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Detailed Understanding of Solvent Effects for the Cationic Ring-Opening Polymerization of 2-Ethyl-2-oxazoline

Maarten Vergaelen,[⊥] Bryn D. Monnery,[*,⊥] Valentin Victor Jerca, and Richard Hoogenboom[*]

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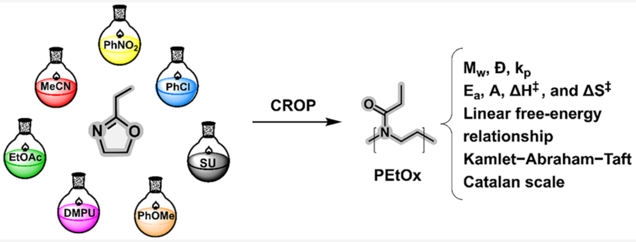

ABSTRACT: Polymerization of 2-ethyl-2-oxazoline (EtOx) has often been in the spotlight for fundamental studies of poly(2-alkyl/aryl-2-oxazoline)s (PAOx) polymerization, especially initiator screening, solvent screening, and copolymerization trends. In this work, we build on previous observations of solvent effects on the cationic ring-opening polymerization (CROP) of EtOx, with additional experimental observations of previously unreported solvents to expand the explored parameter space. Our objective is to find solvents with the lowest activation energy (E_a) and higher Arrhenius preexponential factor (A), which will allow us to produce narrow molar mass distributions at higher molecular weights, in the least time. To achieve this, we examined the various single factors like Dimroth $E_T(30)$ values, the Kamlet−Abraham−Taft (KAT) linear free-energy relationship (LFER) equation(s), and the Catalan LFER equations. Only one of Catalan's equations sufficiently disentangled dipolarity and polarizability to give a good fit due to contradictory effects. It was found that solvent nucleophilicity, electrophilicity, and polarizability affected the E_a, but not dipolarity. All four factors affected the A. This indicates that the E_a is minimized in solvents that do not solvate ions well (i.e. force ion-pairing), and A was minimized in more dipolar solvents that solvate the polymer chains well. A strongly negative activation entropy ($\Delta S^‡$) shows that the propagation reaction is associative. The Catalan LFER allows for the prediction of E_a, A, $\Delta H^‡$, and $\Delta S^‡$, and the derived k_p, across a broad range of solvents.

■ INTRODUCTION

In the two last decades, poly(2-ethyl-2-oxazoline) (PEtOx) has received considerable attention in the field of biomedical and pharmaceutical applications,[1−4] including polymer−prodrug conjugates,[5−7] hydrogels,[8−10] and matrix excipients.[11−15] Furthermore, hydrolysis of PEtOx affords linear poly(ethylene imine) (PEI),[16−18] which is the "gold standard" among cationic polymer transfection agent for delivery of nucleic acids.[16−21] As reproducible synthesis and narrow dispersity (for therapeutics) are key parameters for such biomedical applications, an in-depth understanding of the synthesis of PEtOx via living cationic polymerization is important. In this work, we addressed the question what the best solvent is for the polymerization of EtOx with respect to polymer solubility, monomer reaction rate, and polymer dispersity. The ideal solvent should be a good solvent for the polymer and give rapid polymerization with minimal chain transfer (i.e., low activation energy) leading to low dispersity if combined with fast initiation. PEtOx is soluble in both a broad range of polar and relatively apolar solvents, with chlorobenzene being the least polar solvent known to dissolve PEtOx, while toluene leads to precipitation during EtOx polymerization when targeting high-molar-mass polymers.[22,23] The ideal solvent should not interfere with the cationic ring-opening polymerization (CROP) of PEtOx, while retaining control over molar mass and molar mass distribution, and with a propagation rate as high as possible to minimize reaction times. Litt et al. were the first to survey the effect of solvent for the polymerization of 2-oxazolines in general.[24] In this work, they identified many solvents that reacted with the propagating centers, but they did not determine activation energies, etc. Solvent effects have also been described by Dworak[25] for the CROP of 2-methyl-2-oxazoline (MeOx) and by Monnery et al. for the low-temperature polymerization of 2-isopropyl-2-oxazoline in chlorobenzene.[26]

The initial investigations into the nature of the reactivity of propagating 2-oxazolinium cations were carried out by the groups of Saegusa[27−29] and Kagiya.[30,31] The first study of the effect of the solvent on the polymerization of 2-phenyl-2-oxazoline reported by Kagiya demonstrated that in polar solvents, the activation energy increased with increasing nucleophilicity, while it was unaffected by solvent nucleophilicity in apolar solvents. This is consistent with polymerization by free ions and ion pairs, respectively. This predated the establishment of the Kamlet−Abraham−Taft equation (see below) and can be seen as a pioneering work in this area.

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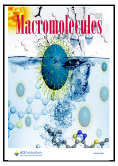

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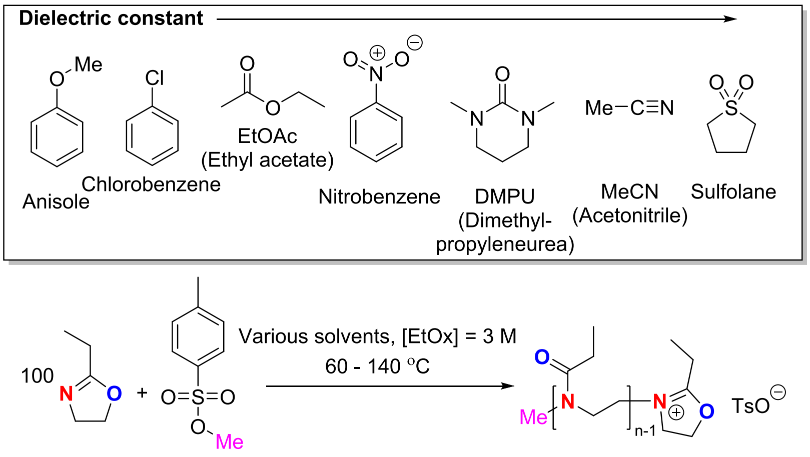
Scheme 1. General Scheme of Investigated Polymerization Solvents for the CROP of EtOx, under Standardized Conditions of [EtOx] = 3 M and [MeOTs] = 0.03 M[a]



[a]Solvents Are Ordered by Their Dielectric Constant.

A wide variety of initiator systems have been studied for EtOx, including alkyl sulfonates, alkyl, benzyl, and acetyl halides, oxazolinium salts, and Lewis acids.[32−37] The initiator may affect the polymerization rate in two ways. First, if the counterion is sufficiently nucleophilic, it can form a σ-bond with the propagating 2-oxazolinium cation, inactivating it as a covalent propagating species, but this is only observed with the lower halides.[25,33] Second, the size of the counterion will affect the propagation rate if it forms a close ion pair with the oxazolinium cation, but if the solvent is polar enough to solvate the ions, then this effect disappears.[26]

Finally, several studies show accelerated EtOx polymerization during copolymerization with a comonomer containing an electron-rich side chain, leading to end-group activation and transition state stabilization.[38−40] Moreover, some extraordinary solvents have been reported to lead to accelerated CROP of EtOx, including ionic liquids[41] and sulfolane.[42] The synthesis of uniform high-molar-mass PEtOx was reported in chlorobenzene.[43] Furthermore, ethyl acetate[44] and benzotrifluoride[23] were reported as greener solvents for the synthesis of PEtOx. Despite that a wide range of different solvents have been reported for the CROP of EtOx, a comprehensive comparative study on different polymerization solvents has never been conducted. Hence, a more in-depth evaluation of the effect of the solvent parameters, such as polarity and polarizability, has also not been reported for the CROP of EtOx.

There are three well-established polarity scales: Reichardt−Dimroth, Kamlet−Abraham−Taft, and Catalan. Reichardt's and Dimroth reported in 1963 that the longest-wavelength electronic absorption band of a particular solvatochromic betaine dye is related to the ionizing power (i.e., polarity and other factors) of the solvent.[45] This value, $E_T(30)$, is often normalized against water (= 1) and tetramethylsilane (= 0) to give E_T^N. This is a highly compounded term, which encompasses dipolarity (permanent dipoles/partial charges of the solvent), polarizability (the ability of a solvent to form temporary dipoles/partial charges), and, to a lesser extent, acidity (electrophilicity) and basicity (nucleophilicity).

The empirical Kamlet−Abraham−Taft (KAT) scale was constructed in an *ad hoc* fashion, with basicity (b.β),[46] acidity (a.α),[47] and dipolarity-polarizability (s·π^*)[48] forming the original three parameters (eq 1), which were reported separately. These were extended with an attempt to separate dipolarity and polarizability with an *ad hoc* correction factor (δ),[49] which can be rearranged:

$$x = x_0 + s\cdot\pi^* + a\cdot\alpha + b\cdot\beta \tag{1}$$

$$x = x_0 + p\cdot\pi^{**} + p\cdot d\cdot\delta + a\cdot\alpha + b\cdot\beta \tag{2}$$

The δ factor is 0.5 for polychlorinated compounds and 1 for aromatic compounds. This is extremely crude, and since it contains a compounded term, it cannot be used for multivariate linear regression. Recently Moreira et al. have devised a methodology to disentangle dipolarity and polarizability in π^* in a manner amenable to linear regression,[50] but with insufficient data points for our use. Additionally, other extensions to the KAT scale have been proposed, such as using the Hildebrand solubility parameter (δ_H) to account for cavity formation in the solvent shell, but it overlaps heavily with other factors, and so is not usually used.[51]

Given these problems, Catalan developed a new equation, with the factors being as pure as possible.[52,53] It was initially proposed with a term conflating dipolarity and polarizability (SPP), much like the KAT π^* (eq 3). The dipolarity (SdP) and polarizability (SP) were then separated (eq 4).[54]

$$x = x_0 + s\cdot\mathrm{SPP} + a\cdot\mathrm{SA} + b\cdot\mathrm{SB} \tag{3}$$

$$x = x_0 + p\cdot\mathrm{SP} + d\cdot\mathrm{SdP} + a\cdot\mathrm{SA} + b\cdot\mathrm{SB} \tag{4}$$

Czerwinski was the first to apply an LFER (E_T and KAT) for the determination of the effect of solvents on radical pulsed laser polymerization (PLP) k_p values.[55] Jeličić et al. used similar LFER's for the determination of the effect of ionic liquids on PLP k_p values.[56−59] Bergenudd et al. attempted to analyze the effect of solvents on the k_p of the atom-transfer radical polymerization (ATRP) of (oligoethylene glycol) methacrylate (OEGMA) but had an insufficient number of data points, and so the fit is statistically meaningless.[60] Smolne and Buback used the KAT equation to analyze the effect of different water-poly(ethylene oxide) mixtures on the k_p of OEGMA by ATRP.[61] Matyjaszewski and co-workers have successfully applied the KAT equation to the ATRP equilibrium.[62,63] The Catalan equations, being introduced

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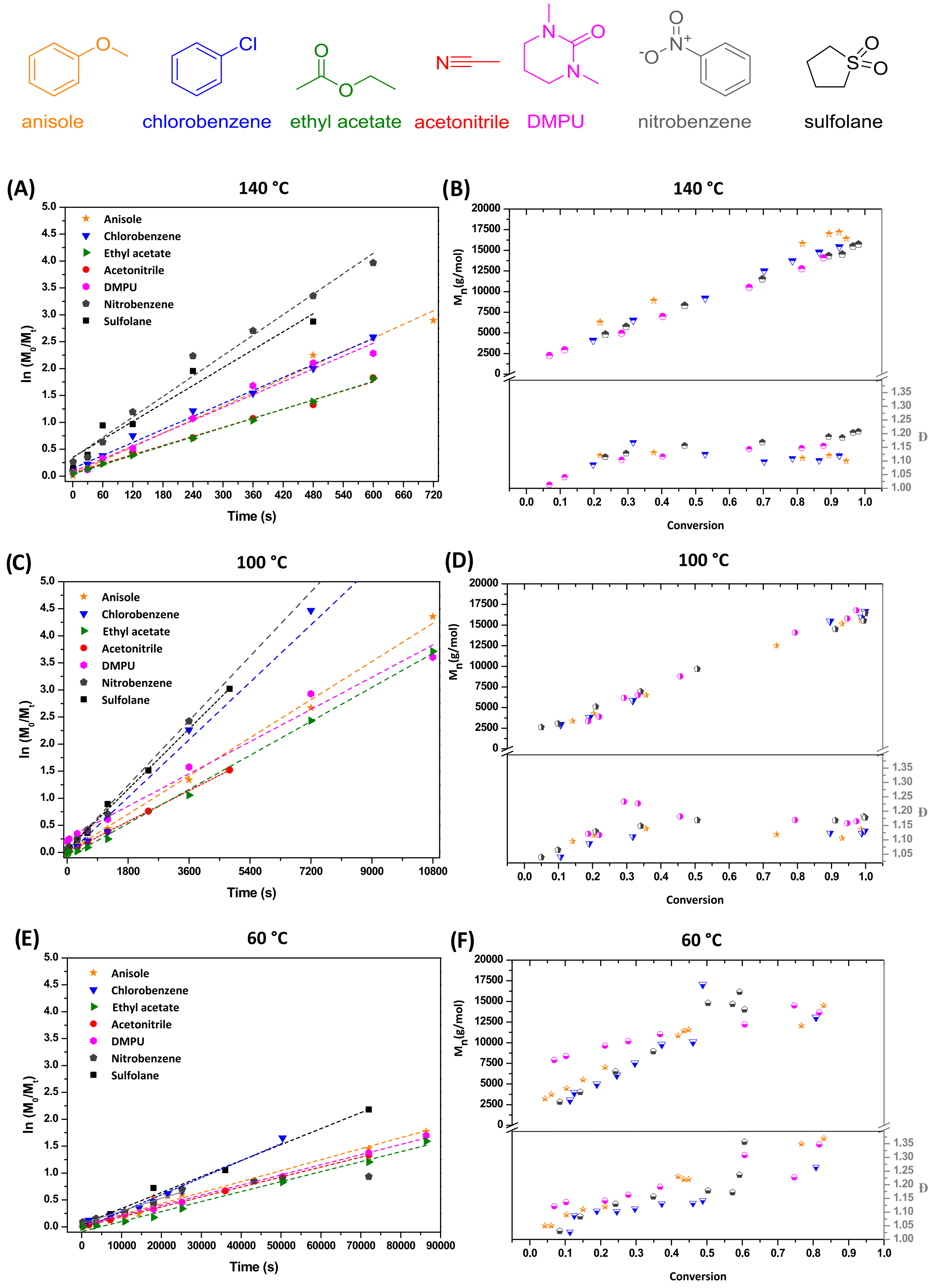


Figure 1. Polymerization kinetics of 2-ethyl-2-oxazoline (3 M) initiated by methyl tosylate (0.03 M) in acetonitrile,[42] anisole, chlorobenzene, DMPU, ethyl acetate,[44] nitrobenzene, and sulfolane[42] at 140 °C (A, B), 100 °C (C, D) and 60 °C (E, F). Only the linear region of the kinetic plots was used for the linear fits. Values for monomer conversion vs time plots for CROP in acetonitrile, sulfolane, and ethyl acetate were previously reported and are not incorporated in the M_n vs conversion plots. A larger zoom of this figure is provided in SI Figure S1 for improved readability.

much later than the KAT equations, have not been applied to the prediction of polymerization parameters, to the best of our knowledge. Ionic polymerizations have apparently confounded analysis by LFER, as shown by the lack of reports of such analysis. In none of the above reports were factors such as E_a and A determined separately, but rather the rate constants were predicted.

In this work, we have determined the polymerization rate constants (k_p) for the polymerization of EtOx with a constant initial monomer concentration (3 M) and initiator concentration (0.03 M methyl tosylate) in seven different solvents at three different temperatures (60, 100, and 140 °C). Our selection of solvents was based upon those reported to be good polymerization solvents for the CROP of EtOx; or theorized to be, including acetonitrile,[22,64] anisole, chlorobenzene,[43,65,66] *N*,*N*′-dimethylpropyleneurea (DMPU), ethyl acetate,[44] nitrobenzene, and sulfolane (Scheme 1).[42] We have determined the Arrhenius and Eyring−Polanyi parameters and analyzed them for correlation with solvent parameters, principally using Catalan's equation. The identification of good correlations would allow us to assess the reaction mechanism and to predict the behavior of the polymerization in other solvents.

RESULTS AND DISCUSSION

Kinetic Studies of the CROP of 2-Ethyl-2-oxazoline in Different Solvents at Varying Temperatures. For the kinetic investigation on the CROP of EtOx, a standard monomer to initiator (M/I) ratio of 100 was chosen, leading to a target DP of 100 repeating units. A monomer concentration of 3 M was chosen as being reasonably representative of previous work that is commonly in the 1−4 M monomer concentration range. Three temperatures were chosen, (60, 100, and 140 °C) covering a wide, commonly used, range and allowing the determination of the Arrhenius parameters for four solvents, namely, anisole, chlorobenzene, DMPU, and nitrobenzene. In addition, we included the previously reported polymerization kinetics for the CROP of EtOx in acetonitrile,[42] sulfolane (with five temperatures),[42] and ethyl acetate.[44] These data sets provided a sufficient number of experimental values for further analysis (Figure 1). Note that a zoom of Figure 1 is included in Supporting Information Figure S1 and the raw SEC traces of previously unpublished kinetic studies are shown in Figure S2.

Linear first-order kinetics were observed for all investigated solvents for the CROP of EtOx and all solvents led to controlled polymerization as indicated by the linear increase of molar mass with conversion and the rather low Đ values (Figure S1). The only exception was the CROP of EtOx in nitrobenzene at 60 °C, which showed undesired termination reactions as the conversion did not further increase after 25,000 seconds, and, therefore, the k_p was determined from the lower reaction coordinates. It is not understood why termination occurred during this polymerization, but it may be speculated that the nitro-group strongly coordinates the living cationic chain end, thereby inactivating it.

Most of the evolutions of molar mass and molar mass distributions (Figure 1) were consistent with fast and full initiation, apart from two of the most apolar solvents (chlorobenzene and ethyl acetate), which showed slow initiation at 60 °C and, therefore, the lower reaction coordinate was excluded for determination of the k_p values. Note that anisole might also show slow initiation, but this could not be identified due to the rather late first data point. This slow initiation might be surpassed using more reactive initiators such as triflates or 2-oxazolinium salts, but for this comparative study, we preferred to keep the initiator constant.[26,36]

The k_p values (Table 1) were determined from eq 5, rearranged into eq 6

Table 1. Propagation Rate Constants (k_p in L·mol·s^{-1}) for the CROP of EtOx in the Seven Different Solvents at 60 °C (333.15 K), 100 °C (373.15 K), and 140 °C (413.15 K)

	k_p (L·mol·s^{-1})		
solvent/temperature (K)	333.15	373.15	413.15
acetonitrile	6.81×10^{-4}	1.31×10^{-2}	1.41×10^{-1}
anisole	6.17×10^{-4}	1.06×10^{-2}	9.16×10^{-2}
chlorobenzene	9.90×10^{-4}	2.07×10^{-2}	1.85×10^{-1}
DMPU	1.18×10^{-3}	1.99×10^{-2}	1.34×10^{-1}
ethyl acetate	6.29×10^{-4}	1.26×10^{-2}	1.46×10^{-1}
nitrobenzene	7.85×10^{-4}	2.21×10^{-2}	2.11×10^{-1}
sulfolane	6.54×10^{-4}	1.20×10^{-2}	9.56×10^{-2}

$$\frac{d[M]}{dt} = k_p \cdot \frac{[I]_0}{[M]_o} \cdot [M]_0 \tag{5}$$

$$k_p = \frac{d[M]}{dt} \cdot \frac{1}{[I]_0} \tag{6}$$

where $\frac{d[M]}{dt}$ is the rate of change of the concentration of the monomer and $[M]_0$ and $[I]_0$ are the initial concentrations of the monomer and initiator, respectively.

Discussion on the Arrhenius Parameters and Trends for the Polymerization of 2-Ethyl-2-oxazoline in Different Solvents. The k_p values were used to estimate the activation energy (E_a) and the effective collision frequency (preexponential factor, A) using the Arrhenius equation (eq 7) in its rearranged form (eq 8), based on the assumption that the three data points represent the expected linear correlation

$$k_p = A\ e^{-E_a/RT} \tag{7}$$

$$\ln\ k_p = \ln A - \frac{E_a}{RT} \tag{8}$$

where R is the gas constant and T is the temperature (K).

The Arrhenius plot (Figure 2) was used to determine the E_a and A in the seven investigated solvents (Table 2). By inspection, it can be observed that E_a is lower in apolar solvents and A is higher in polar solvents. Essentially, more collisions occur in polar solvents, but of those that occur in apolar solvents, more are successful.

Determination of the Activation Enthalpy and Entropy. Using the Eyring−Polanyi equation (eq 9) in its rearranged form (eq 10), the Eyring−Polanyi plot (Figure 3) allows for calculation of the activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) (Table 3)

$$k_p = \frac{\kappa \cdot k_B \cdot T}{h}\ e^{\Delta S^{\ddagger}/R}\ e^{-\Delta H^{\ddagger}/RT} \tag{9}$$

$$\ln \frac{k_p}{T} = \frac{-\Delta H^{\ddagger}}{R} \cdot \frac{1}{T} + \ln \frac{\kappa.\ k_B}{h} \cdot \frac{-\Delta S^{\ddagger}}{R} \tag{10}$$

where κ is the transmission rate constant, k_B is the Boltzmann constant, and h is Plank's constant. Since the propagation reaction is irreversible, it is assumed that the transmission rate

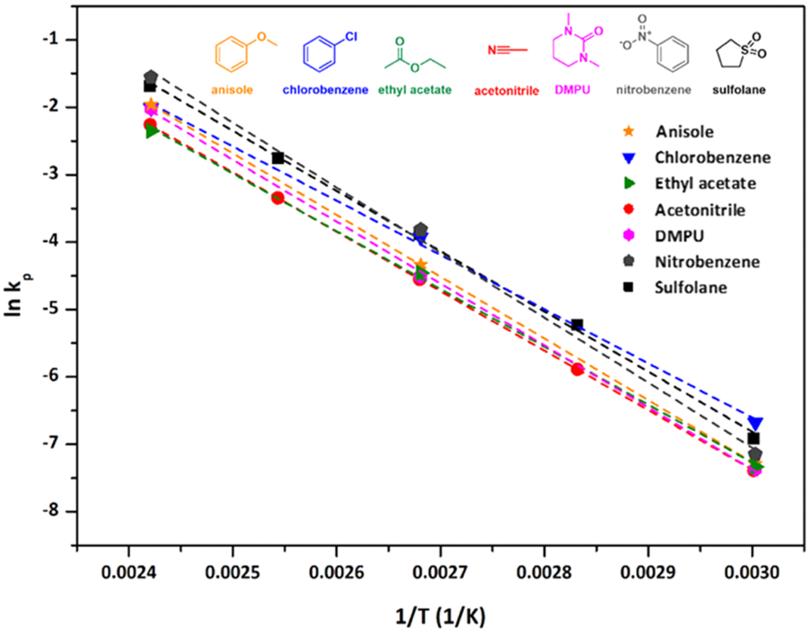


Figure 2. Arrhenius plot, giving the correlation of the ln of the propagation rate constant versus the inverse temperature for the CROP of EtOx in different solvents. Note that five data points are included for the CROP of EtOx in acetonitrile and sulfolane based on literature data.[42,44]

Table 2. Overview of the Arrhenius Parameters for the CROP of EtOx in the Various Solvents

Solvent	E_a (kJ.mol^{-1})	A
Acetonitrile	71.6	1.06×10^8
Anisole	76.3	6.14×10^8
Chlorobenzene	68.0	5.71×10^7
DMPU	77.9	1.03×10^9
Ethyl acetate	71.5	1.10×10^8
Nitrobenzene	80.3	3.28×109
Sulfolane	75.0	5.92×10^8

constant is unity (κ = 1). The $\Delta S^‡$ term being negative is consistent with the propagation being an S_N2 reaction.

Determination of the Relationship of the Solvent with the Reaction Mechanism. Initially, it was attempted to fit the data from Figure 2 and Table 1 and the k_p values for the CROP of EtOx in the different solvents to the solvent properties, *e.g.*, polarity, dipole moment, or dielectric constant of the solvents by univariate regression, but there was no obvious, simple relationship (Table S1).

Next, the Kamlet–Abraham–Taft equation in its' simple form (eq 1) was used, which also did not show a statistical

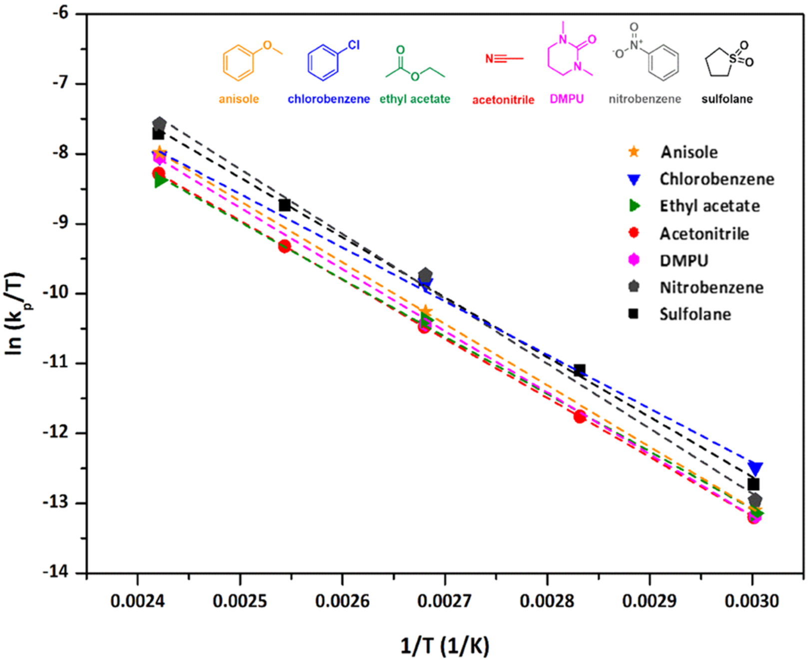


Figure 3. Eyring–Polanyi plot (ln k_p/T vs 1/T) for the CROP of EtOx in the various solvents, retrieved from all of the experiments at different temperatures. Note that five data points are included for the CROP of EtOx in acetonitrile and sulfolane based on literature data.[42,44]

Table 3. Enthalpy of Activation ($\Delta H^{\ddagger}$) and Entropy of Activation ($\Delta S^{\ddagger}$) for Various Solvents Calculated from the Eyring–Polanyi Plot

Solvent	$\Delta H^{\ddagger}$ (kJ·mol^{-1})	$\Delta S^{\ddagger}$ (J·mol^{-1}·K^{-1})
Acetonitrile	68.5	−101.4
Anisole	73.2	−86.8
Chlorobenzene	64.9	−106.6
DMPU	74.9	−82.5
Ethyl acetate	68.4	−101.1
Nitrobenzene	77.2	−72.9
Sulfolane	71.9	−87.1

correlation with the k_p's (Table S2). Given the possibility that the factors comprising k_p were not covarying, we have decomposed the data using the Arrhenius and Eyring–Polanyi theories to derive E_a and A, and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively, which, however, also did not show a significant correlation (Figure S3 and Table S2).

The conflation of dipolarity and polarizability in this equation is a known problem, and a correction factor, δ, is sometimes used to separate them (eq 2).[49] However, this is a nonlinear equation and cannot be analyzed by linear regression.

In contrast to these previous methods, the Catalan eqs 3 and 4 are relatively pure, and eq 4 separates dipolarity and polarizability. Hence, linear regression using both Catalan eqs 3 and 4 was performed for the various factors. The factors x_0, p, d, s, a, and b (as appropriate) were fitted to the solvent factors.

It was found that nitrobenzene simply did not fit with the other investigated solvents. If nitrobenzene was excluded from the fit, then a very strong correlation was found for E_a, A, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$. It must, therefore, be concluded that nitrobenzene is either an interfering solvent or contains interfering impurities despite the extensive purification, which would also explain the termination reactions observed.

With eq 3, in which the solvent polarizability and dipolarity are conflated in a single term (SPP), the SPP term is found to have no statistical relationship with our analyzed coefficients in all cases, leading to a generally poor fit (Table S3). It was, however, a much better fit than eq 1, on the edge of statistical significance. We thus found that eq 3 is inappropriate for analyzing this data, but it was a step in the right direction.

Using eq 4 that separates dipolarity and polarizability led to a much better fit of the data (Table S4, Figure S4). However, it was only significant for A. When the 95% confidence intervals were calculated for E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ that the confidence interval of SdP included zero (0), there was no relationship between these factors and the dipolarity of the solvent. SdP is thus an insignificant variable in those cases; it has no relationship with the measurement, and must be removed.

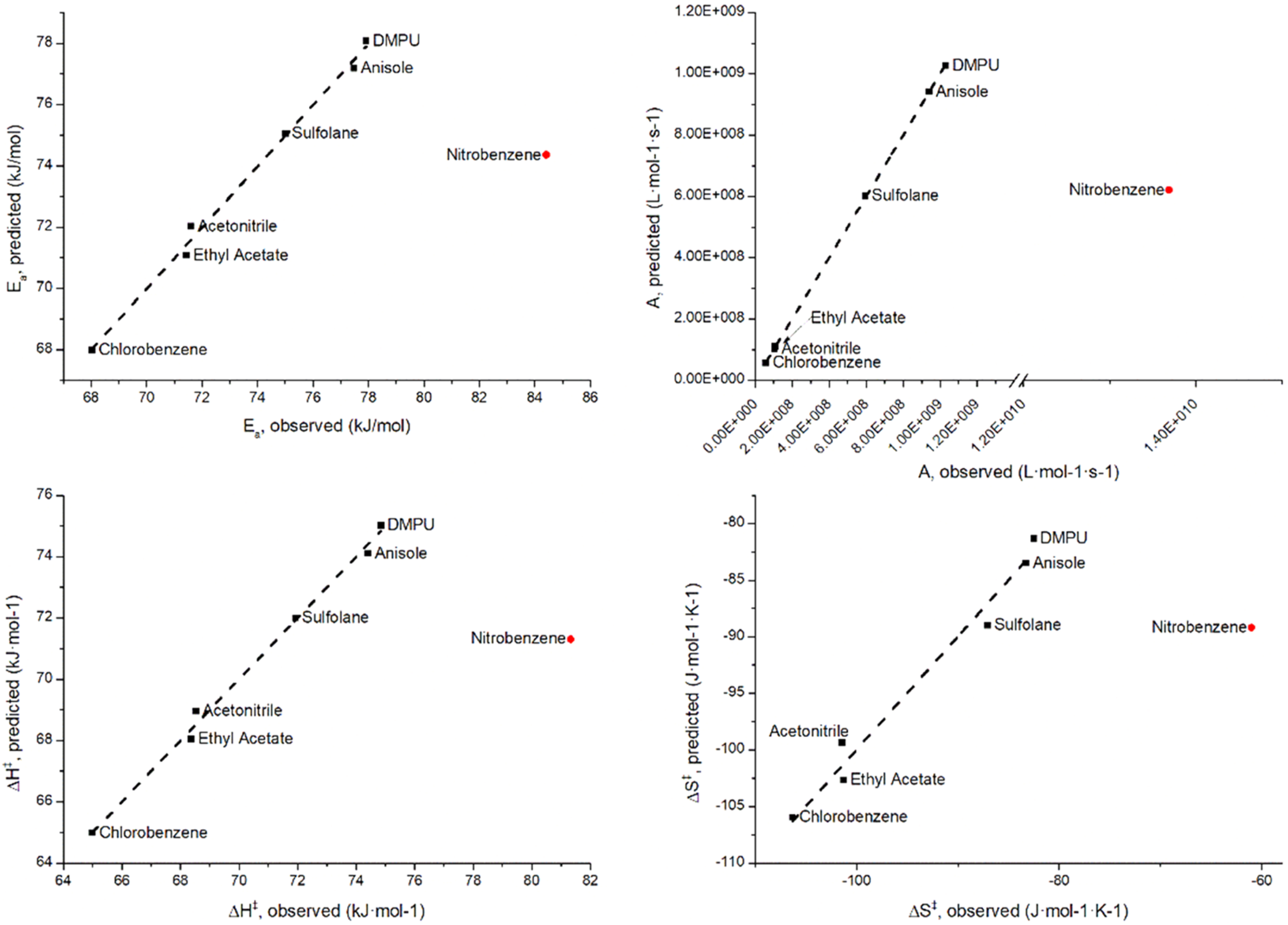


Figure 4. Results of a three-parameter (eq 11, for E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) and four-parameter (eq 4, for A) fit to the Catalan equation. As dipolarity is unrelated to the E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$, it was excluded. Nitrobenzene was excluded as it was found to act as a terminating solvent.

The equation thus was simplified for these factors resulting in eq 11

$$x = x_0 + p{\cdot}\mathrm{SP} + a{\cdot}\mathrm{SA} + b.\ \mathrm{SB} \tag{11}$$

The resulting three-parameter fit for the activation energy and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, combined with a four-parameter fit for the Arrhenius parameter (A) is shown in Figure 4, with the corresponding calculated coefficients being summarized in Table 4. The equations are statistically significant in all cases.

In eqs 4 and 11, dipolarity does not significantly affect $\Delta S^{\ddagger}$ but does affect the preexponential factor, A. The preexponential factor can be decomposed into the collision frequency (Z) and the steric factor (ρ) as per eq 12. In the gas phase, it is simple to calculate Z from first principles and hence derive ρ, but in solution, this is impossible due to diffusion being limited. However, ρ is related to $\Delta S^{\ddagger}$ as per eq 13.

$$A = \rho{\cdot}Z \tag{12}$$

$$\rho \approx \mathrm{e}^{\Delta S^{\ddagger}/R} \tag{13}$$

Hence, since ρ is related to $\Delta S^{\ddagger}$ and this is not related to the dipolarity, the relationship of A and dipolarity must be in the collision frequency, Z. That is, the dipolarity only affects the frequency of collisions. The most reasonable explanation is that in polar solvents, the polymer chain is more extended, and thus the monomer is free to diffuse to the propagating center, whereas in apolar solvents, the chain is collapsed and imposes a diffusion limit on the monomer diffusing into the polymer globule.

This explains the failure of the conflated Catalan equation (eq 3) since the factors are strongly correlated with polarizability, and not correlated with dipolarity, with the terms conflated in SPP the regression cannot disentangle the two, rendering the equation not applicable in this case. This also explains the failure of the Kamlet−Abraham−Taft equation with this reaction since π^* also conflates dipolarity and polarizability in the same manner.

The k_p values cannot be directly calculated by regression (p-value of 0.51, 0.66, and 0.66 for 60, 100, and 140 °C, respectively), since SP has a contrary effect on E_a and A, and direct analysis would require them to co-vary. However, if the calculated values of E_a and A are simply fed back into the Arrhenius equation (eq 7) then an extremely good fit (adj. r^2 = 0.9996) is obtained (Figure 5). Thus, the predicted values can be used to estimate reaction rates.

Solvent Effects in the Mechanism of Polymerization.

It must be stated that nitrobenzene behaves in a way that defies all of the general trends. The observation of a termination reaction at 60 °C suggests that the nitro-group strongly coordinates the living cation, thereby inactivating it.

The propagation rate constants, k_p, are strongly increased by increased solvent polarizability, and moderately increased by increased solvent dipolarity. They are decreased with increased solvent electrophilicity and nucleophilicity.

The activation energy, E_a, and activation enthalpy, $\Delta H^{\ddagger}$, are increased by increased polarizability, electrophilicity, and nucleophilicity. These factors all relate to the solvation of ions, and hence loosen the ion-pairing of the oxazolinium with its counterion. They are insensitive to solvent dipolarity. This is in agreement with Monnery et al. who argued that the ion pair was more reactive due to an increase in ring strain due to charge−dipole repulsion distorting the cationic oxazolinium ring.[26]

Table 4. Coefficients for the (Reduced) Catalan eq 11 and eq 4 for the CROP of EtOx and the Relative Statistical Fit[a]

eq.	x_0	p	d	A	b	error DoF	adjusted r^2	p-value
E_a	59.79 (57.01−62.57)	7.19 (3.20−11.05)	0	93.83 (81.00−106.67)	12.13 (10.04−14.21)	2	0.986	0.00815
A	-1.36×10^9	1.70×10^9	-3.59×10^8	9.35×10^9	1.05×10^9	1	1	0.0136
	$(-1.44 \times 10^9 - 1.28{\times}10^9)$	$(1.62 \times 10^9 - 1.78 \times 10^9)$	$(-4.06 \times 10^8 - 3.11 \times 10^8)$	$(9.08 \times 10^9 - 9.62 \times 10^9)$	$(1.01 \times 10^9 - 1.09 \times 10^9)$			
$\Delta H^{\ddagger}$	56.75−	7.24	0	92.84	12.08	2	0.985	0.00869
	(53.90−59.61)	(3.38−11.11)		(80.01−105.68)	(9.84−14.22)			
$\Delta S^{\ddagger}$	−139.60	34.68	0	236.16	26.18	2	0.948	0.0309
	(−154.24−124.96)	(14.85−54.51)		(168.59−303.73)	(15.21−37.15)			

[a] In all cases, $P < 0.05$ and thus is a significant fit.

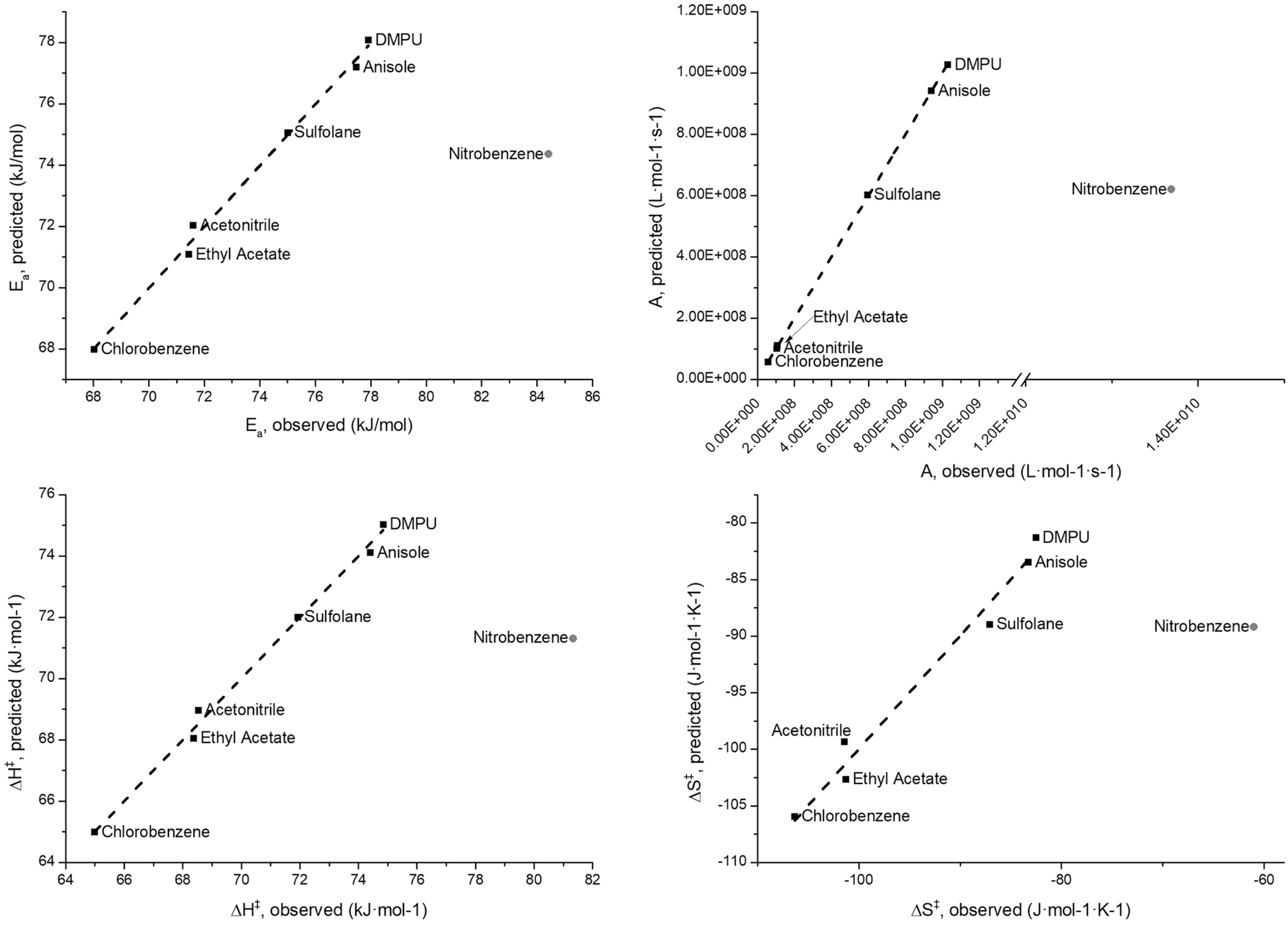


Figure 5. Generalized fit of k_p generated by plotting the product of the Arrhenius equation from predicted values of E_a and A vs observed k_p.

The preexponential factor, A, is very strongly increased with increased polarizability and moderately increased with increases in the other factors.

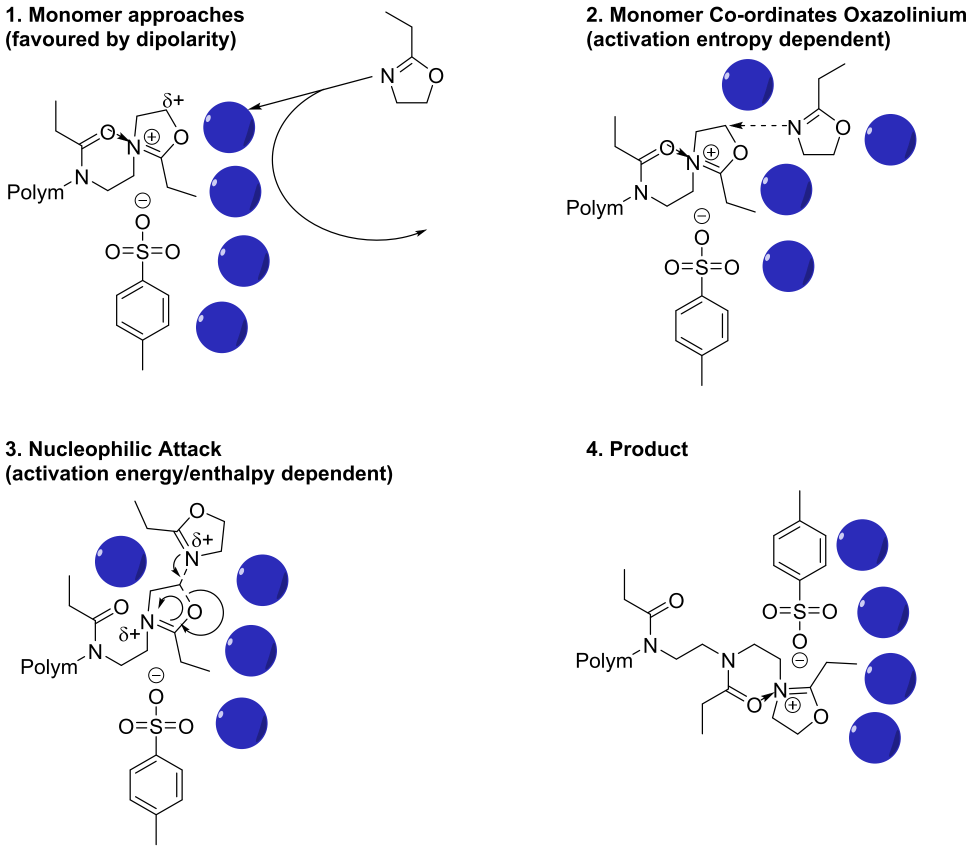
The activation entropy, $\Delta S^{\ddagger}$, is strongly negative. This means that the reaction mechanism is associative, and it relates to the entropy change of the formation of the activated complex (i.e., the insertion of a monomer molecule into the complex following a collision). It is strongly increased by increased polarizability, and moderately by electrophilicity and nucleophilicity (i.e., increased polarizability, etc. means it is easier to insert a monomer into the complex). It is found that it is most difficult to insert a monomer into the oxazolinium complex in chlorobenzene, acetonitrile, and ethyl acetate, and easiest to insert in DMPU, anisole, or sulfolane (the solvents forming two distinct groups). This suggests that the tighter the ion pair, the more difficult the monomer insertion is.

The collision frequency, Z, is increased with increased dipolarity. Since this is related solely to the number of collisions, and not on the success or failure of a collision, it must mean that in a dipolar solvent, more collisions between the oxazolinium end-group and monomer occur. This can be explained by considering the polymer chain in solution. It is a random coil whose tightness or looseness depends upon how well solvated it is. Thus, in a less dipolar solvent, the coil will be more compact, and it will be more difficult for the monomer to diffuse to the oxazolinium, and *vice versa* in a more dipolar solvent. Hence, in a less polar solvent, the probability of a monomer diffusing through the polymer globule to reach the oxazolinium is decreased.

The increase of E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ with the solvent nucleophilicity is expected since the solvent is competing with the nucleophilic monomer. What was unexpected was to find a similar effect for electrophilicity. This must be due to the solvent coordinating either the counterion or the monomer π-system (or both), which are the two electron-rich species in the system. In the former case, it would prevent ion-pairing which is expected to increase the E_a. In the latter case, the solvent would decrease the nucleophilicity of the monomer by forming a complex reducing its ability to insert into the preactivated complex (i.e., decrease $\Delta S^{\ddagger}$), which is the opposite of what is observed. Thus, the primary reason for electrophilicity increasing E_a must be due to increased solvation of the counterion, loosening the ion pair.

Thus, we essentially have a situation wherein if the solvent allows for easy insertion of a monomer (higher $\Delta S^{\ddagger}$), as happens in polar solvents, then E_a and $\Delta H^{\ddagger}$ are increased, making it less likely that a propagation reaction occurs. Therefore, neither polar nor apolar solvents give hugely different k_p values, and the effects of polarity on k_p are contradictory. The general mechanism is per Figure 6, remembering that the $n - 1$ carbonyl donates electron density to the oxazolinium cation.

Predictions for Other Solvents. We have extended the Catalan values for 137 solvents available.[37] We can apply these


1. Monomer approaches (favoured by dipolarity)

2. Monomer Co-ordinates Oxazolinium (activation entropy dependent)

3. Nucleophilic Attack (activation energy/enthalpy dependent)

4. Product

Figure 6. Notional scheme of polymerization. (1) Approach of monomer and repulsion by polymer chain and solvent sphere. (2) Coordination to oxazolinium, displacing a solvent molecule. (3) Nucleophilic attack leading to (4) product which reforms intramolecular dative bonds.

to our equations and assess whether there are potentially better solvents available. We have calculated the E_a (Table S5), A (Table S6), and k_p values (Table S7). We should note that many of these solvents are interfering (such as alcohols, amines, and water) or are poor solvents for PEtOx, such as toluene. These solvents are, hence, only theoretically assessed and could not be used for the CROP of EtOx.

The most important value is E_a, as it also is the prime determining factor in the degree of chain transfer (assuming that the β-elimination E_a is relatively invariant). Here, we find that chlorobenzene is the best available known solvent, as all of the solvents we estimate to have lower E_a do not solvate the polymer.

We should note that the solubility of poly(2-alkyl-2-oxazoline)s in apolar solvents increases as the side chain becomes longer and with some of the larger alkyl side-chain toluene is a good solvent.[70] This is also applied to copolymers with 2-ethyl-2-oxazoline, as above 90 °C toluene is a reasonable solvent for PEtOx.[23] Thus, for future work with such systems, it may be worth exploring solvents such as toluene to further suppress chain transfer.

In terms of the preexponential factor, anisole and sulfolane are close ties for the two best solvents. All of the solvents estimated to give higher values interfere with the polymerization. These solvents are of particular value in the polymerization of block and star polymers, as they can solvate low-molar-mass polymers bearing multiple 2-oxazolinium cations,[71] which chlorobenzene does not.[72]

For the rate constants, temperature has a very significant impact. At lower temperatures, the reaction proceeds faster in apolar solvents, whereas at high temperatures, the reaction proceeds faster in polar solvents. This is due to the increase in molecular energy in the Boltzmann distribution of the system. Since the E_a is lower in apolar solvents then increases in temperature will have less of an effect as a smaller proportion of the distribution will cross the E_a threshold (due to more already being over said threshold). Since the raw collision rate is higher in polar solvents, eventually as the temperature increases the propagation rate will favor the polar solvent.

However, it should be noted that the increased E_a in polar solvents will be accompanied by an increased fraction of chain transfer polymers and that increased temperatures will do likewise. To produce polymers with the lowest content of transfer products, the least polar solvent that dissolves the polymer should be used. For PEtOx with a single propagating oxazolinium, this is chlorobenzene. For PMeOx, this optimal solvent is sulfolane since there are no solvents of lower polarity known that can dissolve PMeOx. For PEtOx with multiple 2-oxazolinium groups, as present during star-polymer synthesis with multifunctional initiators, a more polar solvent such as acetonitrile is required, at least in the lower reaction coordinate.[72] Anisole provided a high collision rate (hence extended random coil) and is far more convenient to use than sulfolane, but it does not dissolve PMeOx. For more apolar polymers, like poly(2-nonyl-2-oxazoline), solvents such as toluene are predicted to be the ideal choice.

■ CONCLUSIONS

In this work, we have studied the kinetics of the polymerization of 2-ethyl-2-oxazoline in constant conditions, varying only the

Table 5. Polarity Properties of the Solvent Used[a]

	Catalan parameters					Kamlet−Abraham−Taft parameters				miscellaneous	
solvent	SPP	SP	SdP	SA	SB	α	β	π^*	Hildebrand δ_H (MPa$^{1/2}$)	dielectric constant	Dimroth $E_T(30)$ (kcal·mol^{-1})
acetonitrile	0.895	0.645	0.974	0.044	0.286	0.19	0.40	0.75	24.3	37.5	45.6
anisole	0.823	0.82	0.543	0.084	0.299	0	0.22	0.73	19.8	4.33	37.1
chlorobenzene	0.824	0.833	0.537	0	0.182	0	0.07	0.71	19.4	5.62	36.8
DMPU	0.924	0.936[b]	0.672[b]	0.026	0.752	0.46	0.87	0.86	21.9	36.12	42.1
ethyl acetate	0.795	0.656	0.603	0	0.542	0	0.45	0.55	18.6	6.02	38.1
nitrobenzene	0.968	0.891	0.873	0.056	0.24	0	0.30	1.01	20.5	34.8	41.2
sulfolane	1.003	0.83	0.896	0.052	0.365	0	0.39	0.98	27.4	44	44

[a] Left: Catalan's parameters, which are used in this work; center: Kamlet−Abraham−Taft parameters,[51,67] the Hildebrand solubility parameter;[68,69] right, dielectric constant (a generalized polarity term), and the Dimroth−Reichardt mixed dipolarity/electrophilicity parameter. [b] Disentangled using Catalan's equations as per the methods.

solvent. Seven solvents were investigated, covering a wide range of usable solvents. Nitrobenzene was mildly interfering in the polymerization, but the other six behaved conventionally. A first attempt to find any correlation between the solvent properties and the propagation rate constants (k_p)/Arrhenius parameters (A, E_a) failed to put any trend forward. Nevertheless, further analysis by Arrhenius and Eyring−Polanyi gave the activation energy, enthalpy and entropy, and preexponential factors. Using these values, regression analysis using the Catalan equation revealed the generalized relationship of these values with solvent parameters, assuming no reaction occurs with the solvent (as suggestively happened with nitrobenzene). This enabled us to clarify the hypothesis, which was consistent with that proposed by Monnery et al. in 2015.[26] In polar solvents, it is easier to insert a monomer into the oxazolinium−solvent complex, but the activation energy is higher. Conversely, in apolar solvents, it is more difficult to insert the monomer into the complex, but the activation energy is lower. This can be explained in terms of ion-pairing.

In general, when aiming to minimize side reactions (certainly required when aiming for higher-molecular-weight PEtOx; and PAOx), the activation energy should be lowered and, therefore, the least polar solvent in which the polymer is soluble should be used.

As a conclusion of this "Arrhenius−Eyring−Polanyi−Catalan" approach, the theoretical reaction kinetic parameters were calculated for a large series of solvents, as a proof of concept of the used methodology and based on the experimental work done for the CROP of EtOx in various solvents.

EXPERIMENTAL SECTION

Materials. Methyl *p*-toluenesulfonate (MeOTs), drying agents (barium oxide, calcium hydride, sodium pallets), potassium hydroxide, and solvents (chlorobenzene, anisole, nitrobenzene, DMPU) (HPLC quality or Acroseal) were purchased from both Sigma-Aldrich and Thermo Fisher/Acros Organics. 2-Ethyl-2-oxazoline (EtOx) was kindly donated by Polymer Chemistry Innovations (PCI). CH_3CN was purified over aluminum oxide by means of a solvent purification system from J.C. Meyer.

Purification of Solvents, Monomer, and Initiator. Anisole, DMPU, ethyl acetate, and nitrobenzene were dried over barium oxide and fractionally distilled. The center-cut fraction was then redistilled from fresh barium oxide.

Acetonitrile was purified by passage through an aluminum oxide column in a nitrogen atmosphere (J.C. Meyer system) and piped directly into a glovebox.

Chlorobenzene was washed three times with concentrated sulfuric acid (i.e., until no discoloration occurs), three times with saturated aqueous sodium bicarbonate, and three times with water. It was dried with magnesium sulfate, filtered, and then dried over barium oxide before distillation onto living P(EtOx) tosylate followed by distillation into a clean receiving vessel.

Sulfolane was slurried over potassium permanganate until the purple color persisted for 1 h. Excess $KMnO_4$ was destroyed by adding methanol dropwise until the mixture was colorless, and the manganese oxide was filtered off. Methanol was removed by rotary evaporation, and the sulfolane was dried over calcium hydride before vacuum distillation.

2-Ethyl-2-oxazoline was fractionally distilled, dried over barium oxide, and redistilled from sodium.

Methyl tosylate was dried over calcium hydride and vacuum-distilled.

Equipment. Conversions for the CROP of the selected 2-oxazoline monomers were monitored by gas chromatography (GC) analysis. GC was performed on an Agilent 7890A system equipped with a VWR Carrier-160 hydrogen generator and an Agilent HP-5 column of 30 m length and 0.320 mm diameter. An FID detector was used and the inlet was set to 240 °C with a split injection ratio of 25:1. Hydrogen was used as carrier gas at a flow rate of 2 mL/min. The oven temperature was increased by 20 °C/min from 50 to 120 °C, followed by a ramp of 50 °C/min. to 240 °C. To determine conversion, t(0) samples were taken and the solvent was used as the internal standard.

All stock solutions and samples were prepared in a VIGOR Sci-Lab SG 1200/750 Glovebox System with an atmospheric water concentration below 0.1 ppm. For the polymerizations, a Biotage Initiator EXP Microwave System with Robot Sixty was used. During the polymerizations, the microwave synthesizer operated at a constant set temperature, which is monitored by an IR sensor, and normal absorption levels were kept constant throughout all experiments.

Size-exclusion chromatography (SEC) was performed on an Agilent 1260-series HPLC system equipped with a 1260 online degasser, a 1260 ISO pump, a 1260 automatic liquid sampler (ALS), a thermostatted column compartment (TCC) at 50 °C equipped with two PLgel 5 μm mixed-D columns in series, a 1260 diode array detector (DAD), and a 1260 refractive index detector (RID). The used eluent is N,N′-dimethylacetamide (DMA) containing 50 mM lithium chloride at an optimized flow rate of 0.5 mL/min. The spectra were analyzed using the Agilent ChemStation software with the GPC add-on. Molar mass and dispersity ($Đ$) values were calculated against polymethylmethacrylate standards from Polymer Standards Service (Mainz, Germany).

Method for Polymerization Kinetic Studies. To perform the kinetic studies, 45 mL stock solutions (3 M EtOx, 0.03 M MeOTs, in the appropriate solvent) were prepared in a glovebox. These were divided into 2.5 mL microwave vials (700 to 800 μL each). For each run, 24 microwave vials were heated for at least seven different times at three different temperatures for each of the polymerization solvents. After the reaction, GC samples were made by sampling 100 μL of the reaction medium and diluting with 900 μL of chloroform for injection (or acetone for ethyl acetate due to the chloroform and ethyl acetate peaks overlapping). Monomer conversion was calculated by the decrease in the integration of the monomer peak when normalized against the solvent peak.

For the SEC analysis, the samples were terminated with 500 μL of a methanolic KOH solution, and 100 μL of this solution was diluted with 900 μL of DMA (supplemented with LiCl) and filtered through 0.13 μm filters before injection.

Catalan Parameters. Catalan parameters were generally taken from the most up-to-date source.[52] Data for DMPU is unpublished, but the reduced Catalan parameters were previously available on the website of Prof. Catalan (note: this website is offline after the retirement of Prof. Catalan),[73] and the SP and SdP parameters were disentangled using eqs 4 and 9 from ref 53. An overview of the employed Catalan parameters and alternative polarity scales is given in Table 5.

Regression Analysis. Simple regression analysis was carried out in Microsoft Excel 2010 using the line of best-fit function. Multivariate analysis was carried out using Matlab 2017b using the linear model function.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.2c01930.

> Zoomed version of Figure 1 (Figure S1); SEC elugrams (Figure S2); results of fit of parameters to the Kamlet-Abraham-Taft eq 1 and Catalan eq 3 (Figures S3 and S4); resulting fits against various literature-derived single factors (Table S1); linear regressions for eqs 1, 3, and 4 (Tables S2−S4); predictions—based on the statistical/mathematical work performed—for an extensive list of polymerization solvents (more than experimentally obtained) for the E_a, A, and k_p's (Tables S5−S7) (PDF)

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Notes

The authors declare the following competing financial interest(s): R.H. is one of the founders of Avroxa BVBA that commercializes poly(2-oxazoline)s as Ultroxa. The other authors have no conflicts to declare.

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■ ABBREVIATIONS

EtOx, 2-ethyl-2-oxazoline; PAOx, poly(2-alkyl/aryl-2-oxazoline)s; CROP, cationic ring-opening polymerization; MW, molecular weight; Đ, dispersity; PEI, poly(ethylene imine); PEtOx, poly(2-ethyl-2-oxazoline); MeOTs, methyl *p*-toluenesulfonate; SP, solvent polarizability; SdP, solvent dipolarity; SA, solvent acidity; SB, solvent basicity; DoF, degrees of freedom; SPP, general polarity term; MeOx, 2-methyl-2-oxazoline; DMPU, *N,N*′-dimethylpropyleneurea; E_a, activation energy; A, preexponential factor/Arrhenius factor; $\Delta H^{\ddagger}$, activation enthalpy of transition state; $\Delta S^{\ddagger}$, activation entropy of transition state; DP, degree of polymerization; M_n, number-average molecular weight

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