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Substituent Effects in Xanthate-Mediated Polymerization of Vinyl Acetate: Ab Initio Evidence for an Alternative Fragmentation Pathway

Michelle L. Coote*,† and Leo Radom*,†,‡

Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia, and School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia

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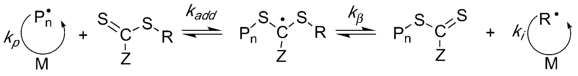
ABSTRACT: High-level ab initio calculations have been performed for the addition and fragmentation steps in reversible addition−fragmentation chain transfer (RAFT) polymerization of vinyl acetate. The RAFT agents considered were a series of xanthates of the form S═C(O−Z′)S−R, where Z′ = methyl, ethyl, iso-propyl, and *tert*-butyl and R = CH_2OCOCH_3 and CH_3. The results indicate that increasing substitution within the Z′ group stabilizes the RAFT adduct radical, thereby reducing the rate of fragmentation of the S−R bond. For the model vinyl acetate system, there is an additional substantial reduction in rate for the bulkier iso-propyl and *tert*-butyl substituents (compared with methyl and ethyl) associated with a sterically induced conformational change in the transition structures. However, the calculated S−R fragmentation rate for Z′ = *tert*-butyl is still not low enough to explain the experimentally observed rate retardation in this system. Instead, the rate retardation appears to be the result of the preferred fragmentation of the O−C bond in the *tert*-butoxy group of the RAFT adduct. This fragmentation pathway is not normally favored in RAFT polymerization. However, in this particular system, the combination of the vinyl acetate radical being a poor homolytic leaving group, the *tert*-butyl radical being a good leaving group, and charge-transfer stabilization of the transition structure for O−C β-scission tips the balance in favor of the O−C β-scission reaction.

Introduction

In recent years, the field of free-radical polymerization has been revolutionalized by the development of techniques for controlling the molecular weight and architecture of the resulting polymer, including nitroxide-mediated polymerization (NMP),[1] atom-transfer polymerization (ATRP),[2] and reversible addition−fragmentation chain transfer (RAFT) polymerization.[3] In all of these processes, control is achieved by protecting the majority of the growing polymer chains from bimolecular termination through their reversible trapping into some dormant form. In the case of RAFT polymerization, thiocarbonyl compounds (known as RAFT agents, **2**) reversibly react with the growing polymeric radical (**1**) via the chain-transfer reaction shown in reaction 1, producing a polymeric thiocarbonyl compound (**4**) as the dormant species.[3]



(1)

1 **2** **3** **4** **5**

To achieve control, a delicate balance of the forward and reverse rates of addition (k_{add} and k_{-add}) and fragmentation ($k_β$ and $k_{-β}$), together with the rates of reinitiation (k_i) and propagation (k_p), is required. It is therefore important to understand the effect of substituents on each of these individual steps, so that RAFT agents (and other reaction conditions) can be optimized for the controlled polymerization of any given monomer.

In the present work, we use ab initio calculations to study the effect of substituents on the fragmentation pathways of the RAFT-adduct radical (**3**) in xanthate-mediated polymerization of vinyl acetate.[4] Controlled free-radical polymerization of vinyl acetate is of particular technological interest because poly(vinyl acetate) is a precursor to poly(vinyl alcohol), which can in turn be cross-linked to a nontoxic hydrogel suitable for biomedical applications (such as oral drug delivery). Since the vinyl acetate propagating radical is relatively unstable and thus highly reactive, it has proved difficult to control via NMP and ATRP or using standard dithioester RAFT agents. In the case of RAFT polymerization, the standard dithioesters actually inhibit polymerization. It is thought that, since the vinyl acetate propagating radical is a poor homolytic leaving group, the fragmentation of the RAFT-adduct radical (**3**) is thus very slow.[5] However, controlled polymerization of vinyl acetate has recently been achieved using either dithiocarbamates or xanthates as RAFT agents.[5−8] It has been suggested[5] that dithiocarbamates and xanthates are successful because they increase the electron density at the radical center and that this destabilizes the RAFT-adduct radical relative to normal dithioester substituents (such as CH_3 and phenyl) and increases the fragmentation rate. The electron-donating OR and NR_2 substituents are also thought to stabilize the thiocarbonyl product of fragmentation (**4**) through their conjugation with the C═S double bond.[5,9,10]

A recent experimental study of substituent effects in xanthate-mediated polymerization of vinyl acetate has provided some support for these ideas.[8] It was found that, for a series of xanthates (S═C(OZ′)SCH_2OCOCH_3, for Z′ = **A**−**H** in Figure 1), control of polymerization *increased* in the order **A** to **G**. At the same time the electron-withdrawing ability of the Z′ group, measured as the ^1H NMR shift on the methylene group of the leaving group (adjacent to the sulfur), *decreased* from **A** to **H**. It was concluded that the improved control of

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† Australian National University.

‡ University of Sydney.

* To whom correspondence should be addressed: e-mail mcoote@rsc.anu.edu.au; radom@chem.usyd.edu.au.

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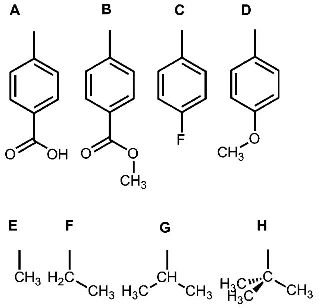
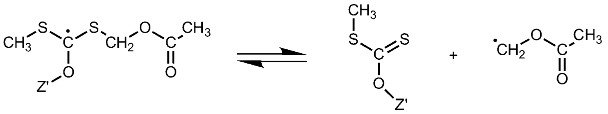


Figure 1. Z′ substituents **A**−**H** in the xanthate agents $S{=}C(OZ')SCH_2OCOCH_3$ considered in ref 8. In the present work we consider substituents **E**−**H**.

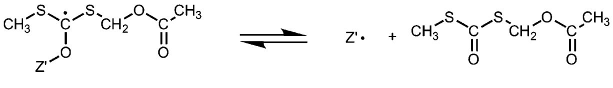
polymerization is correlated with the increasing electron density on the central carbon of the xanthate, and this was thought to correspond to decreased stability of the RAFT-adduct radical. However, an intriguing result from this work was that the xanthate with the least electron-withdrawing Z′ substituent (**H**) actually inhibited the polymerization of vinyl acetate for times of up to 2 days. This result is surprising since, on the basis of the above electronic arguments, this substituent should have led to the least stable RAFT-adduct radical and hence the fastest polymerization rate. It should also have led to the greatest control over the polymerization. It is therefore of interest to reexamine the arguments and to probe the cause of this unexpected inhibition effect.

In the present work we use ab initio molecular orbital calculations to explore the effect of the alkoxy group (Z = OZ′ for Z′ = Me, Et, iso-Pr, and *tert*-Bu; see **E**−**H** of Figure 1) on the addition and fragmentation reactions in xanthate-mediated polymerization of vinyl acetate. In order that the calculations can be performed at an accurate level of theory, we consider the following model reaction 2, in which the nonparticipating group of the RAFT agent is a methyl group and in which the propagating vinyl acetate radical is truncated at the terminal group:



(2)

In addition to the standard fragmentation pathway, we also calculate the rates and enthalpies for a possible side reaction 3 in which the alkoxy group itself fragments:



(3)

In this way, it is hoped to provide more information on the effect of substituents in xanthate-mediated polymerization of vinyl acetate and, in particular, to examine why the O-*tert*-butyl-substituted xanthate leads to inhibition of vinyl acetate polymerization.

Computational Procedures

Standard ab initio molecular orbital theory[11] and density functional theory[12] calculations were carried out using GAUSSIAN 98[13] and MOLPRO 2000.6.[14] Unless noted otherwise, calculations on radicals were performed with an unrestricted wave function. In cases where a restricted-open-shell wave function has been used, it is designated with an "R" prefix.

Barriers and enthalpies were calculated for β-scission of the S−R and O−Z′ bonds in the RAFT adduct radicals $CH_3SC^{\bullet}(O{-}Z')S{-}R$, for R = CH_3 and CH_2OCOCH_3 and Z′ = Me, Et, iso-Pr, and *tert*-Bu. For each species considered, significant effort was taken to try to ensure that the optimized structure was the global (rather than merely the local) minimum-energy structure by first performing extensive conformational searches at the HF/6-31G(d) level. Geometries of the preferred conformations of reactants, products, and transition structures were then reoptimized at the B3-LYP/6-31G(d) level of theory. Finally, improved relative energies were obtained through RMP2/6-311+G(3df,2p) and G3(MP2)-RAD[15] calculations on the B3-LYP optimized structures. For the R = CH_2OCOCH_3 systems, approximate G3(MP2)-RAD barriers and enthalpies were obtained by adding the substituent effect, as calculated at the RMP2/6-311+G(3df,2p) level of theory, to the (exact) G3(MP2)-RAD barriers and enthalpies for the corresponding R = CH_3 systems. We have previously shown that G3(MP2)-RAD provides very good absolute barriers and enthalpies, while RMP2/6-311+G(3df,2p) provides very good relative values, for radical addition to C=S double bonds.[16] More recently, we have confirmed that these levels of theory are also suitable for studying radical addition to C=O double bonds.[17b]

Having obtained the G3(MP2)-RAD barriers at 0 K, the gas-phase rate coefficients for the addition and fragmentation reactions were calculated at 60 °C via standard transition state theory, in conjunction with the harmonic oscillator approximation. The entropies of activation ($\Delta S^{\ddagger}$) were calculated using the B3-LYP/6-31G(d) optimized geometries, and scaled[18] B3-LYP/6-31G(d) frequencies were used to calculate the zero-point vibrational energy, the temperature correction to the barrier, and the vibrational contribution to $\Delta S^{\ddagger}$. An examination of the accuracy of the harmonic oscillator approximation for studying the addition and fragmentation reactions in RAFT polymerization is currently under way. The preliminary indications are that this approximation may lead to errors of up to an order of magnitude in the calculated rate coefficients, and this level of error would be consistent with our recent studies of radical addition to C=C and C≡C bonds.[19] However, we expect that the errors in the *relative* rate coefficients (important for studying substituent effects) will be somewhat reduced through cancellation. Furthermore, it should be stressed that, in contrast to experimental procedures for estimating the individual rate coefficients in RAFT polymerization, the ab initio calculations have no kinetic-based assumptions or assumed empirical parameters other than the fundamental physical constants.

Further details concerning all of the calculations are provided in the Supporting Information. Included therein are GAUSSIAN archive entries corresponding to the optimized geometries of all species (Table S1), corresponding total energies at the higher levels of theory (Table S2), a detailed description of the (textbook) formulas used in calculating the rate coefficients (Table S3), and the calculated temperature corrections and entropies of the individual species (Table S4).

Results and Discussion

Barriers and enthalpies for β-scission of both the S−R and O−Z′ bonds of the RAFT-adduct radicals $CH_3SC^{\bullet}(O{-}Z')S{-}R$ (with R = CH_2OCOCH_3 and Z′ = Me, Et,

Table 1. Barriers and Enthalpies (0 K, kJ mol^{-1})[a] for S−R and O−Z′ β-Scission of RAFT-Adduct Radicals, $CH_3SC\cdot(O{-}Z')S{-}CH_3$ and $CH_3SC\cdot(O{-}Z')S{-}CH_2OCOCH_3$

RAFT-adduct radical	S−R β-scission[b] $\Delta H^{\ddagger}$	S−R β-scission[b] ΔH	O−Z′ β-scission[c] $\Delta H^{\ddagger}$	O−Z′ β-scission[c] ΔH
$CH_3SC\cdot(OZ')S{-}CH_3$				
Z′ = Me	53.4	29.2	62.9	−32.0
Z′ = Et	53.7	29.8	65.4	−18.2
Z′ = iso-Pr	56.8	33.4	63.8	−7.1
Z′ = *tert*-Bu	59.3	37.1	42.9	−14.0
$CH_3SC\cdot(OZ')S{-}CH_2OCOCH_3$				
Z′ = Me	33.2	36.1	50.3	−26.9
Z′ = Et	33.5	39.0	76.7	−10.8
Z′ = iso-Pr	54.3	41.6	63.3	−0.7
Z′ = *tert*-Bu	56.1	43.6	42.3	−9.3

[a] Calculated at the G3(MP2)-RAD level, using B3-LYP/6-31G(d) geometries and including scaled B3-LYP/6-31G(d) zero-point vibrational energies. For the larger $CH_3SC\cdot(O{-}Z')S{-}CH_2OCOCH_3$ systems, an approximate G3(MP2)-RAD level was used (see text). [b] S−R β-scission refers to the reaction $CH_3SC\cdot(OZ')S{-}R \rightarrow CH_3SC(OZ'){=}S + \cdot R$. [c] O−Z′ β-scission refers to the reaction $CH_3SC\cdot(O{-}Z')SR \rightarrow CH_3SC({=}O)SR + \cdot Z'$.

Table 2. Forward (k_{frag}, s^{-1}) and Reverse (k_{add}, L mol^{-1} s^{-1}) Rate Coefficients at 60 °C for β-Scission of the S−R and O−Z′ Bonds in the RAFT-Adduct Radicals $CH_3SC\cdot((O{-}Z')S{-}R$ for R = CH_2OCOCH_3[a]

$CH_3SC\cdot(O{-}Z')S{-}CH_2OCOCH_3$	S−R β-scission[b] k_{frag}	S−R β-scission[b] k_{add}	O−Z′ β-scission[c] k_{frag}	O−Z′ β-scission[c] k_{add}
Z′ = Me	1.2×10^{7}	9.1×10^{5}	1.2×10^{5}	2.5×10^{-5}
Z′ = Et	8.5×10^{6}	2.0×10^{6}	1.0×10^{1}	1.4×10^{-8}
Z′ = iso-Pr	3.5×10^{4}	3.7×10^{4}	4.6×10^{2}	1.2×10^{-5}
Z′ = *tert*-Bu	8.6×10^{3}	4.4×10^{4}	6.2×10^{5}	5.0×10^{-4}

[a] Energies calculated at the approximate G3(MP2)-RAD//B3-LYP/6-31G(d) level of theory and entropies calculated using B3-LYP/6-31G(d) geometries and frequencies (see text). [b] S−R β-scission refers to the reaction $CH_3SC\cdot(OZ')S{-}CH_2OCOCH_3 \rightarrow CH_3SC(OZ'){=}S + \cdot CH_2OCOCH_3$. [c] O−Z′ β-scission refers to the reaction $CH_3SC\cdot(O{-}Z')SCH_2OCOCH_3 \rightarrow CH_3SC({=}O)SCH_2OCOCH_3 + \cdot Z'$.

iso-Pr, and *tert*-Bu) in xanthate-mediated polymerization of vinyl acetate are presented in Table 1, and the corresponding rate coefficients (at 60 °C) are shown in Table 2. The minimum-energy conformations of the RAFT-adduct radicals, transition structures, and product thiocarbonyl or carbonyl compounds for the S−R and O−Z′ β-scission reactions in this system are displayed in Figures 2 and 3, respectively. To assist in the qualitative analysis of the results, we have also calculated the barriers and enthalpies for β-scission of the simpler $CH_3SC\cdot(O{-}Z')S{-}CH_3$ systems (i.e., R = CH_3), and these are included in Table 1 for comparison purposes. In what follows, we examine in turn the effect of substituents on the barriers and enthalpies of the S−R β-scission reactions and the O−Z′ β-scission reactions. We then conclude with a comparison of the alternative fragmentation pathways and thereby suggest a possible explanation for the previously reported[8] rate retardation in the Z′ = *tert*-Bu system.

Effect of Substituents on S−R β-Scission. From Table 1, it can be seen that the enthalpies for β-scission of the S−R bonds of the $CH_3SC\cdot(O{-}Z')S{-}R$ radicals (for both R = CH_3 and R = CH_2OCOCH_3) increase monotonically with increasing alkylation of the Z′ group (i.e., Me < Et < iso-Pr < *tert*-Bu). Now, as reported in ref 8, the electron-donating ability of the O−Z′ group increases in the same order. Indeed, we have noted elsewhere that the electron-donating ability of the Z′ group, as measured by the decreasing ionization energy of the corresponding radical, increases in this order.[17] It would therefore appear that the increase in donation to the electron-deficient center may be stabilizing (rather than destabilizing as previously supposed[8]) the RAFT-adduct radical, thereby leading to the observed increase in the fragmentation enthalpies from Me to *tert*-Bu. Nonetheless, the fragmentation enthalpies are all considerably lower than those previously reported[20] for RAFT radicals of the form $CH_3SC\cdot(Z)S{-}CH_3$ where Z = CH_3 (64.2 kJ mol^{-1}), benzyl (72.3 kJ mol^{-1}), or phenyl (95.2 kJ mol^{-1}). Hence we can confirm that the alkoxy group does in general lower the fragmentation enthalpy relative to normal dithioester RAFT agents and must therefore achieve this through the (relative) destabilization of the RAFT-adduct radical and/or the (relative) stabilization of the product thiocarbonyl compound. We are currently examining the effect of substituents on the radical stabilization energies (RSEs) of a large range of RAFT-adduct radicals, and the preliminary indications are that the RSEs for these xanthate-adduct radicals are of comparable magnitude to those having CH_3 or benzyl (but not phenyl) groups attached to the radical center.[21] This would therefore suggest that the principal effect of the alkoxy substituents in xanthate-mediated polymerization is to stabilize the product thiocarbonyl compound, rather than to destabilize the radical adduct, and this is in accord with other recent studies.[9,10] Finally, we note that the fragmentation enthalpies for R = CH_3 are slightly lower than the corresponding values for R = CH_2OCOCH_3 and that the vinyl acetate moiety is indeed a poor leaving group from the RAFT-adduct radical.

Examining next the barriers, we find that for the methyl leaving group there is a small increase in the fragmentation barriers with increasing alkylation of the Z′ group. These changes in the barrier follow the changes in the fragmentation enthalpies in accordance with the Evans−Polanyi rule.[22,23] However, for the vinyl acetate leaving group, the behavior is more complicated. While there is an increase in the barrier height from Me to *tert*-Bu, the barriers fall into two distinct groups, with the adducts having Z′ = Me or Et showing substantially lower barriers for fragmentation than those having Z′ = iso-Pr or *tert*-Bu. Furthermore, the barriers for the bulkier Z′ substituents are relatively similar for both the methyl and (larger) vinyl acetate leaving groups, while for the smaller Z′ substituents, the barriers are considerably lower for the (more bulky) vinyl acetate leaving group. Thus, it does not appear likely that the substantial difference in barrier height between the Z′ = Me or Et systems and the Z′ = iso-Pr or *tert*-Bu systems may be attributed predominantly to increased steric strain in the transition structures for the latter case.

Nonetheless, it appears that steric factors are contributing to the difference in the barriers for the Z′ = Me or Et and Z′ = iso-Pr or *tert*-Bu cases, but in a more indirect manner. If we examine the minimum-energy conformations of the radicals and transition structures (Figure 2), we see that the substantial increase in barrier height for the iso-Pr and *tert*-Bu substituents is associated with a conformational change in the transition structure as the Z′ substituent becomes more bulky. More specifically, we can see that the vinyl acetate moiety is oriented toward the alkoxy group for the Z′ = Me and Et cases but away from the alkoxy group in the

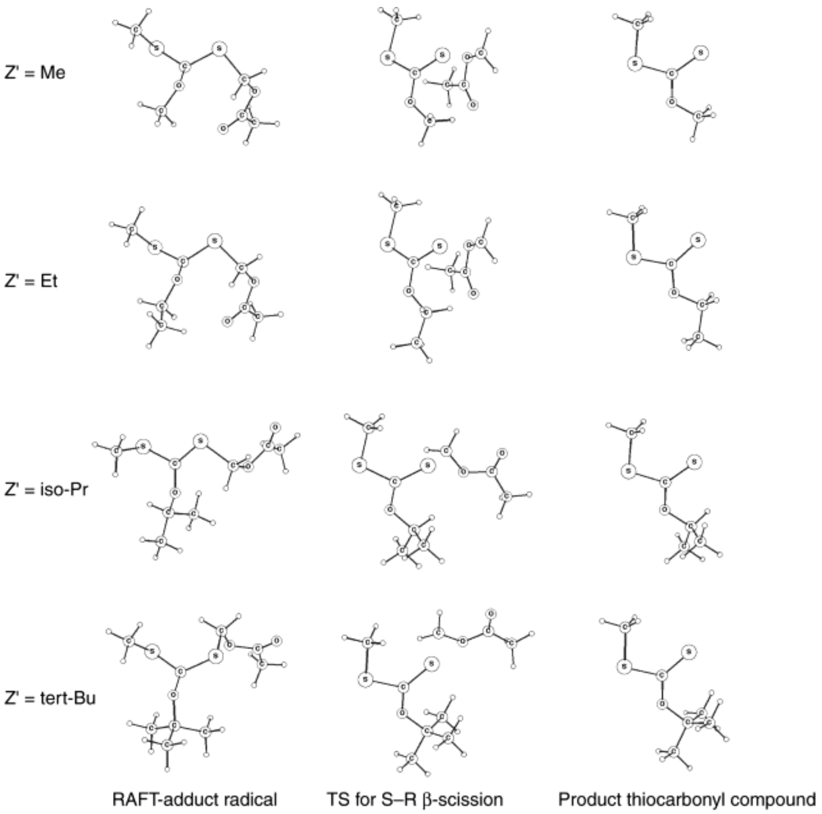


Figure 2. Optimized B3-LYP/6-31G(d) structures of the minimum-energy conformations of species in the S−R β-scission of RAFT-adduct radicals $CH_3SC{\cdot}(OZ')S{-}CH_2OCOCH_3$ ($Z' =$ Me, Et, iso-Pr, *tert*-Bu) to form the vinyl acetate propagating radical (${\cdot}CH_2OCOCH_3$) and the thiocarbonyl compounds, $CH_3SC(OZ'){=}S$.

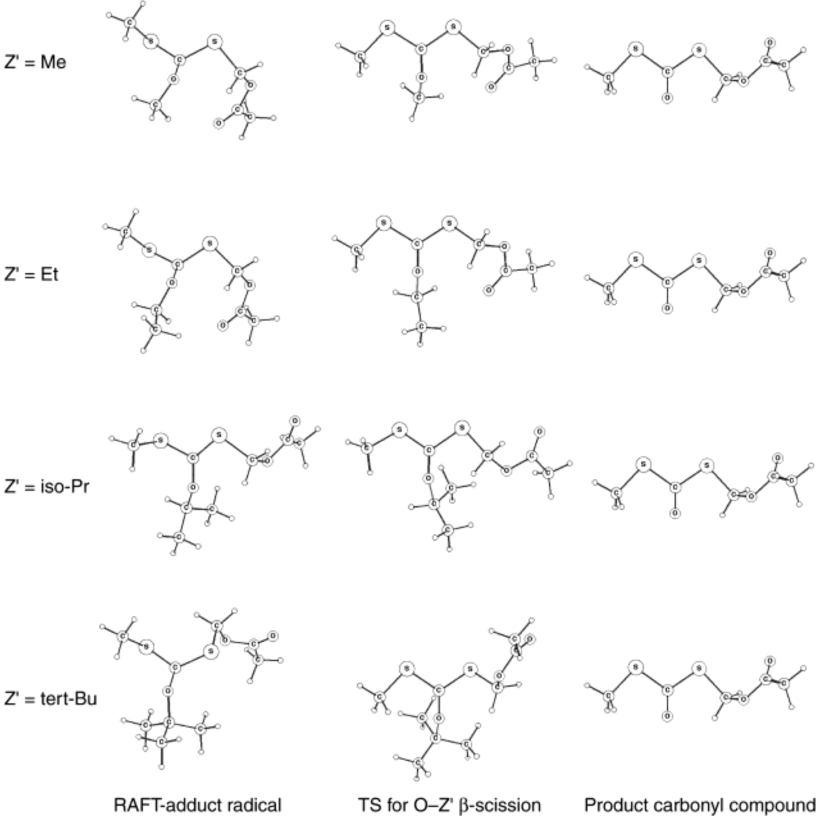


Figure 3. Optimized B3-LYP/6-31G(d) structures of the minimum-energy conformations of species in the O−Z′ β-scission of RAFT-adduct radicals $CH_3SC{\cdot}(O{-}Z')SCH_2OCOCH_3$ ($Z' =$ Me, Et, iso-Pr, *tert*-Bu) to form an alkyl radical (${\cdot}Z'$) and the carbonyl compound $CH_3SC({=}O)SCH_2OCOCH_3$.

bulkier $Z' =$ iso-Pr and *tert*-Bu cases. It would appear that the transition structure is being stabilized in the $Z' =$ Me and Et cases via through-space interactions involving the vinyl acetate moiety and the RAFT agent.

Table 3. Mulliken Charges[a] on the Z′ Fragments in the RAFT-Adduct Radicals ($CH_3SC\cdot(O-Z')SR$) and Transition Structures for O−Z′ β-Scission

	R = CH_3		R = CH_2OCOCH_3	
	$CH_3SC\cdot(O-Z')SR$	Z′ ... O=C(SCH_3)SR	$CH_3SC\cdot(O-Z')SR$	Z′ ... O=C(SCH_3)SR
Z′ = Me	0.35	0.32	0.37	0.24
Z′ = Et	0.37	0.38	0.39	0.28
Z′ = iso-Pr	0.39	0.44	0.40	0.46
Z′ = *tert*-Bu	0.42	0.47	0.42	0.49

[a] Calculated at the RHF/6-31G(d)//B3-LYP/6-31G(d) level of theory.

In contrast, in the bulkier Z′ = iso-Pr and *tert*-Bu cases, steric repulsion forces the vinyl acetate moiety to angle away from the RAFT agent, preventing these through-space interactions and leading to a higher reaction barrier. It is difficult to establish the exact nature of the stabilizing interactions, but it is worth noting that the carbonyl group of the vinyl acetate moiety passes within 2 Å of hydrogens in the Z′ group, and thus hydrogen bonding may be a factor. Although hydrogen bonding between a hydrogen of a C−H bond and a carbonyl oxygen does not normally contribute a strong stabilizing effect for stable compounds, such interactions may be more significant in the (higher energy) transition structures.

The trends in the forward and reverse rate coefficients at 60 °C (Table 2) follow the trends in the corresponding barriers. Thus, the Z′ = Me and Et systems have significantly faster fragmentation rate coefficients than the more bulky Z′ = iso-Pr and *tert*-Bu systems. What is interesting about these data is that all of the fragmentation rate coefficients are considerably faster than those calculated previously[20] for RAFT-adducts having a methyl leaving group and a phenyl ($0.13\ s^{-1}$) or benzyl ($9.8\ s^{-1}$) group in the Z-position. Indeed, the fragmentation rate coefficients for these six systems cover 8 orders of magnitude (at 60 °C) and demonstrate the extreme sensitivity of this reaction to changes in the substituents. For the present xanthate-mediated systems, the "equilibrium constants" ($K_{eq} = k_{add}/k_{frag}$) decrease monotonically from Me ($13.2\ L\ mol^{-1}$) to *tert*-Bu ($0.195\ L\ mol^{-1}$). However, none of the observed equilibrium constants are high enough to place the polymerizations in the regime for which slow fragmentation of the RAFT-adduct radical should lead to rate retardation (i.e., $K_{eq} > 10^6-10^7$).[24] In summary, while the fragmentation rate coefficient of the Z′ = *tert*-Bu substituted system is lower than those for the other xanthate-mediated systems, it is not low enough to account for the rate retardation experimentally observed[8] in this system.

Effect of Substituents on O−Z′ β-Scission. The enthalpies for β-scission of the O−Z′ alkoxy group (Table 1) follow an interesting pattern in both the R = CH_3 and R = CH_2OCOCH_3 cases. In each case we see an increase in the reaction enthalpies from Me to iso-Pr, followed by a small decrease from iso-Pr to *tert*-Bu. Separately, we have examined Z′−X bond dissociation energies in a wide range of compounds and have found that this unusual pattern is repeated for simpler cases such as X = OCH_2 and X = OCH_3.[17] Indeed, experimental evidence for these unusual trends has recently been noted and discussed by Zavitsas and co-workers.[25,26] Prima facie, these results may appear counterintuitive, as one might generally expect Z′−X bond dissociation reactions to become more exothermic from Me to *tert*-Bu in accord with the increasing stability of the product alkyl radical (i.e., •Z′). However, it is important to realize that the relative bond dissociation energies are a function of the relative stabilities of both the reactants and products. In fact, the increasing alkylation of the Z′ group stabilizes not only the product radical but also the O−Z′ bond in the reactant $CH_3SC\cdot(O-Z')S-R$ radical, and it is these competing effects that led to the unusual ordering of enthalpies.

The stabilizing effect of the Z′ group on the O−Z′ bond (which we discuss in detail elsewhere[17]) may be explained as follows. The increasing electron-donating ability of the Z′ group from Me to *tert*-Bu leads to increasing polarization of the O−Z′ bond. This can be seen quite clearly in Table 3, where we list the charge on the Z′ fragment in the RAFT-adduct radicals. Not only is there a significant positive charge for all of the radicals, but this increases substantially in the order Me < Et < iso-Pr < *tert*-Bu. In valence-bond terms, this increased resonance between the covalent (i.e., O−Z′) and ionic (i.e., $O^-Z'^+$) configurations leads to increased stabilization of the O−Z′ bond from Z′ = Me to *tert*-Bu. This effect counteracts the increasing stability of the product •Z′ radicals from Me to *tert*-Bu, and it is only for the most stable *tert*-Bu radical that the radical-stabilizing effect dominates the relative enthalpies.

The barriers for O−Z′ fragmentation follow similar trends to the enthalpies, in that there is initially an increase in barrier with increasing alkylation of Z′, followed by a decrease with further alkylation. However, the quantitative trends (and indeed the qualitative position of the maximum barrier) are somewhat different. To understand the reaction barriers for O−Z′ β-scission, it must be realized that the breaking O−Z′ bond in the transition structure is also stabilized by resonance between the covalent and ionic configurations of the bond (see Table 3). This increasing $O^-Z'^+$ charge-transfer stabilization of the transition structure counteracts to some extent the increasing $O^-Z'^+$ charge-transfer stabilization of the reactant radicals. This is in contrast to the reaction enthalpies where the $O^-Z'^+$ charge-transfer stabilization clearly does not occur in the isolated products. As a result, the maximum barrier occurs for a lower extent of alkylation (i.e., Z′ = Et) than does the maximum enthalpy (i.e., Z′ = iso-Pr).

A clearer indication of the role of charge-transfer effects in the transition structures can be ascertained from the reverse barriers since, in these quantities, the charge-transfer-stabilized transition structure is compared with the isolated reactants (where of course charge-transfer stabilization is not possible). For the R = CH_3 systems, the reverse barriers are 94.9, 83.6, 70.9, and 56.9 $kJ\ mol^{-1}$ for Z′ = Me, Et, iso-Pr, and *tert*-Bu, respectively. There is thus a steady decrease in the barrier despite increasing stability of the reactant alkyl radicals, and this decrease may be attributed to increasing charge-transfer stabilization of the transition structures. Viewed in another way, a stronger (forming) O−Z′ bond is being made by *tert*-butyl than by Me in the reverse direction. For the R = CH_2OCOCH_3 systems, the corresponding reverse barriers are 77.2, 87.5, 64.0, and 51.6 kJ mol^{-1}, respectively. These show a pattern similar to the R = CH_3 systems, except that the Z′ = Me system has a lower barrier than the Z′ = Et system. In this particular case, the lower barrier for Z′ = Me may be the result of the greater reactivity of the $\cdot CH_3$ radical and/or a possible additional stabilizing contribution from the reverse $O^+Z'^-$ ionic configuration (which would be most stable for the best electron-withdrawing Z′ = Me substituent).

As in the case of the S−R β-scission, the trends in the forward and reverse rate coefficients for O−Z′ β-scission at 60 °C (Table 2) follow the trends in the corresponding barriers. The addition reactions have negligible reaction rates at 60 °C. This is not surprising because radical addition to carbonyl compounds is generally quite slow (due to their relatively high singlet−triplet excitation gaps), and in particular, addition to the oxygen center of carbonyl compounds is not generally preferred.[27] The rates of the β-scission reactions vary considerably in line with the barriers, with the highest rates occurring for the Z′ = Me and Z′ = *tert*-Bu cases as these have the lowest barriers. As noted above, the barriers for the β-scission reactions may be considered to be the result of the competing effects of charge-transfer stabilization of the reactant radicals and transition structures, and the hyperconjugative stabilization of the leaving alkyl radical. In the case of Z′ = Me, the (relatively) high fragmentation rate may be attributable to a large reaction exothermicity and possible (minor) stabilization of the transition structure through resonance from *both* the $O^-Z'^+$ and $O^+Z'^-$ ionic configurations. In the case of the Z′ = *tert*-Bu system, the fast fragmentation rate may be attributable to the stabilization of the transition structure through resonance with the $O^-Z'^+$ configuration (which counteracts the corresponding stabilization of the breaking O−Z′ bond) and the relatively large stability of the leaving *tert*-Bu radical.

Comparison of S−R and O−Z′ *β*-Scission. Comparing the barriers and enthalpies for the S−R and O−Z′ β-scission reactions, we note that the O−Z′ β-scission is the thermodynamically preferred reaction, being exothermic in all cases. In contrast the S−R β-scission reaction is strongly endothermic in all cases. Nonetheless, despite this strong thermodynamic preference for O−Z′ β-scission, the kinetic preference is *generally* for S−R β-scission. In other words, if we consider the reverse direction, radical addition to thiocarbonyl compounds occurs with relatively high rates, whereas addition to carbonyl compounds occurs with very low rates.

We have recently compared radical addition to C=O and C=S double bonds in simpler systems and have noted that radical additions to C=S bonds occur with very low barriers compared with additions to carbonyl bonds.[27] One of the main reasons for this difference is the significantly lower (by around 2 eV in simple systems[27]) singlet−triplet excitation gaps for the C=S vs C=O double bonds. Under the curve-crossing model,[28,29] it can be shown that (in the absence of other effects) lower singlet−triplet gaps are correlated with lower barriers for addition, as they indicate a reduced energy cost for the π−π^* electronic excitation that occurs during the addition reaction. Since the addition and β-scission reactions share the same transition structure, one would also expect that, in the absence of other factors, the barriers should be lower for S−C vs O−C β-scission. Of course, in the present reactions, other factors do counter this kinetic preference for S−R over O−Z′ β-scission. In particular, the greater exothermicity of O−Z′ vs S−R β-scission reactions and the favorable charge-transfer stabilization of the O−Z′ β-scission transition structures both help to lower the barrier of O−Z′ β-scission, relative to that of S−R β-scission. Nonetheless, the barriers for O−Z′ β-scission remain higher than the corresponding S−R β-scission barriers for all but the Z′ = *tert*-butyl system. In this system, the significant charge-transfer stabilization of the O−Z′ β-scission transition structure, combined with the greater stability of the *tert*-butyl leaving group, tips the balance in favor of the O−Z′ β-scission reaction.

Why Does S=C(O-*tert*-Bu)-SR Retard Vinyl Acetate Polymerization? Comparing the rates of S−R and O−Z′ β-scission in the vinyl acetate system (Table 2), a possible explanation for the retardation in the Z′ = *tert*-Bu system becomes apparent. Whereas in the Me, Et, and iso-Pr substituted-systems the rate for S−R β-scission is 2−5 orders of magnitude faster than that for O−Z′ β-scission, in the *tert*-Bu case the O−Z′ β-scission reaction is faster by 2 orders of magnitude. Thus, in the *tert*-Bu system, this unexpected side reaction occurs in preference to the normal fragmentation step, producing a relatively stable *tert*-Bu radical, and a relatively unreactive carbonyl compound. In particular, given the extremely low rate coefficients for addition to the O-center of the carbonyl compound, this compound would not be capable of re-forming the RAFT-adduct radical, and the RAFT mechanism would be expected to fail for this system.

The other consequence of this side reaction would be the rapid conversion of the (reactive) vinyl acetate propagating radicals into the (more stable) *tert*-butyl radicals. While the *tert*-butyl radicals would be capable of reinitiating polymerization, the rate of reinitiation would be expected to be relatively slow. For example, the rate of addition of the *tert*-butyl radical to vinyl acetate in solution at 298 K is 4200 L mol^{-1} s^{-1}, while the corresponding methyl addition rate is 14 000 L mol^{-1} s^{-1} under the same conditions.[30] This slow rate of reinitiation might be expected to cause retardation in the early stages of the polymerization, while the RAFT agent is being consumed. Furthermore, during this period, the slow rate of addition would allow chain-stopping side-reactions (such as termination and transfer steps) to compete more effectively, and this might then explain the experimentally observed inhibition in this system. An examination of the low molecular weight products in the failed Z′ = *tert*-Bu system could be used to test this hypothesis. In particular, one might expect to find the carbonyl compounds (of varying chain lengths) and various termination and transfer products involving the *tert*-butyl group.

Conclusions

In the present work we have used ab initio molecular orbital calculations to study addition and fragmentation in a series of xanthate-mediated vinyl acetate polymerizations. The RAFT agents considered were a series of xanthates of the form S=C(O−Z′)S−R, where Z′ = methyl, ethyl, iso-propyl, and *tert*-butyl and R = CH_2OCOCH_3. In general we find that fragmentation of the S−R bond is relatively fast, and the equilibrium constants (i.e.,

k_{add}/k_{frag}) are relatively small. In the simpler R = CH_3 system, there is a small increase in the fragmentation enthalpy and a corresponding increase in the fragmentation barrier, with increasing alkylation of the Z′ group (i.e., Me < Et < iso-Pr < *tert*-Bu). This would suggest that increasing electron donation to the radical center by the Z′ group is stabilizing the RAFT-adduct radical, thereby reducing the fragmentation rate. In the model vinyl acetate system R = CH_2OCOCH_3 there is a more substantial decrease in the fragmentation rate for Z′ = iso-Pr and *tert*-Bu, associated with a sterically induced conformational change in the transition structure.

However, the S−R fragmentation rates are not low enough to explain the experimentally observed[8] inhibition of the Z′ = *tert*-Bu mediated system. Instead, the rate retardation appears to be the result of the preferred fragmentation of the O−C bond in the *tert*-butoxy group of the RAFT adduct. This fragmentation pathway is not normally favored in RAFT polymerization. However in this particular system, the combination of the vinyl acetate radical being a poor leaving group, the *tert*-butyl radical being an excellent leaving group, and the charge-transfer stabilization of the transition structure for O−C β-scission tips the balance in favor of this reaction.

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Supporting Information Available: Tables S1−S4 showing (S1) the B3-LYP/6-31G(d) optimized geometries (in the form of GAUSSIAN archive entries), (S2) the corresponding total energies at RMP2/6-311+G(3df,2p) and G3(MP2)-RAD, (S3) details of the formulas used in the kinetics calculations, and (S4) the temperature corrections and entropies of the individual species. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) It should be noted that RAFT processes employing xanthates as the RAFT agents are sometimes referred to as MADIX (macromolecular design via interchange of xanthates) processes. However, to avoid confusion, we use the more general term of “RAFT” throughout this paper.

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