Aminated poly(ethylene glycol) methacrylate resins as stable heterogeneous catalysts for the aldol reaction in water

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Article info
Article history:
Received 20 September 2019
Revised 16 November 2019
Accepted 18 November 2019

Keywords:
Aminated PEGMA
Aldol reaction
Heterogeneous catalysis
Water
Continuous-flow

Abstract
Amine functionalized silicas have frequently been investigated as potential aldol reaction catalysts. However, active site leaching due to hydrolysis cannot be avoided, limiting the long-term stability of these catalysts in aqueous aldol reactions. Therefore, novel catalysts based on an organic resin have been developed starting from a suspension polymerized poly(ethylene glycol) methacrylate (PEGMA) hydrogel with poly(ethylene glycol) dimethacrylate (PEGDMA) as cross-linker. Amine functionalization was performed by chlorination of the terminal hydroxyl groups in the resulting PEGMA resin and subsequent nucleophilic substitution with an amine precursor, i.e., ethylenediamine (EDA), N,N-dimethylethlenediamine (DED), or methylamine (MA). The successful synthesis of the catalysts was confirmed by 13C NMR, FT-IR, and elemental CHN analysis. Performance evaluation in a batch reactor for the aqueous aldol reaction of acetone with 4-nitrobenzaldehyde resulted in a turnover frequency (TOF) of the PEGMA-EDA catalyst amounting to 6.3 ± 0.4 s⁻¹, which is of the same order of magnitude as that of the corresponding state-of-the-art amine functionalized silica evaluated using hexane as solvent. The PEGMA-DED catalyst exhibited a somewhat lower TOF of 3.1 ± 0.2 s⁻¹, while the PEGMA-MA catalyst did not exhibit any turnover, indicating that the secondary amine in the backbone of the active site in the PEGMA-EDA catalyst is inactive. Continuous-flow evaluation of the PEGMA-EDA catalyst in a packed-bed reactor indicated that, as opposed to a primary amine functionalized silica catalyst, a stable catalytic activity as a function of time on stream could be achieved for at least 8 h and, hence, that no deactivation has occurred in this timeframe.

1. Introduction
Aldol reactions establish carbon-carbon bonds between two carbonyl-containing species and are widely used to synthesize more complex organic molecules from simpler ones. They are typically used in the synthesis of fine chemical [1] and pharmaceutical [2] components. A potential new application is situated in the bio-based industry for the production of liquid fuels from lignocellulosic biomass resources [3]. At present, commercially implemented aldol reactions are typically catalyzed by homogeneous strong bases. Despite their adequate activity, these catalysts are dangerous to handle, pose an environmental risk, and are deactivated upon separation from the product stream [1]. Heterogeneous alternative catalysts with primary or secondary amine sites, particularly those grafted on a mesoporous silica surface, have often been investigated for the model aldol reaction of acetone with 4-nitrobenzaldehyde [4–9]. Secondary amines are generally preferred as active sites when the reaction is performed in an organic solvent, because on primary amines, stable imines of both 4-nitrobenzaldehyde and acetone can form in substantial amounts, leading to active site inhibition, and tertiary amines cannot form the crucial enamine intermediate [4,7]. With secondary amines, care should also be taken that the substituent does not cause a too large steric hindrance [4,10]. Hence, the methylaminopropyl functional group is currently reported as resulting in the highest activity [4]. With water as solvent, imine formation on primary amines was found to be less of an issue [11,12]. In turn, the...
formation of an inhibiting stable iminium ion on secondary amines has been hypothesized to occur to a significant extent in an aqueous environment, resulting in primary amines actually outperforming secondary amines [11]. Water is also advantageous as a solvent, because it is cheap, readily available and not toxic [13]. However, the current state-of-the-art amine functionalized silica catalysts are not stable in water, due to the hydrolysis of Si–O–Si bonds [14,15], which results in structural degradation of the mesoporous silica material and active site leaching [16]. There is, hence, a need for more hydrothermally stable heterogeneous amine catalysts for application in aqueous aldol reactions.

Organic support materials do not contain any Si–O–Si bonds and will thus not be subjected to the same hydrolysis reactions as silica-based materials. Polystyrene is an example of a polymer for which a plethora of different supported L-proline catalysts have already been developed and evaluated in the aqueous aldol reaction [17–24]. Polystyrene is chosen as polymer support for these catalysts, because a hydrophobic environment could be created around L-proline, which is otherwise inactive in water [19,25]. However, no clear information has been reported about the stability of these catalysts, as it is often not reported at all or only reported at complete reagent conversion in repeat batch experiments, which does not provide information about the kinetics of deactivation [26–28]. Other types of amine functionalized organic catalysts, e.g., with intermolecular promoting groups, have also been developed. Hoyt et al. [29] synthesized cooperative acid-base polystyrene polymers with primary amines that were promoted by neighboring hydroxyl or carboxylic acid groups. However, the hydrophobic polymer material could not sufficiently swell in the reaction environment, which resulted in a poor accessibility of the catalytic sites. More recently, Ellebracht et al. [30,31] used cellulose nanocrystals as organic support to create either monofunctional primary amine catalysts, or amine catalysts that are intermolecularly promoted by cooperative acid groups. However, relatively slow aldol reactions were achieved in water/acetone reaction mixtures for the unpromoted catalyst [30]. The promoted catalysts, which were evaluated in an acetonitrile/acetone solvent mixture, exhibited a much higher activity but a poor recyclability [31], likely due to a strong binding of 4-nitrobenzaldehyde in the form of imines on the active site. Recent work has also shown that the primary amines, present in the biopolymer chitosan, are stable in the aqueous aldol reaction but lack an adequate activity [32]. The currently available heterogeneous aminated polymer based catalysts are, hence, either unstable or exhibit a poor activity as compared to the silica-based materials.

In this work, a stable heterogeneous amine functionalized hydrophilic organic resin is developed. A tailored extent of cross-linking ensures that the polymer does not dissolve in the reaction mixture, while preserving the possibility to swell and as such guarantee the active sites accessibility [33]. However, to adequately swell in the reaction mixture, which is in this case a mixture of water as solvent and acetone as excess reagent, it is vital that the polymer is hydrophilic. Hence, the catalysts are based on polyethylene glycol (PEG), which is described as a ‘chameleon type’ polymer, because it has both hydrophilic and hydrophobic properties [34]. As a crosslinked resin, it will swell in water, acetone, ethanol as well as toluene, methylene chloride, and many organic solvents [34]. This versatile swelling behavior allows to efficiently synthesize the catalyst in a dry organic solvent, while allowing the use of its catalytic properties in the aqueous aldol reaction. Combined with its stability under the typical reaction conditions used in the aldol reaction [35], and easy functionalization [36], PEG derived catalysts appear very attractive.

PEG polymers with an average Mn between 360 and 520 and one or two methacrylate endgroups are commercially available, and are respectively denoted as poly(ethylene glycol) methacrylate (PEGMA) or poly(ethylene glycol) dimethacrylate (PEGDMA). A combination of these monomers will then be polymerized via the methacrylate functions into resins via a free-radical suspension polymerization [37]. The endgroups of these polymers are hydroxyl groups, as displayed in Fig. 1.

2. Procedures

2.1. Synthesis and characterisation of PEGMA catalysts

The first step in the catalyst preparation is the synthesis of a cross-linked poly(ethylene glycol) methacrylate resin as displayed in Fig. 1. This synthesis occurs via a suspension polymerization, displayed in Scheme 1, step 1, as described by Tuncel et al. [37]. A stabilizer, PVP (Sigma-Aldrich, K30, MW 40000) is dissolved in 40 mL deionized water for the preparation of the continuous phase. The disperse phase was prepared by mixing 5.5 mL cyclohexanol (Sigma-Aldrich, ReagentPlus, 99%) with 2.0 mL octanol (Acros, 99%), 4.0 mL poly(ethylene glycol) methacrylate (Sigma-Aldrich, average Mn 360) and 0.6 mL poly(ethylene glycol) dimethacrylate (Sigma-Aldrich, average Mn 750). The initiator BPO (0.12 g, Luperco A98, reagent grade, ≥98%) was then dissolved in this homogeneous solution. The disperse phase was added to the continuous phase in a 50 mL glass flask and stirred at 450 rpm for 4 h at 85 °C and for 1 h at 90 °C. After completion, swellable resin beads were obtained which were washed twice with acetone (VWR, 98.5%) and dried overnight on a high vacuum line at 50 °C.

In the next step, the dried hydrogel beads were covered completely with 40 mL dry toluene (Sigma-Aldrich, anhydrous, 99.8%), 0.3 mL of thionyl chloride (Sigma-Aldrich, >99%, Reagent-Plus) and 0.33 mL pyridine (JT Baker, ACS Reagent, 99.8%). The targeted chlorine loading was 0.81 mmol g⁻¹, corresponding to a 30% replacement of the hydroxyl groups. This mixture was stirred for 4 h at 75 °C before being filtered off, washed twice in ethanol (Koptec, 200 proof), and dried overnight on a high vacuum line at 50 °C. To produce a 100% chlorine substituted material (100-PEGMA-Cl), which, in Section 3.1 is used to ensure a higher resolution in the characterization steps, 1.0 mL of thionyl chloride and 1.1 mL of pyridine was used.

Finally, in the last step in Scheme 1, amine and diamines as displayed in Fig. 2 are introduced on the material by Sₙ₂ nucleophilic substitution of the chlorine group. For this, either 5 mL ethylenediamine (Sigma-Aldrich, 99%, ReagentPlus) or 3 mL N,N′-dimethylethlenediamine (Alfa Aesar, 95%) or 15 mL methylamine (2.0 M in THF, Sigma Aldrich) is added to the resin beads dissolved in dry toluene. An equivalent molar amount of di-isopropylethylamine (DIPEA,
Sigma-Aldrich, >99%, ReagentPlus) is added as HCl scavenger. Grafting of the diamines is performed at reflux temperature (110°C) for 24 h, grafting of methylamine is performed at 40°C for 48 h. Afterwards, the obtained catalysts are washed twice in 200 mL ethanol and dried at 50°C on a high vacuum. To obtain a highly functionalized PEGMA-EDA material, which will not be catalytically evaluated but is used in Section 3.1 to obtain a material with a high resolution for characterization, 25 mL of ethylenediamine (Sigma-Aldrich, 99%, ReagentPlus) was used.

CHN analysis of PEGMA catalysts was performed by Atlantic MicroLabs. The active site loading is determined as the concentration of amine groups for the methylamine functionalized catalyst (PEGMA-MA), and half of the concentration of amine groups for the diamines (PEGMA-EDA and PEGMA-DED). Non-spinning Direct Polarization (DP) 13C Nuclear Magnetic Resonance (NMR) spectra were recorded at 60°C with a Bruker AVIII-300. Fourier Transform-Infrared (FT-IR) transmission spectroscopy was performed with a Nicolet iS10 Spectrometer. SEM images of the resin beads were collected with a Hitachi SU 8010 scanning electron microscope.

2.2. Synthesis and characterization of the aminated mesoporous silica catalyst

To compare the stability of the developed PEGMA resin catalyst to the state-of-the-art aminated mesoporous silica, a primary amine functionalized mesoporous silica catalyst (Silica-APS) was synthesized according to the well-known literature procedures [4,7,16,38]. Silicagel 60 (grade 7734, Sigma-Aldrich, pellet diameter between 250 µm and 500 µm) was first heated to 700°C (heating rate of 2°C min⁻¹) and kept at this temperature for 6 h. Afterwards, the silica support is cooled to 120°C and 5 g is diluted in 30 mL toluene (extra dry, Acros). Next, the silane [3-(aminopropyl)trimethoxysilane (98%, APTES, ABCR) is added with a targeted amine loading of 0.3 mmol g⁻¹. The volume of silane required is calculated by assuming the number of free silanols equals 1.1 OH nm⁻² after calcination at 700°C [39]. Subsequently, the mixture is refluxed at 110°C for 24 h under an argon atmosphere. Filtration is then performed to recover the solid sample, followed by washing with chloroform (>99.8%, Roth, <50 ppm H₂O) and drying in vacuum for 24 h at room temperature.

The concentration of amine groups, corresponding to the concentration of active sites, was determined via elemental (CHN) analysis. These measurements were performed on a Thermo Flash 2000 elemental analyzer using V₂O₅ as catalyst, in order to ensure the total oxidation of the sample. The mass percentage of nitrogen in the sample is obtained by referring the obtained peak area to a calibration curve of methionine (USP, 99%) that was obtained prior to the measurements.

2.3. Performance evaluation

The catalyst performance is evaluated for the aldol reaction of acetone (99.6%, Acros) with 4-nitrobenzaldehyde (99%, Acros), resulting in 4-hydroxy-4-(4-nitrophenyl)butan-2-one as aldol product and 4-(4-nitrophenyl)-3-buten-2-one as enone product, see Scheme 2. This reaction was selected because it is the typical benchmark aldol reaction [6,38,40] of which the effects of solvent [11], water [16], type of active site [7] and cooperative effects [4] are well-known.

2.3.1. Batch reactor

The catalyst performance was initially evaluated in a batch-type reactor (Parr 4560 mini, 300 mL), of which the procedure has been reported in previous work [4,16]. The reactor was loaded with an amount of catalyst equivalent with 0.06 mmol active amine sites, 55 g water as solvent and 0.25 g methyl 4-nitrobenzoate (>99%, Sigma-Aldrich) as internal standard. This mixture was then heated to 55°C, under constant stirring. Acetone (45 g) was separately added as HCl scavenger. Grafting of the diamines is performed at reflux temperature (110°C) for 24 h, grafting of methylamine is performed at 40°C for 48 h. Afterwards, the obtained catalysts are washed twice in 200 mL ethanol and dried at 50°C on a high vacuum. To obtain a highly functionalized PEGMA-EDA material, which will not be catalytically evaluated but is used in Section 3.1 to obtain a material with a high resolution for characterization, 25 mL of ethylenediamine (Sigma-Aldrich, 99%, ReagentPlus) was used.
heated to 55 °C and was used to dissolve 0.45 g 4-nitrobenzaldehyde prior to injection in the reactor. The reaction mixture was mechanically stirred at 400 rpm. The time of injection was taken as the start of the reaction (t = 0). The reaction was monitored for 240 min by taking a sample (0.3 mL) of the reaction mixture every 15 min during the first hour and, subsequently, every 30 min for the remaining 3 h. For each experiment, the total decrease of reaction volume due to sampling was less than 5% whereby the effect of sampling on the kinetic data is considered to be negligible. The turnover frequency (TOF) in the batch reactor was determined from the slope of the initial linear part of the conversion of 4-nitrobenzaldehyde as a function of reaction time, the concentration of active amine sites and the initial concentration of 4-nitrobenzaldehyde [28].

2.3.2. Continuous-flow reactor
The stability of the PEGMA-EDA and aminated mesoporous silica catalyst was evaluated in a plug-flow reactor [28], of which the operating procedure has been reported in previous work [16], with a site time of 544 mol$_\text{site}$ s mol$^{-1}$ 4NB. Before loading into the reactor, the PEGMA resin catalyst was swollen in deionized water for 30 min. The feed mixture was composed of 0.45 wt% 4-nitrobenzaldehyde, 44.6 wt% acetone, 54.5 wt% water and 0.25 wt% methyl-4-nitrobenzoate as internal standard.

2.3.3. Sample analysis
The reaction samples were analyzed using a reversed-phase high-performance liquid chromatograph (RP-HPLC), from Agilent (1100 series) on a XDB-C18 column [16]. The HPLC was operated at 30 °C using a gradient method with water (0.1% trifluoroacetic acid, Acros) and 30 v% to 62 v% acetonitrile (HPLC grade, Acros) as solvents. This method separates all the components in a period of 14 min. The components were identified using a UV-detector with a variable wavelength that has been programmed for an optimal absorption for each component. Quantification of the different components in the reaction mixture was performed by relating the peak surface areas of the components to the amount and peak area of the internal standard added to the reactor.

3. Results and discussion

3.1. Catalyst characterization and validation of synthesis procedure

SEM images of the PEGMA resin beads are displayed in Fig. 1S in the Supplementary Information and indicate that spherical beads in the order of 100 μm are indeed formed in the suspension polymerization. As indicated in Fig. 3(a), the DP $^{13}$C NMR of the pristine resin exhibits all the characteristic peaks of polymerized PEGMA, even though the peaks at 43.4 ppm and 47.4 ppm appear to be overlapping and are not individually distinguishable. The first functionalization step is the reaction with thionyl chloride, which, as can be observed in Fig. 3 (b), reduces the intensity of the peak at 61.3 ppm, corresponding to a carbon attached to a hydroxyl group, and increases the peak around 43.6 ppm, corresponding to a carbon attached to Cl. There is some overlap with the peak related to the polymerized methacrylate carbon atom at 47.4 ppm, but a clear shift in the maximum and intensity was found after chlorination. No other peaks have shifted, or appeared. For comparative purposes, the $^{13}$C NMR spectrum of a 100% chlorinated PEGMA material is given in the Supplementary Information Fig. 2S. It is evident from this figure that the peak of a carbon attached to a hydroxyl group, at 61.3 ppm, has entirely disappeared in favor of a larger peak at 43.6 ppm corresponding to C-Cl. While such a highly functionalized material is not used for catalytic purposes, it indicates that the resin can sufficiently swell in dry toluene to allow access to all the hydroxyl sites.

The FT-IR spectrum in Fig. 4 supports the conclusions drawn above. The characteristic peaks associated with the C=H, C=O and C−O vibrations in the polymerized PEGMA molecule are the
most intense and respectively appear at 2900 cm\(^{-1}\), 1720 cm\(^{-1}\) and 1100 cm\(^{-1}\) in Fig. 4(a). The spectrum of the partially chlorinated 30-PEGMA-Cl in Fig. 4(b) shows that the peak associated with hydroxyl groups in PEGMA, around 3500 cm\(^{-1}\), reduces upon reaction with thionyl chloride in favor of a C–Cl peak at 660 cm\(^{-1}\). The spectrum of a 100% chlorinated PEGMA material, as displayed in the Supplementary Information Fig. 3S, indicates a complete loss of the hydroxyl groups in PEGMA, around 3500 cm\(^{-1}\) and an increase in the C–Cl peak at 660 cm\(^{-1}\). No other peaks have appeared or changed shape. There is, hence, no obvious indication that any other than the desired reaction occurred.

Next, the partially chlorine functionalized 30-PEGMA-Cl materials were subject to nucleophilic substitution with a symmetrical diamine to produce the desired catalysts. Reaction with ethylenediamine (EDA) resulted in the PEGMA-EDA catalyst, reaction with N,N\(_2\)-dimethylethylenediamine (DED) resulted in the PEGMA-DED catalyst. The achieved loading is reported in Table 1. While the active site loadings are lower than the targeted loading, the obtained catalysts do allow to assess and compare the activity and stability of the amine sites in the aldol reaction. Fig. 5 and Fig. 6 respectively show the DP \(^{13}\)C NMR results of the PEGMA-EDA and PEGMA-DED catalysts including the peak assignment to the functionalized groups. While there appear peaks in the expected region in the \(^{13}\)C NMR profile, different individual assignment is difficult due to their low intensity. This is due to the relatively low diamine loading (~0.3 mmol \(g^{-1}\)) of the catalysts. The same issue causes the FT-IR spectra of the PEGMA-EDA and PEGMA-DED catalysts to be indistinguishable from the unfunctionalized PEGMA material, as displayed in the Supplementary Information Fig. 4S. However, \(^{13}\)C NMR and FT-IR characterization results of a high-loaded PEGMA-EDA, with a 2.1 mmol \(g^{-1}\) diamine loading corresponding to 88% of the available hydroxyl groups being replaced with EDA, are displayed in Figs. 5S and 6S. The peaks associated with the primary diamine of this high-loaded material are clearly visible in the spectra. Even though this high-loaded material is not evaluated for its catalytic activity because the amine groups would severely sterically hinder each other, it indicates that the desired functionalization indeed occurs under the employed experimental conditions and that there is no indication of undesired side-reactions taking place.

In order to investigate the possible catalytic activity of the secondary amine in the EDA chain of the PEGMA-EDA catalyst, functionalization with methylamine (MA) is also performed to produce PEGMA-MA. In the DP \(^{13}\)C NMR and FT-IR spectra corresponding to this material, no clear peaks relating to the methylamine group can be distinguished due to the low mass percentage of methylamine and the low intensity of secondary amine vibrations in FT-IR. However, its loading as determined from the nitrogen elemental analysis is reported in Table 1 and proves that amine functionalization has occurred.

To compare the stability of the developed catalysts against the state-of-the-art amine functionalized silica catalysts, a primary amine functionalized silica catalyst (Silica-APS) is synthesized according to literature procedures [4] and its active site loading is also reported in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Active site loading ± 5% (mmol (g^{-1}))</th>
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<tr>
<td>PEGMA-EDA</td>
<td>0.43</td>
</tr>
<tr>
<td>PEGMA-DED</td>
<td>0.28</td>
</tr>
<tr>
<td>PEGMA-MA</td>
<td>0.24</td>
</tr>
<tr>
<td>Silica-APS</td>
<td>0.26</td>
</tr>
</tbody>
</table>

3.2. Performance evaluation

Experiments with methylamine functionalized PEGMA-MA yielded no measurable 4-nitrobenzaldehyde conversion, as reported in Table 2. This indicates that the secondary amine, which is formed at the anchoring point to the PEGMA backbone material in the PEGMA-EDA catalyst, is not catalytically active. This is possibly related to the severe steric hindrance that is encountered by

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>TOF (s(^{-1}))</th>
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<tbody>
<tr>
<td>PEGMA-EDA</td>
<td>6.3 ± 0.4 (10^{-4})</td>
</tr>
<tr>
<td>PEGMA-DED</td>
<td>3.1 ± 0.2 (10^{-4})</td>
</tr>
<tr>
<td>PEGMA-MA</td>
<td>0.0</td>
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</tbody>
</table>
the amine site from the neighboring PEG chains. Nucleophilic substitution with \( \text{N}_2\text{N}’\text{-dimethylenediamine} \) generated a tertiary amine which is known to be inactive due to its inability to form an enamine intermediate [4]. Hence, the only catalytically active sites on the PEGMA-EDA and PEGMA-DED catalysts are, respectively, the terminal primary amine and the terminal secondary amine.

Both the PEGMA-EDA and PEGMA-DED catalysts are evaluated for the aldol reaction in a batch reactor and their activity curves are displayed in Fig. 7 in the Supplementary Information. The TOF exhibited by the secondary amine functionalized PEGMA-DED amounts to \( 3.1 \pm 0.2 \cdot 10^{-4} \text{ s}^{-1} \), while that by the PEGMA-EDA amounts to \( 6.3 \pm 0.4 \cdot 10^{-4} \text{ s}^{-1} \). This observation indicates that, in contrast to when an organic solvent such as hexane is used [4,7], primary amine sites are more active with water as solvent than the secondary amine sites [11]. This has been reported previously by Kandel et al. [11] and is attributed to the presence of water shifting the equilibrium away from the inhibiting imine on primary amines while also promoting the formation of inhibiting iminium ions on secondary amines. While comparison with literature reported turnover frequencies should be performed carefully, due to different reaction conditions, the obtained TOF for the PEGMA-EDA catalyst is 4 times higher than the state-of-the-art primary amine functionalized mesoporous silica catalyst that was evaluated in water [12], and is comparable to the TOF of this primary amine functionalized silica catalyst evaluated in hexane [4]. This difference in activity for both catalysts using water is most likely related to a difference in adsorption behavior in the catalyst pores resulting in a different local polarity environment [12,41,42].

![Graph](image)

**Fig. 7.** Conversion as a function of time on stream for the PEGMA-EDA catalyst (●) and the Silica-APS catalyst (●) in the aldol reaction of acetone with 4-nitrobenzaldehyde. (\( T = 55 ^\circ \text{C} \), \( P = 180 \text{ kPa} \), site time = \( 544 \text{ mol}_{\text{cat}}.\text{s}.\text{mol}^{-1} \), 0.45 wt% 4-nitrobenzaldehyde, 44.6 wt% acetone, 54.5 wt% water, 0.25 wt% IS). Line is a guide for the eye.

### 3.3. Comparison of PEGMA-EDA stability to the state-of-the-art aminated silica

Reusability of the PEGMA catalysts was not evaluated in the Parr® batch reactor because the small resin beads were difficult to completely recover after a first run. To avoid errors while filtering and recycling a catalyst in consecutive batch tests, the stability of the PEGMA-EDA catalyst has been evaluated in a packed-bed plug-flow reactor [28] and is compared at the same reaction conditions, to the stability of the current state-of-the-art primary amine functionalized mesoporous silica catalyst. The catalytic activity, expressed as 4-nitrobenzaldehyde conversion, versus time on stream is displayed in Fig. 7 for both catalysts.

The PEGMA-EDA catalyst exhibited a constant conversion as a function of time on stream for at least 8 h. On the other hand, at these reaction conditions, the state-of-the-art primary amine functionalized mesoporous silica exhibited an initial activity that is almost 4 times lower than that of the PEGMA-EDA catalyst, as could be expected from the TOF results in the batch reactor. Additionally, it can be observed the amine functionalized mesoporous silica loses most of its activity in the first 3 h on stream, which is likely caused by leaching of the active sites [14,16]. This is attributed to the large amounts of water present in the reactor. Clearly, these reaction conditions are far from optimal for the activity and stability of the Silica-APS catalysts in the aldol reaction. However, water was previously found to be required for these catalysts to prevent site-blocking species being formed on the amine sites [16]. Yet, deactivation by hydrolysis and subsequent leaching of active sites remained an inherent problem with amine functionalized mesoporous silica catalysts. This was shown in our previous experimental work, where a lower water contents in an organic solvent such as DMSO [16] also resulted in deactivation with time on stream, albeit to a lesser extent, i.e., losing about a third of its activity in the first 10 h on-stream. On the contrary, in this work the PEGMA-EDA catalyst appears to exhibit a much better resistance against deactivation during the aldol reaction even when exposed to high water concentrations. This clearly demonstrates the potential of amine functionalized resin catalysts. Moreover, in contrast to the more widely used polystyrene resin catalysts [29], the catalyst developed in this work sufficiently swells in high-polarity solvents such as water to allow access to the active sites, resulting in a TOF that can rival with the current state-of-the-art materials [4,12,31]. Hence, the developed catalyst based on PEGMA resins opens up bright perspectives for future application in reactions using water as solvent.

### 4. Conclusions

For the first time, a highly active heterogeneous amine catalyst is developed that exhibits a stable activity in the continuous-flow aldol reaction of acetone with 4-nitrobenzaldehyde. The catalyst support material was synthesized via a free radical suspension polymerization of a (polyethylene glycol) methacrylate (PEGMA) monomer and poly(ethylene glycol) dimethacrylate (PEGDMA) as cross-linker. Chlorine functionalization of a part of the hydroxyl groups was performed with thionyl chloride. Subsequent amine functionalization was then performed by nucleophilic substitution of different diamines and amines on the partly chlorinated material. The successful chlorination and amine functionalization was confirmed by \(^{13}\text{C} \) NMR and FT-IR measurements, which yielded no indications of undesired side-reactions taking place during the catalyst synthesis. Elemental CHN analysis was performed to quantify the active sites.

Functionalization was performed with ethylenediamine (EDA), N,N-dimethylethylenediamine (DED) and methylamine (MA) respectively resulting in a primary amine catalyst and two secondary amine catalysts. Evaluation of their kinetic performance was done in a batch reactor for the aldol reaction of acetone with 4-nitrobenzaldehyde using 50 vol% water as solvent and 50 vol% acetone as excess reagent. The PEGMA-MA catalyst did not exhibit any turnover, indicating that the secondary amine in the backbone of the active site on the PEGMA-EDA catalyst is most likely not contributing to the observed activity. A TOF of \( 6.3 \pm 0.4 \cdot 10^{-4} \text{ s}^{-1} \) was reported for the PEGMA-EDA catalyst, which is in the same range as the currently best performing promoted heterogeneous amine catalysts that were evaluated in hexane, and \( 3.1 \pm 0.2 \cdot 10^{-4} \text{ s}^{-1} \) for the PEGMA-DED catalyst.

The most active PEGMA catalyst, i.e. the PEGMA-EDA catalyst, was also evaluated in a packed-bed continuous-flow reactor under the same reaction conditions as the batch reactor and exhibited a stable conversion with time on stream for at least 8 h, indicating...
stable catalyst behavior. This is in stark contrast with the current state-of-the-art primary amine functionalized mesoporous silica catalysts which exhibited a lower activity and deactivated completely after only 3 h on stream under the same reaction conditions. The developed PEGMA-based catalysts, hence, open up new perspectives for the application in continuous-flow aldol reactions using water as solvent.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Acknowledgment

The authors acknowledge financial support from the Research Foundation - Flanders (FWO) through Grant Number V401719N and the European Research Council under the European Union’s Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 615456. J.L. is a postdoctoral fellow of the Research Foundation - Flanders (FWO) (1222218N). C.W.J. acknowledges support from the United States Department of Energy, Basic Energy Sciences through Catalysis Science contract DE-FG02-03ER15459.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2019.11.027.

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