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INTERPRETATION OF MEMBRANE  
PERFORMANCE RESULTS BY APPLICATION  
OF SPIEGLER - KEDEM THEORY**

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# From Reaction Solvent to Crystallization Solvent, Membrane Assisted Reaction Workup and Interpretation of Membrane Performance Results by Application of Spiegler–Kedem Theory

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**ABSTRACT:** Within practically all multistep synthetic sequences used to prepare molecular entities, a step can be found in which a change of solvent is required. Presently this is nearly always carried out by distillation process. Alternatives to distillation do, however, exist such as the nonthermal membrane based solvent exchange. Although highly efficient and useful in several circumstances, this technique is seldom carried out within an industrial setting, possibly due to some uncertainty as to the issues to be confronted. By making use of a practical example in which the Refametinib intermediate DIM-DAB (2) undergoes a solvent exchange from the reaction solvent THF to its crystallization solvent ethanol, these issues are illustrated and explained. Furthermore, the at first sight seemingly arbitrary rejection profile of DIM-DAB (2) over various membranes is explained by applying Spiegler–Kedem theory. Use of this modeling leads to a more targeted membrane screening phase, in which solute rejection is determined in a particular solvent over a number of membranes. Moreover, this model can also be used to simulate membrane performance in a solvent exchange without necessarily requiring the experimental demonstration. The simulation increases the efficiency of the experimental work by allowing a more comprehensive view of membrane performance. This in turn leads to more informed decisions of which membrane is the most suited to the requirements of the process.

## INTRODUCTION

The IMI CHEM21 project is a major project involving both industry and academia and aimed at the development of sustainable methods for the production and development of molecules within the pharmaceutical industry. Within the framework of this project there was interest from the industrial partners for the development of a safe, selective, economic and sustainable method to reduce an aromatic nitro group to an amine in highly functionalized aromatics. This seemingly simple transformation results, with many catalysts, in concomitant reduction of other groups such as halogens.<sup>1</sup> As part of the IMI CHEM21 initiative, efficient methods were developed to effect this transformation in batch and flow reactors<sup>2–4</sup> using hydrogenation and heterogeneous catalysts of nonprecious transition metals. These intensified processes were used to synthesize the aniline key intermediate DIM-DAB (2)<sup>5,6</sup> for the

synthesis of the API refametinib (BAY 86-9766, RDEA119) which is being developed by Ardea Biosciences, Inc. for cancer indications (see Scheme 1). However, despite the elegant and efficient intensification of the reaction step, to achieve intensification in a manufacturing process, the downstream separation and isolation of the product also needs to be considered. Separations used in reaction workup or product isolation can account for up to 70% of the global capital and operational costs incurred in an industrial process; therefore, the necessity of intensification of this part of a process is clear.

In the reaction highlighted in this communication, the reduction is carried out in THF and product 2 is isolated via a crystallization process from ethanol. The present method to accomplish the necessary solvent exchange is a distillation process. Although this method is successful, alternatives were investigated to determine if this process could be made more efficient, from either an energy or process point of view. One possible alternative method to distillation is organic solvent nanofiltration (OSN),<sup>7</sup> a mild separation method reliant upon membranes stable in organic solvents. Membrane performance is typically characterized by the membrane rejection and Flux. In this work volumetric Flux  $J$  is used, defined as the volume of solvent passing through the membrane per unit area and unit time.  $J$  is expressed as  $L\ m^{-2}\ h^{-1}$  or, if normalized to the trans membrane pressure used, as  $L\ m^{-2}\ h^{-1}\ bar^{-1}$  and then termed permeance. Solute rejection  $R$  is a function of the solute concentrations in the permeate  $C_p$  and the retentate  $C_r$  and expressed as a percentage.

Conceptually an OSN separation can be linked to a flow reactor, resulting in a continuous reaction–isolation process, in this example a solvent switch from reaction solvent to crystallization solvent. The use of membranes to perform solvent exchange has already been reported several years ago<sup>8–10</sup> and has proved to be a useful and very efficient method in several situations. It remains, however, a technique that is seldom considered by process chemists in an industrial setting, possibly due to the lack of membrane equipment within industrial research laboratories or due to a certain amount of unclarity of the issues that will be confronted if such an OSN solvent exchange is to be attempted.

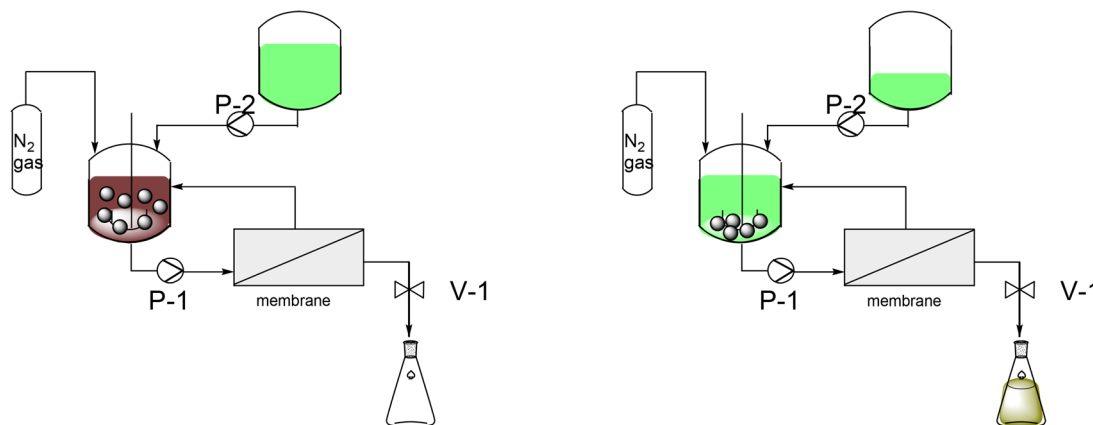
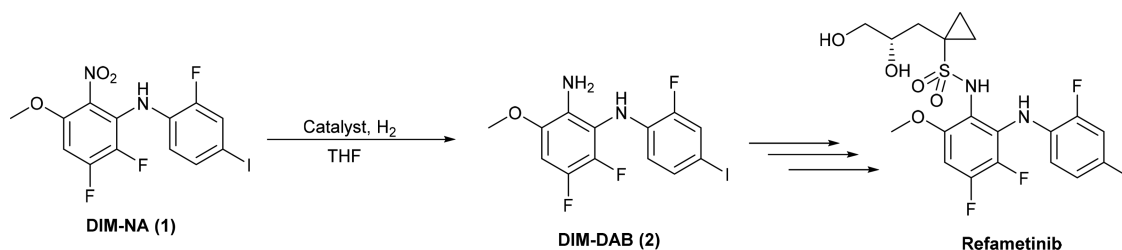
The process used to accomplish the solvent exchange is shown schematically in Figure 1. A solution of the solute is passed over a membrane that has high rejection, preferably

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Scheme 1. Synthesis of Key Intermediate DIM-DAB 2 from Nitroaniline DIM-NA 1



**Figure 1.** Schematic diagram of a solvent switch via a membrane process. The left image shows the starting situation, and the right image shows the final situation of the constant volume diafiltration process. P-1 is a circulation pump, P-2 is a diafiltration pump, and V-1 is a valve.

total, for the solute. Solvent 2, the solvent in which **2** will be finally crystallized from, in this case ethanol (green in Figure 1), is added via a constant volume diafiltration process,<sup>11</sup> washing the initial solvent, THF (brown in Figure 1), out of the system. This membrane-based washing process will inevitably require more than one diafiltration volume. One diafiltration volume is the volume of washing solvent equivalent to the volume of the original feed solution. In this short communication, the issues confronted when performing a solvent exchange by a membrane process are illustrated by means of the solvent exchange from THF to ethanol for the aromatic amine **2**.

### FACTORS INFLUENCING THE CHOICE OF MEMBRANE

The initial decision to be made when considering a membrane solvent switch process is the membrane to be used. To date this usually involves a membrane screening phase, in which solute rejection is determined in a particular solvent over a number of membranes. Indeed, despite the fact that several models have been developed to predict membrane performance,<sup>7</sup> predicting membrane rejection is particularly difficult. This is because rejection in OSN is dependent on solvent–solute–membrane interactions<sup>12,13</sup> and thus can change when the solvent is changed. This is even more complicated when solvent mixtures are involved as is inevitably the case on effecting a solvent switch via a diafiltration process. For the solvent switch to be successful, high rejection of the solute is an absolute necessity. If this is not the case, significant quantities of the solute can be lost to the permeate. The main criteria for choosing a membrane are as follows.

- **Molecular mass of 2:** Membrane rejection is not necessarily governed exclusively by size exclusion. As indicated above, affinity aspects similar to those seen in chromatography

also play a role. However, for these affinity aspects to come into play molecules must be sufficiently close to the membrane surface to interact with it. With a very open membrane or a membrane of large pore size this surface solute interaction is significantly reduced. Thus, for the relatively small molecule **2**, a tight membrane will be required.

- **Solvents:** High rejection is a requirement in both solvents. As mentioned above, rejection can change on changing the polarity or solubility characteristics of the solvent used. In this case the Hansen solubility parameters<sup>14</sup> for THF and ethanol are very different, the total solubility parameter being 19.4 MPa<sup>1/2</sup> for THF and 26.5 MPa<sup>1/2</sup> for ethanol.<sup>15</sup> Furthermore, THF is a solvent that many of the polymeric membranes are unstable in those that are stable in this solvent are usually those that are stabilized by cross-linking.
- **Concentration:** As ethanol is a crystallization solvent during the membrane process, it is advisable to remain at a concentration below that where crystallization occurs. Solubility data for **2** in THF, ethanol, and THF/H<sub>2</sub>O, (95:5 v/v%) are listed in Table 1.

**Table 1.** Solubility Data of **2** at 25 and 50 °C

Solvent	Solubility	
	25 °C	50 °C
THF	3.12 M	4.17 M
THF/H <sub>2</sub> O	1.54 M	2.95 M
EtOH	0.13 M	0.2 M

Thus, to successfully carry out the solvent exchange in the present case, the membrane required is a tight membrane that is stable in both THF and ethanol.

Table 2. Some Characteristics of the Membranes Chosen for Inclusion in the Membrane Screening

Entry	Membrane	Type	Source	MWCO (g/mol)	Water permeance at 20 °C (Lm <sup>2</sup> h <sup>-1</sup> bar <sup>-1</sup> )	Contact angle (deg)
1	0.9 nm TiO <sub>2</sub>	ceramic	Inopor	450	31	20
2	0.9 nm C <sub>1</sub> TiO <sub>2</sub> <sup>a</sup>	ceramic	Vito	450	7	46
3	0.9 nm PPA-TiO <sub>2</sub> <sup>b</sup>	ceramic	Vito	450	0.8	80
4	Solsep-10206S	polymeric	Solsep	300		63
5	AMS S-3012	polymeric	AMS techn	180		55
6	Duramem-200	Polymeric	Evonik	200	0.8	45

<sup>a</sup>0.9 nm C<sub>1</sub> TiO<sub>2</sub> is a 0.9 nm TiO<sub>2</sub> membrane with a separation layer modified with methyl groups. <sup>b</sup>0.9 nm PPA TiO<sub>2</sub> is a 0.9 nm TiO<sub>2</sub> membrane with a separation layer modified with phenyl phosphoric acid groups.

With this information in hand, the following membranes were selected to be included in the screening phase. Some characteristics of these membranes are listed in Table 2. Included are contact angle and water permeance, as both parameters can be used as indicators of the surface polarity of membranes. Hydrophilic membranes and consequently those with a high surface polarity, will give higher water permeance and contact angles that tend to zero. Surface modification of ceramic membranes with organic layers reduces the surface polarity in comparison to the unmodified membranes, and consequently decreases water permeance and increases contact angle.

The molecular weight cutoff (MWCO), which is defined as the molecular weight of the solute that is rejected for 90%, is also reported for the membranes. However, some caution is required with this figure, as it is highly dependent on the solvent used for its determination.<sup>16,17</sup> The MWCO values mentioned in the table are the values as communicated by the membrane suppliers; for the modified membranes we know that the MWCO is not changed by our modification.<sup>13</sup>

## RESULTS AND DISCUSSION

A limiting factor in the initial screening was the solubility of **2** in ethanol. Membrane rejection and permeance were determined for a 0.1 M solutions of **2** in THF and ethanol. Listed in Table 3 is a summary of the screening results.

Table 3. Membrane Screening Results<sup>a</sup>

Membrane	Membrane type	Temp (°C)	Retention <b>2</b> (%)		Av. Permeance (Lm <sup>-2</sup> h <sup>-1</sup> bar <sup>-1</sup> )	
			THF	EtOH	THF	EtOH
0.9 nm TiO <sub>2</sub>	Ceramic	25	63.8	20	5.2	1.22
0.9 nm C <sub>1</sub> TiO <sub>2</sub>	Ceramic	25	97	50	2.8	0.23
0.9 nm PPA-TiO <sub>2</sub>	Ceramic	25	53.0	13.9	0.26	0.031
Solsep-10206S	Polymeric	25	56.8	41	0.12	0.23
AMS S-3012	Polymeric	25	35.4	36	0.03	0.04
Duramem-200	Polymeric	25	98.2	94.9	0.19	0.18

<sup>a</sup>Experimental concentration of solute 0.1 M.

## INTERPRETATION OF THE MEMBRANE SCREENING RESULTS

At first sight, these rejection results may seem somewhat arbitrary and difficult to interpret. However, they become rather more explainable if one takes into consideration Spiegler–Kedem theory and how this relates to solvent–solute–membrane interactions.

Spiegler–Kedem theory describes the transport of a solute through a membrane and splits it up into two terms, the first

one related to diffusion and thus solubility effects, and the second related to convection, pore size, and molecular volume. In the Spiegler–Kedem eq 1,  $P_{\text{diff}}$  is the solute permeability due to diffusion,  $\Delta x$  is the membrane thickness,  $C$  is the solute concentration, and  $\sigma$  is the reflection coefficient which is dependent on the ratio of the solute size and membrane pore size.

$$J_{\text{solute}} = P_{\text{diff}} \Delta x (dc/dy) + C(1 - \sigma)J \quad (1)$$

This equation can be further solved to calculate solute rejection  $R$ . The result shows clearly that rejection is a function of the reflection coefficient  $\sigma$ , and the ratio of solvent and solute permeabilities  $J/P_{\text{diff}}$ . Note, when  $J/P_{\text{diff}}$  is very large, solute rejection will approach a limiting value, equal to the reflection coefficient  $\sigma$ , dependent upon the solute volume, size, and membrane pore size. In this case solute transport is dominated by convection and rejection is due to size exclusion. In all other situations diffusion influences the solute transport mechanism and rejection is lower than the reflection coefficient ( $\sigma$ ).

$$R = \frac{(1 - F)\sigma}{1 - \sigma F} \quad (2)$$

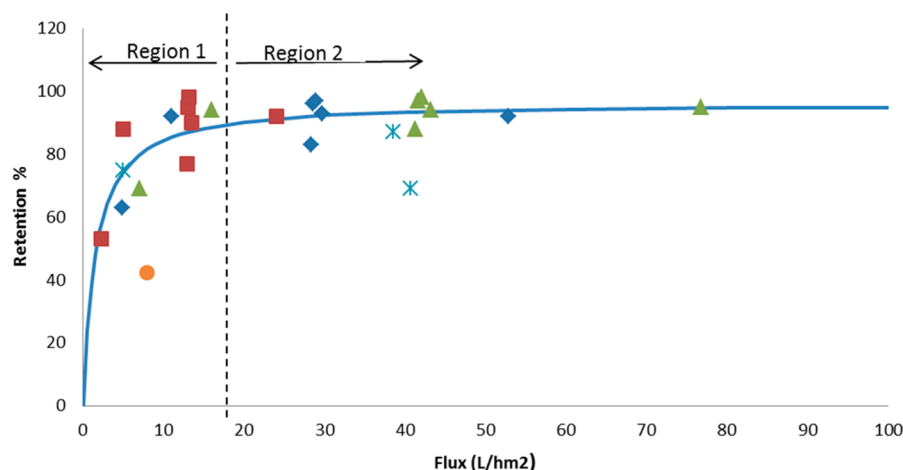
$$F = \exp(-(1 - \sigma)J/P_{\text{diff}}) \quad (3)$$

The experiments performed in this work used a number of ceramic membranes of very similar pore size, and thus very similar reflection coefficient  $\sigma$ . However, these membranes differ in surface polarity, which will have an effect upon the solvent and solute permeabilities, and thus on  $J/P_{\text{diff}}$ . Therefore, we expected that the ratio  $J/P_{\text{diff}}$  was the more important factor in determining the experimentally observed rejection of **2**. By taking into account the membrane MWCO and the solute size (394 Da), a good estimation for  $\sigma$  was made.<sup>18</sup> Subsequently, using eqs 2 and 3, it was possible to derive from the measured retentions and fluxes an estimate of  $P_{\text{diff}}$  for each membrane and both solvents. Table 4 lists the results of the ratio  $J/P_{\text{diff}}$  for all situations. Note that the accuracy of  $J/P_{\text{diff}}$  is rather low when the retentions and thus  $J/P_{\text{diff}}$  values are high. This is because in that situation, a small change in  $\sigma$  causes a significant change in  $J/P_{\text{diff}}$ . However, as can be seen below, this does not have any effect on the interpretation and conclusions of this paper.

In a previous study<sup>15</sup> a similar approach based on Spiegler–Kedem theory was used to understand the observed solute rejection with a solute that was highly soluble in all solvents used. The solute in question was a polystyrene of 580 Da and several solvents were employed. This leads to the observation that, if retention was plotted against flux (see Figure 2), two distinct regions were observed. As the polystyrene had high solubility in all solvents, solute–solvent interactions were practically constant, and thus the dominant interaction determining membrane performance is the membrane–solvent

Table 4.  $J/P_{\text{diff}}$  and  $(J/P_{\text{diff}})\cdot\eta$  Results for the Membrane–Solvent Combinations Used

Membrane	Temp (°C)	THF				Ethanol			
		$P_{\text{diff}}$ (Lm <sup>-2</sup> h <sup>-1</sup> )	$J/P_{\text{diff}}$	$(J/P_{\text{diff}})\cdot\eta$ (mPa·s)	Rejection (%)	$P_{\text{diff}}$ (Lm <sup>-2</sup> h <sup>-1</sup> )	$J/P_{\text{diff}}$	$(J/P_{\text{diff}})\cdot\eta$ (mPa·s)	Rejection (%)
0.9 nm TiO <sub>2</sub>	25	1.1	4.73	2.18	63.8	3.2	0.38	0.42	20
0.9 nm C <sub>1</sub> TiO <sub>2</sub>	25	0.05	56.0	25.76	97	0.22	1.05	1.16	50
0.9 nm PPA-TiO <sub>2</sub>	25	0.18	1.41	0.65	53.0	0.17	0.18	0.20	13.9
Duramem-200	25	0.001	190.0	87.4	98.2	0.007	25.7	28.3	94.9
SolSep-10206S	25	0.085	1.41	0.65	56.8	0.31	0.74	0.81	41

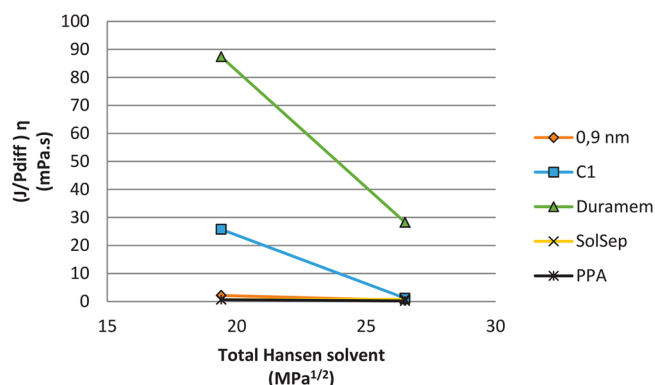


**Figure 2.** Compilation of all measured polystyrene retentions on a 1 nm TiO<sub>2</sub> ceramic membrane with a phenyl modified separation layer, plotted as a function of the flux during the measurement. The retentions for solvents methyl cyclohexane, EtAc, toluene, MEK, THF, DCM, and DMF at 16 bar are shown by the green triangles, at 11 bar by the blue diamonds, and at 5 bar by the red squares. The crosses are the retentions for solvents cyclohexane, MIK, and DCM-DMF (50–50) measured at 11 bar. The orange point is the retention for solvent IPA. The blue curve is the best fit of the Spiegler–Kedem theory to all experimental data. Adapted with permission from ref 15. Copyright 2016 Elsevier.

interaction. In region 1, affinity between the solvent and the membrane surface is nonideal and thus diffusion transport dominates. As a consequence the nature of the solvent has a strong influence on the observed rejections. In region 2, membrane–solvent affinity is higher, leading to convection being the dominating transport mechanism. In this region  $\sigma$  and thus size exclusion is controlling membrane rejection. The fit with the Spiegler–Kedem theory in Figure 2 could be made with one constant  $P_{\text{diff}}$  value and  $\sigma$  equal to the maximal retention observed. As in this study low solute concentrations were used (1 g/L), concentration polarization effects can be neglected.

In the present example, because the solvent exchange is going to a solvent, ethanol, in which 2 is 24 times less soluble than in THF, the solute–solvent interactions will become far more important than in the previously reported system. These solute–solvent interactions become visible on comparison of the  $J/P_{\text{diff}}$  ratios (Table 4). As solvent viscosity ( $\eta$ ) also has a role to play in membrane flux, the  $J/P_{\text{diff}}$  values have been normalized to the solvent viscosity. These values can be plotted against the total Hansen solubility parameters for the solvents (Figure 3). From the information in Table 4 and Figure 3, a number of observations become more obvious, including:

- High rejection is achieved when the ratio of  $J/P_{\text{diff}}$  is large ( $\geq 10$ ), and conversely, low rejection occurs when this ratio is small;
- For nearly all membranes  $P_{\text{diff}}$  was higher in ethanol resulting in a lower  $J/P_{\text{diff}}$ ;
- With tight membranes, such as the Duramem, both  $J$  and  $P_{\text{diff}}$  are low. But  $P_{\text{diff}}$  is still much lower than  $J$ , so this



**Figure 3.**  $(J/P_{\text{diff}})\cdot\eta$  vs total Hansen parameter for the solvents at 25 °C.

keeps the ratio  $J/P_{\text{diff}}$  large (about 10 or higher, and thus high rejection). This significantly low  $P_{\text{diff}}$  in comparison to  $J$  may be expected, as with the tight (polymer) membranes, molecules are transported through the membrane via the interstitial spaces between the polymer chains rather than via a “classic” pore. In this case, molecular mass and volume will become more important. Thus, for the Duramem membrane the retentions stay high, also in ethanol, due to the greater role of the  $\sigma$ -factor in the rejection equation;

- Compared to the Duramem membrane, the C<sub>1</sub> modified membrane has a similar surface polarity, but the pores are bigger. This explains the measured higher flux, and the

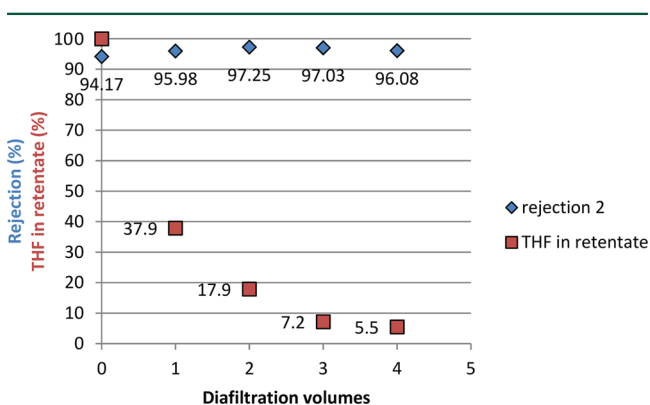
derived higher  $P_{\text{diff}}$ . However, the ratio  $J/P_{\text{diff}}$  is always lower for the  $C_1$  modified membrane than for the Duramem membrane, meaning that the pore size must have a greater influence on  $P_{\text{diff}}$  than on  $J$  (as pore size decreases,  $J/P_{\text{diff}}$  values increase).

- With both the Solsep-10206S and 0.9 nm PPA-TiO<sub>2</sub> membranes,  $J/P_{\text{diff}}$  in THF and ethanol is very low (order of 1), and as a consequence, rejection is very low in both solvents over both membranes. With these two membranes the solute–membrane affinity plays a greater role, leading to extra large  $P_{\text{diff}}$  values, large in comparison to  $J$ , which is low in both solvents. Together this leads to a ratio of the two which is quite small.
- In Figures 3, a line is drawn through the two points for each membrane (evolution is assumed to be linear; further studies with intermediate polarity solvents will show if this is a correct assumption). The intercepts of all lines with the  $x$  axis are very similar, and also very similar to the Hansen solubility parameter of the solvent at which point crystallization can be expected.

### ■ DEMONSTRATION OF THE SOLVENT SWITCH VIA CONSTANT VOLUME DIAFILTRATION

Because the Duramem-200 membrane was identified as the only membrane that gave high rejection of **2** in both solvents, this membrane was chosen to demonstrate the solvent switch process. The experiment was carried out at 25 °C because at 50 °C, although higher membrane permeance and higher final concentrations of **2** in ethanol are possible, the  $J/P_{\text{diff}}$  and as a consequence rejection in ethanol, is somewhat lower at 50 °C than that at 25 °C. To demonstrate the process, THF was washed through the membrane with 4 diafiltration volumes. The starting concentration of the solute in the feed was 0.1 M, the same as that used for the screening experiments.

Rejection of **2** remained above 90% throughout the process, as may have been expected from the screening results. The average rejection of **2** during the whole process was 96.1%, and leakage of the reaction product through the membrane was relatively minor being on the order of 12% of the original quantity in the feed. After 4 diafiltration volumes THF was reduced to 5 (w/w %). Figure 4 shows w/w % of THF in the retentate.



**Figure 4.** Rejection of **2** and retentate content of THF during the solvent exchange.

Membrane permeance during the process remained reasonably stable, albeit relatively low. At the concentration that these experiments were carried out, no evidence of membrane fouling due to precipitation of **2** was observed, as the stability of

membrane permeance would suggest. Average process permeance amounted to 0.225 L m<sup>2</sup> h<sup>-1</sup> bar<sup>-1</sup>. Based on this average permeance the expected volume of permeate produced per hour under the same operating conditions and using a commercial sized spiral wound module can be calculated and is reported in Table 5. Whereas rejection performance of this

**Table 5.** Expected Hourly Volume of Permeate Generated under 20 bar Pressure on Commercial Spiral Wound Membrane Modules

Module	Nominal size (inches)	Active membrane area (m <sup>2</sup> )	Hourly volume permeate (L)
1812	1.8 × 12	0.11	0.50
2512	2.5 × 12	0.17	0.76
2540	2.5 × 40	1.80	8.10
4020	4.0 × 20	2.00	9.00
4040	4.0 × 40	5.40	24.30

membrane is good, for scale up ideally permeance should be higher.

### ■ SOLVENT SWITCH CALCULATION

The diafiltration in the demonstration with Duramem-200 was stopped after 4 diafiltration volumes had been washed through the membrane. At that moment 5% of residual THF remained in the retentate. As it is possible that 5% THF is too high for the crystallization to be successful, the number of diafiltration volumes required to reduce the THF quantity to ≤0.5 wt % was calculated. Furthermore, based on the average rejection noted during the solvent switch process, i.e. 96.1%, also the losses of **2** via permeation through the membrane were calculated using eq 4.<sup>19</sup>

$$\text{Remaining solute (i)} = Q_{(i)} \times e^{-(1-R) \cdot N} \quad (4)$$

where  $Q_{(i)}$  is the initial quantity of solute (i) in the system,  $N$  is the number of diafiltration volumes, and  $R$  is rejection. The concentration of **2** at the initial point of the calculation was set to be the same as that in the demonstration process which was 40 g/L (0.1 M). Results of this calculation are shown in Figure 5 and Table 6.

The modeling was then extended to predict the progress of the solvent exchange if the  $C_1$  modified ceramic membrane had been used. The  $C_1$  membranes is the only other membrane with rejection of **2** higher than 95% in either of the solvents. For this simulation, solute rejection was calculated for each half diavolume via Spiegler–Kedem theory. The results are shown in Figure 6 and Table 7. The order of the columns in Table 7 shows also the order of the calculations performed: the diavolume leads to the amount of THF in the retentate; this allows calculation of the total Hansen parameter of the retentate; following the interpolation in Figure 3 then  $(J/P_{\text{diff}})\eta$  can be determined. Subsequently  $J/P_{\text{diff}}$  was calculated using the viscosity of the solvent mixtures determined using Chemcad software, and finally the rejection of **2** was derived using eqs 2 and 3, and the concentration of **2** in the retentate was calculated using eq 4. The object of this simulation was to gain a more comprehensive view of which is the most suited membrane for the solvent exchange process without the necessity of carrying out all the experimental work. Indeed, based solely on the screening results, this modified ceramic membrane would not have been chosen for the diafiltration process because of the low rejection in ethanol. The screening tests, however, give only the solute rejection at the two extreme points of the

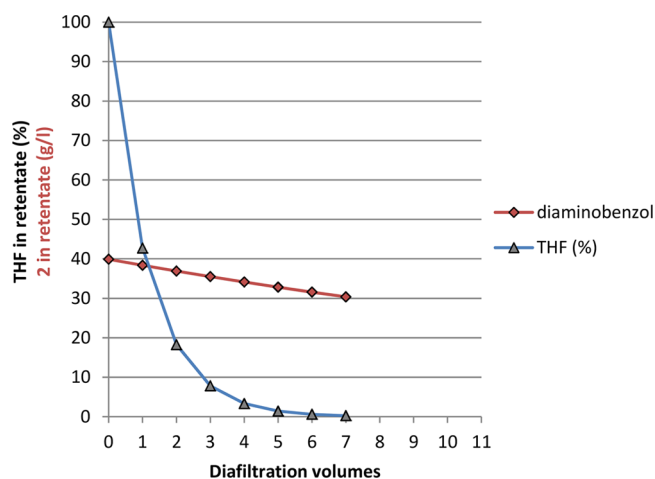


Figure 5. Simulation of solvent switch process with a Duramem-200 membrane.

Table 6. Solvent Exchange Simulation Data Using a Duramem-200 Membrane

Diafiltration volumes	2 in retentate (g) <sup>a</sup>	2 in permeate (g) <sup>a</sup>	THF in retentate (% w/w)
0	39.9	0	100
1	38.4	1.5	42.7
2	36.9	3.0	18.2
3	35.5	4.4	7.8
4	34.1	5.8	3.3
5	32.8	7.0	1.4
6	31.6	8.3	0.61
7	30.4	9.5	0.26

<sup>a</sup>Based on average process rejection of 96.1%.

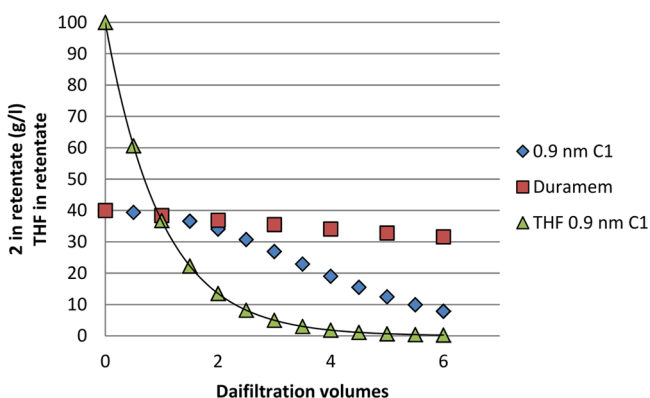


Figure 6. Simulation of the solvent exchange process using a 0.9 nm TiO<sub>2</sub> with a separation layer modified with methyl groups (0.9 nm C<sub>1</sub> TiO<sub>2</sub>).

solvent system, and there remains the possibility that the solute rejection in the solvent mixture could be far higher than that of pure ethanol. As can be seen from the calculated results, quantities of 2 in the retentate remain similar to that with the Duramem membrane up to two diafiltration volumes; thereafter, they begin to differ. However, as this simulation shows, THF is being removed from the system faster than with the Duramem membrane. Indeed, after two diafiltration volumes, the quantity of THF in the retentate is approximately 12%. This is due to the larger pore size of this membrane, giving less resistance to the solvents.

## CONCLUSIONS

This study is intended to highlight, by means of a practical example, the issues faced when considering a solvent switch using a membrane process. By making use of Spiegler–Kedem theory, the at first sight, seemingly arbitrary rejection results become understandable. In this particular case, when going from a strong solvent for the solute to one in which solute–solvent interactions are being approached, the changing solvent–solute interactions strongly influence the solute rejection. This leads to a new as yet unreported membrane performance region in which rejection is controlled more by the diffusion than size exclusion, and thus retentions are relatively low. Unlike region 1 of Figure 2, the importance of diffusion is now dictated by a low solute–solvent affinity, and not by a low solvent–membrane affinity. Further to being used to explain the observations made during the membrane screening, an understanding of the factors affecting rejection can be used to make any membrane screening phase more targeted and thus shorter. In the case highlighted, where the second solvent is the crystallization solvent and thus limits of solute solubility are being approached, the results are capable of predicting the total Hansen solubility parameter of the solvent mixture at which crystallization will occur. Moreover, application of Spiegler–Kedem theory was also used to simulate the diafiltration process with a membrane that, based on the screening results, would not necessarily have been applied in the solvent exchange process. Without the need for experimentation, this demonstrated the extent of success this process would have achieved. The simulation gives the possibility of obtaining a more comprehensive view of the most appropriate membrane for the task in hand. This initial report focuses on a particular solvent exchange of industrial interest and is thus somewhat narrow in scope. Further studies are being carried out to explore and broaden the scope and demonstrate the utility of application of Spiegler–Kedem theory to solvent–solute–membrane interactions, and specifically in situations where the solvent–solute affinity becomes low. Also experimental verification of the modeled diafiltration results is actively being pursued.

## EXPERIMENTAL SECTION

**General.** The solvents used in this study, THF and ethanol, were all technical grade purchased from VWR (Belgium) and used without prior purification. Commercially available membranes selected for this study were Solsep membranes (Solsep, Apeldoorn, The Netherlands), AMS membranes (AMS Technologies Ltd., Or-Yehuda, Israel), Duramem (Evonik MET Ltd., London, UK), and Inopor ceramic membranes (Inopor, Veilsdorf, Germany). The C<sub>1</sub> and phenyl phosphoric acid (PPA) modified ceramic membranes were Inopor membranes modified in-house using methods described elsewhere<sup>20</sup> to have *n*-alkyl or phosphoric acid groups on the top layer of the membrane. Ceramic membranes used in this work, both commercial and modified, were asymmetric tubular TiO<sub>2</sub> membranes; length 120 mm, outer diameter 10 mm, inner diameter 7 mm, and a top layer thickness of approximately 50 nm. Polymeric membranes were flat sheets. All membrane experiments were performed in a cross-flow filtration unit made in-house, pressurized with nitrogen gas. Filtration experiments were performed with a cross-flow velocity of 2 m/s, and unless stated otherwise, polymeric membranes were used with a transmembrane pressure of 20 bar, and ceramic membranes, with 10 bar.

**Table 7. Solvent Exchange Simulation Data Using a 0.9 nm TiO<sub>2</sub> with a Separation Layer Modified with Methyl Groups (0.9 nm C<sub>1</sub> TiO<sub>2</sub>)**

Entry	Diafiltration volumes	THF in retentate (% v/v)	Total Hansen solubility (MPa <sup>1/2</sup> )	(J/P <sub>diff</sub> )-η (mPa·s)	J/P <sub>diff</sub>	Rejection 2 (%)	2 in retentate (g)
1	0	100	19.40	25.76	56.00	97	40.0
2	0.5	57.8	22.40	15.37	21.65	94.5	39.40
3	1	34.1	24.08	9.54	11.22	90.8	38.34
4	1.5	20.3	25.06	6.15	6.41	85.5	36.61
5	2	12.2	25.63	4.16	4.12	79.5	34.05
6	2.5	7.4	25.98	2.96	2.91	73.5	30.73
7	3	4.4	26.18	2.25	2.18	67.6	26.92
8	3.5	2.7	26.31	1.82	1.76	62.6	22.89
9	4	1.63	26.38	1.56	1.50	59.2	19.02
10	4.5	1.0	26.43	1.40	1.33	56.3	15.51
11	5	0.6	26.46	1.30	1.23	54.4	12.46
12	5.5	0.4	26.47	1.24	1.16	52.9	9.92
13	6	0.2	26.48	1.21	1.10	51.0	7.84

Flux during the filtration is calculated using eq 5 and has symbol  $J$ , where  $V$  is the permeate volume,  $A$  is membrane area, and  $t$  is unit time.

$$J = \frac{V}{At} \quad (5)$$

Solute rejection ( $R$ ) is a function of the solute concentrations in the permeate  $C_p$  and the retentate  $C_r$  and is expressed as a percentage.  $R$  is calculated following eq 6.

$$R = \left(1 - \frac{C_p}{C_r}\right) \times 100 \quad (6)$$

5,6-Difluoro-*N*<sup>1</sup>-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine (Dim-DAB, 2) was supplied by Bayer AG (Wuppertal, Germany).

Analysis was carried on a Waters UPLC with a UV/vis PDA detector. A Waters Acquity BEH C18 column was used with dimensions 2.1 mm × 100 mm, 1.7 μm. A solvent gradient of water and acetonitrile buffered with 0.1% formic acid was used as mobile phase. The column temperature was 40 °C, and the detector was used with a wavelength of 297 nm.

**Membrane Pretreatment.** The AMS membranes are supplied “wet”: after cutting the required membrane piece they are submerged in water for 30 min prior to use. All other polymeric membranes were supplied in a “dry” form in flat sheets and needed to be preconditioned. To this end, a membrane piece was cut out with an effective membrane area of 100 cm<sup>2</sup> and placed in a cross-flow filtration cell. Then the solvent to be used in the experiment was added to the OSN unit, and the membrane was saturated in the solvent by bringing it under 10 bar pressure until the first drops of permeate were observed. Subsequently, the pressure was released and the membrane was allowed to equilibrate for a minimum of 4 h. The membrane was then conditioned by bringing the unit under 20 bar pressure and allowing approximately 50 mL of solvent to permeate. Pure solvent was then further permeated through the membrane until a stable flux was obtained. Ceramic membranes can be used directly without the need for pretreatment.

**General Procedure for Membrane Screening.** A solution of 2 (0.1 M) in the solvent to be used in the experiment (THF or ethanol) was added to the filtration unit and fitted with the appropriate and if required preconditioned membrane. Cross-flow circulation was started, and the system allowed equilibration at 25 °C (±2 °C). The unit was brought

under pressure, 20 bar for polymeric membranes or 10 bar for ceramic membranes. After a stable flux was reached, 50 mL of permeate were collected and samples were taken for analysis. The pressure was released, and the temperature in the unit brought to 50 °C (±2 °C). After a stable flux was reached, 50 mL of permeate were collected and samples were taken for analysis. This procedure was repeated for each membrane and each solvent.

**Solvent Exchange from THF to Ethanol.** A solution of 2 (23.6 g, 59.8 mmol) in THF (600 mL) was added to the filtration unit fitted with a preconditioned Duramem-200 membrane. The unit was equilibrated to 25 °C (±2 °C) with circulation of the solution. The system was brought under 20 bar pressure and subjected to constant volume diafiltration with ethanol, until 4 diafiltration volumes had been washed through the membrane. For analysis, regular sampling of both the permeate and retentate was carried out.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) Blaser, H.-U.; Steiner, H.; Studer, M. Selective Catalytic Hydrogenation of Functionalized Nitroarenes: An Update. *Chem-CatChem* 2009, 1, 210–221.
- (2) Loos, P.; Alex, H.; Hassfeld, J.; Lovis, K.; Platzek, J.; Steinfeldt, N.; Hübner, S. Selective Hydrogenation of Halogenated Nitroaromatics to Haloanilines in Batch and Flow. *Org. Process Res. Dev.* 2016, 20, 452–464.
- (3) Baramov, T.; Loos, P.; Hassfeld, J.; Alex, H.; Beller, M.; Stemmler, T.; Meier, G.; Gottfried, M.; Roggan, S. Encapsulated



Cobalt Oxide on Carbon Nanotube Support as Catalyst for Selective Continuous Hydrogenation of the Showcase Substrate 1-Iodo-4-nitrobenzene. *Adv. Synth. Catal.* **2016**, *358*, 2903–2911.

(4) Said, M. B.; Baramov, T.; Herrmann, T.; Gottfried, M.; Hassfeld, J.; Roggan, S. Continuous Selective Hydrogenation of Refametinib Iodo-nitroaniline Key Intermediate DIM-NA over Raney Cobalt Catalyst at kg/day Scale with Online UV–Visible Conversion Control. *Org. Process Res. Dev.* **2017**, *21*, 705–714.

(5) Xiao, D.; Zhu, L.; Wang, S.; Liang, Z.; Hu, W. Novel 6-arylamino pyridone sulfonamides and 6-arylamino pyrazinone sulfonamides as mek inhibitors. WO 2010/145197 A1, 2010.

(6) Maderna, A.; Vernier, J.-M. Preparation of (R)- and (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and protected derivatives thereof. WO2011/009541 A1, 2011.

(7) Marchetti, P.; Solomon, M. F. J.; Szekely, G.; Livingston, A. G. Molecular Separation with Organic Solvent Nano filtration: A Critical Review. *Chem. Rev.* **2014**, *114*, 10735–10806.

(8) Livingston, A.; Peeva, L.; Han, S.; Nair, D.; Luthra, S. S.; White, L. S.; Freitas Dos Santos, L. M. Membrane separation in green chemical processing: solvent nanofiltration in liquid phase organic synthesis reactions. *Ann. N. Y. Acad. Sci.* **2003**, *984*, 123–41.

(9) Livingston, A. G. WO2002076588(A1) solvent exchange.pdf. WO 02/076588 A1, 03.10.2002, 2002.

(10) Lin, J.; Livingston, A. Nanofiltration membrane cascade for continuous solvent exchange. *Chem. Eng. Sci.* **2007**, *62*, 2728–2736.

(11) Constant volume diafiltration is a process in which solvent is added to the OSN unit at a rate that is equivalent to the rate at which solvent permeates through the membrane. Thus, solvent volume within the unit remains constant.

(12) Marchetti, P.; Butté, A.; Livingston, A. G. NF in organic solvent/water mixtures: Role of preferential solvation. *J. Membr. Sci.* **2013**, *444*, 101–115.

(13) Rezaei Hosseinabadi, S.; Wyns, K.; Meynen, V.; Carleer, R.; Adriaenssens, P.; Buekenhoudt, A.; Van der Bruggen, B. Organic solvent nanofiltration with Grignard functionalised ceramic nanofiltration membranes. *J. Membr. Sci.* **2014**, *454*, 496–504.

(14) Hansen, C. M. *Hansen Solubility Parameters A User's Handbook*; CRC Press: Boca Raton, FL, 2007.

(15) Hosseinabadi, S. R.; Wyns, K.; Meynen, V.; Buekenhoudt, A.; Van der Bruggen, B. Solvent-membrane-solute interactions in organic solvent nanofiltration (OSN) for Grignard functionalised ceramic membranes: Explanation via Spiegel-Kedem theory. *J. Membr. Sci.* **2016**, *513*, 177–185.

(16) Zwijnenberg, H. J.; Dutczak, S. M.; Boerrigter, M. E.; Hempenius, M. A.; Luiten-Olieman, M. W. J.; Benes, N. E.; Wessling, M.; Stamatialis, D. Important factors influencing molecular weight cut-off determination of membranes in organic solvents. *J. Membr. Sci.* **2012**, *390–391*, 211–217.

(17) See Toh, Y. H.; Loh, X. X.; Li, K.; Bismarck, A.; Livingston, A. G. In search of a standard method for the characterisation of organic solvent nanofiltration membranes. *J. Membr. Sci.* **2007**, *291*, 120–125.

(18) By comparing the molecular weight cut-off with the molecular weight of the solute, an estimation of  $\sigma$ , the maximal rejection that can be expected from the membrane, can be derived. For each batch of a particular membrane, the MWCO was determined; within a particular batch of membranes the MWCO remains constant, as has previously been observed in the article: Buekenhoudt, A.; Bisignano, F.; De Luca, G.; Vandezande, P.; Wouters, M.; Verhulst, K. Unravelling the solvent flux behaviour of ceramic nanofiltration and ultrafiltration membranes. *J. Membr. Sci.* **2013**, *439*, 36–47.

(19) Mulder, M. *Basic Principles of Membrane Technology*, 2nd ed.; Kluwer Academic Publishers: Dordrecht, 1996.

(20) Mustafa, G.; Wyns, K.; Vandezande, P.; Buekenhoudt, A.; Meynen, V. Novel grafting method efficiently decreases irreversible fouling of ceramic nanofiltration membranes. *J. Membr. Sci.* **2014**, *470*, 369–377.