Ligand reorganization energies as a basis for the design of synergistic metal ion extraction systems

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In the extraction of alkaline earth cations by acidic organophosphorus extractants, a correlation has been demonstrated between the effectiveness of the stereoisomers of dicyclohexano-18-crown-6 as synergists and the strain energy associated with conversion of the unbound crown ether to its complexed form.

Metal ion separations comprise an important part of numerous industrial processes and constitute an essential first step in many chemical analyses. Among metal ion separation methods, liquid–liquid extraction (LLX) has found particularly wide use, a consequence of its selectivity, physical simplicity, and ease of scale-up. The extraction of a metal ion from an aqueous phase into an organic solvent requires, among other things, that electroneutrality be maintained. For neutral extractants, this is accomplished by coextraction of anions into the organic phase:

$$M^{n+}{}_{(aq)} + n\,X^{-}{}_{(aq)} + E_{(org)} \Leftrightarrow MX_n\cdot E_{(org)}$$

For common inorganic anions (*e.g.* Cl^-, NO_3^-), satisfactory metal extraction requires the use of organic solvents capable of either efficiently solvating a hydrophilic anion or of dissolving high concentrations of water,[1,2] a requirement that significantly reduces the number of practical LLX solvents. This limitation can be largely overcome, however, by employing organophilic anions, in particular, the anionic form of any of a number of alkylphosphoric, carboxylic or sulfonic acid extractants. Frequently, combinations of neutral and acidic extractants exhibit synergistic properties, yielding metal ion extraction greater than the sum of that observed for the individual extractants. Strong, size-selective synergism has been reported, for example, for alkaline earth cation extraction by certain combinations of crown ethers (CE) and organophosphorus acids (HA).[3,4] Despite numerous reports describing synergistic effects,[5–7] there have been few systematic investigations of the factors governing their magnitude. As a result, guidelines for the design of synergistic systems capable of the efficient and selective extraction of a desired cation are lacking. Recently, Hay *et al.*[8,9] have shown that ligand reorganization energies calculated using molecular mechanics methods can be employed to make quantitative predictions of the relative metal ion binding affinities of a variety of ligands containing a fixed number of donor atoms but differing in conformation. In the present work, we demonstrate that these methods provide the basis of a systematic approach to the design of synergistic metal ion extraction systems.

The crown ether dicyclohexano-18-crown-6 (DCH18C6) has five different stereoisomers,[10] each varying with respect to *cis/trans* isomerism at the point of ring fusion and *syn/anti* isomerism between cyclohexano substituents across the macrocyclic cavity. For the extraction studies, distribution ratios ($D_M = [M]_{org}/[M]_{aq}$) for Ca^{2+}, Sr^{2+} and Ba^{2+} were determined between aqueous buffers (pH ≈ 1.5–5) and toluene solutions of individual DCH18C6 stereoisomers and/or bis-*n*-octyl-, bis-2-ethylhexyl- or bis(diisobutylmethyl)-phosphoric acid [abbreviated HDOP, HDEHP and HD(DiBM)P, respectively] using standard radiometric methods. Continuous variation studies showed metal extraction to be negligible for the crown ether alone, permitting the synergistic constant to be defined simply as the ratio of the extraction constants in the presence and absence of DCH18C6 for each dialkylphosphoric acid. Acid dependency studies (Fig. 1), in which metal distribution ratios were determined as a function of pH at constant HA concentration either alone or in the presence of a stereoisomer of DCH18C6, indicated that while no significant synergistic effects are observed for Ca^{2+}, the extraction of both Sr^{2+} and Ba^{2+} is synergized by addition of DCH18C6. In nearly all cases, the magnitude of the synergistic effect was found to vary in the order:

cis-syn-cis (A) > *cis-anti-cis* (B) > *cis-trans* (E) >
trans-syn-trans (C) ⩾ *trans-anti-trans* (D)

Slope analysis of these acid dependences, along with similar treatment of the extractant dependencies of the D_M values at constant pH and consideration of the continuous variation results, permits delineation of the equilibria describing alkaline earth cation extraction in these systems. In the absence of DCH18C6, the equilibrium expression can be written as follows:

$$K_{ex} = ([M(HA_2)_2\cdot nHA]_{org}[H^+]_{aq}{}^2)/([M^{2+}]_{aq}[(HA)_2]_{org}{}^{(2+n/2)})$$

where $n = 1$ for Ca^{2+} and 2 for Sr^{2+} and Ba^{2+}. For Sr^{2+} and Ba^{2+} in the presence of DCH18C6, this expression becomes:

$$K_{ex,s} = ([M(HA_2)_2\cdot DCH18C6]_{org}[H^+]_{aq}{}^2)/([M^{2+}]_{aq}[(HA)_2]_{org}{}^2\,[DCH18C6]_{org})$$

[The use of $(HA)_2$ to represent the alkylphosphoric acid in both sets of equilibria follows from the known dimeric state of these acids in toluene[5,11] and the absence of interaction between DCH18C6 and HA in the organic phase, confirmed by vapor pressure osmometry.] The synergistic constant, K_s, is defined as the ratio of $K_{ex,s}$ to K_{ex}, and corresponds to the organic phase reaction that leads to the formation of the final Sr^{2+} or Ba^{2+} complexes:

$$M(HA_2)_2\cdot 2HA_{(org)} + DCH18C6_{(org)} \rightleftharpoons M(HA_2)_2\cdot DCH18C6_{(org)} + (HA)_{2\,(org)}$$

Fig. 2 depicts the relationship between the synergistic constants (*i.e.* the magnitude of the synergistic effect) for strontium and barium extraction and the ligand reorganization energy,[8,9] ΔU_{reorg}, for the complexation of Sr^{2+} and Ba^{2+} by the various stereoisomers of DCH18C6. The ligand reorganization energy represents the extent to which complex formation between the crown ether and a metal ion induces steric strain in the crown ether and, therefore, indicates the degree of binding site preorganization characteristic of each stereoisomer. Ligand reorganization energy is defined as the sum of two structural reorganization components: the energy required to convert the free ligand from its minimum energy conformer to one

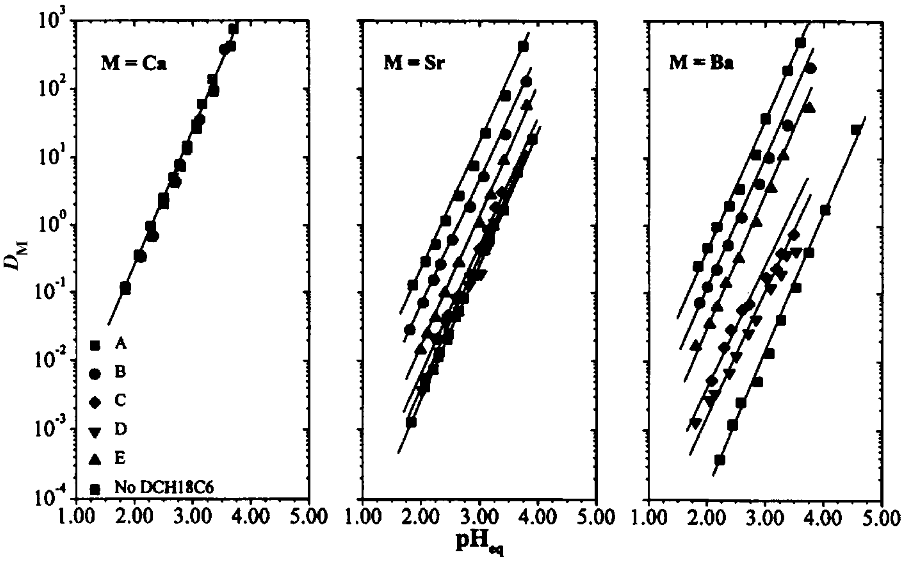

Fig 1. D_M *vs.* equilibrium pH for Ca^{2+}, Sr^{2+} and Ba^{2+} extraction by bis-*n*-octylphosphoric acid (HDOP) in toluene, both alone and in the presence of the stereoisomers of DCH18C6. Conditions: [HDOP] = 0.10 M; [DCH18C6] = 0.025 M in toluene; $[M(NO_3)_2]$ = 0.001 M; T = 23 ± 2 °C. (The least squares lines have a fixed slope of 2, consistent with the extraction equilibria.)

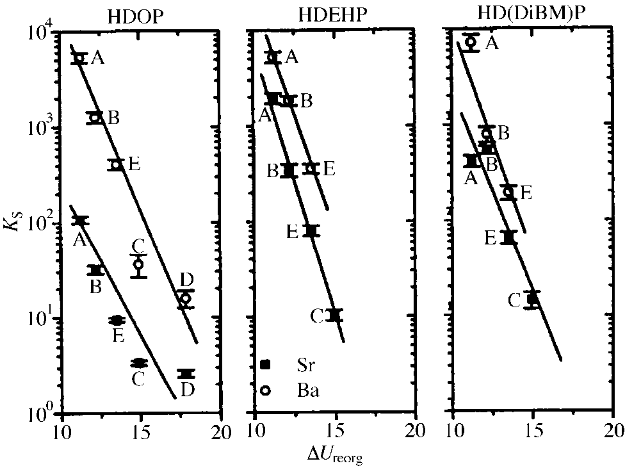

Fig 2. Relationship between the synergistic constants for Sr^{2+} and Ba^{2+} extraction and the ligand reorganization energy of the DCH18C6 stereoisomers.

predisposed for binding, ΔU_{conf}, and the energy difference between the binding conformer and the ligand conformation in the metal complex, ΔU_{comp}. Ligands highly preorganized for binding (*i.e.* 'sterically efficient' ligands) exhibit small ΔU_{reorg} values. As shown in Fig. 2, there exists an inverse linear relationship between log K_s and ΔU_{reorg}, providing strong evidence that the primary factor determining the magnitude of synergistic effects is the reorganization energy (and therefore, the metal ion binding affinity) of the neutral ligand, in this case, the various DCH18C6 stereoisomers. It appears that steric factors related to branching of the alkyl chains of the organophilic acid anion also play a role (Fig. 2), but the influence of these factors is clearly more limited.

To our knowledge, this work represents the first report of a correlation between the magnitude of a synergistic effect and ligand reorganization energies and thus, the first demonstration of the utility of molecular mechanics methods in guiding the design of synergistic metal ion separation systems. Given the widespread interest in crown ether-based separation processes and the enormous variety of both macrocyclic polyethers and organophilic acid anions available, these results are certain to have a significant impact on the development of improved systems for both analytical-scale and large-scale metal separations.

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