別記様式第３号－１

学 位 論 文 の 要 旨

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学位論文題目	Synthesis, characterization, and stability evaluation of novel hybrid nanoparticles, and their biomedical and chemical applications （新規ハイブリッドナノ粒子の調製、分析、安定性の評価と、その生物医学的及び化学的応用）

本論文は貴金属ナノ粒子の調製、分析、安定性の評価と、その生物医学的及び化学的応用についての研究成果をまとめたものである。

第１章は序論であり、貴金属ナノ粒子研究の歴史的背景と、既知の調製方法についての一般的な知見について述べている。この章では、ナノ粒子コロイド溶液の安定化と分析方法について紹介するとともに、ナノ粒子触媒及びナノ粒子を利用した抗がん剤の薬物輸送システムについての先行研究を示した。

第２章は、末端にスルホ基を有するアルキルスルファニルアニリンを還元剤兼安定化剤として用いた有機分子－金ハイブリッドナノ粒子の調製法の開発について述べている。末端にスルホ基を有するアルキルスルファニルアニリン溶液は、塩化金酸水溶液と弱アルカリ性条件下で反応して、極めて安定な金ナノ粒子溶液を生じた。得られたナノ粒子の粒径は11.2 ± 5.9 nmであり、良好な分散性を示した。^{1}HNMR、FT-IR等の各種分光学的測定によって、得られた粒子の特徴と安定性について検討した。

第３章では、ハイブリッド金ナノ粒子の生物医学的応用を検討している。先に得られたハイブリッド金ナノ粒子に抗がん剤を導入した、新しい抗がん剤－ナノ粒子複合体の開発を検討した。

検討の結果、DNAリンカーを介して抗がん剤パクリタキセルを結合した金ナノ粒子の調製に成功し、このナノ粒子ががん細胞に対して強い細胞毒性を示すことを確認した。抗がん剤－ナノ粒子複合体の細胞毒性は、パクリタキセル単体の細胞毒性よりも強く、今回開発した抗がん剤－ナノ粒子複合体が、新しい薬物輸送システムとして機能しうると推測した。

第４章では、アルキルスルファニルアニリンと結合したポリビニルアルコールによって安定化された白金ナノ粒子を触媒とする官能基選択的な還元反応について述べている。固定化白金ナノ粒子が、芳香族ニトロ化合物をはじめとするさまざまな化合物の還元反応において繰り返し利用に耐える触媒であり、通常の白金触媒に比べて反応性が高いことを示した。また、ハロゲンを含む芳香族ニトロ化合物に対して極めて高い官能基選択性を示し、炭素－ハロゲン結合を侵すことなくニトロ基のみを還元することが明らかになった。

第５章は総括として、一連の研究で得られた成果をまとめている。アルキルスルファニルアニリンを基盤とする貴金属ナノ粒子の安定化剤の有用性と、その応用について総括した。

別記様式第４号

Summary of Doctoral Dissertation

Title of Doctoral Dissertation

Synthesis, characterization, and stability evaluation of novel hybrid nanoparticles, and their biomedical and chemical applications

Name: Mahmoud Ibrahiem Mohieeldin Darwish

This thesis mainly comprises of 5 chapters.

Chapter 1. General introduction and literature review of noble metal nanoparticles

It gives general historical aspects of noble metal nanoparticles and previous attempts of their preparation. This chapter discusses nanoparticles stabilization in colloidal solutions and methods of characterization. Moreover, it gives information about surface modifications of gold nanoparticles either by covalent approach (thiol modification) or ionic approach (electrostatic interaction). Furthermore, this chapter introduces the applications of metal-based nanoparticles as a nanocatalytic system and anti-cancer drug delivery system.

Chapter 2. Spontaneous preparation, characterization, and stability evaluation of highly stable gold nanoparticle stabilized with ω-sulfonylated alkylsulfanylaniline

In this chapter, the preparation of new reductive stabilizers, ω-sulfonylated alkylsulfanylanilines have been developed. Highly stabilized Au NP has been synthesized by the spontaneous reaction of $HAuCl_4$ and ω-sulfonylated alkylsulfanylanilines in an aqueous solution of pH 8. The reaction yielded a spherical

sulfonylated-**Au NP** with an average particle size of 11.2 ± 5.9. The peculiarities of the prepared sulfonylated-**Au NP** were examined by UV-visible spectroscopy, ^{1}H NMR, transmission electron microscope (TEM), and Fourier transform infrared (FTIR) spectra. Sulfonylated-**Au NP** which has been prepared by this method was tolerant in highly acidic or basic conditions, and stable in concentrated salt solutions such as PBS, a common biological medium. Moreover, the sulfonylated-**Au NP** have successfully redispersed after drying to powder, and even after keeping the dried powder of sulfonylated-**Au NP** in the air at room temperature for at least 2 weeks, the powdered sulfonylated-**Au NP** was redispersed to give stable sulfonylated-**Au NP** solution. Surface modification of the sulfonylated-**Au NP** was also examined.

These advantages suggested that sulfonylated-**Au NP** can be an attractive alternative for citrate- or ascorbate-stabilized Au NP, particularly in biological and medicinal applications.

Chapter 3. Biomedical application of gold nanoparticles for anti-cancer drug delivery by conjugation with paclitaxel through DNA-oligonucleotides linker

In this chapter, the synthesis and characterization of a novel paclitaxel-DNA-Au NP bio-conjugate was achieved for targeted drug delivery of paclitaxel. This chapter presents the loading of paclitaxel on the surface of Au NP via DNA linker. This has been done through the modification of paclitaxel by the reaction with succinic anhydride to form carboxyl terminated succinyl paclitaxel (ST). ST reacted with amino terminated DNA oligonucleotides via peptide bond formation to form thiol-terminated ST-DNA. ST-DNA was loaded on the Au NPs surface through ligand exchange reaction whereas SH group replaces NH_2 on the surface of Au NP to form nano-bioconjugate. This is attributed to the fact that, SH group strongly coordinates on Au NP surface more than NH_2 group.

The cytotoxicity of the nano-bioconjugate was tested against breast cancer cells (SK-BR3) and brain cancer (Neuro 2a). The cytotoxicity of paclitaxel was greatly enhanced in case of nano-bioconjugate than that of the free paclitaxel or ST as it was evaluated by 3-(4,5-dimethylazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay. Therefore, this anti-cancer drug delivery strategy enhances the solubility, stability, and effectivity of the drug to fight against the cancerous cells, which is considered a hopeful strategy in the treatment of oncological diseases.

Chapter 4. Preparation and characterization of platinum nanoparticles stabilized by a polymer modified with sulfonyl aniline and their application as a highly efficient, recyclable, chemo-selective, and broad spectrum nanocatalyst

In this chapter, stable platinum nanoparticles (Pt NP) with efficient nanocatalytic activity, recyclability, and chemo-selectivity have been prepared. The polymer (**PVA-ATB**), which used as a reductive stabilizer, has been prepared from acrylated polyvinyl alcohol modified with 4-aminothiobenzene. This polymer was used to form **PVA-ATB-Pt NP** (nanocatalyst) spontaneously, in a one-step reaction. Stable and small-sized nanoparticles were formed at pH 8. The synthesized nanoparticles showed a good catalytic reduction activity as demonstrated by the standard hydrogenation of *p*-nitrophenol. It was found that **PVA-ATB-Pt** exhibited a higher turnover number and a higher apparent rate constant when compared to other nanocatalysts in the literature. Furthermore, the nanocatalyst could be reused for at least six successive catalytic cycles.

The nanocatalyst also possessed the ability to catalyze the conversion of 4-bromonitrobenzene to 4-bromoaniline with high chemo-selectivity and no concurrent debromination reaction.

Moreover, the nanocatalyst possessed broad spectrum of nanocatalysis such as the

catalytic reduction of hexacyanoferrate (oxidation reduction reaction). Also, it could catalyze the catalytic hydrogenation of carbon-carbon double bond. Furthermore, the nanocatalyst could catalyze organic dyes degradation (methyl orange and methylene blue dyes) to less toxic and beneficial compounds.

Chapter 5. Summary of the results

The results of this study have been summarized. This study achieves a development in the field of nanotechnology in terms of synthesis, characterization, stability evaluation of noble meal nanoparticles and their biomedicinal and chemical applications. It gives a wide scope for preparation of metal nanoparticles by using newly developed reductive stabilizers such as ω-sulfonylated alkylsulfanylanilines and **PVA-ATB**. The characterization, stability evaluation, examination of the optical properties, and other peculiarities of metal nanoparticles (gold and platinum nanoparticles) have been evaluated. Moreover, their applications in chemistry and medical field as nanocatalyst and anti-cancer drug delivery have been evaluated.