A SYNTHETIC, ELECTRICALLY NEUTRAL CARRIER FOR Co²⁺

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Recently, the complexing of alkali and alkaline earth metal cations by neutral molecules $\begin{bmatrix} 1 & 4 \end{bmatrix}$ has gained new impetus due to the observation of the formation of complexes between such ions and carrier antibiotics $\begin{bmatrix} 5 \end{bmatrix} \begin{bmatrix} 6 \end{bmatrix}$. Synthetic lipophilic ligands of high selectivity for Ca^{2^+} are especially attractive in view of their use as carriers in investigations concerning biological systems $\begin{bmatrix} 7 \end{bmatrix}$ and as membrane components for ion selective electrodes $\begin{bmatrix} 8 \end{bmatrix}$.

According to calculations on model systems, and assuming oxygens to be the coordinating atoms, such a carrier should be a multidentate ligand having preferably six coordinating atoms $[\mathfrak{s}]$. To discriminate between mono- and divalent cations the thickness of the ligand layer should be as small as possible $[\mathfrak{s}]$; in addition, both ligand and complex should be lipid-soluble. To achieve a high selectivity for Ca^{2^+} relative to other alkaline earth metal cations, the coordinating oxygen atoms should form a rather fixed cavity with a radius of around 1 $^{\mathsf{A}}$. Since rapid cation exchange is necessary, however, the ligand system must have an adequate flexibility so that a compromise between selectivity, i.e., high formation constant for Ca^{2^+} , and flexibility of the ligand will have to be made $[\mathfrak{g}]$. To eliminate competitive reactions with protons, the ligand should not contain functional groups participating in acid-base reactions under working conditions. The preparation of a number of molecules meeting these requirements will be described elsewhere [10]. In fig. 1 the structure of one representative is given.

FIGURE 1 Structure of Carrier for Ca²⁺ Using filter paper (Type VCWP, Millipore Corporation, Bedford, Mass., USA) impregnated with a 20% by weight solution of ligand (fig. 1) in p-nitroethylbenzene as the membrane in the cell assembly (see [8])

Ag;AgCl, 0.01M KCl membrane sample solution 0.1M NH_4NO_3 KCl(satd.), Hg_2Cl_2 ;Hg (1) and 0.1M aqueous solutions of the chlorides of the different cations, the selectivity sequence

is obtained. The comparison of this sequence with the one obtained analogously by impregnating the membrane with pure p-nitroethylbenzene:

Rb
$$^{\circ}$$
 K $^{\circ}$ Cs > Ba > Na >> Li $^{\circ}$ Sr $^{\circ}$ Ca > Mg (3)

clearly demonstrates the ligand's preference of Ca^{2+} over the other cations studied (see column 4 in table 1). Using equation (4) to describe the EMF of the cell (1), the selectivity constants $K_{\text{CaM}}^{\text{Pot}}$ given in table 1 are obtained through equation (5).

$$EMF = E_{o} + \frac{2.303 \text{ RT}}{2F} \log(a_{Ca}^{2} + K_{CaM}^{Pot} a_{Mz}^{2/z})$$
 (4)

$$\log k_{CaM}^{Pot} = \frac{(EMF_2 - EMF_1)2F}{2.303 RT} - \log a^{(2/z)-1}$$
 (5)

T : absolute temperature a : ion activities

R : gas constant z : charge of the interfering ion F : Faraday constant E_{σ} : temperature dependent constant EMF_1 : EMF of the cell assembly (1) with a 0.1M solution of calcium chloride as the sample

EMF₁ : EMF of the cell assembly (1) with a 0.1M solution of calcium chloride as the sample
EMF₂ : EMF of the cell assembly (1) with a 0.1M solution of the interfering cation chloride as the sample

TABLE 1 Selectivity Constants KPot (0.1M solutions)

Cation M	membrane with		
	ligand(20% by weight in p-nitroethylbenzene)	p-nitroethylbenzene	effect of ligand on K CaM *)
Ca ²⁺	1	1	1
Rb ⁺	2·10 ⁻¹	8 •10 ⁶	2.5.10-8
κ ⁺	9·10 ⁻²	6 •10 ⁶	1.5·10 ⁻⁸
Ba ²⁺	8·10 ⁻²	1.3·10 ⁴	6.2·10 ⁻⁶
Cs ⁺	6·10 ⁻²	з •10 ⁶	2 ·10 ⁻⁸
Sr ²⁺	10 ⁻²	10	10 ⁻³
Na ⁺	7•10 ⁻³	1.2°10 ⁴	5.8·10 ⁻⁷
Li ⁺	3*10 ⁻³	40	7.5·10 ⁻⁵
Mg ²⁺	3·10 ⁻⁵	4 •10 ⁻²	7.5·10 ⁻⁴

^{*)} Ratio of values in column 2 over those in column 3

The interaction of the ions with the ligand can be observed by NMR spectroscopy (see fig. 2 and table 2). Both in ¹H and ¹³C resonance the groups showing the largest shifts due to complexation are those adjacent to the oxygen atoms suitable for coordination. In contrast to the cryptates [1], this ligand shows rapid exchange with alkali and alkaline earth metal

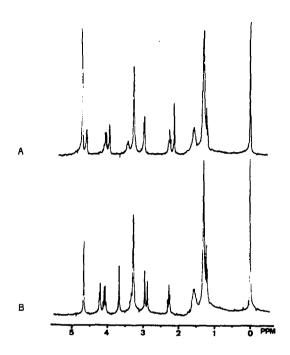


FIGURE 2. 270 MHz Proton Magnetic Resonance Spectra of the Ligand (see fig.1) Measured in Methanol-d₄. A:ligand after addition of an excess of Ca(SCN)₂. B:free ligand.

TABLE 2. 1 H and 13 C Chemical Shifts (ppm) of the Ligand (see fig.1) and its Complex with Ca^{2+} •)

Position	¹ H (270 MHz)		¹³ C (22.63 MHz)	
(fig.1)	free ligand	complex (Ca ²⁺)	free ligand	complex (Ca ²⁺)
1	1.22	1.22	14.6	14.6
2	4.09/4.12	4.10/4.12	61.1	61.4
4			175.1	175.6
5	2.29	2.29	35.0	35.1
6	1.57	1.59	25.9	25.9
7-11	1.31	1.31	27.9-30.4	27.9-30.3
12	1.31	1.31	27.7	27.8
13	1.57	1.59	27.9-30.4	27.9-30.3
14	3.33	3.46	50.1	∿49.5
16			171.1	172.3/172.0
17	4.24/4.25	4.64	70.4	70.6/69.9
19	3.70	4.00	71.5	70.8
N-CH ₃	2.95/2.88	3.00/2.99	34.5/33.5	∿34.5/∿33.7

^{*) 270} MHz FT proton magnetic resonance spectra were run on a Bruker-Spectrospin HFX-270 spectrometer equipped with an FT unit, and the 22.63 MHz FT 13C magnetic resonance spectra on a Bruker—Spectrospin HFX-10 spectrometer equipped with an FT unit B-SC-FFT-12. The chemical shifts are given in ppm relative to TMS in the solvent methanol.

cations*). Assuming rapid exchange, complex formation constants can be calculated from the chemical shifts of a given nucleus in the free ligand, in a nearly equimolar mixture of ligand and metal ion, and in the complex. Using the shift of the protons at C-17 the largest formation constant found for the cations studied is that obtained for Ca²⁺, in agreement with sequence (2). Assuming a 1:1-type complex the formation constants in methanol are around 1000 and 10 for Ca²⁺ and K respectively.

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References

- B. Dietrich, J. M. Lehn, J. P. Sauvage, Tetrahedron Letters 34, 2885, 2889 (1969);
 - J. M. Lehn, J. P. Sauvage, Chem. Commun. 440 (1971).
- [2] C. J. Pedersen, J. Amer. Chem. Soc. 89, 7017 (1967);
 - C. J. Pedersen, H. K. Frensdorff, Angew. Chem. internat. Edit. 11, 16 (1972).
- J. J. Christensen, J. O. Hill, R. M. Izatt, Science 174, 459 (1971).
- R. J. Levins, Analyt. Chemistry 43, 1045 (1971).
- Z. Štefanac, W. Simon, Chimia 20, 436 (1966).
- W. E. Morf, W. Simon, Helv. Chim. Acta 54, 2683 (1971); presented at the Symposium on Molecular Mechanisms of Antibiotic Action on Protein Biosynthesis and Membranes, June 1971, University of Granada, Spain.
- E. W. Moore in R. A. Durst: Ion-Selective Electrodes, Nat. Bur. Stand. (US) Special Publication 314, Washington, 1969.
- W. Simon, H. R. Wuhrmann, M. Vašák, L. A. R. Pioda, R. Dohner, Z. Štefanac, Angew. Chem. internat. Edit. 9(6), 445 (1970).
- H. Diebler, M. Eigen, G. Ilgenfritz, G. Maass, R. Winkler, II. I.C.C.C., Haifa, 1968; Pure Appl. Chemistry 20, 93 (1969).
- [10] D. Ammann, E. Pretsch, W. Simon, Helv. Chim. Acta, in preparation.
- *) The splitting of some signals (N-CH_q; H on C-17) is probably due to the hindered rotation