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Sonochemical Synthesis of Small Boron Oxide Nanoparticles

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Abstract

Synthesis of small boron oxide nanoparticles is reported. A sonochemical approach in the presence of a capping agent was employed to produce approximately 4–5 nm sized B₂O₃ nanoparticles, including the ¹⁰B isotopically enriched form. The morphology and composition of the nanoparticles were established using TEM and electron diffraction respectively. XPS and FTIR spectroscopy provided information about the surface functionalization of the B₂O₃ nanoparticles, which can be further modified through a facile, one-step ligand exchange process. The toxicity of the synthesized nanoparticles was investigated in CHO cells, indicating that these systems were non-toxic up to 1.7 mM concentrations

Synopsis

A sonochemical treatment was performed on bulk B₂O₃ in the presence of a capping agent to produce small (4–5 nm) B₂O₃ nanoparticles, including the ¹⁰B isotopically enriched form. The morphology and composition of the bulk material and nanoparticle product were established using electron microscopy and diffraction. The surface functionalization of the B₂O₃ nanoparticles, and their toxicity in CHO cells have been investigated.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ASSOCIATED CONTENT

Supporting Information. Experimental and characterization details, FTIR, NMR, TGA, XPS, TEM, SEM, cell studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Nanoscale architectures of oxide-based materials have been extensively developed due to their diverse applications in the areas ranging from photonics to drug delivery.^{1–3} The properties of nanomaterials can be altered by simply tuning their morphology, which is very beneficial to tailor materials for specific applications. Although efforts at nanostructuring metal and non-metal oxides (e.g., TiO₂, Fe₂O₃, SiO₂, Al₂O₃) have garnered much attention over the years, we were surprised at the lack of available synthetic methods for producing well-defined nanoscale B₂O₃ systems. Bulk B₂O₃ is a common component in oxide glasses and ceramics for large-scale industrial uses such as optical glasses, insulation fiberglass and fire retardants.^{4–5} Additionally, B₂O₃-glasses are also used in radiation shielding^{6–7} and dielectric applications.⁸ However, processing options for bulk B₂O₃ require high temperatures for melting and sintering, as well as specialized equipment. The development of nanoscale B₂O₃ would therefore be potentially useful for creating solution-processable coating materials, or for fabricating novel composite materials that contain discrete amounts of B₂O₃ nanoparticles.

Computational predictions on the structure and morphologies of nano-B₂O₃ have been theoretically explored;⁹ however, experimental endeavors to synthesize nanoscale boron oxide remain sparse. Prior attempts at nanostructuring boron oxide-based materials have primarily used ball-milling, which presents limitations with respect to the size and homogeneity of the nanoproducts formed.^{10–13} Furthermore, due to the reactivity of B₂O₃ with water, it is not feasible to apply solution-based synthetic routes (co-precipitation, hydrothermal, and aqueous sol-gel) that precipitate out insoluble metal oxides. In this work, we report a nanostructuring strategy aimed at division of the bulk material. As a result, the developed sonochemical method allows for the preparation of uniform, small (4–5 nm), spherical B₂O₃ nanoparticles utilizing bulk B₂O₃ powder as the starting material.

We commenced our work by performing a probe sonication treatment on amorphous bulk B₂O₃ powder (Figure 1a) in the presence of oleic acid serving a dual role as the reaction medium and capping agent. Oleic acid was chosen due to its biocompatibility, high boiling point, and widespread use in stabilizing nanoparticles.^{14–15} The B₂O₃ nanoparticles formed from this treatment get rapidly capped with oleic acid which limits the reaction domain and prevents nanoparticle aggregation, similar to the surface modification observed in metal oxide nanoparticles.^{14–15} The composition, morphology and surface modification of the oleic acid-capped B₂O₃ nanoparticles (OA-B₂O₃ NPs) were characterized by transmission

electron microscopy (TEM), selected area electron diffraction (SAED), Fourier transform infrared (FTIR) spectroscopy, and X-ray photoelectron Spectroscopy (XPS).

Examining the morphology using TEM illustrated that the product from the sonochemical reaction consisted of uniform spherical nanoparticles with an average size of 4.31 ± 0.54 nm in diameter (Figure 1b and Figure S1). This is in stark contrast to the micron-sized platelets comprising the bulk B_2O_3 starting material (Figure 1a). High-resolution TEM coupled with SAED on the nanoparticles displayed polycrystalline rings (Figure S2), which were indexed to B_2O_3 (JCPDS# 00–006-0634). Even though B_2O_3 is typically amorphous, it appears that the prolonged heat treatment arising from the high temperature associated with probe sonication led to the formation of crystalline domains in the B_2O_3 nanoparticles. The FTIR spectrum of the OA- B_2O_3 NPs (Figure 1d) displayed the typical stretching frequencies of B_2O_3 and oleic acid (Figure S3), confirming the presence of oleic acid on the nanoparticles. A detailed peak assignment of IR frequencies with corresponding vibrational modes is provided in Table S1.^{16–18} We can further utilize the IR stretching frequencies to provide insight on the mechanism of capping on B_2O_3 nanoparticles.^{14,19} Upon closer inspection of the $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ IR bands (Figure S4), we calculated ν to be 247 cm^{-1} , which points towards a $k^1-O-C-O$ interaction of oleic acid with the boron sites in the nanoparticle.^{14,19} The surfaces of the bulk B_2O_3 and OA- B_2O_3 NPs were analyzed by XPS (Figure 1e). The B 1s peaks (Figure 1e) shift from 189.5 eV in bare bulk B_2O_3 to 188.6 eV in OA- B_2O_3 NPs, indicating that the surface B-O environment in OA- B_2O_3 NPs has been altered upon capping. The O 1s XPS spectra of OA- B_2O_3 NPs (Figure 1e) also exhibited a binding energy shift to 528.0 eV, compared with 529.4 eV in bulk B_2O_3 . Further resolution of the O 1s peaks (Figure S5) indicated the presence of two peaks that are assigned to the B-O and O=C-O binding sites.^{20–21} ^{11}B MAS NMR spectroscopy of bulk B_2O_3 and OA- B_2O_3 NPs revealed a change in chemical shift from 4.6 to 6.2 ppm respectively (Figure S6). The observed chemical shift of bulk B_2O_3 is consistent with B_2O_3 ,²² and the downfield shift for OA- B_2O_3 NPs is attributed to deshielding that occurs due to the binding of non-bridging oxygens²² (COO^- in this case). The zeta potential value of OA- B_2O_3 NPs was measured as -51.3 mV (Table S2), which is indicative of the presence of negatively charged functional groups, such as the carboxylate groups of oleic acid. Moreover, the highly negative zeta potential value shows that the OA- B_2O_3 NPs possess good colloidal stability.²³ During our investigations, we also performed control reactions on bulk B_2O_3 to determine the optimal conditions for synthesizing B_2O_3 nanoparticles. Microwave treatment of bulk B_2O_3 in oleic acid yielded B_2O_3 nanoparticles with a broad size distribution (Figure S8) whereas probe sonication reactions of B_2O_3 in the presence of other capping agents (dextran, PEG) produced large fragments that lacked a well-defined morphology (Figure S9). Therefore, we established that the combination of probe sonication with oleic acid as the capping agent is more effective for preparing uniform, small (4–5 nm) B_2O_3 nanoparticles.

In order to explore processing options for B_2O_3 NPs, the next step in our synthetic protocol entailed surface modification of the OA- B_2O_3 NPs with carboxymethyl-dextran (CMD), a water-soluble capping agent (Figure 2). This is essential to solubilize the nanoparticles for various aqueous-based applications.²⁴ We performed a phase transfer reaction on OA- B_2O_3 NPs using a saturated solution of CMD and characterized the resulting mixture by various analytical techniques. While the resulting NPs became soluble in water, their morphology

remained unchanged based on TEM analysis, suggesting successful synthesis of CMD-capped B_2O_3 nanoparticles (CMD- B_2O_3 NPs, Figure 1c). Consistent with this hypothesis, the FTIR spectrum of the CMD- B_2O_3 NPs (Figure 1d) displayed stretching frequencies of B_2O_3 and carboxymethyl-dextran (Figure S3), with the ν of 190 cm^{-1} indicating a bridging bidentate capping of the B_2O_3 NPs through the carboxylate group (Figure S4). XPS analyses (Figure 1e) on CMD- B_2O_3 NPs exhibited a B 1s peak at 188.5 eV, comparable to the B–O environment in OA- B_2O_3 NPs. The O 1s spectra (Figure S5) revealed the presence of B–O, O=C–O and O–H sites,^{20–21} signifying a slight change in surface environment occurring as a result of ligand exchange. This trend consistent with that observed for OA- B_2O_3 NPs, owing to the similarities in the surface binding group of oleic acid and carboxymethyl-dextran. Indeed, the zeta potential of CMD- B_2O_3 NPs was measured as -33.5 mV (Table S2), which is ascribed to the anionic carboxylate groups on the surface. Likewise, the high negative zeta potential value indicates that the CMD- B_2O_3 NPs are also stable as colloidal dispersions.²³

There has been a long-standing history in the development of boron-rich compounds suitable for boron neutron capture therapy (BNCT). This technology is potentially promising for treatment of metastatic tumors (*e.g.*, glioblastoma carcinoma) and skin cancers.²⁵ Recently, there has been a revived interest in this approach given the breakthroughs achieved in medical neutron generation that do not rely on nuclear reactors. These developments further drive the need to create boron-rich scaffolds that are non-toxic and amenable to functionalization. To date, boron-based nanomaterials synthesized for potential use in BNCT include boron nanocomposites, boron nitride, boron carbide, and various boronated and boron-functionalized nanostructures.^{25–37} However, their relatively large sizes and morphologies could lead to a lower nanomaterial cellular uptake. Additionally, larger nanomaterials ($>50\text{ nm}$) have difficulty penetrating the blood brain barrier,³⁸ and show increased accumulation in the body.³⁹ Considering these shortcomings, we synthesized bulk isotopically labelled $^{10}B_2O_3$ (Figure S10, procedure adapted from Ref 40) with the aim of extending the above discussed nanostructuring methodologies to the bulk $^{10}B_2O_3$ powder. We successfully obtained products consisting of spherical OA- $^{10}B_2O_3$ NPs (Figure 3a), and CMD- $^{10}B_2O_3$ NPs (Figure 3b) having an average particle diameter of $4.9 \pm 0.9\text{ nm}$ (Figure S12). SAED on the OA- $^{10}B_2O_3$ NPs (Figure 3a) showed polycrystalline rings that were indexed to a mixture of B_2O_3 polymorphs (JCPDS #00–006–0634 red, #00–006–0297 yellow). The FTIR and XPS spectra for the OA-capped and CMD-capped $^{10}B_2O_3$ NPs (Figures S13 and S14) are in agreement with the observations for the corresponding B_2O_3 nanoparticles (Figure 1d, 1e) and substantiate the respective surface functionalization.

This straightforward two-step synthesis of biocompatible $^{10}B_2O_3$ NPs is especially useful when compared with the multi-step routes currently applied to make molecular ^{10}B -enriched boron-rich BNCT agents²⁵. Particularly, the synthesis of derivatized boron clusters for BNCT proceed through several intermediates, and utilize higher cost $^{10}B_2H_6$ or $^{10}B_3H_8$ starting materials. In contrast, the above-discussed nanochemistry presents an inexpensive and scalable route towards making ^{10}B -enriched B_2O_3 -based BNCT agents from commercially available $^{10}B(OH)_3$ or $^{10}B_2O_3$. In order to investigate the toxicity of the nanoparticles, we employed a flow cytometry assay on Chinese hamster ovarian (CHO) cells in which the cells were incubated with B_2O_3 and $^{10}B_2O_3$ nanoparticles for 24 hours, and analyzed via fluorescence activated cell sorting (FACS). Dose-dependent studies showed

that the nanoparticles were non-toxic for concentrations ranging from 0.003 pM to 0.4 pM (Figure 3c). Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was utilized to determine the B₂O₃ and ¹⁰B₂O₃ sample concentrations listed in Figure 3c. Furthermore, we observed that even administering B₂O₃ NPs concentrations as high as 1.7 mM proved to be non-toxic to the CHO cells (Figure S15). The theoretical boron content per B₂O₃ nanoparticle of 4 nm diameter was calculated to be ~1500 boron atoms. Therefore, this concentration corresponds to a maximum value of $\sim 6.6 \times 10^{13}$ boron atoms per cell, which is several orders of magnitude greater than the BNCT required minimum of 1×10^{11} boron atoms. The apparent cell growth observed for cells incubated with OA-B₂O₃ NPs and OA-¹⁰B₂O₃ NPs is consistent with findings that suggest that oleic acid improves cell growth of CHO cells.⁴¹

In summary, this work establishes a facile, one-step process for the synthesis of small (4–5 nm), spherical B₂O₃ nanoparticles. There are several unique aspects to this work; the first being the use of non-toxic, inexpensive reagents and ambient reaction conditions. Typically, stronger conditions such as high temperatures and pH, or the use of strong reducing agents are required to yield uniformly sized nanoparticles.^{42–43} The second interesting aspect is the ease of modifying the surface functionalization of the B₂O₃ nanoparticles. Stirring the nanoparticles in solutions of a capping agent is sufficient to produce surface modifications, unlike current methods for functionalizing boron-based nanostructures which involve coupling,^{44–45} chemical reactions,⁴⁶ or milling.^{47–48} An additional noteworthy aspect of the current work is the observed non-toxicity of the ¹⁰B₂O₃ nanoparticles, making them prospective candidates for boron neutron capture therapy (BNCT). Considering that ¹⁰B-enriched boron oxide is already being produced on the industrial scale for nuclear applications, these results provide a scalable and efficient entry towards an expanded toolbox of boron-rich hybrid nanomaterials.^{49–52}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Kolmakov A; Moskovits M Chemical Sensing and Catalysis by One-dimensional Metal-oxide Nanostructures. *Annu. Rev. Mater. Res* 2004, 34, 151–180.

2. Laurent S; Forge D; Port M; Roch A; Robic C; Vander Elst L; Muller RN Magnetic Iron Oxide Nanoparticles: Synthesis, Stabilization, Vectorization, Physicochemical Characterizations, and Biological Applications. *Chem. Rev* 2008, 108, 2064–2110. [PubMed: 18543879]
3. Yu X; Marks TJ; Facchetti A Metal Oxides for Optoelectronic Applications. *Nature Mater.* 2016, 15, 383–396. [PubMed: 27005918]
4. Schubert DM, In Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCHVerlag, online, 2015, Vol. 6, pp 187–204.
5. Schubert DM, In Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley & Sons, New York, 2011, Vol. 4, pp 1–68.
6. Sayyed MI; Elhouichet H Variation of Energy Absorption and Exposure Buildup Factors with Incident Photon Energy and Penetration Depth for Boro-tellurite (B₂O₃-TeO₂) Glasses. *Radiat. Phys. Chem* 2017, 130, 335–342.
7. Singh H; Singh K; Gerward L; Singh K; Sahota HS; Nathuram R ZnO-PbO-B₂O₃ Glasses as Gamma-ray Shielding Materials. *Nucl. Instr. Meth. Phys. Res. B* 2003, 207, 257–262.
8. Rhim SM; Hong S; Bak H; Kim OK Effects of B₂O₃ Addition on the Dielectric and Ferroelectric Properties of Ba_{0.7}Sr_{0.3}TiO₃ ceramics. *J. Am. Ceram. Soc* 2000, 83, 1145–1148.
9. Fullerton SK; Maranas JK A Molecular Dynamics Study of the Structural Dependence of Boron Oxide Nanoparticles on Shape. *Nano Lett.* 2005, 5, 363–368. [PubMed: 15794626]
10. Kim J; Uhm YR; Lee MK; Lee HM; Rhee CK Neutron Shielding Characteristics of Nano-B₂O₃ Dispersed Poly Vinyl Alcohol. In Transactions of the Korean Nuclear Society Spring Meeting May 29 2008 29–30.
11. Kalfa OM; Yalginkaya Ö; Türker AR Synthesis of nano B₂O₃/TiO₂ Composite Material as a New Solid Phase Extractor and its Application to Preconcentration and Separation of Cadmium. *J. Hazard. Mater* 2009, 166, 455–461. [PubMed: 19135793]
12. Al-Rashdi B; Tizaoui C; Hilal N Copper Removal from Aqueous Solutions Using Nano-scale Diboron Trioxide/Titanium Dioxide (B₂O₃/TiO₂) Adsorbent. *Chem. Eng. J* 2012, 183, 294–302.
13. Chang LC; Chiou BS Effect of B₂O₃ Nano-Coating on the Sintering Behaviors and Electrical Microwave Properties of Ba (Nd₂– xSmx)Ti₄O₁₂ Ceramics. *J. Electroceramics* 2004, 13, 829–837.
14. Zhang L; He R; Gu H-C Oleic Acid Coating on the Monodisperse Magnetite Nanoparticles. *Appl. Surf. Sci* 2006, 253, 2611–2617.
15. Mahdavi M; Ahmad MB; Haron MJ; Namvar F; Nadi B; Rahman MZA; Amin J Synthesis, Surface Modification and Characterisation of Biocompatible Magnetic Iron Oxide Nanoparticles for Biomedical Applications. *Molecules* 2013, 18, 7533–7548. [PubMed: 23807578]
16. Hanst PL; Early VH; Klemperer W Infrared Spectrum and Molecular Structure of B₂O₃. *J. Chem. Phys* 1965, 42, 1097–1104.
17. Buc D; Bello I; Caplovicova M; Mikula M; Kovac J; Hotovy I; Chong YM; Siu GG Analysis of Magnetron Sputtered Boron Oxide Films. *Thin Solid Films.* 2007, 515, 8723–8727.
18. Boroica L; Radu D; Medianu R FTIR Spectra of Glasses from BaO-B₂O₃-TiO₂ System. *J. Optoelectron. Adv. M* 2008, 10, 3217–3220.
19. Perez JPL Preparation and Characterization of Surface Functionalized Boron Nanoparticles for Fuel and Propellant Applications. Ph.D. Thesis The University of Utah, Salt Lake City, UT, 2013.
20. Wilson D; Langell MA XPS Analysis of Oleylamine/Oleic Acid Capped Fe₃O₄ Nanoparticles as a Function of Temperature. *Appl. Surf. Sci* 2014, 303, 6–13.
21. Moon OM; Kang BC; Lee SB; Boo JH Temperature Effect on Structural Properties of Boron Oxide Thin Films Deposited by MOCVD Method. *Thin Solid Films* 2004, 464–465, 164–169.
22. Kroeker S; Stebbins JF Three-coordinated Boron-11 Chemical Shifts in Borates. *Inorg. Chem* 2001, 40, 6239–6246. [PubMed: 11703125]
23. Riddick TM Control of Stability through Zeta Potential; Zeta Meter, Inc.: Staunton, VA, 1968.
24. Thanh NTK; Green LAW Functionalisation of Nanoparticles for Biomedical Applications. *Nano Today* 2010, 5, 213–230.
25. Hawthorne FM The Role of Chemistry in the Development of Boron Neutron Capture Therapy of Cancer. *Angew. Chem. Int. Ed. Engl* 1993;32, 950–984.

26. Yinghuai Z; Peng AT; Carpenter K; Maguire JA; Hosmane NS; Takagaki M Substituted Carborane-appended Water-soluble Single-wall Carbon Nanotubes: New Approach to Boron Neutron Capture Therapy Drug Delivery. *J. Am. Chem. Soc* 2005, 127, 9875–9880. [PubMed: 15998093]
27. Mortensen MW; Sørensen PG; Bjørkdahl O; Jensen MR; Gundersen HJG; Bjørnholm, T. Preparation and Characterization of Boron Carbide Nanoparticles for Use as a Novel Agent in T Cell-guided Boron Neutron Capture Therapy. *Appl. Radiat. Isot* 2006, 64, 315–324. [PubMed: 16290943]
28. Yinghuai Z; Cheng Yan K; Maguire JA; Hosmane NS Recent Developments in Boron Neutron Capture Therapy (BNCT) Driven by Nanotechnology. *Curr. Chem. Biol* 2007, 1, 141–149.
29. Ciofani G; Raffa V; Menciassi A; Cuschieri A Folate Functionalized Boron Nitride Nanotubes and their Selective Uptake by Glioblastoma Multiforme Cells: Implications for their Use as Boron Carriers in Clinical Boron Neutron Capture Therapy. *Nanoscale Res. Lett* 2009, 4, 113–121.
30. Hosmane NS; Yinghuai Z; Maguire JA; Kaim W; Takagaki M Nano and Dendritic Structured Carboranes and Metallocarboranes: From Materials to Cancer Therapy. *J. Organomet. Chem* 2009, 694, 1690–1697.
31. Zhu Y; Lin Y; Zhu YZ; Lu J; Maguire JA; Hosmane NS Boron Drug Delivery via Encapsulated Magnetic Nanocomposites: a New Approach for BNCT in Cancer Treatment. *J. Nanomater* 2010, 24–31.
32. Mandal S; Bakeine GJ; Krol S; Ferrari C; Clerici AM; Zonta C; Cansolino L; Ballarini F; Bortolussi S; Stella S; Protti N; Bruschi P; Altieri S Design, Development and Characterization of Multi-functionalized Gold Nanoparticles for Biodetection and Targeted Boron Delivery in BNCT Applications. *Appl. Radiat. Isot* 2011, 69, 1692–1697. [PubMed: 21641810]
33. Achilli C; Grandi S; Ciana A; Guidetti GF; Malara A; Abbonante V; Cansolino L; Tomasi C; Balduini A; Fagnoni M; Merli D Mustarelli P; Canobbio I; Balduini C; Minetti G Biocompatibility of Functionalized Boron Phosphate (BPO₄) Nanoparticles for Boron Neutron Capture Therapy (BNCT) Application. *Nanomedicine* 2014, 10, 589–597. [PubMed: 24161383]
34. Kuthala N; Vankayala R; Li Y-N; Chiang C-S; Hwang KC Engineering Novel Targeted Boron-10-Enriched Theranostic Nanomedicine to Combat against Murine Brain Tumors via MR Imaging-Guided Boron Neutron Capture Therapy. *Adv. Mater* 2017, 29, 1700850.
35. Zhu Y; Hosmane NS Nanostructured Boron Compounds for Cancer Therapy. *Pure Appl. Chem* 2017, 90, 653–663.
36. Oleshkevich E; Teixidor F; Rosell A; Viñas C Merging Icosahedral Boron Clusters and Magnetic Nanoparticles: Aiming toward Multifunctional Nanohybrid Materials. *Inorg. Chem* 2018, 57, 462–470. [PubMed: 29257676]
37. Ay AN; Akar H; Zaulet A; Vinas C; Teixidor F; Zumreoglu-Karan B Carborane-layered Double Hydroxide Nanohybrids for Potential Targeted- and Magnetically Targeted-BNCT Applications. *Dalton Trans.* 2017, 46, 3303–3310. [PubMed: 28225126]
38. Chen W; Mehta SC; Lu DR Selective Boron Drug Delivery to Brain Tumors for Boron Neutron Capture Therapy. *Adv. Drug Deliv. Rev* 1997, 26, 231–247. [PubMed: 10837545]
39. Longmire M; Choyke PL; Kobayashi H Clearance Properties of Nano-sized Particles and Molecules as Imaging Agents: Considerations and Caveats. *Nanomedicine* 2008, 3, 703–717. [PubMed: 18817471]
40. Balci S; Sezgi N A; Eren, E. Boron Oxide Production Kinetics Using Boric Acid as Raw Material. *Ind. Eng. Chem. Res* 2012, 51, 11091–11096.
41. Schmid G; Zilg H; Eberhard U; Johannsen R Effect of Free Fatty Acids and Phospholipids on Growth of and Product Formation by Recombinant Baby Hamster Kidney (rBHK) and Chinese Hamster Ovary (rCHO) Cells in Culture. *J. Biotechnol* 1991, 17 155–167. [PubMed: 1366984]
42. Wang X; Zhuang J; Peng Q; Li Y A General Strategy for Nanocrystal Synthesis. *Nature* 2005, 437, 121–124. [PubMed: 16136139]
43. Frey NA; Peng S; Cheng K; Sun S Magnetic Nanoparticles: Synthesis, Functionalization, and Applications in Bioimaging and Magnetic Energy Storage. *Chem. Soc. Rev* 2009, 38, 2532–2542. [PubMed: 19690734]
44. Mortensen MW; Bjørkdahl O; Sørensen PG; Hansen T; Jensen MR; Gundersen HJG; Bjørnholm T Functionalization and Cellular Uptake of Boron Carbide Nanoparticles. The First Step Toward T

- Cell-guided Boron Neutron Capture Therapy. *Bioconjug. Chem* 2006, 17, 284–290. [PubMed: 16536457]
45. Joni IM; Balgis R; Ogi T; Iwaki T; Okuyama K Surface Functionalization for Dispersing and Stabilizing Hexagonal Boron Nitride Nanoparticle by Bead Milling. *Colloids Surf. A* 2011, 388, 49–58.
46. Zhi CY; Bando Y; Tang CC; Huang Q; Golberg D Boron Nitride Nanotubes: Functionalization and Composites. *J. Mater. Chem* 2008, 18, 3900–3908.
47. Van Devener B; Perez JPL; Anderson SL Air-stable, Unoxidized, Hydrocarbon-dispersible Boron Nanoparticles. *J. Mater. Res* 2009, 24, 3462–3464.
48. Perez JPL; McMahon BW; Anderson SL Functionalization and Passivation of Boron Nanoparticles with a Hypergolic Ionic Liquid. *J. Propul. Power* 2013, 29, 489–495.
49. Axtell JC; Saleh LMA; Qian EA; Wixtrom AI; Spokoyny AM Synthesis and Applications of Perfunctionalized Boron Clusters. *Inorg. Chem* 2018, 57, 2333–2350. [PubMed: 29465227]
50. Qian EA; Wixtrom AI; Axtell JC; Saebi A; Jung D; Rehak P; Han Y; Mouly EH; Mosallaei D; Chow S; Messina M; Wang J-Y; Royappa AT; Rheingold AL; Maynard HD; Kral P; Spokoyny AM Atomically Precise Organomimetic Cluster Nanomolecules Assembled via Perfluoroaryl-Thiol S_NAr Chemistry. *Nature Chem.* 2017, 9, 333–340. [PubMed: 28485398]
51. Jung D; Saleh LMA; Berkson ZJ; El-Kady MF; Hwang JY; Mohamed N; Wixtrom AI; Titarenko E; Shao Y; McCarthy K; Guo J; Martini IB; Kraemer S; Wegener EC; Saint-Cricq P; Ruehle B; Langeslay RR; Delferro M; Brosmer JL; Hendon CH; Gallagher-Jones M; Rodriguez J; Chapman KW; Miller JT; Duan X; Kaner RB; Zink JJ; Chmelka BF; Spokoyny AM A Molecular Cross-Linking Approach for Hybrid Metal Oxides. *Nature Mater.* 2018, 17, 341–348. [PubMed: 29507417]
52. Ramachandran R; Salguero TT Nanostructuring of Strontium Hexaboride via Lithiation. *Inorg. Chem* 2018, 57, 4–7. [PubMed: 29256604]

Figure 1.

(a) SEM image of bulk B_2O_3 (b) Low-magnification TEM image of OA- B_2O_3 NPs, inset high-magnification TEM image (c) Low-magnification TEM image of CMD- B_2O_3 NPs, inset high-magnification TEM image (d) ATR-IR spectra of bulk B_2O_3 , OA- B_2O_3 NPs and CMD- B_2O_3 NPs (e) B 1s and O 1s XPS spectra of bulk B_2O_3 , OA- B_2O_3 NPs and CMD- B_2O_3 NPs.

Figure 3. (a) TEM image of OA-¹⁰B₂O₃ NPs, inset SAED with labeled indices for prominent rings (b) HRTEM image of CMD-¹⁰B₂O₃ NPs (c) Flow cytometry of CHO cells incubated with no nanoparticles, OA-B₂O₃ NPs, OA-¹⁰B₂O₃ NPs, CMD-B₂O₃ NPs, or CMD-¹⁰B₂O₃ NPs for 24 hours. Dead cells were characterized as exhibiting fluorescence greater than 10². Error bars represent the standard deviation of three replicate samples.