Preorganized *endo*-Dicarboxylic Host Macrocycles having Superior Extraction Selectivity for Small Alkaline Earth Metal Ions

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Novel preorganized host macrocycles with defined cavity size and two convergent carboxylic acid groups extract small alkaline earth metal ions in a liquid two-phase system with high selectivity, in particular Ca^{2+}, unlike the alkali metal ions.

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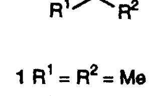
endo-Functional hosts with preorganized cavities are rare,[1] in particular if carboxylic groups are involved.[2] On the other hand, hosts with proton ionizable functions are promising complexants and extraction agents for metal ions rendering superfluous the phase transfer of additional anionic species.[3] For binding of divalent metal ions, two carboxylic groups have already been arranged as convergent functions of a rigid molecular cleft.[4,5]

We report a new host design which is a preorganized macrocyclic structure with two convergent carboxylic acid functions kept in a noninteractive distance. Examples are the macrorings **1** and **2** being different in the substitution of the diphenylmethano building blocks.

Compounds **1** (mp > 265 °C) and **2** (mp > 250 °C) were obtained in 12 and 24%, respectively, when methyl 2,6-bis(bromomethyl) 4-*tert*-butyl-benzoate[6] and 2,2-bis(4-hydroxyphenyl)propane (Janssen) or 1,1-bis(4-hydroxyphenyl)cyclohexane[7] were reacted in the presence of 2 equiv. of Cs_2CO_3 in dried DMF using high dilution[8] and subsequent hydrolysis of the isolated esters with CsOH.



1 $R^1 = R^2 = Me$
2 $R^1, R^2 = -(CH_2)_5-$

Both modelling studies (MM2, program HYPERCHEM 3) and a successful crystal structure of an inclusion complex of **1** with EtOH[9] revealed two energy minimum conformations **A** (low-step type) and **B** (calix-like) for each favoured *endo* orientation of the carboxylic groups (Fig. 1). From calculations, conformers **A** are lower in relative host energy than conformers **B** (145 *vs.* 163 kJ mol^{-1} for **1** and 212 *vs.* 217 kJ mol^{-1} for **2**). Conformers **B**, however, seem more suitable for binding of metal ions due to the smaller distance of the carboxylic groups (5.56 *vs.* 6.73 Å for **1** and 5.02 *vs.* 6.34 Å for **2**).† Moreover, geometry optimization calculations show that **2** provides the carboxylic groups in a somewhat smaller distance (5.02 *vs.* 5.56 Å for conformers **A** of **2** and **1**, respectively). For both compounds no low energy conformation with an exo orientation of acidic groups were found.

As expected, compounds **1** and **2** are very efficient extractants for alkaline earth metal ions whereas alkali metal ions are practically not extracted (<0.7%) under the choosen experimental conditions‡ (Fig. 2) demonstrating a striking extraction selectivity of alkaline earth over alkali metal ions. A distinct preference of Ca^{2+} over Mg^{2+}, Sr^{2+} and Ba^{2+} is also evident from Fig. 2 for both compounds.

The observed Ca^{2+} selectivity is essentially more pronounced for compound **2** under competitive extraction conditions with Mg^{2+}, Sr^{2+} and Ba^{2+} caused by specific discrimination effects of the higher extracted over the lower extracted metal ion (Fig. 2), thus yielding higher efficiency in the separation of Ca^{2+} from larger alkaline earth metal ions as expected from single ion experiments.

This selectivity for Ca^{2+} in general is obviously a result of optimum balance between dehydration and binding to the ligand. Nevertheless, strongly hydrated Mg^{2+} ion is still extracted to a rather high extent, and for **1** extraction of Mg^{2+} surpasses even the extraction of Sr^{2+} and Ba^{2+} which is perhaps the most important finding showing originality of the present host design. When comparing the net extraction efficiencies of the two hosts, the more lipophilic **2** is superior.

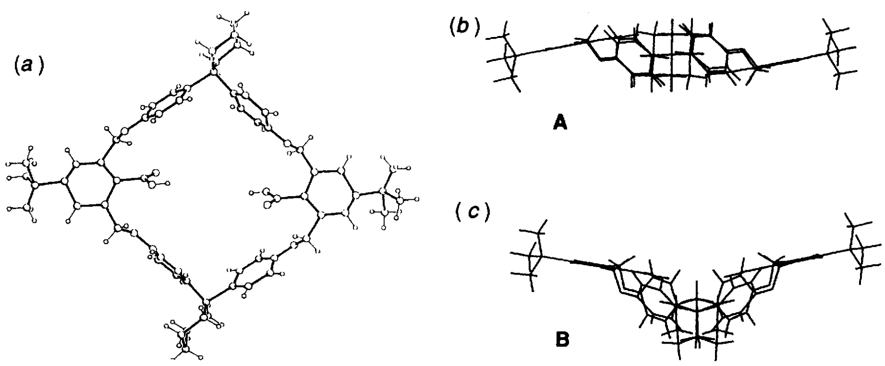


Fig. 1 (*a*) Conformation of **2** found in the crystal structure of a solid ethanol inclusion complex and (*b*,*c*) two energy minimum conformations **A** (low-step-type) and **B** (calix-like) of compound **2** calculated by molecular mechanics in the gaseous phase

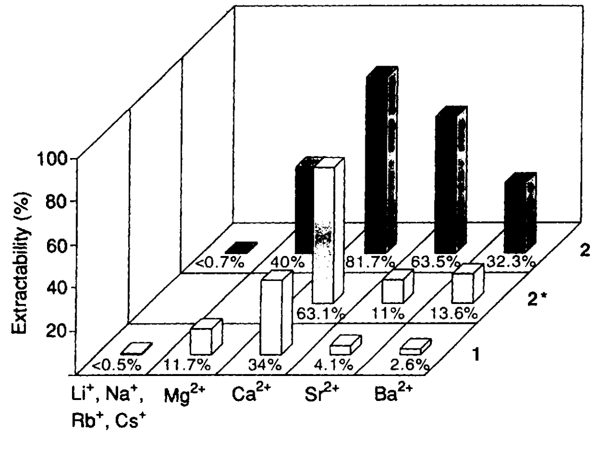


Fig. 2 Extractabilities in single ion extraction with **1** and **2** and competitive extraction experiments with **2** (row 2*). $[M(NO_3)_n] = 1 \times 10^{-4}$ mol dm^{-3}; pH = 8.5 (TEA/HCl-buffer); [**1**] or [**2**] = 1×10^{-3} mol dm^{-3}/CHCl$_3$.

Favoured extractability of alkaline earth metal ions from aqueous into an organic phase can be controlled by the solvent polarity. About two orders of magnitude higher distribution ratios of the metal ion ($D_M = c_{M(org)}/c_{M(w)}$) are obtained for Ca^{2+}, Sr^{2+} and Ba^{2+} extraction with **2** into *n*-decanol instead of chloroform under identical conditions (Fig. 2). This behaviour arises from additional interactions between the complexed metal ion and solvent molecules that complete the coordination sphere (usual coordination numbers of alkaline earth metal ions are between 6 and 8[12]). It becomes clear if the composition of the extracted complex is taken into account. A nonlinear regression analysis of data sets of distribution ratios in dependence on ligand concentration points to both 1 : 1 and 2 : 1 ligand : metal ion ratio in the formed complex in chloroform. In *n*-decanol a complex composition of one metal ion, one ligand and one alcohol molecule was proved.

The results obtained show that host design footing on a rigid cavity with convergent dicarboxylic acid functions kept in a noninteractive distance is a source for highly selective complex forming agents of cations. To modify the nature, the distance and the number of endo orientated functional groups in this framework appears to be a promising task.

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

Received, 6th May 1994; Com. 4/02696I

Footnotes

† Estimated cavity sizes based on the distances of oxygen atoms of carboxylic groups reduced by its van der Waals dimensions of approximately 3.0 Å (ref. 10) yield 2.5–3.2 Å for **1** and 1.9–2.6 Å for **2** corresponding to ionic diameter of Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} (1.7–2.9 Å, ref. 10, 11).

‡ Liquid–liquid extraction investigations were performed in micro reaction vials (0.5 cm^3 of each phase) at 25 ± 1 °C in the system metal nitrate–triethanolamine (TEA)–hydrochloric acid–water/extractant–organic solvent at a pH of 8.5. After a shaking time of 30 min equilibrium was achieved and all samples were centrifuged. In case of Ca^{2+}, Sr^{2+} and Ba^{2+} the metal ion concentration in both phases was determined by radiotracer technique (Isocommerz GmbH) in a γ-counter Cobra II and a liquid-scintillation counter Tricarb 2500 (both from Canberra–Packard), respectively. The Mg^{2+} concentration was determined by atomic absorption (AAS 2100/Perkin Elmer) only in the aqueous phase.

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