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ORIGINAL RESEARCH

A "turn-on" fluorescent microbead sensor for detecting nitric oxide

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Lan-Hee Yang[1,2]
Dong June Ahn[3]
Eunhae Koo[1]

[1]Advanced Materials Convergence Division, Korea Institute of Ceramic Engineering and Technology, Seoul, Republic of Korea; [2]Department of Biomicrosystem Technology, Korea University, Seoul, Republic of Korea; [3]Departments of Biomicrosystem Technology, Chemical & Biological Engineering, KU-KIST Graduate School, Korea University, Seoul, Republic of Korea

Abstract: Nitric oxide (NO) is a messenger molecule involved in numerous physical and pathological processes in biological systems. Therefore, the development of a highly sensitive material able to detect NO in vivo is a key step in treating cardiovascular and a number of types of cancer-related diseases, as well as neurological dysfunction. Here we describe the development of a fluorescent probe using microbeads to enhance the fluorescence signal. Microbeads are infused with the fluorophore, dansyl-piperazine (Ds-pip), and quenched when the fluorophore is coordinated with a rhodium (Rh)-complex, ie, $Rh_2(AcO^-)_4$(Ds-pip). In contrast, they are able to fluoresce when the transition-metal complex is replaced by NO. To confirm the "on/off" mechanism for detecting NO, we investigated the structural molecular properties using the Fritz Haber Institute *ab initio* molecular simulations (FHI-AIMS) package. According to the binding energy calculation, NO molecules bind more strongly and rapidly with the Rh-core of the Rh-complex than with Ds-pip. This suggests that NO can bond strongly with the Rh-core and replace Ds-pip, even though Ds-pip is already near the Rh-core. However, the recovery process takes longer than the quenching process because the recovery process needs to overcome the energy barrier for formation of the transition state complex, ie, NO-$(AcO^-)_4$-(Ds-pip). Further, we confirm that the Rh-complex with the Ds-pip structure has too small an energy gap to give off visible light from the highest unoccupied molecular orbital/lowest unoccupied molecular orbital energy level.

Keywords: nitric oxide, microbead, fluorescence, rhodium complex, *ab initio* molecular simulation

Introduction

Since nitric oxide (NO) was identified as an endothelium-derived relaxation factor in 1987,[1,2] NO has become of interest in many scientific and technological areas. For instance, NO is now known to be a ubiquitous messenger molecule in the cardiovascular, nervous, and immune systems, and is a major factor in tumor progression.[3–12] Therefore, detection and manipulation of the NO concentration in biological systems is crucial in treating cardiovascular and many types of cancer-related diseases, as well as neurological dysfunction. However, because NO is highly reactive, it is rapidly and easily converted to other species,[6,13] making it very difficult to detect and monitor concentrations in vivo.

Much effort has gone into developing efficient methods for detection of NO, including electrochemicals, electron paramagnetic resonance spectroscopy, chemiluminescence, and fluorescence detection.[14–19] Compared with other methods, fluorescence detection can provide highly spatial and temporal data on the distribution of both intracellular and extracellular NO. Lippard et al have been developing reversible, fluorescence-based NO detection adducts using fluorophores coordinated with metal-complex scaffolds.[20] However, because the fluorophore adducts do not function as NO sensors in aqueous medium, a silastic polymer-based membrane was used as a NO-

Correspondence: Eunhae Koo
Advanced Materials Convergence Division, Korea Institute of Ceramic Engineering and Technology,
77, Digital-ro 10 Gil, Guemcheon-gu, Seoul 153-801, Republic of Korea
Email ehkoo@kicet.re.kr