137. Selective Transport Membranes and their Applicability for Novel Sensors

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(27.VI.86)

Selective transport of given substrates through artificial membranes can be achieved by incorporation of electrically neutral or charged carriers. Such mediated transport described for alkali and alkaline-earth metal cations is reported here for the first time for certain anions using cobyrinate-type ionophores, and it is also conceivable to be realized for nonionic substrates (*e.g.* glucose). The fundamental requirements for corresponding co-transport and counter-transport membrane systems are set forth in view of a design of novel substrate-selective sensors for analytical-chemical applications.

Introduction. – A large number of potentiometric or amperometric membrane electrode systems for the selective determination of given substrates has been introduced and has found widespread application in analytical chemistry, especially in clinical-chemical routine analysis (for a review, see [1–3]). All relevant sensors of this type described so far can be classified in three categories:

1) Systems which are based on a highly selective substrate-permeable resp. substrate-extracting membrane as the detector unit (*e.g.* ion-selective electrodes, ion-selective field-effect transistors).

2) Systems which are composed of a poorly selective substrate-permeable membrane and a selective internal detector unit (*e.g.* gas-sensing electrodes).

3) Systems in which a substrate-specific reaction is combined with sensors of the type 1) or 2) (*e.g.*, enzyme electrodes and related biosensors).

However, another, completely novel construction principle is conceivable to be realized for electrochemical, optical, and other membrane-based sensor systems:

4) Sensors which are composed of a highly selective substrate-transport membrane and a poorly selective internal detector unit.

The required high permeability of the membrane can be achieved either by incorporating substrate-selective channels (only for the case of bilayer lipid membranes of *ca.* 10-nm thickness) or by introducing selective carriers, *i.e.* mobile complexing agents for the substrates. Since the preparation of sufficiently stable bilayers for analytical purposes as well as the tailoring of channels of given selectivities are far from being realized [4], we focus in the following on carrier-based membranes for selective substrate transports.

Theory. – If a membrane (m) incorporating a carrier L is interposed between two solutions (s) containing substrates N, these species can move across the membrane by carrier translocation upon complex formation:

$$\mathrm{N\,(s) + L\,(m)} \overset{K_N}{\rightleftharpoons} \mathrm{NL\,(m)}$$

For simplicity, a 1:1 stoichiometry of the substrate/carrier complexes is assumed. The complexation parameters K_N characterizing the substrate-distribution equilibria must not necessarily be identical for the two membrane/solution interfaces (′) resp. (″) *i.e.*

$$\bar{c}'_{NL} = K'_N c'_N \bar{c}'_L\ ; \quad \bar{c}''_{NL} = K''_N c''_N \bar{c}''_L \tag{1a, b}$$

where the concentrations $\bar{c}$ of the subscripted species refer to the membrane boundaries, and the concentrations c refer to the external solutions. Assuming a constant total concentration of the carrier in the membrane, one can write the relation:

$$\bar{c}_L + \sum_N \bar{c}_{NL} = \bar{c}_{L,tot} \tag{2}$$

Hence, the flux J_N of a given substrate across the membrane at zero-current steady-state can be described as

$$J_N = J_{max} \frac{\bar{c}'_{NL} - \bar{c}''_{NL}}{\bar{c}_{L,tot}} \tag{3}$$

where the maximum transport rate J_{max} depends on the diffusion coefficient $\bar{D}$ of free and complexed carrier, on the total carrier concentration $\bar{c}_{L,tot}$, and on the membrane thickness d:

$$J_{max} = \bar{D}\bar{c}_{L,tot}/d \tag{4}$$

Finally, the following flux equation is obtained from *Eqns. 1–3*:

$$J_N = J_{max}\left[\frac{K'_N c'_N}{1 + \sum_N K'_N c'_N} - \frac{K''_N c''_N}{1 + \sum_N K''_N c''_N}\right] \tag{5}$$

and the concomitant, time-dependent concentration changes in the external solutions are related as follows:

$$V''\,dc''_N/\mathrm{d}t = -\,V'\,dc'_N/\mathrm{d}t = A\,J_N \tag{6}$$

where V' and V'' are the volumes of the two solutions, and A is the active membrane area. *Eqns. 5* and *6* apply to the facilitated or carrier-mediated transport of any electrically neutral [5] [6] or charged substrate across a membrane that conforms to the present simple model.

One example is the mediated diffusion of a single salt $N = \mathrm{M^+X^-}$ at zero current, that is, the simultaneous transport of cations and anions across a membrane containing an electrically neutral carrier selective for cations (or for anions). In this case, the substrate-distribution parameters K'_N and K''_N are identical with the overall salt-extraction constant K_{MX}, and *Eqn. 5* can be transformed into

$$J_M = J_X = J_{max}\left[\frac{1}{1 + K_{MX}\, c''_M\, c''_X} - \frac{1}{1 + K_{MX}\, c'_M\, c'_X}\right] \tag{7}$$

Obviously, *Eqn. 7* predicts transport up to diffusion equilibrium where it finally holds that

$$c_M^{\prime\prime eq}\, c_X^{\prime\prime eq} = c_M^{\prime eq}\, c_X^{\prime eq} \tag{8}$$

However, this equilibration transport proceeds with the maximum rate only as long as

$$K_{MX}\, c''_M\, c''_X \ll 1 \quad \text{and} \quad K_{MX}\, c'_M\, c'_X \gg 1 \tag{9a, b}$$

Extremely interesting is the case where the first solution contains one of the permeating ions (*e.g.* X^-) in excess, whereas the second solution is initially free from permeants:

$$c_M'^o \ll c_X'^o \; ; \quad c_M''^o = c_X''^o = 0 \qquad (10a, b)$$

Here, the following equilibrium concentrations are established in the second solution (for $V' \approx V''$; see *Eqns. 8* and *10*):

$$c_M''^{eq} = c_X''^{eq} \approx \frac{V'}{V''} c_M'^o \qquad (11)$$

Evidently, the high concentration gradient of one species across the membrane leads to a *co-transport* of the other species and to its quantitative accumulation (against its concentration gradient) on the other side of the membrane. The conditions for favorable dynamics of this equilibration process are, according to *Eqns. 9–11* (see. *Fig. 1*):

$$K_{MX}\, c_M'^o\, c_X'^o \gg 1 \quad \text{and} \quad K_{MX}\, (c_M'^o)^2 \ll 1 \qquad (12)$$

Selective transport membrane systems of this type, involving an appropriate detection for the permeants arising in the inner solution ("), may become highly valuable analytical devices.

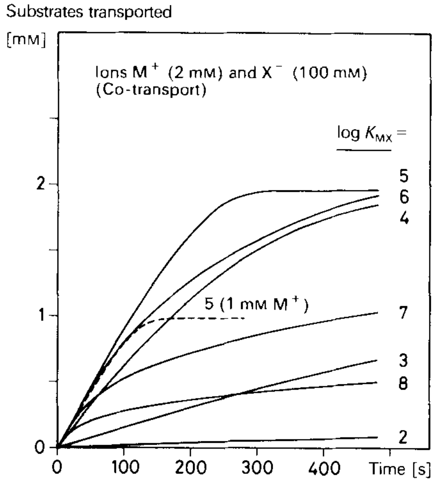

Fig. 1. *Equilibrating transport of cations and anions through a carrier membrane.* The electrolyte concentrations transferred from soln. *1* into soln. *2* are given as a function of time for different values of the salt-extraction constant K_{MX}. Initial concentrations in soln. *1*: 2 mM M^+ (except for dashed curve), 100 mM X^-. The following parameters were used for the calculations according to *Eqns. 6* and *7*: $A = 1\ \text{cm}^2$, $V' = V'' = 10^{-1}\ \text{cm}^3$, $d = 10^{-3}$ cm, $\bar{D} = 10^{-7}\ \text{cm}^2/\text{s}$, and $\bar{c}_{L,tot} = 10^{-5}\ \text{mol/cm}^3$.

Another example, where the basic flux *Eqns. 5* and *6* apply, is the mediated transport of ions of a given charge z (cations or anions) across membranes that contain electrically charged carriers [7] [8] or combinations of charged and neutral carriers [9]. In this case, the presence of at least two permeating substrates N, namely the ions I^z and J^z, is required for inducing a transport at zero current. If the stabilities of the involved ion/carrier complexes are sufficiently high, *Eqn. 5* yields the following description [7–9]:

$$J_I = -J_J = J_{max} \left[\frac{c_I'}{c_I' + K_{IJ}\, c_J'} - \frac{c_I''}{c_I'' + K_{IJ}\, c_J''} \right] \qquad (13)$$

in which the complex-stability ratios K'_J/K'_I and K''_J/K''_I have obviously been replaced by the coefficient K_{IJ} which characterizes the selectivity of the membrane transport system for the substrate J^z relative to I^z. According to *Eqn. 13*, this transport selectivity has no influence on the concentration ratios established at the final equilibrium state ($J_I = J_J = 0$):

$$c_I''^{eq}/c_J''^{eq} = c_I'^{eq}/c_J'^{eq} \tag{14}$$

On the other hand, the coefficients K_{IJ} are found to be decisive for the rate of equilibration [8] [9] since the requirements for maximum transport are

$$c_I' \gg K_{IJ}\, c_J' \quad \text{and} \quad c_I'' \ll K_{IJ}\, c_J'' \tag{15}$$

This implies that the selectivity of the carriers between the two permeating ions must be relatively poor (depending on the ion concentrations), whereas the preference of these substrates over other competing ions should be as high as possible [8] [9]. An especially interesting system is created, when the first solution initially contains only the substrate I^z, and the second one only the substrate J^z at a much higher concentration (for $V' \approx V''$), *i.e.*

$$c_I'^{o} \ll c_J''^{o}\,; \quad c_I''^{o} = c_J'^{o} = 0 \tag{16}$$

In this case, a real *counter-transport* is induced, resulting in a nearly complete accumulation of the species I^z on the other side of the membrane. One then obtains:

$$c_I''^{eq} = \frac{V'}{V''}\, c_J'^{eq} \approx \frac{V'}{V''}\, c_I'^{o} \tag{17}$$

and the boundary conditions for a fast equilibrating transport are found to be (see *Fig. 2*):

$$K_{IJ} \ll 1 \quad \text{but} \quad K_{IJ} \gg c_I'^{o}/c_J''^{o} \tag{18}$$

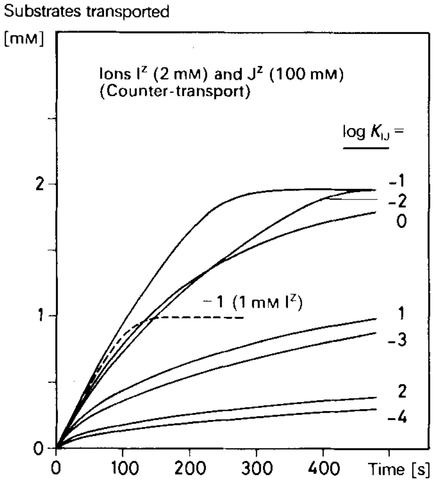

Fig. 2. *Equilibrating transport of two ions of the same charge through a carrier membrane.* Initial concentrations: 2 mM I^z in soln. *1* (except for dashed curve), 100 mM J^z in soln. *2*. The ion concentrations transferred from one soln. into the other one are given as a function of time for different values of the selectivity coefficient K_{IJ}. Calculations according to *Eqns. 6* and *13* using the same parameters as in *Fig. 1*.

This constitutes again a basis for the development of promising membrane-transport devices for analytical chemistry.

A drawback of the co-transport and counter-transport systems, as discussed above, is that the permeating substrates must approach a *Donnan* equilibrium distribution across the membrane. This is the basic requirement for such systems (see *Eqns. 11* and *17* and *Figs. 1* and *2*) to exhibit a strict correlation between the input concentration, $c_M'^{\circ}$ resp. $c_I'^{\circ}$, and the output concentration, c_M'' resp. c_I''. This equilibration process generally makes for a slow response of corresponding sensors, on one hand, and it involves considerable changes of the substrate concentrations in both solutions, on the other hand. Kinetic measurements in the early period of equilibrating transport would usually not be successful, however, since the maximum rate of substrate permeation depends only on membrane parameters and geometric factors (see *Eqns. 5* and *6* for any substrate N):

$$\left(\frac{\mathrm{d}c_N''}{\mathrm{d}t}\right)_{\max} = \frac{A}{V''} J_{max} \tag{19}$$

The only situation, where the initial transport rates become concentration-dependent, is found when only a minor fraction of the carriers are loaded by the substrate of interest. Accordingly, the following requirements must then be met for the permeation of a single neutral substrate such as an ion pair M^+X^-:

$$K_{MX}\, c_M'^{\circ}\, c_X'^{\circ} \ll 1 \quad \text{and} \quad K_{MX}\, c_M''^{\circ}\, c_X''^{\circ} \approx 0 \tag{20a, b}$$

In this case, the highest possible rate for the permeant at steady state is determined by

$$\left(\frac{\mathrm{d}c_M''}{\mathrm{d}t}\right)_{\circ} = \left(\frac{\mathrm{d}c_X''}{\mathrm{d}t}\right)_{\circ} \approx \frac{A}{V''} J_{\max} \cdot K_{MX}\, c_M'^{\circ}\, c_X'^{\circ} \tag{21}$$

Evidently, kinetic measurements in the second solution can then yield straightforward information on the substrate concentrations in the first solution (see *Fig. 3*), *e.g.*

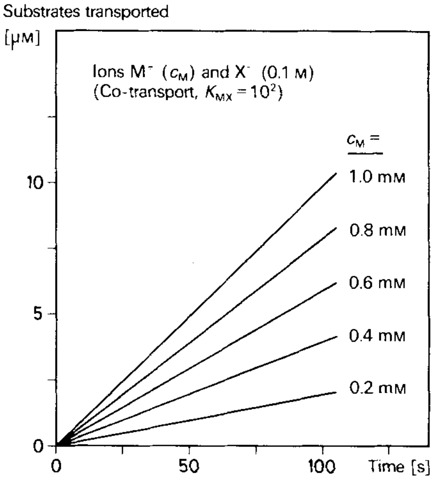

Fig. 3. *Initial transport of cations and anions through a carrier membrane.* The electrolyte concentrations transferred into soln. *2* are given as a function of time for an initial anion concentration of 100 mM and a varying cation concentration c_M. A salt-extraction constant of 10^2 and the parameters in *Fig. 1* were used for the calculations.

$$\left(\frac{\mathrm{d}c''_{\mathrm{M}}}{\mathrm{dt}}\right)_{\mathrm{o}} \approx \mathrm{const} \cdot c'^{\mathrm{o}}_{\mathrm{M}}, \quad \text{for } c'^{\mathrm{o}}_{\mathrm{X}} = \mathrm{const}' \tag{22}$$

Another interesting system is created when two substrates I^z and J^z are offered on the same side of the membrane and are translocated simultaneously (*competitive transport*, driven by a counter-transported species). Again, the permeant I^z to be determined should occupy only a relatively small fraction of carriers in the membrane, *i.e.*

$$c'^{\mathrm{o}}_{\mathrm{I}} \ll K_{\mathrm{IJ}}\, c'^{\mathrm{o}}_{\mathrm{J}} \quad \text{and} \quad c''^{\mathrm{o}}_{\mathrm{I}} \approx 0 \tag{23}$$

Then the highest possible transport rate for I^z becomes

$$\left(\frac{\mathrm{d}c''_{\mathrm{I}}}{\mathrm{dt}}\right)_{\mathrm{o}} \approx \frac{A}{V''}\, J_{\mathrm{max}} \cdot c'^{\mathrm{o}}_{\mathrm{I}} / K_{\mathrm{IJ}}\, c'^{\mathrm{o}}_{\mathrm{J}} \tag{24}$$

as shown in *Fig. 4*:

$$\left(\frac{\mathrm{d}c''_{\mathrm{I}}}{\mathrm{dt}}\right)_{\mathrm{o}} \approx \mathrm{const} \cdot c'^{\mathrm{o}}_{\mathrm{I}}, \quad \text{for} \quad c'^{\mathrm{o}}_{\mathrm{J}} = \mathrm{const}' \tag{25}$$

For corresponding sensors an amperometric detection seems to be especially suited, because the resulting electric current would become directly proportional to the concentration to be determined.

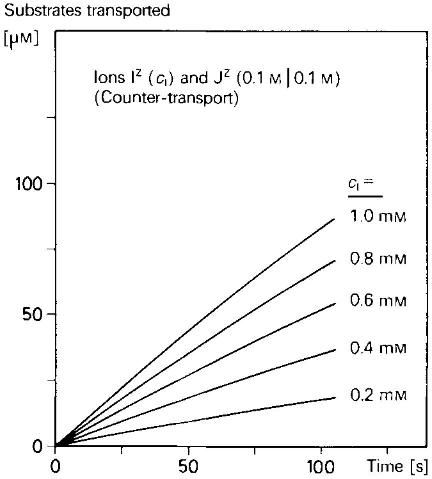

Fig. 4. *Initial transport of two ions of the same charge through a carrier membrane.* The ion concentrations transferred in opposite directions from one soln. into the other one are given as a function of time. Soln. *1* initially contains 100 mM J^z and varying concentrations c_I of I^z, soln. *2* contains 100 mM J^z. A selectivity coefficient of 10^{-1} and the parameters in *Fig. 1* resp. *2* were used for the calculations.

Discussion of Results. – With the exception of a variety of potentiometric ion-selective membrane electrodes which are based on a distribution equilibrium of the sensed ions rather than on their permeation, no analytically relevant sensor systems were described so far that make use of a selective carrier-mediated transport of substrates through membranes. Therefore, the following discussion will be restricted to a review of some promising developments and potential candidates in the field of this new sensor technology.

A considerable number of contributions reported on neutral-carrier-mediated transports (*co-transport, 'symport'*) of alkali and alkaline-earth metal salts through stirred organic phases or similar model membranes (for a review, see [10–18]). The primary aim of these studies was to demonstrate the ionophoric action and the cation-selectivity behavior of some naturally occurring compounds and especially of synthetic lipophilic complexing agents. Most interestingly, the maximum rate or efficiency of the transport was usually obtained for systems where the overall extraction constant K_{MX} of the permeating salt M^+X^- was in the range of about 10^4 to 10^6 M^{-2} [12] [17]. This is in excellent agreement with the theoretical results illustrated in *Fig. 1*. The reason for the existence of an optimum is that, at lower values of K_{MX}, a too low amount of electrolyte is extracted into the organic phase while, at higher values of K_{MX}, saturation of the carriers with the permeants occurs. At both extremes, the driving force for the facilitated salt diffusion within the membrane becomes insufficient. In most reports, a co-transport of cations was driven or at least supported by an anion-concentration gradient, as is the case in *Fig. 1*, but it is also possible to realize an uphill transport of anions by applying a cation-concentration gradient [13]. However, no practical applications of co-transport membrane systems in analytical chemistry have been reported so far. Very promising are, for example, recent attempts aiming at the separation of the enantiomers of biogenic ammonium ions by membranes based on electrically neutral, enantioselective complexing agents [18].

Counter-transport ('antiport') systems for *cationic substrates* were described around 1970, when monensin, fatty acids, and other cation-selective carriers were introduced in appropriate bulk membranes (for a review, see [7] [8] [17] [19–25]). Since these negatively charged ligands undergo easy protonation/deprotonation reactions at the phase boundaries, an external pH gradient is usually applied as the driving force for cation transport through the membrane. The counter-transported species were in most cases alkali or alkaline-earth metal ions. By far the highest selectivity of cation transport was achieved, however, when combinations of synthetic neutral carriers for specific cations with classical proton carriers were used instead of single negatively charged ligands [9].

Very recently, several derivatives of vitamin B_{12} were synthesized which are perhaps the first real examples of positively charged carriers that exhibit outstanding selectivity for certain *anionic substrates* in bulk membranes [26] [27]. Corresponding membrane electrodes behave as NO_2^--sensitive devices, the potentiometric selectivity factor being $\sim 10^{-5}$ for Cl^- and ~ 1 for SCN^- relative to the primary ion. The preliminary results in *Fig. 5* demonstrate that basically the same membranes induce a carrier-mediated permeation of anions. So far, this is the first documentation of anion counter-transport by artificial membranes. According to theory [8] [9] (see also *Fig. 2*), the maximum rate of counter-transport is expected when the selectivity between the two involved substrates is $K_{IJ} \approx 1$. In contrast, heavily reduced transport rates should result either for $K_{IJ} \ll 1$, where the species I predominates in the membrane phase, or for $K_{IJ} \gg 1$, where J predominates. These predictions are confirmed by the experimental findings in *Fig. 5*. When coupled to an oppositely directed SCN^- transport, a flux of NO_2^- ions of about 10^{-12} mol cm^{-2} s^{-1} is observed which roughly corresponds to the maximum transport rate for such ~ 0.1-mm thick solvent polymeric membranes at zero current [8] [9]. The transport rate is considerably lowered, however, when the SCN^- ions are replaced by Cl^- ions which are much less favored by the anion-selective carrier membrane (see. *Fig. 5*).

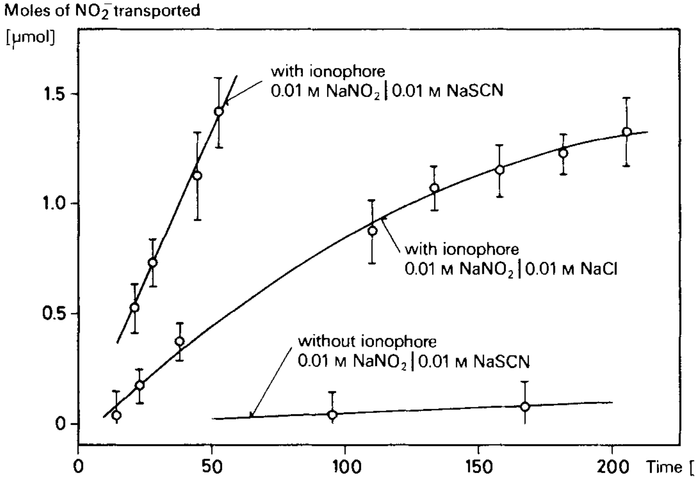

Fig. 5. *Zero-current transport of NO_2^- ions through solvent polymeric bulk membranes containing an anion-selective carrier (a cobyrinate).* The driving forces are anion concentration gradients as indicated between soln. *1* (NO_2^-) and soln. *2* (SCN^- or Cl^-). The transport of NO_2^- into soln. *2* is measured by differential pulse polarography.

Extremely promising would be the development of selective transport membranes for *electrically neutral substrates.* In fact, non-electrolytic, non-volatile species cannot be directly determined by means of the conventional potentiometric sensor techniques. Their analysis upon a carrier-mediated separation step would, therefore, be a highly welcome and attractive possibility. First attempts in this field were made by *Behr* and *Lehn* [28], who reported on the selective transport of amino acids through a liquid membrane by lipophilic carrier molecules. The driving force for this selective pumping process resulted from coupling to acid/base reactions and to cation concentration gradients. Another highly specific transport membrane system was introduced later for biogenic amines [29]. The schematic representation in *Fig. 6* clearly shows that a similar

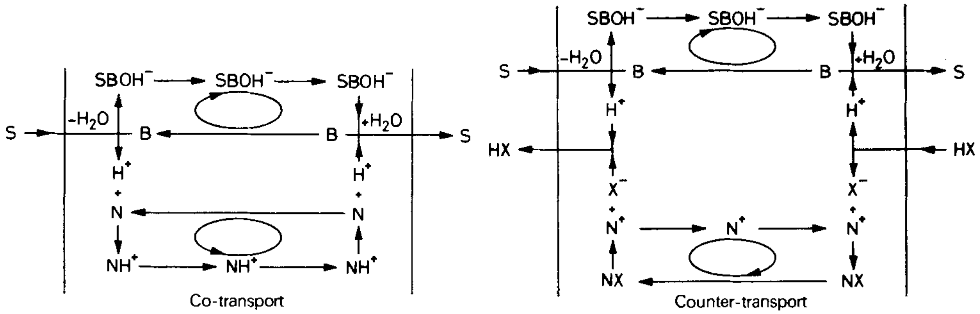

Fig. 6. *Mechanisms suggested for a carrier-mediated co-transport* (left) *and counter-transport* (right) *of glucose and similar substrates through artificial membranes.* Symbols: S: substrate, B: (alkylphenyl) boronic acid or related carrier, $SBOH^-$: substrate-carrier complex, N (left): organic amine (proton carrier) for cotransport of species H^+, N^+ (right): organic ammonium ion (anion-exchanger) for countertransport of species X^-.

carrier mechanism is feasible for the selective transport of glucose or other relevant compounds. Work aiming at the development of such a new glucose-sensing system is in full progress.

This work was partly supported by the *Swiss National Science Foundation* and by *Ciba Corning Diagnostics Corp.*

Experimental Part

General. Chemicals and solvents: decane-1, 10-diyl-diglutarate-bis (1-butylpentyl)ester (*ETH 469*; *Fluka, p.a.*, for ion-selective electrodes); poly(vinyl chloride) (PVC; *Fluka, purum p.a.*, for ion-selective electrodes); aquocyano-Co (III)-heptakis(2-phenylethyl) cobyrinate perchlorate (carrier; synthesis according to [27]); THF (*Fluka, puriss. p.a.*); NaCl (*Merck, p.a.*); $NaNO_2$ (*Merck*, 'reinst'); NaSCN (*Fisher Scientific Co.*); H_2O (deionized and doubly distilled from quartz vessels).

Membrane Preparation. The solvent polymeric membranes were prepared according to [30] using 1 wt.-% carrier, 66 wt.-% *ETH 469* (respectively, 67 wt.-% for membranes without carrier) and 33 wt.-% PVC. In contrast to [30], the three membrane components (total mass: 216 mg) were dissolved in 3 ml of THF, and the soln. was poured into a glass ring of 59 mm of i.d. Finally a membrane of about 50-μm thickness was obtained.

Transport Cell Assembly. A cell assembly of the following type was used: soln. *1* | membrane | soln. *2*. The transport cell, manufactured from *Teflon*, had a total volume of 60 ml. The internal diameter was 4 cm, resulting in an active membrane area of 12.6 cm^2. Soln. *1* was 0.01 M $NaNO_2$ and soln. *2* was 0.01 M NaSCN or NaCl. The solns. were continuously stirred during the transport experiments.

Procedure. The nitrite concentration arising from membrane transport in soln. *2* was determined by differential pulse polarography. 1 ml of the sample soln. was taken from the transport cell and mixed with the reagents indicated in [31]. The soln. was degassed, and a differential pulse polarogram was recorded. A triple standard addition was made, and the initial sample concentration was calculated from the four polarographic curves. For details, see [31]. The reduction of the sample volume in the transport cell was compensated by addition of 1-ml aliquots of the stock soln. *2*.

Apparatus. Polarographic curves were recorded with a *Metrohm Polarecord E506* in conjunction with a *E505* polarography stand equipped with mechanical drop timer.

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