ChemComm

COMMUNICATION



View Article Online View Journal | View Issue



Cite this: Chem. Commun., 2015, 51, 4854

Received 8th January 2015, Accepted 11th February 2015

DOI: 10.1039/c5cc00168d

www.rsc.org/chemcomm

Oxalic acid complexes: promising draw solutes for forward osmosis (FO) in protein enrichment[†]

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Highly soluble oxalic acid complexes (OACs) were synthesized through a one-pot reaction. The OACs exhibit excellent performance as draw solutes in FO processes with high water fluxes and negligible reverse solute fluxes. Efficient protein enrichment was achieved. The diluted OACs can be recycled *via* nanofiltration and are promising as draw solutes.

The demand for proteins is steadily increasing, effective protein production is needed. Protein enrichment is an essential step in protein production. As most proteins are labile and heat sensitive, athermal enrichment technologies are preferred. Membrane technology has gained importance in biotechnology due to its mild operating conditions and superior separation ability.¹ Microfiltration, ultrafiltration and nanofiltration (NF) have been extensively used for protein enrichment. However, these pressure-driven processes are usually energy intensive and severe membrane fouling is often encountered. In contrast, forward osmosis (FO) employs the osmotic pressure difference to induce water transport. Not only does it consume less energy but also results in lower fouling because of no hydraulic pressure involved.^{2–5} These features make FO very attractive in protein enrichment.^{6,7}

As the osmotic pressure gradient across the membrane is the driving force for FO processes, draw solutes with characteristics of high osmotic pressures, low reverse fluxes and easy regeneration are crucial to fulfil protein enrichment. Most conventional draw solutes of inorganic salts are not suitable for protein enrichment because they have severe reverse salt fluxes.^{6,8} The permeated salts may denature the feed proteins.⁷ A variety of novel draw solutes have been proposed recently.^{9–15} However, most novel draw solutes either undergo complicated synthesis procedures^{10,15} or have relatively low water fluxes.^{9,11,14} To satisfy the aforementioned requirements, Fe³⁺ and Cr³⁺ complexes with oxalic acid (OA) as ligands and Na⁺ as counterions (denoted as Na–Fe–OA and Na–Cr–OA, respectively) were investigated as draw solutes in this work. Such substances possess lots of hydrophilic groups and are ionizable in water which make them desirable as draw solutes.

Na–Fe–OA and Na–Cr–OA were synthesized according to a modified method.¹⁶ Quantitative yields were achieved in their syntheses. Fig. 1(a) shows the proposed structure of Na–Fe–OA. Na–Cr–OA is structurally similar to Na–Fe–OA (Fig. S1(a), ESI†). The proposed structures were confirmed by single-crystal X-ray crystallography (Fig. 1(b); Fig. S1(b), Tables S1 and S2, ESI†).

Both complexes consist of an octahedral anion framework and three Na⁺ (Na₃ and Na₄ in Na–Fe–OA occupy special positions with 50% occupancy for each atom. The same situation occurred in Na₁ and Na₂ of Na–Cr–OA). The octahedral framework contains a metal core and three five-membered rings. This is a desirable scaffold as it not only contributes to the stability of OACs, but also reduces their reverse flux in FO and makes OACs easily recyclable. Despite the configural similarity, Fe³⁺ and Cr³⁺ complexes are different in their crystal structures owing to their differences in metal electronic structures. The distances between the metal core and its directly connected



Fig. 1 (a) Proposed and (b) X-ray single crystal structures of Na-Fe-OA.

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 $[\]dagger$ Electronic supplementary information (ESI) available. CCDC 1042529 and 1042530. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc00168d

oxygens (M–O) are shorter in Na–Cr–OA than in Na–Fe–OA, indicating a stronger interaction of Cr–O than Fe–O. Meanwhile, the distance between carbon and the terminal oxygen is generally shorter in Na–Cr–OA than in Na–Fe–OA. These data imply a stronger dissociation ability of Na–Cr–OA than Na–Fe–OA. Hence, the former has a higher osmotic pressure than the latter at the same concentration, as confirmed by the experimental results (Fig. S5, ESI†).

The coordination between OA and Fe³⁺ or Cr³⁺ was confirmed by FTIR (Fig. S2, ESI[†]). In both complexes, the peak at ~3500 corresponds to the O–H groups of the crystal water. The absorptions at 1648–1690 cm⁻¹ and 1252–1265 cm⁻¹ correspond to C=O and C–O groups, respectively, indicative of the presence of carboxylic groups.^{17,18} The lower stretching frequencies of C=O ranging from OA (1690 cm⁻¹) to OACs (1660–1670 cm⁻¹) are a result of perturbation at the hydroxyl site leading to the weakening of C=O through conjugation. The absorption at ~560 cm⁻¹ in OACs is due to the metaloxygen bond (M–O), as verified in the similar complexes.¹⁹ All these results manifest the successful coordination between OA ligands and the metal cores.

The detailed compositions of Na–Fe–OA and Na–Cr–OA were determined by TGA measurements (Fig. S3, ESI[†]). The thermal decomposition of both OACs takes place in two stages. The weight loss in the first stage occurring at 45–150 °C is associated with the loss of the crystal water. With a further increase in temperature, the dehydrated intermediates undergo the second-stage of decomposition (240–480 °C) where the organic components are evaporated in the form of CO and CO₂ with metal oxides remaining. Na–Cr–OA exhibits higher thermal stability than Na–Fe–OA. The OACs have a similar thermal decomposition mechanism as those with similar structures.^{18,20,21} The TGA study shows that the observed weight losses are very close to the calculated ones for both OACs (Table S3, ESI[†]).

The relative viscosities (η_r) of Na–Fe–OA, Na–Cr–OA and OA are recorded in Fig. S4(a) (ESI[†]). The highest concentration of 1.5 M was used for Na-Fe-OA and OA due to their limited solubility. η_r increases with an increase in draw solute concentration for all compounds, and the increment is larger at higher concentrations. OACs with Na–Fe–OA have the largest η_r at the same concentration. As the viscosity of a draw solution has a negative effect on water flux in FO processes, Na-Cr-OA may perform better than Na-Fe-OA when other conditions are the same. However, the effect of viscosity on FO performance may be insignificant for these OACs because they have much lower η_r than other draw solutes such as Na–Fe–CA¹⁸ and PAA–Na compounds²² as shown in Fig. S4(b) (ESI[†]). Even at their highest studied concentrations, OACs exhibit much lower η_r . This is possibly due to the fact that OACs have smaller molecular sizes than Na-Fe-CA¹⁸ and PAA-Na compounds.²²

Fig. S5 (ESI[†]) displays the relationship between osmotic pressure and draw solution concentration for these two OACs using OA as a reference. Due to the colligative properties, the osmotic pressure increases with increasing concentration of both OACs and OA. Among them, Na–Cr–OA has the highest osmotic pressure, followed by Na–Fe–OA and then OA at the



Fig. 2 FO performance of 1 M Na–Fe–OA and Na–Cr–OA using TFC-PES₁ and TFC-PES₂ membranes (feed: DI water, PRO mode).

same concentration. This could be ascribed to the higher dissociation degree of Na–Cr–OA than Na–Fe–OA, as presented in the X-ray single-crystal structural studies. More ionic species may be present in the OAC solutions than in the OA solution. In addition, the increment of osmotic pressure is not proportional to the increment of concentration possibly due to the reduced ionic dissociation at higher draw solution concentrations.

The suitability of OACs as draw solutes was determined via FO. Fig. 2 shows the FO performance of 1 M OACs using both TFC-PES₁ and TFC-PES₂ hollow fiber membranes under the PRO mode (draw solution facing the selective layer) and DI water as the feed. The two membranes were prepared using different dope formulations and spinning conditions as described elsewhere.^{23,24} Both complexes exhibit good performance in terms of high water fluxes and insignificant reverse solute fluxes. Na-Cr-OA outperforms Na-Fe-OA, consistent with the observations in both osmotic pressure and X-ray single crystal structure analyses. The TFC-PES₂ membrane surpasses the TFC-PES₁ membrane under the same conditions in FO. Better performance may be obtained if a more ideal FO membrane is available. In every condition, the amount of OAC lost when treating a 1 L feed solution is negligible with $J_s/J_w \approx 0$. This reveals the advantage of using OACs as draw solutes. To assess the effect of concentration on FO performance, Na-Cr-OA at various concentrations was studied using the TFC-PES₂ membrane. NaCl was also included as a benchmark (Fig. 3). Under all conditions, the water flux increases with increasing draw solute concentration, in line



Fig. 3 Comparison of FO performance between Na–Cr–OA and NaCl: (a) water flux, (b) reverse flux (TFC-PES₂ membrane, feed: DI water).

with the change of osmotic pressure (Fig. S5, ESI[†]). The PRO mode consistently outperforms the FO mode (draw solution facing the support layer) in terms of water flux. Interestingly, Na–Cr–OA outperforms NaCl under the PRO mode but is inferior to NaCl under the FO mode at high concentrations. This is due to the low diffusion coefficient of Na–Cr–OA because of its large structure. Thus, it has more severe internal concentration polarization than NaCl. However, Na–Cr–OA has an insignificant reverse flux compared to NaCl. As a consequence, the replenish cost for Na–Cr–OA as a draw solute is minimal and the feed contamination can be significantly avoided. These unique characteristics are essential for protein enrichment because proteins can be denatured easily by salts.⁶

To study protein enrichment via FO, both Na-Cr-OA and NaCl at 1.0 M were used to concentrate bovine serum albumin (BSA) solutions under the PRO mode. Fig. S6 (ESI[†]) shows a comparison of the changes of BSA concentration over time. After 3 hours, the enrichment percentages are 52.5% and 32.5% for Na-Cr-OA and NaCl, respectively, consistent with the observation when using DI water as the feed (Fig. 3), Na-Cr-OA is more efficient than NaCl to enrich the protein solution. The possible structural change of BSA after FO was determined by CD measurements (Fig. 4). The CD spectra show no significant difference between the original and the concentrated BSA enriched by Na-Cr-OA, demonstrating that BSA remains intact in its configuration. In contrast, there is a noticeable detour in the CD spectra of BSA concentrated by NaCl. The BSA undergoes significant conformation changes after the FO process due to the effects of severe reverse NaCl flux.⁶ Therefore, Na-Cr-OA exhibits another advantage as a draw solute in protein enrichment.

Fig. 5 displays the water flux and solute rejection as a function of Na–Cr–OA concentration *via* an NF process. The details of the pressure-driven NF process has been depicted elsewhere.^{18,21} Both water production and rejection decrease with increasing feed concentration as a result of reduced effective driving forces. Concentration polarization and membrane fouling may also contribute to the reduction. Nevertheless, a solute rejection of more than 97% is achieved when the Na–Cr–OA concentration increases from 0.05 to 0.19 M over 3.6 hours. The recycled OACs have been reused and show the same FO performance as the fresh OACs. To further concentrate the draw solution and



Fig. 4 CD spectra of original and concentrated BSA via FO.



improve the water productivity, one may explore other suitable NF membranes and study other membrane processes such as membrane distillation.^{7,10}

In summary, OACs were synthesized *via* a facile but efficient one-pot reaction. Their unique features such as expanded structure, high solubility and ionizability in water enable them to be used as draw solutes with excellent FO performance superior to the conventional NaCl draw solute. OACs are especially efficient for protein enrichment *via* FO without denaturing proteins. They can be easily regenerated by an NF process. Their performance can be further improved if a more ideal FO membrane is available. This encouraging outcome demonstrates the suitability of OACs as draw solutes for FO processes and inspires future exploration of novel draw solutes for protein enrichment.

This research is supported by the National Research Foundation, Prime Minister's Office, Singapore, under its Competitive Research Program entitled, "Advanced FO Membranes and Membrane Systems for Wastewater Treatment, Water Reuse and Seawater Desalination" (grant number: R-279-000-336-281 and R-278-000-339-281). Special thanks are also given to Mr Chunfeng Wan for his valuable help.

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