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A noncovalent, fluoroalkyl coating monomer for phosphonate-covered nanoparticles

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To Paul Wender, who taught us as undergraduate (AYC) and graduate (TJW) students to 'suspend the constraints of reality'

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ABSTRACT

Gadolinium-containing phosphonate-coated gold nanoparticles were prepared and then non-covalently coated with an amphiphilic fluorous monomer. The monomer spontaneously self-assembles into a non-covalent monolayer shell around the particle. The binding of the shell utilizes a guanidinium–phosphonate interaction analogous to the one exploited by the Wender molecular transporter system. Particle–shell binding was characterized by a 27% decrease in ^{19}F T_1 of the fluorous shell upon exposure to the paramagnetic gadolinium in the particle and a corresponding increase in hydrodynamic diameter from 3 nm to 4 nm. Interestingly, a much smaller modulation of ^{19}F T_1 is observed when the shell monomer is treated with a phosphonate-free particle. By contrast, the phosphonate-free particle is a much more relaxive ^{1}H T_1 agent for water. Together, these observations show that the fluoroalkylguanidinium shell binds selectively to the phosphonate-covered particle. The system's relaxivity and selectivity give it potential for use in ^{19}F based nanotheranostic agents.

1. Introduction

The development of 'smart' nanoparticulate medicinal entities is an emerging area at the interface of chemical and clinical sciences. For example, novel drug delivery systems and imaging agents based on drug-loaded polymers or nanoparticles have appeared recently,[1] and are making way into the clinic.[2] Nanotechnology further offers opportunities to design combined therapeutic plus diagnostic agents, or 'theranostic' systems; examples of such include paramagnetic nanoparticles for MRI imaging,[3] ^{64}Cu-loaded liposomes for PET imaging,[4] and others.[5]

One key factor to controlling the in vivo behavior of these systems is the ability to control their surface properties.[6] Along these lines, we are pursuing the development of monomeric organic compounds that engage in predictable self-assembly around nanoparticulate molecular probes and that have the ability to control the bioactivity of the former by modifying their size, surface, and access to the external aqueous milieu.[7]

We present here a general strategy for applying a (poly)ethyleneglycol (PEG)-terminated fluoroalkyl coating to a phosphonate-covered nanoparticle agent and illustrate the use of bioorthogonal ^{19}F magnetic resonance relaxivity to track the behavior of the coating monomer as it associates with the particle. The coating monomer (**1**, Fig. 1) exploits a guanidinium head group, which can interact with particle surface phosphonate groups through a double hydrogen bonding system analogous to the one used by the Wender molecular transporter system for its initial adhesion to cell surfaces.[8] Particles utilizing such core–shell interactions have various clinical applications, such as vectors for gene delivery, as investigated in the Wender lab.[9] Monomer **1** further features a fluoroalkane region that enables the self-assembly of a fluorous, Teflon-like layer that can limit the particle's exposure to its aqueous surroundings.

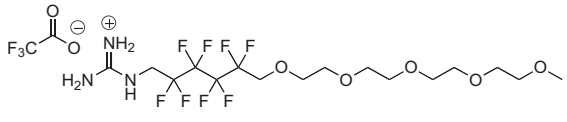

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Fig. 1. Structure of monomer **1**.

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We have previously characterized the binding of monomer **1** with small-molecule phosphonates,[10] and we hypothesize that a particle with a phosphonate surface can utilize the same interaction(s) to bind species **1**, thus enabling the self-assembly of a monolayer coating around a particle (Fig. 2). Incorporating a paramagnetic species into such a particle can thus enable the use of monomer **1** as a ^{19}F MRI contrast system for an appropriately filtered, T_1-weighted image plane. Although ^{19}F MRI-based nanotheranostic technology is not as well developed as the analogous ^{1}H MRI based systems, ^{19}F MRI based systems are beginning to emerge,[11,12] and offer important bioorthogonality unavailable to other imaging modalities.[13] We show here potential utility of monomer **1** as a flexible tool for the installation of ^{19}F groups on the surface of a phosphonate-covered nanoparticle and illustrate the corresponding modulation in ^{19}F T_1 upon particle-**1** binding. We further illustrate **1**'s selectivity for a phosphonate surface over a phosphonate free particle and illustrate that the coverage provided by **1** corresponds to a monolayer in aqueous solution.

2.2. NMR properties of monomer 1

Shell monomer **1** exhibits 3 different peaks in the ^{19}F NMR spectrum, which can be rigorously assigned by a combination of ^{19}F–^{13}C HMBC and ^{13}C–^{1}H HSQC NMR spectra (see Supporting information). The most downfield signal (−117.9 ppm, peak A) corresponds to the fluorine CF_2 group nearest the guanidine of **1**. An upfield (−123.5 ppm, peak C) multiplet corresponds to the two central CF_2 groups, and the middle peak of the ^{19}F spectrum (−119.8 ppm, peak B) corresponds to the fluorines closest to the PEG tail: see Supporting information regarding the ^{19}F signal assignments. The T_1 relaxation times were measured in 25 mM pH=7.6 TRIS–HCl buffer and were found to be 457(8) ms, 436(7) ms, and 497(7) ms for peaks A, B, and C, respectively. These data are summarized in Fig. 3.

2.3. Design and synthesis of paramagnetic nanoparticles

Our design for a template nanoparticle is based on a very simple gold-centered structure, which is decorated with a periphery of

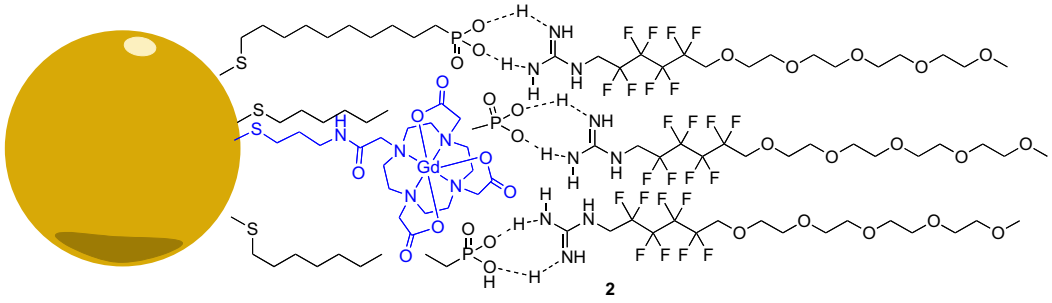
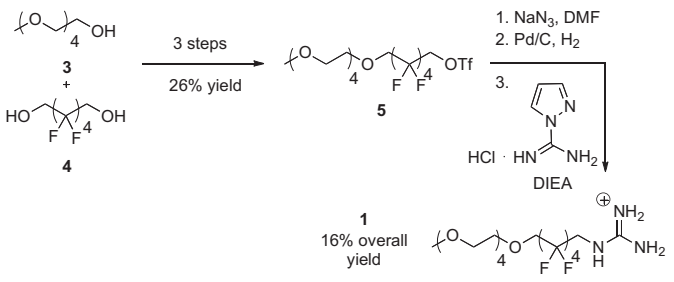


Fig. 2. Hypothetical interactions between phosphonate core and guanidine shell to yield shell coated phosphonate particle **2**.

2. Results and discussion

2.1. Design and synthesis of shell monomer 1

Shell monomer **1** features a guanidinium head group, which is designed to participate in hydrogen bonding with phosphonates on the periphery of a particle. This is attached to a fluorous phase group[14] that prevents intercalation of the shell in to the interior of the particle and limits the particle's exposure to its surroundings. Appropriate fluorous starting materials for this design are readily available side products from Teflon synthesis.[15] A hydrophilic PEG chain is then appended as a solubilizing group. Scheme 1 summarizes the synthesis of monomer **1**, which we have previously reported.[10] This route relies on the intermediacy of a bench top-stable alkyl triflate (**5**), which is a versatile starting material for fluoroalkyl amines.



Scheme 1. Synthesis of monomer **1**.

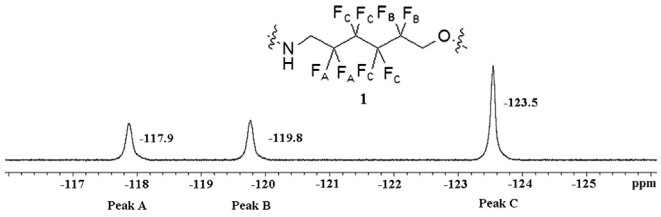


Fig. 3. NMR properties of **1**.

thiol-terminated phosphonic acid surfactants (Fig. 4). The selection of this construction is based on its popularity in several scaffolds currently being developed for drug delivery and clinical imaging applications.[16] It enables concise size control and flexibility of surface functionalization.[17,18] In this section we present synthetic routes for paramagnetic particles functionalized with both [Gd(DOTA)] and phosphonate peripheries.

A 1.5 nm phosphine-stabilized gold core (**10**) was first synthesized based on previously reported conditions.[19] Thiols **6** and **7** were assembled onto the gold core via interfacial ligand exchange in a biphasic water/dichloromethane system (Scheme 2A).[20] The resulting particles form visible aggregates at neutral pH, but are stable in a pH=7.6 TRIS–HCl buffer. Monomer **1** spontaneously self assembles onto particles **8** immediately upon introduction to an aqueous solution of **8** to yield hybrid gadolinium-phosphonate particles **2**.

Phosphonate-free particles **9** are apparently unstable to aggregation when prepared according to the procedure above, but in situ deprotection of trityl-protected thiol **11** followed by treatment with $HAuCl_4$ can be used to generate these particles (Scheme 2B).[21] This