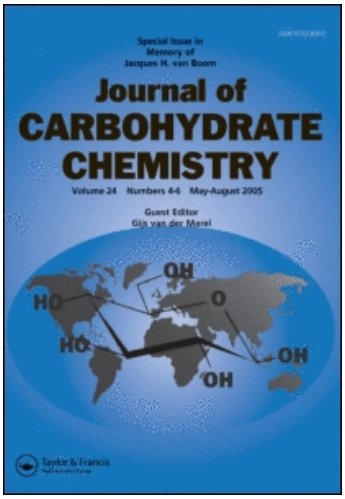


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COMMUNICATION

# SYNTHESIS OF HYDROPHILIC ULTRAFINE NANOPARTICLES COORDINATED WITH CARBOHYDRATE CLUSTER

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## ABSTRACT

A hydrophilic phosphine oxide (1) as a suitable ligand for semiconductor nanoparticles was synthesized. The hydrophilicity of the phosphine oxide was enhanced by introduction of three mannose moieties to the end of the molecule via amide linkages. The ligand 1 was able to coordinate to the CdSe/ZnS nanoparticle making the newly formed hydrophilic complex.

*Key Words*: Nanoparticles; Carbohydrate cluster

Semiconductor nanocrystals and nanoparticles can exhibit unique photonic properties such as the absorption and emission of photons, properties which can be used for medical and pharmaceutical purposes. It is necessary that the nanoparticles be soluble in common solvents for practical applications, and efforts have been made to make

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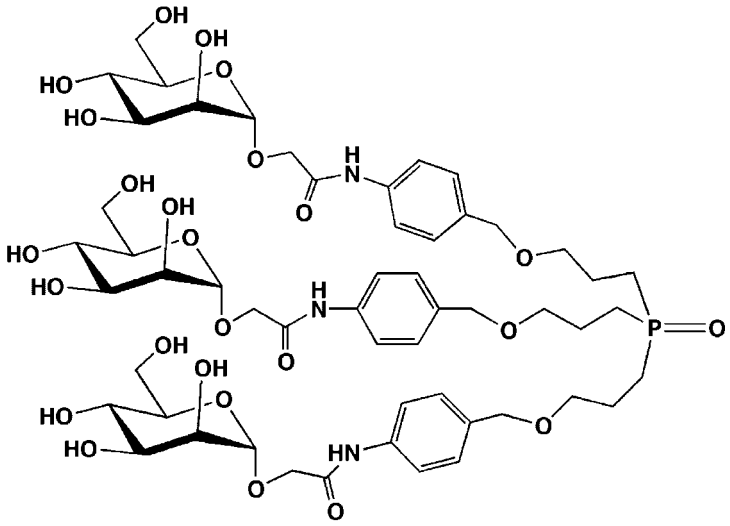

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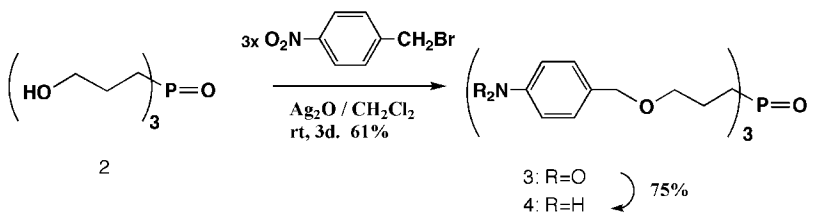
***Figure 1.*** Targeted hydrophilic ligand for the nanoparticles.



these materials suitably soluble. Phosphine oxides can coordinate transition metals and semiconductor nanocrystals. Katari[1] and Dabbousi[2] reported that transition metals combine with trioctylphosphine oxide (TOPO) as a ligand to form semiconductor ultrafine nanoparticles. These nanoparticles are soluble in organic solvents such as chloroform and toluene through coordination with the hydrophobic TOPO, but not soluble in polar solvents such as water and ethanol. We are interested in applying such spectrometrically useful nanoparticles to luminescence diagnostic agents using a hydrophilic or water-soluble ligand instead of TOPO. Bawendi and coworkers have addressed this problem[3] by employing ionic functional groups such as carboxylate salts to solubilize the nanoparticles. However, water solubility of the nanoparticle is significantly affected by the pH and ionic strength of the aqueous solution, and the nanoparticles exhibit no peculiar biological activity such as cell recognition. These facts prompted us to synthesize hydrophilic and stable nanoparticles that can overcome these problems. Thus we designed and synthesized molecule **1** (Figure 1) composed of these hydrophilic α-



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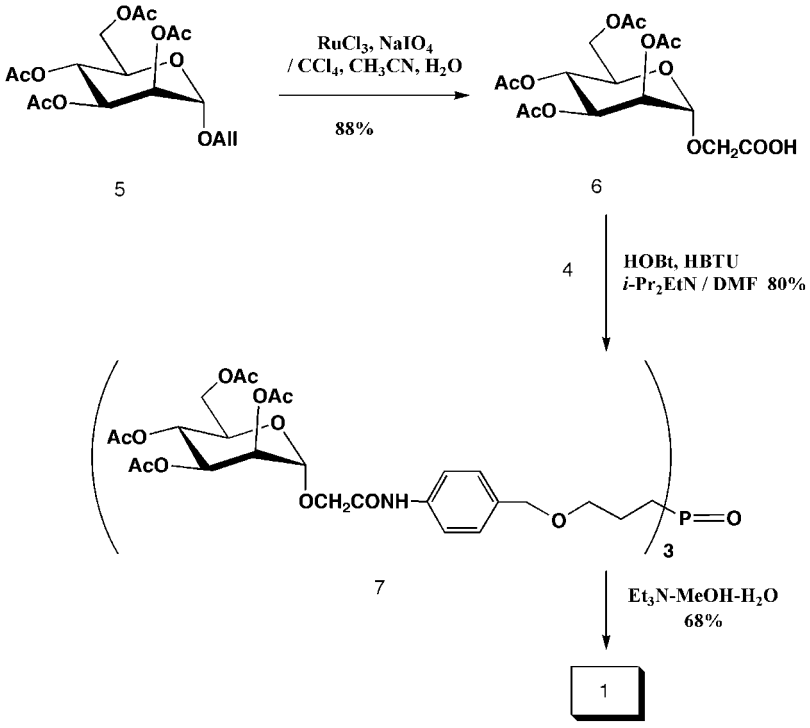
***Scheme 1.*** Synthesis of tris [(4-aminobenzyl) oxypropyl] phosphine oxide (4) from 2.

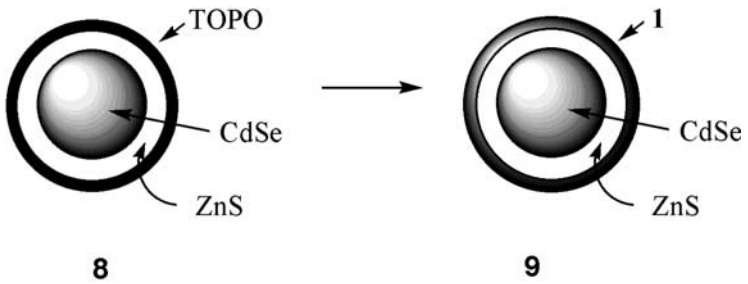
mannopyranosyl moieties linked to phosphine oxide, which can be examined in order to determine the affinity of the mannose units to specific proteins such as Concanavalin A. We demonstrated the increased hydrophilicity through coordination of **1** to the semiconductor nanoparticles.

We selected a commercially available phosphine oxide [**2**, tris(3-hydroxypropyl)phosphine oxide] as the ligand-core possessing a tris(3-hydroxypropyl) group, and added a linker at the end of **2**. As shown in Scheme 1, the 4-nitrobenzylation of **2** was first examined. Although **2** showed a slight or no solubility in common solvents such as $CH_2Cl_2$, THF, benzene and pyridine, a longer reaction time (10 days) using 4-nitrobenzyl bromide and $Ag_2O$ in $CH_2Cl_2$ did produce the desired tris[(4-nitrobenzyl)oxypropyl]phosphine oxide (**3**)[4] in 96% yield. The use of benzene as the solvent produced a similar result, but THF and pyridine did not provide the desired compound. AgOTf was used in $CH_2Cl_2$ in place of $Ag_2O$, although the yield of **3** was low. The AgOTf-THF system,[5] which completely dissolved **2**, did not afford **3** at all. The three nitro groups of **3** were then reduced with zinc powder in aq AcOH to yield **4** in 75%.

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl trichloroacetimidate[6] was converted to the corresponding allyl glycoside (**5**) using TMSOTf as a promoter in 54% yield together with the corresponding β-isomer (23%). The allyl α-glycoside **5** was then oxidized to give the carboxylic acid (**6**) with $RuCl_3$-$NaIO_4$ in $CCl_4$-$CH_3CN$-$H_2O$[7] in 88% yield (Scheme 2). The coupling reaction of **4** and **6** was performed with *O*-benzotriazol-1-yl-*N*, *N*, *N*′, *N*′-tetramethyluronium hexafluorophosphate (HBTU) and *N*-




***Scheme 2.*** Conversion to the targeting compound 1.




***Scheme 3.*** Schematic of the cross sections of the synthesized nanoparticles.

hydroxybenzotriazole (HOBt) in the presence of $i$Pr$_2$EtN in DMF at $-20$°C, and the desired triamide (**7**)[4] was obtained in 67% yield as the key intermediate. The solvolysis of **7** was carried out with $Et_3N$ in aq MeOH and the targeted compound **1**[4] was obtained in 85% yield after purification with HPLC (C18). We assigned the structures of **3**, **7** and **1** from their $^1$H NMR spectra which showed the high symmetries of these tris-substituted phosphine oxides.

We selected the luminescing CdSe/ZnS core/shell type nanoparticle,[2] where the cadmium selenide core crystal is covered with zinc sulfide shell crystals via epitaxial crystal growth on the CdSe core. The CdSe/ZnS was then coordinated with TOPO to give CdSe/ZnS-TOPO (**8**) as reported by Dabbousi et al.[2] Finally, we coordinated the carbohydrate-derived phosphine oxide (**1**) to the nanoparticle (**8**). To the stirred dispersion of **8** in EtOH was added an excess amount of **1** and the mixture was refluxed. A clear EtOH solution was produced indicating that we had obtained the hydrophilic semiconductor nanoparticle (**9**) due to the replacement of TOPO with hydrophilic **1** (Scheme 3).

In summary, we have designed and synthesized a hydrophilic phosphine oxide (**1**) as a suitable ligand for semiconductor nanoparticles. The hydrophilicity of the phosphine oxide was enhanced by introduction of three mannose moieties to the end of the molecule via amide linkages. These results indicate that the ligand **1** was able to coordinate to the CdSe/ZnS nanoparticle making the newly formed complex significantly more hydrophilic than CdSe/ZnS-TOPO.

## REFERENCES

1. Katari, L.E.B.; Colvin, V.L.; Alivisatos, A.P. X-ray photoelectron spectroscopy of CdSe nanocrystals with applications to studies of the nanocrystal surface. J. Phys. Chem. **1994**, *98*, 4109–4117.
2. Dabbousi, B.O.; Rodriguez-Viejo, J.; Mikulec, F.V.; Heine, J.R.; Mattoussi, H.; Ober, R.; Jensen, K.F.; Bawendi, M.G. (CdSe)ZnS core-shell quantum dots: Synthesis and characterization of a size series of highly luminescent nanocrystallites. J. Phys. Chem., B **1997**, *101*, 9463–9475.
3. Inventor: Bawendi, M.G.; Mikulec, F.V.; Sundar, V.C. Biological Applications of Semiconductor Nanocrystals, USA, WO 2000017642 (A2), March 30, 2000.

4. Physical data for key compounds are given below, values of δH were measured at 25°C. Chemical shifts are expressed in ppm downfield from the signal for internal $Me_4Si$ for solutions in $CDCl_3$, and for the solutions in $D_2O$, in ppm downfield from the signal for $Me_4Si$, by reference to internal DHO (4.65). **3**: $\delta_H$ (500 MHz, $CDCl_3$) 8.12 (d, 2Hx3, J = 8.3Hz, Ph), 7.40 (d, 2Hx3, J = 8.8Hz, Ph), 4.53 (s, 2Hx3, PhC$H_2$), 3.52 (m, 2Hx3, $OCH_2$), 1.92 – 1.74 (m, 4Hx3, $PCH_2CH_2$). Anal. Calcd for $C_{30}H_{36}N_3PO_{10}\cdot 0.5H_2O$ (638.67): C, 56.41; H, 5.85; N, 6.58. Found: C, 56.51; H, 5.77; N, 6.62. 7: $\delta_H$ (500 MHz, $CDCl_3$) 8.17 (s, 1Hx3, NH), 7.57 (m, 2Hx3, Ph), 7.29 (m, 2Hx3, Ph), 5.41 (m, 1Hx3, H-2), 5.40 (dd, 1Hx3, $J_{2,3} = 3.2$Hz, H-3), 5.32 (t, 1Hx3, $J_{3,4} = J_{4,5} = 9.7$Hz, H-4), 4.97 (s, 1Hx3, H-1), 4.47 (s, 2Hx3, PhC$H_2$), 4.31 (m, 2Hx3, H-6a, 1/2$OCH_2CO$), 4.13 (m, 2Hx3, H-6b, 1/2$OCH_2CO$), 4.03 (m, 1Hx3, H-5), 3.51 (m, 2Hx3, $OCH_2$), 2.18, 2.11, 2.17, 2.14 (each s, 3Hx4x3, $CH_3CO$), 1.91 – 1.78 (m, 4Hx3, $PCH_2CH_2$), MALDI-MS: $m/z = 1704.4$ (calcd for $C_{78}H_{103}N_3PO_{37}$ 1704.60 $[M+H]^+$), 1726.4 (calcd for $C_{78}H_{102}N_3PO_{37}Na$ 1726.58 $[M+Na]^+$), 1742.4 (calcd for $C_{78}H_{102}N_3PO_{37}K$ 1742.55 $[M+K]^+$). **1**: $\delta_H$ (500 MHz, $D_2O$) 7.27 (d, 2Hx3, J = 8.5Hz, Ph), 7.21 (d, 2Hx3, J = 8.5Hz, Ph), 4.77 (d, 1Hx3, $J_{1,2} = 1.6$Hz, H-1), 4.44 (s, 2Hx3, PhC$H_2$), 4.28, 4.19 (ABq, 2Hx3, J = 15.4Hz, $OCH_2CO$), 3.93 (dd, 1Hx3, $J_{2,3} = 3.4$Hz, H-2), 3.74 (dd, 1Hx3, $J_{3,4} = 8.9$Hz, H-3), 4.70 (dd, 1Hx3, $J_{5,6a} = 2.1$Hz, $J_{gem} = 12.1$Hz, H-6a), 4.59 (dd, 1Hx3, $J_{5,6b} = 5.5$Hz, H-6b), 3.52 (t, 1Hx3, $J_{4,5} = J_{4,5} = 8.9$Hz, H-4), 3.48 (m, 1Hx3, H-5), 3.42 (m, 2Hx3, $OCH_2$), 1.65 – 1.54 (m, 4Hx3, $PCH_2CH_2$), MALDI-MS: $m/z = 1222.5$ (calcd for $C_{54}H_{78}N_3PO_{25}Na$ 1222.45 $[M+Na]^+$), 1238.5 (calcd for $C_{54}H_{78}N_3PO_{25}K$ 1238.43 $[M+K]^+$).
5. Tamura, J.; Horito, S.; Yoshimura, J.; Hashimoto, H. Effect of complexation of silver ion with the glycosyl donor and acceptor on the regio- and stereoselectivity in the β-mannopyranosylation of 1,3-Di-*N*-benzyloxycarbonyl-2-deoxystreptamine using silver triflate as a promoter in tetrahydrofuran. Carbohydr. Res. **1990**, *207*, 153–165.
6. Mori, M.; Ito, Y.; Ogawa, T. Total synthesis of the mollu-series glycosyl ceramides α-D-Man*p*-(1 → 3)-β-D-Man*p*-(1 → 4)-β-D-Glc*p*-(1 → 1)-cer and α-D-Man*p*-(1 → 3)-[β-D-Xyl*p*-(1 → 2)]-β-D-Man*p*-(1 → 4)-β-D-Glc*p*-(1 → 1)-cer. Carbohydr. Res. **1990**, *195*, 199–224.
7. Kim, B.M.; Sharpless, K.B. Cyclic sulfates containing acid-sensitive groups and chemoselective hydrolysis of sulfate esters. Tetrahedron Lett. **1989**, *30*, 655–658.

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