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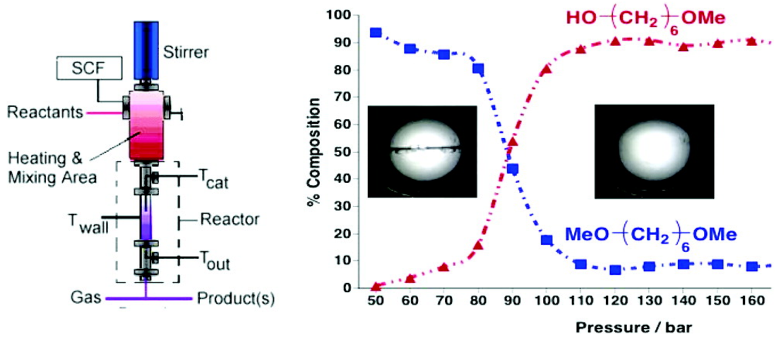
J. Am. Chem. Soc., **2005**, 127 (1), 293-298• DOI: 10.1021/ja044814h • Publication Date (Web): 17 December 2004



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Selective Monoprotection of 1,*n*-Terminal Diols in Supercritical Carbon Dioxide: A Striking Example of Solvent Tunable Desymmetrization

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Abstract: The reaction between 1,*n*-terminal diols ($n = 3$ or 6) with simple alcohols (MeOH, EtOH, and *n*-PrOH) in supercritical CO_2 over an acid catalyst (Amberlyst 15) leads to two possible products, a mono- and a bis-ether. At 150 °C, the selectivity of the reaction with 1,6-hexanediol and MeOH can be switched from 1:20 in favor of the bis-ether at 50 bar to 9:1 in favor of the desymmetrized mono-ether at 200 bar. It is demonstrated that the switch in selectivity is associated with the phase state of the reaction mixture, with monophasic conditions favoring the mono-ether and biphasic conditions favoring the bis-ether. A rationalization of this effect is also presented.

Introduction

Over the past 10 years, there has been a significant expansion in the number and, indeed, the diversity of reactions that have been successfully conducted in supercritical fluid (SCF) systems.[1−5] This rapid chain of developments has been driven by a wide variety of factors, including the following:

(i) The use of SCFs to isolate highly sensitive (labile/unstable) materials that are difficult or impossible to isolate by more traditional methods.[6−11]

(ii) The exploitation of the hybrid properties of SCFs, most notably, the enhanced solubility of gases, lower diffusion coefficients, and moderate heat transfer properties, affords an increase in the rates of reaction, for example, in the catalytic reduction[12,13] of CO_2 with H_2 and the hydrogenation of a wide range of organic substrates.[14−16]

(iii) The use of supercritical CO_2 ($scCO_2$) as a cleaner alternative to conventional solvents (for example, in polymerization reactions).[17]

(iv) The use of the high compressibility of SCFs to tune the outcome of a reaction, particularly attempting to switch the reaction between one product and another merely by changing the pressure.

This tuning of chemical reactions is perhaps the most appealing aspect of SCFs, but there are surprisingly few examples where it has been achieved in practice. For example, in an elegant study on the photodimerization of isophorone, Johnston and co-workers[18] showed that varying the pressure of $scCO_2$ caused a switch between head-to-head and head-to-tail dimers. There have been a number of studies on the shifting of chemical equillibria, for example, in the rotamerization[19,20] or tautomerization[21−23] of many organic molecules. There are a number of examples where variation of the SCF density by manipulation of the reaction pressure has been used to control the chemoselectivity of reactions. Sellin and co-workers report a pressure-dependent switch in the products of Rh-catalyzed hydroformylation of 1-hexene; only aldehydes were formed at pressures above 190 bar, but at lower pressures, alcohols were also observed.[24] Similarly, there are reports of pressure tuning

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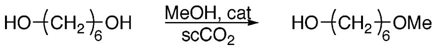
10.1021/ja044814h CCC: $30.25

Scheme 1. Desymmetrization of 1,6-Hexanediol with MeOH (molar ratio of 1:100) Carried Out over the Commercially Available Resin Amberlyst 15



$$HO{-}(CH_2)_6{-}OH \xrightarrow[scCO_2]{MeOH,\ cat} HO{-}(CH_2)_6{-}OMe$$

of the *exo*:*endo* ratios in Diels−Alder-type cycloadditions.[25,26] Perhaps one of the most striking examples of a tunable reaction is the acid-catalyzed diastereoselective oxidation of cysteine and methionine derivatives found by Rayner and co-workers.[27] By varying the density of the SCF, the authors were able to increase the diastereoselectivity of the oxidation to values in excess of 95%. By contrast, when an identical reaction is carried out in conventional solvents, no selectivity is observed at all.

Previously, our group has reported the development of a wide range of selective reaction systems, all carried out continuously by employing $scCO_2$ as the reaction medium. Reactions include hydrogenation,[28,29] Friedel−Crafts alkylation,[30] acid-catalyzed condensation reactions,[31] hydroformylation,[32] and more recently the asymmetric hydrogenation of prochiral olefins.[33] This paper concerns just one of these reactions, the acid-catalyzed etherification of symmetrical 1,*n*-terminal diols with low molecular weight aliphatic alcohols. This reaction was first reported by us some years ago.[31] At that time, the reaction was remarkable because it led to the efficient desymmetrization of the diol by selectively etherifying only one of the chemically equivalent hydroxyl moieties.

Desymmetrization reactions are interesting because they offer the possibility of expanding the range of potential applications for a given starting material. In principle, a wide range of renewable feedstocks, including glucose and other polysaccharides, such as starch, could be processed to yield nonpetroleum-derived building blocks for application in synthesis.[34,35] This requires chemical differentiation between similar functionalities within a molecule, which is not so easy. Traditionally, synthetic chemists approach this problem by employing multistep protecting group strategies.[36] Over the past 15 years, the number of desymmetrization reactions has increased significantly. Successful strategies have been as diverse as elegant catalysis,[37−42] the application of selective enzymatic transformations,[43] controlled extraction using mixed solvent systems,[44,45] or supercritical dimethyl ether.[46]

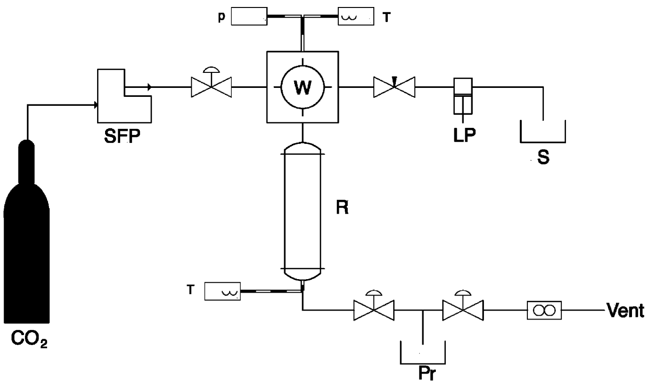


Figure 1. Schematic diagram of the laboratory scale supercritical flow reactor. The CO_2 is pressurized and delivered by a pneumatic reciprocating pump, SFP, running in constant pressure mode [NWA, PM-101]. Organic substrates, S, are delivered at a constant rate via a standard HPLC pump, LP [Anachem, Gilson 305]. All feed streams are mixed in a heated mixer unit fitted with a large aperture sapphire window, W (∅ = 40.0 × 28.5 mm), before being passed through a packed catalyst bed, R (10.00 mL in volume). Products, Pr, are collected between two single stage depressurization valves [NWA, PE-103]; depressurized gases are then vented at this point. T and p are temperature and pressure monitors, respectively.

This paper reports our observation that the desymmetrization of diols in $scCO_2$ (Scheme 1) is an outstanding example of a pressure tunable reaction. In what follows, we investigate the selective alkylation of symmetrical diols in some detail. We examine the reaction of a variety of diols with simple alcohols and demonstrate that the pressure effect is relatively general and that the switch in selectivity between mono- and bis-alkylated products is directly related to the vapor−liquid phase equilibrium in the reaction mixture.

Experimental Section

Safety Note: The experiments described in this paper involve the use of high pressures and require equipment with the appropriate pressure rating. It is the responsibility of individual researchers to verify that their particular apparatus meets the necessary safety requirements. The various components that we describe work well, but they are not necessarily the only equipment of this type available nor are they the most suitable for the purpose.

The apparatus used for the main part of this study is similar to that described previously[31] but with an important modification, the inclusion of a window in the premixer. This sapphire-windowed mixer (NWA GmbH) allows the phase state of the reaction mixture to be viewed immediately upstream from the reactor; a more detailed description of this component is published elsewhere.[47] The principal features of the equipment are shown schematically in Figure 1.

In addition, a number of higher precision experiments were carried out on a much smaller, fully automated instrument, which can be operated continuously for up to 5 days, while collecting aliquots of products at high pressure for direct GLC analysis. Parameters that can be controlled by on-line automation include flow rate of $scCO_2$ (Jasco, PU-1580-CO_2), flow rate of organic substrates (Jasco, PU-980), system pressure (Jasco, BP-1580−81), catalyst bed temperature, and GLC sample rate (Shimadzu, GC17a with an automated in-line, high-pressure

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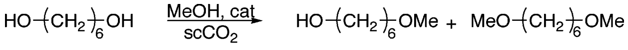
Scheme 2



$$HO{-}(CH_2)_6{-}OH \xrightarrow[scCO_2]{MeOH,\ cat} HO{-}(CH_2)_6{-}OMe + MeO{-}(CH_2)_6{-}OMe$$

1 1m 1b

Table 1. Effect of Changing the Temperature on the % Composition of the Organic Material Recovered from the Reaction of 1,6-Hexanediol (**1**) with MeOH in scCO$_2$[a]

T (°C)	**1** (%)	**1m** (%)	**1b** (%)
110	91	8.5	0.5
120	46	52	2
130	20	71	9
140	7	78	15
150	4	86	10
160	0	44	56
170	0	3	97

[a] All reactions were carried out isobarically (200 bar); CO$_2$ was delivered at a flow rate of 0.65 L min^{-1} (CO$_2$ flow was measured after expansion at STP); organic substrates were delivered volumetrically (0.5 mL min^{-1}) by an HPLC pump.

sampling system). A full description of the rapid optimization instrument appears elsewhere.[48]

Analysis of reaction products from the non-automated experiments was carried out by gas liquid chromatography (Shimadzu GC-17A), using a DB-5 liquid-phase capillary column (30 m, 0.25 mm od, 0.25 μm df) and a flame ionization detector, the response of which was precalibrated for each component. Initial product identification was carried out by nominal mass GC−MS using a Thermo-Finnigan Polaris-Q instrument fitted with a similar analytical column. Sample ionization was carried out by using both electron impact (EI) at 70 eV and chemical ionization (CI) methods, employing CH$_4$ as the reagent gas.

All chemicals (Aldrich) were used without further purification. Standard grade CO$_2$ (Cryoservices (U.K.) Ltd., 99.88% purity) was used as supplied. Amberlyst 15 (Batch No. FA003356) was purchased from Lancaster Chemicals Ltd.

Results and Discussion

Reaction of 1,6-Hexanediol (1) with MeOH. A series of isobaric reactions (at 200 bar in scCO$_2$) were carried out to test the effect of temperature on the reaction in Scheme 2; the results are summarized in Table 1. From the table, it can be clearly seen that (i) the amount of unreacted 1,6-hexanediol (**1**) decreases with temperature, reaching 0% at temperatures ≥160 °C, (ii) the mono-methylated product, **1m**, is formed preferentially at lower temperatures under these conditions, (iii) the yield of **1m** reaches a maximum at 150 °C with a selectivity approaching 9:1 over the bis-methylated product, **1b**, and (iv) the selectivity switches dramatically in favor of **1b** when the temperature is increased to 170 °C. Overall, these observations are consistent with the sequential formation of **1m** and **1b** and are precisely what might be anticipated on thermodynamic grounds.

By contrast, a quite unexpected effect was observed when the pressure was varied at a constant temperature of 150 °C, as shown in Figure 2. As the pressure was decreased from 200 bar (as used in the first experiment), the selectivity of the reaction switched completely from 9:1 in favor of **1m** to 1:20 in favor of **1b** at 50 bar. At ca. 90 bar, approximately equal amounts of the two products, **1m** and **1b**, were formed. On the other hand, the amount of residual **1** was hardly changed over the entire pressure range. Broadly similar results were obtained with ratios of **1** to MeOH between 1:100 and 1:10.

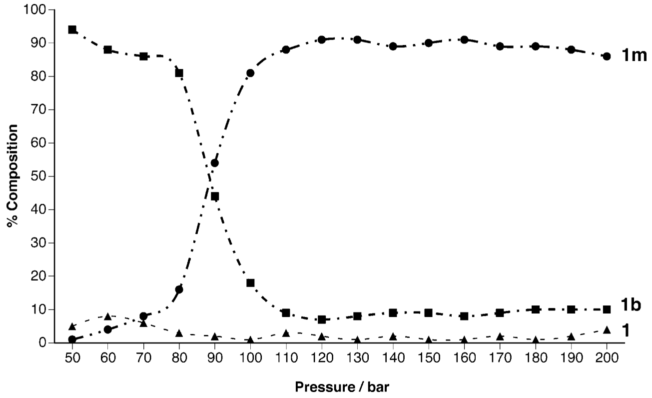


Figure 2. Plot showing the distribution of products in the reaction of 1,6-hexanediol (**1**) with methanol (1:100) as a function of pressure. The data series are labeled as follows: (▲) 1,6-hexanediol, (■) bis-ether (**1b**), and (●) mono-ether (**1m**). All of the reactions were carried out at 150 °C over Amberlyst 15 in a reactor tube of 10 mL volume. CO$_2$ was delivered at a flow rate of 0.65 L min^{-1} (CO$_2$ flow was measured after expansion at ambient temperature and pressure), and organic substrates were delivered at 0.5 mL min^{-1}.

This switch in selectivity is one of the more striking pressure effects that has been observed in any SCF reaction. Why does the switch occur? Our immediate observation was that the reaction mixture in the premixer (see Experimental Section) was monophasic at high pressures and biphasic at low pressures. We now show that this phase separation is likely to be the underlying cause of the switch in selectivity.

In any experiment of this type, one might expect some statistical variation in the determination of the reaction selectivities. Therefore, to demonstrate that the minor variations in the yields at high pressure in Figure 2 are nothing more than statistical, long and very careful experiments were performed using the automated reactor system[48] which can collect and analyze a much larger number of samples than can conveniently be processed manually (see Experimental Section). The results are shown in Figure 3, which shows that (i) as expected, most of the fluctuations at high pressure disappear under more carefully controlled conditions, (ii) doubling the pressure from 200 to 400 bar had a negligible effect on the selectivity, even though the residence time was increased substantially,[49] and (iii) the data at low pressures are “noisier” than in the results shown in Figure 2, consistent with the automated withdrawal of random aliquots from a biphasic mixture, thereby emphasizing the phase difference between low- and high-pressure experiments.

The phase behavior of multicomponent reaction mixtures can be quite a complicated topic[50] because the composition of the reaction mixture changes as the reaction proceeds.[51] In this case, we have the advantage that the mixture is relatively dilute in **1**; therefore, the phase equilibrium will be dominated by CO$_2$ and MeOH, the concentration of which will be relatively constant.

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(49) In a monophasic supercritical reaction mixture flowing through a tubular reactor, the residence time will increase with increasing density of the reaction mixture (which in turn depends on the reaction pressure) provided that the overall mass flow of material remains unchanged. As pointed out in the paper, the effect of pressure on the residence time of reaction mixtures in the multiphase region of the phase diagram is considerably more complicated.

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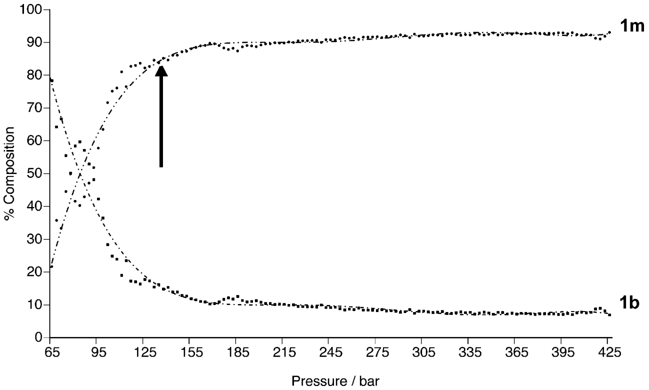

Figure 3. Automated experiment plot showing the distribution of products in the reaction of 1,6-hexanediol (**1**) with MeOH (1:100) as a function of pressure. The data series are labeled as follows: (■) bis-ether (1b) and (●) mono-ether (1m). Each data point was recorded after a stepwise change in pressure (3 bar at a time), and all reactions were carried out at 150 °C over Amberlyst 15 in a tubular reactor of 10 mL volume. CO_2 was delivered as a liquid at a flow rate of 1.00 mL min^{-1} (CO_2 was liquefied at −10 °C at a bottle pressure of 56 bar), and organic substrates were delivered at 0.5 mL min^{-1}. The arrow on the diagram indicates the approximate dew point of the reaction mixture at 150 °C; see also, Figure 5.

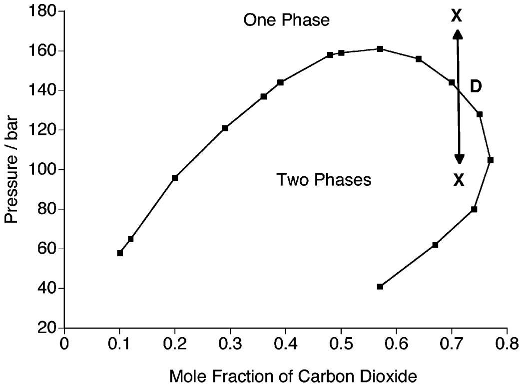

Figure 4. Isothermal phase behavior for CO_2 and MeOH at 150 °C. The area inside the critical loci curve represents the two-phase region, and the area outside represents the one-phase region. The arrow indicates the mole fraction of CO_2 (0.702) and the pressure range of our reaction mixtures.

This considerably simplifies the relationship between phase behavior and selectivity in this reaction. The relationship is further simplified by the fact that the temperature is constant during the switch in selectivity. Thus, Figure 4 shows the *p*-*x* phase envelope for $CO_2 + MeOH$ at 150 °C with the high- and low-pressure extremes of our experiment superimposed. In such a system, there is a particular pressure, the so-called “dew-point” (D), where a liquid phase first appears as the pressure is decreased. As the pressure is decreased further, the volume of the liquid phase increases.

If our interpretation of this reaction is correct, the key parameter is not the relative volumes of the gas and liquid phases but rather the partitioning of **1** between the two phases, which of course will depend on not only the volume of the gas phase but also its density. Thus at high pressures, where the system is all in a single phase, **1** would necessarily be entirely in the gas phase. Similarly, at low pressures when the density of the CO_2 is low, the majority, if not all of **1**, would be found dissolved in the liquid phase. Thus, the most significant point on the plots in Figures 2 and 3 are not the crossing points where the overall selectivity switches from **1m** to **1b** but the point at which the high selectivity for **1m** initially begins to drop. This point, indicated with an arrow in Figure 3, represents the dew point of the reaction mixture where the first trace of liquid is formed and **1** begins to partition into the new phase. How then can the dew point be detected in an opaque tubular reactor?

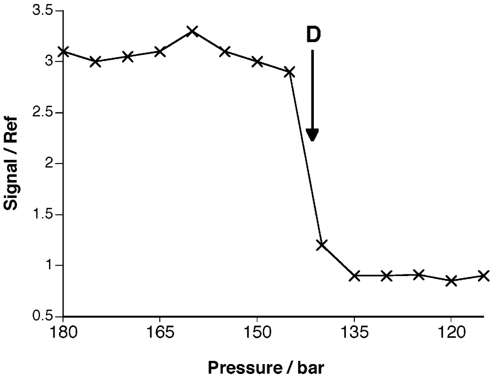

Figure 5. Signal obtained from the optic fiber reflectometer (ref 52). Each data point was recorded after a stepwise change in pressure, and all measurements were carried out at 150 °C in an empty tubular reactor (ref 52). The magnitude of the signal is expected to change quite dramatically around the point where a phase transition is expected as a direct result of a significant change in the density of the substrate in immediate contact with the tip of the fiber. In this case, the signal drops significantly (in the region of point D); this indicates the formation of a droplet of condensed phase on the tip of the fiber, thus corresponding to the dew point of the system. CO_2 was delivered as a liquid at a flow rate of 1.00 mL min^{-1} (CO_2 was liquefied at −10 °C at a bottle pressure of 56 bar), and a solution of MeOH and **1** (100:1 mol ratio) was delivered at 0.5 mL min^{-1}.

Even in well thermostated, precision view-cells, the identification of a dew point can be quite challenging. In our premixing view-cell, such a delicate measurement is really not practicable, particularly, because the rapidly rotating stirrer will inevitably disperse any droplets of liquid. Therefore, a new approach is required. Fortunately, we have recently developed an optic fiber reflectometer which responds to a very thin film of liquid in immediate contact with the optic fiber.[52] The probe operates by measuring the intensity of light reflected from the cut end of the optic fiber; this intensity depends on the difference between refractive indices of the fiber and the fluid around it. Liquids being denser than gases have higher refractive indices and, therefore, reduce the intensity of reflected light.

To estimate the dew point of our reaction mixture, the optic fiber was installed in an empty tubular reactor.[53] Figure 5 shows the reflectometer signal as a function of pressure, and one can clearly see a discontinuity indicating a dew point at ca. 140 bar. This is precisely the pressure region at which the selectivity of the reaction begins to change (see the arrow in Figure 3), thus further supporting the link between phase behavior and selectivity.

Reaction of 1 with EtOH and *n*-PrOH. If the change in selectivity were due to phase separation, one would expect to observe a similar change in selectivity, but at slightly different pressures, in the etherification of **1** with other alcohols.

Figure 6 shows that this is indeed the case; when **1** is reacted with EtOH at 150 °C, there is a pressure dependence in product selectivity with desymmetrization at high pressures and full

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(52) Avdeev, M. V.; Konovalov, A. N.; Bagratashvili, V. N.; Popov, V. K.; Tsypina, S. I.; Sokolova, M.; Ke, J.; Poliakoff, M. *Phys. Chem. Chem. Phys.* **2004**, *6*, 1258−1263.

(53) In principle, such fibers are small enough to be introduced into the center of the catalyst bed, but since this reaction generates water, which is likely to separate from $scCO_2$, we have carried out the measurements in a reactor tube in the absence of catalyst.

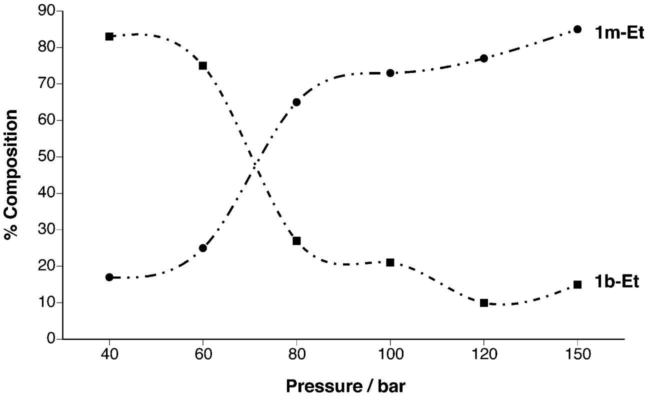


Figure 6. Plot showing the change in selectivity of the reaction of 1,6-hexanediol (**1**) with ethanol (1:100) as a function of pressure. As the reaction pressure is increased, the selectivity changes to favor the mono-ether (**1m**-Et), just as it occurs in the reaction with MeOH.

Table 2. Effect of Changing the Pressure on the % Composition of the Organic Material Recovered from the Reaction of 1,6-Hexanediol (**1**) with *n*-PrOH in scCO$_2$[a]

pressure (bar)	**1** (%)	**1m-Pr** (%)	**1b-Pr** (%)
40	1	28	71
70	1	54	45
100	3	78	19
200	4	84	12

[a] All reactions were carried out isothermally (150 °C); CO$_2$ was delivered at a flow rate of 0.65 L min^{-1} (CO$_2$ flow was measured after expansion at STP); organic substrates were delivered volumetrically (0.5 mL min^{-1}) by a suitable HPLC pump.

etherification at lower pressures. Similar results are found with *n*-PrOH (see Table 3).

Although these experiments provide further evidence that phase separation and selectivity are linked, the reactions in EtOH and *n*-PrOH are of limited synthetic value since we have already shown that acid-catalyzed reactions under these conditions lead to formation of Et$_2$O and *n*Pr$_2$O.[31]

Reaction of 1,3-Propanediol (2) with MeOH. The desymmetrization[54] is not restricted to 1,6-hexanediol (**1**); Figure 7 shows the results of reacting 1,3-propanediol (**2**) with MeOH. As before, the reaction has pressure-dependent selectivity with a high yield of the desymmetrized product **2m** at high pressures. It is striking, however, that the switchover in selectivity between **2m** and **2b** occurs much more gradually than for the corresponding switch between **1m** and **1b**. As mentioned above, the switch in selectivity reflects the partitioning of the diol between the liquid and gas phases. It is probable, therefore, that these differences reflect the greater solubility of **2** compared to that of **1** in scCO$_2$. We now suggest why monophasic conditions favor desymmetrization whereas biphasic conditions favor the formation of the fully etherified products.

Conclusions

For a supercritical reaction to be successful, it should offer significant advantages over more traditional alternatives. The reaction discussed in this paper is an example where the use of scCO$_2$ gives rise to a remarkable change in the selectivity of the reaction products merely by changing the pressure of the system. Our experiments have shown that, at an appropriate temperature, the selectivity in the etherification of 1,*n*-terminal diols can be switched almost completely between mono- and bis-ethers. This switch appears to be closely linked to the phase state of the reaction mixture, with monophasic conditions yielding largely mono-ethers and biphasic generating bis-ethers. The connection between phase state and selectivity can probably be best understood in terms of residence time of the reaction mixture in the reactor and the local concentration of the reactants on the catalyst surface.

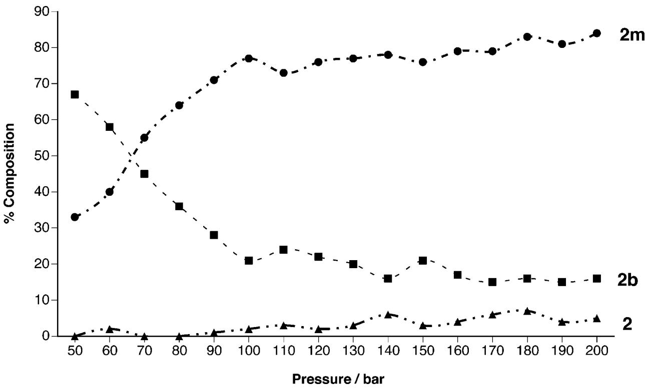
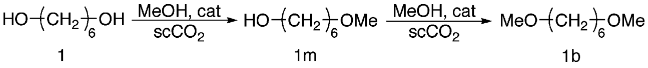


Figure 7. Plot showing the distribution of products in the reaction of 1,3-propanediol with methanol (1:100) as a function of pressure. The data series are labeled as follows: (▲) 1,3-propanediol (**2**), (■) bis-ether (**2b**), and (●) mono-ether (**2m**). All of the reactions were carried out at 150 °C over Amberlyst 15 in a reactor tube of 10 mL volume. CO$_2$ was delivered at a flow rate of 0.65 L min^{-1} (CO$_2$ flow was measured after expansion at ambient temperature and pressure), and organic substrates were delivered at 0.5 mL min^{-1}.

Scheme 3



$$\underset{1}{\mathrm{HO{-}(CH_2)_6{-}OH}} \xrightarrow[\mathrm{scCO_2}]{\mathrm{MeOH,\ cat}} \underset{1m}{\mathrm{HO{-}(CH_2)_6{-}OMe}} \xrightarrow[\mathrm{scCO_2}]{\mathrm{MeOH,\ cat}} \underset{1b}{\mathrm{MeO{-}(CH_2)_6{-}OMe}}$$

The etherification of diols appears to take place sequentially; that is, via the mono-etherified species (see Scheme 3). Our starting reaction mixture is composed of three components, scCO$_2$, the starting diol, and an alkylation source (i.e., MeOH). Under monophasic reaction conditions, all of these three components will necessarily have the same residence time (or distribution of residence times over the catalyst bed). However, at lower pressures when the reaction mixture separates into more than one phase, the residence time of the condensed phase will become longer than that of the gas phase simply because the liquid phase is denser than the gas. Longer residence times should, in principle, favor the formation of the fully alkylated product, the bis-ether. However, the experiment illustrated in Figure 3, where CO$_2$ was used at high pressure, shows that extending the residence time by itself is not enough to produce the observed change in selectivity. Therefore, there must be a second effect. This, we believe, is the effect of surface tension that causes the liquid film to wet the surface of the catalyst within the bed. This wetting will result in a simultaneous increase in the relative concentrations of organic substrate and the acidic groups of the catalyst producing a double acceleration of the reaction rate. Finally, the presence of increased concentrations of H$_2$O generated by the reaction may enhance the acidity of the acidic sites, thereby accelerating the reaction rate further.

In this paper, we have reported pressure-sensitive reaction tuning for two different diols and three different alkylating alcohols. Preliminary results from our laboratory suggest that

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(54) We have already shown that 1,5-pentanediol and 1,4-butanediol undergo almost quantitative intramolecular cyclization to generate the appropriate oxacycle; see also, ref 31.

this switch in selectivity is also observed in the selective etherification of alicyclic diols. Furthermore, pressure-dependent switching in the selectivity of the esterification of both diols and diacids is also evident. Thus, we believe that, in the absence of competing cyclization reactions, the pressure tuning of selectivity in acid-catalyzed reactions will turn out to be relatively widespread.

Acknowledgment. We thank all of our colleagues in the Clean Technology Group at The University of Nottingham, in particular, to Messrs. P. Stephenson, P. Clark, P. Gooden, B. Walsh, and A. Chapman. We also thank Messrs. M. Guyler, M. Dellar, P. Fields, R. Wilson, and D. Litchfield of the Chemistry Workshops for their invaluable technical assistance. We are grateful to Professors V. N. Bagratashvili, P. G. Jessop, and Drs. J. R. Hyde, J. Ke, F. R. Smail, R. Amandi, S. K. Ross, and M. V. Avdeev for helpful discussions. We thank Thomas Swan & Co. Ltd., the CRYSTAL Faraday Partnership, The EU (CPF-CO_2), and the EPSRC (GR/S25227/01) for financial support.

JA044814H