorimetry, light scattering, surface tensiometry, and pulse-gradient spin−echo NMR. Solubility, solubilization, metal binding, and micelle “seeding” experiments were also carried out. Chain-conformation and supramolecular assembly into remarkable molecular “scrolls” were investigated by X-ray analysis and electron microscopy, respectively. One of the more interesting properties of the asterisks is that they remain monomeric in water despite having as many as 19 hydrophobic aromatic rings exposed to the water. The reasons for this behavior, and the possibility of exploiting it for constructing enzyme models free from aggregation equilibria, are discussed.

## Introduction

This paper deals with molecules that have six semirigid arms projecting from a benzene-ring core. Each of the arms terminates in an anionic group (R = phosphate in the structure below), thereby imparting water solubility to otherwise highly water-insoluble molecules. The compounds were prepared in three different “generations” according to whether the arms each possess one, two, or three aromatic rings. For example, generation-3 molecules have a total of 18 aromatic rings within the six arms. Previously reported compounds, where R = i-Pr, called asterisks, inspired the design of our systems.[1] Recent additional examples of various multiarmed aromatics are also available.[2−6] But syntheses of water-soluble asterisks, and examination of their colloidal properties, have no counterpart in past work.



Would our asterisks behave similarly to anionic micelles or dendrimers to which they have a vague resemblance? Would the molecules interlock their arms in water? Would an asterisk solubilize small hydrophobic molecules or metal ions between its arms? Answering such questions was a prime concern of ours. Yet, admittedly, pursuit of the project also appealed to us aesthetically. It was pleasurable to imagine asterisk molecules darting through water—like six-sided snow-flakes bandying about in the wind.

Characterizing the solution properties of the asterisks utilized the following: UV−vis and fluorescence spectroscopies, calorimetry, light scattering, surface tensiometry, and pulse-gradient spin−echo NMR in addition to studies of solubility, solubilization effects, and metal binding. Solid-state properties were also examined via X-ray analysis and electron microscopy. As stated previously, a balanced perspective in colloid chemistry can be best achieved by multiple methods, each of which reveals only a fragment of reality.[7]

## Synthesis

The synthetic strategy used to obtain the water-soluble asterisks is shown in Scheme l. In general terms, the hydroxyl of 4-thiomethylphenol was first protected with R, after which the sulfur was demethylated to give thiol-**1.** The latter was used to displace the six chlorines of hexachlorobenzene to produce a first-generation asterisk system **A-l**. Similar chemistry with preformed arms **2** and **3** (made from **1**) gave second and third generation asterisks **A-2** and **A-3**. Removing the protecting

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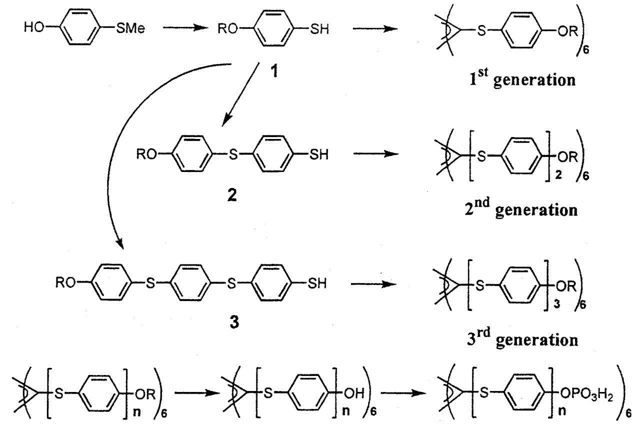
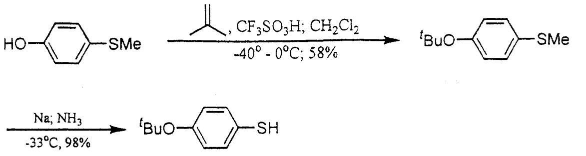
***Scheme 1.*** Synthetic Strategy for Making Water-Soluble Asterisks, Where R = Protecting Group



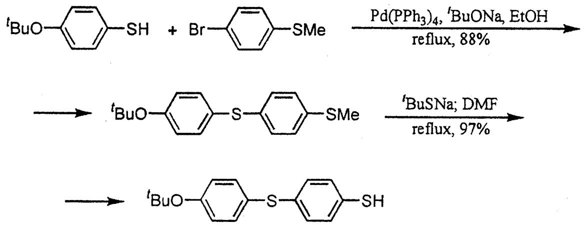
group R, and endowing the resulting terminal hydroxyls with phosphates, led to the water-soluble asterisks. The apparent simplicity of the scheme belies the many difficulties encountered in its pursuit. Impaired solubility and slow reaction rates, relative to those of low molecular weight counterparts, were common with the asterisks. Poor yields were unacceptable since we needed sufficient compound for multiple tests. The following brief discussion of how these problems were overcome seems, generally speaking, relevant to the design of supramolecular systems in which *p*-phenylene sulfide "wires" are a desired structural element.

The choice of protecting group R on the oxygen was critical.[8] It needed to be stable in the presence of strong bases and nucleophiles. And it had to be easily removed in high yield (a stipulation made more acute by the presence of six such groups per molecule). The triisopropylsilyl group failed us because subsequent demethylation of the sulfur by two different routes (t-BuSNa in dimethylformamide (DMF) and Na in $NH_3$)[9,10] gave low yields due to decomposition or byproducts. We ended up using the *tert*-butyl group despite the fact that its installation (eq 1) took place with only a moderate yield of 58%.[11] On the other hand, the demethylation of sulfur was now almost quantitative.



(1)

Interconnecting the aromatic rings within the arms required the coupling of aromatic thiolates with aromatic halides. Of two previously described methods for accomplishing this feat ($Cu_2O$ and Pd catalysis),[12,13] the latter was far more effective (eq 2). Rather than again using $Na/NH_3$ to liberate the thiol (which risked Birch-type interference), we carried out a high-yield demethylation with sodium alkanethiolate. The resulting thiol could be purified satisfactorily by vacuum distillation on a Kugelrohr.

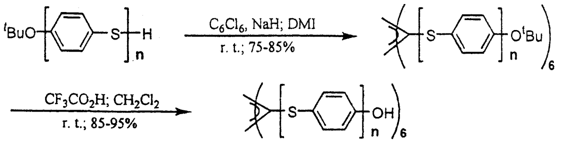


(2)

Simple extension of the synthetic procedure used for generation-2 arms (eq 2) to make generation-3 arms was complicated by formation of dimeric and tetrameric byproducts that could not be removed chromatographically. An approach, combining both Cu and Pd chemistry (Scheme 2), was therefore required.[1] With the three thiols of eqs 1 and 2 and Scheme 2 in hand, we were ready to prepare the asterisks.

Asterisks were synthesized according to the MacNicol procedure[1,14] in which the aryl thiolates (1.2-fold/Cl excess) were reacted with hexachlorobenzene in 1,3-dimethyl-2-imidazolidinone (DMI) at room temperature for 1−3 days (eq 3). (It was fortunate that our thiolates were protected with a *tert*-butyl protecting group because later attempts to use 4-hydroxythiophenol in the MacNichol procedure gave only inseparable mixtures despite reported successes to the contrary in the literature).[15] The coupling products were purified by column chromatography and then deprotected with trifluoroacetic acid.

All three generations of hexaphenols form clathrates with ether; even a high vacuum for several days does not destroy them. The hexaphenols are soluble in ether, acetone, and methanol, but only generation-l readily dissolves in basic water. Air-oxidization is rapid, as might be expected. Treatment of the generation-l hexaphenol with acetyl chloride or benzoyl chloride gave crystalline hexaacyl compounds suitable for X-ray analysis (reported later in the paper). Phosphorylation was effected quantitatively using a 2.5-fold excess/(hydroxyl of $POCl_3$) (eq 4).[16] Intermediates were subsequently hydrolyzed with water at room temperature (generation-l) or 40−50 °C (generations-2 and -3). Acidification of aqueous solutions with concentrated HCl caused the fully protonated hexamonophosphates, designated **A-l**, **A-2**, and **A-3**, to precipitate.



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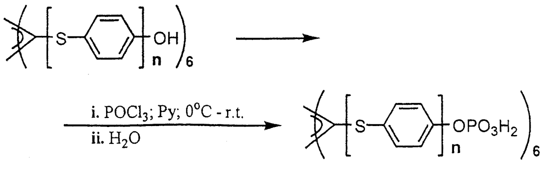

(4)

## Physical Studies

To confine the paper to a reasonable length, the data are presented in a concise format that retains the principal information derived from the various physical methods.

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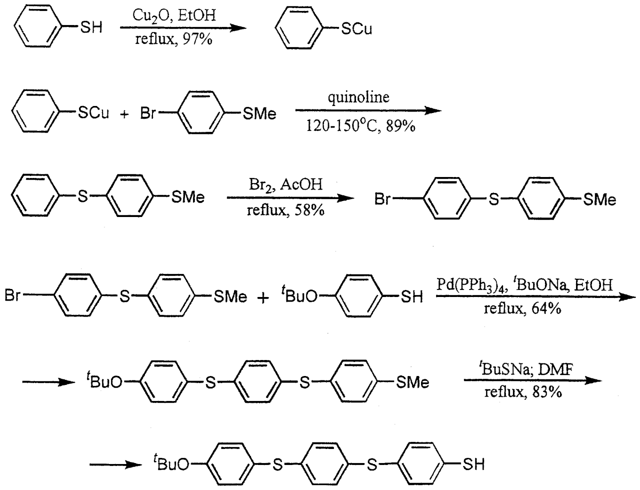
***Scheme 2.*** Synthesis of the Generation-3 Arm



**General Properties.** Compounds **A-l**, **A-2**, and **A-3** are bright yellow compounds that are insoluble in most organic solvents (hexane, $CH_2Cl_2$, $CHCl_3$, ether, and THF) but highly soluble in dimethyl sulfoxide (DMSO). Water-solubility, determined semiquantitatively using a spectrophotometric assay, is pH-dependent, as indicated by the following: (a) **A-l** is highly soluble from pH = 2 to pH = 10 (only in concentrated HCl does **A-l** fail to dissolve); (b) **A-2** becomes highly soluble above pH = 8; and (c) the solubility of **A-3** is low (ca. $4 \times l0^{-4}$ M) at pH = 8 but increases more than l0-fold at pH = 10. Obviously, two opposing factors dictate solubility: the degree of phosphate ionization and the length of the arms. Water-solubility of **A-3**, for example, requires the formation of the phosphate dianion, whereas the two smaller asterisks dissolve in the monoanionic state.

**UV−Vis Spectrophotometry.** Departures from Beer−Lambert linearity in plots of absorbance vs concentration would imply self-assembly of the asterisks. Thus, UV−vis absorbance measurements were carried out at 25.0 °C in 0.l0 M degassed aqueous KOH using the following concentration ranges: (a) **A-l**, 0.0l−l0 mM; (b) **A-2**, 0.0l−3 mM; and (c) **A-3**, 0.0l−3 mM. Such large concentration ranges were made possible by using, and interrelating, eight wavelengths of widely differing absorptivities between 390 and 460 nm (part of a long “tail” ranging from 320 to 460 nm and accounting for the compounds’ yellow color). Linear plots over the indicated concentration ranges (not shown) were an indication (although not a direct proof) that none of the asterisks aggregates in water.

**Flourescence.** All three asterisks fluoresce in basic aqueous solutions (0.l0 M KOH in degassed Milli-Q water). The following excitation and emission maxima at l.0 mM were recorded for characterization purposes: (a) **A-l**, 432 nm, 536 nm; (b) **A-2**, 446 nm, 538−539 nm; (c) **A-3**: 448 nm, 539−540 nm. Relative fluorescence intensities at 0.30 mM increase from 1 to 3 to 12 upon going from **A-l** to **A-2** to **A-3**.

**Differential Scanning Calorimetry.** Calorimetric studies were performed on near-saturated basic solutions of the three asterisks in order to determine if they undergo thermally induced phase transitions Thus, heating and cooling aqueous samples in a Hart Scientific differential scanning calorimeter (DSC) at a rate of 10 $^o$C/h between 10 and 90 °C gave no peak indicative of a cooperative phase transition such as that found with phospholipid assemblies.[17] Self-assembly, driven by hydrophobic association of the asterisks’ aromatic arms, either fails to occur or, if it does take place, the corresponding phase transitions must fall outside our experimental temperature range.

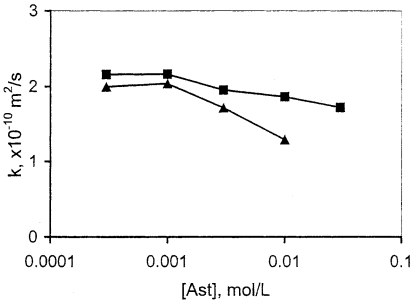


***Figure 1.*** Diffusion coefficients *k* obtained from FT-PGSE NMR for **A-1** (■) and for **A-2** (▲). The lines are eye guides.

**Dynamic Light Scattering.** Dynamic light scattering (DLS) measurements, performed on a Coulter N4 sub-micrometer particle sizer, were carried out to determine if any aggregates existed at 1−3 mM concentrations in basic water (0.l0 M NaOH). Experiments were performed at different scattering angles of 30, 63, and 90° on optically clear solutions. The data did not reveal particles larger than 5−7 nm, the resolution threshold of the instrument. According to the DLS data, therefore, aggregates of **A-1**, **A-2**, and **A-3,** if they form at all, must be micelle size or smaller

**Fourier Transform Pulsed-Gradient Spin−Echo NMR.** Fourier transform pulsed-gradient spin−echo NMR (FT-PGSE) was used to obtain the diffusion rates of the asterisks in water.[18,19] If micelle-sized aggregates are formed, then past experience would have us expect the diffusion rates to decrease 3−4-fold.[20] Measurements were performed using Shigami special precision NMR tubes and a 600 MHz INOVA 600 spectrometer: 0.l0 M NaOD/$D_2O$, 0.3−30 mM **A-l**, and 0.3−10 mM **A-2**. (Unfortunately, broadened signals for **A-3** are too weak to allow FT PGSE NMR studies on our largest asterisk.)

Results of the study are shown in Figure 1. The diffusion rates for **A-l** and **A-2** are seen not to differ substantially, nor is there the marked concentration dependence that one generally finds when a conventional surfactant passes through its critical micelle concentration. Once again, no aggregation of the asterisks in water is indicated.

The diffusion data allowed the calculation of the particle diameters from the Stokes−Einstein equation and the diffusion coefficient $D$ (cm$^2$/s) according to $D = k_B T/3\pi\eta d$, where $k_B$ is the Boltzmann constant (erg/K), $T$ is the temperature (K), $\eta$ is the viscosity (P) (assumed to be that of water), and $d$ is the diameter of the particle (cm). Both **A-1** and **A-2** asterisks have apparent hydrodynamic diameters of 2.3 ± 0.1 nm, a value consistent with the monomolecular state. It is surprising that **A-2** manifests the same size as **A-1,** an observation whose origins may be related to folding of the asterisks in water (to minimize hydrocarbon−water contact) and to the inherent assumptions of the Stokes−Einstein equation (i.e. that the

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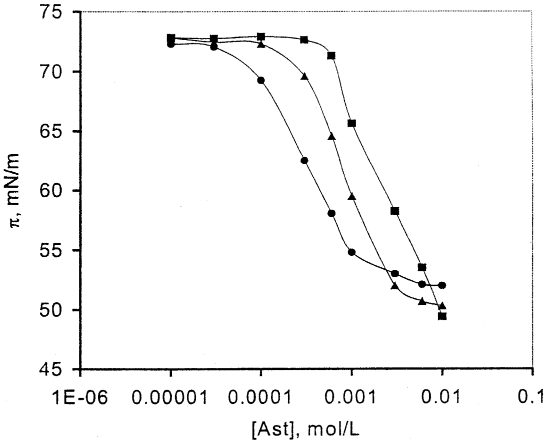

***Figure 2.*** Surface tension/concentration plots for **A-1** (■), **A-2** (▲), and **A-3** (●). The lines are eye guides.

molecules are spherical). In a subsequent section, X-ray data will disclose more detailed information on asterisk conformers.

**Surface Tensiometry.** The ability to decrease the surface tension of water ranks as one of the most commonly reported properties of amphiphilic substances.[21] A conventional surfactant adsorbs at the air/water interface with the polar headgroup embedded in the water and the hydrophobic tail projecting into the air. It was unclear how the asterisks would behave since they have six ion-terminated arms radially disposed about a central benzene ring. Surface tension measurements were made with a Kibron $\mu$Trough (0.l mM KOH in Milli-Q water; 25.0 °C; 300 $\mu$L samples; three to four repeats per concentration ranging from 0.01 to 10 mM), and the data are given in Figure 2. It is seen that all three asterisks are mildly surface-active, reducing the surface tension from 72 to near 50 mN/m (or dyn/cm) as compared to 30−40 mN/m for many conventional surfactants.[21] The decline in surface tension occurs over a l0-fold concentration range (as opposed to more precipitous declines with most conventional surfactants), suggesting that adsorption at the air/water interface is unaccompanied by discrete micelle formation. When the plots in Figure 2 level off, the air/water interface is saturated with loosely packed asterisks having, in all likelihood, the central core and an unknown portion of the six arms exposed to the air. As would be expected, saturation is reached first with **A-3**, then with **A-2**, and last with **A-l**.

**Solubilization.** Most amphiphilic molecules self-assemble in water into micelles, vesicles, etc., which are capable of solubilizing hydrophobic molecules in water. The fact that the asterisks fail to aggregate allowed a welcome opportunity to study hydrophobic association to a *single* multiionic molecule unburdened by aggregation equilibria. Since **A-3**, for example, possesses 19 aromatic rings, there would seem to be ample "exposed" surface area for the asterisk to hydrophobically bind, and therefore to solubilize, nonpolar compounds that would not ordinarily dissolve in water. The question, in other words, was whether the asterisks would behave like "unimolecular micelles".

Mesitylene (1,3,5-trimethylbenzene) was selected as a test compound for the following reasons: (a) It is a liquid with a low intrinsic solubility in water of about 0.4 mM (much lower than that of benzene or toluene). (b) Mesitylene, having nine identical methyl protons, can be analyzed by NMR with relatively high sensitivity. (c) A high boiling point (162−164 °C) minimizes errors caused by volatilization. Thus, 1 mL of asterisk solution (0.3−3 mM in 0.l M NaOD/D$_2$O) was stirred with excess (100 $\mu$L) mesitylene for 30 min after which the layers were allowed to separate overnight. The aqueous layers were then analyzed by proton NMR using a known quantity of methanol as an internal reference to quantify the mesitylene content.

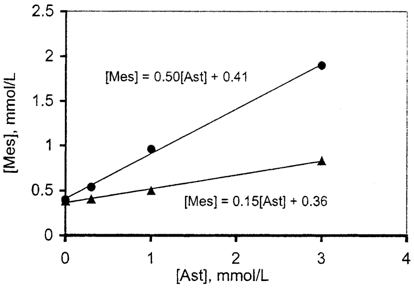

***Figure 3.*** Dependence of mesitylene solubility on **A-2** (▲) and on **A-3** (●) concentrations. Graphs represent averaged data from three consecutive series of experiments.

An NMR spectrum of the water layer without asterisk showed two mesitylene methyl signals: (a) a 1.76 ppm peak corresponding to tiny amounts of suspended mesitylene which persisted despite the long period allowed for phase separation; (b) a 2.23 ppm peak corresponding to dissolved (aqueous) mesitylene. As **A-2** or **A-3** was added to the water, the 2.23 ppm peak gradually shifted to 1.96 or 2.09 ppm, respectively. Presumably, bound mesitylene "senses" the presence of both water and aromatic host. Although **A-l** has no solubilization capacity, **A-2** and **A-3** can solubilize 0.15 and 0.50 mesitylene molecules/(asterisk molecule) (Figure 3). Stated in another way, at 3 mM **A-3** the mesitylene solubility in water increases almost 5-fold over and above its "natural" value.

How does the solubilization capacity of the asterisks compare with that of micelles? Answering this question is complicated by a sensitivity of micellar solublization to surfactant and additive structure. Typically, ca. 20−40 ethylbenzene molecules, for example, are soliblized per 100-molecule micelle composed of 12-carbon ionic surfactants.[22] On a per-surfactant-molecule basis, therefore, **A-3** is equivalent to a conventional surfactant. If consideration is given to the high molecular weight of **A-3,** and to its restricted solubility as a monomer, then **A-3**'s overall solubilization capacity is not competitive with micelles. Asterisks are thus best viewed as water-soluble compounds that weakly complex aromatic guests.

**Cooperative Effects.** The question arose whether the anionic asterisks, might "seed" micelle formation of a cationic surfactant (e.g. *n*-dodecyltrimethylammonium bromide or DTAB). The study of mixed micelles, a venerable area of colloid chemistry,[23] has shown large reductions in critical micelle concentration (CMC) when two surfactants of opposite charge are mixed.[24] Such systems are different, however, from an asterisk/DTAB

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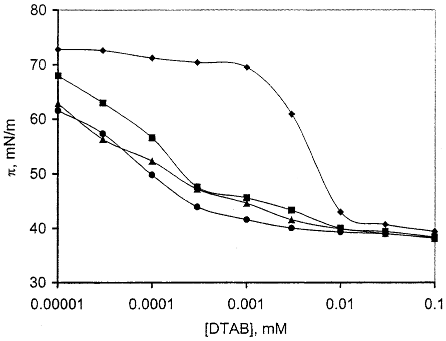

***Figure 4.*** Surface tension/concentration dependence for DTAB in 0.5 mM NaOH/Milli-Q water (♦) and in the same solvent in the presence of 1.0 × $10^{-6}$ mol/L of asterisks: **A-1** (■), **A-2** (▲), and **A-3** (●). The lines are eye guides.

pair where one of the components, namely, the asterisk, is not in and of itself a micelle-forming molecule. Any enhanced assembly of DTAB caused by an asterisk can be attributed to an effect at the molecular level.

As seen in Figure 4, all three asterisks, at a remarkably low concentration of l.0 μM in 0.5 mM NaOH, sharply reduce the surface tension of aqueous DTAB solutions below DTAB's CMC of ca. 5 mM. For example, l.0 μM **A-3** causes the surface tension of l mM DTAB to decrease from 70 to 42 mN/m. Clearly, 1 asterisk molecule/(1000 DTAB molecules) efficiently promotes DTAB adsorption at, and saturation of, the air/water interface. Although the data do not supply proof that assembly into micelles is likewise favored by the asterisks, it seems likely that DTAB micellization should respond similarly to the interfacial assembly with regard to the presence of these additives. Micelle-like NMR peak-broadening of DTAB below its CMC (along with reduced diffusion rates measured by PGSE NMR) brought on by micromolar levels of **A-l** (data not shown) supports this speculation.

**Metal Binding.** Addition of $Hg^{2+}$, an ion with a known affinity for sulfur, to aqueous solutions of **A-1** caused the solution's yellow color to intensify. (Corresponding experiments with **A-2** and **A-3** could not be carried out because $Hg^{2+}$ precipitates in the basic solutions necessary to dissolve these asterisks.) UV−vis spectrophotometry showed absorbance increases at wavelengths above 350 nm. Eight wavelengths between 400 and 490 nm yielded consistent Job plots[25] with maxima at 0.5 (not shown), indicative of a 1:1 complex. No further metal binding studies were pursued.

**X-ray Studies.** Compounds **A-l**, **A-2**, and **A-3** are all amorphous solids that decompose above 160 °C. The corresponding generation-l hexaphenol could, however, be completely acetylated to give a high-melting (199−202 °C) solid from which X-ray-quality crystals were obtained by crystallization (chloroform/hexane). Figure 5 shows the X-ray structure. As was previously reported for other asterisks, the arms on the central benzene ring alternate in a 1,3,5-up/2,4,6-down (or *ababab*) arrangement.[14,15] In contrast, the generation-l hexabenzoate has a 1,2,5 up/3,4,6-down (or *aabbab*) configuration (Figure 6). The majority of known hexasubstituted benzenes assume *ababab* conformations, although two other instances of *aabbab* variations (with six β-naphthylthio or six 2-methylphenylthio groups) have been reported.[14,15] Since the hexaacetate and hexabenzoate differ only in their terminal para-substituents, space-filling requirements, as opposed to intramolecular repulsions near the benzene core, seem to determine the solid-state conformations. Neither the hexaacetate nor the hexabenzoate crystal lattices show lattice porosity favorable to formation of inclusion compounds as found with certain other hexasubstituted benzenes.[26] One speculates that the *aabbab* conformation would be favored over the *ababab* conformation in water due to the former's greater intramolecular contact among the apolar arms, but there is no evidence supporting this contention.

**Molecular Scrolls.** Upon carrying out the phosphorylation given in eq 4, we observed that long needles of **A-l** precipitate from the acidic solution. Optical and electron microscopy revealed that these fibers (several millimeters long and up to 0.5 mm wide) had a scroll-like appearance (Figure 7). Molecular scrolls have been reported previously,[27] but the ones in Figure 7 are particularly beautiful. When the scrolls were washed with acetone, they began to unroll and wrinkle (Figure 8). Scrolling demonstrates the strong tendency of **A-1** to self-assemble into uniform molecular sheets that are ca. 4 μm thick. It is possible that the molecules fill space (like hexagonal kitchen tile) with intermolecular hydrogen-bonding among the phosphomonoesters serving as an adhesive force at the six "corners".

## Discussion

There are but few instances in which the colloidal properties of amphiphilic aromatics in water have been defined. Compared to the aliphatic chains of conventional surfactants, aromatic rings possess a reduced hydrophobicity[28] and a greater rigidity, both of which disfavor the assembly process in water. Micelles, after all, are a disordered array of molecules where the hydrocarbon chains prefer to twist and turn in a tangled brush-heap not unlike that found in hydrocarbon solvents themselves.[29] Even a single cis double bond in a surfactant's chain elevates the CMC by 3−4-fold because the permanent chain bend reduces the ability to pack freely into a disorganized, multimolecular assembly.[30] A benzene ring within an aliphatic chain does lower the CMC but only by an amount equivalent to that of 3.5 methylenes.[31] Moreover, since aromatics do not "freeze" water molecules as effectively as do aliphatic chains,[32] solvent release upon aggregation (with its attendant entropic benefits) is less capable of counteracting the concurrent electrostatic repulsion among the assembled headgroups. In summary, packing difficulties and an impaired hydrophobicity of aromatic rings explain a key feature of water-soluble asterisks: Asterisks prefer the monomeric state in water despite having as many as 19 aromatic rings. UV−Vis, DSC, DLS, FT-PGSE NMR, and tensiometry affirm this conclusion.

Several years ago we explored the ability of an amphiphilic polycyclic aromatic, namely, 1-pyrenesulfonic acid, to self-assemble in water.[32] 1-Pyrenesulfonic acid is a 16-carbon hydrocarbon with four coplanar aromatic rings. Although the compound has many fewer aromatic rings than the asterisks, it

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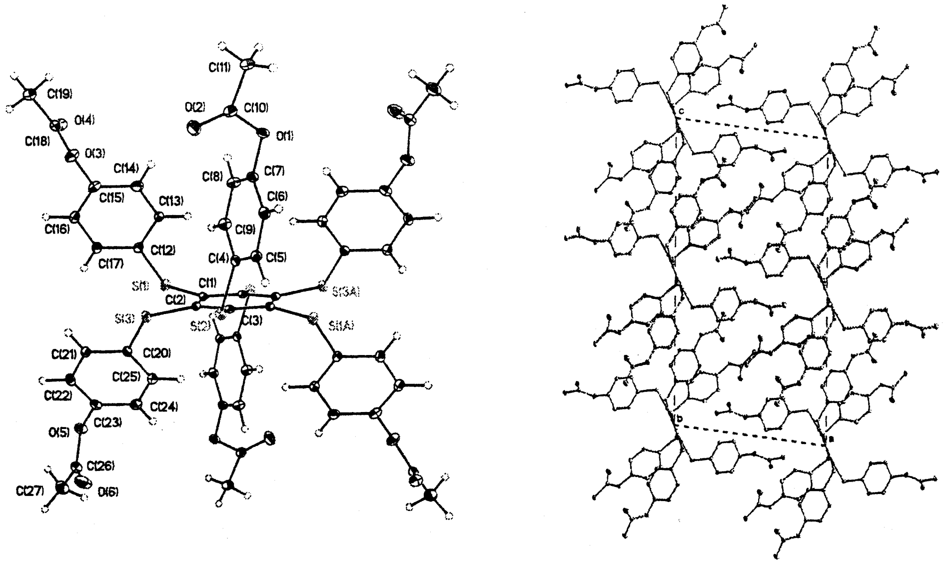

***Figure 5.*** X-ray picture of the first-generation asterisk terminating at each arm with an acetoxy group and sharing an *ababab* configuration.

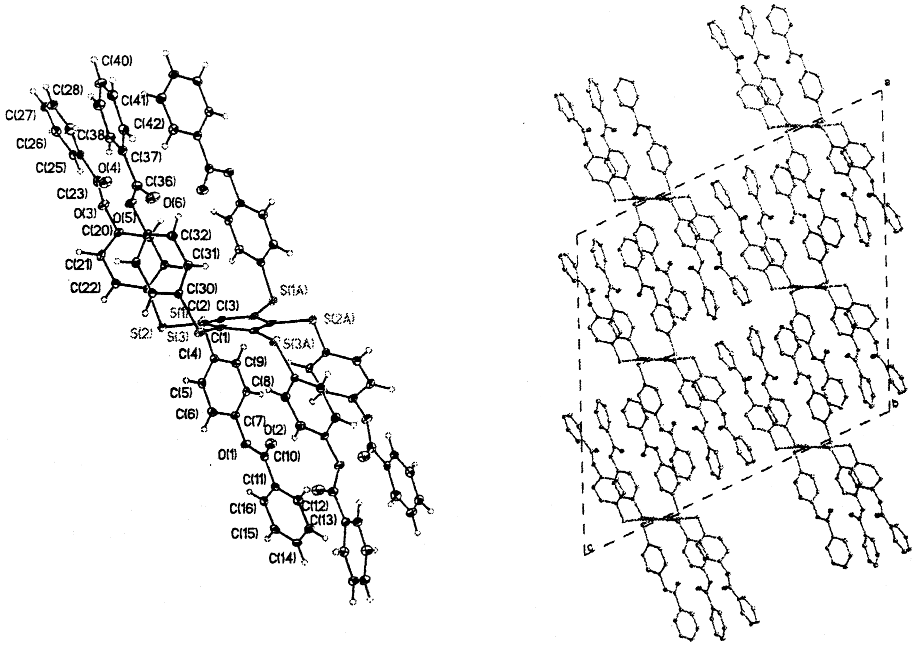

***Figure 6.*** X-ray picture of the first-generation asterisk terminating at each arm with a benzoyloxy group and sharing an *aabbab* configuration.

is flat and, it would seem, well set up for hydrophobically driven $\pi-\pi$ stacking. In actual fact, 1-pyrenesulfonic acid merely dimerizes in water. Even at 50 mM (a concentration 100-fold greater than the CMC of sodium hexadecyl sulfate), dimerization of 1-pyrenesulfonic acid is only 50% complete. It is clear that aromatic/aromatic association in water is far less efficient than aliphatic/aliphatic association. But why, one may ask, does simple pyrene dimerization overshadow its multimolecular stacking? As seen in the next paragraph, an attempt to address this question discloses some important properties of aromatics relevant to the asterisks.

Monte Carlo studies of benzene in water suggest that water molecules "close to the benzene molecule show only small deviations from what is found in pure water".[33] Expressed in another way: Water structure is only modestly perturbed by the presence of a benzene molecule. Theory also tells us that the first hydration shell of benzene consists of 23 water molecules.[34] Of these, 21 comprise a hydrophobic "in-plane" hydration. The other two water molecules solvate the benzene on either side of the ring at the center via weak hydrogen-bonding between the water protons and the $\pi$-cloud. Computer simulations were also carried out on a benzene dimer embedded in 510 water molecules.[35] Two distinct energy minima were detected. One of them corresponds to a contact interaction in which two benzenes reside back-to-back only 4.3 Å apart. The other represents a solvent-separated dimer with a 5.l Å separation. Although six water molecules are situated at the edges of the complex, no water lies directly between the two benzene rings. In summary, mildly structured water gathers primarily at

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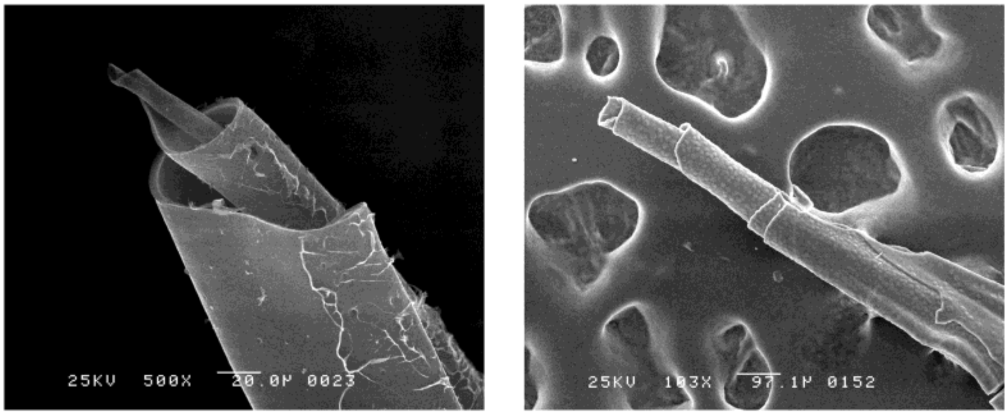

***Figure 7.*** SEM images of **A-1** scrolls that precipitate from acidic water. Bars = 20 $\mu$m (left) and 97 $\mu$m (right).

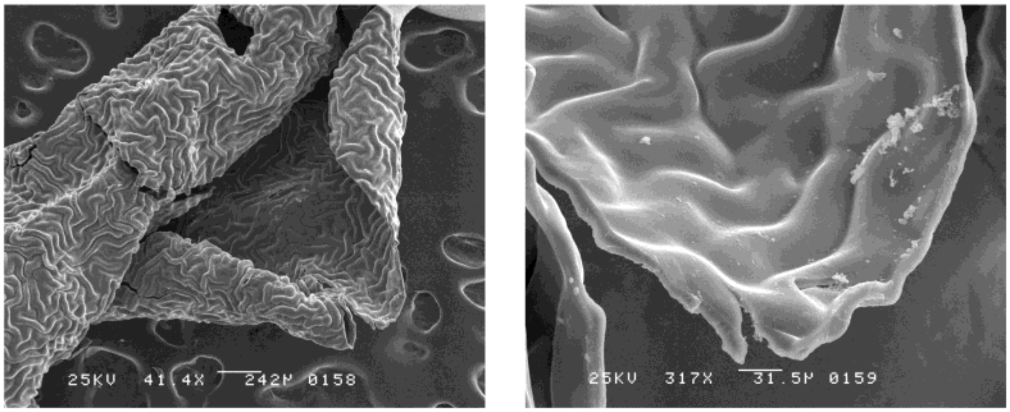

***Figure 8.*** SEM images of **A-1** scrolls washed with water and dried in air. Bars = 242 $\mu$m (left) and 31.5 $\mu$m (right).

the periphery of the benzene rings rather than above or below the rings where the actual hydrocarbon–hydrocarbon contact takes place. One can only speculate that multimolecular stacking is not observed because this creates internal benzene rings whose edges, where most of the hydration of monomeric aromatics normally occurs, are not optimally solvated. The entropic benefits of releasing weakly bound water during stacking are seemingly insufficient to compensate for a sterically impaired “edge” solvation.

The upshot of the pyrene behavior and the theoretical computations is that the asterisks, even **A-3** with its six arms containing three aromatic rings each, would not necessarily be expected to self-assemble in water. Strong solvation of the ionic groups in water, coupled to weak solvation of the aromatic rings, may succeed in dragging these molecules into water, but there the asterisks remain—unassembled—until the solubility limit is reached. The principles involved here are useful because they reveal a strategy for constructing enzyme models that are at once (a) water soluble, (b) possessive of hydrophobic sites that can bind substrates, and (c) free from complicating self-assembly equilibria. The strategy, of course, is to construct the models from solubilized aromatics bearing catalytic groups. By employing aromatic instead of aliphatic binding sites, one sacrifices a degree of hydrophobic substrate association but one gains in ensuring the monomeric state of the enzyme model.

The asterisks display two properties of particular interest: They solubilize mesitylene in water, and they trigger micelle formation of a conventional surfactant. With regard to solubilization, it was pointed out that **A-3** can solubilize up to 0.5 molecule of mesitylene/(asterisk molecule) (Figure 3). This is more-or-less equivalent to the capabilities of a micellized conventional surfactant. But when consideration is given to the molecular weight of **A-3**, it is seen that in fact **A-3** is not a particular efficient solubilizer. Perhaps the same solvation factors that discourage aggregation of **A-3** also discourage binding of small aromatics. A much bigger effect was observed with asterisks “seeding” the assembly of DTAB, a conventional cationic surfactant. For example, only 1.0 $\mu$M of **A-l**, **A-2**, or **A-3** (it does not seem to make much difference which) causes a massive decrease of the surface tension from 70 to 41–45 mN/m in the presence of 1.0 mM “submicellar” DTAB (Figure 4). Apparently, a single asterisk molecule can provide a nucleus around which a surfactant of opposite charge can self-assemble. Although the efficiency by which the asterisks accomplish this feat is remarkable, the phenomenon itself is not new. For example, it is known that low concentrations of dyes can sometimes lower the CMC of surfactants.[36] Micelle seeding is a worthy of a more systematic investigation.

Finally, we should mention the solid-state properties of generation-l asterisks. The conformation in the crystal lattice (i.e. the relative disposition of the six arms) is highly dependent upon a substituent (acetyl or benzoyl) at the terminal carbon of the arms (Figures 5 and 6). Difficult-to-predict packing factors, as opposed to intramolecular steric effects near the core, must control the configuration. Compound **A-l** itself precipitates from water as uniform sheets that coil into scrolls (Figure 7). Although the molecular basis of this supramolecular assembly is not yet understood, its great beauty should be appreciated. And one

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(36) Mukerjee, P.; Mysels, K. J. *J. Am. Chem. Soc.* **1955**, *77*, 2937.

wonders if the phenomenon is more general—if other multinuclear aromatics can self-assemble into sheets and scrolls when hydrogen-bonding units are suitably positioned at critical contact points.

## Experimental Section

**Physical Methods.** Certain details and references pertaining to the physical methods are given in the text; additional details are available from the Supporting Information.

**Synthesis.** Yields, references, etc., pertaining to the procedures for synthesizing the asterisk arms (eqs 1 and 2; Scheme 2) are given in the text. Additional details are available from the Supporting Information. Procedures for assembling the asterisks themselves are given below, where **A**-*n*−X refers to an asterisk of generation ***n*** and terminal group X.

**A-*n*−O*t*Bu.** An arylthiophenol (7.2 mmol) and hexachlorobenzene (2.85 g, 1 mmol) were dissolved in 1,3-dimethyl-2-imidazolidinone (25 mL), and the solution was degassed with argon for 1 h and cooled in an ice bath after which sodium hydride (0.35 g, 14.4 mmol) was added with vigorous stirring. Hydrogen began to evolve, the mixture became a yellowish-brown, and a bright yellow solid began to precipitate. The mixture was allowed to warm to room temperature and stirred for 12 (generation-l), 24 (generation-2), or 48 h (generation-3). The suspension was then cooled to 0 °C, 50 mL of ice-cold 1 M HCl was added, and the resulting mixture was poured in 200 mL of distilled water. Precipitate was removed by filtration, washed with water several times, and dissolved in chloroform. The chloroform solution was shaken with water and brine and then dried over sodium sulfate. Removal of solvent on a rotary evaporator produced a bright yellow solid that was purified by column chromatography on silica (96:4 $CHCl_3$/EtOAc; benzene/EtOAc with 0−2% gradient; and hexane/benzene with 66−100% gradient plus benzene/EtOAc with 0−2% gradient for generations-1, -2, and -3, respectively). Yields of purified material ranged from 74 to 84%. Products from all three generations gave a satisfactory $^1$H and $^{13}$C NMR, FAB HRMS, and C,H,S elemental analysis.

**A-*n*−OH.** A *tert*-butylated asterisk derivative (1 mmol) was dissolved in 20 mL of dichloromethane, degassed for 1 h with argon, and mixed with 20 mL of trifluoracetic acid. The solution was stirred for 1 h and then evaporated to dryness to give a yellow solid residue that was dried under reduced pressure. After the product was dissolved in ethyl ether, the ether was washed with water, dried over sodium sulfate, and removed. The resulting solid was chromatographed on silica (ether/methanol with 0−6% gradient; ether/methanol with 0−4% gradient; ether/methanol with 0−4% gradient for generations-1, -2, and -3, respectively. Yields of purified material ranged from 74 to 93%. All three products gave the expected $^1$H and $^{13}$ C NMR and FAB HRMS (for generations-1 and -2) or FAB MS (for generation-3). C,H,S elemental analyses agreed only to within 0.7 absolute % due to the strong adhesion to ether that even vacuum pumping could not fully remove. An X-ray structure of **A-1**−OH**,** and its acetyl and benzoyl derivatives, affirmed the structure assignment.

**Compounds A-l, A-2, and A-3.** A solution of **A-*n***−OH (0.41 mmol) in pyridine (5 mL) was cooled in an ice bath and mixed with phosphorus oxychloride (0.55 mL, 6 mmol). Stirring at 0 °C was continued for 2 h, after which the solution was allowed to warm slowly to room temperature and diluted with 25 mL of dry ether. The resulting precipitate was removed by filtration, leaving a filtrate that was taken to dryness under reduced pressure. After 40 mL of water was added to the solid, the mixture was stirred for 1 h. During that period, a yellow syrup on the walls dissolved (creating a viscous turbid solution), and a yellow material began to precipitate. Addition of 5−10 mL of concentrated HCl caused further precipitation of a solid that was removed by filtration and dried under reduced pressure over phosphorus pentoxide. Yields ranged from 78 to 82%. Suitable $^1$H and $^{13}$ C spectra were obtained, although the presence of bound water complicated the C,H,S elemental analyses. Purity of the compounds was affirmed by single $^{31}$P NMR signals (DMSO-$d_6$) of −3.49, −3.70, and −3.35 ppm for **A-1**, **A-2**, and **A-3,** respectively. Structural identity was affirmed by mass spectral data in two cases. FAB HRMS. Calcd for **A-1:** 1302.8425. Obsd: 1302.8400. FAB MS. Calcd for **A-2:** 1949.8549. Obsd: 1949.9.

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**Supporting Information Available:** Experimental details, analytical data for all new compounds, and crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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