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Thermally Reversible Polymer Linkages. 1. Model Studies of the Azlactone Ring

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ABSTRACT: Our research focuses on the use of 2-oxazolin-5-ones ("azlactones") in thermally reversible reactions with phenols, forming linkages to be used for recyclable polymers. In this work, model studies of the azlactone ring-opening reaction with para-substituted phenol nucleophiles have been useful in elucidating an unusual mechanism of reaction for phenols in concentrated solution, wherein protonation of the azlactone nitrogen is rate controlling at early reaction times. In addition, the ring opening has been determined to be reversible at temperatures below 300 °C when electron-withdrawing substituents are placed para on the phenol ring. Thus the model studies have (1) enhanced current knowledge of azlactone chemistry pertinent to polymer chemistry and (2) shown that this system has the potential for development into thermally reversible covalent linkages for stepwise polymerization and cross-linking.

Introduction

2-Oxazolin-5-ones ("azlactones") have been used in polymer chemistry both as monomers and cross-linking agents.[1-9] The radical polymerization of 2-vinylazlactones results in azlactone-functionalized polyethylenes that are susceptible to nucleophilic ring opening of the azlactone ring (Figure 1). Similarly, bisazlactones may be polymerized via stepwise ring opening with difunctional nucleophiles.

Our proposed research involves the possibility of using the nucleophilic ring-opening reaction of azlactones as a thermally reversible process for polymer linkages. Thus this chemistry may be used for recyclable covalent cross-linking or polymerization (Figure 1).

There are several instances in the literature of polymer linkages that are thermally reversible; for example, physical cross-linking by hydrogen bonding and crystallization,[10-16] ionic attraction,[17-22] and glassy phase formation[23-28] are all known in the formation of thermoplastics. However, these methods do not yield linkages of covalent integrity. Consequently, the physical properties and processability of these networks are usually inferior to those of irreversibly cross-linked covalent networks.

A solution to this problem is to develop a reversible *covalent* linkage suitable to give the necessary mechanical integrity in the envisioned polymer systems. Herein also lies the possibility of reversible chain extension, from which monomer can be regenerated. Only a few instances of thermally reversible covalent polymer linkages are known in the literature. These consist of Diels–Alder 4+2 cycloadditions[29,30] anhydride formation,[31,32] and nitroso dimerization.[33,34]

In this paper we report the results of a mechanistic study of the reversible nucleophilic ring-opening reaction of a model azlactone by phenol nucleophiles. The model system was used to investigate the potential for effective cross-linking and stepwise polymerization reactions as shown in Figure 1, as well as to study the mechanism of the reaction in a quantitative manner. Presently we are transferring this chemistry to the polymer systems shown.

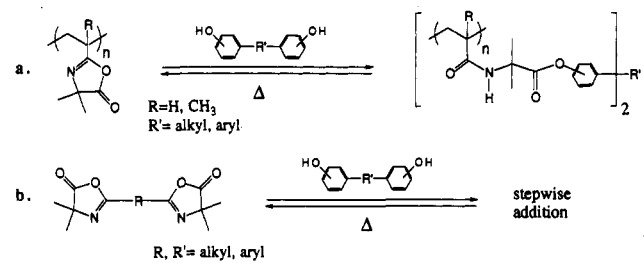

Figure 1. Envisioned schemes for thermally reversible azlactone linkages to be used in polymer chemistry. (a) Reversible cross-linking of poly(2-vinyl-4,4-dimethyl-2-oxazolin-5-one) with bisphenols. (b) Reversible chain extension of bisazlactones and bisphenols.

We have proposed an appropriate azlactone/nucleophile model system and have studied it in some detail. A model azlactone, 2-isopropyl-4,4-dimethyl-2-oxazolin-5-one (I) was chosen to mimic the chemistry of a polymerized vinyl moiety at the 2 site of the azlactone ring (see Figure 1a). Substitution at the 4 site is necessary to avoid acid–base side reactions (Figure 2). The nucleophiles in these studies were *p*-nitrophenol, phenol, and *p*-methoxyphenol, and it was postulated that the "trigger temperature" for the reverse reaction of ring-opened adducts III could be tailored through the use of functional groups to provide reversibility within "practical" temperature ranges for the envisioned applications (200–300 °C).

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Proton NMR spectroscopy has proven to be a reproducible and accurate nondestructive method for the measurement of both the disappearance of I and the appearance of III. All quantitative data reported herein are measured by the NMR method described in the Experimental Section.

Experimental Section

All chemicals were purchased from Aldrich Chemical Co. and were used without further purification except for hexane, which was distilled from Na–K alloy immediately prior to use.

Synthesis of 2-isopropyl-4,4-dimethyl-2-oxazolin-5-one (I): Synthesis of the model compound was accomplished in two steps. In the first step, isobutyryl chloride was used to acylate 2-methylalanine with according to the method of Iwakura et al.[35] Certain modifications of the reported technique were necessary: 3 equiv of isobutyryl chloride used instead of 1 equiv; violent mechanical stirring plus efficient cooling required to maximize yield and prevent overheating of the heterogeneous mixture formed during the reaction. After acidification of the reaction mixture with 1 equiv of HCl, sufficient H_2O was added to form two layers in the reaction flask. Slow stirring of the layers for 12–24 h resulted in all of the product being located in the top layer. The layers were separated, and the top layer was added directly to boiling toluene; heating was continued until all the material was dissolved. At this point excess H_2O could be removed by pipetting. Crystals resulting from a second dissolving in boiling toluene gave 15% yield of pure *N*-isobutyryl-2-methylalanine by melting point (150–152 °C) and elemental analysis: calcd (found) C, 55.5 (55.4); H, 8.7 (8.7); O, 27.7 (27.7); N, 8.1 (8.1).

Cyclodehydration of the *N*-isobutyryl-2-methylalanine was completed via reaction with 1.1 equiv of dicyclohexylcarbodiimide in dry hexane; 50 mL of hexane/g of *N*-isobutyryl-2-methylalanine was sufficient to allow magnetic stirring of the heterogeneous mixture. Hexane was removed by rotary evaporation, and the product fractionated under vacuum by using standard Schlenk techniques and immediately transferred to a Vacuum Atmospheres drybox to prevent hydrolysis of the azlactone ring. Yield was 75% of crude product for the cyclization step.

Characterization was accomplished by ^1H NMR ($CDCl_3$: δ 1.17, d, 6 H; δ 1.32, s, 6 H; δ 2.74, sept, 1 H), ^{13}C NMR ($CDCl_3$: δ 18.6, CH_3; δ 24.5, CH_3; δ 29.0, CH; δ 65.1, C; δ 167.8, C; δ 181.6, C), and elemental analysis: calcd (found) C, 61.94 (61.95); H, 8.39 (8.44); O, 20.65 (20.60); N, 9.03 (8.99).

Synthesis of open-ring adducts of isopropylazlactone and para-substituted phenols (III): Isopropylazlactone was used directly in hexane solution from the synthesis above, without distillation. Addition of an equimolar amount (assuming 75% yield from the cyclization step) of the desired phenol derivative plus 5 mol % of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was followed by reflux for 2–3 h under argon. Purification was by rotary evaporation of hexane, followed by recrystallization from $EtOH/H_2O$.

The synthesis of adduct IIIa equired rotary evaporation of hexane before the addition of the *p*-nitrophenol and the esterification to be run neat, at 80 °C/24 h in order to maximize yields. Despite extra precaution, yields of IIIa were extremely low (about 5% after five recrystallizations) as compared to IIIa and IIIb (about 75% after two recrystallizations).

Characterizations were via ^1H NMR and elemental analysis:

compd	atom	% calc	% found	mp, °C
IIIa	C	57.14	57.02	105
	H	6.16	6.21	
	O	27.18	27.22	
	N	9.52	9.51	
IIIb	C	67.45	67.22	133
	H	7.68	7.74	
	O	19.25	19.40	
	N	5.62	5.59	
IIIc	C	64.50	64.43	130
	H	7.58	7.63	
	O	22.91	22.93	
	N	5.01	4.99	

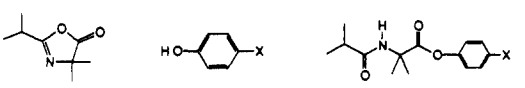

Figure 2. Model compounds for the mechanistic study of the envisioned polymer systems. I: 2-isopropyl-4,4-dimethyl-2-oxazolin-5-one. II: functionalized phenols. III: adducts of I and II.

Reaction solutions and analysis: All solutions were mixed in a Vacuum Atmosphere Dri Lab Model HE-43-4 drybox under argon atmosphere. The atmosphere was maintained at ≤10 ppm H_2O and O_2 as shown by chemical testing (diethylzinc). All NMR spectra were run on a Varian XL-200 (200 MHz) Fourier transform spectrometer. Temperature was regulated to ±0.1 °C inside the NMR probe as well as in the drybox. Where heating inside the drybox was necessary, a silicon oil bath connected to a variable-voltage transformer was used. A typical reaction solution was made by addition of the appropriate weight of reagents to a volumetric tube inside the drybox, followed by addition of deuterated solvent to the correct volume. Reactions were then carried out in vials inside the drybox with removal of aliquots for NMR measurement or in a single NMR sample tube removed from the drybox with a septum. In some cases, acetonitrile was also added directly to the reaction solution or in a sealed capillary to the NMR tubes as an internal standard.

The reaction was followed by ^1H NMR as shown in a typical example (Figure 3). Undesirable hydrolysis products were detectible by ^1H NMR through the appearance of "splitting" in the absorption due to species III (the hydrolysis product, *N*-isobutyryl-2-methylalanine, appears slightly upfield of the absorption due to IIIa–c) and by the appearance of the chemical shift due to species II without the concomitant presence of I. Furthermore, the inclusion of internal standard to the ^1H NMR reaction solutions showed that III grew in at the expected rate based on the measured disappearance of I in the measurement of forward reactions.

The reverse reaction was also monitored via ^1H NMR by removing the reaction solutions from the drybox in medium-walled NMR tubes or in heavy-walled reaction vessels equipped with a constriction, stopcock, and ground-glass joint. The vessels were then sealed by oxygen/acetylene torch after three freeze–pump–thaw cycles on a standard Schlenk line. Heating at the desired temperature was accomplished by immersing the vessels in a ceramic heating mantle filled with sand and regulated at the desired temperature ±5 °C.

The reverse addition of IIIa to form I and IIa was also accomplished by heating the neat adduct in a small distillation apparatus under vacuum. The distillation was set up in the drybox by adding IIIa to the flask to be heated, then removing the apparatus under argon, and immediately applying vacuum via Schlenk line. Heating was accomplished in a sand bath as described above. The temperature was slowly ramped up until the adduct was observed to have completely disappeared from the heated flask. Products were determined by washing the catch flask with CH_3CN and running the resulting mixture through a Waters Model 590 liquid chromatograph at 0.5 mL/min of 60% CH_3CN(aq). The chromatograph was equipped with a NovaPak C18 reverse-phase column, a Spectroflow 757 UV detector set at 254 or 215 nm, and Perkin-Elmer LC-25 refractive index detector.

Since I, IIa–c, and IIIa–c were characterized in the purified form by standard techniques, it was easily determined that it in the absence of water, reactions other than the desired forward and reverse reactions did not occur. Coinjection of I or the hydrolysis product of I (or IIIa–c) in HPLC analysis confirmed whether or not any hydrolysis had occurred.

Results and Discussion

^1H NMR examination of the forward reaction of I and IIa is shown in Figure 3. Several reactions of equimolar I and II were observed in both dilute (0.1 M) and concentrated (0.5 M) solutions in several solvents. The dilute solutions were examined for the purposes of obtaining kinetic data; however, the reaction has negligible

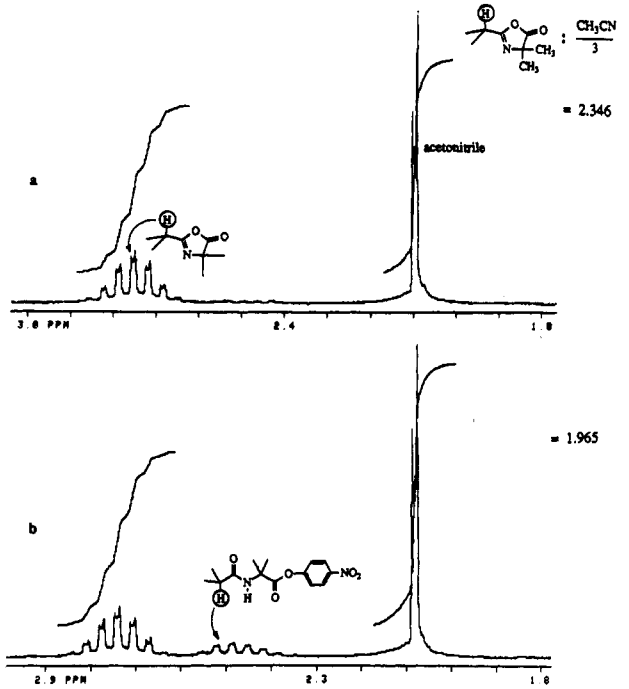

Figure 3. Method of internal standard using acetonitrile for ^1H NMR analysis at (a) $t = 0$ and (b) $t = 24$ h for the reaction of I and IIa in $CDCl_3$/27 °C.

reactivity under these conditions. In addition, concentrated solutions are of interest for the purposes of the model study, since the envisioned step polymerizations and cross-linking schemes (Figure 1) will involve concentrated solutions. Therefore, the results concerning the forward reaction of I and II are for the concentrated solutions unless otherwise stated. On the other hand, the ring closure of adducts III were initially carried out in dilute solution (0.1 M) in order to maximize the extent of the ring-closure reaction.

The most outstanding characteristic of the forward reactions of isopropylazlactone and the phenol nucleophiles used is that they are quite slow. Kinetics (DMSO solution) for the uncatalyzed reaction appeared to be second order overall, first order each in I and II for solutions 0.1 M in both reagents. However, correlation is extremely poor for these reactions as they require days for a measurable amount of reaction to take place and several weeks to react to an extent that rate constants could be estimated. For instance, a solution 0.1 M in I and IIa gave an approximate second-order rate constant of 6×10^{-7} L/mol s at room temperature. When the reaction was run at 100 °C, negligible reaction was observed after 18 h. An examination of the "true order" of the reaction at 0.5 M indicates that, initially, the reaction approaches 0.5 order in each reagent (see Table I). In this technique, initial rates are measured at a single temperature for varying initial concentrations of the reagent in question; a plot of ln k_{init} vs ln [concentration]$_{init}$ then gives a line whose slope is the order of that reagent.[36]

Studies were then conducted with 0.5 M solutions as these were of measurable reactivity and were found to obey first-order overall reactivity, with half-order dependence on I and IIa–c at early times. Although correlation of the curves in Table I were poor, this evidence was used in conjunction with the fitted overall first-order plots to determine that the order in both reagents is 0.5 for the concentrated solutions.

For phenol nucleophiles IIa–c, the forward reaction exhibited a retardation effect at 5–20% reaction, depending on the phenol derivative used (see Figure 4). Presumably, this is due to contributions from the reverse

Table I
Investigation of the True Order of the Reaction of I and IIa at 27 °C, 0.5 Equimolar in DMSO-d_6[a]

[azlactone]$_0$, mol/L	[*p*-nitrophenol]$_0$, mol/L	rate$_0$, mol/L s
0.510 ± 0.010	0.507	2.2×10^{-5}[b]
0.510 ± 0.010	0.345	9.5×10^{-6}[b]
0.510 ± 0.010	0.259	7.0×10^{-6}[b]
0.510 ± 0.010	0.173	1.2×10^{-5}[b]
0.516	0.510 ± 0.010	1.7×10^{-5}[c]
0.345	0.510 ± 0.010	1.2×10^{-5}[c]
0.261	0.510 ± 0.010	1.3×10^{-5}[c]
0.167	0.510 ± 0.010	8.0×10^{-6}[c]

[a] Low correlation was seen for the measurement of the disappearance of IIa due to difficulty in the quantitative measurement of aromatic protons relative to acetonitrile. [b] ln rate$_0$ vs ln [*p*-nitrophenol]$_0$, slope = 0.58 (order in *p*-nitrophenol), correlation = 0.55. [c] ln rate$_0$ vs ln [azlactone]$_0$, slope = 0.61 (order in azlactone), correlation = 0.94.

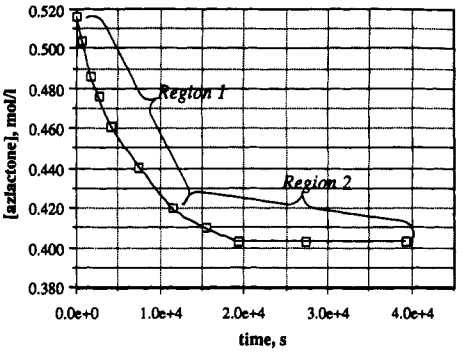

Figure 4. Concentration vs time plot for the disappearance of I by ^1H NMR. The data are linear to a first-order plot in region 1 (correlation = 0.998).

reaction as the forward reaction proceeds but is probably not an equilibrium, since further reaction (albeit extremely slow) is seen to occur over several weeks thereafter. For the purpose of kinetic measurement, however, no further data were used after this point since the observed reactivity may be due simply to slow precipitation of the open-ring adduct or evaporation of 1. Since the reaction at early times follows the expected order, the kinetic data reported above apply to the initial portion of the reaction only. Consequently, all reported rate constants should be considered to be relative measures of reactivity only.

Pseudo-first-order conditions were employed, wherein IIa was used at the maximum concentration possible, corresponding to 3.68 M in DMSO-d_6 at 27 °C. I was used at 0.5 M. The chemical shift of I was upfield of the shift observed in the equimolar solutions, causing the shifts of the methine protons of I and IIIa to overlap. This is probably due to the increase in polarity of the solvent medium. The data could not be quantified, and furthermore these conditions were not indicative of the system being modeled; thus these studies were not pursued further.

Relative reactivities were measured by examining side-by-side reaction solutions of I and IIa–c at 24 h after mixing. Rate data suggest that the point of retardation of the reaction as observed in Figure 3 has been reached by the 24-h time period. Table II shows the results of 1:1 reactions of I with II after 24 h at room temperature in various solvents, as measured by ^1H NMR. The order of reactivity of IIa–c was initially unexpected since IIa was the weakest phenol nucleophile used. It is, however, the most ionized of the nucleophiles IIa–c in solution.

Nonnucleophilic bases such as tertiary amines have been observed to reverse this reactivity trend (see Experimental Section, synthesis of open-ring adducts using DBU); in our own experiments, trifluoroacetic acid and H_2SO_4 (fuming) also reverse the phenol reactivity order in addition

Table II
Observed Equilibrium after 24 h at 27 °C for the Reaction of I with IIa–c in Various Solvents, As Measured by ^{1}H NMR[a]

nucleophile II	solvt	[III]/[I][II] at 24 h
IIa	$CDCl_3$	4.7
	DMSO	2.0
	chlorobenzene	9.3
IIb	$CDCl_3$	0.14
	DMSO	0.21
	chlorobenzene	0
IIc	$CDCl_3$	0
	DMSO	0
	chlorobenzene	0

[a] All solutions are 0.5 M in I and II. No catalysts were present in the solution.

Table III
Reaction Coordinate after 24 h at 26–27 °C in $CDCl_3$ for the Reaction of I with IIa–c As Measured by ^{1}H NMR[a]

nucleophile II	$[F_3CCOOH]/[I]$ at $t = 0$	[III]/[I][II] at 24 h
IIa	1/15 (catalytic)	7.3
IIb		0.48
IIc		4.0
IIa	1/5	17
IIb		1.5
IIc		11
IIa	1/3	12
IIb		3.0
IIc		45
IIa	1/1	32
IIb		66
IIc		2.2×10^3

[a] All solutions are 0.5 M in I and II with varying equivalents of trifluoroacetic acid added.

to causing an overall reactivity enhancement of the reaction; acetic acid (acetic acid-d_4 was used) does not exhibit the same effect, although a general enhancement of reactivity was observed.

Solutions 0.5 equimolar in I and II were reacted with varying amounts of trifluoroacetic acid in $CDCl_3$ at room temperature as shown in Table III. Reversal in the order of nucleophile reactivity is observed at 1 equiv of trifluoroacetic acid at the 24-h mark. Notably, the trifluoroacetic anion participates in the reaction, but not to a large extent; open-ring adducts of phenol predominate. This is mechanistically significant because if trifluoroacetic acid is the primary proton donor, then the nucleophilic species are mainly trifluoroacetic anion and protonated phenol: trifluoroacetate anion is the stronger nucleophile, yet both nucleophiles participate in the reaction. Also notable is the fact that trifluoroacetic acid reacted alone with I does not react to a large extent in 24 h and appears to follow a different reaction pathway. No apparent rate retardation is seen over a 24-h period as is observed for the phenol nucleophiles.

The product of reaction of I with trifluoroacetic acid may involve nucleophilic participation or initial attack by trifluoroacetate anion followed by ring closure and subsequent reopening by II, or both. The peaks for both products appear to grow in simultaneously, so it is impossible to judge whether one or both of these mechanisms are in operation. Kinetic isotope experiments, described below, were required to determine what the rate-controlling step of the reaction might be.

Other protonic acids were studied in analogous solutions, based on the results with trifluoroacetic acid. Reactions 1:1 in I and IIa–c, with varying amounts of acetic acid-d_4 or fuming H_2SO_4 were run in $CDCl_3$ at 26 °C over 24 h. While general reactivity was *slightly* enhanced, acetic acid did not affect reversal in the reactivity of IIa–c up to 2 equiv of acetic acid; additionally, negligible reactivity was seen with acetic acid and I alone. There was no evidence of nucleophilic participation in the products formed by the reaction of I and IIa–c in the presence of acetic acid. Thus a protic acid must be a strong enough proton donor to react with I alone in order to affect the reversal of reactivity of IIa–c. Fuming sulfuric acid caused a reversal in the reactivities of IIa–c analogous to that with trifluoroacetic acid. This reversal in reactivity was observed at 0.5 equiv or less of H_2SO_4. Additionally, evidence of nucleophilic participation was present in these ^{1}H NMR spectra, as the open-ring products of II vs sulfonate anion with I exhibited different chemical shifts (see Figure 5).

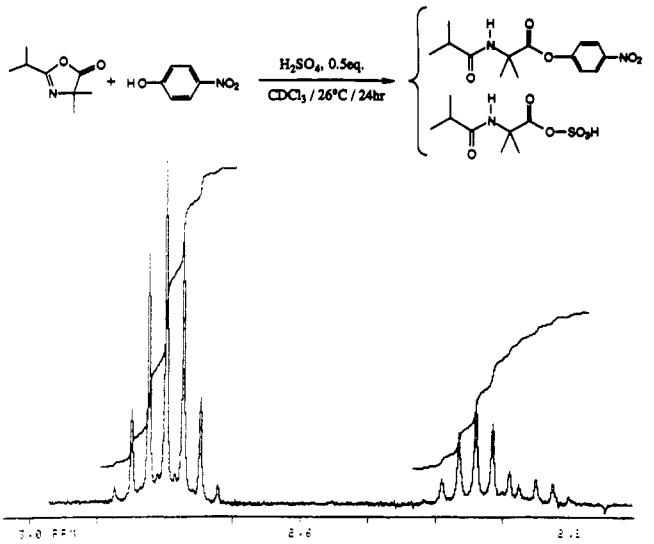

Figure 5. Reaction of equimolar I and IIc in the presence of 0.5 equiv of fuming sulfuric acid after 24 h of reaction time (26 °C, $CDCl_3$). The methine proton of adduct IIIa is centered at approximately δ 2.34; that of the open-ring adduct of I and H_2SO_4 appears at about δ 2.25 ppm.

Thus, in the case of protonic acids, stronger acids promote reactivity of the least acidic phenols. Additionally, stronger protonic acids cause apparent nucleophilic participation in this ring-opening reaction.

$AlCl_3$ was also used to study acid catalysis of the forward reaction without the possibility of nucleophilic participation. In reaction solutions analogous to those in Table III it appears (although the ^{1}H NMR spectra of solutions with $AlCl_3$ are poor) that an analogous reversal of reactivity in IIa–c occurs at $\leq$0.5 equiv of $AlCl_3$.

At this point, the mechanism at early times appeared to be as shown in Figure 6, that is, protonation of the azlactone nitrogen by the nucleophile followed by ring opening. Thus in uncatalyzed additions, IIa is expected to be the most reactive nucleophile since it is the most acidic of the three analogues. Acid catalysis causes phenol rather than phenolate to be the reactive nucleophile, and hence the reversal in reactivity was observed. However, the previous experiments do not address which of these first two steps is rate controlling for the reaction: is there a fast preequilibrium for the protonation of the azlactone ring, followed by slow nucleophilic attack, or is protonation of the azlactone nitrogen rate controlling? The fact that trifluoroacetate anion does not compete appreciably with *p*-nitrophenol as a nucleophilic indicates that, in concentrated solution, protonation of the azlactone ring may be involved in the rate-controlling step during the initial portion of the reaction.

To address this question, primary kinetic isotope studies were undertaken. These experiments involved measurement of the rate of the uncatalyzed reaction of phenol (IIb) and phenol-d_6 (IIb′) with I under identical conditions.

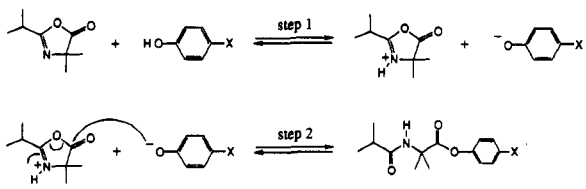

Figure 6. Proposed mechanism for the reaction of I and IIa–c.

The theory of the experiment asserts that protic acids dissociate at a faster rate than deuterated acids; however, deuterated acids have a higher pK_a at equilibrium than protic acids. Therefore, if protonation by the phenol hydroxyl proton is involved in a rate-controlling step, we would expect IIb to react at a faster rate than IIb'. Other phenol analgues are assumed to react by the same mechanism as phenol itself. Solutions were 0.5 equimolar in the reagents; DMSO-d_6 was used as solvent. Figure 7 shows the ^1H NMR spectra of the two reaction solutions at the same point of reaction. IIb reacts at a faster rate than IIb' during this early portion of the reaction (~5% reaction of protonated phenol is shown in Figure 7). The first 5% of the reaction of IIb with I gave $k^{rel}_H = 1.15 \times 10^{-6}$ s^{-1}, $k^{rel}_D \approx 2.11 \times 10^{-7}$ s^{-1}, or $(k_H/k_D)^{rel} \approx 5.45$. At long times (≥8% reaction; several days) that is, after the point of rate retardation as seen in Figure 4 had been reached, the rate of reaction of IIb' with I was qualitatively observed to exceed that of IIb.

Thus at early reaction times, protonation of the azlactone ring by phenol in concentrated solution apparently is rate controlling for these weak nucleophiles. In less strict agreement with this assertion is an Arrhenius activation energy of 77.5 kJ/mol (correlation = 0.999) as measured by 0.5 M solutions of I and IIa (30, 40, and 50° C). Again, values of k_{obs} were measured in the linear region only (i.e., the first 5–20% reaction) for the concentrated solutions and so are not rigorously accurate.

Additional primary kinetic isotope studies were conducted under the same conditions as outlined above except the dilute (0.1 M) solutions were examined. Kinetic measurements resulted in $(k_H/k_D)^{rel} < 1$, as was expected. H_2O and D_2O were also examined and exhibit the same trends of kinetic isotope effect as phenol (that is, $(k_H/k_D)^{rel} > 1$) in 0.5 M solutions.

The reasons for the observations at early times of the forward reaction in concentrated solution may be due to a higher degree of order required for the proton transfer in a less-solvated system. The envisioned reaction in this case would be a fast combination of I and II, followed by a rate-controlling breakup of the intermediate to protonated I and phenolate anion:

$$\text{I} + \text{II-H} \rightarrow (\text{I/II-H}) \qquad \text{(fast)}$$

$$(\text{I/II-H}) \rightarrow \text{I-H}^+ + \text{II}^- \qquad \text{(slow)}$$

$$\text{I-H}^+ + \text{II}^- \rightarrow \text{III} \qquad \text{(fast)}$$

This situation does not appear to exist in the dilute solution; therefore, less-solvated systems cause the observed effect.

At later reaction times, it was found previously (see Figure 3) that the reaction was no longer first order overall, and it was postulated that contributions from the reverse reaction (the ring closure of I) are responsible. This may bear relation to the observation that the rate of phenol-d_6 was found to exceed that of phenol-H_6 at later times of reaction. It is unknown whether the exact mechanism of ring opening changes at this point.

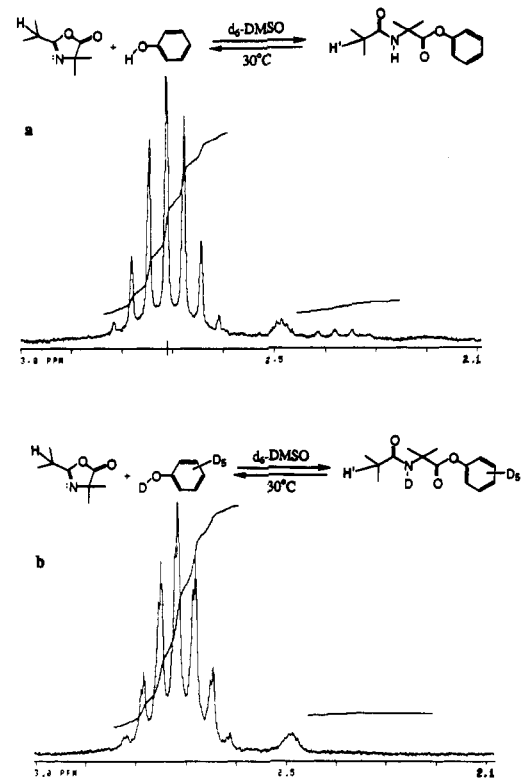

Figure 7. ^1H NMR spectra showing the reaction of I with (a) phenol (IIb) and (b) phenol-d_6 under identical conditions. Both spectra were taken at t = 47 304 s. The absorbance at δ 2.48 is due to protic impurities in DMSO-d_6.

The reverse reaction has also been examined in model studies of IIIa–c. The three ring-opened adducts of I and IIa–c were synthesized and purified as described in the Experimental Section.

The adducts were then heated for 24-h periods in dilute (0.1 M) DMSO-d_6 solution to determine whether the reaction was reversible; i.e., can I and IIa–c be re-formed? It became clear early on in these studies that water must be rigorously excluded in order to avoid the preferential hydrolysis of the ester linkage at elevated temperatures. Thus the reactions were carried out in sealed heavy-walled tubes after mixing the solutions in the drybox. Hydrolysis was detectible by careful evaluation of the NMR spectra, as described in the Experimental Section.

In the case of the IIIa, the reverse reaction becomes significant at about 200 °C, with 3:1 I:IIIa observed after 24 h at 250 °C (see Figure 8); at 24 h/300 °C, this ratio increased to 5:1. IIIb and IIIc were not observed to reverse at 300 °C. Thus leaving group ability is significant for the ring-closing reaction. This information appears to be anomalous with observations of the forward reaction at first glance. However, if the point along the reaction coordinate observed at the point of rate retardation seen in Figure 4 is *not* a true equilibrium, then it is probable that at equilibrium, IIc reacts to a further extent than IIa. In other words, at equilibrium less IIIa would be formed than IIIc and hence the more facile reversibility of IIIa. Long heating times caused degradation of the materials in the sealed tubes and extensive proton exchange of DMSO; thus equilibrium was not established for the reverse reaction.

Additional evidence for the reversal of the ring-opening reaction of IIIa was obtained by heating the neat adduct in a small distillation apparatus under vacuum. This technique has two advantages: first, the adduct is not exposed to heat for long periods of time; second, the reverse reaction could be "driven" by the removal of I and IIa from the reaction flask. Between 235 and 250 °C, the IIIa

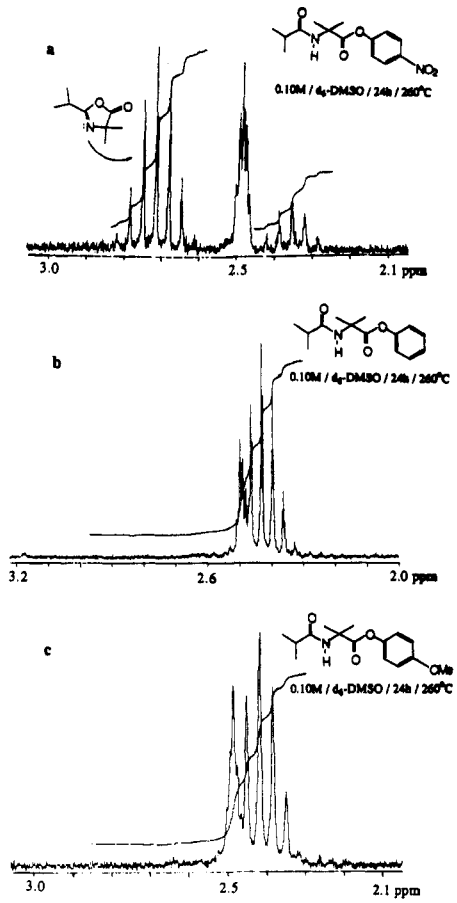

Figure 8. ^{1}H NMR spectra of dilute solutions of IIIa–c after 24 h at 260 °C. The ratio of I:IIIa in spectrum a is 3:1. The large protic DMSO peak at δ 2.5, due to accelerated proton exchange at 260 °C, does not permit accurate measurement of the ratio [I][II]:[III].

was observed to disappear from the heated flask. The materials in the catch flask were determined by HPLC to be I and IIa, along with some IIIa. It was confirmed by co-injection that hydrolysis of the ester linkage was not responsible for the appearance of IIa.

Conclusions

The mechanism of the nucleophilic ring opening of 2-isopropyl-4,4-dimethyl-2-oxazolin-5-one (I) by phenol derivatives (IIa–c) has been studied, and the model has allowed several observations that will be useful in predicting the behavior of the corresponding polymerizations and cross-linking schemes. In concentrated solutions without acid or base catalysts, the reaction is slow with an apparent rate retardation occurring early on in the forward reaction. The rate-controlling step at early reaction times in concentrated solution is attributed to the protonation of the azlactone ring by the nucleophile, while the retardation effect observed to operate over long times is thought to involve an equilibrium concentration of protonated azlactone, with nucleophilic attack as the rate-controlling step. Clearly, a catalyst will be needed to affect substantial yields within reasonable time periods. This will be crucial when designing the corresponding step polymerizations and cross-linking schemes.

The range of thermal reversibility of adducts III is dependent on substituents placed para on the phenol ring, where electron-withdrawing substituents favor reversibility at lower temperatures. We can predict that in both stepwise polymerizations and cross-linking applications, electron-withdrawing substituents placed on a bisphenol structure will allow thermal reversibility at lower temperatures.

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