Supplementary Information

One-step ligand exchange and switching from hydrophobic to water-stable hydrophilic superparamagnetic iron oxide nanoparticles by mechanochemical milling

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Detailed Experimental Section

Materials: All chemicals were used as received without further purification. Iron(III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) (reagent grade, ≥98%, purified lumps), iron(II) chloride tetrahydrate ($FeCl_2 \cdot 4H_2O$) (puriss. p.a., ≥99.0%), toluene (anhydrous, ≥99.8%), hexane (CHROMASOLV®, for HPLC, ≥95%), chloroform ($CHCl_3$) (CHROMASOLV® Plus, for HPLC, ≥99.9%, contains amylenes as stabilizer), sodium phosphate monobasic (BioPerformance Certified, ≥99%), Trizma® base (Primary Standard and Buffer, ≥99%), and 4,5-dihydroxy-1,3-benzenedisulfonic acid disodium salt monohydrate (Tiron) (97%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium acetate trihydrate (99–101%), sodium phosphate dibasic heptahydrate (ACS), and Tris hydrochloride (Molecular Biology) were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Sodium oleate ($C_{18}H_{33}ONa$) (>97.0%) was purchased from TCI America (Portland, OR, USA). ACS reagent grade hydrochloric acid (HCl), methanol (MeOH), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetic acid, hydrogen peroxide (30%), and potassium hydroxide (KOH) were obtained from ACP Chemicals Inc. (Montreal, QC, CAN). Ethanol (anhydrous) (EtOH) was obtained from Commercial Alcohols Inc. (Brampton, ON, CAN).

All buffers and solutions were prepared using deionized (DI) water from a Barnstead™ Diamond TII water purification system (>15 MΩ·cm) (Thermo Fisher Scientific, Waltham, MA, USA) or Milli-

Q® Reference (18.2 MΩ·cm) or Academic water purification system (min. 18 MΩ·cm, typically 18.2 MΩ·cm) (EMD Millipore Corporation, Billerica, MA, USA). For the synthesis of IONP-OA, water was deoxygenated by N_2(g) bubbling for 30 minutes. For the purification of IONP-OA, nanoparticles were centrifuged at 4000 ×*g* using a Sorvall RC 6 Plus centrifuge (Thermo Fisher Scientific, Waltham, MA, USA) using a swinging bucket rotor (SH-3000BK) or a PK120R centrifuge (ALC International, Cologno Monzese, MI, ITA) equipped with a T450 fixed angle rotor. When required, nanoparticles were redispersed in solution via analog vortex mixer (VWR International, Radnor, PA, USA). All sonications were performed using a Bransonic® model 2510 ultrasonicator (Branson Ultrasonic Corp., Danbury, CT). When required, buffers were filtered with 0.45 μm or 0.22 μm (PVDF, Thermo Scientific, Rockwood, TN, USA) syringe filters to reduce dust particles.

Synthesis of IONP-OA: Magnetic iron oxide nanoparticles stabilized with oleic acid (OA) were prepared according to the method as described in Korpany *et al.*[1] with minor modification as follows. After the reaction mixture was pelleted by centrifugation, the pale orange supernatant was removed from each nanoparticle pellet and the pellets were stored at -20 °C until purification was continued. To continue the purification, the retained pellets were defrosted to room temperature and purification was resumed as normal, by re-dispersing the pellets in hexane and subsequently re-precipitating with EtOH, as outlined in Ref. 1.

Synthesis of IONP-Tiron: The oleic acid-substituted IONPs (5 mg) and Tiron (25 mg, 50 mg, 75 mg or 100 mg) were placed into a 10 mL stainless steel milling jar, along with 2 stainless steel milling balls (7 mm diameter, 1.3 g each). The mixture was then milled using a Retsch MM400 shaker mill for either 30 min or 60 min at a frequency of 30 Hz. Unless otherwise specified, 10 μL toluene was added as a LAG liquid additive prior to milling. The resulting powders were analyzed by powder X-ray diffraction and stored under nitrogen.

Purification of IONP-Tiron: Purification of mechanochemically prepared IONP-Tiron was done using a technique conventionally used for purification of ligand-exchanged IONPs. Specifically, 5 mg of the milled reaction mixture was weighed into a glass vial. Then, 0.5 mL of 95% MeOH (i.e. 95% MeOH, 5% DI water) was added to the mixture, and the mixture was sonicated with several very brief pulses in a bath sonicator to mix and break up aggregates. A handheld neodymium (NdFeB) magnet was applied to the glass vial for 2 minutes to magnetically isolate the nanoparticles. The resulting supernatant was carefully removed by pipette and the pellet retained. 0.5 mL of fresh 95% MeOH was added to the pellet, mixture sonicated with several very brief pulses and then centrifuged at 6500 rpm (4105 ×*g*) (Sorvall PICO, Thermo Fisher Scientific (Waltham, MA, USA)) at room temperature for 15 minutes to pellet the nanoparticles. After centrifugation, the supernatant was carefully removed by pipet and the recovered pellet dried completely under nitrogen flow. The purified nanoparticle pellet was immediately re-dispersed or stored at -20 °C until further use.

Powder X-ray diffraction (PXRD): PXRD patterns were collected using a Bruker D2 powder diffractometer equipped with a Cu-K_α (λ=1.54060 Å) source and Lynxeye detector. The minimum and maximum detector discriminant values were set at 0.180 V to 0.220 V respectively to filter X-ray fluorescence from Fe. The patterns were collected in the range 5° to 40° 2θ. Analysis of PXRD patterns was conducted using Panalytical X'Pert Highscore Plus software.

When required, IONP-Tiron was further purified for PXRD as follows. Approximately 50 mg of the crude reaction mixture after milling (5 mg IONP-OA, 100 mg Tiron, milled for 60 minutes at 30 Hz with 10 μL toluene) was weighed into each of three 5 dram glass vials. Then, 5 mL of fresh 95% MeOH was added to each mixture followed by brief sonication (10, 1 second pulses) in a bath sonicator to ensure complete mixing. Nanoparticles were then magnetically isolated, as previously described, for 10 minutes at room temperature. After isolation, the resulting supernatants were carefully removed by pipet and 5 mL of fresh 95% MeOH was added to each vial to further wash the nanoparticles. The mixtures were once again briefly sonicated, then transferred to 3 × 15 mL centrifuge tubes, and subsequently centrifuged at 4000 ×*g* (Sorvall RC 6 Plus, SH-3000BK swinging bucket rotor) for 30 minutes at 20 °C to pellet the nanoparticles. After centrifugation, the resulting supernatants were carefully removed by pipet and 50 μL of fresh 95% MeOH was added to each nanoparticle pellet. Each nanoparticle mixture was vortexed and sonicated briefly (10, 1 second pulses each) to redisperse the nanoparticles. The resulting nanoparticle mixtures were transferred to a single 5 dram glass vial and dried down under nitrogen flow. Purified nanoparticles were stored under N_2(g) at -20 °C until characterization.

Fourier-Transform Infrared Attenuated Internal Reflectance Spectroscopy (FTIR-ATR): FTIR-ATR spectra were recorded between 4000 and 400 cm^{-1}, with 4 cm^{-1} resolution, on a Spectrum Two™ FTIR spectrometer equipped with a diamond ATR accessory (PerkinElmer Inc., Waltham, MA, USA). Spectrum recording and data processing was performed using Spectrum™ FTIR software (PerkinElmer Inc., Waltham, MA, USA).

Tiron reference spectra were acquired from unmodified solid Tiron deposited directly on the diamond ATR crystal. IONP-Tiron was purified prior to spectra acquisition as follows. 15.9 mg of the ligand exchange reaction mixture (5 mg IONP-OA, 100 mg Tiron, milled for 60 minutes at 30 Hz with 10 μL toluene) was weighed out in a clean glass vial. The purification of the resulting IONP-Tiron nanoparticles was followed as previous, except 1.6 mL wash volumes were used instead of 0.5 mL. After purification, the resulting purified nanoparticle pellet was redispersed in 100 μL of fresh 95% MeOH. Nanoparticle solutions were drop-cast as films onto the ATR crystal from $CHCl_3$ for as-prepared IONP-OA and from 95% MeOH for IONP-Tiron. Nanoparticle films were allowed to dry completely in air at room temperature prior to spectra acquisition.

Transmission Electron Microscopy (TEM) Imaging: Nanoparticle shape and size were evaluated by TEM imaging using a FEI Tecnai™ T12 TEM operating at 120 kV. IONP-OA TEM samples were prepared by submerging and incubating a 400-mesh carbon coated copper grid (Ted Pella Inc., Redding, CA, USA) in the as purified IONP-OA in hexane for 30 seconds. After 30 seconds, the grid was removed from the nanoparticle solution and left to dry in air at room temperature.

IONP-Tiron (prepared with 100 mg Tiron) TEM samples were prepared by purifying (as previously described) 5 mg of the reaction mixture after mechanochemical grinding (5 mg IONP-OA, 100 mg Tiron, milled for 60 minutes at 30 Hz with 10 μL toluene) and redispersing the purified nanoparticle product in 0.5 mL of 20 mM sodium phosphate buffer pH 7.09. IONP-Tiron (prepared with 25 mg Tiron) TEM samples were prepared by purifying (as previously described, except using 0.4 mL 95% MeOH washes) 4 mg of the reaction mixture after mechanochemical grinding (5 mg IONP-OA, 25 mg Tiron, milled for 60 minutes at 30 Hz with 10 μL toluene), and redispersing the purified nanoparticle product in 1 mL of 20 mM sodium phosphate buffer pH 7.09. Both nanoparticle solutions were briefly vortexed and sonicated (10 very brief pulses each) to ensure full nanoparticle redispersal prior to the plating of TEM samples. 20 μL of each prepared IONP-Tiron solution was deposited on the carbon-side

of a 400-mesh carbon coated copper grid (Ted Pella Inc., Redding, CA, USA). The droplet was incubated for 5 minutes at room temperature, then excess removed with filter paper. All prepared TEM samples were left to completely dry in air at room temperature prior to imaging.

Nanoparticle diameters (equivalent diameter) were determined from TEM images using the software Pebbles v.2.0.1[2] and statistics were obtained OriginPro v.8.5.1 (OriginLab Corporation, Northampton, MA, USA). Equivalent diameter was calculated by Eq. 1:

$$d = r \cdot 2 \cdot SF \quad (1)$$

where d is the equivalent diameter (nm), r the equivalent radius (pixel) determined by Pebbles, and SF is the image scale factor (nm/pixel).

Electrophoretic Mobility and Zeta (ζ) Potential Measurements: As zeta potential measurements can be effected by the concentration of the sample analyzed, an effort was made to ensure the nanoparticle concentration between samples tested was relatively similar. Samples were purified with the same method as previous, however, with adjustments to amount of crude reaction mixture purified in order to obtain similar nanoparticle concentrations for electrokinetic measurements (Table S1). It was observed that purification wash volume had an influence on the solubility of the nanoparticles during purification, therefore wash volumes were also adjusted to accommodate for alterations in the amount of crude reaction mixture processed (Table S1). In most cases, the nanoparticles required 30 minutes centrifugation time, an increase from 15 minutes when smaller reaction mixture amounts are purified, in order to sufficiently pellet the nanoparticles (Table S1). The need for increased centrifugation time for samples prepared for zeta potential is likely due to the increase in amount of crude reaction mixture processed and corresponding increase in wash volumes.

For electrokinetic measurements, purified nanoparticles were immediately dispersed in 1.65 or 1.6 mL filtered 20 mM sodium phosphate pH 7.00 or pH 7.19 (Table S1) and briefly vortexed (10 pulses) and sonicated (10 pulses) to fully redisperse. In some cases, purified nanoparticle solids were frozen at -20 °C under N_2(g) until measurements were to be obtained. For each sample, electrokinetic measurements were obtained using a ZetaPlus analyzer (Brookhaven Instruments, Holtsville, NY) at 25 °C, acquiring ten runs, with each run comprised of three cycles. When needed, the Dixon's *Q*-test was used to detect and reject single outliers in a data set at a confidence level of 95%. Runs for each sample were averaged, and mean and standard error reported in Table 1. The ZetaPlus software was used to calculate zeta potential (ζ) from electrophoretic mobility (μ) by the Smoluchowski equation (Eq. 2)

$$\mu = \frac{\zeta \varepsilon}{\eta} \quad (2)$$

where ε is the dielectric constant and η the viscosity of the medium.

Concentration Determination of Iron Oxide Nanoparticles: The concentration of iron in solutions of IONP-Tiron was spectrophotometrically determined by the complexation of iron(III) with Tiron based on previous literature assays[3-8]. A standard curve was constructed from samples prepared from a 1.000 mg Fe^{3+}/mL stock solution which was both prepared and diluted with 3.75 mM HCl(aq), as outlined in Table S2. 250.0 mL of 1.000 mg Fe^{3+}/mL was prepared in a 250.0 mL volumetric flask by dissolving

1.2100 g of $FeCl_3 \cdot 6H_2O$ quantitatively in 3.75 mM HCl(aq). For the construction of the standard curve, Fe^{3+} standard samples were prepared in triplicate from the prepared Fe^{3+} stock solution.

In a typical assay, 100 µL of IONP-Tiron solution or 400 µL prepared Fe^{3+} standard sample was aliquoted to a glass vial. 100 µL of 37% HCl was added to the nanoparticle or Fe^{3+} standard sample. The glass vial was capped, and heated for 10 minutes at approximately 70 °C via water bath to complete nanoparticle digestion. After 10 minutes, a clear yellow solution was obtained. Before continuing, 300 µL of DI water was added to the digested nanoparticle samples in order to keep nanoparticle sample and standard assay volumes consistent. 100 µL of the digested nanoparticle sample or standard was aliquoted to another glass vial. 100 µL of freshly prepared 0.1 M or 0.5 M H_2O_2 was added to nanoparticle samples in order to oxidize Fe^{2+} to Fe^{3+}. 25 µL of 0.1 M H_2O_2 was previously found sufficient to oxidize approximately 0.57–1.42 g/L of iron[8]. Here, 0.5 M H_2O_2 was used if the approximate concentration of iron was unknown. 100 µL of DI water was added for samples used for the standard curve determination, instead of 100 µL H_2O_2, as it was assumed that all of the iron was present as Fe^{3+}. After H_2O_2 or DI water was added, samples were incubated at room temperature for 10 minutes before proceeding. 200 µL 0.25 M Tiron(aq) was subsequently added to the assay solutions and a rapid color change occurred, from yellow to blue-green, indicating the chelation of iron by Tiron at acidic pH[9]. 350 µL of 0.2 M Tris buffer pH 9.3–9.5 was added to each assay solution, followed by 50 µL 4M KOH(aq). Upon addition of KOH(aq), the solutions turned red, indicating the presence of an iron-Tiron complex at alkaline pH[9]. After the addition of KOH, assays were incubated at room temperature for 15 minutes for full color development to occur.

UV–visible absorption spectra of all assays were collected from 800–400 nm using a 0.3 cm quartz micro spectrophotometer cell (Spectrocell, Oreland, PA, USA or Starna Cells Inc., Atascadero, CA, USA) by a Cary 100 Bio spectrophotometer (Agilent Technologies Inc., Santa Clara, CA, USA). For the construction of the standard curve, assays were diluted by a factor of 4 with 0.2 M Tris buffer pH 9.3–9.5 (2.400 mL added) prior to UV–visible spectra acquisition. For nanoparticle samples, samples were diluted with sufficient 0.2 M Tris buffer 9.3–9.5 in order to get $A_{480\ nm}$ readings within the linear region of the standard curve. Using the prepared Fe^{3+} standard samples (Table S2) an extinction coefficient at 480 nm for Fe^{3+} ($\varepsilon(Fe^{3+}, 480\ nm)$) (Eq. 5), using absorbance at 480 nm ($A_{480\ nm}$) (Eq. 4), was calculated by applying the Beer-Lambert Law (Eq. 3):

$$A = \varepsilon l c \quad (3)$$

$$\varepsilon(Fe^{3+}, 480\ nm) = A_{480\ nm} / (l \cdot c) \quad (4)$$

$$\varepsilon(Fe^{3+}, 480\ nm) = m / l \quad (5)$$

where A is the absorbance of the sample, ε is the extinction coefficient at a specific wavelength, l the pathlength of the cuvette, and c is the concentration of the absorbing species. m refers to the calculated slope of the linear regression (Figure S4) of absorbance vs. concentration of Fe^{3+} from the data obtained for the standard samples prepared in Table S2. For the standard curve, assays performed in triplicate were averaged for each concentration of Fe^{3+}, and linear regression was performed on the averaged data using OriginPro v.8.5 (OriginLab Corporation, Northampton, MA, USA) to obtain the slope, m.

Solubility Measurements: Solubility of ligand exchanged nanoparticles was determined by the visual examination of redispersed purified ligand exchange products. Solid, dried IONP-Tiron product obtained from purified ligand exchange mixture (5 mg IONP-OA, 100 mg Tiron, milled for 60 minutes

at 30 Hz with 10 μL toluene) was redispersed in 20 mM sodium phosphate buffer pH 7.19, 20 mM sodium acetate buffer pH 5.00, 0.2 M Tris buffer pH 9.26, DI water, DMSO, or DMF. Products were briefly vortexed (10 pulses) and sonicated (via bath sonicator, 10 pulses) before solubility determinations were made.

Magnetometry: Samples for magnetic measurements were prepared as follows. IONP-OA was used as-prepared, without further purification. For IONP-Tiron, 41.2 mg of milled reaction mixture (5 mg IONP-OA, 100 mg Tiron, 60 min mill time, 30 Hz) was purified as previously described, except 4 mL of 95% MeOH was used to wash the nanoparticles at each step, nanoparticles were magnetically isolated for 10 minutes, and centrifugation at 6,500 rpm was performed for 30 minutes.

Superconducting quantum interference device (SQUID) magnetometry measurements were carried out using a Quantum Design MPMS XL-7S magnetic property measurement system. Each powder sample was loaded in a gelatin capsule, which was sealed with a thin strip of Kapton tape. The capsule was inserted in a diamagnetic clear plastic straw fixed to the MPMS sample rod. For both zero-field-cooled (ZFC) and field-cooled (FC; applied field was 10 mT) measurements, the samples were first cooled to 1.9 K in the absence (ZFC) or presence (FC) of an applied magnetic field, before being warmed to 300 K under 10 mT while magnetization was measured. ZFC measurement preceded FC. Magnetization vs applied magnetic field strength loops were measured at temperatures of 300 K and 1.9 K, with applied magnetic field strength up to ±7 T. Magnetization was normalized per mass of sample (note on units: 1 emu g^{-1} = 1 A m^2 kg^{-1}).

Additional Figures

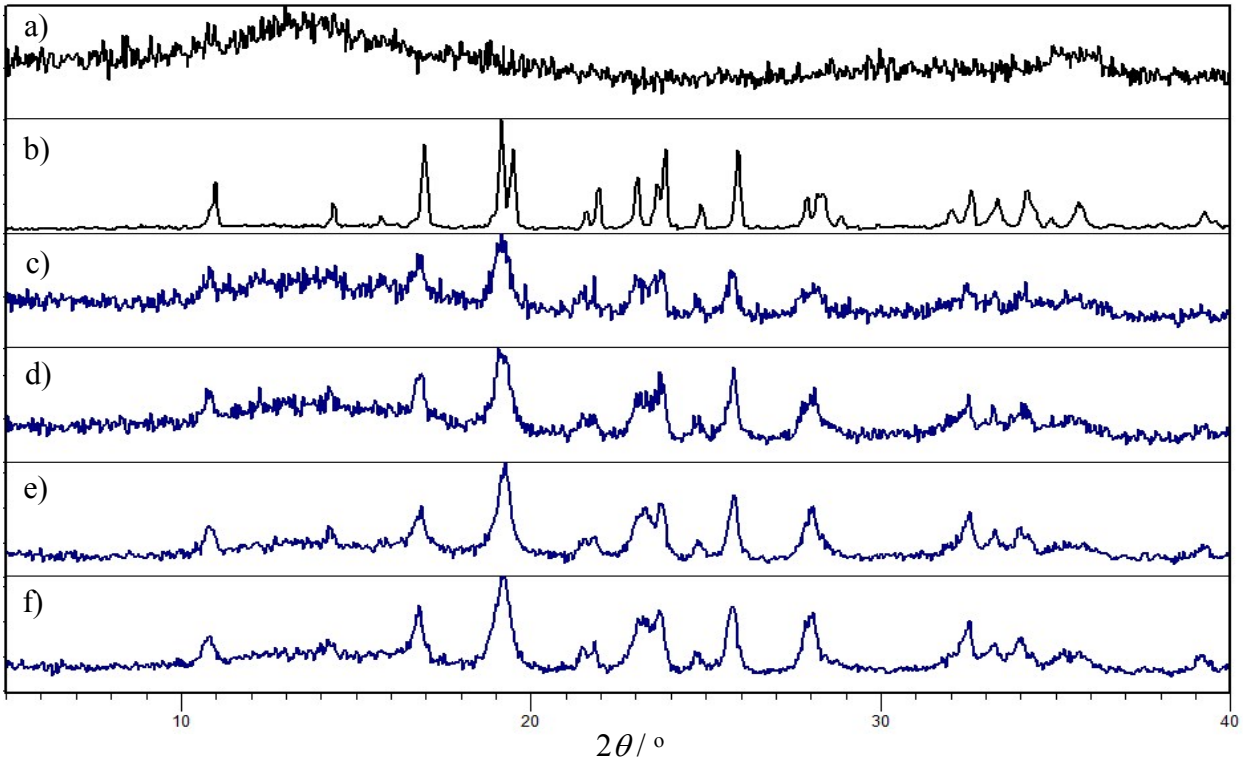

Figure S1. Powder X-ray diffraction patterns of: a) IONPs synthesized from solution; b) commercial Tiron; mechanochemically prepared samples made by 30 min LAG (10 μL toluene) of 5 mg IONPs with: c) 25 mg; d) 50 mg; e) 75 mg and f) 100 mg Tiron.

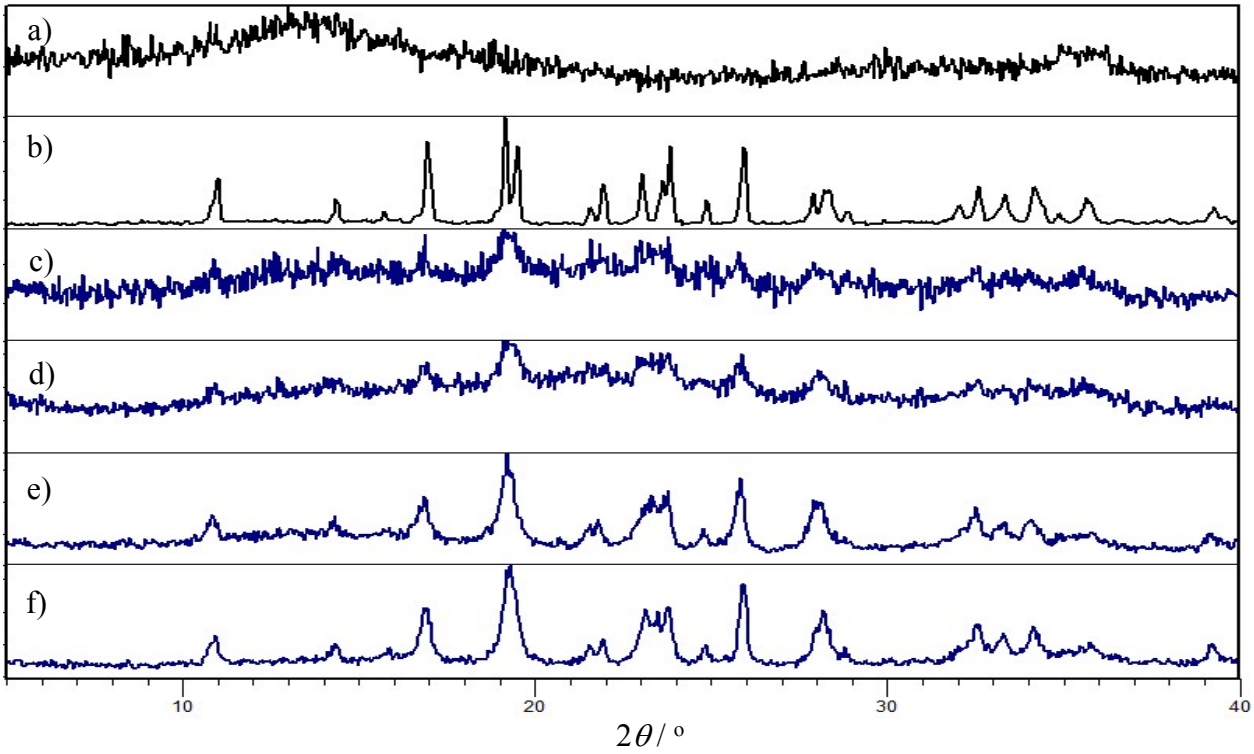

Figure S2. Powder X-ray diffraction patterns of: a) IONPs synthesized from solution; b) commercial Tiron; mechanochemically prepared samples made by 60 min LAG (10 μL toluene) of 5 mg IONPs with: c) 25 mg; d) 50 mg; e) 75 mg and f) 100 mg Tiron.

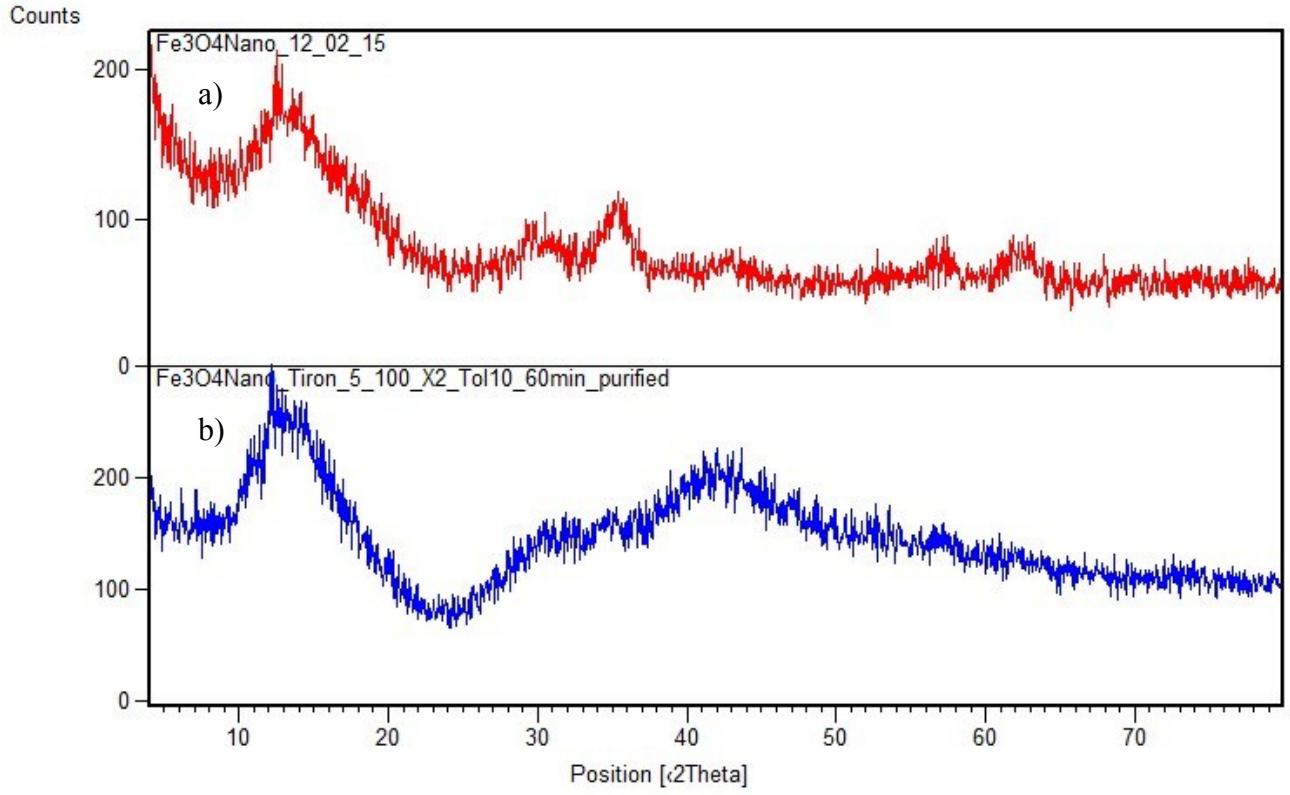

Figure S3. Powder X-ray diffraction patterns of: a) IONPs synthesized from solution; b) mechanochemically prepared samples made by 60 min LAG (10 μL toluene) of 5 mg IONPs with 100 mg Tiron, purified as described in Supplementary Information.

Table S1. Purification and redispersal of IONP-Tiron for samples prepared for electrokinetic measurements.

Sample[a]	Amount of reaction mixture processed (mg)	Wash volumes (mL)	Centrifugation time (min)	pH[d]	Volume of buffer added for redispersal (mL)
100 mg Tiron, 30 min[b]	30.1	3.0	45	7.00	1.65
75 mg Tiron, 30 min	23.7	2.3	45	7.00	1.65
50 mg Tiron, 30 min	16.6	1.6	30	7.00	1.65
25 mg Tiron, 30 min	9.4	0.9	30	7.00	1.65
100 mg Tiron, 60 min, neat	30.2	3.0	30	7.19	1.6
100 mg Tiron, 60 min, 50 µL DMF	30.2	3.0	30	7.19	1.6
100 mg Tiron, 60 min	30.3	3.0	30	7.19	1.6
75 mg Tiron, 60 min	23.5	2.3	30	7.19	1.6
50 mg Tiron, 60 min	16.5	1.6	30	7.19	1.6
50 mg Tiron, 60 min[c]	16.4	1.6	30	7.00	1.65
25 mg Tiron, 60 min	9.7	0.9	30	7.00	1.65

a Unless otherwise specified, samples were prepared by milling the specified amount of Tiron with 5 mg of IONP-OA and 10 µL toluene.
b Minutes specified in the sample details refer to the mill time of the reaction.
c Repeat sample, for comparison, corresponding to -47.96 ± 0.92 mV in Table 1 redispersed in 20 mM sodium phosphate buffer pH 7.00 (instead of pH 7.19) for electrokinetic measurements.
d Nanoparticle samples were redispersed in 20 mM sodium phosphate buffer at the stated pH.

Table S2. Composition of standard samples prepared for the construction of the standard curve for Fe^{3+}.

Standard Sample #	µL Fe^{3+} stock (1.000 mg/mL)	µL HCl(aq) (3.75 mM)	Final Fe^{3+} concentration (µg/mL)	UV–vis assay concentration (µg/mL)
0	0	400.0	0	0.00
1	40.0	360.0	100	2.50
2	80.0	320.0	200	5.00
3	120.0	280.0	300.0	7.50
4	160.0	240.0	400.0	10.00
5	200.0	200.0	500.0	12.50
6	240.0	160.0	600.0	15.00
7	280.0	120.0	700.0	17.50
8	320.0	80.0	800.0	20.00
9	360.0	40.0	900.0	22.50
10	400.0	0.0	1000.0	25.00

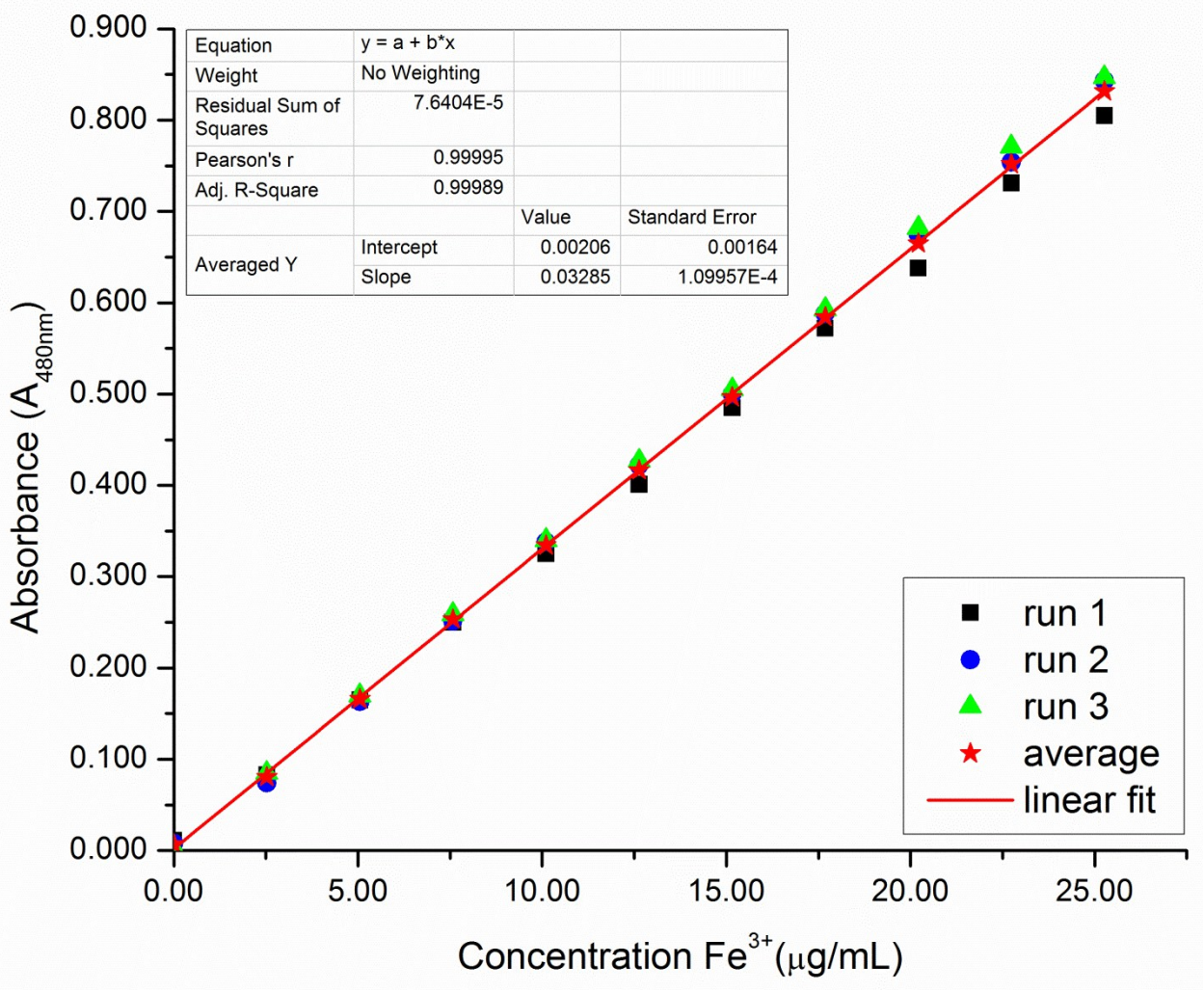

Figure S4. Linear fit of standard curve for Fe^{3+} complexed with Tiron. The extinction coefficient for the iron-Tiron complex in the assay developed was calculated using Eq. 5 and found to be $\varepsilon(Fe^{3+}, 480\ nm) = 109.5\ (mg/mL)^{-1}\ cm^{-1}$, $6.23\ mM^{-1}\ cm^{-1}$.

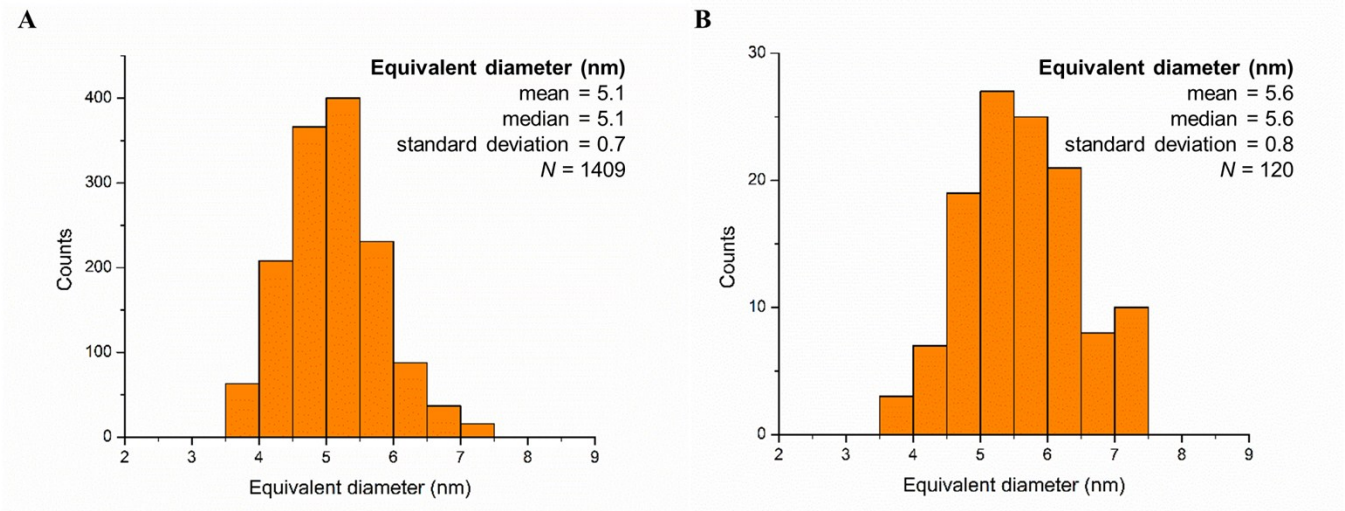

Figure S5. Nanoparticle equivalent diameter histograms and statistics showing the size distribution of *N* particles for (A) IONP-OA and (B) IONP-Tiron for TEM samples presented in Figure 1.

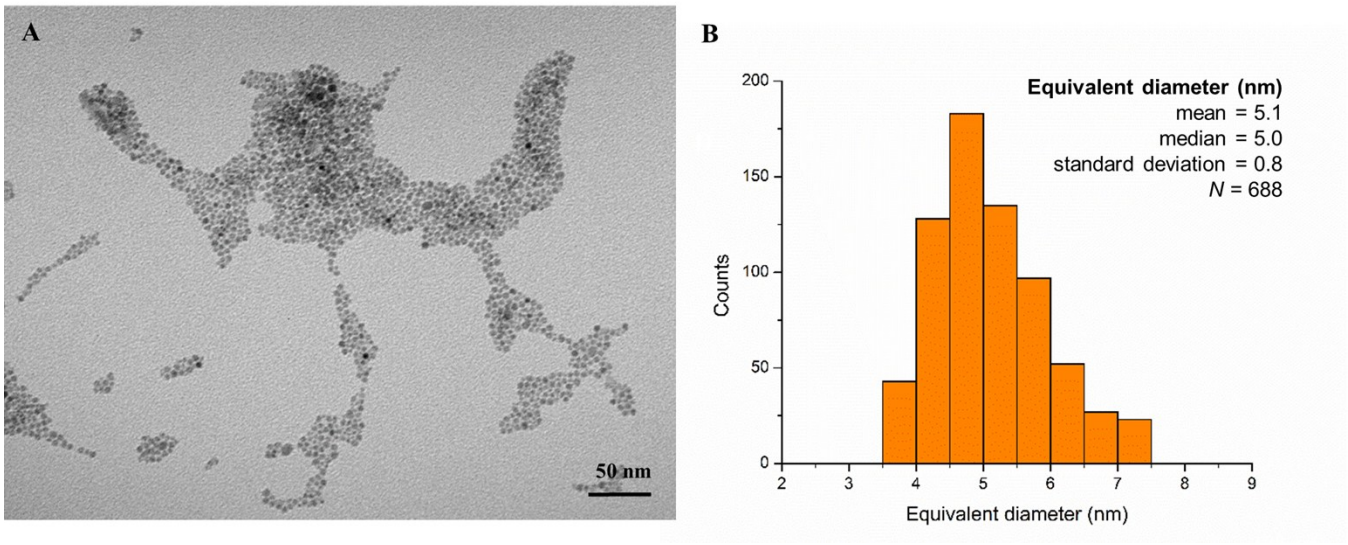

Figure S6. (A) TEM image of IONP-Tiron (5 mg IONP-OA, 25 mg Tiron, milled for 60 minutes at 30 Hz with 10 μL toluene) and (B) associated nanoparticle equivalent diameter histogram and statistics showing the size distribution of *N* particles.

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