ACS Catalysis

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Influence of Poly(ethylene glycol) Structure in Catalytic Macrocyclization Reactions

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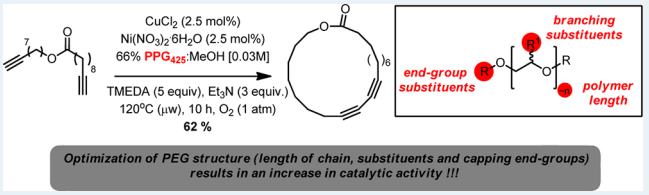
Supporting Information

ABSTRACT: The first evaluation of the structural effects of six different poly(ethylene glycol) (PEG)-derived polymers in MeOH mixtures on their aggregation abilities, ability to control dilution effects, and catalysis has been performed through examining surface tension measurements and the isolated yields of a model Glaser−Hay macrocyclization reaction of diyne **3**. Three different structural effects were studied involving (1) the presence of capping groups on the terminal hydroxyl functionalities of the polymers, (2) the length of the polymer chain, and (3) the effects of branching alkyl groups in the polymer backbone. The data obtained provides important guidelines for conducting macrocyclizations using PEG/solvent mixtures, suggesting that macrocyclizations are most efficient at high ratios of PEG/MeOH and when employing medium-length lipophilic branched poly(propylene glycol) (PPG) polymers. In particular, the use of PPG bearing terminal uncapped hydroxyl groups allows for a significant reduction in the catalyst loading. The macrocyclization studies reinforce that the aggregation characteristics of PEG-derived solvents can be harnessed in catalysis, particularly in reactions in which control of concentration effects is important.

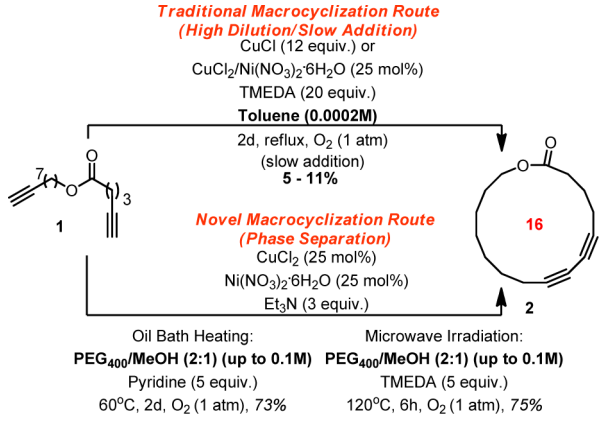


KEYWORDS: *macrocyclization, poly(ethylene glycol), acetylenes, surface tension, concentration*

Concentration effects play an important role in the development of synthetic methodologies. For example, the rate of bimolecular reactions can be significantly accelerated or decelerated through changes in the reaction concentration. The specific concentration of reactive intermediates in chemical transformations can be controlled by using biphasic mixtures,[1−3] through phase transfer catalysis, or both. The nature of a given reaction's solvent and its concentration have become increasingly scrutinized in organic synthesis as chemists weigh the efficiency of a chemical transformation against the environmental impact and costs associated with the use of that solvent under the principles of green chemistry.[4] Maintaining this balance becomes increasingly difficult when considering the preparation of highly valuable compounds. Macrocycles are a class of molecules whose unique structural features[5] have allowed them to find application in diverse fields of the chemical industry, including agrochemical, pharmaceutical, petrochemical, cosmetics, and materials science. Despite the abundance of possible applications, macrocycles are not as broadly investigated as other cyclic compounds because of the difficulties associated with their synthesis.[6] The control of concentration effects is intrinsically key to conducting efficient macrocyclization reactions that avoid problematic oligomerization. Maintaining a relatively low concentration of a given substrate via high dilution, often using toxic, volatile organic solvents, is commonly employed[7] to inhibit intermolecular reactions among substrates. The large volumes of solvent required can be problematic when conducting reactions on larger scales, and the disposal or recycling of the solvents is either environmentally damaging or energy-inefficient.[8]

In a program aimed at developing new catalytic macrocyclization strategies, our group recently reported a strategy for conducting Glaser−-Hay macrocyclization reactions at high concentrations (Scheme 1).[9] The macrocyclization procedure employed Cu catalysis and mixtures of poly(ethylene glycol)

Scheme 1. Comparing Macrocyclization Routes to Diyne 2



Received: January 24, 2013
Revised: March 6, 2013
Published: March 8, 2013

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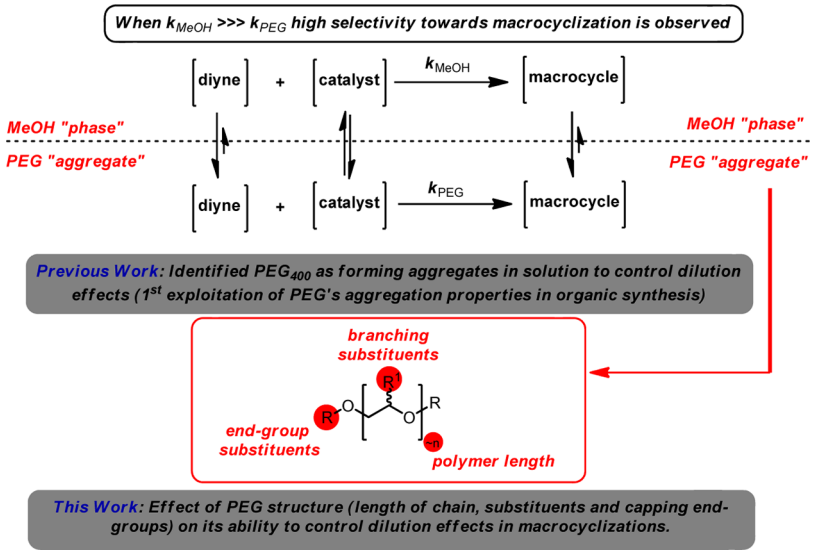
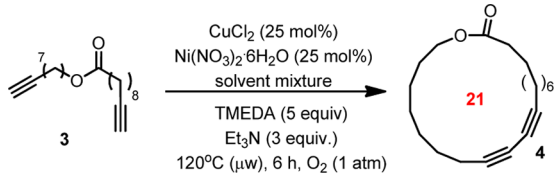


Figure 1. The proposed origin of selectivity in Glaser–Hay macrocyclization reactions employing PEG_{400}/MeOH mixtures.

Table 1. Yields of Macrocycle 4 at Various Ratios of PEG in MeOH



entry	% solvent/MeOH	solvent	yield **4** (%)[a]	entry	solvent	yield **4** (%)[a]	entry	solvent	yield **4** (%)[a]
1	0		24	17		24	33		24
2	10		40	18		46	34		43
3	33		56	19		53	35		45
4	50	PEG_{190}	59	20	PEG_{1450}	61	36	PPG_{425}	49
5	66		69	21		68	37		62
6	80		71	22		55[b]	38		56
7	90		42[b]	23		45[b]	39		58
8	100		5[b]	23		5[b]	40		9[b]
9	0		24	25		24	41		24
10	10		30	26		36	42		44
11	33	PEG_{250}	36	27		43	43		54
12	50	(OMe)	36	28	Pluronic	49	44	PEG_{400}	62
13	66		38[b]	29		59	45		75
14	80		44[b]	30		62	46		77
15	90		46[b]	31		42[b]	47		56[b]
16	100		15[b]	32		24[b]	48		5[b]

[a]All compounds were isolated by silica gel flash chromatography. Unless otherwise stated, all remaining starting material **3** was oligomerized.[17] [b]Remaining mass balance was recovered **3**.

$(PEG)_{400}$/MeOH as a solvent combination, which was postulated to form aggregates and control the dilution effects. The methodology afforded the diyne **2** and a series of related industrially relevant macrolactones in good to high yields in 48 h, at concentrations ranging from 150 to 500 times greater than traditional protocols. The slow rate of the macrocyclization was subsequently improved upon through the development of a microwave heating strategy.[9b]

Although the aggregation properties of poly(propylene glycol) (PEG) solvents have been well documented in the literature, no report of their use in organic synthesis had been previously reported. Consequently, a mechanistic investigation was undertaken to understand the origin of efficient macrocyclization. Surface tension measurements confirmed the presence of aggregates in PEG_{400}/MeOH mixtures (Figure 1). As such, the acyclic diyne, the catalysts, and the resulting macrocycle all theoretically exist in equilibrium between the two phases. Subsequent investigations revealed that the acyclic diyne preferentially solubilized within the PEG aggregate[10] and that the rate of reaction was significantly higher in MeOH than in PEG_{400}. We concluded that high selectivity for macrocyclization vs oligomerization could be achieved when there is a significant preference for the substrate to exist in a certain "phase" in which the rate of cyclization is very slow. Diffusion of the substrate into a separate "phase" in small concentration

dx.doi.org/10.1021/cs400050g | ACS Catal. 2013, 3, 773–782

where the rate of cyclization is significantly greater would result in selective formation of macrocycles such as **2**.[11]

The development of a macrocyclization protocol in which PEG was used to control concentration effects was the first report of exploiting PEG's aggregation properties[12] in organic synthesis. This was surprising, given the advantages to using PEG as a solvent in organic synthesis.[13] PEG_{400} has already been used as a "green" solvent, particularly in cross-coupling transformations,[14] because it is a water-soluble hydrophilic polymer that is relatively nontoxic, nonvolatile, inexpensive, and thermally stable.[15−17] The use of PEG in macrocyclization to partially replace existing toxic and volatile organic solvents was viewed as a step toward the development of a "green" macrocyclization protocol. An additional advantage to using PEG-derived solvents is the wide variety of structurally distinct PEG-derived polymers that are commercially available. Indeed, PEG polymers can be obtained in varying chain lengths and with different functionalities attached to or replacing the terminal hydroxyl groups. Various poly(propylene glycols) (PPGs) can also be obtained and could be viewed as derivatives of PEG in which a branching Me group is located upon the polymer backbone. At first glance, it was unknown what effects these structural modifications to PEG_{400} would have upon the efficiency and selectivity of the macrocyclization reaction previously developed. However, we were motivated by the potential for further improvements in catalytic efficiency and a more detailed understanding of PEGs ability to control concentration effects. Consequently, herein, we report the first investigation of the effect of PEG structure on catalysis and its ability to control concentration effects in Glaser−Hay macrocyclization reactions.

RESULTS AND DISCUSSION

The cyclization of the acyclic diyne **3** to macrocyclic diyne **4** under previously developed catalytic conditions at high concentration was investigated using different PEG or PPG polymers. The isolated yield of macrocycle **4** was determined at eight different ratios of PEG/MeOH (Table 1).[18] In general, the yield of **4** tends to increase with an increase in the PEG/MeOH ratio. At a specific high ratio of PEG/MeOH that is characteristic of each PEG polymer studied, catalyst inhibition is observed, the yields of **4** drop, and the remaining mass balance is reisolated acyclic diyne **3**.[19] To investigate the effect of aggregation on the yield of the macrocyclization, surface tension measurements for each PEG/MeOH combination were also obtained.[20] The plot of the surface tension experiments were conducted at 60 °C,[21] and the resulting measurements (in red, Figures 3, 5, 7, and 8) were then overlaid with the isolated yields of macrocycle **4** (in green, Figures 3, 5, 7, and 8) that were obtained at the various ratios of PEG/MeOH. Depicted on each of the plots (Figures 3, 5, 7, and 8) is a region highlighted in gray, which indicates the PEG/MeOH ratios in which catalyst inhibition is observed and the remaining mass balance in reisolated diyne **3**.

With six different PEG/PPG polymers in hand, the effect of structural modifications of PEG polymers on their ability to promote Glaser−Hay macrocyclization at high concentration could be investigated. Three key structural features of the PEG solvents were to be explored: (1) the effect of "capping" the terminal hydroxyl groups of the PEG polymer, (2) the effects of the polymer length, and (3) the effect of branching in the PEG polymer (i.e., increased hydrophobicity).

"Capping" of the Terminal Hydroxyl Groups of PEG. The terminal hydroxyl groups of PEG polymers can participate in a number of chemical transformations to allow for the further functionalization of PEG polymers for various applications.[22] Consequently, a number of PEGs bearing differently substituted hydroxyl groups are commercially available. In an effort to study the effect of the terminal hydroxyl groups on both the aggregation characteristics of the PEG and its ability to promote macrocyclization of acyclic diyne **3**, $PEG_{250}(OMe)$ was identified as an ideal PEG for study (Figure 2).[23] The two "capping" groups of the hydroxyl

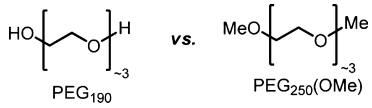


Figure 2. Short-chain PEG polymers have different "capping" groups.

functionalities in $PEG_{250}(OMe)$ are simple methyl groups, which minimizes the contribution of the capping groups themselves on the macrocyclization reaction. In addition, PEG_{190}, another commercially available PEG polymer, has a similar average molecular weight, allowing for a more accurate comparison of the similarities and differences between the two PEG solvents.

When comparing the surface tension measurements obtained for ratios of PEG_{190}/MeOH (Figure 3, top) and $PEG_{250}(OMe)$/MeOH (Figure 3, bottom), both solvents exhibit a nonlinear increase in the surface tension. The S-shaped increase in surface tension is characteristic of aggregate formation in solution; however, the surface tension measurements between the two PEG polymers changes as the ratio of PEG/MeOH increases. As the ratio of PEG/MeOH increases, the surface tension of mixtures of PEG_{190}/MeOH increases much more dramatically than for the "capped" $PEG_{250}(OMe)$/MeOH. More importantly, the ability of each PEG solvent to promote macrocyclization of diyne **3** was also very different. In solvent mixtures of PEG_{190}/MeOH, the isolated yield of macrocycle **4** increases from 24% at 100% MeOH to a maximum of ∼71% yield at 80% PEG_{190}/MeOH. At all the different ratios of PEG_{190}/MeOH, no starting acyclic diyne **3** was recovered, and the formation of oligomers was observed.[17] When the ratio of solvents was further increased to 90% PEG_{190}/MeOH, a significant drop in the isolated yield of **4** was observed (42%). Macrocyclization of **3** in 100% PEG_{190} provided only traces of **4**. Interestingly, at 90% and 100% PEG_{190}/MeOH, the remaining starting material **3** could be recovered, suggesting that the high ratios of PEG_{190}/MeOH caused some degree of catalyst deactivation.[24] The ability of $PEG_{250}(OMe)$/MeOH solvent mixtures to promote macrocyclization of diyne **3** was markedly different. The isolated yield of macrocycle **4** also increased with the ratio of $PEG_{250}(OMe)$/MeOH; however, the yields of **4** were almost always much lower than what was obtained in the PEG_{190}/MeOH solvent mixtures.

The yields of **4** using $PEG_{250}(OMe)$/MeOH do not vary as dramatically as they do in PEG_{190}/MeOH, just as the surface tension does not rapidly increase to same degree in $PEG_{250}(OMe)$/MeOH as it does in PEG_{190}/MeOH mixtures. The maximum yield of **4** when using the "capped" PEG was observed at 90% $PEG_{250}(OMe)$/MeOH, although the yield of **4** again dropped to 15% at 100% $PEG_{250}(OMe)$. Again, in contrast to what was observed with PEG_{190}/MeOH, the

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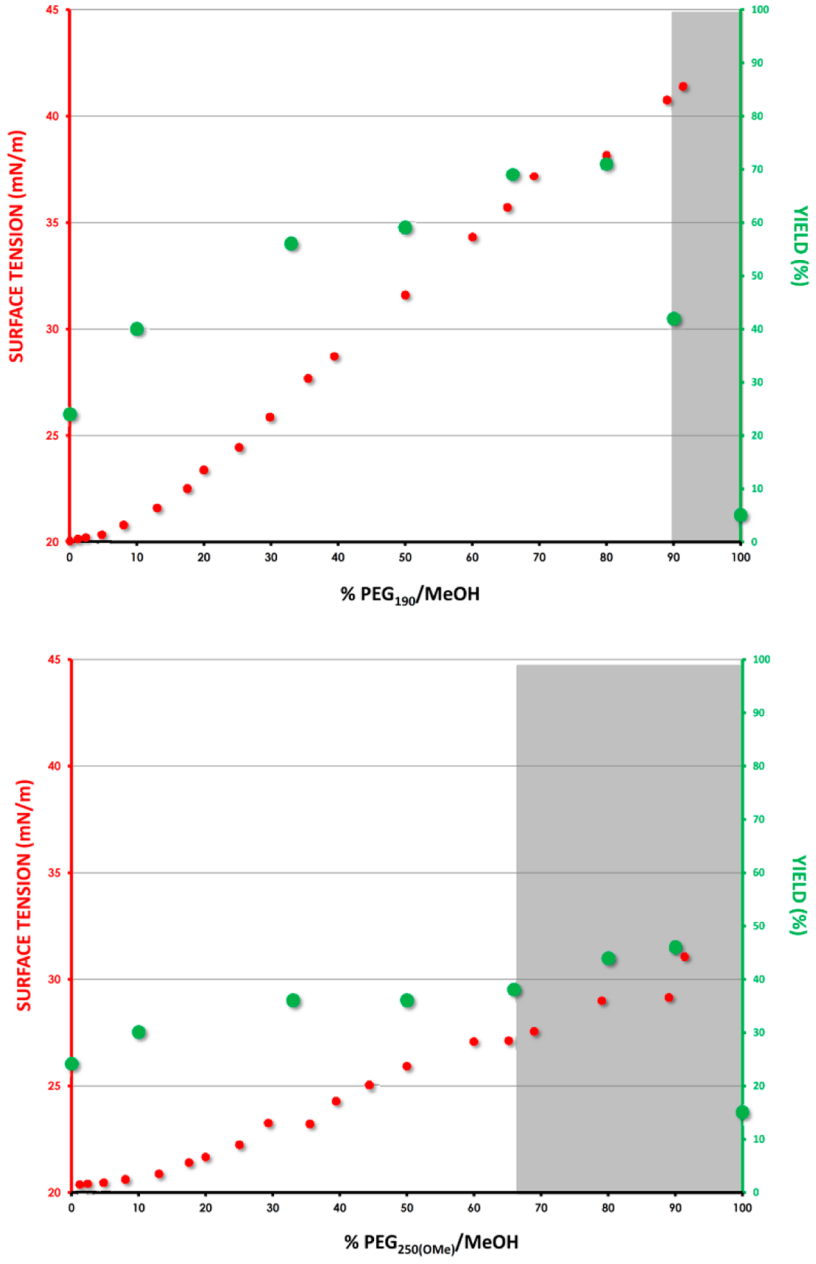
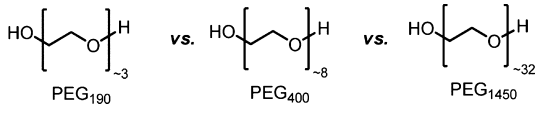


Figure 3. The effect of using a "capped" PEG polymer $PEG_{250}(OMe)$ (bottom) versus PEG_{190} (top) when promoting macrocyclic Glaser–Hay coupling (**3** → **4**) at high concentration (0.03 M). Surface tension measurements (red) and isolated yields (green) are plotted on the same figure. The region highlighted in gray indicates PEG/MeOH ratios in which catalyst inhibition is observed and the remaining mass balance is reisolated diyne **3**.

$PEG_{250}(OMe)$/MeOH solvent mixture displayed catalyst inhibition at much lower ratios of $PEG_{250}(OMe)$/MeOH (~66% $PEG_{250}(OMe)$/MeOH), perhaps accounting for the lower yields of **4** observed. Taken as a whole, these results suggest that the terminal hydroxyl groups of PEG polymers play an important role in aggregation, and PEGs having terminal hydroxyl groups are much more efficient at promoting the Glaser–Hay macrocyclization at high concentrations.

Different Chain Lengths of PEG. The chain length of PEG polymers can be exploited to alter their solubility properties, where the interior of a PEG polymer normally becomes increasingly hydrophobic as the number of ethylene glycol units multiply. Small-chain PEGs, such as PEG_{190}, are normally free-flowing liquids, whereas larger-chain PEGs, such as PEG_{1450}, are available as solids that can be melted to act as a solvent at elevated temperatures (Figure 4). Because the hydroxyl groups of the PEG polymer were identified to be important for aggregation and obtaining high yields of macrocycle product **4**, three different PEG polymers (PEG_{190}, PEG_{400}, and PEG_{1450}), all having terminal hydroxyl groups, were chosen to evaluate the benefit of increased chain length.



PEG_{190} PEG_{400} PEG_{1450}

Figure 4. PEG polymers having different chain lengths.

dx.doi.org/10.1021/cs400050g | *ACS Catal.* 2013, 3, 773–782

In general, the surface tension plots for all three solvent mixtures studied utilizing different chain-length polymers of PEG displayed a nonlinear increase in the surface tension between 100% MeOH and ~15−30% PEG/MeOH, resulting in an S-shaped curve signaling the presence of aggregates in solution (Figure 5, PEG_{190} (top), PEG_{400} (middle), PEG_{1450} (bottom)). Regardless of the chain length of the PEG used, all the solvent mixtures had rapid increases in surface tension as the ratio of PEG/MeOH increased. Notably, the shorter PEG_{190}/MeOH never reaches a plateau, but the longer PEG_{400}/MeOH mixture does have its surface tension plateau at ~70% PEG_{400}/MeOH. It was not possible to obtain surface tension data for the PEG_{1450}/MeOH mixtures at ratios above 70% PEG_{1450}/MeOH because PEG_{1450} is a solid and forms saturated suspension at high ratios at 60 °C. The macrocyclization of acyclic diyne **3** was also investigated in each PEG/MeOH mixture; the isolated yields of macrocycle **4** are plotted in Figure 5 (PEG_{190} (top), PEG_{400} (middle), PEG_{1450} (bottom)). All three different chain lengths gave high yields of the macrocycle **4** at their optimal PEG/MeOH ratio. For PEG_{190}/MeOH and PEG_{400}/MeOH, the maximum yields of 71% and 77% occurred at a ratio of 80% PEG/MeOH, whereas the longer PEG_{1450} had a lower maximum yield (69%) at a lower ratio of 66% PEG_{1450}/MeOH. Note that isolated yields for macrocycle **4** were obtained at high ratios of PEG_{1450}/MeOH, since PEG_{1450} is a liquid at the elevated temperatures in the microwave. The biggest difference when comparing the behavior of all three PEG chain lengths in that the longer PEG_{1450} tended to show lower yields and caused catalyst inhibition at lower ratios of PEG/MeOH (catalyst inhibition was observed at 90% PEG_{190} or PEG_{400}/MeOH and at 66% PEG_{1450}/MeOH). In summary, short- and medium-chain-length PEG polymers can be used as solvents to efficiently promote Glaser−Hay macrocyclization at high concentration when high ratios of PEG/MeOH are employed. Large-chain polymers can be problematic as a result of greater levels of catalyst inhibition at the high ratios of PEG/MeOH normally needed to promote efficient cyclization.

Branched Polymers of PEG: PPG and Pluronic. PPG polymers have a Me group along the ethylene subunit of the polymer and have been found to be slightly more toxic than PEG.[25] PPG formed from polymerization of *rac*-propylene oxide affords an atatic polymer, and polymerization from the optically pure epoxide monomer or polymerization with chiral catalysts affords the isotatic polymer.[26] For the evaluation of branched PEG-derived polymers in controlling the effective molarity in macrocyclization reactions, the cheaper, commercially available atatic polymers were chosen for investigation. The addition of the Me group along the backbone makes PPG much more lipophilic than PEG, but PPG still prefers a tightly wound helix conformation in aqueous solution.[27−29] To study the effects of branching in the macrocyclization reactions, two separate branched polymers having different chain lengths were identified for study (Figure 6).

First, because PEG_{400} was identified as the optimal PEG solvent to date, PPG_{425} was evaluated, since it has a similar chain length and molecular weight and surface tension measurements of mixtures of PPG_{425}/MeOH were obtained (Figure 7). The surface tension measurements of PPG_{425}/MeOH closely mirror those obtained for mixtures of PEG_{400}/MeOH, in that an S-shaped curve was observed with a plateau occurring at approximately 70% PPG_{425}/MeOH. The surface tension measurements for PPG_{425}/MeOH, however, do not exhibit the steep increase in surface tension between 40% and 60% PPG_{425}/MeOH that is observed in the same region for mixtures of PEG_{400}/MeOH. When the macrocyclization of diyne **3** was investigated at different ratios of $Pluronic_{1100}$/

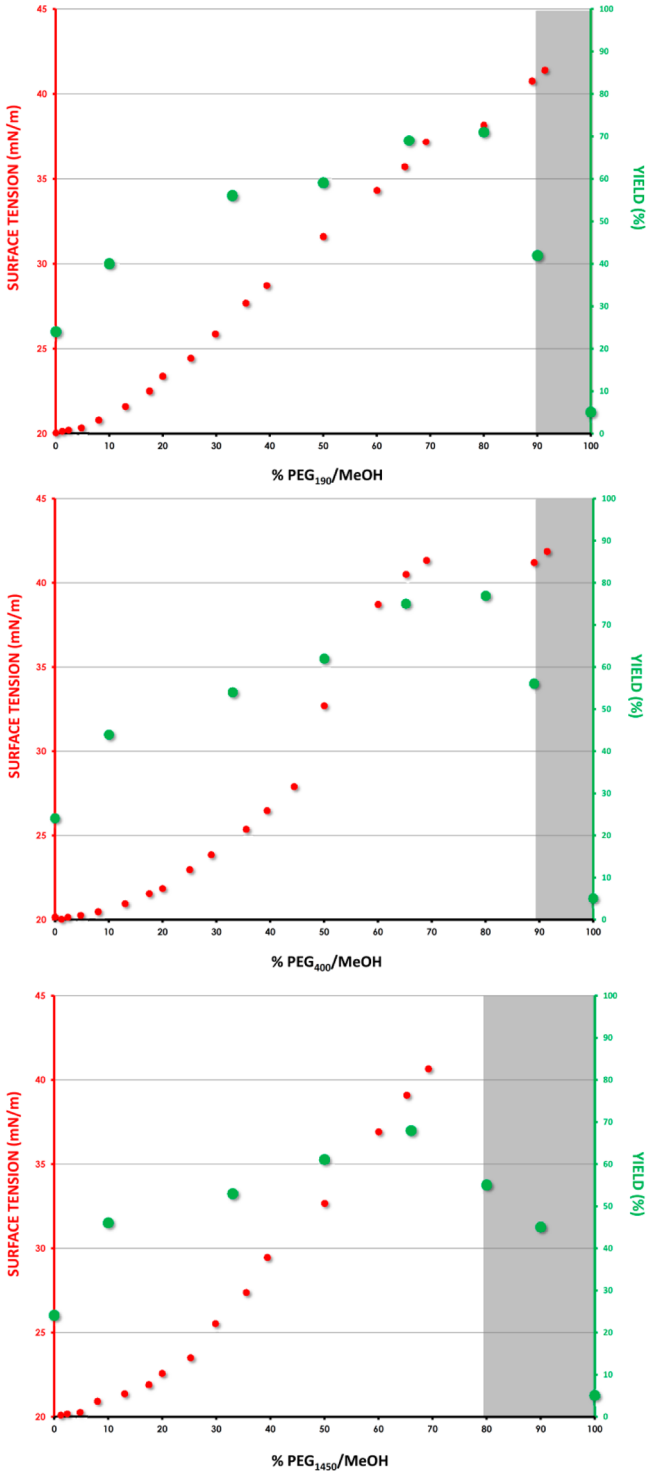


Figure 5. The effect of using different polymer lengths of PEG polymer (PEG_{190} (top), PEG_{400} (middle), PEG_{1450} (bottom)) when promoting macrocyclic Glaser−Hay coupling (**3** → **4**) at high concentration (0.03 M). Surface tension measurements (red) and isolated yields (green) are plotted on the same figure. The region highlighted in gray indicates PEG/MeOH ratios in which catalyst inhibition is observed and the remaining mass balance is reisolated diyne **3**.

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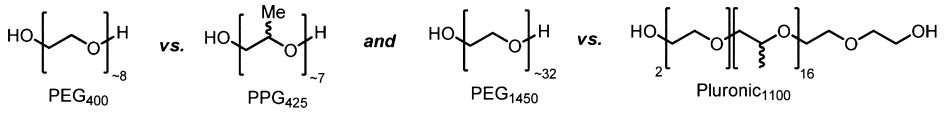

Figure 6. Comparison of different PEG polymers having different chain lengths and branching substituents.

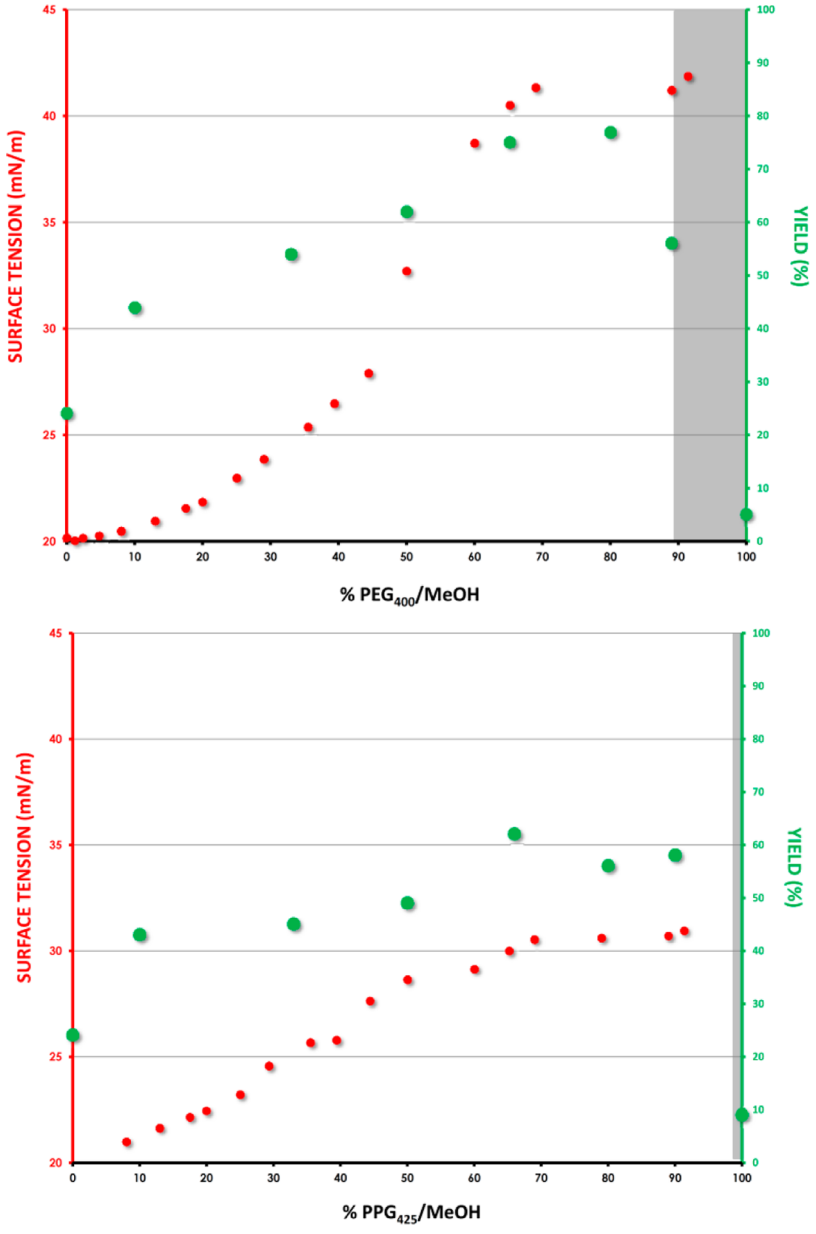

Figure 7. The effect of using branched polymers of short-chained PEGs (PEG400 (top) and PPG425 (bottom)) when promoting macrocyclic Glaser–Hay coupling (**3** → **4**) at high concentration (0.03 M). Surface tension measurements (red) and isolated yields (green) are plotted on the same figure. The region highlighted in gray indicates PEG/MeOH ratios in which catalyst inhibition is observed and the remaining mass balance is reisolated diyne **3**.

MeOH, the yields of macrocycle **4** reached a maximum 62% isolated yield at 80% Pluronic$_{1100}$/MeOH. Overall yields were similar or only slightly lower than those obtained in PEG$_{1450}$/MeOH mixtures (see Table 1 to compare isolated yields). One distinct difference observed with PPG$_{425}$/MeOH mixtures was that there was much less catalyst inhibition, and polymerization of the starting acyclic diyne **3** was observed, even when the macrocyclization was conducted in 100% PPG$_{425}$/MeOH. The lack of catalyst inhibition could be due to an increased solubility preference for the catalyst in MeOH, as opposed to the PPG$_{425}$ aggregates, although further work is necessary to elucidate the origin of the reactivity in PPG$_{425}$ mixtures.

The effects of branching in PEGs on the macrocyclization reaction of **3** were also investigated with longer polymer lengths. To make comparisons with the previously studied PEG$_{1450}$, Pluronic$_{1100}$ was chosen for study. Pluronic$_{1100}$ is a well-defined block polymer having two ethylene oxide units at each terminus and 16 *rac*-propylene units (Figure 6). The

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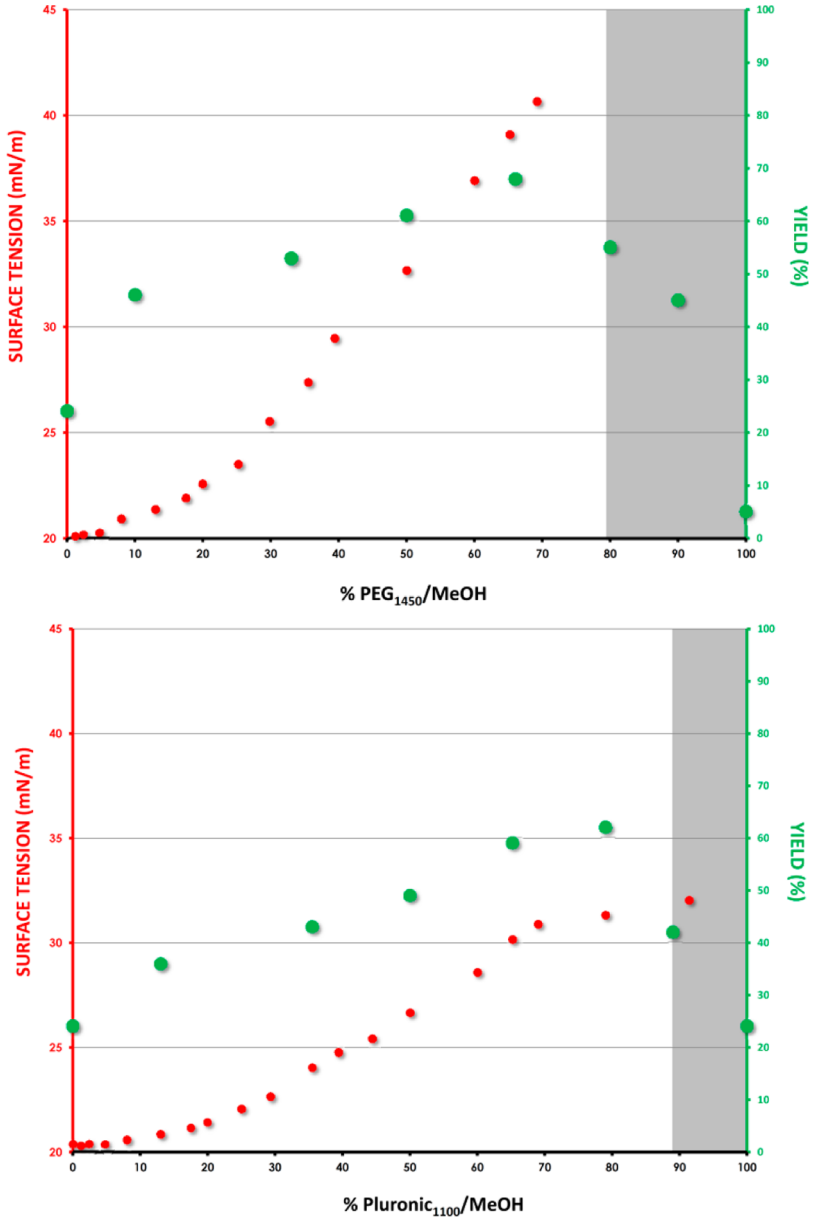

Figure 8. The effect of using branched polymers of long-chained PEGs (PEG1450 (top) and Pluornic1100 (bottom)) when promoting macrocyclic Glaser–Hay coupling (**3** → **4**) at high concentration (0.03 M). Surface tension measurements (red) and isolated yields (green) are plotted on the same figure. The region highlighted in gray indicates PEG/MeOH ratios in which catalyst inhibition is observed and the remaining mass balance is reisolated diyne **3**.

resulting polymer has surfactant properties that are useful in cosmetic and pharmaceutical applications, most often for increasing the solubility of lipophilic substances in aqueous environments.[30] Pluronics have also been evaluated for various drug delivery applications and were shown to have their own inherent biological activity due to their propensity to incorporate into cellular membranes.[31] In contrast with the surface tension measurement observed for PEG_{1450}/MeOH, the surface tension measurements of $Pluronic_{110}$/MeOH could be obtained even up to 100% $Pluronic_{1100}$/MeOH, since $Pluronic_{1100}$ is a liquid at room temperature. (Figure 8). The surface tension measurements for $Pluronic_{1100}$/MeOH do not exhibit a steep increase in surface tension between 40% and 60% $Pluronic_{1100}$/MeOH that is observed in the same region for mixtures of PEG_{1450}/MeOH, but a distinct plateau and S-shaped curve were observed, confirming the aggregation of $Pluronic_{1100}$/MeOH mixtures at high ratios. When the macrocyclization of diyne **3** was investigated at different ratios of $Pluronic_{1100}$/MeOH and the yields of macrocycle **4** reached a maximum 62% isolated yield at 80% $Pluronic_{1100}$/MeOH, overall yields were similar or only slightly lower than those obtained in PEG_{1450}/MeOH mixtures (see Table 1 to compare isolated yields). As was observed with PPG_{425}/MeOH mixtures, the branching in $Pluronic_{1100}$/MeOH mixtures allows for much less catalyst inhibition at high ratios of $Pluronic_{1100}$/MeOH when compared with PEG_{1450}/MeOH. The reduction in catalyst inhibition can easily be observed when comparing the yields of macrocycle **4** at 100% $Pluronic_{1100}$ (24%) and 100% PEG_{1450} (<5%).

Because catalyst inhibition was observed to a much lesser degree when reactions were performed in branched polymer solvents, such as PPG_{425} and $Pluronic_{1100}$, it was believed that

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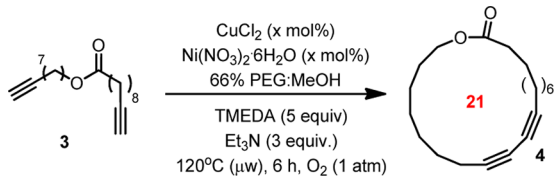
these solvents could allow for a reduction in the catalyst loading used to promote macrocyclization. Consequently, the catalyst loading in the cyclization of diyne **3** to macrocycle **4** was investigated in mixtures of 66% PEG_{400}/MeOH and 66% PPG_{425}/MeOH (Table 2). When the catalyst loading of the Cu and Ni catalysts was decreased in the macrocyclization of diyne **3** using a 66% PEG_{400}/MeOH solvent mixture, the yields of the desired macrocycle **4** also decreased (entries 1−4). Although the yield of macrocycle **4** was 75% when using a 25 mol % catalyst loading, macrocycle **4** was isolated in 67% yield when decreasing the catalyst loading to 10 mol %. The use of even lower catalyst loadings of 5 or 2.5 mol % resulted in even lower overall yields (54% and 35%, respectively) of the desired macrocycle **4** and large quantities of reisolated **3**. In contrast, when the catalyst loading of the Cu and Ni catalysts was decreased in the macrocyclization of diyne **3** using the branched polymer solvent (66% PPG_{425}/MeOH), the yields of the desired macrocycle **4** were either maintained or increased (Table 2, entries 5−8). When the mol % of the Cu/Ni catalyst system was dropped from 25% to 10%, the yield of macrocycle **4** increased from 62% to 81%. Because reducing the catalyst loading is expected to slow the rate of reaction, it could consequently increase the selectivity for cyclization vs oligomerization and explain the increase in the isolated yield of **4**. When the catalyst loading in the macrocyclization of diyne **3** using 66% PPG_{425}/MeOH was dropped to 5 mol %, the yield of macrocycle **4** remained high (74%), and the remaining mass balance was recovered unreacted diyne **3**. Finally, the catalyst loading was dropped to 2.5 mol %, which resulted in a very slow macrocyclization. However, if the reaction time was slightly increased (from 6 to 10 h), the macrocycle **4** could be isolated in exactly the same yield as was obtained with a catalyst loading 10 times higher (entry 8 versus 5, Table 2).

Table 2. Effect of PEG Structure on the Catalyst Loading in the Macrocyclization To Form 4



entry	solvent	catalyst loading (x mol %)	yield **4** (%)[a]
1	PEG_{400}	25	75
2		10	67[b]
3		5	54[b]
4		2.5	35[b]
5	PPG_{425}	25	62
6		10	81
7		5	74[b]
8		2.5	62[b,c]

[a]All compounds were isolated by silica gel flash chromatography. Unless otherwise stated, all remaining starting material **3** was oligomerized.[17] [b]Remaining mass balance was recovered **3**. [c]Reaction time was 10 h (O_2 was bubbled through the solution a second time after 5 h).

In summary, the first evaluation of the structural effects of PEG-derived polymers and their aggregation abilities for exploitation in organic synthesis has been described. The evaluation of six different PEG polymers in MeOH mixtures for their ability to control dilution effects has been performed through examining surface tension measurements and the isolated yields of a model Glaser−Hay macrocyclization reaction of diyne **3**. Three different structural effects were studied involving (1) the presence of capping groups on the terminal hydroxyl functionalities of the polymers, (2) the length of the polymer chain, and (3) the effects of branching alkyl groups in the polymer backbone. The data obtained for isolated yields of macrocycle **4** provide important guidelines for conducting macrocyclizations using PEG/solvent mixtures: (1) regardless of the nature of the PEG solvent, the macrocyclizations exhibit greater efficiency at high ratios of PEG/MeOH, normally affording high yields and often recovered unreacted starting material, and (2) very high ratios (>90% PEG/MeOH) often result in catalyst inhibition and lower yields. Importantly, when comparing the structural features of the various PEGs, other valuable insights come to light: (1) the terminal hydroxyl groups are important for inducing aggregation and provide surface tension graphs with a well-defined S-shaped curve and overall higher yields of macrocycle **4** than when using "capped" PEGs; (2) long chained PEGs can provide a more lipophilic environment, but result in much greater degrees of catalyst inhibition at the high ratios of PEG/MeOH normally needed for efficient macrocyclization, which resulted in lower yields of macrocycle **4**; and (3) polypropylene-containing PEGs (PPG_{425} and $Pluronic_{1100}$) provided good yields of macrocycle **4** and are much more lipophilic than PEG, making them interesting alternatives for substrates that have problematic solubility. It should be noted that PPG_{425} and $Pluronic_{1100}$ mixtures exhibited very high catalyst reactivities, even at very high ratios (>90% PEG/MeOH), which resulted in greater levels of oligomerization observed and less efficient macrocyclization selectivity (i.e., macrocyclization vs oligomerization); however, the increase in catalyst reactivity when compared with other PEG solvents could be exploited to develop macrocyclization reactions with reduced catalyst loadings. When macrocyclization was conducted in 66% PPG_{425}/MeOH, the catalyst loading could be reduced 10-fold (from 25 to 2.5 mol %) and afford high yields of the desired macrocycle product.[32]

The macrocyclization studies outlined herein reinforce that the aggregation characteristics of PEG-derived solvents can be harnessed in organic synthesis and are not limited to exploitation in medicinal chemistry and materials science. It is expected that as the properties of these solvents continue to be explored, they will become increasingly employed in catalysis. In particular, the high catalyst activities observed in branched PEG solvents could be especially useful in other fields of catalysis in which the "green" characteristics of PEG solvents are desired in concert with high catalyst activities. Considering the wealth of other synthetic processes that suffer from concentration effects,[33] it is reasonable to assume that PEG or PEG/solvent mixtures could be used to improve such processes or provide alternatives to traditional aqueous/organic biphasic reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

Surface tension data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the Natural Sciences and Engineering Research Council of Canada (NSERC), Université de Montreal and the Centre for Green Chemistry and Catalysis (CGCC) for generous funding. A.-C.B. thanks NSERC (Vanier Graduate Scholarship), the FQRNT and CGCC for graduate scholarships.

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