Carrier mediated transport through supported liquid membranes; determination of transport parameters from a single transport experiment

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This paper describes a time-dependent transport model for carrier assisted cation transport through supported liquid membranes. The model describes the flux of salt as a function of time and two parameters *viz.* the diffusion coefficient of the cation complex (D), and the extraction constant (K_{ex}). Simulations of transport experiments indicate that high extraction constants (K_{ex}) are responsible for the decrease in the transport rate in time.

A simulation program (CURSIM) was designed that is capable of determining the essential transport parameters D and K_{ex} from only one time-dependent transport experiment. The non-linear curve-fitting 'Down-hill Simplex' technique, gives directly the best-fit values of D and K_{ex}.

The CURSIM method was tested by evaluation of the transport of $KClO_4$ by different calix[4]arene-crown-5 carriers and by valinomycin. Comparison of the results with those obtained previously by the initial flux approach, which requires a series of different experiments, shows a good agreement of both methods.

In living matter, selective facilitated transport of cations through cell membranes is provided by macrocyclic antibiotics such as valinomycin. Valinomycin was the first protein recognized to facilitate the selective transport of K^+ through mitochondria.[1]

Reusch and Cussler were the first to mimic facilitated transport by making use of an artificial set-up which consists of two aqueous phases that are separated by a water-immiscible organic phase to which a receptor (crown ether carrier) is added to facilitate selective transport.[2] Since then, carrier facilitated transport has been investigated extensively.

For industrial applications, carrier facilitated separations of alkali and alkaline earth cations,[3] heavy metal ions[4] and radioactive cations[5] are being investigated because of its high separation factors, that can be achieved under mild conditions, with low energy requirements and the ability to transport 'uphill', *i.e.* against the concentration gradient. To meet industrial demands, the hollow fibre supported liquid membrane (SLM) has been developed.[6]

In supramolecular chemistry, liquid membranes are frequently used to evaluate complexation and transport properties of a novel type of receptors. Membrane transport has been achieved by carriers which selectively recognize and transport cationic, anionic, neutral and zwitterionic species.[7]

In our work we use supported liquid membranes in which the organic phase containing the receptor (or carrier) is immobilized in the pores of a macroporous polymer sheet that separates two aqueous phases (Fig. 1). The geometry is described in detail in the Experimental section.

Mathematical models have been derived to describe transport through liquid membranes. Reusch and Cussler were the first to derive a model for the cation assisted transport through SLMs as ion pairs[2] that can be used to describe transport through non-polar membrane solvents. Izatt *et al.* derived a similar model in which ion-pair formation in the aqueous phases was included.[8]

We have developed a mathematical model that describes carrier-mediated transport of cations as solvent-separated ions through supported liquid membranes filled with relatively polar solvents.[9] This model is derived from the various equilibria that can be defined at both interfaces of the membrane (Fig. 2).

The transport can be described by the following consecutive steps; (i) partitioning of salt from the aqueous (source) phase to the membrane phase defined by a partition constant K_p, (ii) complexation of the cation in the membrane phase defined by a

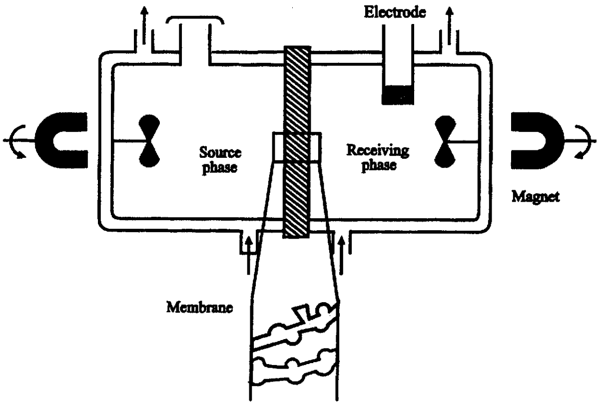


Fig. 1 Experimental set-up of a supported liquid membrane

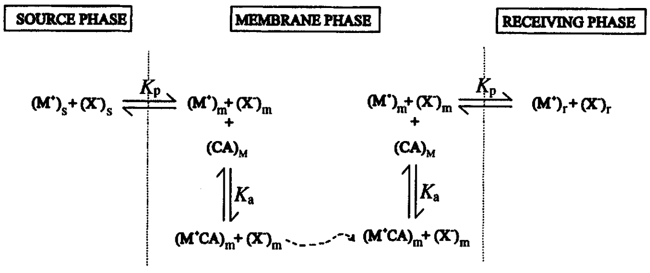


Fig. 2 Schematic representation of the equilibria at the source phase-membrane interface

complexation constant K_a, (iii) diffusion of the cation complex to the receiving side of the membrane, and (iv) decomplexation followed by partitioning of salt to the other aqueous (receiving) phase.

The flux equation

Assuming that all chemical equilibria at the interfaces are kinetically fast on the timescale of the transport process, and that resistances in the aqueous phases can be neglected, the flux is determined only by diffusion of the complex through the membrane. In this case, the flux can be described by Fick's first law. When transport occurs predominantly *via* the complex and not *via* the free salt, the flux is proportional to the concentration gradient of the complex over the membrane [eqn. (1)], where

$$J_{M^+} = \frac{D}{d}([LM^+]_{ms} - [LM^+]_{mr}) \qquad (1)$$

J_{M^+} = flux, D = diffusion coefficient,[10] d = membrane thickness, $[LM^+]_{ms}$ = complex concentration in the membrane at the source interface and $[LM^+]_{mr}$ = complex concentration in the membrane at the receiving interface.

Single monovalent cations will be transported as a complex of 1:1 stoichiometry (Fig. 2). In this case, the complex concentrations in the membrane can be expressed as a function of the aqueous external salt concentrations and the extraction constant K_{ex} ($K_{ex} = K_aK_p$), and substitution in eqn. (1) leads to eqn. (2), where a_r = salt concentration in the receiving phase,

$$J_{M^+} = \frac{D}{2d}\Bigl[-K_{ex}a_s^2 + \sqrt{(K_{ex}a_s^2)^2 + 4K_{ex}a_s^2L_0} + K_{ex}a_r^2 - \sqrt{(K_{ex}a_r^2)^2 + 4K_{ex}a_r^2L_0}\Bigr] \qquad (2)$$

a_s = salt concentration in the source phase and L_0 = initial carrier concentration in the membrane phase.

From eqn. (2) it is clear that the properties of a receptor acting as a carrier can be described by D and K_{ex}. The diffusion coefficient D determines the transport velocity of the complex through the membrane phase, whereas the extraction constant K_{ex} determines the ability of the carrier to extract a cation from the aqueous phase.

The initial flux approach

In the literature, transport parameters are usually determined from initial flux measurements. In these experiments the conditions are such that the amount of transported species can be neglected, which means that in eqn. (2) the salt concentration in the receiving phase (a_r) is almost 0. The initial flux (J_0) is described by eqn. (3), where $a_{s,0}$ = initial salt concentration in the source phase.

$$J_0 = \frac{D}{d}[LM^+]_{ms} = \frac{DK_{ex}a_{s,0}}{2d}\left[\sqrt{\left((a^2_{s,0} + 4\frac{L_0}{K_{ex}}\right)} - a_{s,0}\right] \qquad (3)$$

When the initial flux J_0 is measured at different initial salt concentrations in the source phase ($a_{s,0}$), D and K_{ex} can be determined from eqn. (3) by least-squares analysis. A disadvantage of the initial flux approach is that for a reasonably accurate determination of D and K_{ex} it requires at least 6 transport experiments at different initial salt concentrations. Furthermore, when the carrier has a high extraction constant the initial flux approach is relatively insensitive towards the value of the extraction coefficient. Therefore, we have investigated another and more general method for the determination of the membrane transport parameters.

Results and discussion

Description of the time-dependent model

In the literature, time dependency of transport has been addressed by Behr *et al.* for counter ion transport through Bulk Liquid Membranes (BLM).[11] Using numerical simulations, they were able to simulate competitive transport as a function of time. Ibáñez *et al.* derived an analytical equation to describe time dependency of the assisted transport of ion-paired cations through a BLM.[12]

When we describe the cation assisted transport *as a function of time*, the concentration of salt in the receiving phase (a_r) is described by law of conservation for the receiving phase [eqn. (4)], where V_r = volume of the receiving phase and A_m = membrane surface.

$$V_r\frac{da_r}{dt} = A_m \times J_{M^+} \qquad (4)$$

The salt concentrations in the source phase and the receiving phase are related by the mass balance for the total system. When the amount of salt in the membrane phase is neglected, eqn. (5) is obtained.

$$a_s = a_{s,0} - \frac{V_r}{V_s}a_r \qquad (5)$$

Substitution of eqn. (5) in eqn. (2) leads to the flux equation [eqn. (6)].

$$J_{M^+} = \frac{D}{2d}\left\{-K_{ex}\left(a_{s,0} - \frac{V_r}{V_s}a_r\right)^2 + \sqrt{\left[K_{ex}\left(a_{s,0} - \frac{V_r}{V_s}a_r\right)^2\right]^2 + 4K_{ex}\left(a_{s,0} - \frac{V_r}{V_s}a_r\right)^2L_0} + K_{ex}a_r^2 - \sqrt{(K_{ex}a_r^2)^2 + 4K_{ex}a_r^2L_0}\right\} \qquad (6)$$

In this equation, the flux J_{M^+} only contains the salt concentration in the receiving phase as an unknown variable. Substitution in the law of conservation [eqn. (4)] and subsequent numerical integration using the fourth order Runge–Kutta procedure[13] enables us to calculate the salt concentration in the receiving phase as a function of time.

Simulations of transport experiments

The influence of the transport characteristics D and K_{ex} on the transport rate can be illustrated by simulations using the parameter values for V_s, V_r, A_m and d as present in our experimental set-up (Fig. 1). The Runge–Kutta integration technique was applied in the form of a Turbo Pascal program. Figs. 3 and 4 show the effect of K_{ex} on the concentration of salt in the receiving phase and on the flux through the membrane phase, respectively.

According to eqn. (6) the flux increases linearly with an increasing diffusion coefficient, but the influence of the extraction constant on the transport cannot simply be predicted from eqn. (6). Therefore, transport simulations have been carried out, by varying the extraction constant (Figs. 3 and 4). Based on these simulations we can conclude that variation of the extraction constant has a large influence on the time-dependent behaviour of transport. At low K_{ex} values ($K_{ex} < 10$ dm^3 mol^{-1}), the carrier will not be saturated, and consequently the initial fluxes are low and remain constant in time. When the extraction constant increases ($K_{ex} \approx 40$ dm^3 mol^{-1}), the carrier is saturated at the source phase interface, which is reflected in a maximal initial flux which remains virtually constant in time. However, at very high extraction constant ($K_{ex} > 100$), fluxes decrease with time. This behaviour can be explained by the

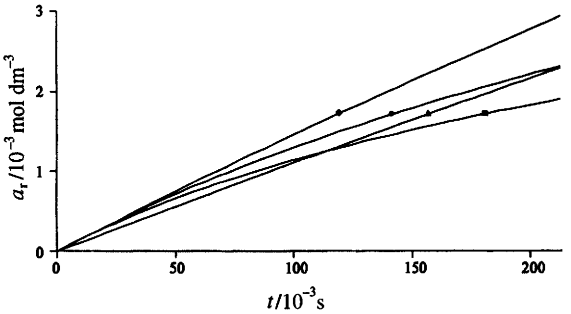


Fig. 3 Simulations of the salt activity in the receiving phase (a_r) as a function of time for different extraction constants (K_{ex}). K_{ex}: 3 (▲), 40 (◆), 900 (●) and 3000 dm^3 mol^{-1} (■).

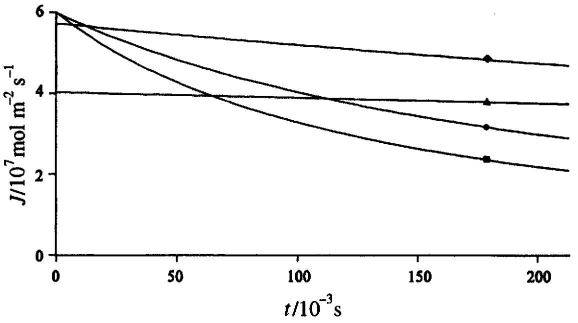


Fig. 4 Simulations of the flux (J) through the membrane phase as a function of time for different extraction constants (K_{ex}). K_{ex}: 3 (▲), 40 (◆), 900 (●) and 3000 dm^3 mol^{-1} (■).

increasing complex concentration inside the membrane phase at the receiving side of the aqueous phase. This reduces the complex concentration gradient (Δ[Complex]/Δd) over the membrane phase and therefore according to Fick's law the flux will decrease. From Fig. 3 it is also clear that the total amount of transported material is no measure for the extracting ability of the carrier.

CURSIM; the design of a curve-fitting system for time-dependent transport

In order to determine D and K_{ex} from one single time-dependent transport experiment, a curve-fitting system (CURSIM) has been designed and is implemented in a Turbo Pascal program. In principle, curve-fitting is based on the description of experimental data by a mathematical equation containing $p_1 \ldots p_m$ adjustable parameters. In our case $p_1 = D$ and $p_2 = K_{ex}$, hence the number of adjustable parameters is 2. By varying both parameters, an absolute minimum is searched that reflects the situation in which the difference between model and experiment is minimal. When we assume that only one set of transport parameters (D^*, K_{ex}^*) can describe a given experimental curve, the curve-fitting method will result in the desired transport parameters. However, in order to eliminate the possibility that a local optimum is obtained and consequently incorrect values of D and K_{ex}, the CURSIM system has been divided into three steps; (i) the search for the best fit transport parameters D^* and K_{ex}^* by the actual curve-fitting technique, (ii) an evaluation of the results to prove that the best-fit obtained is a global result, and (iii) the determination of the variance σ^2 in D^* and K_{ex}^*.

The first step involves the search for the optimal transport parameters D^* and K_{ex}^* starting from initial starting values (D^i, K_{ex}^i). Using these initial values, the transport behaviour is simulated according to the model. The deviation between the model and the experimental data is expressed in terms of its least squares [eqn. (7), N = the total number of data points ($a_{r,exp}$,t_i)].

$$\sigma^2(D, K_{ex}) = \frac{1}{N-2}\sum_{i=1}^{N}[a_{r,exp}(t_i) - a_{r,model}(t_i; D, K_{ex})]^2 \qquad (7)$$

Iteratively, a new set D and K_{ex} is chosen and the corresponding least-squares deviation σ^2 (D, K_{ex}) is calculated. The best-fit solution is defined by its minimal least-squares. In the literature many techniques of multi-dimensional minimization or curve-fitting have been reported.[14] For our CURSIM method, the downhill Simplex method of Nelder and Mead has been implemented.[15] The Simplex method involves the repeated observation of a system response (inverse least-square value $1/\sigma^2$), as a function of the values of D and K_{ex}.

The selection of new variables can be visualized by the movement of a geometrical construct (a simplex) over a response surface. The simplex has a number of vertices equal to one more than the number of dimensions of the factor space. In our case the simplex is visualized by a triangle. The coordinates of the vertex in this three dimensional space are set by D, K_{ex} and $1/\sigma^2$. During the optimization process, the simplex is moved by the repeated replacement of its worst vertex and seeking for hills or ridges. Practically this will be reached when all vertices end in the same end point [D^*, K_{ex}^*, $(1/\sigma^2)^*$].

Having obtained the best fit parameters D^*, K_{ex}^*, the question whether the optimum is local or global has to be addressed. This is done by repeating the curve-fit analysis using different initial values D^i and K_{ex}^i. These initial values have to cover a large physical area of the parameter space. When these different initial values lead to identical best-fit values, it is very likely that the best-fit values D^* and K_{ex}^* are global.

A second evaluation method is the construction of a surface area plot. This is a three dimensional plot of the system response ($1/\sigma^2$) as a function of D and K_{ex}. It allows a more detailed examination of the surface near the best-fit. When the best fit is precise, a single and sharp peak in the solution set of D^* and K_{ex}^* should be observed. A broad peak is an indication of an inaccurate estimate. If the optimum is global, the variances in both D^* and K_{ex}^* have to be estimated by the introduction of errors in the experimental input parameters (V_s, V_r, d_m, A_m, $a_{s,0}$, L_0)[16] followed by a second simplex iteration procedure. The difference between the resulting estimations D_{error}^* and $K_{ex,error}^*$ and the optimal parameters D^* and K_{ex}^* is taken as a measure for the variance.

Application range of CURSIM

In general, the curve-fitting of an experiment with N data points can be written as a set of N equations [eqn. (12)]: A typical

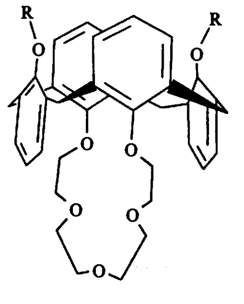
$$\begin{aligned} a_{r,exp}(t_1) &= a_{r,model}f(t_1, K_{ex}, D) \\ \cdot \quad & \quad \cdot \\ \cdot \quad & \quad \cdot \\ \cdot \quad & \quad \cdot \\ a_{r,exp}(t_N) &= a_{r,model}f(t_N, K_{ex}, D) \qquad (12) \end{aligned}$$

time-dependent transport experiment lasts for 24 hours and gives a total number of 3000 data points. In this case, there are two possibilities: (i) the flux does not decrease in time and the curve of activity *vs.* time is linear, or (ii) the flux does decrease in time and the curve will not be linear.

When the flux remains constant in time a straight line is obtained when the salt concentration in the receiving phase is plotted as a function of time. The set of N equations is written as a linear combination of the first data point [eqn. (13)].

$$N^*a_{r,exp}(t_0) = N^*a_{r,model}f(t_0, K_{ex}, D) \qquad (13)$$

In this case, eqn. (12) reduces to one equation [eqn. (13)] containing two variables, and no single best-fit solution will be



1 R = ethoxy
2 R = isopropoxy

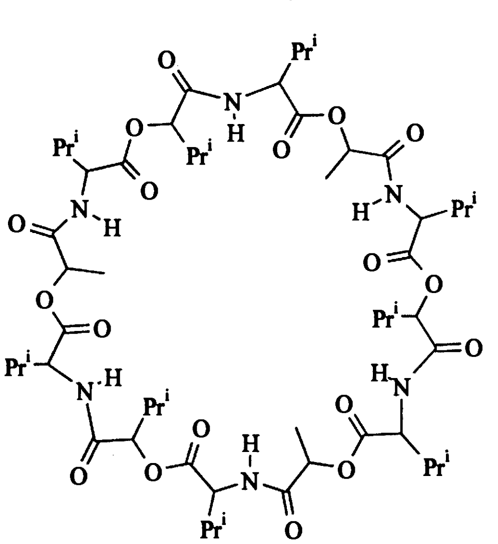


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Fig. 5 **1** 1,3-Diethoxy calix[4]crown-5, 1,3 alternate, **2** 1,3-diisopropoxy calix[4]crown-5, 1,3 alternate and **3** valinomycin used as carriers in membrane transport experiments

Table 1 Transport parameters of carriers **1**–**3** for the assisted transport of $KClO_4$ as determined with the initial flux method and by the CURSIM method

	Initial flux		CURSIM	
Carrier[a]	10^{12} D/ m^2 s^{-1}	10^{-3} K_{ex}/ dm^3 mol	10^{12} D/ m^2 s^{-1}	10^{-3} K_{ex}/ dm^3 mol^{-1}
1	10.6 ± 1.1	>25	10.1 ± 1.9	43.2 ± 2.4
2	11.6 ± 1.3	>25	13.6 ± 3.0	35.9 ± 1.8
3	9.4 ± 1	2–10	10.4 ± 2.3	6.1 ± 0.3

[a] The structures of the carriers are displayed in Fig. 5.

obtained. However, in the case of a non-linear increase of the activity of salt as a function of time, the set of equations is not reduced and the CURSIM system can be applied to determine D and K_{ex}.

Determination of transport parameters; performance of CURSIM

In order to test the performance of CURSIM, various time-dependent transport experiments were carried out. For our transport model we assume that no ion pairs are formed in the membrane. This is justified when relatively low carrier concentrations are used in conjunction with polar membrane solvents. In our experiments the carrier concentration was 0.01 mol dm^{-3} and the solvent was *o*-nitrophenyl octyl ether ($\varepsilon_r = 24$). The absence of an external transport resistance was verified, because of the constant fluxes at different stirring rates (300–900 rpm) of the aqueous phases.[17]

The carriers that were used in the experiments are the functionalized calix[4]arene-crown-5 receptors **1** and **2**, both designed for the selective complexation of potassium and synthesized according to literature procedures.[18] For comparison valinomycin **3**, the known natural potassium selective ionofore, was used.[19] The structures of the carriers are depicted in Fig. 5.

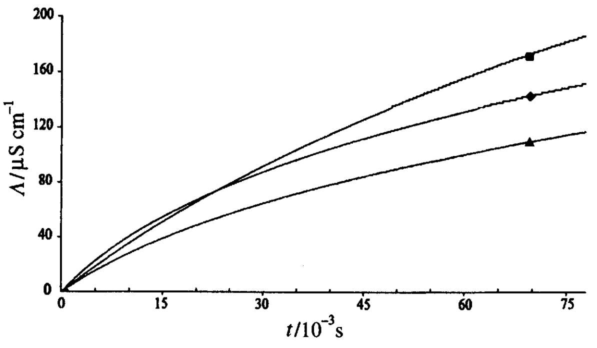

Fig. 6 Time-dependent transport experiments of $KClO_4$ ($a_{s,0}$ = 0.1 M); conductivity in the receiving phase as a function of time for compounds **1**–**3**: **1** (▲), **2** (◆), **3** (■)

Because the measurements extended over a longer period of time (24 h), the carriers have to be very lipophilic. In all cases the original flux was restored after replacement of both aqueous phases after 24 h of transport. Therefore, it was concluded that the carrier did not leach out to the aqueous phases during the time of the experiment.

Previously, we have reported data for transport parameters D and K_{ex} from transport experiments *via* the initial flux method.[18] These data are included in Table 1 for comparison with the results obtained by CURSIM. For the high values of K_{ex} only lower limits are given, because in this range the initial flux method is rather inaccurate. This is due to the fact that the extraction constant is derived as the initial slope of the plot of J_0 *vs.* $a_{s,0}$. If a carrier is used with a very high extraction constant, saturation of the carrier is already reached at very low concentrations of salt in the source phase. When J_0 is plotted as a function of $a_{s,0}$ a maximum flux is obtained almost instantaneously and the determination of the initial slope to obtain K_{ex} is very inaccurate. For the same reason, the diffusion coefficient D can be determined very accurately from the maximum value for J_0.

Time-dependent transport measurements using carriers **1**–**3** were carried out by measuring the conductivity in the receiving phase with a time interval of 30 s (Fig. 6).

Subsequent calculation of the concentration and the corresponding activity from the Debye–Hückel equation[20] is carried out to give a file which contains the data of the activity of salt as a function of time. The D^* and K_{ex}^* values obtained with the CURSIM method are summarized in Table 1.

A representation of the response surfaces around the best-fit parameters was calculated. These are depicted in Fig. 7. The response surfaces for carriers **1**–**3** are normalized in such a way that the height of the maximum response is below 10^4.

Comparison of the results of the initial flux approach and CURSIM shows that both methods are in good agreement (Table 1). The results itself are very surprising, because it shows that the binding of potassium (K_{ex}) by the calix[4]crown-5 derivatives is much higher than by valinomycin.[12]

The variances given in Table 1 are reasonable, and also from the three-dimensional plot of the response surface, it can be concluded that the optimum is very sharp. When starting from different values K_{ex}^i and D^i in the parameter space, a rapid iteration process towards the optimum can be observed. Less than 100 iteration steps are sufficient to reach the optimum value. These results indicate that CURSIM is a very powerful tool in the evaluation of transport parameters and related association constants ($K_a = K_{ex}/K_p$) of new carriers.

Compared with the initial flux method, where transport measurements of at least six different initial salt concentrations

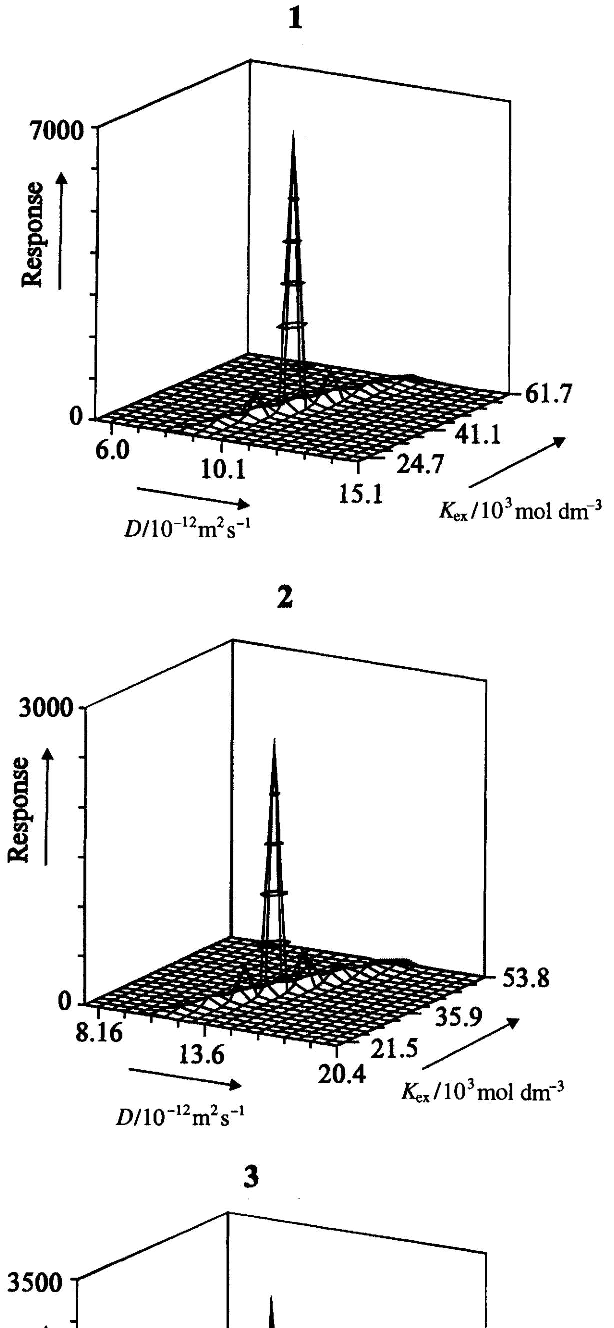

Fig. 7 Response-surfaces of compounds **1**–**3** from a time-dependent transport experiment of a source phase concentration of 0.1 M $KClO_4$ with 0.01 M of carrier in NPOE-Accurel (T = 298 K)

are needed for an accurate determination of D^* and K_{ex}^*, the information of only one time-dependent transport experiment is sufficient to obtain the desired parameters with the CURSIM method. Furthermore, in the case of carriers with a high extraction constant the initial flux method is only able to determine D^* accurately, whereas with the CURSIM method highly accurate values for both D^* and K_{ex}^* are obtained.

Experimental

Simulations

Simulations were carried out using average values for the variables that play a role in the membrane set-up; V_r = 53 [cm^3], V_s = 53 [cm^3], A_m = 13.4 [cm^2], $a_{s,0}$ = 0.1 [mol dm^{-3}]; $a_{r,0}$ = 0 [mol dm^{-3}]; L_0 = 0.01 [mol dm^{-3}]; d = 0.1 [cm]. The starting values for the transport parameters D and K_{ex} were varied in the ranges: D = (1 × 10^{-12} to 15 × 10^{-12} [m^2 s^{-1}]); K_{ex} = (1 to 1 × 10^4 [dm^3 mol^{-1}]).

Transport measurements

The transport experiments were performed in an apparatus that consists of two identical cylindrical compartments (half-cell volume 50 cm^3; effective membrane area 13 cm^2) made of glass. Stirring was accomplished by a flat-bladed turbine positioned at the centre of the half-cells and driven by a magnet outside the compartment at a stirring rate of 900 rpm. At this stirring rate the transport is governed by diffusion of the complex through the membrane phase, *e.g.* all external transport resistances can be neglected.

The geometry of the cell has been designed in such a way that efficient stirring of the aqueous phases is achieved without obstruction of the membrane phase. For mathematical simplification, the volumes of the source phase and receiving phase cells are equal.

The compartment was double-walled for thermostatting using a water bath (Tamson, TC). All measurements were performed at 25 °C.

The membrane was positioned between the cylindrical compartments containing the two aqueous phases. The supported liquid membrane consisted of a thin macroporous polypropylene film (Accurel; thickness d = 100 μm, porosity Θ = 64%). The carrier was dissolved in *o*-nitrophenyl octyl ether (NPOE). The membrane was submerged in this solution under vacuum (2 × 10^{-3} Pa) for 15 min. The membrane was wiped carefully with a tissue to remove excess fluid at the outside of the support.

The aqueous solutions used as the source phase were prepared with doubly distilled and deionized water and doubly distilled deionized water was used as the receiving phase. The transported perchlorate salts were determined by monitoring the conductivity (Radiometer CDM 83) as a function of time. The concentration was calculated using a salt constant that correlates the conductivity to the concentration. The activity was determined by calculation of the activity coefficient at the different concentrations using the Debye–Hückel equation.

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10 In order to obtain the 'real' diffusion constant through NPOE D_{true}, the diffusion constant resulting from transport experiments D has to be corrected for the tortuosity τ and porosity θ of the membrane.

$$D_{\text{true}} = \frac{D\tau}{\theta}$$

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16 The determination of each parameter in the model is attended with an experimental error affecting the accuracy of the ultimate estimation. For each parameter (V_s, V_r, A_m, d_m, $a_{s,0}$, L_0) the error is estimated in an additive way; the experimental errors in all parameters are added in order to obtain the maximum deviation ($V_s = V_s + 5\%$; $V_r = V_r - 5\%$; $A_m = A_m + 5\%$; $d_m = d_m - 10\%$; $a_{s,0} = a_{s,0} + 10\%$; $L_0 = L_0 + 5\%$).

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