Hyper-polarizing organic phase and its use for polyion sensing in blood plasma

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Ion-selective optodes (ISOs) have emerged as an optical variant of ion-selective electrodes (ISEs) allowing the optical detection of ionic species based on ion exchange between analytes and optical reporters. Being freed from external equipment, ISOs have been miniaturized down to the nanoscale (<100 nm) using various optical signal transducers such as chromoionophores, solvatochromic dyes and quantum dots. While the nanoISOs have shown promising performance for the detection of small ions such as alkali ions (K^+, Na^+, Li^+) and biologically relevant ions (Ca^{2+}, Mg^{2+}, Cl^-), those for polyion quantification have suffered from severe interference in the complex samples whole blood, blood plasma and serum. Indeed, the signal of ISOs in plasma was found to already saturate in the absence of the target polyion in our experiment and as reported earlier.[1]

In this contribution we will describe a newly developed sensor working through a novel sensing mechanism based on "hyper-polarizing organic phase" where the solvatochromic dye is strongly polarized by the negatively charged organic molecule DNNS (dinonylnaphthalenesulfonate ion) which is known to be a good ligand of protamine, an arginine-rich polycationic protein.[2] The solvatochromic dye accordingly shows a high polarity signal in the organic phase, which is, surprisingly, higher than that in an aqueous environment. In the presence of protamine, DNNS incorporated in the nanoparticle-based sensor interacts with protamine rather than the solvatochromic dye, turning the optical signal back to non-polarity. In this manner hyper-polarization is used as an optical signal transduction mechanism.

The newly developed sensor has shown greatly improved selectivity where even arginine, the main repeating moiety of protamine, does not induce signal transduction at all while the conventional ion-exchange type exhibited interference from arginine. Several thermodynamic parameters involving DNNS/protamine and DNNS/arginine interaction will be shown to explain the cause of this improved selectivity. Owing to the high selectivity, this sensor has enabled polyion detection in plasma for the first time as an optical nanoparticle-based sensor. The sensor was finally applied to quantify heparin, a polyanionic saccharide used as an anticoagulant during surgery, in various patient plasma samples.

[1] X. Xie, J. Zhai, G. A. Crespo, E. Bakker, *Anal. Chem.* **2014**, 86, 8770–8775.
[2] Y. Soda, K. J. Robinson, R. Nussbaum, E. Bakker, *Chem. Sci.* **2021**, 12, 15596-15602