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Preparation of aminated microfiltration membranes by degradable functionalization using plain PEI membranes with various morphologies

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Abstracts

Membranes have been introduced as support for chromatographic separations to overcome drawbacks of particle supports, in particular the diffusion-restricted adsorption rate. However, only very few membrane types fulfill the requirements concerning the processability, permeability, number of active sites, swellability and unspecific protein adsorption. Membranes from polyimides could be an attractive alternative because of their easy fabrication by degradable functionalization if the polymer reduction by degradation can be limited. It suggests a great influence of membrane morphology on the process of pore opening. Hence various structured PEI membranes were aminated by degradable functionalization using DETA as a modifier. In contrast to sponge-like structures, the macrovoidal structures are beneficial because they combine a strong pore opening with a low reduction in membrane thickness. On the other hand, the separation properties of the virgin membrane have only a marginal influence on the pore opening process because of their equilibration after a short treatment time. The number of covalently bound functions could be strongly increased by a double functionalization process using a high-volume polyamine as a modifier in the second step indicating the presence of residual imide groups of the basic polymer after the primary DETA treatment. After optimized preparation, the resulting aminated membrane is characterized by a large pore size, a high number of binding sites and, because of the very thin, gel-like protection layer of amine, low unspecific adsorption sites suggesting effective low-cost separation on basis of adsorption.

Keywords: Membrane preparation and structure, microporous and porous membranes, affinity membranes, polyimide, amination,

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1. Introduction

Membranes have been introduced as supports for chromatographic separations in the past to overcome drawbacks of particle supports like the compressibility of the mostly soft support gels, the high pressure drops along the column and particularly the diffusion restricted adsorption rate. The convective flow governs the transmembrane flux resulting in considerably higher adsorption rates because of the shorter diffusion ways. As a consequence, high productivity and low production costs can be realized especially if low quantities of the product have to be separated from large volumes during the production. However, the separation profile of the membrane has to guarantee that all components can permeate unrestricted through the support membrane to avoid pore blocking. This requires membranes with pore sizes in the range of 0.5 to 5 μm . Additionally to the common requirements, application of adsorptive membranes in the biotechnological and medical field need to be sterilizable and often a disposable use is desired. Thus thermal stability and low costs of the membranes are important facts to be taken in account.

Nonsolvent induced membrane formation (NIPS) using water as a nonsolvent is the most commonly applied process to prepare membranes [7] because this process is simple and thus limits the production costs significantly. However, the asymmetric membranes prepared in this way usually possess an ultrafiltration separation profile. Therefore, the pore sizes are too small for application of these membranes in adsorptive separation processes. On the other hand, typical engineering polymers like polysulfones, polyamides or poly(vinylidene fluoride), which are commercially available as membranes with microfiltration separation profile and different pore sizes, do not possess enough active sites for the binding of ligands [6,9] and are furthermore characterized by a high unspecific protein adsorption because of their hydrophobicity [10]. Only membranes from vinyl alcohol polymers [11,12], new developed cellulose based materials [13,14] and partially polyamides [15,16] fulfill the requirements with respect to processability, number of active sites, swellability and protein adsorption behavior. Therefore, new membrane types have to be developed in order to optimize adsorptive separations.

Our own investigations document that polyimides, carrying a priori no active sites for ligand binding, can be easily functionalized by surface modification with nucleophilic modifiers using wet-chemistry [17]. When choosing a suitable modifier, the functionalization can be combined simultaneously with a pore opening in which the separation profile of the treated membrane will be transferred from the ultrafiltration into the microfiltration range [18]. The pore opening is initiated by degradation of the functionalized polyimide [19]. Principally, it could be verified that polyimide membranes prepared by NIPS can be modified in a one-step process into hydrophilic microfiltration membranes with large pore diameter and a large number of active sites (amine groups) which makes these membrane types attractive for adsorptive applications either in the functionalized form or in the bioactive after further binding of ligands to the functional groups. However, the degradation process is connected with membrane thickness and, therefore, the porous membrane volume usable for adsorption processes is reduced. As a conclusion, the reduction in polymer volume has to be limited as much as possible to avoid a stacking of too many membranes to realize the desired stack volume.

The reduction of the membrane volume should be restricted if a membrane with larger pores and/or a membrane with a higher degree of asymmetry in the morphology is designed and applied as a virgin membrane for simultaneous functionalization and pore opening process. Insofar it can be suggest that an optimal choice of the virgin membrane type is of importance for high performance supports.

The aim of this investigation is the preparation of microfiltration membranes from poly(ether imide) (PEI) membranes by degradative functionalization with a reduced polymer volume reduction opened possibilities for effective applications in the field of protein separation. Plain membranes with various structured morphology were used for degradative functionalization differing in the mean pore size and in the morphological structure. The treated membranes were characterized by variation in the separation profile, loss of membrane thickness and content of amine function as binding sites, all related to the modification step. In the second part, the content of active sites will be strongly increased by double functionalization: In the first step degradation dominates the membrane properties whereas functionalization dominates in the second step leading to functionalized membranes with large pore diameters and a very high content of chemical functions. The results verify that a suitable morphology of the virgin membrane is a prerequisite for an effective pore opening resulting in highly functionalized membranes that are beneficial for application in adsorptive separations.

2. Experimental

2.1 Materials

In this study asymmetric PEI flat membranes (membrane polymer PEI: Ultem 1000[®], General Electric, USA) with ultrafiltration properties and different morphologies prepared on a polyester nonwoven support were used as the initial membrane for membrane modification in heterogeneous phase. The membranes are fabricated by NIPS using water as coagulant in the pilot equipments of GKSS from PEI dissolved in different solvents, partially under addition of additive. In one case poly(benzimidazole) (PBI), a commercial product of Celanese, USA was added to the PEI solution [20], in another case sodium lauryl sulfate (SDS) or lithium chloride (LiCl) were added. All used reagents like the solvents (N-methylpyrrolidone (NMP), N,N-dimethylacetamide (DMAc), γ -butyrolactone (GBL)), the additives LiCl or SDS, the modifiers (diethylene triamine (DETA) and poly(ethylene imine) (Pei), $M_n = 60\text{kg/mol}$) as well as the test substances (dextran of different molecular weights, Acid Orange II), are commercial products from Sigma-Aldrich, Fluka or Merck and were applied as purchased. Characteristic data of the applied membranes are listed in **Table 1**; the morphology of selected samples is presented in **Figure 1**.

Table 1: Characteristic data of the investigated virgin membranes

Membrane designation	Membrane morphology	Membrane thickness		Polymer mass [mg cm ⁻²]	Water permeability [lm ⁻² h ⁻¹ kPa ⁻¹]	Pore diameter D ₅₀ [nm]	Cut-off [kg mol ⁻¹]
		Membrane + nonwoven [μm]	Membrane [μm]				
Reference [18]	sponge	196	-	3.3	3.0	3.8	20
ST 1	sponge	205	45	3.2	9.1	6.8	90
ST 2	sponge	246	92	4.3	10.6	4.2	300
ST 3	sponge	213	57	3,5	11.2	6,7	70
MT 1	finger	205	50	3.1	0.16	2.3	8
MT 2	finger	207	52	3.2	1.35	5.4	20

Figure 1: SEM morphology of the cross section of selected plain membrane types from PEI (a – ST 1; b – ST 2; c – MT 1; d – MT 2)

2.2 Membrane modification

First, the dry PEI flat membrane was wetted by contacting with a water/1-propanol solution (1:1) for 30 min, and then carefully rinsed with deionized water, except for the membranes prepared by addition of LiCl or PBI, which are never-dried products.

DETA treatment: The wet membrane was mounted onto a stainless steel cylinder with a stirrer guide and fixed with clamping rings. This device was immersed into a thermostat bath, which contains the modifying solution DETA. The PEI membrane was modified on the active-layer side. The concentration of modifying solution DETA was generally 4 wt.-%. All reactions were carried out at 90°C and a stirring rate of 40 rpm ($4.188 \text{ rad}\cdot\text{s}^{-1}$) for the time indicated. After quenching in cool deionized water, the membrane was demounted, thoroughly washed with deionized water to remove adsorbed modifier and stored in wet state at 4°C until use or first dried at room temperature (RT) and then at 100°C up to a constant weight (about 3 h).

Pei treatment: The DETA modified membrane was modified in a second step by 2 wt.-% solutions of Pei in water for 30 min under the conditions of DETA treatment and further posttreated in analogy to DETA posttreatment. It was reported that under such functionalization conditions a maximum of amine groups was observed with a high reproducibility [21].

2.3 Characterization of the membranes

Water permeability and pore diameter: Water permeabilities of the membranes and rejections of the virgin membranes were determined in a dead-end mode at 0.05 MPa in a stirred ultrafiltration cell (Berghoff, Type GN 10-400, Germany). The ultrafiltration experiments of the virgin membranes were carried out first with distilled water, then with a test solution. The test solution was a 0.1 wt.-% aqueous solution of a dextran mixture with molecular weights from 650 to 1410000 D. Size distribution of dextrans in permeate, in retentate and in original solution were analyzed by size exclusion chromatography (SEC) (Shimatzu, Germany). From the results of SEC the average pore diameter (D_{50}) was calculated by assuming a logarithmic normal distribution of the pore size [22]. The water permeability of the treated membranes was determined with the same arrangement but at a pressure of 0.05 MPa (low-intensity treatment) or 0.01 MPa (high-intensity treatment). Additionally the average pore size of selected membranes with microfiltration properties were measured with Capillary Flow Porometer, type 6 (Porous Materials, Inc, USA) and Porewick as the wetting liquid.

Morphology: The morphology was evaluated by Scanning Electron Microscopy (SEM). After exchange of water of the wetted membranes with graduated water/ethanol solution and drying at RT, the membranes were fractured in liquid nitrogen and coated with gold/palladium (80/20 wt.-%) (EAP 101, Gatan, USA). The prepared samples were investigated using a LEO 1550 VP electron microscope with Schottky emitter (LEO, Germany) at an acceleration voltage of 3 kV.

Membrane thickness: The membrane thickness was estimated by micrometer gauge at ten different locations of the membrane surface and the data were averaged.

Polymer mass: Polymer mass per membrane area was estimated by determination of loss of membrane mass after dissolving the polymer in DMAc for 2 h at 80°C under gentle stirring. Generally, the polymer layer of DETA-treated membranes was completely soluble under the applied conditions and therefore completely removed during the solvent treatment.

Amine content: The Acid Orange II assay [23] was used for the determination of the content of amine according to the description in [17]. Briefly, membrane samples of

defined size (1.33 cm^2) are immersed in a solution of $500 \text{ }\mu\text{mol/l}$ Acid Orange II in distilled water at pH 3 (diluted HCl) at which a protonation of amines takes place. After shaking for 24 h at RT the samples were thoroughly washed with water at pH 3. If content of dye was too low (discoloring during adsorption process) the adsorption step was repeated. The amount of bound dye was quantified after detachment in distilled water at pH 12 (diluted NaOH). The detachment was achieved after 15 min shaking at RT. After that the optical density of the solution was measured spectrometrically at a wavelength of 492 nm using Spectra Fluor Plus spectrometer (Tecan, Germany). The concentration of amine groups was determined with help of a calibration curve under assumption that one amine group is complexed with one equivalent value of Acid Orange II.

BET area: The pore area of selected samples was determined with BET technique using the device ASAP 2010 (Micrometrics, Germany).

3. Results and discussion

3.1 Investigation of virgin membranes with different morphologies and different separation characteristics

With respect to the general morphology, membranes can be distinguished into sponge-like and macrovoidal membranes. In previous investigations [18], results of one membrane type with sponge-like morphology were reported to discuss the basis of the membrane modification principle. Related to the general preparation process (NIPS), the variation of the average membrane pore size in direction of higher pore diameter is very limited as well as the preparation of much sponge-like morphology with strongly different separation properties. The generation of such morphology is generally a challenge for membrane researchers. Insofar the variation in pore diameter was only possible in the limits of membrane fabrication by NIPS. The experimental investigations were therefore focused on the variation in the general morphology.

3.1.1 Sponge-like structures

In a first series of investigations, membranes with sponge-like morphology were prepared and treated with DETA to aminate the membrane and to open their pore system. Results of the change in water permeability in dependence on the treatment time are presented in **Figure 2** for different membrane types, which differ in the permeability of the virgin membranes. For a better comparison to previous investigations, data of the former investigated membrane type are included as a dotted line in this figure.

Figure 2: Dependence of water permeability of sponge-like PEI membrane types on the DETA treatment time

The results verify that the dependencies are comparable for all investigated membrane types except at the beginning of the modification process and except for the membrane type using PBI as an additive. At low treatment times, the differences in the water permeabilities of the virgin membrane are documented but leveled off at treatment times of about 10 min and pore opening was equalized with progress in treatment time. Similar water permeabilities are obtained independent of the permeability/pore size of the virgin membrane. Probably defects initiated by the nonwoven or partial finger pores attributes to marginal differences if the thickness of the polymer layer is further reduced. However, a suitable reproducibility is given for treatment times of up to 60 min. Insofar treatment times higher than 60 min are unfavorable for a further increase of pore size for this membrane type. In general the tendency to open the pore system is smaller if PEI/PBI blend membranes are investigated, which is probably due to the nondegradability of PBI in the polymer matrix under the applied conditions.

In **Figure 3** the reduction in membrane thickness (**a**) and polymer mass (**b**) of this basic membrane type are shown for two selected membranes in dependence on the treatment time with DETA solution.

Figure 3: Reduction in membrane thickness (a) and polymer mass (b) of sponge-like PEI membrane types in dependence on the DETA treatment time

As can be seen, membrane thickness and polymer mass were reduced with the treatment intensity. The differences between the two selected types are related to the degree of structural asymmetry. In order to generate comparable water permeabilities, a larger reduction in membrane thickness and a bigger loss in polymer mass is necessary for type ST 2 in comparison to ST 1. Smaller pores generate a higher surface for the degradation process and therefore a higher degradation rate. To support this hypothesis the amine group content of the covalently aminated membranes are determined for both membrane types in dependence on the treatment time. Data are presented in **Figure 4** and correspond to the polymer mass.

Figure 4: Influence of DETA treatment time on the amount of free amine groups of PEI membranes with sponge-like morphology

The higher amine content generally observed for type ST2 is a strong indication for a higher surface area accessible for the degradation process and supports the postulation of differences in degree of structural asymmetry between both membrane types.

3.1.2 Macrovoidal structures

In a second series, two different types of PEI membranes with macrovoidal structures were used for investigations in analogy to the experiments of the sponge-like membrane types. Besides the differences in separation properties (table 1) of both types, the morphology varied in the start point of the finger pores in the membrane cross section (Figure 1): Whereas the finger pores of type MT 1 started immediately beneath the active layer, the finger pores of type MT2 begins at a sponge-like transition layer beneath the active layer. According to the differences in average pore size and morphology, differences in the behavior by DETA treatment can be expected.

Data of water permeability in dependence on the DETA treatment time are presented in **Figure 5**. A typical dependency of water permeability on the treatment time of the sponge-like membrane structure is included in this figure as a dotted line.

Figure 5: Dependence of water permeability of macrovoidal PEI membrane types on the DETA treatment time

The water permeability is increased as expected with the treatment time, but the dependency is strongly different from the sponge-like membrane type: In the first minutes of treatment, a marginally increase in water permeability is observed. The differences in the average pore sizes of the virgin membranes are equilibrated after about 30 min treatment time. A plateau of water permeability is reached characterizing the permeability of the transition layer between the sponge-like and the macrovoidal morphology and the opening of the finger pores begins followed by the permeability of the complete opened finger pore layer. Insofar the start point of the finger pores in the membrane cross section dominates the time point at which a considerable increase in water permeability and therefore in the pore size is observed. It is advantageous if the finger pores start immediately beneath the active layer. Under these conditions high water permeability resulted and a high average pore diameter at low treatment intensity was reached relatively independent of the pore size of the virgin membrane. On the other hand, the results demonstrate that a significantly higher water permeability/pore size can be generated if virgin membranes with finger pores were used in comparison to sponge-like structures. SEM micrographs of the cross section near the active layer (a) and the treated surface (b) of the selected membrane type MT1 document the changes in morphology during DETA treatment (**Figure 6**).

Figure 6: SEM morphology of cross section (a) and DETA treated surface (b) in dependence on the treatment time

First the active layer is degraded, opened the sponge-like transition layer, which will be removed to open the finger pore layer. This process of polymer degradation generates pores in the micrometer range as shown in run b. The opening of the finger pores starts at about 30 min treatment time and is completed at about 50 min treatment time using this membrane type. (Note the differences in the bars of part b.) Despite the high porosity and large pore sizes the membrane is mechanically stable. The data of reduction in membrane thickness and loss in polymer mass are shown in **Figure 7 a and b** in dependence on the treatment time with DETA for macrovoidal structure types.

Figure 7: Reduction in membrane thickness (a) and polymer mass (b) of macrovoidal PEI membrane types in dependence on the DETA treatment time

In particular the reduction in membrane thickness is considerable lower for macrovoidal structure types than for sponge-like structure types. Additionally the content of amine groups generated by the DETA treatment is comparable to the results of sponge-like structure types (not shown here in detail) with opened pore systems suitable for adsorptive membrane applications.

3.2 Preparation of highly aminated PEI membranes with microfiltration separation profile by double functionalization

According to the results on top, degradative amination of PEI membranes is a beneficial technique for the preparation of adsorptive membranes from membranes with ultrafiltration separation profile. Generally, membranes with macrovoidal morphology offer an effective opening of the pore system by degradation suggesting a completely unrestricted permeation of high-volume molecules through the pore system of the membrane adsorber bed. After one second, a high number of functions similar to a gel-like protective layer are required to realize high binding sites and to avoid unspecific adsorption of the polymeric support material by hydrophobic interactions. In general, both requirements can not be fulfilled completely with low-volume functionalization agents such as DETA but they are necessary for an effective pore opening [18]. On the other hand, high-volume polyamines generate a

covalently bound gel-like layer with a high amount of chemical functions [17], which guaranty a lot of binding sites at a simultaneous protection of the polymeric background. If free imide groups are present after the first treatment process with the pore opening agents DETA, these groups can be used for a covalent binding of polyamines in a second functionalization step.

In order to realize such a two-step process, PEI membranes were treated first with the DETA bath and subsequently with a Pei bath after rinsing the membrane between both steps. Data of the amine group determination, a very sensitive parameter of free imide groups, are pictured in **Figure 8** in dependence on the DETA treatment time using the ST 1 and MT 1 membranes as examples. The data of the one-step treatment with DETA are also included in this figure as a reference symbolized by a dotted line (MT 1 membrane).

Figure 8: Variation of the amount of free amine groups of PEI membranes after double functionalization: first step: DETA treatment with variable treatment time; second step: Pei treatment with fixed treatment time (30 min)

The results manifest a strong increase in amine group content if in a second step additional amination with Pei is employed. Differences exist in the absolute value if membranes with different morphology are applied. Under identical posttreatment conditions sponge-like structures are related to higher amine group content, an indication for the generally smaller pore size of sponge-like morphologies. These investigations lead to the important conclusion that after the first treatment step residual imide groups are present which can be used for further covalent functionalization resulting in a gel-like protection layer with a high amount of binding sites.

Following this double functionalization route, a control of changes in water permeability is necessary. Data of changes in water permeability as result of the second functionalization step are shown in **Figure 9** for two selected membrane types.

Figure 9: Influence of the second functionalization step on the water permeability of PEI membranes with various morphology in dependence on the DETA treatment time

The data document clearly that the functionalization with the high-volume molecule Pei diminished the water permeability of the membrane and thus their pore size. This reduction in water permeability is dramatic for membranes with sponge-like morphologies and suggests a limited permeation of large volume molecules during the application in an adsorptive separation processes. In contrast pore sizes can be realized with macrovoidal structure type, which suggest an unlimited permeation of high volume molecules despite the observed reduction in water permeability. Insofar this structure type fulfills all requirements for applications in an adsorptive separation processes after a double functionalization process.

4. Conclusions

Functionalized membranes with microfiltration separation profile are advantageously applied as supports for adsorptive separation techniques in the past but generally only few membrane types fulfill the requirements for adsorptive separations. Depending on the field of use, some membrane characteristics become important besides the general requirements. E.g. in therapeutic blood purification steam-sterilizability and low membrane costs are prerequisites for an extensive application because of the desired disposable use. Therefore the preparation of the adsorptive support membrane has to be realized in a continuous short time process by surface functionalization of commercial membranes. Membranes from commercial polyimides offer a great potential in application as adsorptive supports because they can be steam-sterilized and functionalized easily by wet-chemical means causing a simultaneous functionalization and pore opening. As expected, the membrane morphology of the virgin polyimide membrane influences strongly the preparation process and the observed membrane properties suggest an optimal membrane support for adsorptive separations. The results of investigations lead to the following conclusions:

- By optimal choice of the morphology of the virgin membrane to be processed a strong pore opening can be connected with a marginal reduction in membrane thickness and loss in polymer mass. In general virgin membranes with macrovoidal morphologies in which the finger pores begin to grow immediately beneath the active layer prove advantageously in comparison to

sponge-like structures because of the strong change in pore size initiated by the opening of the finger pore system of the membrane. In contrast, the virgin membrane permeability was found to be relatively ineffective in the frame of investigated variation of ultrafiltration separation profile.

- Simultaneous functionalization and pore opening requires a low molecular weight aminic modifier. After a suitable pore opening, residual imide groups are still present which can be used for a further covalent binding of polyamines increasing considerably the content of functional groups and generating a very thin gel-like aminic layer on all surfaces. The latter covers the background of the support polymer completely and suggests a very low unspecific adsorption.

In summary, the membrane supports were prepared under optimal conditions (45 min DETA, 10 min Pei, macrovoidal morphology) resulted in an aminated membrane with 0.8 μm mean pore size, an amine group content of 1200 nmolcm^{-2} membrane (= ca. 560 μmolg^{-1} polymer) and a BET area of ca. 5 m^2g^{-1} while showing a marginal reduction in membrane thickness as a result of the modification process.

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