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Tenacic Acids: a New Class of Tenacious Binders to Metal Oxide Surfaces

Rajesh Komati,[b] Carl A. Mitchell,[b] Anastasia LeBeaud,[b] Huy Do,[b] Galina Z. Goloverda*[a] and Vladimir L. Kolesnichenko*[a]

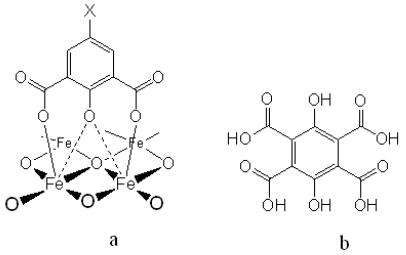
Abstract: The backbone of 2-hydroxyisophthalic acid was identified as a potential metal oxide anchor because of the perfect alignment of all three of its donor groups for binding to inorganic surfaces. It can therefore be used in the design of organic linkers for metal oxide-based hybrid materials. Optimized and scalable methods for the synthesis of 2-hydroxyisophthalic acid (1) and its 5-substituted derivatives: 5-bromo- (2), 5-sulfooxy- (3), 5-hydroxy- (4), and 5-PEG600 (5) are presented. Dynamic Light Scattering (DLS) demonstrated that (2) inhibits $Fe(OH)_3$ precipitation when Fe^{III} aqueous solutions are titrated with NaOH, while similar titrations in the presence of the structurally-related isophthalic and salicylic acids, both missing the third donor group, show turbidity at pHs as low as 2.3 and 3.5, respectively. The adduct synthesized from 4.5 nm γ-Fe_2O_3 nanoparticles and (5) is water-, alcohol- and CH_2Cl_2-soluble, and forms stable aqueous colloids in the pH range of 4.4-8.7. Moreover, at a pH close to neutral these colloids survive at 100ºC, demonstrating the high practicality of 2-hydroxyisophthalic acid for nanoparticulate inorganic/organic hybrid material design.

Introduction

Many areas of modern technology rely on composite materials with a broad spectrum of chemical and physical properties. For example, nanoparticulate imaging and delivery agents for theranostic applications often contain a superparamagnetic iron oxide core and an organic shell with a targeting peptide, fluorescent dye, or drug molecule attached.[1-6] Similarly, materials for photovoltaics are commonly made up of a semiconductor with an attached dye or quantum dot sensitizer.[7-10] Normally, a linker whose structure and composition are optimized for binding, connects the two components in these materials. Metal oxides, for instance, can be connected to organic parts of the material by including oxygen-donor ligands in the linker. A primary goal of this work was to develop new linkers with an easily functionalizable structure and a coordinating head with optimal binding capacity for metal oxide surfaces.

For a biomedical application, it is important that the nanoparticulate adduct be hydrolytically stable, which can be secured by the nature of the linker's coordinating head. When designing such a head, an aqueous metal ion complexation equilibrium would be an advantageous, yet simple, model system to examine. Stronger ligands might seem to be the obvious choice for this purpose. For example, anionic chelators/complexones such as alpha-hydroxycarboxylic acids (citric, tartaric, etc.),[11] derivatives of catechol,[12-16] and phosphonic acids,[17-19] have been found to be effective colloid stabilizing agents. On the other hand, the complexones often bind so strongly to a SINGLE metal center that they leach metal ions from the surface, leading to nanoparticle degradation,[18,20] and in the extreme, to its complete dissolution if enough complexone is present. The molecular geometry of an ideal linker's coordinating backbone would have its donor atoms positioned for a MULTIPLE-SITE attachment to metal oxide surface in a bridging binding mode.

Even though our earlier experience with phthalic and isophthalic acids showed that they were relatively weak ligands for iron oxide nanoparticles as compared to citric and tartaric acids,[11] the aromatic acids were still more appealing due to their higher propensity for derivatization. We proposed to strengthen the aromatic linker head's binding capacity by adding a phenolic OH-group between the two carboxylates in the isophthalate metal oxide-coordinating core. The idea was that the resulting tridentate ligand would preferentially bind in a bridging mode to at least two neighboring metal ions (η^3:μ-bridging), as shown in Scheme 1a. The ligand presented in this scheme is 2-hydroxyisophthalic acid, and to the best of our knowledge, there are no reports in the literature on its surface and colloidal chemistry.



Scheme 1. (a) A hypothetical binding mode of 2-hydroxyisophthalic acid to the solid iron oxide surface; (b) quinol tetracarboxylic acid.

Our target molecule may be also viewed as a derivative of salicylic acid, which is known to form moderately strong complexes with metal ions in aqueous solutions.[21] Considering the binding mode displayed in Scheme 1a, it appeared reasonable to expect that an extra carboxyl group added to the salicylic acid molecule would not contribute to the strength of a single metal ion complexation. However, the resulting molecule might be an effective bridging ligand for binding to an inorganic surface with minimal risk of leaching metal ions out. Since no derivatives of 2-hydroxyisophthalic acid are commercially available, one of the aims of this work was its synthesis and functionalization.

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The first report of derivatives of 2-hydroxyisophthalic acid was made by John U. Nef (1862-1915) as early as in 1888.[22] Focusing on the synthesis of the carboxylate derivatives of p-benzoquinone, Nef performed a multiple-step synthesis to obtain quinol tetracarboxylic acid. The structure of quinol tertacarboxylic acid, with its two identical sets of functional groups facing in opposite directions (Scheme 1b), might be advantageous for supramolecular chemistry and photovoltaics. However, hybrid materials for biomedical applications would benefit more from a family of “single-faced” ligands that can be chemically modified at the site of substituent X (Scheme 1a).

There are only four synthetic procedures found in the literature for the preparation of unsubstituted,[23-27] 4,6-disubstituted[28-30] and 5-substituted[31-33] derivatives of 2-hydroxyisophthalic acid. To the extent of our knowledge, the only attempt to directly functionalize 2-hydroxyisophthalic acid suffered from low yield and ill characterization.[24] There were several reports on the coordination chemistry of 2-hydroxyisophthalic acid with copper(II), where this ligand was generated *in situ* by oxidation of isophthalic acid with Cu(II).[34-39]

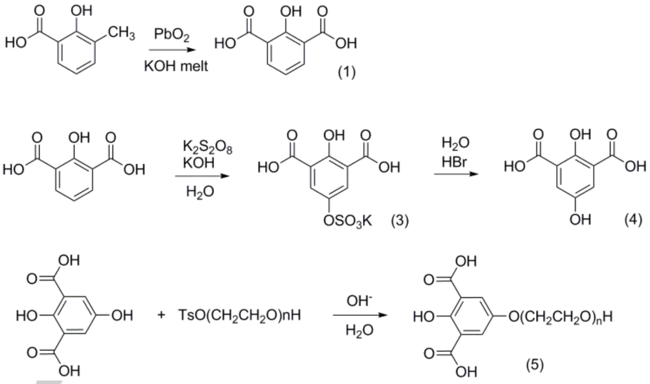
Relatively scarce studies of 2-hydroxyisophthalic acid and its derivatives include solution phase beryllium complexation,[27] structural coordination chemistry,[34-41] luminescence properties,[41] supramolecular chemistry,[26,42,43] crystal structure and acid/base properties,[44] and hydrolysis kinetics.[45,46]

Herein we report the synthesis of an unsubstituted acid (1) and of its 5-substituted derivatives with X = Br (2), OSO_3^- (3), OH (4) and PEG600 (5) substituents. Also, we demonstrate a high affinity of 2-hydroxyisophthalate backbone to metal oxide surfaces, and the ability of its derivatives to stabilize iron oxide aqueous colloids via electrostatic and steric mechanisms.

Results and Discussion

Ligands synthesis and properties Synthesis of the parent 2-hydroxyisophthalic acid (1) was accomplished by PbO_2 oxidation of 3-methylsalicylic acid in KOH melt[23-25] (Scheme 2). Our modification of this method helped to reduce the amount of time needed for the reaction and to eliminate the fire and inhalation hazards without any loss in yield or quality of the product. This relatively stable substance can be easily purified by recrystallization from hot water (from which it crystallizes as a monohydrate) or by vacuum sublimation at 200°C. Its room-temperature (22°C) solubility in water was found to be 2.6 g/L. The substance is a triprotic acid with pKa’s 1.92, 4.57 and 11.1 (details will be reported elsewhere). The monohydrate loses its crystallization water above 100°C and the anhydrous compound melts with decomposition at 253-255°C. The substance resists oxidation by oxygen or lead(IV) oxide, but its benzene ring undergoes electrophilic aromatic substitution via nitration, azo-coupling[47] and Elbs persulfate oxidation (details are given below) reactions, which opens up a variety of pathways for its derivatization.

Synthesis of 5-bromo-2-hydroxyisophthalic acid (2) was completed by Duff formylation[48,49] of 5-bromosalicylic acid followed by oxidation with sodium chlorite. Synthesis of 2-hydroxy-5-(sulfooxy)isophthalic acid potassium salt (3) was accomplished by Elbs persulfate oxidation[50] of (1). This compound was used as a precursor for the formation of 2,5-dihydroxyisophthalic acid (4), synthesized through its bromide-assisted acidic hydrolysis. Synthesis of the 2-hydroxyisophthalic acid conjugate with polyethylene glycol (PEG-600) (5) was accomplished in two steps, starting with intermediate (4). In the first step, PEG-600 was tosylated with tosyl chloride in the presence of triethylamine. In order to minimize the formation of the ditosylated derivative, the synthesis was performed with a large excess of PEG and in a dilute dichloromethane or chloroform solution. In the second step, nucleophilic substitution of the tosylated PEG-600 with (4) in basic aqueous solution yielded the target conjugate, which was freed from the sodium tosylate by-product and excess PEG by elution through a base-activated DOWEX-1 resin column.



Scheme 2. Synthesis of 2-hydroxyisophthalic acid and its 5-substituted derivatives.

Interaction with metal oxide surfaces. The affinity of 2-hydroxyisophthalic acid to inorganic oxide surfaces was first evidenced by thin-layer chromatography (TLC). 2-hydroxyisophthalic acid, 5-hydroxyisophthalic acid, and salicylic acid were compared side-by-side on normal phase TLC plates impregnated with UV_{254} fluorescent indicator. Using an eluent of 8:2 (v/v) ethyl acetate/acetic acid the R_f values were 0.41, 0.75 and 0.78, respectively, indicating a significantly stronger binding of the named (1) acid to silica, which is a relatively acidic oxide.

The affinity of 2-hydroxyisophthalate moiety to iron oxide surfaces was then evaluated by testing its ability to inhibit the precipitation of iron(III) hydroxide from aqueous solutions of Fe^{III} against the same ability of the structurally related isophthalic and salicylic acids (which have only two coordinating groups on the ring). Three aqueous solutions containing iron(III) and one of the above acids were prepared and titrated with a NaOH solution while monitoring by Dynamic Light Scattering (DLS). Solution (a) contained 5-bromo-2-hydroxyisophthalic acid (2) (Fe:L = 2:3); solutions (b) and (c) contained salicylic and 5-hydroxyisophthalic acids (Fe:L = 1:3), respectively. The acid (2) was superior to the reference salicylic and 5-hydroxyisophthalic acids, as it was the only one able to inhibit precipitation of iron hydroxide under neutral and basic conditions (Fig.1).

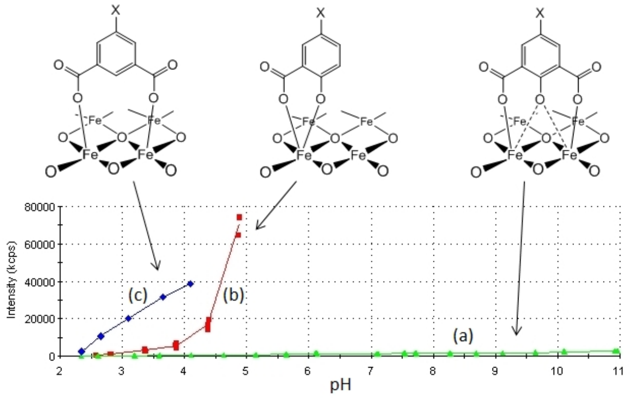


Figure 1. Light scattering as a function of pH in the DLS-monitored titration of iron(III) aqueous solutions containing 5-bromo-2-hydroxyisophthalate (solution a, green curve), salicylate (solution b, red curve), and isophthalate (solution c, blue curve). Note: higher light scattering intensity is due to a greater aggregation. The former effectively inhibits precipitation of hydrated iron(III) oxide in the reference reaction $Fe^{3+} + 3OH^{-} \rightarrow Fe(OH)_3$.

Based on visual evidence - ligand-free (except for H_2O and Cl^-) Fe^{III} solutions turn from yellow to deep red-purple upon addition of (1) or (2) – and UV-Vis data (Fig.S24), it can be concluded that the solution (a) at low pH contained iron in a form of coordination complex. This observation is in line with the known property of iron(III) to complex salicylic acid,[21] but not isophthalic acid, which did not cause any notable color change. As the pH was raised during titration, the characteristic colors in (a) and (b) rapidly faded, resulting in a clear orange solution with (a) and turbid orange one with (b); the originally clear yellow isophthalate-containing solution (c) rapidly turned turbid orange at a pH as low as 2.5. The DLS and UV-Vis data (Fig.S24) evidenced that the most likely form of iron in (a) above pH 5 was colloidal iron(III) hydroxide. It is our hypothesis that the original (pH 2) iron 2-hydroxyisophthalate complex in this solution is not particularly strong and the equilibrium shifts significantly towards its dissociation as the pH is raised. Thus, the complex undergoes partial dissociation, hydroxylation, and condensation, resulting in the formation of very small iron (hydr)oxide nanoparticles with (2) coating the surface – likely with the same binding mode as in the original complex (Scheme 1a). This also correlates with 2-hydroxyisophthalate complexation stoichiometry with Be and complex stability trends for Be, Al, Cr, Fe, Cu, Zn, Cd and Pb ions.[27]

2-hydroxyisophthalate-coated Fe_2O_3 nanoparticles Inorganic nanoparticles, coated with common small-molecule ligands, usually form aqueous colloids stabilized by an electrostatic mechanism (electrical double-layers). It is likely that this scenario is in place in a solution (a), Figure 1, at higher pHs. Generally, the stability of such colloids is affected by the pH and ionic strength of the medium. The same complexing agent, but chemically modified with a spacer attached to its backbone, can stabilize the nanoparticles' colloid through a steric mechanism, which is pH-insensitive. Depending on the nature of the spacer, this agent can also facilitate solubility of the nanoparticulate adduct in different solvents. For example a spacer composed of hydrocarbon chains can make the inorganic/organic adduct lipophilic while a polyether-like spacer can make it amphiphilic. In this study we have chosen PEG600 as a suitable spacer and conjugated it with 2-hydroxyisophthalate moiety to produce (5). This choice was justified for very small iron oxide nanoparticles used in this study. [15,51,52]

The 4.5 nm maghemite (γ-Fe_2O_3) nanoparticles were synthesized in a form of a surfactant-free non-aqueous (diethylene glycol) colloid. This was accomplished by high-temperature hydrolysis of chelated iron(II,III) alkoxide complexes, followed by room-temperature oxygenation. Minor modification of our earlier reported method[11,53] simplified the procedure and permitted more accurate control over the total concentration of iron in the resulting colloids. As we have shown,[11,53] the reaction conditions used for these syntheses are sufficient for converting all iron precursors into non-aggregated nanoparticles in quantitative yield (TEM image and XRD are shown in Fig. S25). Diethylene glycol colloids of the obtained 4.5 nm nanoparticles were reacted with (1) or (5) producing the surface-coated nanoparticulate adducts. The added amount of ligand was based on the known nanoparticles' concentration and size. The reaction stoichiometry was calculated so that each ligand molecule bound to two metal atoms on the nanoparticle's surface[11] (see p. S27 in SI file for details).

The DLS-monitored pH titrations were performed on aqueous Fe_2O_3 colloids (1.0 g of stock diethylene glycol colloid per 10 mL total volume) with the initial Fe^{III} concentration of 0.005M (Fig 2). A ligand-free Fe_2O_3 colloid (control) could be kept peptized only at pH values of 5.5 and lower (red curve in Fig.2). Colloids containing particles coated with the parent acid (1) showed the opposite behavior: at low pH the colloids aggregated; stable aqueous colloids formed in the pH range of 5.2 to 8.2 (blue curve in Fig. 2). This observation was in line with the expected electrostatic colloid stabilization mechanism, which is pH-dependent.

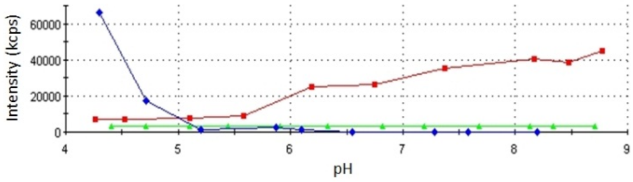


Figure 2. Light scattering as a function of pH in Fe_2O_3 (4.5 nm) aqueous colloids: the original ligand-free colloid (red), a colloid with nanoparticles coated with 2-hydroxyisophthalic acid (blue), and a colloid containing particles coated with 2-hydroxyisophthalic acid-PEG600 conjugate (green). Note: higher light scattering intensity is due to a greater aggregation.

In order to obtain pH-insensitive colloids, we used (5) as an amphiphilic steric stabilizing agent. Nanoparticulate adduct of 4.5 nm Fe_2O_3 with (5), isolated in solid form, was found to be water-, methanol-, ethanol- and dichloromethane-soluble. According to DLS, it has formed stable aqueous colloids in the studied range of pHs from 4.4 to 8.7 (green curve in Fig. 2) and contained particles with a hydrodynamic diameter of 12 nm.

Moreover, these colloids remained unchanged at neutral pH even after heating to 100°C.

Further evidence of binding of the 2-hydroxyisophthalate moiety to Fe_2O_3 nanoparticles was obtained from FT-IR spectra of both adducts: with (1) and (5) (isolated in pure form) and from the combustion analysis for the adduct with (1). The IR spectra showed expected vibrational bands of the coordinated aromatic carboxylate ligand (Fig. S26); spectrum of the adduct with (5) showed additional vibrational bands corresponding to oligo-ethylene oxide side substituent. Combustion analysis for Fe_2O_3 adduct with (1) detected that the content of Fe_2O_3 was 79.8%. Calculation (see p. S27 in SI file for details), based on assumption that 2-hydroxyisophthalate ligand is doubly-deprotonated and bound to two surface iron atoms on the 4.5 nm nanoparticle, gave the Fe_2O_3 content of 80.28%.

Conclusions

In conclusion, our hypothesis that 2-hydroxyisophthalic acid has its two carboxyl groups and phenolic -OH ideally aligned for strong binding to inorganic surfaces was supported. This moiety would be a good precursor for an adjustable linker's synthesis. Because this acid and its derivatives are not commercially available, the parent acid and its 5-substituted derivatives with X = Br, OSO_3^-, OH and a conjugate with PEG600 have been synthesized. The 2-hydroxyisophthalic acid derivatives inhibit precipitation of iron(III) hydroxide from neutral and alkaline aqueous solutions. The 5-(PEG600) derivative makes 4.5 nm γ-Fe_2O_3 nanoparticles not only water-, ethanol- and dichloromethane-soluble, but also capable of forming heat-resistant aqueous colloids at neutral pH, and stable colloids at room temperature in the studied pH range of 4.4-8.7.

The described findings, great potential for simple derivatization and high stability open up a variety of applications for 2-hydroxyisophthalic acid as a precursor in the synthesis of linkers for organic/inorganic composite materials for biomedical and solar energy uses. We define this acid and its derivatives as being tenacious to metal oxide surfaces and propose to name them "tenacic acids".

Experimental Section

General All reagents and solvents were of the reagent grade purchased from ACROS or Aldrich. NMR spectra were recorded on Agilent 400MR spectrometer. Routine electrospray mass-spectra were obtained on a Thermo Finnigan TSQ Ultra instrument. High-resolution mass spectra were obtained on Thermo Q-Exactive LC/MS/MS System and on Agilent Technologies 6530 Accurate Mass QTofLC/MS (at the University of Texas at Austin mass-spectrometry facility). Dynamic light scattering (DLS) experiments were performed with a Malvern Zetasizer Nano ZS instrument combined with a MPT-2 automatic titrator. The initial concentrations were: Fe^{III} - 1.5 mmol/L, (2) – 2.25 mmol/L, salicylic and 5-hydroxyisophthalic acids – 4.5 mmol/L, NaOH (titrant) – 0.25M. In the experiments with Fe_2O_3 nanoparticles and (1) and (5), the initial $[Fe^{III}]$ was 5×10^{-3}M, [L] was 5.5×10^{-4}M, and titrations were done with 0.01M NaOH and HCl. The elemental analyses were performed by Galbraith, Inc. Powder X-ray diffractogram was obtained using Rigaku MiniFlex II diffractometer. TEM images were obtained on JEOL JEM 2010 transmission electron microscope. FT-IR spectra were obtained on Thermo Nicolet 380 spectrometer.

2-hydroxyisophthalic acid (1). A 250-mL stainless steel beaker was charged with 120 g of the granular $KOH{\cdot}H_2O$ and 25 mL of water. After cooling for 5 minutes, 20.0 g of 3-methyl salicylic acid were added to the solution gradually while stirring with nickel spatula, followed by 120 g of PbO_2. The resulting mixture was flame-heated while intensive stirring with a Bunsen burner. During 10-15 minutes heating session, the mixture turned thicker first, and then softened, then liquefied, briefly boiled, and changed its color from black to red. Heating was continued until the melt became free-flowing and Pb_3O_4 formed as red crystals. The reaction mixture was allowed to cool; the solidifying melt was loosened by stirring. After cooling, the solid was treated with 300 mL of deionized water and stirred until KOH melt dissolved and Pb_3O_4 separated from the solution. The crystalline red Pb_3O_4 fraction was separated by decantation, and the yellow-orange microcrystalline fraction was separated by a brief centrifuging. The precipitates were washed with additional 2×50 mL of water, and all aqueous solutions were combined. The resulting solution was acidified with the solution of sulfuric acid: 51 mL of a concentrated H_2SO_4 in 100 mL of water. Addition of sulfuric acid was continued until the pH dropped to 7-8; the precipitation of $PbSO_4$ at this point was complete. The precipitated lead sulfate was separated by centrifuging, and rinsed with water to improve the yield of the product. The separated supernatant solution was further acidified with the remaining sulfuric acid; this caused precipitation of the target product **(1)**. After cooling in an ice bath, the solid was filtered off on a medium glass frit, washed with 0.1M HCl until a drop test with $BaCl_2$ solution was negative, then with icy water, and finally transferred in a dish and air-dried. Yield of an off-white powder was 20.4 g (85%). No further purification was needed for most purposes, however if desired, the substance can be recrystallized from hot water. All lead-containing by-products were washed with water, dried and recycled. Anal. Calc'd for $C_8H_6O_5{\cdot}H_2O$: C, 48.00; H, 4.04. Found: C, 48.35; H, 4.02. HRMS (ESI) calc'd. for $C_8H_6O_5$ [M - H] 181.0142, found 181.0139. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.93 (d, *J* = 7.6 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 1H).

5-bromo-2-hydroxyisophthalic acid (2) The solution of 5-bromosalicylic acid (1.74 g, 8 mmol) and hexamethylenetetramine (4.48 g, 32 mmol) in 20 mL of trifloroacetic acid was stirred at 90˚C for 12 h. After completion and cooling to room temperature, 100 mL of 1 M HCl were added and the reaction mixture was stirred for 6 h. The organic product was extracted with ethyl acetate (3×100 mL). Combined organic layers were washed with water and dried over sodium sulfate. Ethyl acetate was removed under reduced pressure to get the 1.49 g of 5-bromo-3-formylsalicyclic acid (a) with a 76 % yield.

To a solution of (a) (0.74 g, 3 mmol) in 6 mL of DMSO, sodium dihydrogenphosphate (0.094 g, 0.783 mmol) solution in 2 mL of water was added. To this stirring solution, sodium chlorite (0.577 g, 6.38 mmol) in 20 mL of water was added dropwise and the reaction mixture was stirred at room temperature about 3 h. After completion, the pH was lowered to 2 by addition of sulfuric acid and the solution was cooled to ~10°C. After 3 hours, the precipitate was filtered off and dried under vacuum to get 0.519 g of the pure product with 62% yield.

Anal. Calc'd for $C_8H_5O_5Br{\cdot}H_2O$: C, 34.43; H, 2.53. Found: C, 34.92; H, 2.43. HRMS (ESI) calc'd. for $C_8H_5O_5Br$ [M - H] 258.9248, found 258.9240. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.95 (s).

2-hydroxy-5-(sulfooxy)isophthalic acid, K salt (3) (a) Ten mmol (2.00 g) of the recrystallized **(1)** was suspended in 20 mL of water; 17.0 mL of 5.0M aqueous NaOH was added, resulting in a complete dissolution of the acid. The solution was chilled on ice. A solution of 10 mmol of $Na_2S_2O_8$ (2.38 g) in 10 mL of water was added dropwise under stirring. Rate of the addition was adjusted so that the temperature did not exceed 10°C. The reaction solution was sealed and left at room temperature for ~8 hours.

(b) The ice-chilled reaction solution was acidified with 1M HCl to pH ~1. Unreacted 2-hydroxyisophthalic acid **(1)** was quickly extracted with four portions of 25 mL of MTBE/CH2Cl2 (2:1) mixture (the organic solution was rotary-evaporated and the unreacted **(1)** (0.6 g) was recovered and reused in the next sulfatation procedure. A solution of potassium bisulfate (20 mmol, 2.7 g) in 10 mL of water was added to the reaction solution with agitation, and the solution was left at ~10°C overnight. A crystalline product was isolated by filtration and washing with concentrated $KHSO_4$ solution before it was used for synthesis of **(4)**. For the analytical purposes, a pure substance was obtained by washing with 10 mL of chilled 0.1M HCl, then with MTBE and dried under open air at ambient temperature and then at 105°C. The yield of the off-white powder was 1.50 g (70%). For analysis, the sample was dried at 110°C overnight followed by combustion at 800°C; the residue was identified as K_2SO_4. Calcd: 27.5%. Found: 26.9%. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.71 (s). ESI-MS calc'd. for $C_8H_6SO_9$ [M-H] 277, found 277; [½M-H] 138, found 138. Fragmentation of these peaks followed the expected path in MS-MS runs.

2,5-dihydroxyisophthalic acid (4) A suspension of **(3)** (1.10 g, 3.48 mmol) in 20 mL of water was mixed with 6 mL 25% HCl and 0.2 g of NaBr. The reaction mixture was brought to 80°C and stirred for about 2 hours. As reaction progressed, the solution turned clear and by the end of the reaction, a white crystalline precipitate formed. The reaction mixture was cooled down to a room temperature and a white precipitate was filtered, washed with 0.1 M chilled HCl and dried to produce 2,5-dihydroxyisophthalic acid **(4)** (0.65 g) as a white powder with an isolated yield of 86%. Anal. Calc'd for $C_8H_6O_6{\cdot}H_2O$: C, 44.45; H, 3.74. Found: C, 44.55; H, 3.49. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.36 (s). ESI-MS calc'd. for $C_8H_6O_6$ [M-H] 197.0092, found 197.0086.

2-hydroxy-5-(PEG600)isophthalic acid (5) (a) PEG600 tosylation. A solution of 6.0 g (10 mmol) of PEG600 in 10 mL of dichloromethane was mixed with 0.382 g (2 mmol) of tosyl chloride dissolved in 2 mL of dichloromethane. A 1.4 mL portion of trimethylamine (10 mmol) was added to the resulting solution dropwise while stirring. After 12 hours of aging at ambient conditions, the resulting colorless solution was rotary evaporated, and the residue was redissolved in 10 mL of toluene. The byproduct triethylammonium chloride, crystallized out as colorless needles, was filtered off, washed with toluene, and the combined toluene solution was rotary-evaporated and then dried at 60°C and 80 mbar pressure yielding 6.24 g of oily colorless product.

(b) A 55 mg (0.25 mmol) portion of **(4)** was dissolved in 5.0 mL of 0.10M aqueous NaOH under nitrogen blanket and pH of the solution was adjusted to 10. Tosylated PEG600 (1.0 g of 20% reagent) was added with intensive stirring. The reaction solution was heated overnight at 96°C under nitrogen protection. After cooling, new 1 g portion of tosylated PEG600 was added and heating was resumed for another 12 hours. After cooling, the solution was diluted with equal volume of water and acidified with 0.1M HCl to pH 1. The reaction solution was treated with base-activated DOWEX-1 resin on the column, which caused adsorption of the product, unreacted dihydroxyisophthalic acid and tosic acid. The unreacted PEG600 was removed by flushing the column with water, followed by 0.1M HCl to isolate the product. The resulting aqueous solution was evaporated in vacuum at 60°C to dryness; the oily residue was dissolved in chloroform, the leftovers of tosic acid were extracted with water, and the organic layer was dried with drierite and evaporated yielding 50 mg of the product (not optimized). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 2H); 3.65 (s, 80H). ESI-MS [M-H], found: cluster of peaks 505.40-1077.44 spaced by m/z 44.0 (CH_2CH_2O), with maximum at m/z 769.3490. Calcd for $C_8H_5O_6(CH_2CH_2O)_{13}H$ (-H): 769.3489. Fragmentation of every ion from this cluster gave the same pattern typical for all 2,5-dihydroxyisophthalic acid derivatives: m/z = 108, 152 and 196.

Diethylene glycol γ-Fe_2O_3 colloid. All reagents were used in the form of stock solutions in diethylene glycol: $FeCl_3$ and $FeCl_2$ - 0.5 mol/kg each; H_2O - 1 mol/kg; and NaHdeg - 1.3 mol/kg (obtained by reacting Na metal with diethylene glycol). All manipulations (except for oxygenation) were done in the nitrogen atmosphere of a glovebox. In a typical procedure, solutions of $FeCl_3$, $FeCl_2$, H_2O and NaHdeg were mixed in the following proportion*: 6 g (3 mmols) + 3 g (1.5 mmols) + 7 g (7 mmols) + 10 g (13 mmols). The obtained green-brown solution was mixed with 64 g of diethylene glycol and the temperature was raised from 25 to 180°C in 20 min. Heating at this temperature was continued for ~2 hours, and then at 220°C for ~1 hour. The resulting colloid was completely homogeneous, so no purification was necessary. Overall iron concentration in the obtained this way Fe_3O_4 colloids was [Fe] = 0.050 mol/kg.

*Note: special care should be taken when these solutions are transferred and mixed, as their high viscosity can cause serious deviations from the desired reaction stoichiometry, what in turn, can alter the properties of the resulting colloid.

Colloids of γ-iron(III) oxide (maghemite) were obtained by room temperature oxygenation of the magnetite colloids with dry O_2 for 1 week. Vigorous stirring helped to speed up the process. During oxygenation, the color of the solutions changed from brown-black to deep orange-brown.

γ-Fe_2O_3 nanoparticulate adduct with (1). A 10 mL aliquote of 0.010M aqueous monobasic sodium 2-hydroxyisophthalate was added to 20 g of diethylene glycol γ-Fe_2O_3 colloid (0.050 mol/kg) under intensive stirring. After 1 hour at room temperature, the resulting homogeneous solution was heated at 100°C for 1 hour, cooled and mixed with 10 mL of water. No visible change was noted: the colloid was transparent deep red. This colloid was acidified with 0.1M hydrochloric acid to pH ~3. This caused coagulation. The solid was separated from solution using magnet, washed with water (3×50 mL) and dried under open air at ~40°C and finally at 105°C for 1 hour. The isolated yield of dark brown solid was 78 mg. The samples for combustion analysis were dried at 150°C until constant weight.

γ-Fe_2O_3 nanoparticulate adduct with (5). A 0.5 mL aliquote of 0.011M methanol solution of 5-(PEG600)-2-hydroxyisophthalic acid was added to 1.0 g of diethylene glycol γ-Fe_2O_3 colloid (0.050 mol/kg) under intensive stirring. After 1 hour at room temperature, the resulting homogeneous solution was heated at 100°C for 1 hour, cooled, mixed with 1 mL of water, heated again for 1 hour at 100°C and finally at 60°C overnight. No visible change was noted: the colloid was transparent deep red. The solvent was evaporated under high vacuum at 50°C yielding dark red-brown solid. This solid was dissolved in ethanol and dichloromethane (1:1), the solution was centrifuged and decanted to remove the by-product NaCl and evaporated. Solid residue was washed with MTBE and dried to yield 9.6 mg of the product.

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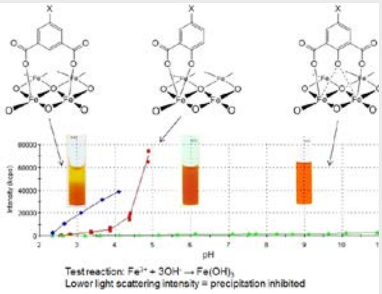
FULL PAPER

Synergistic effect of the three donor groups in 2-hydroxyisophthalic acid secures its strong covalent binding to metal oxide surfaces. Herein we have demonstrated its ability to form stable adducts with iron oxide at a wide range of pHs, drastically improving their practicality in functional hybrid materials' design.



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Tenacic Acids: a New Class of Tenacious Binders to Metal Oxide Surfaces