Effect of Aqueous PEG or PPG Solvents on Reaction Selectivity and Gibbs Energies

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Low molecular weight polyethylene glycol (PEG 300), polypropylene glycol (PPG 425), and their aqueous solutions are investigated for use as novel, nonvolatile, environmentally friendly reaction solvents. The kinetics and selectivities of a S_N1 and a Diels-Alder reaction (reactions commonly used in pharmaceutical synthesis) in the polyglycol-H_2O solutions are reported. Reaction rate constants and product selectivities in the polyglycol-H_2O solvents were comparable to those observed in the traditional organic solvents used with these reactions. Gibbs free energy calculations show that the reactants and reaction transition states for the S_N1 and Diels-Alder reactions are stabilized in the presence of the polyglycol-H_2O solvents. © 2004 American Institute of Chemical Engineers *AIChE J,* 50: 511–517, 2004
Keywords: polyglycols, PEG 300, PPG 425, environmentally benign solvents, reaction kinetics, Gibbs free energies

Introduction

The demand for environmentally friendly reaction solvents to lower VOC or toxic air emissions has grown, partly spurred by various government regulations. Alternative solvents have been the subject of much research in recent years including studies of supercritical CO_2, near critical water, ionic liquids, aqueous-organic two-phase systems (using phase transfer catalysts), and other organic solvents such as ethyl lactate (Chandler et al., 1998; Rosa et al., 2000; Sherman et al., 1998; Tundo et al., 2000; Watkins, 2002).

We have been investigating aqueous solutions of low molecular weight PEG and PPG as useful, safe, environmentally friendly alternative reaction solvents for pharmaceutical synthesis. PEG and PPG are relatively nontoxic and nonvolatile. PEG is certified as being safe for ingestion (Harris, 1992) and is currently used in cosmetic products, biological products, and medicines (Rieger, 1991; Zalipsky and Harris, 1997). Low molecular weight PPG is nonirritating to the skin and is also used in cosmetic products (Rieger, 1991). Both PEG 300 and PPG 425 are biodegradable (Dow MSDS sheets). Another consideration is their ability to dissolve various organic compounds. We have previously reported that the solubility of several organic compounds is quite high in the polyglycol-H_2O solutions (Leininger et al., 2002, 2003). Because of their low volatility, use of these polyglycol-H_2O solvents would reduce volatile emissions, as well as being useful for higher temperature operations.

The objective of this research was to investigate using polyglycol-H_2O solutions as reaction solvents, specifically for fine chemical and pharmaceutical-type reactions. Previously, reaction rate constants for three different classes of organic reactions (S_N1, S_N2, and Diels-Alder) were measured in the polyglycol-H_2O solutions and compared to those obtained in traditional organic solvents (Leininger et al., 2003). It was found that reaction rate constants in the polyglycol solvents were comparable or higher for the S_N1 and Diels-Alder reactions, but lower for the S_N2 reaction. This current study further examines the effect of the polyglycol-H_2O solutions on reaction kinetics by examining additional S_N1 and Diels-Alder reactions, with an emphasis on product selectivity since each of these reactions may yield two isomeric products. In addition, we have interpreted the kinetic results by calculating the Gibbs free energy of both the reactants and the transition states in the various solvents.

Materials and Methods

S_N1 reaction: hydrolysis of 1-chloro-3-methyl-2-butene

The hydrolysis of 1-chloro-3-methyl-2-butene to form two isomers (Figure 1) was investigated in aqueous polyglycol solutions and in traditional S_N1 solvents such as methanol-H_2O

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and acetone-H_2O under homogeneous, liquid-phase conditions. The chemicals used (as received) were 95% pure 1-chloro-3-methyl-2-butene, 98% pure 2-methyl-3-buten-2-ol, 99% pure 3-methyl-2-buten-1-ol, 99+% pure methanol, 99+% pure acetone, pure polypropylene glycol ($M_n = 425$), and pure polyethylene glycol ($M_n = 300$), all from Aldrich. Impurities in 1-chloro-3-methyl-2-butene (95% pure) were accounted for in the calibration curves and in the GC analysis.

All reactions were conducted in closed glass vials or in a Kontes, 50 mL jacketed glass reaction beaker with temperature control. Initial concentrations of 1-chloro-3-methyl-2-butene were usually 0.1 mol/L; however, data were also obtained with initial concentrations of 0.7 mol/L and 2.0 mol/L. For PEG solvents with 10 mass % H_2O or less and 20 mass % H_2O-PPG 425, gas chromatography (Varian Model 3350 with a FID detector and an Alltech, capillary column, coated with AT-1 phase) was used to obtain concentration-time data. For PEG solvents with greater than 10 mass %, *in situ* conductivity readings were used to follow the extent of the reaction. As the reactions are only slightly equilibrium limited (ca. 95% conversion at equilibrium), rate constants were obtained from initial rate data. For all of the reactions, gas chromatography was used to determine the product distribution (2-ol: 1-ol ratio).

Room temperature solubility measurements were made for 1-chloro-3-methyl-2-butene in the polyglycol-H_2O solutions. Small volumes of the liquid reactant were added to the solvents, mixed, and visual inspection was used to determine if complete dissolution occurred. By decreasing the amount of added solute, a narrower and more accurate solubility range was determined. For all the solubility values reported in Table 1, the solute is completely soluble at the lower value and some insoluble liquid is present at the upper value. Therefore, the solubility of the compounds falls within the given range. Errors associated with the values given in the tables (volume measurement errors) are estimated to be 5%–10%.

Table 1. Solubility of Reactants in Various Solvents (22°C)

	Solubility (mol/L)	
Solvent	1-chloro-3-methyl-butene	Cyclopentadiene
PPG 425	Miscible	
95% PPG425-H_2O	4.1–4.3	
90% PPG425-H_2O	2.5–2.8	2.2–2.8
80% PPG425-H_2O	0.81–1.15	1.3–1.9
70% PPG425-H_2O	0.59–0.62	0.84–0.93
64% PPG425-H_2O	0.37–0.47	
PEG	Miscible	
90% PEG300-H_2O	1.2–1.5	1.0–1.3
80% PEG300-H_2O		0.64–0.84
90% Acetone-H_2O	Miscible	
80% Acetone-H_2O	1.7–1.9	
90% Methanol-H_2O	Miscible	
80% Methanol-H_2O	1.5–1.8	

Diels-Alder reaction between cyclopentadiene and ethyl vinyl ketone

The reaction between cyclopentadiene and ethyl vinyl ketone to form two stereoisomers (Figure 2) was studied in the polyglycol-H_2O solutions and compared to results obtained in ethanol and 1-propanol, both commonly used solvents for such reactions. This reaction was studied under homogeneous, liquid-phase conditions. 99.5+% pure 1-propanol, dicyclopentadiene and 97% pure ethyl vinyl ketone were obtained from Aldrich and used as received. The experimental procedure was adapted from Blokzijl et al. (1991) for the same reaction. Dicyclopentadiene was cracked to form cyclopentadiene. The cyclopentadiene solution was then chilled, diluted with solvent, and used immediately. Gas chromatography (Alltech column with 0.25 micron AT-1 coating and FID detector) was used to determine the purity of the cracked cyclopentadiene, as well as to follow the cyclopentadiene concentration over time. Reaction results from Blokzijl et al. (1991) were repeated and used to identify the two product peaks in chromatograms. Data obtained at very low (0.004 mol/L) concentrations were not used because of interference from impurities in the reaction solution at that level.

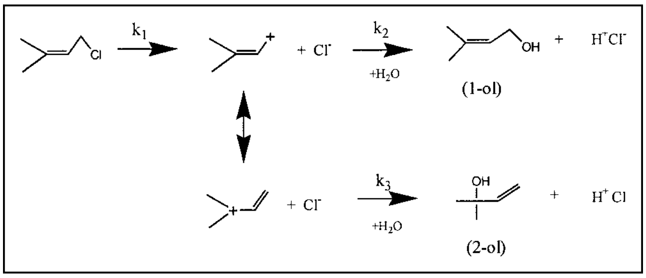

Figure 1. S_N1 reaction: the hydrolysis of 1-chloro-3-methyl-butene.

The reaction forms two isomers: 3-methyl-2-buten-1-ol and 2-methyl-3-buten-2-ol.

For this reaction, kinetic data were obtained in pure PEG 300, pure PPG 425, and pure 1-propanol as well as in 10 mass % water in the polyglycols. Different initial reactant concentrations were used to verify that the reaction was second order. The reactions proceeded to about 90% conversion. Product selectivities were investigated in these solvents as well as in 40 mass % H_2O in 1-propanol and in 30 mass % H_2O in PEG 300 and PPG 425-H_2O.

The room temperature solubilities of cyclopentadiene in aqueous PEG and PPG solutions are shown in Table 1. The *CRC Handbook of Chemistry and Physics* (1982) reports cyclopentadiene to be completely miscible in ethanol. Ethyl vinyl ketone (the co-reactant) was found to have a solubility of over 4 mol/L in 90% PPG 425-H_2O.

Gibbs free energies

The Gibbs free energy of activation (and the rate constant of the reaction) depends on both the reactant Gibbs free energy

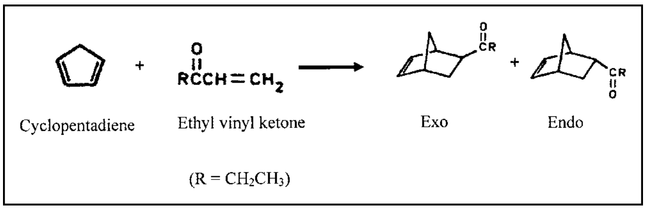

Figure 2. Diels-Alder reaction between cyclopentadiene and ethyl vinyl ketone to form two stereoisomers (exo and endo forms).

(G^R) and the transition state Gibbs free energy (G^{TS}). The Gibbs free energy of the reactants and of the transition state in each solvent was determined by the procedure of Buncel and Wilson (1979, 1980). These calculations were done for the S_N1 reaction, the Diels-Alder reaction, and for a previously-studied S_N2 reaction (Leininger, 2002).

The change in the Gibbs energy of activation in going from solvent I to solvent II ($\Delta G^{\neq}_{\mathrm{I}\rightarrow\mathrm{II}}$), was found using experimental rate constants and the following relation

$$\ln \frac{k_I}{k_{II}} = -\frac{G_I^{\neq} - G_{II}^{\neq}}{RT} = -\frac{\Delta G^{\neq}_{I\rightarrow II}}{RT} \tag{1}$$

where k_{I} is the rate constant in solvent I, k_{II} is the rate constant in solvent II, $G_{\mathrm{I}}^{\neq}$ is the activation energy of the reaction in solvent I, and $G_{\mathrm{II}}^{\neq}$ is the activation energy of the reaction in solvent II. (This relation assumes that the transmission coefficients in the two reaction media are identical.)

The change in the reactant's Gibbs energy (at low reactant concentration) when going from solvent I to solvent II ($\Delta G^R_{\mathrm{I}\rightarrow\mathrm{II}}$) was estimated from the activity coefficients of the reactant in the solvents (Abraham, 1974)

$$\Delta G^R_{I\rightarrow II} = -RT \ln \frac{\gamma_I}{\gamma_{II}} \approx -RT \ln \frac{\gamma_I^{\infty}}{\gamma_{II}^{\infty}} \tag{2}$$

where γ_{I} is the activity coefficient of the reactant in solvent I, γ_{II} is the activity coefficient of the reactant in solvent II, $\gamma_{\mathrm{I}}^{\infty}$ is activity coefficient of the reactant at infinite dilution in solvent I, and $\gamma_{\mathrm{II}}^{\infty}$ is activity coefficient of the reactant at infinite dilution in solvent II. Activity coefficients at infinite dilution were found using the UNIFAC group-contribution method (Smith et al., 1996) and original UNIFAC-VLE parameters (Fredenslund and Sorensen, 1994). In these calculations PEG 300 was represented using 6 ethylene oxide monomers (corresponding to a MW of 282 g/mol) and PPG 425 with 7 propylene oxide monomers (corresponding to a MW of 424 g/mol). For the second-order S_N2 and Diels-Alder reactions, the change in each reactant's Gibbs energy ($\Delta G^R_{\mathrm{I}\rightarrow\mathrm{II}}$) was calculated and the energies were summed together for the two reactants (Haberfield et al., 1972; Buncel and Wilson, 1979, 1980).

The change in the Gibbs free energy of the transition ($\Delta G^{TS}_{\mathrm{I}\rightarrow\mathrm{II}}$) was then obtained from the Gibbs reactant free energy change ($\Delta G^R_{\mathrm{I}\rightarrow\mathrm{II}}$) and the measured change in the Gibbs free energy of activation ($\Delta G^{\neq}_{\mathrm{I}\rightarrow\mathrm{II}}$)

$$\Delta G^{TS}_{I\rightarrow II} = \Delta G^{\neq}_{I\rightarrow II} + \Delta G^R_{I\rightarrow II} \tag{3}$$

For these calculations, the reactant free energy (G^R) and the transition state free energy (G^{TS}) were reported for each solvent with respect to a reference solvent.

Results and Discussion

S_N1 reaction: hydrolysis of 1-chloro-3-methyl-2-butene

Reaction Kinetics. As expected, this hydrolysis reaction followed first-order kinetics in all of the solvents examined. The first-order rate constants (based on haloalkene disappearance) in PPG 425-H_2O, PEG 300-H_2O, methanol-H_2O, and acetone-H_2O are shown in Figure 3. From multiple reaction runs, the error in the rate constants was estimated to be ±5–10%. Figure 3 shows that as the concentration of H_2O is increased in the solvent, the rate constants increase. At low water concentration, reactions in the acetone and methanol solutions yield significantly higher rate constants, with the aqueous PPG 425 solutions yielding the lowest rate constants. However, at higher water content, aqueous PPG 425 solutions have rate constants comparable to those in traditional solvents. Since the rate constants increase strongly with water content while the reactant solubility only modestly decreases (Table 1), the maximum possible reaction rate (product of solubility and rate constant) follows a trend similar to the rate constants.

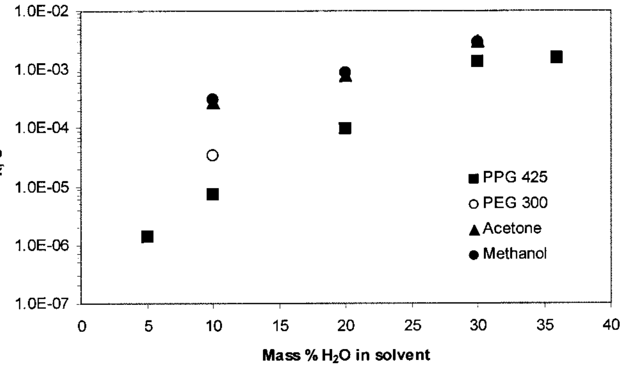

Figure 3. Rate constants (based on haloalkene disappearance) for the hydrolysis of 1-chloro-3-methyl-2-butene in polyglycol and traditional solvents at 22°C.

The rate constants for this reaction are different than those obtained for the previously studied S_N1 hydrolysis reaction of 2-chloro-2-methylpropane (Leininger et al., 2003). For that S_N1 reaction, the rate constants in the PEG 300-H_2O solutions and 90 mass % PPG 425-H_2O solution were 2–3 orders of magnitude greater than those obtained in the traditional organic solvents at low water concentrations. However, for the hydrolysis of 1-chloro-3-methyl-2-butene, rate constants in the polyglycol solutions are an order of magnitude lower at low water concentrations, but are similar at higher water concentrations. Interpretation of these kinetic results in terms of the Gibbs free energies of reactant and transition states is discussed below.

Product Selectivity. The reaction mechanism in Figure 1 suggests that the product distribution depends on which carbocation resonance structure is more stable. The literature reports that tertiary carbocations are more stable than primary carbocations (Vollhardt and Schore, 1994) favoring the 2-ol product. Figure 4 shows the 2-ol:1-ol ratios observed in the various solvents using an initial 1-chloro-3-methyl-2-butene concentration of 0.1 mol/L. It was estimated that the error in the 2-ol:1-ol ratios were approximately ± 5%. In H_2O, the 2-ol:1-ol ratio has been reported as 5.7 (DeWolfe and Young, 1956). Figure 4 shows that the 2-ol:1-ol ratios are greatest in the PPG 425 solutions with values ranging from 4.1 to about 4.8 indicating little dependence of selectivity on water content. In the acetone-H_2O solutions, the 2-ol:1-ol ratio is about 2.2 when 10 mass % water is present and increases significantly to about 3.6 when 30 mass % water is present. In the literature, it has been

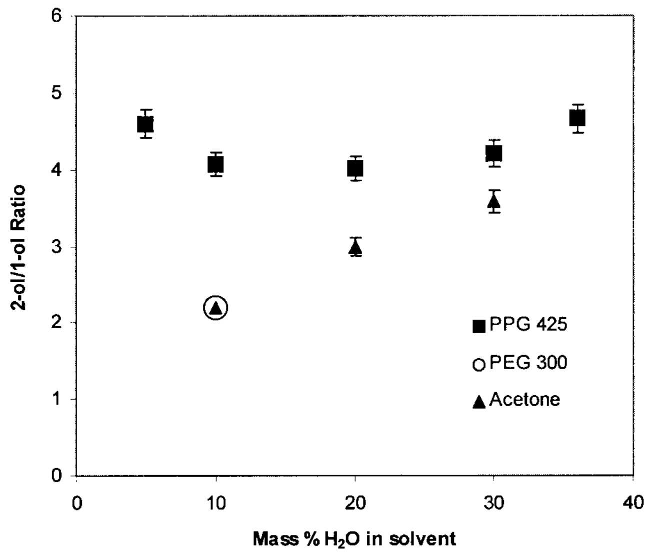

Figure 4. Solvent effects on the product ratio (2-ol:1-ol) for the hydrolysis of 1-chloro-3-methyl-2-butene at 22°C.

Initial reactant concentration = 0.1 mol/L.

shown that increasing the polarity of common solvents increases the 2-ol:1-ol ratio for this particular reaction (DeWolfe and Young, 1956, 1964). The fact that the PPG-H_2O solution does not behave like this leads to the hypothesis that the relative stability of the two resonance forms does not change when water is added to the PPG-H_2O solutions. This is interesting given that the first-order rate constant is significantly affected by the addition of water. The selectivity obtained in 90 mass % PEG 300-H_2O is similar to that in the 90 mass % acetone-H_2O solution, but not to that in 90% PPG 425-H_2O despite the similarities between the PPG and PEG molecules. Product selectivity was affected by initial reactant concentrations in 90% PPG-H_2O with the ratio increasing to 8.1 when the reactant was increased to 2 mol/L.

Reaction Yields. Reaction yields for the acetone-H_2O solutions were the highest with values around 80–90%. For the PPG 425-H_2O solutions, the yields are around 70–80% while, in 90 mass % PEG 300-H_2O solution, the yield is only about 40%. It is likely that side reactions between 1-chloro-3-methyl-2-butene and the alcohol groups on the polyethylene glycol molecule are responsible for the lower reaction yields in the PEG 300 solutions. This also seemed to occur in the methanol solutions. It appears that the alcohol groups on the polypropylene glycol molecule are less reactive than those in PEG 300 or methanol.

Temperature Effects. Because the aqueous polyglycol-H_2O solvents are less volatile, reactions in high glycol concentration solutions can be run at high temperatures without the use of high pressure. This is an important design advantage of the polyglycol-H_2O solvents. Values of the reaction rate constant at 22°, 35°, and 45°C in 70% PPG-H_2O solutions corresponded to an activation energy of 76 kJ/mol.

Diels-Alder reaction between cyclopentadiene and ethyl vinyl ketone

Reaction Kinetics. The rate constants for the second-order Diels-Alder reaction between cyclopentadiene and ethyl vinyl ketone are shown in Figure 5. (The rate constants for reaction in ethanol, 1-propanol, and for 10 mass % H_2O in 1-propanol at 25°C were obtained from Blokzijl et al. (1991)). Our experimentally measured rate constant in 1-propanol of 7.5×10^{-4} m^3/kmol*s corresponds within 2% of the value reported by Blokzijl et al. (1991). All kinetics were based on following the disappearance of cyclopentadiene. An error estimate for the rate constant values using data from multiple reaction runs is ± 10–15%.

For the pure solvents, rate constants are the highest in the 1-propanol solution. However, both PEG 300 and PPG 425 solvents yield rate constants that are comparable to those obtained in 1-propanol and ethanol. Similar to other Diels-Alder reaction results reported in the literature, the rate constants increase with the addition of water, approximately doubling with the addition of 10 mass % water. Diels-Alder rate constant accelerations have been attributed to hydrophobic effects, hydrogen bonding interactions, and polarity (Otto et al., 1994; Engberts, 1995; Cativiela et al., 1996; van der Wel et al., 1996; Otto and Engberts, 2000). These results are analyzed further below by calculating the Gibbs free energies of both the reactants and transition states.

Product Stereoselectivity. The endo:exo ratios obtained in various solvents are shown in Figure 6. The endo:exo ratios in pure PEG 300 and PPG 425 solutions are similar to each other, but lower than that in pure 1-propanol. The endo:exo ratio increased in all solvents when water was added. However, the ratio increased more in the PEG 300-H_2O and PPG 425-H_2O solutions than in 1-propanol, so that the ratios in the 70 mass % PEG 300-H_2O and 70 mass % PPG 425-H_2O solutions were comparable to that in the 60 mass % 1-propanol-H_2O solution.

It has been proposed in the literature that Diels-Alder reaction endo:exo ratios can be influenced by a number of solvent properties: solvophobic interactions, hydrogen bonding, and polarity interactions (Ahmad-Zadeh Samii et al., 1985; Cativiela et al., 1994, 1996; Jenner, 1994; Otto and Engberts, 2000). From our kinetic data alone, it is difficult to determine if the differences in the product ratio are caused from solvophobic interactions, hydrogen bonding, and/or polarity interaction as

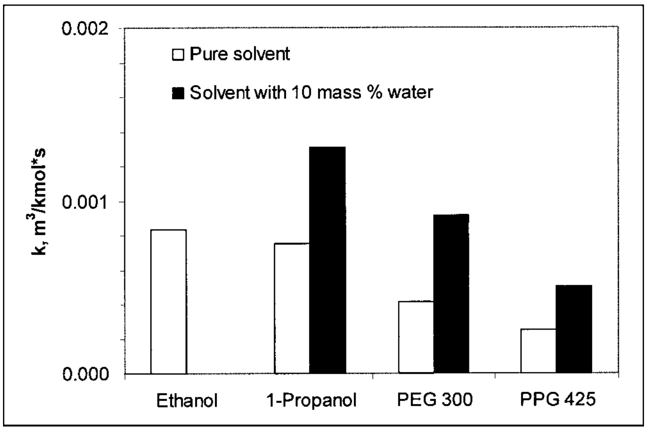

Figure 5. Rate constants for the reaction between cyclopentadiene and ethyl vinyl ketone in various solvents at 22°C.

Rate constants in ethanol and 1-propanol from Blokzijl et al. (1991).

all the solvents tested are polar, can hydrogen bond, and would most likely have solvophobic interactions with the Diels-Alder reactants.

Gibbs free energy interpretation of kinetics

S_N1 Reaction. As described in the Methods section, the changes in reactant free energy and the transition state free energy with respect to a reference solvent (95% PPG 425-H_2O) were calculated. Figure 7a shows these results for the hydrolysis of 1-chloro-3-methyl-2-butene in different solvents in terms of the decrease in Gibbs activation energy ($-\Delta G^{\neq}_{I\rightarrow II}$), while Figure 7b shows a qualitative free energy comparison. As water is added to the PPG 425-H_2O solutions, the transition state is more stabilized. The reactant energy (G^R) is only slightly de-stabilized in the PPG 425-H_2O solutions as water is added which corresponds to the slight decrease in 1-chloro-3-methyl-2-butene solubility. The reactant energies and transition state energies are similar in the 70 mass % PPG-H_2O solution and the 70 mass % acetone-H_2O solution, which corresponds to the similar reaction rates, although the acetone solution has a slightly lower transition state free energy.

We repeated these calculations using the reaction kinetics previously obtained for the hydrolysis of 2-chloro-2-methylpropane (Leininger et al., 2003) and found that the S_N1 transition state was significantly more stabilized (10–15 kJ/mol) in the 90 mass % PEG 300-H_2O solutions than in the 90 mass % acetone-H_2O or 90 mass % methanol-H_2O. S_N1 transition states generally seem to be stabilized in polyglycol-H_2O solutions.

Diels-Alder Reaction. Changes in Gibbs reactant free energies and transition state energies in going from pure PPG 425 (reference solvent) to other solvents were calculated for the Diels-Alder reaction between cyclopentadiene and ethyl vinyl ketone (Figures 8a and b.) These two figures show that the 90 mass % PPG 425-H_2O solution stabilizes the transition state of this reaction the most with 90 mass % 1-propanol-H_2O stabilizing the transition state the least. However, because the reactant free energy is higher in the 1-propanol solution (leading to lower solubility), the rate constant is higher. This corresponds with the concept that solvent solvophobicity increases Diels-Alder rate constants. However, it is important to note that, even though rate constants are lower in the polyglycol-H_2O solutions when compared to the 1-propanol-H_2O solution, the transition state is actually more stabilized in the polyglycol-H_2O solutions. This is a favorable result, because it tends to lower the activation energy of the reaction without decreasing reactant solubility.

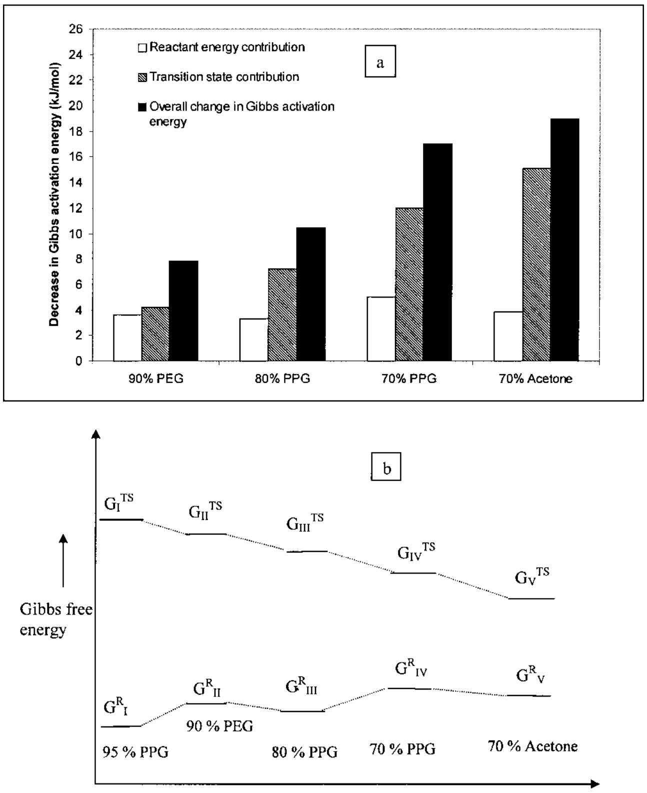

Figure 7. Changes in the Gibbs free energies for the hydrolysis of 1-chloro-3-methyl-2-butene in various solvents using 95% PEG 425-H_2O as the reference solvent.

(a) Overall decrease in Gibbs energy showing the contributions from the reactant energy and the transition state energy changes; (b) qualitative Gibbs energy diagram showing the results from part a (not to scale).

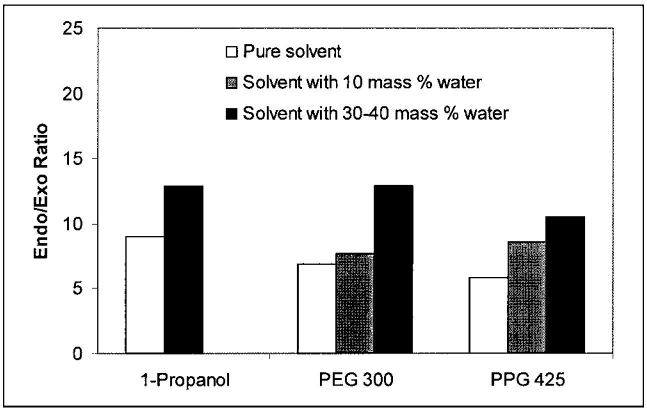

Figure 6. The effect of solvent on product selectivities (endo:exo) for the reaction of cyclopentadiene and ethyl vinyl ketone at 22°C.

S_N2 Reaction. We also calculated the free energy changes for a previously-studied S_N2 reaction (Leininger, 2002) between 1-bromobutane and diethylamine in traditional organic solvents (acetonitrile, and 1-butanol) and in aqueous polyglycol solutions. PPG 425 and PEG 300 solvents stabilized the transition state for the reaction more than did acetonitrile or 1-butanol solvents, but they also increased the reactant free energies resulting in an overall lower rate constant. (Data not shown.)

Conclusions

(1) These results, along with those previously reported (Leininger et al., 2002, 2003), support the idea that low molecular weight polyethylene glycol (PEG 300) and polypropylene glycol (PPG 425) and their aqueous solutions can be used as environmentally friendly reaction solvents for typical pharmaceutical synthesis reactions.

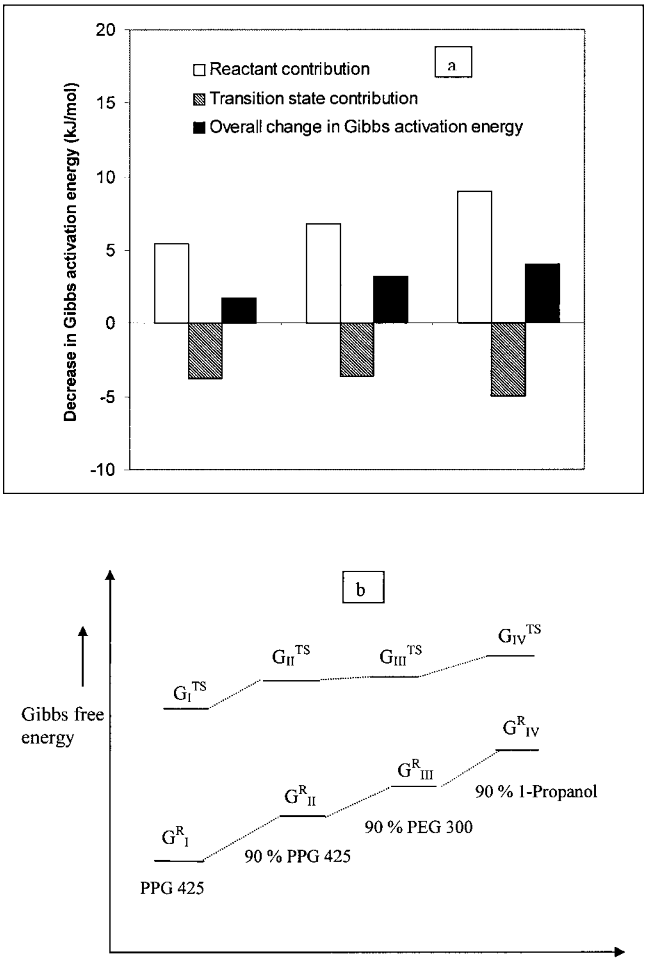

Figure 8. Changes in the Gibbs free energies for the reaction between cyclopentadiene and ethyl vinyl ketone in various solvents using pure PEG 425 as the reference solvent.

(a) Overall decrease in Gibbs energy showing the contributions from the reactant energy and the transition state energy changes; (b) qualitative Gibbs energy diagram showing the results from part a (not to scale).

(2) Kinetics: For the hydrolysis of the 1-chloro-3-methyl-2-butene (S_N1) reaction, the rate constants obtained at low water content were about an order of magnitude lower than those in the conventional solvents (methanol-H_2O and acetone-H_2O). At higher water content, the rate constants in the PPG 425-H_2O solutions were comparable. Reactant solubility was also quite high in the polyglycol-H_2O solutions so significant reaction rates were obtained at the various solvent compositions. For the Diels-Alder reaction between ethyl vinyl ketone and cyclopentadiene, the rate constants in the PPG 425 and PEG 300 solutions were comparable to those observed in 1-propanol and ethanol solvents.

(3) Product selectivity: For the hydrolysis of 1-chloro-3-methyl-2-butene, the 2-ol:1-ol ratio was highest in PPG 425-H_2O solutions as compared to aqueous acetone or PEG solutions. Adding water increased the 2-ol:1-ol ratio in the acetone solutions, but had little effect in PPG 425 solutions. For the Diels-Alder reaction studied, the endo:exo ratio in the pure solvents was about 30% lower in PEG 300 and PPG425 than in 1-propanol. Adding water increased the endo:exo ratio significantly in all solvents.

(4) Gibbs free energies: In comparison to conventional solvents, the transition states for the S_N1 and the Diels-Alder reactions were stabilized in the polyglycol-H_2O solutions. This is a favorable result since this lowers the activation energy without lowering reactant solubility.

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