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Understanding the Colloidal Stability of Nanoparticle-Ligand Complexes: Design, Synthesis, and Structure-Function Relationship Studies of Amphiphilic Small-Molecule Ligands

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Abstract: For effective application of nanoparticles, their amenability to in-solution processing must be addressed, and stable, homogeneous solvent conditions are required. Although organic ligands have been used as surface-modifying reagents for nanoparticles to increase their colloidal stability and homogeneity in solution, the structure-function relationships of nanoparticle-ligand complexes remain elusive and controversial. Herein, a series of novel amphiphilic small-molecule ligands was designed, synthesized, and applied as surface-modifying reagents for aqueous, transparent TiO₂ and ZrO₂ nanoparticles. The colloidal stability of the resulting nanoparticle-ligand complexes was found to depend not only on the chain length but also on the relative balance between hydrophobicity and hydrophilicity. The structure of the ligands can be fine-tuned to achieve "flexible colloidal stability," significantly increasing complex stability in a variety of organic solvents.

Introduction

Over the past decade, nanotechnology has grown remarkably, such that it now accounts for a substantial fraction of current research in both academic and industrial fields. Nanoparticles rank among one of the most important platforms in the repertoire of technologically useful materials due to their unique electrical, magnetic, and optical physicochemical characteristics, which would be difficult to replicate in other materials because of the extremely high specific surface area.1 Extensive efforts to produce nanoparticles of well-defined size and morphology have led to the development of important classes of functional materials and devices.² For such applications to be successful, the amenability of nanoparticles to in-solution processing must be addressed, and stable, homogeneous solvent conditions are required. Although various organic ligands have been devised and used as surface-modifying reagents to increase the stability and homogeneity of nanoparticles in solution,³ the structurefunction relationships of such nanoparticle-ligand complexes remain elusive and are often controversial.⁴ Traditional colloidal models are often inadequate for predicting the properties of nanoparticles in solution, which have only recently been described both experimentally and theoretically.⁵ Furthermore,

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careful attention must be paid to the choice of ligand, with consideration given to the nanoparticles, solvents, and additives, even if present in small amounts, as slight differences can significantly affect in-solution properties. Although polymeric and/or oligomeric ligands are generally better than small molecules, their modes of action can be complex.

We have been investigating the use of oligomeric, amphiphilic ligands composed of a hydrophobic alkyl chain and a hydrophilic ethylene glycol chain, with a terminal phosphoric acid as an anchoring group (Figure S1).⁶ When the ligand was mixed with aqueous nanoparticles, the resulting nanoparticle-ligand complexes aggregated and could be collected via centrifugation. The recovered complexes exhibited flexible colloidal stability in a variety of organic solvents. Folding of either the alkyl or ethylene glycol chain in respective polar or less-polar solvents could explain the variations in affinity. However, the ligand we have focused on is an oligomeric mixture characterized by high structural variation, including a variety of both alkyl and ethylene glycol chain lengths in combination with phosphoric acid and phosphoric mono- and di-esters (Figure S2). Described herein is the design and synthesis of well-defined novel amphiphilic smallmolecule ligands and the results of structure-function relationship studies.

Results and Discussion

The present work began with the design of amphiphilic smallmolecule ligands via a reliable synthesis route (Scheme 1). In order to avoid generating diastereomers, n-alkyl chains were selected as hydrophobic moieties. As for hydrophilic moieties, although there are several functional group options, for example alcohols, carboxylic acids, and amines, they can also function as potential anchoring groups, thus promoting the formation of undesired complexes. On the other hand, ethylene glycol chains are promising, as they are non-reactive and pH neutral. Due to synthesis concerns, phosphonic acid was chosen as the anchoring group instead of phosphoric acid, which is widely used as an anchoring group for various oxide surfaces.⁷ Based on this design and retrosynthetic approach, the novel amphiphilic small-molecule ligands were synthesized from the corresponding dibromoalkane and oligoethylene glycol monomethyl ether in 3 steps, which included Williamson, Michaelis-Arbuzov, and hydrolysis reactions (Scheme 2; see Supporting Information for synthesis details).

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Scheme 1. Design and Retrosynthetic Approach for Synthesizing Novel Amphiphilic Small-Molecule Ligands.



Scheme 2. Representative Route for the Synthesis of Novel Amphiphilic Small-Molecule Ligands.

Considering that self-assembled organic monolayers have been widely studied using octyl and longer ligands,⁸ octyl-triethylene glycol phosphonic acid (1, **C8:EG3**) was initially synthesized (Figures 1 and 2). When ligand (1) was mixed with aqueous transparent TiO₂ nanoparticles (Figures 3 and S3, 4 nm by DLS), the resulting nanoparticle-ligand (1) complexes aggregated, with the solution assuming a white, cloudy appearance (Figure 4). This could be explained by masking of the surface hydrophilic hydroxyl groups by the phosphonic acid molecules anchored onto the surface of the TiO₂ nanoparticles through covalent bonds,⁹ which decreased the affinity of the TiO₂ nanoparticles for the aqueous solution (Figure 4, <1 equiv.).



Figure 1. Structures of the Novel Amphiphilic Small-Molecule Ligands Examined in this Work.



Figure 2. Representative ¹H-NMR Spectrum of the Novel Amphiphilic Small-Molecule Ligands.







Figure 4. Schematic Illustration and Photographs of the Ligand (1) Anchoring Behavior.

The complexes were collected via centrifugation (Figure S4) and characterized by ¹H-NMR (Figure S5), FT-IR (Figure S6), and elemental analysis. Both NMR and IR spectra showed peaks corresponding to the expected structure, and elemental analyses indicated that the amount of ligand (1) loaded was approximately 4.3 μ mol/m². It should be noted that no

aggregation occurred, and the solution remained transparent when excess ligand (1) was added (Figure 4, >1 equiv.). Formation of a stable bilayer under the condition of excess ligand (1) could possibly have led to the exposure of hydrophilic phosphonic acid molecules, thus increasing the affinity of the complexes for the aqueous solution.

The colloidal stability of the recovered complexes was then investigated by DLS and TEM in methanol as a typical polar solvent and toluene as a typical less-polar solvent, at a concentration of 3.0wt% in each solvent (Figures 5 and S7). While the solution remained transparent for complexes in methanol (Figure S8, 10 nm by DLS), in toluene, the complexes aggregated and the solution assumed a white, cloudy appearance (Figure S8, 53 nm by DLS). Although TEM images were taken under vacuum conditions after evaporating the solvents, they likely reflected the colloidal conditions. Namely, primary particle size was similarly maintained in both solvents; however, larger aggregates were observed in toluene, which was in accordance with the white, cloudy appearance.



Figure 5. Photographs and TEM Images of Solutions of the Nanoparticle-Ligand (1) Complexes at 3.0wt% in Methanol (Left) and Toluene (Right).

Based on these observations, it would be reasonable to conclude that a more hydrophobic ligand would yield complexes with flexible colloidal stability. Therefore, octyl-diethylene glycol phosphonic acid (2, C8:EG2) and octyl-monoethylene glycol phosphonic acid (3, C8:EG1) were synthesized based on the concept of a shortened hydrophilic ethylene glycol chain and were utilized as surface-modifying reagents for aqueous transparent TiO₂ (Figures S9–S12). The amount of each ligand (2, 3) loaded was estimated at 4.6 µmol/m² based on elemental analysis, suggesting that stable monolayers were formed. Although the hydrophobicity was indeed increased for both ligands (2, 3), the colloidal stability of the complexes was not as expected (Figure 6). The nanoparticle-ligand (3) complexes were barely stable in toluene (DLS unmeasurable), whereas the colloidal stability of the nanoparticle-ligand (2) complexes in toluene was even lower. However, both complexes were stable in methanol (Figures S13 and S14; 10 and 5 nm by DLS, respectively). This result clearly indicates that the colloidal stability of the complexes is not directly determined by the hydrophobicity or hydrophilicity of the ligand.





Figure 6. Photographs of Solutions of the Nanoparticle-Ligand (3) Complexes at 3.0wt% in Methanol (Left) and Toluene (Right).

The design was then altered based on the concept of extending the hydrophobic alkyl chain. Thus, decyl-triethylene glycol phosphonic acid (4, C10:EG3) and dodecyl-triethylene glycol phosphonic acid (5, C12:EG3) were synthesized and utilized as surface-modifying reagents for aqueous transparent TiO₂ (Figures S15-S19). The formation of stable monolayers was confirmed based on estimated amounts of ligands (4, 5) loaded (5.0 µmol/m² and 4.6 µmol/m², respectively). To our delight, both ligands (4, 5) yielded complexes exhibiting flexible colloidal stability (Figures 7 and S20), meaning that they were stable in both methanol (Figures S21 and S22; 10 and 9 nm by DLS, respectively) and toluene (Figures S21 and S22; 12 and 14 nm by DLS, respectively). The colloidal stability of the nanoparticleligand (5) complexes was further studied by SAXS in methanol (Figures S23) and toluene (Figure S24) at a 3.0wt% in each solvent. The results were better than expected; the nanoparticleligand (5) complexes were estimated to be 4 nm in both solvents, which agreed well with the primary particle sizes. Taken together, these data indicate that the nanoparticle-ligand (5) complexes are flexibly stable in both polar methanol and less-polar toluene.



Figure 7. Photographs and TEM Images of Solutions of the Nanoparticle-Ligand (5) Complexes at 3.0wt% in Methanol (Left) and Toluene (Right).

The question then arose as to whether the observed flexible colloidal stability of the complexes was simply the result of steric repulsion due to the chain lengths and/or the result of the relative balance between hydrophobicity and hydrophilicity. To obtain further insights into the structure-function relationship, octyl-tetraethylene glycol phosphonic acid (**6**, **C8:EG4**) was then designed and synthesized. As compared with ligands (**4**, **5**), ligand (**6**) had a similar chain length but different hydrophobicity and hydrophilicity. In this case, the addition of ligand (**6**) did not induce any aggregation of the complexes in aqueous solution, and no complexes were recovered by centrifugation (Table 1 and Figures 8 and S25; 12 nm by DLS). Although the possibility

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that ligand (6) was not anchored to the surface of the TiO₂ nanoparticles could not be entirely ruled out, it is much more likely that even a slight difference in the relative balance between hydrophobicity and hydrophilicity has a substantial impact on the colloidal stability of the complexes. The critical micelle concentration (CMC) of ligands (1-6) was also measured to assess the relative balance between hydrophobicity and hydrophilicity (Figures S26-S31). The CMC of ligands (2-5) was estimated to be significantly lower than that of ligand (1), suggesting that ligands (2-5) are more hydrophobic than ligand (1). In particular, the CMC values of ligands (2-4) were very similar, whereas the functions were greatly different. These results clearly indicate that not only the relative balance between hydrophobicity and hydrophilicity but also steric repulsion due to chain length is indeed important for the ligands. By contrast, the CMC of ligand (6) seemed to be very high compared with ligands (4, 5), suggesting that the relative balance between hydrophobicity and hydrophilicity must also be considered in ligand design.

	in MeOH	in Toluene	in H_2O
TiO ₂ -ligand (1) Complexes	10 nm	53 nm	-
TiO ₂ -ligand (2) Complexes	10 nm	-	-
TiO ₂ -ligand (3) Complexes	7 nm	-	-
TiO ₂ -ligand (4) Complexes	10 nm	12 nm	-
TiO ₂ -ligand (5) Complexes	9 nm	14 nm	-
TiO ₂ -ligand (6) Complexes	-	-	12 nm

Table 1. Summary of DLS Data for Nanoparticle-Ligand (1-6) Complexes.



Figure 8. Schematic Illustration and Photographs of Ligand (6) Anchoring Behavior.

The scope and limitations of the flexible colloidal stability were then investigated using various organic solvents and nanoparticle-ligand (5) complexes as a model (Figure 9). To our satisfaction, the complexes gave transparent solutions in a wide range of organic solvents (Figures S32–S37; 9–13 nm by DLS and 3–4 nm by SAXS) in addition to methanol and toluene. In acetonitrile, the complexes aggregated and the solution assumed a white, cloudy appearance (17 nm by DLS), whereas in hexane, the complexes were barely stable (DLS unmeasurable). Although these results might simply suggest that the solvents were too hydrophobic or hydrophilic, it is still possible that the modes of action of the ligands are more complex than we assume.



Figure 9. Photographs of Solutions of Nanoparticle-Ligand (5) Complexes at 3.0wt% in Various Organic Solvents.

To further demonstrate the generality of the novel amphiphilic small-molecule ligand, nanoparticle-ligand complexes were finally prepared using larger-size aqueous transparent TiO₂ nanoparticles (Figure S38; 15 nm by DLS) and ZrO₂ nanoparticles (Figure S39; 4 nm by DLS) with ligand (5) (Figures 10 and S40–S42). The amount of ligand (5) loaded onto each nanoparticle type was estimated at approximately 9.7 and 8.0 μ mol/m², respectively. Gratifyingly, both nanoparticle-ligand (5) complexes exhibited good flexible colloidal stability and assumed a transparent appearance in methanol (Figures 11, 12, and S43–S46; 10 nm by DLS for each ligand).



Figure 10. Photographs and TEM Images of Aqueous Transparent TiO_2 (Above) and ZrO_2 (Below) Nanoparticles (15 nm and 4 nm by DLS, respectively).



Figure 11. Photographs and TEM Images of Solutions of TiO₂ Nanoparticle-Ligand (5) complexes at 3.0wt% in Methanol (Left) and Toluene (Right).



Figure 12. Photographs and TEM Images of Solutions of ZrO₂ Nanoparticle-Ligand (5) complexes at 3.0wt% in Methanol (Left) and Toluene (Right).

Conclusions

In conclusion, we designed a series of novel amphiphilic smallmolecule ligands and established a reliable and effective route for their synthesis. The synthesized ligands were utilized as surface-modifying reagents for aqueous transparent TiO_2 and ZrO_2 nanoparticles. The colloidal stability of the resulting nanoparticle-ligand complexes was investigated by DLS, TEM, and SAXS measurements in methanol as a typical polar solvent and toluene as a typical less-polar solvent. We demonstrated that flexible colloidal stability can be achieved for the complexes by fine-tuning the ligand structure. Both steric repulsion caused by chain length and the relative balance between hydrophobicity and hydrophilicity have a substantial impact on the solubility of the complexes. We believe that the results described herein will prove advantageous, facilitating the design of new ligands and expanding the applications for nanoparticles.

Experimental Section

General Procedure for Williamson Reactions: To a solution of the respective oligoethylene glycol monomethyl ether (15.0 mmol) in THF (40 mL) stirring at r.t., NaH (60% dispersion in paraffin liquid, 900 mg, 22.5 mmol) was added. The resulting reaction mixture was stirred at r.t. for 10 min, and the respective dibromoalkane (22.5 mmol) was then added. The resulting reaction mixture was stirred at r.t. overnight, diluted with MeOH (40 mL), and concentrated in vacuo. Silica gel column chromatography (hexane/EtOAc = 4/1-1/1) gave the corresponding products S1–S6 in 22–54% yield as a pale-yellow oil.

General Procedure for Michaelis-Arbuzov Reactions: The respective substrates **S1–S6** (5.0 mmol) were added to triethyl phosphite (1.73 mL, 10.0 mmol). The resulting reaction mixture was stirred at 140°C for 24 h and concentrated in vacuo. Silica gel column chromatography (EtOAc/MeOH = 20/1) gave the corresponding products **S7–S12** in 74–97% yield as a colorless oil.

General Procedure for Hydrolysis Reactions: To a solution of the respective substrates **S7–S12** (3.0 mmol) in CH_2Cl_2 (30 mL) stirring at r.t., TMSBr (30.0 mmol) was added. The resulting reaction mixture was stirred at r.t. for 24 h, diluted with water (60 mL), and the organic layer was separated. The aqueous layer was saturated with NaCl and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was dried over Na_2SO_4 , filtered, and concentrated in vacuo. Silica gel column chromatography (EtOAc/MeOH = 1/1) gave the corresponding amphiphilic small molecule ligands **1–6** in 42–65% yield as a white solid.

Preparation of TiO₂ Nanoparticle-Ligand Complexes: To a solution of the respective ligands **1–6** (85.9–132 mg, 0.32 mmol, 5.4 µmol/m²) in water (9.0 g) stirring at r.t., aqueous TiO₂ nanoparticles (20wt%, 1.0 g, 295 m²/g) were added. The resulting reaction mixture was stirred at r.t. for 3 h and centrifuged at 30,000 g for 5 min. The recovered precipitate was washed with water and concentrated in vacuo to give the corresponding nanoparticle-ligand complexes as a white powder.

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Keywords: nanoparticle-ligand complex • structure-solubility relationship • amphiphilic small-molecule ligand • flexible solubility • phosphonic acid

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A series of novel amphiphilic small-molecule ligands was designed, synthesized, and applied as surface-modifying reagents for aqueous, transparent TiO_2 and ZrO_2 nanoparticles. The structures of the ligands can be fine-tuned to achieve "flexible colloidal stability," significantly increasing complex stability in a variety of organic solvents.

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