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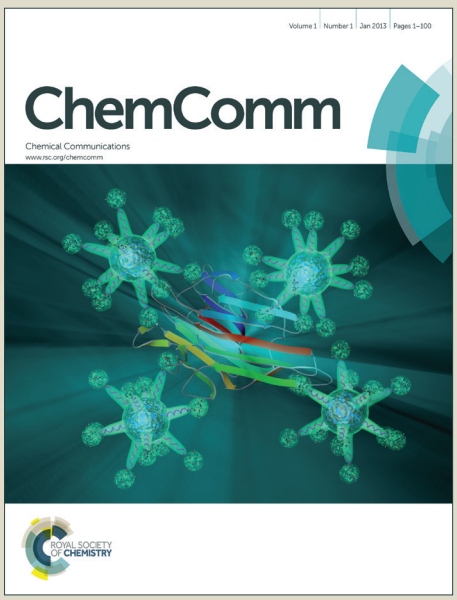

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Ionophore-Based Ion-Exchange Emulsions as Novel Class of Complexometric Titration Reagents

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Complexometric titrations rely on a drastic change of the pM value at the equivalence point with a water soluble chelator forming typically 1:1 complexes of high stability. The available chemical toolbox of suitable chelating compounds is unfortunately limited because many promising complexing agents are not water soluble. We introduce here a novel class of complexometric titration reagents, a suspension of polymeric nanospheres whose hydrophobic core is doped with lipophilic ion-exchanger and a selective complexing agent (ionophore). The emulsified nanospheres behave on the basis of heterogeneous ion exchange equilibria where the initial counter ion of the ion-exchanger is readily displaced from the emulsion for the target ion that forms a stable complex in the nanosphere core. Two different examples are shown with Ca^{2+} and Pb^{2+} as target ions. The lack of protonatable groups on the calcium receptor allows one to perform Ca^{2+} titration without pH control.

Complexing agents for metal ions are today widely used in complexometric titrations, gravimetry, heavy metal detoxification, spectrophotometry, solvent extraction, and chromatography.[1] Complexometric titration (chelometry) is a well-established approach for the determination of metal ions where the complexing agent is used to drastically decrease the concentration of so-called free metal ion in solution at the equivalence point. This change is typically visualized electrochemically with ion-selective electrodes or optically with indicator dyes. [1e, 2]

As proposed by Schwarzenbach[3] , for a reagent to serve in a titration procedure, (i) the reaction must be rapid; (ii) it must proceed stoichiometrically; and (iii) the change in free energy

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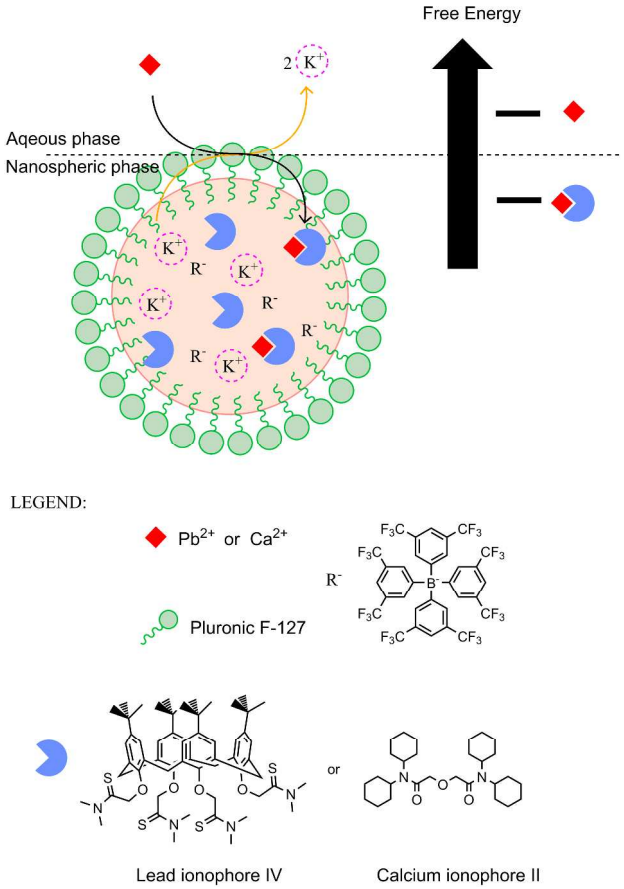

Scheme 1. Ion-selective emulsions containing nanospheres as complexing agent and structures of the compounds used in this work. The nanosphere core is made of dodecyl 2-nitrophenyl ether (D-NPOE) and the hydophobic sub-structure of Pluronic F-127. The complexation reaction comprises (1) ion exchange between target ion (Ca^{2+} or Pb^{2+}) in aqueous phase and the counter ion of R^- (K^+) in the organic phase and (2) the complexation reaction between target ion and the receptor, which lowers the solvation energy for the target ion and provide the driving force for its uptake into the nanospheres.

must be sufficiently large.

Until today, complexometric titrations made use of chelators that undergo homogeneous complexation reactions. Water soluble polyaminocarboxylic acid chelators such as ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) are the most widely used chelators, forming complexes of sufficient stability with nearly all polyvalent cations.[1b, 4] Because of this, their selectivity is not always satisfactory. To ensure adequate selectivity, additional masking agents are required and/or the pH of the solution needs be carefully controlled. For example, calcium titrations with EDTA must be performed above pH 10.[5] In addition, when chelators are used as antidotes for heavy metal intoxication, the potential toxicity of these compounds also requires attention.[1b] For instance, the chelator 2,3-dimercaptopropanol (British Anti Lewisite, BAL), an early antidote for Hg^{2+}, was later found to be toxic because of its ability to accumulate organic and inorganic mercury in the brain.[6]

We propose here a new chemical principle for the design of complexometric titration reagents. Instead of relying on the complexation to occur in homogeneous phase, we make use of nanosphere containing emulsions doped with ion-exchanger and hydrophobic receptor. This makes it possible to move the complexation reaction from the aqueous phase to an organic environment, where many more receptor molecules with highly tunable binding selectivities are available. Moreover, such a design also allows further modification of the nanoparticle matrix material to reduce bio-toxicity.

The principle is shown in Scheme 1. The emulsion is doped with a lipophilic ion-exchanger whose counter ion is readily displaced by the ion of interest. While the relative preference of one (uncomplexed) ion over another is governed by the Hofmeister lipophilicity sequence, the hydrophobic receptor in the particle core forms additionally a stable and selective complex of defined complex stoichiometry with the target ion. While the receptor drives the selective uptake by the nanoscale reagent, the ion-exchanger defines the quantity of extractable ions.

Adequate lipophilic ion receptors, also known as ionophores, have been used in the design of highly selective optical and electrochemical ion sensors for some time with great success [7]. The complexation reaction between the ionophore and target ions is typically diffusion controlled. Together with a small size of less than 100 nm in diameter that ensures a rapid phase transfer process, the first requirement for the complexing agent is fulfilled. The stoichiometry is typically known, thus the second requirement is also fulfilled. Note that the complex stoichiometry is much less critical than with homogenous titrations since one quantifies the amount of extractable ions by the amount of the ion exchanger if the receptor is in sufficient molar excess. Such ionophores exhibit binding constants that are often very high, for divalent ions up to 25 orders of magnitude,[8] and thus fulfil the third requirement stated above for complexing agents.

The Ca^{2+} and Pb^{2+} selective emulsions were prepared by a precipitation method,[9] where a tetrahydrofuran (THF) solution containing calcium ionophore II (ETH 129) or lead ionophore IV, potassium tetrakis[3 ,5-bis(trifluoromethyl)phenyl]borate (KTFPB), dodecyl 2-nitrophenyl ether (D-NPOE) and surfactant Pluronic F-127 was injected into vortexing water to form a self-assembled nanosphere suspension. The ion-selective emulsions were obtained after removal of THF. The resulting emulsion exhibits monodipersity and is stable for at least four weeks.

In the complexometric titration of Ca^{2+} and Pb^{2+}, the calcium or lead ion-selective emulsions were used as complexing agents and potentiometric ion-selective electrodes were employed as endpoint detectors. Three different concentrations of lead and calcium were explored for the titration experiment shown in Fig. 1. Accurate titration curves were obtained with relative errors of less than 3%. The results showed satisfactory agreement with theoretically

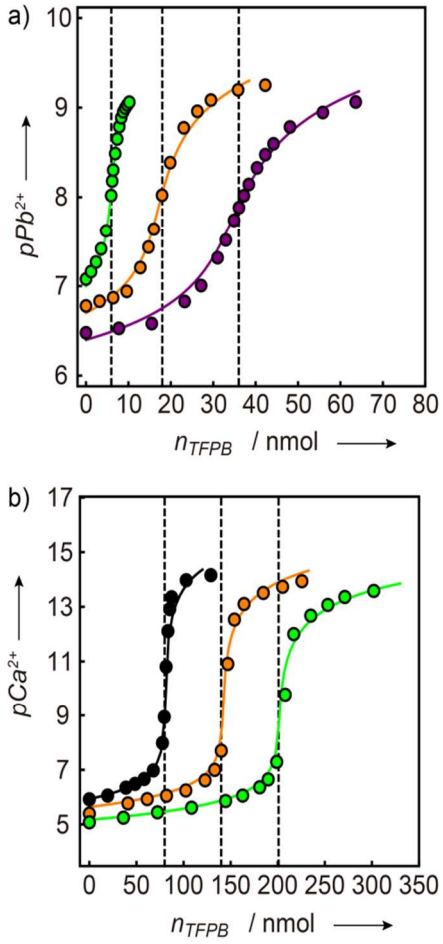

Fig. 1 (a) Potentiometric titration curves for 10^{-7} M (green), 3×10^{-7} M (orange), 6×10^{-7} M (purple) Pb^{2+} in unbuffered solutions (amounts of Pb^{2+} in solution: 3 nmol, 9 nmol, and 18 nmol). (b) Potentiometric titration curves for 4×10^{-6} M (black), 7×10^{-6} M (orange), 10^{-5} M (green) of Ca^{2+} in unbuffered water, corresponding to total amounts of 40 nmol, 70 nmol, and 100 nmol. The dashed vertical lines shows the expected endpoints.

expected equivalence points as indicated by the vertical dotted lines, which were calculated on the basis of number of moles of added ion-exchanger, which defines the amount of extractable ions from the sample. The response time is less than 1 min before the endpoint as shown in Fig. S1, which is essentially given by the time response of the potentiometric detector. The emulsion containing only TFPB was confirmed to not function properly for Ca^{2+} or Pb^{2+} titration because it lacks selectivity.

As an early stage application, the calcium level in the river Arve (Geneva, Switzerland) was determined as 1.40 mM ± 0.06 mM SD using a calcium selective emulsion as complexing agent for Ca^{2+}. This titration compares favorably with an EDTA titration at pH 10 using EBT as endpoint indicator (1.37 mM ± 0.01 mM SD). The

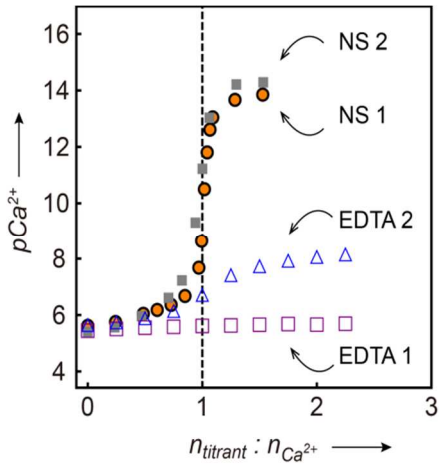

Fig. 2 Comparing calcium selective emulsion with EDTA as complexing agents for the potentiometric titrations of 4 µM calcium. NS 1: titration in non-buffered water by calcium selective emulsion; NS 2: titration in 1mM pH 7.0 Tris-HCl by emulsion; EDTA 1: titration in non-buffered water by EDTA; EDTA 2: titration in 1 mM pH 7.0 Tris-HCl by EDTA. The dashed vertical line marks the endpoint.

results also indicate that the selectivity of the nanospheres is sufficient for this application.

As mentioned above, most available chelators for complexometric titrations require careful pH control or the use of additional masking agents. For the emulsion based calcium chelator, this is generally not necessary because the interference by H^+ is very small, owing to the lack of protonatable groups on the calcium receptor. Fig. 2 shows a comparison of titration curves between calcium selective emulsions and conventional calcium chelator EDTA. As established for EDTA, the lack of a pH buffer results in the disappearance of the endpoint with EDTA. On the other hand, the emulsion-based titrant gives essentially the same endpoint transitions for an unbuffered sample and one buffered at pH 7.0. Fig. 3 even demonstrates the successful titration of calcium under acidic conditions (pH 4). At pH 7.0, the titration curves using the emulsions are much sharper than EDTA owing to the stronger Ca^{2+} binding affinity of calcium ionophore II.

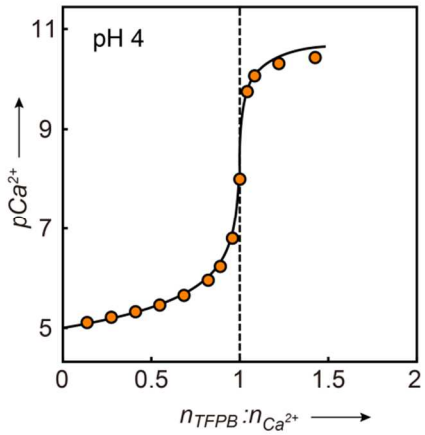

Fig. 3 Potentiometric titration curve for 10^{-5} M $CaCl_2$ in pH 4 HCl solution with calcium selective emulsion as titration reagent. Dashed vertical line marks the expected endpoint.

In summary, we propose here ion-selective nanosphere containing emulsions as a new family of complexing reagents. The nanospheres work on the basis of heterogeneous ion exchange equilibria. Ca^{2+} and Pb^{2+} selective emulsions were shown here as initial examples for complexometric titrations. The ion-selective nanospheres can quantitatively bind calcium or lead ions, even without pH control. Chelators such as EDTA have been widely applied for chelometry but the selectivity and working pH range has not really evolved in the past 60 years. This work opens up new chemical avenues to attain binding affinities and selectivities that have so far not been achievable with homogeneous binding approaches.

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