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Research Article

# Empirical Optimization of Peptide Sequence and Nanoparticle Colloidal Stability: The Impact of Surface Ligands and Implications for Colorimetric Sensing

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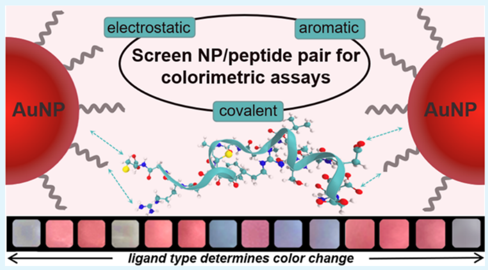
**ABSTRACT:** Surface ligands play a critical role in controlling and defining the properties of colloidal nanocrystals. These aspects have been exploited to design nanoparticle aggregation-based colorimetric sensors. Here, we coated 13-nm gold nanoparticles (AuNPs) with a large library of ligands (*e.g.*, from labile monodentate monomers to multicoordinating macromolecules) and evaluated their aggregation propensity in the presence of three peptides containing charged, thiolate, or aromatic amino acids. Our results show that AuNPs coated with the polyphenols and sulfonated phosphine ligands were good choices for electrostatic-based aggregation. AuNPs capped with citrate and the labile-binding polymers worked well for dithiol-bridging and $\pi-\pi$ stacking-induced aggregation. In the example of electrostatic-based assays, we stress that the good sensing performance requires aggregating peptides of low charge valence paired with charged NPs of weak stability or *vice versa*. We then present a modular peptide containing versatile aggregating residues to agglomerate a variety of ligated AuNPs for colorimetric detection of the coronavirus main protease. Enzymatic cleavage liberates the peptide segment, which in turn triggers NP agglomeration and thus rapid color changes in <10 min. The protease detection limit is 2.5 nM.




**KEYWORDS:** *surface ligand, colorimetric sensor, inorganic nanocrystal, peptide design, nanoparticle aggregation, main protease*

## 1. INTRODUCTION

The aggregation of metallic colloids leads to a bathochromic shift in their surface plasmon resonance (SPR) band and results in a pronounced color change.[1,2] The ultimate color formation is a function of the core composition,[3] particle morphology,[4−6] and surface chemistry,[7,8] which modulate the resonant coupling of light and free electrons in metallic nanostructures. For instance, the aggregation of gold nanoparticles (AuNPs) dramatically changes the dispersion color visually from red to purple/blue by the naked eye due to the strong sensitivity of SPR to the interparticle distance combined with the high molar absorption coefficients.[9,10] Such aggregation-induced plasmonic coupling has been exploited as an optical signal transduction strategy in colorimetric sensors with widespread use in bioanalytical applications.[11−14]

The realization of plasmonic coupling broadly demands either chemical linking (*e.g.*, S−Au bond,[15,16] conjugation,[17] recognition interactions,[18,19] *etc.*) or changes in the environment (*e.g.*, ionic strength,[20] solvent polarity,[21] ligand hydrophilicity,[22] *etc.*). Over the past two years, our group has designed a set of colorimetric sensors to study proteases through an array of NP types, proteases, and aggregation mechanisms.[5,6,16,23−26] However, we have not yet systematically investigated the effects of surface chemistry. Surface chemistry plays a critical role in endowing colloidal stability and interfacial functionality—these factors determine how nanoparticles adapt to the chemical or environmental stimuli and thus manifest in interparticle crosslinking and colorimetric sensing.[1,27−29] The depth and diversity of the ligand field provide choices spanning from metal complexes,[30] small organic compounds,[7,28] polymers,[31,32] and other biomacromolecules (*e.g.*, peptides,[16,24,33] proteins,[34] oligonucleotides[18]). These can tailor the versatile interfaces between nanoparticles and biological systems. Modifying surfaces with ligands allows us to tune interparticle interactions, such as the Coulombic and hydrophobic interactions, hydrogen and covalent bonds, or combinations thereof.[1,7] Clearly, it is beneficial to screen the optimally desired ligands to improve the performance of

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