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Understanding the bioavailability and sequestration of different metal cations in the presence of a biodegradable chelant *S,S*-EDDS in biological fluids and natural waters

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HIGHLIGHTS

- S,S-EDDS is a biodegradable alternative to EDTA for chelation of metal cations?
- The possible use of S,S-EDDS as chelant in hydrosphere and biosphere is tested.
- Contrarily to EDTA, S,S-EDDS may be used in the presence of Ca^{2+} and Mg^{2+}.
- Complex formation is mainly exothermic and the reactions are entropic in nature.
- EDDS use, instead of EDTA, is suggested when $(c_{Ca} + c_{Mg}) > 1.5 \cdot c_{EDTA}$.

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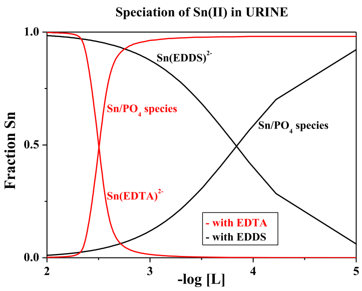
GRAPHICAL ABSTRACT



ABSTRACT

Ethylenediamine-N,N'-disuccinic acid is a biodegradable alternative to EDTA, therefore its use for the sequestration of Ca^{2+}, Sn^{2+}, Cu^{2+}, Zn^{2+} and Fe^{3+} is analyzed. New data on its binding ability towards these cations were obtained with potentiometric, voltammetric and calorimetric measurements at different ionic strengths and at $T = 298.15$ K. Real multi-component fluids, namely fresh water, urine, sea water, saliva and blood plasma were chosen as case studies to evaluate the sequestering ability of EDDS in comparison with EDTA. Speciation diagrams were drawn in selected conditions, considering all interactions among the "natural" components of the fluid and those studied in this work, EDDS and EDTA ($c_L = 1$ mmol dm^{-3}) as sequestering agents and the cited metal cations ($c_M \sim 10^{-5}$ mol dm^{-3}). The comparison of the sequestering ability of EDDS and EDTA is done using pM and $pL_{0.5}$. In blood plasma the plasma mobilizing index was adopted. It was found that EDDS is a good alternative to EDTA, which tends to bind Ca^{2+} and Mg^{2+} more than EDDS. In particular, EDTA cannot be used as a sequestrant for Sn^{2+} when $c_{Ca} > c_{EDTA}$. EDDS is more efficient than EDTA at pH < 8, particularly in urine, where carbonate is absent. In sea water, the sequestering ability of EDDS towards Fe^{3+} is higher than that of EDTA. In blood

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plasma, the PMI of EDDS towards Cu^{2+} is higher than that of EDTA. Thermodynamic information, in terms of ΔH and ΔS, for the protonation and metal complex formation reactions are reported.

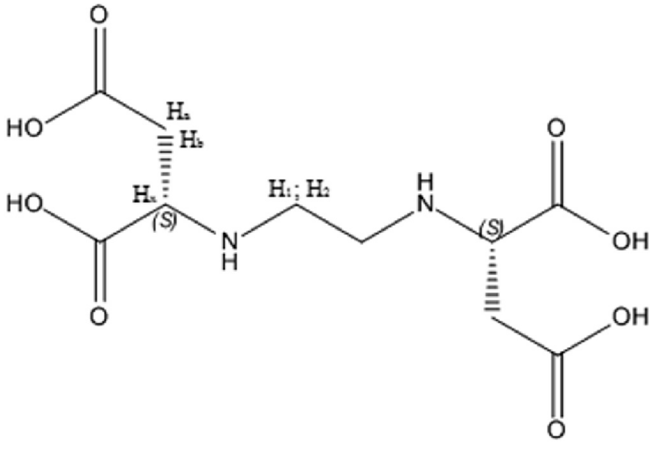
1. Introduction

The presence and the concentration of metal cations in natural fluids is a point of great consideration for the scientists and for the entire society, because regards the evaluation of the health level of an ecosystem and for the implications that pollution caused by the presence of metal cations has for food chain.

Generally, the fate of the metal cations in the biosphere cannot be easily predicted; they can be precipitated as carbonates or hydroxides (*e.g.* Cu^{2+} or Fe^{3+}), bio-accumulated by organisms (*e.g.* Hg^{2+}), organicated by bacteria (*e.g.* Hg^{2+}, Sn^{2+} or Pb^{2+}), oxidized or reduced depending on the pE (E = electron activity) value of the fluid. In each of the above cases, the spectrum of the effects caused by the metal overload in living organisms, in concurrence with other risk factors, may be quite relevant. For example, the copper overload is responsible of the Wilson's disease, and the overload of other metal or organo-metal cations in the living organisms is potentially responsible of other problems of functional, enzymatic or physiological nature.

In the light of these considerations, the knowledge of a remediation procedure could be important, and often complexones, such as EDTA or phosphonates, have been used for this purpose. In the last years this research group has undertaken studies to determine the sequestering ability of complexones (see, *e.g* De Stefano et al., 2014a; De Stefano et al., 2014b; Crea et al., 2014). However, Crisponi et al. (Crisponi et al., 2015) recently claimed some doubt about the chelation therapy applied to humans, related to the side effect of the removal of essential metal cations (*i.e.*, Ca^{2+} and Mg^{2+}) together with the toxic ones.

EDDS, see structure in Scheme 1, consists of two aspartic acid units linked by an ethylene bridge and can exist in three stereoisomers. The synthesis, reported by different authors (Neal and Rose, 1968; Orama et al., 2002; Schowanek et al., 1997; Takahashi et al., 1997), can be realized according to two paths. The first, which uses ethylendiamine and maleic anhydride as reactants, produces a mixture of *S,S* (25%), *R,R* (25%) and *R,S* (50%) diastereoisomers; the second, which needs L-aspartic acid and 1,2-dibromoethane as reagents, is stereo-selective and leads to the formation only of the *S,S* compound. Orama et al. (Orama et al., 2002) reported that the stability of the metal complexes with the *S,S* form is likely to be equal to that of the *R,R* form by symmetry, and slightly higher (0.3–0.5 log *K* units) than that of the *R,S* form, claiming the existence of a small stereospecificity due to the differences in the coordination geometry between the (*S,S*) and (*R,S*) forms of the ligand. This molecule has the advantage that the *S,S* form is readily biodegradable (Schowanek et al., 1997; Anastas, 2014), since it is based on the naturally occurring amino acid L-aspartic acid. Tandy et al. (Tandy et al., 2006) reported that in soils it is degraded in 7–11 days, with an half life of 4.18–5.60 days.



Scheme 1. Chemical structure of S,S-EDDS.

EDDS is a structural isomer of EDTA and shows similar stability of the metal complexes, except for the alkaline earth ones and Ca^{2+} in particular, for which the stability of the EDDS complexes is lower than that of EDTA ones (May and Muray, 1991; Whitburn et al., 1999; Martell et al., 2004; Pettit and Powell, 2004). This last property is of great interest, because in some of the case studies and in general when selective chelation is requested, EDDS may be used also in the presence of Ca^{2+} and Mg^{2+}. In general, the stability of complexes of Ca^{2+} with secondary or primary amines is lower than the corresponding Mg^{2+} ones (May and Muray, 1991; Martell et al., 2004; Pettit and Powell, 2004; De Stefano et al., 1999). The acute toxicity is very low, and it can be used without limitations in pre-harvesting. US EPA data (United States-Environmental Protection AgencyEnvironmental Protection Agency, 2015) reports that the oral LD_{50} (rats) > 2700 mg kg^{-1}, dermal LD_{50} (rats) > 2000 mg kg^{-1}, inhalation LC_{50} (rats) > 1.49 mg dm^{-3}.

Currently, *S,S*-EDDS is used as laundry detergent (the tri-sodium salt) to replace phosphorous containing chelants (Hartman, 1996), in hair products to stabilize peroxide solutions and as enhancer of biocides (Fowles et al., 2007), for the metal removal in waste water and soil washing treatment (Tandy et al., 2006; Yip et al., 2009a, 2009b; Tsang et al., 2009), in photographic development stage (Takahashi et al., 1997), in pulp bleaching (Seccombe and DournelSolvay, 2010), and in many agricultural applications, for example in the metal cation delivery in the foliar treatment (Gonzalez et al., 2007). In 2002, total production of EDDS achieved 10,000 tons. Nowadays, EDDS is a chelating reagent available in Europe on a large scale, and the demand for *S,S*-EDDS acid has been growing at the rate of 15% per year (Kołodynska and Ning, 2011).

For these reasons, the use of the *S,S*-EDDS as chelant for Ca^{2+}, Sn^{2+}, Cu^{2+} Fe^{3+} and Zn^{2+} is investigated in this paper, owing to new data on the binding ability of EDDS towards these cations, determined with potentiometric, voltammetric and calorimetric measurements at different ionic strengths. A critical literature analysis was necessary to select the most reliable data for the M/EDDS systems and those relative to the network of interaction between the “natural” components (*e.g.*, chloride, carbonate, citrate, urea). The case studies object of this work have been chosen for their importance in nature and are: fresh water, urine, sea water, saliva and blood plasma, whose composition in terms of ions was taken from different works (Whitfield and Pytkowicz, 1979; Lentner, 1983; De Stefano et al., 1994; Millero, 1996; Crea et al., 2015) or experimental data, as in the case of urine.

Among the selected metal cations, Sn^{2+} was not deeply studied in the past and it is worth to spend some words about it. Although Sn^{2+} is generally not considered among the worst pollutants, its