

NANO EXPRESS

Open Access

Synthesis and characterisation of biologically compatible TiO₂ nanoparticles

Richard W Cheyne^{1,2}, Tim AD Smith², Laurent Trembleau¹ and Abbie C Mclaughlin^{1*}

Abstract

We describe for the first time the synthesis of biocompatible TiO₂ nanoparticles containing a functional NH₂ group which are easily dispersible in water. The synthesis of water dispersible TiO₂ nanoparticles coated with mercaptosuccinic acid is also reported. We show that it is possible to exchange the stearic acid from pre-synthesised fatty acid-coated anatase 5-nm nanoparticles with a range of organic ligands with no change in the size or morphology. With further organic functionalisation, these nanoparticles could be used for medical imaging or to carry cytotoxic radionuclides for radioimmunotherapy where ultrasmall nanoparticles will be essential for rapid renal clearance.

Introduction

Organically functionalised inorganic nanoparticles are being increasingly studied as a result of their many technological applications. In particular, the synthesis of inorganic nanoparticles for biomedical applications is being widely researched. Biomedical applications of inorganic nanoparticles include biosensing [1], targeted drug delivery agents [2] and contrast agents in magnetic resonance imaging (MRI) [3,4]. Surface-coated superparamagnetic iron oxide nanoparticles have been extensively employed as magnetic resonance signal enhancers that can resolve the weakness of current MRI techniques. Most recently, it has been shown that by conjugating surface-coated Au-Fe₃O₄ nanoparticles to both herceptin and *cis*-platin, the nanoparticles can act as target-specific nanocarriers to deliver platin into Her2-positive breast cancer cells with strong therapeutic results [5]. Furthermore, these nanoparticles can act as both a magnetic and optical probe for tracking the platin complex in cells and biological systems. However, the iron oxide nanoparticles commonly used as MRI contrast agents have a radius of over 50 nm so that they have a limited extravasation ability and are subject to easy uptake by the reticuloendothelial system [6,7]. In order to enhance biological targeting efficiency, ultrasmall nanoparticles with greatly reduced hydrodynamic sizes are desired. Recently, ultrasmall (core size of 4.5 nm) c(RGDyK)-coated Fe₃O₄ nanoparticles have been synthesised [8], and

results show a dramatic increase in cellular uptake. These nanoparticles were synthesised via thermal decomposition of Fe(CO)₅ in the presence of the ligand 4-methycatechol (4-MC). The 4-MC-coated nanoparticles were then conjugated with a peptide c(RGDyK) via the Mannich reaction. There has been much research into the synthesis and properties of TiO₂ nanoparticles since surface-modified TiO₂ nanoparticles have many applications including photocatalysis [9] and photoelectric conversion [10,11]. Such research has shown that it is facile to make surface-coated TiO₂ nanoparticles with an ultrasmall core size of 3 to 5 nm [12,13]. However, the study of TiO₂ nanoparticles for biological applications, which have been shown to be non-toxic at low doses [14] (5 mg/kg body weight), has thus far been limited as such TiO₂ nanoparticles are generally synthesised via a nonhydrolytic method and hence are non-dispersible in water. There are a couple of examples of functionalised TiO₂ nanoparticles which are dispersible in water [15,16]; however, in these reports, a broad size distribution is evidenced (3 to 8 nm).

In this paper, we show that it is possible to synthesise ultrasmall TiO₂ nanoparticles with a core size of 5 nm with a range of coated short-chain organic functional groups which are comparable in size to diabodies which exhibit rapid renal excretion [17]. The organically functionalised nanoparticles are highly dispersible in a range of solvents, and results show that when coated with aspartic acid or mercaptosuccinic acid, the nanoparticles are easily dispersible in water. Hence, for the first time, ultrasmall biocompatible TiO₂ nanoparticles containing a functional

* Correspondence: a.c.mclaughlin@abdn.ac.uk

¹The Chemistry Department, University of Aberdeen, AB24 3 UE, UK
Full list of author information is available at the end of the article

NH₂ or SH group have been synthesised. With further organic functionalisation and conjugation to a targeting moiety such as a single-chain antibody fragment or to biotin, these nanoparticles could be used to carry multiple short-lived radionuclides including ^{99m}Tc and ⁶⁷Ga for medical imaging or to cytotoxic radionuclides for radioimmunotherapy where ultrasmall nanoparticles will be essential for rapid renal clearance.

Results and discussion

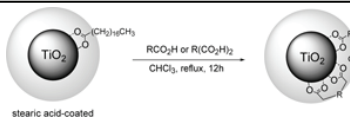
Nanoparticle preparation

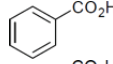
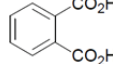
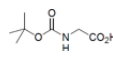
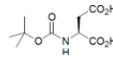
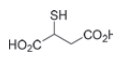
The two-phase thermal synthesis of titanium dioxide nanoparticles was adapted from a previously described procedure [13]. Typically, a solution of *tert*-butylamine dissolved in water was added to a Teflon-lined steel autoclave. Separately, titanium(IV) *n*-propoxide and stearic acid (SA) were dissolved in toluene and added to the autoclave. The autoclave was sealed and heated to 180°C for 16 h and allowed to cool to room temperature. TiO₂ nanoparticles were recovered by precipitation with acetonitrile and isolated by filtration. The “SA-coated” nanoparticles are dispersible in chloroform and methanol but are not dispersible in water or acetonitrile. The approximate number of SA molecules bound to each nanoparticle core was calculated to be 500 by following an established procedure [12].

Surface functionalisation

Exchange of the TiO₂-bound stearic acid chains with various carboxylic acids was performed by reacting SA-coated nanoparticles with excess acids in refluxing chloroform. The resulting nanoparticles could be recovered by removal of solvent, re-suspension in acetonitrile, and filtration. The nanoparticles were dispersed in appropriate solvents, and nuclear magnetic resonance (NMR) spectra were taken. The degree of ligand exchange was determined by integration of the relevant signals of the distinct functional groups in the proton NMR spectra. The results are reported in Table 1. Approximately 37% of the stearic acid chains could be exchanged by benzoic acid (Benz) synthesised under these conditions. Exchange with phthalic acid led to the formation of non-dispersible nanoparticles, and the XRD powder pattern obtained indicates a large proportion of unbound phthalic acid that could not be removed. Synthesis of aspartic acid (Asp) and glycine (Gly) nanoparticles without the protective Boc group were unsuccessful, presumably due to the poor solubility of *l*-aspartic acid and glycine in chloroform. Only about 25% of the stearic acid chains could be exchanged by Boc-glycine (Boc-Gly). But ligand exchange with the bidentate ligands mercaptosuccinic acid (Mercapto) or Boc-aspartic acid (Boc-Asp) was almost quantitative as observed by proton NMR (¹H NMR). The Boc group

Table 1 Exchange of the TiO₂-bound stearic acid chains with various carboxylic acids



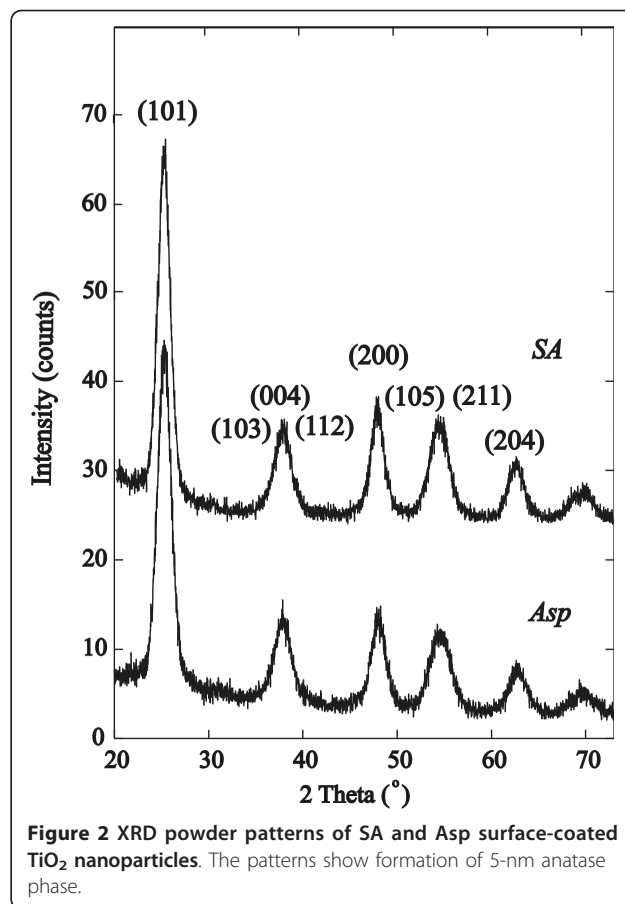
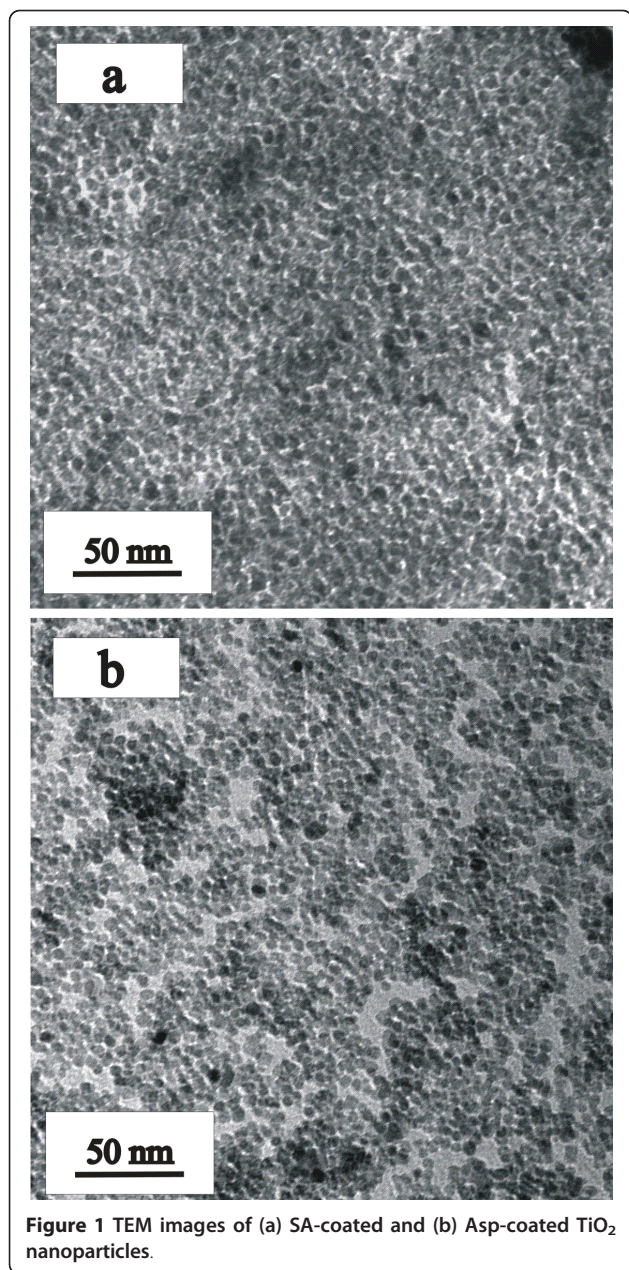
Entry	Carboxylic acid (ligand)	Ligand exchange (%)
1		37 ^{a,b}
2		20 ^{c,d}
3		25 ^{a,b} (30)
4		>95 ^{c,b} (>95 ^e)
5		>95 ^f

^aDetermined by ¹H NMR (400 MHz, CDCl₃). ^bXRD powder pattern indicated essentially pure nanoparticles. ^cThe nanoparticles were not dispersible in any solvent. ^dBased on the recovery yield of ligand in acetonitrile. ^eDetermined by ¹H NMR (400 MHz, D₂O) after removal of the Boc group using HCl/dioxane (ammonium hydrochloride salt is obtained). ^fDetermined by ¹H NMR (400 MHz, D₂O)

was later cleaved with 4 M HCl in dioxane. The resulting nanoparticles from both exchanges were easily dispersed in water (ca. 5 mg/ml), and the dispersion is stable for days without precipitation.

Characterisation of surface-functionalised nanoparticles

The TEM images of SA- and Asp-coated TiO₂ nanoparticles are presented in Figure 1. The TEM images for the other coated nanoparticles and higher magnification images are displayed in the Additional file (Figures S1 and S2 in Additional file 1). The higher magnification shows that the nanoparticles prepared are spherical with a uniform diameter of 5 ± 1 nm, but that the nanoparticles agglomerate. Such agglomeration/aggregation of TiO₂ nanoparticles is well documented and can be tuned by altering the pH (for example see references [9,18,19]). The mean hydrodynamic radius was determined using dynamic light scattering, and the results are displayed in Table 2 and confirm that when dispersed in solution, the coated TiO₂ nanoparticles form agglomerates which vary in size from 141 to 601 nm. Powder X-ray diffraction (XRD) patterns of SA- and Asp-coated nanoparticles are shown in Figure 2. The diffraction patterns show that the anatase phase (JCPDS no. 21-1272) is formed, and the crystallite size was calculated at 5 nm using the Scherrer formula which is in good agreement with the TEM images [20]. The XRD patterns of the Benz, Boc-Gly, Boc-Asp, Mercapto and Gly surface-modified TiO₂ nanoparticles are displayed in Figures S3 and S4 in Additional file 1. There is no



change in particle size or crystal structure upon surface modification.

The presence of the various surface coatings were confirmed by Fourier transform infrared spectroscopy (FTIR) and ¹H NMR measurements. The spectrum of pure stearic acid shows the C = O stretch vibration at 1,700 cm⁻¹. This band is completely converted into three new bands in the spectrum of stearic acid-coated TiO₂ nanoparticles as previously reported [12]. Two different carboxylate binding sites can be identified, a bridging complex ($\nu_a = 1,620 \text{ cm}^{-1}$, $\nu_s = 1,455 \text{ cm}^{-1}$) and a bidentate complex ($\nu_a = 1,521 \text{ cm}^{-1}$, $\nu_s = 1455 \text{ cm}^{-1}$). The infrared (IR) spectrum of the Benz-coated nanoparticles (Figure S5 in Additional file 1) shows no evidence of the free acid C = O stretch, and carboxylate peaks are detected at 1,630, 1,513 and 1,411 cm⁻¹, while C = C aromatic stretches are detected at 1,599 and 1,448 cm⁻¹. Upon ligand exchange with Boc-l-aspartic acid and subsequent removal of the Boc group, a change in the IR spectrum is evidenced (Figure 3). The carboxylate peaks shift to 1,506 and 1,410 cm⁻¹, and the C-N stretching vibration is detected at 1,151 cm⁻¹. The N-H bend is

Table 2 Mean hydronamic radius for the different carboxylic acid-coated TiO₂ nanoparticles determined from DLS measurements

Carboxylic acid (ligand)	Mean hydrodynamic radius (nm)
SA	141
Mercapto	192
Asp	202
Gly	508
BA	601

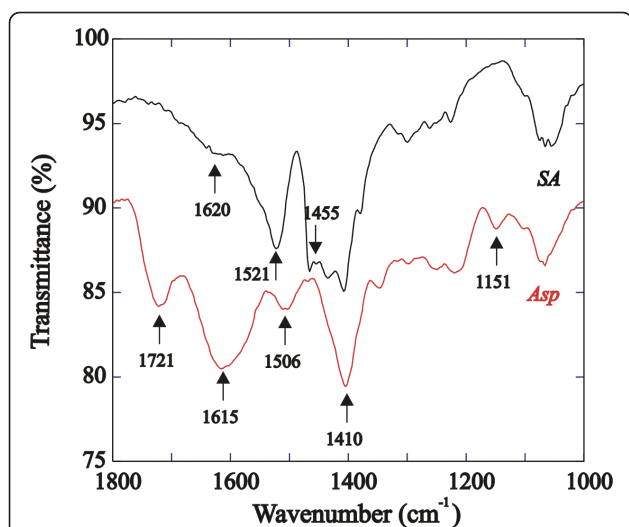


Figure 3 Solid-state ATR-FTIR spectra of SA-coated (top) and Asp-coated (bottom) TiO₂ nanoparticles.

detected by the presence of the strong peak at 1,615 cm⁻¹, demonstrating the presence of a primary amine; however, a C = O stretch observable at 1,721 cm⁻¹ suggests that not all of the carboxylate groups are bound to the TiO₂ core. Two broad peaks are observed at 3,316 and 3,166 cm⁻¹ which correspond to N-H stretch peaks; the broadness of the peaks suggests H bonding interactions between adjacent molecules. The IR spectra of Benz-, Boc-Gly-, Boc-Asp-, Mercapto- and Gly-coated nanoparticles are displayed in Figure S5 in Additional file 1.

The Asp nanoparticles were further investigated by NMR. The proton NMR spectrum of free aspartic acid (Figure 4) shows a doublet of doublets at 4.09 ppm (³J = 4.4 Hz; ³J = 6.8 Hz) and two doublets of doublets at 3.05 ppm (²J = 18 Hz; ³J = 4.4 Hz) and 2.98 ppm (²J = 18 Hz; ³J = 6.8 Hz). For the aspartic acid-coated nanoparticles, these signals are significantly shifted downfield (0.05 to 0.17 ppm) and they are slightly broadened. Curiously, the geminal coupling constant for the CH₂ group has apparently disappeared as the CH group appears as a triplet (*J* = 5.6 Hz) and the CH₂ group appears as a

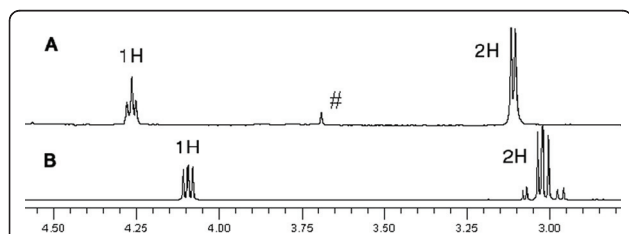


Figure 4 Part of the ¹H NMR spectrum (400 MHz) in D₂O. For Asp-coated nanoparticles (A) and free aspartic acid-coated nanoparticles (B). Number sign, residual dioxane from Boc deprotection.

doublet (*J* = 5.2 Hz). Since the two methylene hydrogens are diastereotopic, the most likely explanation to this anomaly is that the chemical environment of both nuclei is such that they have almost identical chemical shifts. The discrepancy in the coupling constants (5.6 versus 5.2 Hz) can be explained by the signals given by the doublet and triplet appearing slightly broad. A two-dimensional (2D) correlation spectroscopy (COSY) experiment on these nanoparticles confirmed this coupling (Figure 5). The strong correlation clearly seen between the CH triplet (4.25 ppm) and the CH₂ doublet (3.09 ppm) indicates that despite the unusual coupling constants obtained from the ¹H NMR, the nuclei in question are spin coupled. This validates their identities and indicates that the nanoparticle contains aspartic acid as a ligand albeit in a slightly altered chemical state to that of the free acid.

Conclusions

In summary, we have created a facile route to synthesise ultrasmall surface-coated TiO₂ nanoparticles with a range of organic coatings. Furthermore, the surface-coated nanoparticles are incredibly robust so that it is possible to perform ligand exchange reactions on the outer capping groups without disturbing the overall size or structure morphology of the nanoparticles. Results suggest that ligand exchange is most successful with bidentate ligands as a result of the availability of two carboxylic acid groups which bind to the TiO₂ core.

This two-step approach toward the synthesis of surface-modified TiO₂ nanoparticles allows for fine tuning of the nanoparticle core size in the first step before surface modification with suitable ligands in the second. By separating the surface modification step from that of the nanoparticle formation, this method allows for the

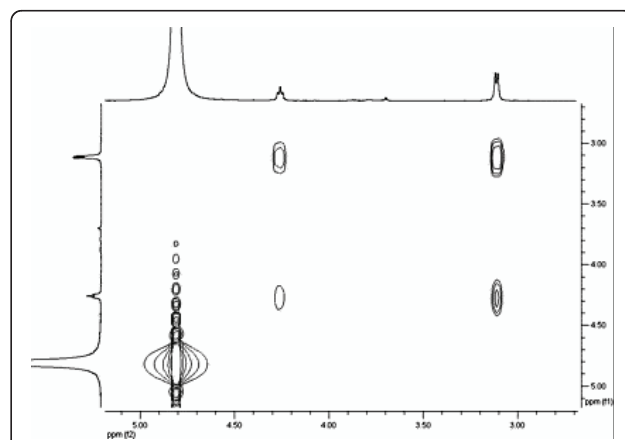


Figure 5 2D COSY NMR spectrum (400 MHz, D₂O) of aspartic acid-coated TiO₂ nanoparticles.

production of identical nanoparticle cores before differentiation by surface modifications. Additionally, the use of bifunctional ligands to form the nanoparticle coating allows for the possibility of post-synthesis modifications to further functionalise the nanoparticle. This may be beneficial for use in biological applications as the initial surface functionalisation can convey improved water solubility before addition of more biologically relevant moieties. With further organic functionalisation and conjugation to a targeting moiety, the biological applications of the nanoparticles described here include the transport of multiple short-lived radionuclides including ^{99}Tc and ^{67}Ga for medical imaging or to cytotoxic radionuclides for radioimmunotherapy. The biological potential of these new nanostructures is currently being investigated.

Experimental procedures

General

All ligand exchange reactions were performed under an argon atmosphere. All reagents were purchased from Sigma-Aldrich (Sigma-Aldrich Company Ltd, Dorset, England) and used without further purification. Cleavage of Boc protecting groups was achieved by stirring in 4 M HCl/dioxane for 3 h under argon.

Analytical measurements

Routine ^1H NMR and COSY data for TiO_2 nanoparticles were obtained at 400 MHz on a VarianUnity INOVA instrument (Agilent Technologies Ltd, UK). Infrared spectra were obtained from 400 scans at 4 cm^{-1} resolution using a Nicolet 380 spectrometer (Thermo Electron Corporation, Franklin, MA, USA) fitted with a diamond attenuated total reflectance (ATR) platform. IR and NMR data reported were obtained at room temperature. Room temperature X-ray diffraction patterns were collected for the organically coated TiO_2 nanoparticles on a Bruker D8 Advance diffractometer (Bruker AXS Ltd, Coventry, UK) with twin Gobel mirrors using $\text{Cu K}\alpha_1$ radiation. Data were collected over the range $20^\circ < 2\theta < 80^\circ$, with a step size of 0.02° . Transmission electron microscopy images were obtained for the organically coated TiO_2 nanoparticles on a Philips CM10TEM (FEI Ltd, Netherlands). Dynamic light scattering (DLS) was performed using a Malvern mastersizer (Malvern Instruments Ltd, Malvern, UK).

Synthesis of titanium dioxide nanoparticles

Titanium dioxide nanoparticles were synthesised by a two-phase thermal approach adapted from a previously described procedure [13]. Typically, a solution of 0.15 mL of *tert*-butylamine (1.43 mmol) dissolved in 14.5 mL of water was added to a 45-mL Teflon-lined steel autoclave.

Separately, 0.225 g of titanium(IV) *n*-propoxide (0.792 mmol) and 0.75 g of stearic acid (2.64 mmol) were dissolved in 14.5 mL of toluene and added to the autoclave without additional stirring. The autoclave was sealed and heated to 180°C for 16 h and allowed to cool to room temperature. The TiO_2 nanoparticles were recovered by precipitation with 90 mL of acetonitrile and isolated by filtration. Off-white solid; ^1H NMR (CDCl_3); δ 0.88 (*t*, 3H), 1.25 (*s*, 30H) and 2.03 (*s*, 2H); IR ν_{max} 2,960, 2,915, 2,848, 1,620, 1,521, 1,455, 1,400, 1,300, 1,258, 1,220 and $1,066\text{ cm}^{-1}$.

Procedure for surface modification of nanoparticles

A solution of carboxylic acid (150 mg) in 5 mL chloroform was added to a reaction vessel containing a dispersion of "SA-coated" TiO_2 nanoparticles (100 mg) in 10 mL chloroform. The reaction was stirred for 18 h under reflux. The resultant surface-modified nanoparticles were recovered by evaporation of the solvent *in vacuo*, re-suspension in acetonitrile and filtration. Unbound starting material was removed by repeated washings of the nanoparticles with acetonitrile.

Benzoic acid exchanged TiO_2

Off-white solid; 86% yield; ^1H NMR indicates an incomplete exchange (37%) of stearic acid with benzoic acid; ^1H NMR (CDCl_3); δ 0.88 (*t*, 3H), 1.28 (*s*, 28H), 1.65 (*t*, 2H), 2.34 (*t*, 2H), 7.42 (*t*, 1.2H), 7.53 (*t*, 0.6H) and 8.06 (*d*, 1.2H); IR ν_{max} 2,956, 2,919, 2,849, 1,630, 1,599, 1,513, 1,448 and $1,411\text{ cm}^{-1}$.

Glycine exchanged TiO_2

Synthesis was performed from Boc-glycine. Cleavage of the protecting group was achieved by stirring the resulting nanoparticles under argon in 4 M HCl/dioxane for 3 h. Off-white solid; 91% yield; ^1H NMR indicates an incomplete exchange (30%) of stearic acid with glycine; ^1H NMR (CDCl_3); δ 0.88 (*t*, 3H), 1.25 (*s*, 30H), 2.02 (*d*, 2H), 2.33 (*s*, 1H), 3.75 (*s*, 1.4H); IR ν_{max} 3,319, 3,115, 2,991, 2,928, 1,742, 1,613, 1,495, 1,435, 1,406, 1,337, 1,305, 1,248, 1,118, 1,066 and 901 cm^{-1} .

Aspartic acid exchanged TiO_2

Synthesis was performed from Boc-aspartic acid. Cleavage of the protecting group was achieved by stirring the resulting nanoparticles under argon in 4 M HCl/dioxane for 3 h. Off-white solid; >95% yield; ^1H NMR (D_2O); δ 1.40 (*s*, 0.4H), 2.03 (*s*, 0.4H), 2.13 (*s*, 0.3H), 3.09 (*d*, 2H, $J = 5.2\text{ Hz}$), 4.25 (*t*, 1H, $J = 5.6\text{ Hz}$); COSY clearly shows coupling between the protons of the doublet (δ 3.09) and triplet (δ 4.25); IR ν_{max} 3,316, 3,166, 2,970, 2,910, 1,721, 1,615, 1,506, 1,410, 1,346, 1,296, 1,253, 1,220, 1,151 and $1,066\text{ cm}^{-1}$.

Phthalic acid exchanged TiO₂

Off-white solid; purification not possible; resulting nanoparticles not dispersible.

Mercaptosuccinic acid exchanged TiO₂

Synthesis was performed using mercaptosuccinic acid. To reduce the possibility of oxidation occurring between mercaptosuccinic acid moieties, the reaction was performed under anhydrous conditions but in an otherwise identical manner to previous exchange reactions. Pale-yellow solid; >95% yield; ¹H NMR (D₂O); δ 2.62 (*m*, 1H) and 2.91 (*m*, 1H); IR ν_{max} 2,915, 2,848, 1,685, 1,535, 1,515, 1,442 and 1,384 cm⁻¹.

Additional material

Additional file 1: Supplementary data. X-ray diffraction, TEM and spectroscopic data for coated titanium nanoparticles.

Acknowledgements

We thank Mr Kevin Mackenzie for making TEM measurements. This work was supported by the Breast Cancer Campaign.

Author details

¹The Chemistry Department, University of Aberdeen, AB24 3 UE, UK ²School of Medical Sciences, University of Aberdeen, AB25 2ZD, UK

Authors' contributions

ACM, LT and TADS designed the study; RC performed the experiments with help from ACM, LT and TADS; All authors contributed to drafting the manuscript; All authors edited and approved the manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 31 August 2010 Accepted: 14 June 2011

Published: 14 June 2011

References

1. Miller MM, Prinz GA, Cheng SF, Bounnak S: **Detection of a micron-sized magnetic sphere using a ring-shaped anisotropic magnetoresistance-based sensor: A model for a magnetoresistance-based biosensor.** *Appl Phys Lett* 2002, **81**:2211.
2. Jain TK, Morales MA, Sahoo SK, Leslie-Pelecky DL, Labhasetwar V: **Iron oxide nanoparticles for sustained delivery of anticancer agents.** *Mol Pharm* 2005, **2**:194.
3. Modo M, Bulté JW: **Cellular MR imaging.** *Mol Imaging* 2005, **4**:143.
4. Modo MMJ, Bulté JWM: *Molecular and Cellular MR Imaging* Boca Raton: CRC; 2007.
5. Xu CJ, Wang BD, Sun SH: **Dumbbell-like Au-Fe₃O₄ Nanoparticles for Target-Specific Platin Delivery.** *J Am Chem Soc* 2009, **131**:4216.
6. Moghimi SM, Hunter AC, Murray JC: **Long-circulating and target-specific nanoparticles: Theory to practice.** *Pharm Rev* 2001, **53**:283.
7. Neuberger T, Schopf B, Hofmann H, Hofmann M, von Rechenberg BJ: **Superparamagnetic nanoparticles for biomedical applications: Possibilities and limitations of a new drug delivery system.** *J Magn Mater* 2005, **293**:483.
8. Xie J, Lee HY, Xu CJ, Hsu AR, Peng S, Chen XY, Sun SH: **Ultrasmall c (RGDYK)-coated Fe₃O₄ nanoparticles and their specific targeting to integrin alpha(v)beta(3)-rich tumor cells.** *J Am Chem Soc* 2008, **130**:7542.
9. Wang BQ, Jing LQ, Qu YC, Li SD, Jiang BJ, Yang LB, Xin BF, Fu HG: **Enhancement of the photocatalytic activity of TiO₂ nanoparticles by surface-capping DBS groups.** *Applied Surface Science* 2006, **252**:2817.
10. Cahen D, Hodes G, Gratzel M, Guillemoles JF, Riess I: **Nature of photovoltaic action in dye-sensitized solar cells.** *J Phys Chem B* 2000, **104**:2053.
11. Jensen H, Fermin DJ, Moser JE, Girault HH: **Organization and reactivity of nanoparticles at molecular interfaces. Part 1. Photoelectrochemical responses involving TiO₂ nanoparticles assembled at polarizable water vertical bar 1,2-dichloroethane junctions.** *J Phys Chem B* 2002, **106**:10908.
12. Beek WJE, Janssen RA: **Photoinduced electron transfer in heterosupramolecular assemblies of TiO₂ nanoparticles and terthiophene carboxylic acid in apolar solvents.** *J Adv Funct Mater* 2002, **12**:519.
13. Pan DC, Zhao NN, Wang Q, Jiang SC, Ji XL, An LJ: **Facile synthesis and characterization of luminescent TiO₂ nanocrystals.** *Adv Mater* 2005, **17**:1991.
14. Fabian E, Landsiedel R, Ma-Hock L, Wiench K, Wohlleben W, van Ravenzwaay B: **Tissue distribution and toxicity of intravenously administered titanium dioxide nanoparticles in rats.** *Arch Toxicol* 2008, **82**:151.
15. Niederberger M, Garnweitner G, Krumeich F, Nesper R, Cölfen H, Antonietti M: **Tailoring the surface and solubility properties of nanocrystalline titania by a nonaqueous in situ functionalization process.** *Chem Mater* 2004, **16**:1202.
16. Kotsokhegchia T, Cellesti F, Thomas A, Niederberger M, Tirelli N: **Preparation of ligand-free TiO₂ (anatase) nanoparticles through a nonaqueous process and their surface functionalization.** *Langmuir* 2008, **24**:6988.
17. Cai WB, Olafsen T, Zhang XZ, Cao QZ, Gambhir SS, Williams LE, Wu AM, Chen XB: **PET imaging of colorectal cancer in xenograft-bearing mice by use of an F-18-labeled T84.66 anti-carcinoembryonic antigen diabody.** *J Nucl Med* 2007, **48**:304.
18. Reyes-Coronado D, Rodriguez-Gattorno D, Espinosa-Pesqueira ME, Cabb C, De Cross R, Oskam G: **Phase-pure TiO₂ nanoparticles: anatase, brookite and rutile.** *Nanotechnology* 2008, **19**:145605.
19. Jiang JK, Oberdorster G, Biswas P: **Characterization of size, surface charge, and agglomeration state of nanoparticle dispersions for toxicological studies.** *J Nanoparticle Res* 2009, **11**:77.
20. Nanda J, Sapra S, Sarma DD, Chandrasekharan N, Hodes G: **Size-selected zinc sulfide nanocrystallites: Synthesis, structure, and optical studies.** *Chem Mater* 2000, **12**:1018.

doi:10.1186/1556-276X-6-423

Cite this article as: Cheyne et al: Synthesis and characterisation of biologically compatible TiO₂ nanoparticles. *Nanoscale Research Letters* 2011 **6**:423.

Submit your manuscript to a SpringerOpen® journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Immediate publication on acceptance
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► springeropen.com