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## Driving an equilibrium acetalization to completion in the presence of water

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Formation of an acetal from a carbonyl substrate by condensation with an alcohol is a classical reversible equilibrium reaction in which the water formed must be removed to drive the reaction to completion. A new method has been developed for acetalization of carbonyl substrates by diols in the presence of water. Complexation of poly(4-styrenesulfonic acid) with poly(4-vinylpyridine) generates a catalytic membrane of polymeric acid at the interface between two parallel laminar flows in a microchannel of a microflow reactor. The catalytic membrane provides a permeable barrier between the organic layer and water-containing layer in the reaction, and permits discharge of water to the outlet of the microreactor to complete the acetalization. Condensation of a variety of carbonyl substrates with diols proceeded in the presence of water in the microflow device to give the corresponding acetals in yields of up to 97% for residence times of 19 to 38 s.

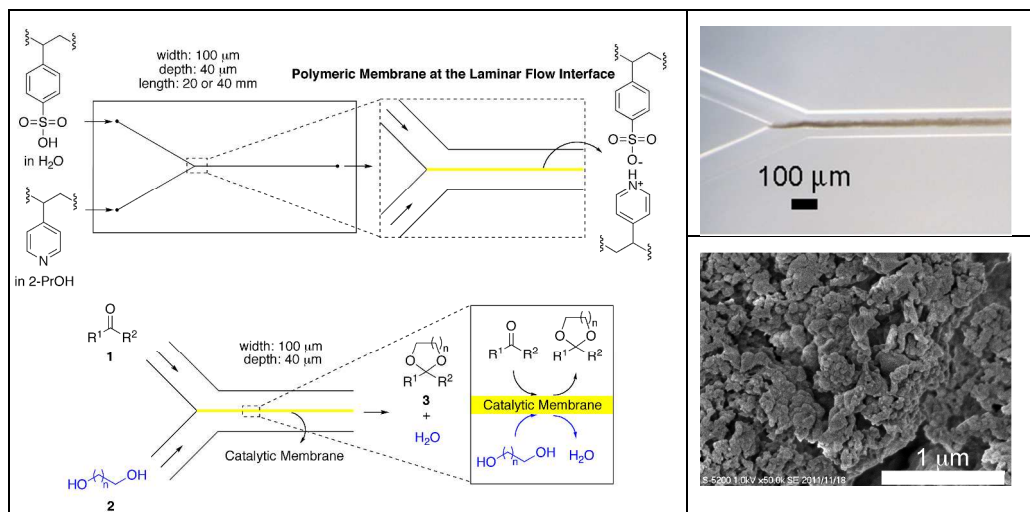
### Introduction

It is widely accepted in the chemical and biochemical literature that equilibrium constants for reversible catalytic, noncatalytic, and enzymatic chemical reactions all have constant values. Under equilibrium conditions, the concentrations of the products reach steady values that are determined by entropy.<sup>1</sup> The acetalization of a carbonyl substrate by an alcohol is a representative example of a reversible reaction that reaches equilibrium.<sup>2,3</sup> This reaction is one of the most basic and classical reversible reactions in organic chemistry in which the products and reactants are in equilibrium. In the case of the reversible reaction of a carbonyl substrate with a diol, the only products are the corresponding acetal and water. To drive the reaction toward completion by shifting the equilibrium, the water that is formed must be removed by physical<sup>4</sup> or chemical methods.<sup>5,6</sup> For example, the standard preparation of the acetal from cyclohexanone (**1a**) and ethylene glycol (**2a**) described in *Organic Syntheses* involves performing the reaction in the presence of 4-toluenesulfonic acid as an acid catalyst in refluxing benzene for six hours with azeotropic removal of water by means of a Dean–Stark condenser; this procedure gives the acetal, 1,4-dioxaspiro[4.5]decane (**3a**), in 75–85% yield (Figure 2b).<sup>4</sup> This is the most basic method for acetal formation. When this reaction is performed at 50 °C under equilibrium conditions without the use of the Dean–Stark condenser, the product **3a** is obtained in a low yield (see below). Therefore, even in classical organic transformations, there are serious problems that need to be overcome

conceptually to permit equilibrium and reversible reactions to proceed to completion.

Recently, microchannel systems that offer many fundamental and practical advantages have been developed for organic transformations.<sup>7–15</sup> By using our molecular convolution methodology, we have been able to fabricate a range of palladium-containing polymeric membrane catalysts inside microchannel reactors at the laminar flow interfaces in the channels.<sup>16–19</sup> A catalytic membrane is formed along the center of a microchannel and then two reactants are introduced from opposite sides of the membrane and flow through the divided channel in contact with the large-area interfacial surfaces of the membrane from the front and the rear, thereby realizing an instantaneous chemical reaction. We surmised that a catalytic membrane inside a microflow reactor might provide a phase barrier between a layer of a solution of a carbonyl compound in an organic solvent and a layer of a diol in an acetalization reaction.<sup>20–24</sup> The dehydrative condensation reaction should proceed under the influence of the driving force of permeation of the reactants through the catalytic membrane, so that the resulting product and water are separated from one another and taken up into the organic solvent and diol layers, respectively. Eventually, water is discharged in the diol layer emerging from the outlet of the catalytic membrane-containing microflow reactor, driving the equilibrium in the direction of completion of the acetalization reaction (Fig. 1, left). We developed a novel microchannel reactor containing a catalytic polymer acid membrane at the interface between two parallel laminar layers of reactant and we applied it in the acetalization of a number of carbonyl substrates with several diols in the presence of water

to give the corresponding acetal products in yields of up to 93% within residence times of 19–38 s.



**Fig. 1.** Schematic showing the preparation of the polymeric acid catalyst membrane-containing microchannel reactor (top left) and its application in acetal formation by a flow reaction (bottom left), together with an optical micrograph of the microreactor (top right) and a scanning electron micrograph of the polymeric acid membrane (bottom right).

## Results and discussion

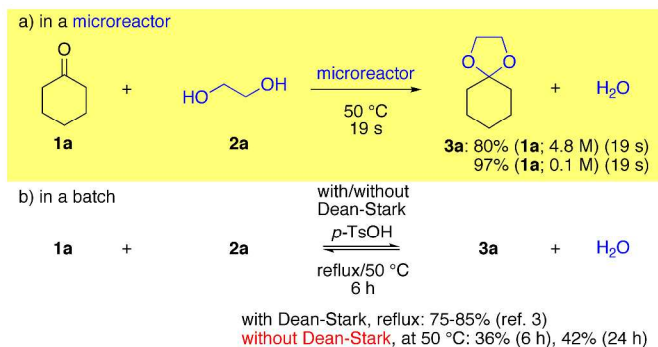
The preparation of the polymeric acid membrane in the microchannel is shown schematically in Fig. 1. Whitesides and co-workers originally reported the deposition of a polymer membrane at a laminar interface between solutions of a sulfonate salt and a polymeric ammonium salt.<sup>25–27</sup> However, to the best of our knowledge, apart from our previous studies,<sup>16–19</sup> there have been no reports in the literature on interfacial deposition of membranes with the aim of using them as catalytic membranes. We formed a catalytic acid membrane inside a glass microchannel reactor with a Y-junction and a channel pattern measuring 100  $\mu\text{m}$  wide, 40  $\mu\text{m}$  deep, and 20 or 40 mm long.<sup>28</sup> A 60 mM aqueous solution of poly(4-styrenesulfonic acid) and a 1.0 mM solution of poly(4-vinylpyridine) in propan-2-ol were continuously injected from syringe pumps into the opposite branches of the Y-shaped microchannel of the microreactor at 24  $^{\circ}\text{C}$  at equal flow rates of 10  $\mu\text{L min}^{-1}$ . A two-phase parallel laminar flow formed in the central microchannel, and a polymeric membrane precipitated at the interface between the two phases. Optical micrographs showed that a sheet of polymeric membrane 20  $\mu\text{m}$  thick, 40  $\mu\text{m}$  high, and 20–40 mm long was formed at the interface between the laminar flows in the microchannel (Fig. 1, right top). A high-resolution scanning electron micrograph revealed that the membrane had a mesoporous structure that provided a large surface area (Fig. 1, right bottom). Elemental analysis indicated that the ratio of poly(4-styrenesulfonic acid) to poly(4-vinylpyridine) in the membrane was 1.75:1. Attenuated total reflectance infrared spectroscopic studies showed that, whereas the C=N stretching absorption of the pyridine ring in poly(4-vinylpyridine) is normally observed at 1470  $\text{cm}^{-1}$ , the

polymeric membrane showed a new absorption peak at 1550  $\text{cm}^{-1}$  and no peak at 1470  $\text{cm}^{-1}$ . This indicated that the pyridine moiety in poly(4-vinylpyridine) had reacted with the poly(4-styrenesulfonic acid) to give the corresponding pyridinium sulfonate salt. The membrane in the microreactor contained 0.02  $\mu\text{mol}/10 \text{ mm}$  of sulfonate. When water at neutral pH was introduced from the inlet and passed through the microflow reactor, the water at the outlet remained at a pH of 7.

Having prepared the polymeric acid membrane-containing microreactor, we proceeded to investigate the formation of an acetal in a flow reaction (Fig. 2).<sup>29–34</sup> Ethylene glycol (**2a**) and a 4.8 M solution of cyclohexanone (**1a**) in toluene were introduced from the opposite branches of the Y-shaped channel into the central membrane-separated channel at 50  $^{\circ}\text{C}$  and a flow rate of 0.2  $\mu\text{L min}^{-1}$  for the cyclohexanone and 0.1  $\mu\text{L min}^{-1}$  for ethylene glycol. The two parallel laminar layers were passed through the membrane-separated channel with a residence time of 19 s. The organic/ethylene glycol microstream that emerged from the channel was collected at the outlet.

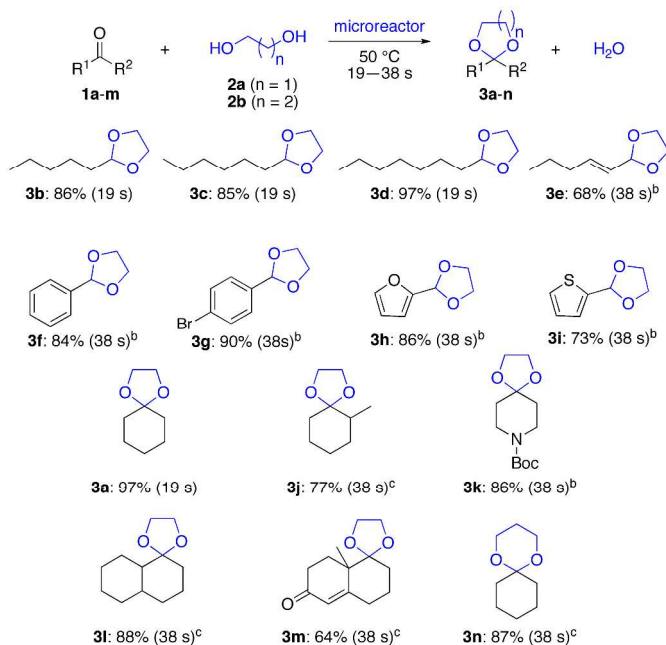
The chemical conversion and the structure of the products were determined by gas chromatography and  $^1\text{H}$  NMR spectroscopy, respectively. We were pleased to find that the microchannel reactor with the poly(4-styrenesulfonic acid)–poly(4-vinylpyridine) membrane successfully promoted the catalytic reaction of ketone **1a** with diol **2a** at 50  $^{\circ}\text{C}$  to give acetal **3a** with 80% yield within a residence time of 19 s.<sup>33,34</sup> A 0.1 M solution of **1a** similarly afforded the acetal in 97% yield. Furthermore, the polymeric acid catalyst-containing microchannel reactor showed superior performance in acetal formation without any additional mechanism for removal of water. The catalytic membrane in the microflow device

provides a phase barrier between the organic solvent and water-containing diol layers, so that the water that forms is discharged from the outlet of the microreactor, driving the formation of the acetal toward completion. In contrast, the formation of the acetal from ketone **1a** with diol **2a** without separation of water in toluene at 50 °C under batch conditions gave **3a** in 36% and 42% yield in 6 and 24 hours, respectively.



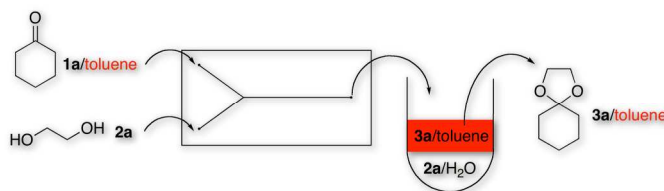
**Fig. 2.** Formation of the acetal in the microreactor and in batch experiments.

We then used the polymeric acid-containing microchannel reactor to prepare acetals from a range of aldehydes and ketones with various diols. The formation of acetals from the aliphatic aldehydes hexanal (**1b**), heptanal (**1c**), and octanal (**1d**) with **2a**, carried out under similar conditions, gave 2-pentyl-1,3-dioxolane (**3b**; 86%), 2-hexyl-1,3-dioxolane (**3c**; 85%), and 2-heptyl-1,3-dioxolane (**3d**; 97%), respectively, within a residence time of 19 s (Fig. 3); no polymerization side reactions were observed. (2*E*)-Hex-2-enal (**1e**) was converted into acetal **3e** in 68% yield at 80 °C and a residence time of 38 s; decomposition of the acid-labile substrate and product as well as deconjugation of the olefin were not detected. The reaction of the aromatic aldehydes benzaldehyde (**1f**) and 4-bromobenzaldehyde (**1g**) with **2a** in the microchannel reactor at 80 °C gave the corresponding 1,3-dioxolanes **3f** and **3g** in 84% and 90% yield, respectively. Hetaryl aldehydes **1h** and **1i** similarly reacted with **2a** to give acetals **3h** and **3i** in 86% and 73% yield, respectively. The reaction of 2-methylcyclohexan-1-one (**1j**) with diol **2a** gave 6-methyl-1,4-dioxaspiro[4.5]decane (**3j**) in 77% yield, and the corresponding reaction of *tert*-butyl 4-oxopiperidine-1-carboxylate (**1k**) gave the 1,3-dioxolane **3k** in 86% yield without damage to the acid-sensitive *tert*-butoxycarbonyl group. The reaction of bicyclic octahydronaphthalen-1(2*H*)-one (**1l**) gave acetal **3l** in 88% yield. The monoacetal from the Wieland–Miescher ketone **1m** gave the corresponding monoacetal **3m** in 64% yield in which no deconjugation of the alkene was observed. The reaction of cyclohexanone (**1a**) with propane-1,3-diol (**2b**) gave the corresponding 1,3-dioxane **3n** in 87% yield.



**Fig. 3.** Formation of acetals from aldehydes or ketones with diols in the polymeric acid catalyst-containing microchannel reactor. *Reaction conditions*: **1** (0.1 M, toluene, flow rate: 0.1  $\mu\text{L min}^{-1}$ ), **2** (neat, flow rate: 0.1  $\mu\text{L min}^{-1}$ ); <sup>a</sup> microchannel reactor (length: 20 mm), 50 °C; <sup>b</sup> microchannel reactor (length: 40 mm), 80 °C; <sup>c</sup> microchannel reactor (length: 40 mm), 100 °C.

The collected stream emerging from the outlet automatically separated to permit isolation of the acetal product with high purity. The upper layer of the collected sample, which consisted of a toluene phase containing the acetal, was decanted by continuous pumping (Fig. 4). Therefore, a desired acetal can be readily and automatically obtained by using our microdevice system without the need to consider any equilibrium and reversible reactions.



**Fig. 4.** Automatic separation of the product stream from the microflow acetalization reaction in the microreactor.

## Conclusions

In conclusion, we have developed a novel catalytic system for equilibrium and reversible reactions. A novel polymeric acid membrane was prepared inside a microchannel reactor at the interface between two laminar flows through ionic interaction of poly(4-styrenesulfonic acid) with poly(4-vinylpyridine). The

microchannel reactor was used to form acetals from various aldehydes and ketones, without additional separation of water, to give the corresponding acetal products. The flow acetalization system permitted automatic separation of the products (which were present in the toluene layer) and water (which was present in the diol layer). Attempts are underway to apply this novel concept to a variety of equilibrium and reversible reactions.

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## Notes and references

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- J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford Univ. Press, Oxford, 2001.
- P. G. M. Wuts, T. W. Greene, *Green's Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, ed. 4, 2006.
- P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, ed. 3, 2005.
- R. A. Dagnault, E. L. Eliel, *Org. Synth., Coll. Vol.* **5**, 1973, 303–304.
- R. Noyori, S. Murata, M. Suzuki, *Tetrahedron* 1981, **37**, 3899–3910.
- J. Otera, N. Dan-oh, H. Nozaki, *Tetrahedron* 1992, **48**, 1449–1456.
- T. With, *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weinheim, 2008.
- J. Yoshida, *Flash Chemistry: Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, Oxford, 2008.
- R. L. Hartman, K. F. Jensen, *Lab Chip* 2009, **9**, 2495–2507.
- B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* 2007, **107**, 2300–2318.
- K. Geyer, T. Gustafsson, P. H. Seeberger, *Synlett* 2009, 2382–2391.
- A. Kirschning, W. Solodenko, K. Mennecke, *Chem.–Eur. J.* 2006, **12**, 5972–5990.
- C. Wiles, P. Watts, *Eur. J. Org. Chem.* 2008, 1655–1671.
- K. Jähnisch, V. Hessel, H. Löwe, M. Baern, *Angew. Chem. Int. Ed.* 2004, **43**, 406–446.
- J. Kobayashi, Y. Mori, S. Kobayashi, *Chem.–Asian J.* 2006, **1–2**, 22–35.
- Y. Uozumi, Y. M. A. Yamada, T. Beppu, N. Fukuyama, M. Ueno, T. Kitamori, *J. Am. Chem. Soc.* 2006, **128**, 15994–15995.
- Y. M. A. Yamada, T. Watanabe, K. Torii, Y. Uozumi, *Chem. Commun. (Cambridge)* 2009, 5594–5596.
- Y. M. A. Yamada, T. Watanabe, T. Beppu, N. Fukuyama, K. Torii, Y. Uozumi, *Chem.–Eur. J.* 2010, **16**, 11311–11319.
- Y. M. A. Yamada, T. Watanabe, A. Ohno, Y. Uozumi, *ChemSusChem* 2012, **5**, 293–299.
- Examples of membrane-based reaction systems or membrane-related reaction systems of acetalizations or similar condensations were shown in references 20–24. C. X. A. da Silva, V. L. C. Gonçalves, C. J. A. Mota, *Green Chem.* 2009, **11**, 38–41.
- I. Agirre, M. B. Güemez, H. M. van Veen, A. Motelica, J. F. Vente, P.L. Arias, *J. Membrane Sci.* 2011, **371**, 179–188.
- J. Ma, M. Zhang, L. Lu, X. Yin, J. Chen, Z. Jiang, *Chem. Eng. J.* 2009, **155**, 800–809.
- A. P. Rathod, K. L. Wasewar, C. K. Yoo, J. Catal. 2014, on web, <http://dx.doi.org/10.1155/2014/539341>
- I. A. Arisketa, *Dissertation in the University of the Basque Country*, 2010.
- P. J. A. Kenis, R. F. Ismagilov, G. M. Whitesides, *Science* 1999, **285**, 83–85.
- B. Zhao, N. O. L. Viernes, J. S. Moore, D. J. Beebe, *J. Am. Chem. Soc.* 2002, **124**, 5284–5285.
- H. Hisamoto, Y. Shimizu, K. Uchiyama, M. Tokeshi, Y. Kikutani, A. Hibara, T. Kitamori, *Anal. Chem.* 2003, **75**, 350–354.
- Purchased from the Institute of Microchemical Technology, Co., Ltd., (Kanagawa, Japan; <http://www.i-mt.co.jp>).
- C. Wiles, P. Watts, S. J. Haswell, *Tetrahedron* 2005, **61**, 5209–5217.
- C. F. Carter, I. R. Baxendale, M. O'Brien, J. B. J. Pavey, S. V. Ley, *Org. Biomol. Chem.* 2009, **7**, 4594–4597.
- C. Wiles, P. Watts, *Chem. Commun. (Cambridge)* 2007, 4928–4950.
- M. Rueping, T. Bootwicha, H. Baars, E. Sugiono, *Beilstein J. Org. Chem.* 2011, **7**, 1680–1687.
- The formation of the acetal did not proceed in the absence of the polymeric acid membrane under similar conditions.
- This result suggests that one tiny flow device could produce 2 moles of **3a** in one year.