

New methodologies for the functionalization of superparamagnetic nanoparticles; cross olefin metathesis.

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Last years have witnessed an exponential growth in the use of magnetic nanoparticles in biomedical applications. Iron oxide nanoparticles, particularly, have gained a dominant role because of their physicochemical properties and low toxicity. Due to their ability to affect the relaxation rate of water protons, these particles are used as contrast agents in magnetic resonance imaging (MRI). Besides, depending on the r_2/r_1 ratio value they can be used both as “positive”, hyperintense signal, or “negative”, hypointense signal, contrast agents. The superparamagnetism of these particles is the most remarkable feature, meaning a much stronger signal in magnetic resonance imaging than that produced by traditional paramagnetic contrast agents.

When using these nanoparticles in biomedical imaging to the most important aspect is the functionalization of the surface with new molecules. This prevents aggregation and allows the activation of these particles with different biomolecules. The modification of the surface should be done, ideally, by covalent bonding. Olefin metathesis offers many of these features thanks to the new family of catalysts, especially Hoveyda-Grubbs 2nd generation. The metathesis mechanism reorganizes the carbon atoms of two C=C bonds, generating two new ones in the presence of a catalyst. This kind of reaction allows access from the easily prepared olefins to those that are cumbersome to obtain, being an efficient and stereoselective synthesis of the more substitute olefins in mild conditions. All of these advantages make the metathesis of alkenes one of the most powerful tools in synthetic chemistry, but as far as we know, it has not been applied for the functionalization of iron oxide superparamagnetic nanoparticles.

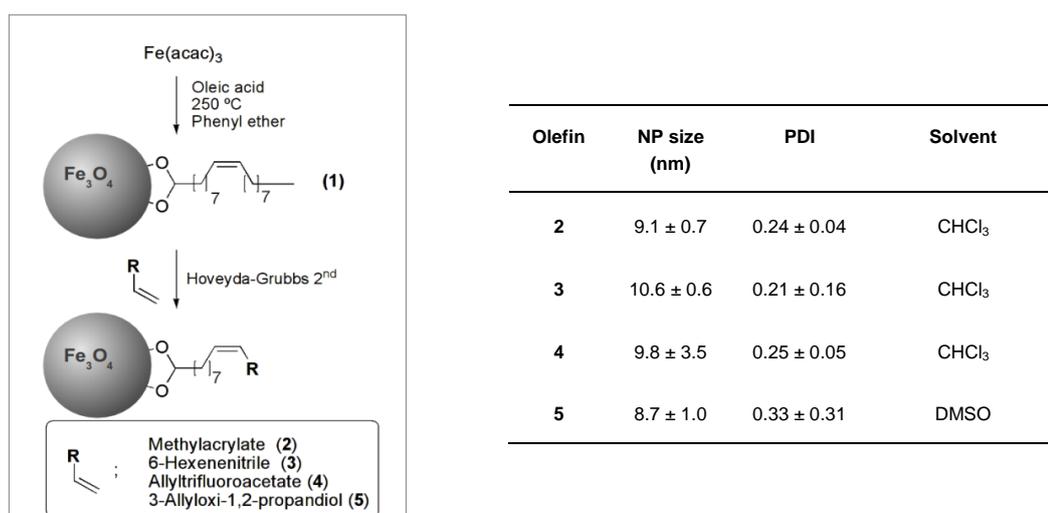


Figure 1.- General metathesis synthesis and summary of the averaged sizes.

Here we present the functionalization of superparamagnetic iron oxide nanoparticles by the use of olefin metathesis reaction. In a first step we synthesized iron oxide nanoparticles by the decomposition of organic precursor, iron acetyl acetonate, under mechanical stirring and N_2 atmosphere, obtaining hydrophobic Fe_3O_4 NPs, with oleic acid as surfactant, superparamagnetic behavior and hydrodynamic size of 8 nm. As a proof of concept of our approach, the cross metathesis was made between the double bond in oleic acid structure and four different molecules with a terminal olefin; methyl acrylate, hexenitrile, allyltrifluoroacetate and 3-allyloxi-1,2-propandiol, in presence of catalytic amounts (4%mol) of Hoveyda-Grubbs 2nd generation catalyst. These new NPs were fully characterized by, DLS, TEM, VSM and FTIR, showing the success of the reaction and excellent values for the hydrodynamic size as can be seen in the Figure 1.

For biomedical applications the nanoparticles must show a high stability in aqueous solution. To this end one approach is to choose an appropriate ligand that renders water stable nanoparticles with an easy final modification of the synthesized hydrophobic particles. For this reason we synthesized sample **2**. After the metathesis the ester bond in **2** was hydrolyzed rendering water stable sample **6** due to the presence of the terminal carboxylic acid ± 10 nm (PDI 0.30 ± 0.07 , N=3) of hydrodynamic size in water were obtained, which involves the possibility of direct application in vivo as contrast agent for MRI. These NPs were fully characterized. The physicochemical properties of the inorganic were studied by TEM and VSM, which demonstrated the superparamagnetic behavior of the sample. The presence of the acid was probed through the FTIR spectrum and the profile of the ζ potential for the NPs, which exhibit their stability in physiological conditions, with a value of -37 ± 5 mV at pH 7, and the typical profile for NPs stabilized by a carboxylic acid.

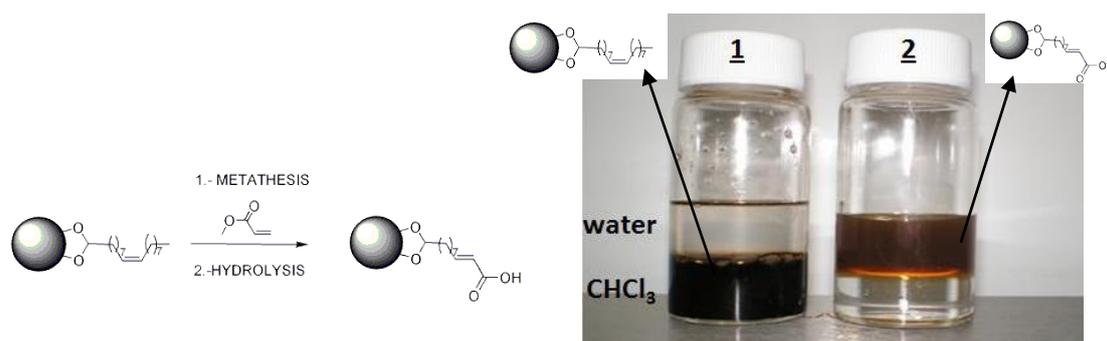


Figure 2.- Hydrolysis of NPs (2) with methyl acrylate, generating hydrophilic NPs.

In this work we demonstrate, for the first time, the use of the cross olefin metathesis reaction for the functionalization of iron oxide nanoparticles with four ligands, allowing the incorporation of different functional groups as alcohols, ester, acid or nitrile. Using appropriate catalyst and reaction conditions it is possible to modify the structure of the surfactant without self-metathesis, as demonstrated with the hydrodynamic size, TEM images and FT-IR spectra reported here. This simplifies the synthesis of hydrophobic and hydrophilic nanoparticles with applications in different fields.

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