Magnetic nanoantioxidants with improved radical-trapping stoichiometry as stabilizers for inhibition of peroxide formation in ethereal solvents

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Graphite-coated magnetic cobalt nanoparticles (CoNPs) decorated with hindered phenolic antioxidant analogues of 2,6-di-tert-butyl-4-methylphenol (BHT, E321) provided easily removable nanoantioxidants capable of preventing the autoxidation of organic solvents as tetrahydrofuran (THF).

Tetrahydrofuran (THF) is one of the most popular ethereal solvents and together with ethyl ether, cyclopentyl methyl ether and 2-methyltetrahydrofuran, forms peroxides upon storage in the presence of O2 via an autoxidation mechanism1. Peroxides are highly unstable and represent an explosion hazard at concentrations above 100 ppm2–5. Autoxidation is a radical chain reaction sustained by peroxyl radicals (ROO•) which causes the oxidative degradation of organic compounds under mild conditions, leading to the formation of a variety of unwanted and in some case toxic and/or dangerous compounds including peroxides and epoxides1,6. Chain-breaking antioxidants (AH) counteract autoxidation by quenching the chain-carrying peroxyl radicals (Eq. 1–2)7.

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\text{ROO}^\cdot + \text{AH} \rightarrow \text{ROOH} + \text{A}^\cdot
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\text{ROO}^\cdot + \text{A}^\cdot \rightarrow \text{non-radical products}
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The hindered phenol butylated hydroxytoluene (BHT, 2,6-di-tert-butyl-4-methylphenol, E 321) is the stabilizer of choice for ethereal solvents, to which it is typically added in 100–300 ppm concentrations8. However, there are some limitations in the use of BHT, for example, it is incompatible with methods requiring high optical purity due to its UV absorbance, and must be avoided with solvent purification systems (such as Pure Solv™ Micro or similar apparatuses) that permit the dispensing of small quantities of dry solvent9. In fact, BHT interacts with the filter material clogging the system, that allows only inhibitor-free solvents. Thus, to avoid dangerous peroxides formation, THF and other ethereal solvents have to be purchased frequently and in small quantities, limiting the effectiveness of these apparatuses. Indeed, an ideal solvent stabilizer should be easily and quantitatively removed just before use.

We imagined that this problem could be solved by using oxidation inhibitors linked to magnetic nanoparticles that allows their removing by decantation using a magnet (Fig. 1).

The possibility to use nanomaterials as radical trapping agents represents a relatively unexplored frontier of the development of novel nano-supported antioxidants. Their small dimensions endow unique properties, which can be used to improve the performances of antioxidants, and to obtain hybrid materials that have been named "nanoantioxidants"10. Some relevant examples include the superoxide dismutase activity of several metal and metal-oxide nanoparticles11,12, the covalent link of gallic acid to the surface of silica nanoparticles to obtain a non-migrating antioxidant10, and the combined inclusion and surface linkage of antioxidants.
to halloysite nanotubes (such as diphenylamine derivative for polymer stabilization)\textsuperscript{13–15}. We have previously reported the preparation of soft ferromagnetic cobalt nanoparticles (CoNPs) decorated on the surface with Trolox (a water-soluble analogue of vitamin E)\textsuperscript{16}.

A problem affecting the efficiency of nanoantioxidants is that the number of radicals trapped by phenols linked to the surface of nanomaterials is usually smaller than 2, that is the value expected from reactions 1 and 2, because of the occurrence of dimerization between the surface-bound phenoxyl radicals. Herein, we describe the synthesis of novel magnetic nanoantioxidants opportunely designed to increase the efficiency of radical trapping by the insertion of bulky groups in ortho position to the reactive OH group, and their use for the stabilization of tetrahydrofuran from oxidative degradation.

**Results and Discussion**

As magnetic nanoparticles, we choose commercially available soft ferromagnetic CoNPs of about 30 nm of diameter functionalized on the surface with azido groups (Turbobeads Click, CoNPs-N\textsubscript{3}) with a functional group-loading as 0.1 mmol/g\textsuperscript{17–19}, that we previously reported to be suitable for the development of antioxidant systems. In fact, the metallic core is coated with roughly three graphitic layers that increases its stability and avoids pro-oxidant effects, as reported, for instance, for iron oxide magnetic nanoparticles\textsuperscript{20,21}. The presence of azido groups allows the functionalization by a copper (I) catalysed azide-alkyne cycloaddition (CuAAC)\textsuperscript{22} to obtain CoNPs-Antiox. As pendants, we chose BHT-like molecules because steric crowding around its phenoxyl group is expected to prevent the stoichiometry reduction (number of radicals trapped by each molecule) due to radical-radical coupling, and because BHT is the molecule of choice for solvents and polymers stabilization\textsuperscript{23–27}.

Two different BHT-like pendants were prepared, depending on the position of the linkage respect the reactive phenolic group (compounds 1 and 2) (Fig. 2). The BHT moiety was separated from the alkyne functional group, needed for the CuAAC reaction, by a chain of nine carbon atoms. Commercially available 10-undecyn-1-ol was oxidized to 10-undecynoic acid\textsuperscript{28} which, in a one-pot procedure, through a Friedel-Crafts acylation with 2,6-di-tert-butylphenol catalysed by trifluoroacetic anhydride followed by a Clemmensen reduction promoted by activated zinc, concentrated HCl and acetic acid, allowed the isolation of BHT-like derivative 1 in 44% overall yield.

**Figure 1.** Schematic preparation, use and removal of nano-magnetic stabilizer systems.

**Figure 2.** Synthesis of BHT-like derivatives 1 and 2 suitable for the functionalization of CoNPs-N\textsubscript{3}. (a) 2,6-di-tert-butylphenol, (CF\textsubscript{3}CO\textsubscript{2})\textsubscript{O}, rt, 3 h; (b) activate Zn, HCl, CH\textsubscript{3}COOH, EtOH, reflux, 15 h; (c) SOCl\textsubscript{2}, MeOH, rt, 1 h; (d) MeMgBr, Et\textsubscript{2}O, rt, 16 h; (e) 2-tert-butyl-4-methylphenol, CH\textsubscript{3}SO\textsubscript{3}H, 1,2-DCE, rt, 24 h.
The second BHT-like alkyne derivative 2, suitable for the functionalization of CoNPs-N3, was prepared from 10-undecenoic acid, used as common starting material, that was esterified with SOCl₂ and methanol²⁹,³⁰ and then reacted with an excess of methyl magnesium bromide to give the corresponding tertiary alcohol³¹. After a non-trivial optimization of the reaction conditions, the Friedel-Crafts alkylation of 2-tert-buty1-4-methylphenol with this tertiary alcohol, using CH₃SO₃H as catalyst, allowed the isolation of alkyne 2 in 27% overall yield (Fig. 2).

The derivatives 1 and 2 (10 equiv) were reacted with CoNPs-N3 (1 equiv) using CuI (0.5 equiv) in the presence of triethylamine (TEA, 5 equiv) as base and anhydrous toluene as solvent (Fig. 3). The suspension was sonicated [μ]] at room temperature under nitrogen for 24 h. After a second addition of the same amount of CuI, the sonication was continued for further 12 h. The use of an excess of alkyne and a "stoichiometric" amount of the "catalytic" copper salt is mandatory since to have the complete functionalization of the surface azido groups as pointed out by FT-IR (vide infra). The nanoparticles were recovered from the reaction mixture with the aid of a neodymium-based magnet and washed with toluene (2 × 9 mL). From this solution alkynes 1 and 2, used in excess, were recovered and recycled. Trace of residual Cu(I) salt "trapped" on CoNPS surface were removed by washing with a solution of 33% NH₃/EtOH (2/1, 5 mL) under sonication for 30 min. Then the solution was removed, and the nanoparticles washed with, in sequence, water (2 × 4 mL), EtOH (2 × 4 mL) and DCM (2 × 4 mL). Each washing step consisted of suspending the particles in the solvent, sonication (5 min) and retracting the particles from the solvent by the aid of the magnet. The functionalization of CoNPs-N3 to CoNPs-A80 (3) and CoNPs-A94 (4) could be easily detected by FT-IR (KBr pellets). From the complete disappearance of the N₃ stretching peak at 2090 cm⁻¹ we considered that the yield of the functionalization was 100% and relying on manufacturer data to assess the particle loading (0.1 mmol/g) it was possible to calculate the corresponding amount of antioxidant moieties (Fig. 3)³².

The antioxidant activity of the CoNPs-A80 (3) and CoNPs-A94 (4) was assessed by measuring the inhibition of the autoxidation of cumene (isopropylbenzene), a reference substrate for autoxidation studies, initiated by azobis(isobutyronitrile) (AIBN) at 30 °C in benzonitrile (see Scheme S1 in the ESM)³³. The reaction was followed by using an automatic gas absorption apparatus, based on a pressure transducer, built in our laboratory³⁴. Figure 4 show the typical oxygen consumption traces recorded during the autoxidation of cumene in the presence of BHT and of the CoNPs-Antiox 3 and 4 in benzonitrile. CoNPs-Antiox generated an inhibition period, which was similar to that caused by BHT when used at a concentration corresponding to the molarity of the active phenolic moiety present on the nanoparticles, considering the quantitative functionalization of all the pending azide groups (see Fig. 4). By using a well assessed kinetic treatment (see ESM)²⁶, from the O₂ consumption traces the rate constants for the reaction with peroxyl radicals were determined as (7.0 ± 0.6) × 10⁹ M⁻¹s⁻¹ for BHT, in good agreement with the literature value considering the kinetic solvent effect²⁴,²⁵, and (4.0 ± 0.5) × 10⁹ or (2.6 ± 0.5) × 10⁹ M⁻¹s⁻¹ for the BHT moieties present on CoNPs-A80 3 and CoNPs-A94 4, respectively.

The slightly lower k₉₅₀ value of CoNPs-Antiox 3 and 4 is likely due to steric shielding experienced on the surface of the nanoparticle. The stoichiometry of radical trapping (n) was determined as 2.2 ± 0.2 for BHT and 2.3 ± 0.2 or 2.4 ± 0.2 for each BHT moiety present on CoNPs-A94 4 and CoNPs-A80 3, respectively. The unexpected large n value of 3 may derive from the occurrence of secondary radical trapping mechanisms involving the formation of quinone methides and regeneration of the phenolic moiety by solvent addition³⁶. These results can be compared to those obtained with unhindered phenols (such as Trolox⁴,¹⁶ or curcumin¹⁵) covalently linked to the surfaces of nanomaterials, as they were found to trap about one ROO• radical per molecule of antioxidant. This remarkable difference enlightens the role of the bulky tert butyl groups in stabilizing the phenoxyl radicals and ensuring a good antioxidant effect to surface-bound phenols.

The efficacy of 3 (CoNPs-A80) and 4 (CoNPs-A94) as stabilizers for ethereal solvents was evaluated by monitoring the development of hydroperoxides in THF by using a commercially available colorimetric assay (see Section 1 in the ESM).

In the presence of hydroperoxides in concentration higher than 1 mg/L, the colour of the test strip turns from white to blue and a quantification can be done by comparison to a colour scale (Fig. 5 inset C). The determination

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Figure 3. Functionalization of CoNPs-N₃ under CuAAC conditions; Left: FT-IR (KBr pellets) spectrum of CoNPs-N₃ (curve a) and FT-IR spectra of CoNPs-A80 3 (curve c) and CoNPs-A94 4 (curve b).
of peroxides formation in THF was done in a series of THF samples containing BHT, CoNPs-Antiox 3 and 4 all at 250 ppm (referred to the phenolic moieties) stored in clear glass vials at ambient light under continuous stirring. These conditions have been chosen to accelerate the oxidation and reduce the times of investigation. Actually, we proved that without continuous mixing the rate of peroxides formation increases sensibly. As shown in Fig. 5 inset C, after six day the THF sample without stabilizer reached a concentration of peroxides bigger than 100 mg/L as evident from the stick turning dark blue, the samples with BHT is about 1 mg/L, while those with CoNPs-A94 4 and CoNPs-A80 3 (both 0.18 mg/mL, corresponding to 18 µM of linked BHT units). Magnetic nanoparticles adhered to the stir bar (inset A) but were homogeneously dispersed in solution when stirring was switched on (inset B).

In conclusion, magnetic nanoparticles CoNPs-Antiox 3 and 4 behave as good antioxidants able to inhibit the oxidative degradation of THF, an ethereal solvent of widespread use, with the possibility to simply remove the inhibitor with the aid of a magnet. The presence of bulky substituents ortho to the reactive OH group allowed to obtain a radical trapping stoichiometry superior to that of other phenols bound to nanomaterials. This approach avoids time and energy consuming procedures to remove stabilizers from easily oxidizable solvents or the use of potentially dangerous inhibitors-free solvents. Although, costs of CoNPs stabilizers reported are much higher than BHT, the problems related with the use of ethereal solvents without stabilizers in automatic drying
dispersers may indicate a niche market for these materials. Indeed, we have preliminary similar result on the inhibition of peroxide formation in diethyl ether. Future work will aim to explore the possibility to improve the dispersion in organic solvents of different polarity and to obtain nanomagnetic stabilizers able to prevent non-oxidative decompositions.

Methods

General information. 1H- and 13C-NMR spectra were recorded with Varian Gemini 200 or Varian Mercury Plus 400. FT-IR spectra were recorded with FT Infrared Spectrometer 1600 Perkin-Elmer in CDCl3 solutions or KBr. GC-MS spectra were recorded with a QMD 100 Carlo Erba. ESI-MS spectra were recorded with a JEOL MStation JMS700. Melting points were measured with Stuart SMP50 Automatic Melting point. All the reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F 254) and the products were visualized with acidic vanillin solution. Silica gel 60 (230–400 mesh) was used for column chromatography. Commercially available reagents and catalysts were used as obtained from freshly open container without further purifications. Dry solvents were obtained by Pure SolvTM Micro Solvent Purification Systems. CHCl3 was washed 10 times with deionized water, dried on anhydrous CaCl2. Et3N was distilled over KOH. Cobalt nanoparticles (diameter 30 nm) which have a covalent azide functionality (0.1 mmol/g). Reactions with CoNPs were carried out under sonication with an ultrasonic bath (Sonorex RK 255 H-R, Bandelin). All air and moisture sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere using cannulas and septa. Solvents were dried following standard procedures. Commercial zinc dust (<0.1 mm) was activated by stirring for 4 min with 2% HCl. The zinc was immediately filtered in vacuo, washed to neutrality with water, and then washed with ethanol, acetone, and Et2O. The resulting powder was dried at 90 °C under vacuum for 10 min and immediately used.

Synthesis of new compounds. Undec-10-ynoic acid. To a solution 0.05 M of 10-undecyn-1-ol (971 mg, 5.77 mmol) in acetone (160 mL), Na2Cr2O7x2H2O (4304 mg, 14.44 mmol) and deionized water (5 mL) were added at 0 °C. Then conc. H2SO4 (1.5 mL) was added dropwise at 0 °C and the reaction mixture was left under magnetic stirring for 15 min. and filtered. The filtrate was extracted with AcOEt (3 × 30 mL) and the organic phase was washed with water (3 × 30 mL) and brine (40 mL), dried over Na2SO4 and concentrated in vacuo. The desired product was obtained as a white solid without any further purification (1000 mg, 94% yield). 1H-NMR (CDCl3, 200 MHz) δ 1.26–1.67 (m, 12 H), 2.51 (t, J = 8.0 Hz, 2 H), 5.04 (s, 1 H), 6.98 (s, 2 H). 13C-NMR (CDCl3, 100 MHz) δ 18.4, 28.5, 28.7, 29.1, 29.5, 29.6, 30.3, 32.0, 34.2, 36.0, 68.0, 84.8, 124.8, 133.47, 135.50, 151.6. IR (CDCl3, cm−1) ν 3643, 3308, 2931, 2857, 2116, 1458, 1435. MS (ESI) m/z 355.58 [M-H]−. Undec-10-ynoic acid methyl ester. Thionyl chloride (600 μL, 8.24 mmol) was added at −15 °C to a solution of undec-10-ynoic acid (750 mg, 4.12 mmol) in anhydrous MeOH (21 mL). The reaction mixture was left under magnetic stirring at room temperature for 1 h, then the solvent was evaporated. After the dilution with water, the mixture was extracted with EtO2 (4 × 20 mL), washed with water until pH = 7 and finally with brine. The organic phase was dried over Na2SO4 and concentrated in vacuo, affording the desired ester as a yellow oil without any further purification (701 mg, 87%). 1H-NMR (CDCl3, 200 MHz) δ 1.31–1.67 (m, 12 H), 1.93 (t, J = 2.6 Hz, 1 H), 2.19 (dt, J = 7.2 Hz, J = 2.6 Hz 2 H), 2.51 (t, J = 8.0 Hz, 2 H), 5.04 (s, 1 H), 6.98 (s, 2 H). 13C-NMR (CDCl3, 100 MHz) δ 18.4, 28.5, 28.7, 29.1, 29.5, 29.6, 30.3, 32.0, 34.2, 36.0, 68.0, 84.8, 124.8, 133.47, 135.50, 151.6. IR (CDCl3, cm−1) ν 3643, 3308, 2931, 2857, 2116, 1458, 1435. MS (ESI) m/z 355.58 [M-H]−: Undec-10-ynoic acid methyl ester. Thionyl chloride (600 μL, 8.24 mmol) was added at −15 °C to a solution of undec-10-ynoic acid (750 mg, 4.12 mmol) in anhydrous MeOH (21 mL). The reaction mixture was left under magnetic stirring at room temperature for 1 h, then the solvent was evaporated. After the dilution with water, the mixture was extracted with EtO2 (4 × 20 mL), washed with water until pH = 7 and finally with brine. The organic phase was dried over Na2SO4 and concentrated in vacuo, affording the desired ester as a yellow oil without any further purification (701 mg, 87%). 1H-NMR (CDCl3, 200 MHz) δ 1.31–1.67 (m, 12 H), 1.93 (t, J = 2.6 Hz, 1 H), 2.18 (dt, J = 7.2 Hz, J = 2.6 Hz 2 H), 2.30 (t, J = 7.4 Hz, 2 H), 3.66 (s, 3 H). 2-Methyl-dodec-11-yn-2-ol. In a Schlenk tube, to a solution of undec-10-ynoic acid methyl ester (1009 mg, 5.15 mmol) in anhydrous Et2O (20 mL), methylmagnesium bromide (3.0 M in Et2O, 8 mL, 26.00 mmol) was added dropwise at −78 °C. The mixture was left under magnetic stirring, and N2 atmosphere allowing warming to room temperature, then after 15 h it was quenched with ice and acidified to pH 4 with acq. HCl 3 N. The so-obtained suspension was extracted with AcOEt (3 × 20 mL), then collected organic phases were washed with water (3 × 10 mL), dried over anhydrous Na2SO4 and evaporated in vacuum, furnishing a crude that was purified through flash column chromatography (petroleum ether/AcOEt 5/1) affording the desired product as a colourless oil (973 mg, 96%). 1H-NMR (CDCl3, 200 MHz) δ 1.20 (s, 6 H), 1.29–1.53 (m, 14 H), 1.93 (t, J = 2.6 Hz, 1 H), 2.17 (dt, J = 7.2 Hz, J = 2.6 Hz 2 H). 13C-NMR (CDCl3, 100 MHz) δ 18.4, 24.3, 28.4, 28.7, 29.0, 29.2, 29.5, 30.1, 44.0, 68.1, 71.0, 84.8. IR (CDCl3, cm−1) ν 3607, 3308, 2934, 2858, 2116, 1467. 2-Tert-Butyl-6-(1,1-dimethyl-undec-10-ynyl)-4-methylphenol (2). A solution of 2-methyl-dodec-11-yn-2-ol (200 mg, 1.02 mmol) and 2-tert-butyl-4-methylphenol (170 mg, 1.04 mmol) in 1,2-DCE (6 mL) was added dropwise at 0 °C to a suspension of CH2SOH (439 mg, 4.57 mmol) in 1,2-DCE (1 mL). The resulting red solution was left under magnetic stirring at room temperature, monitored by TLC (elucent: petroleum ether/Et2O 4/1 and petroleum ether). After 24 h the reaction was quenched with saturatedaq. NaHCO3, then the resulting mixture was diluted with DCM (30 mL) and washed with saturated aq. NaHCO3 (3 × 10 mL) and water (3 × 10 mL). The organic phase was dried over
anhydrous Na₂SO₄ and evaporated in vacuo furnishing a yellow oil that was purified by silica gel column chromatography (petroleum ether followed by petroleum ether/DCM 10/1), giving the desired product 2 as a yellow oil (94 mg, 27% yield). 1H-NMR (CDCl₃, 400 MHz) δ 1.04–1.39 (m, 10 H), 1.40–1.43 (s, 9 H), 1.46–1.54 (m, 24 H), 1.77–1.79 (m, 2 H), 1.94 (t, J = 2.6 Hz, 1 H), 2.17 (dt, J = 7.0 Hz, J = 2.6 Hz, 2 H), 2.28 (s, 3 H), 5.02 (s, 1 H), 6.91 (s, 1 H), 6.99 (s, 1 H). 13C-NMR (CDCl₃, 100 MHz) δ 18.40, 18.43, 21.3, 25.1, 28.5, 28.7, 29.0, 29.19, 29.24, 30.2, 30.3, 34.2, 37.7, 41.8, 84.8, 125.5, 126.6, 128.0, 134.1, 135.5, 151.5. IR (CDCl₃, cm⁻¹) ν 3632, 3308, 2931, 2857, 1434, 1386. MS (ESI) m/z 283.50 [M-58]-, 341.58 [M-H]⁻.

The nanoparticles were recovered from the reaction mixture with the aid of a neodymium-based magnet and washed with toluene (2 × 10 mL) sequentially. Each washing step consisted of suspending the particles in the solvent, sonication (5 min) and retracting the particles from the solvent by the aid of the magnet. After the last washing step, the particles were dried in vacuum overnight and recovered as a black solid of 111 mg. IR (KBr, cm⁻¹) ν 3435, 2919, 2851, 1620, 1430, 1261, 1095.

**CoNPs-A94 (4).** Turbobeads Click (100 mg, 0.1 mmol/g azide-loading, 0.01 mmol) were washed with degassed toluene (3 × 1 mL) and suspended in the same solvent (4 mL) by sonication (10 min) before 1 (33 mg, 0.1 mmol,) TEA (7 μL, 0.05 mmol) and CuI (1 mg, 0.005 mmol) were added. The resulting slurry was sonicated for 24 h at room temperature under a nitrogen atmosphere, then a second crop of CuI (1 mg, 0.005 mmol) was added and the mixture sonicated for additional 12 h. The nanoparticles were recovered from the reaction mixture with the aid of a neodymium-based magnet and washed with toluene (2 × 9 mL). Adventitious trace of residual Cu(I) salts were removed by washing with a solution of 33% ammonia/EtOH (2/1, 5 mL) under sonication for 30 min, then the solution was removed and the nanoparticles washed twice with, in sequence, water (2 × 4 mL), EtOH (2 × 4 mL) and DCM (2 × 4 mL) sequentially. Each washing step consisted of suspending the particles in the solvent, sonication (5 min) and retracting the particles from the solvent by the aid of the magnet. After the last washing step, the particles were dried in vacuum overnight and recovered as a black solid of 98 mg. IR (KBr, cm⁻¹) ν 3400, 2952, 2919, 1601, 1457, 1261, 1099.

**Data availability**

Electronic Supplementary Material: Further details of autoxidation experiments, semi-quantitative determination of the peroxides, NMR spectra are available in the online version of this article at www.nature.com/articles/s41598-019-53531-5.

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Author contributions

C.V. conceived the experiments and wrote the manuscript; A.S. and L.T. carried out the synthetic work, supervised by C.V. and S.M. conceived the study; A.B. conducted the autoxidation experiments supervised by R.A., S.M., R.A. and C.V. analysed the results. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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