JOC Note

Factors Affecting the Relative and Absolute Rates of β-Scission of Alkoxythiocarbonyl Radicals and Alkoxycarbonyl Radicals

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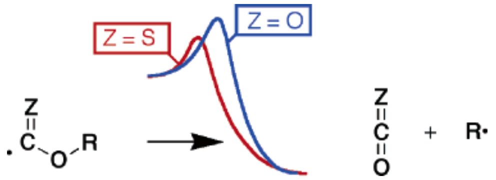

High-level ab initio calculations demonstrate that alkoxythiocarbonyl radicals ($\mathrm{ROC^{\bullet}{=}S}$) undergo β-scission significantly faster than alkoxycarbonyl radicals ($\mathrm{ROC^{\bullet}{=}O}$) despite having similar exothermicities. The relatively low reactivity of the $\mathrm{ROC^{\bullet}{=}O}$ radicals is reduced further by electron-donating R groups and arises from the large polarization of the $\mathrm{C^{\bullet}{-}O}$ bonds of the reactant radicals. The results suggest that the generation of alkyl radicals from $\mathrm{ROC^{\bullet}{=}S}$ should be particularly efficient when the R group bears radical-stabilizing and/or electron-accepting groups, such as CN.

In recent years, xanthic anhydrides have emerged as useful reagents in organic synthesis, providing a convenient tin-free reaction for generating carbon radicals from alcohols and for exchanging a C−O bond for a C−S bond under very mild conditions.[1] At the core of the process, alkoxythiocarbonyl radicals ($\mathrm{ROC^{\bullet}{=}S}$) undergo β-scission to extrude carbon oxysulfide and produce the corresponding alkyl radicals,[1,2] and the rapidity of this reaction is key to its importance. However, little is known about the kinetics of this reaction and its dependence on the alkyl substituents—information that is vital for optimizing the process and identifying its scope and possible limitations.

One intriguing question is why the β-scission of alkoxythiocarbonyl radicals ($\mathrm{ROC^{\bullet}{=}S}$) is faster than that of their oxygen analogues, alkoxycarbonyl radicals ($\mathrm{ROC^{\bullet}{=}O}$). These latter radicals are known to be comparatively resistant to the loss of carbon dioxide,[3,4] and though the exact rates are not known, there is evidence from both experiment[1b] and ab initio calculations[5] that their β-scission rates may be orders of magnitude slower than those of their $\mathrm{ROC^{\bullet}{=}S}$ counterparts. This difference in reactivity is somewhat counterintuitive. For instance, from a thermodynamic viewpoint, the reactions might have been expected to have similar rates, given that in each case the leaving group is the same and a similar O−R bond is broken and C=O bond is formed. Indeed, a previous theoretical study confirmed that the β-scission *enthalpies* for $\mathrm{CH_3OC^{\bullet}{=}O}$ and $\mathrm{CH_3OC^{\bullet}{=}S}$ were approximately equal.[5] It is thus clear that the β-scission *kinetics* depend on additional factors, and it is important to unravel and understand this interplay of factors to facilitate the design of optimal reagents.

To identify the scope and limitations of xanthic anhydrides as a source of alkyl radicals in organic synthesis, in the present work we examine and explain the difference in reactivity between corresponding $\mathrm{ROC^{\bullet}{=}S}$ and $\mathrm{ROC^{\bullet}{=}O}$ β-scission reactions and explore the effects of R substituents on the reaction. To this end, using high-level ab initio molecular orbital calculations, the enthalpies, Arrhenius parameters, and reaction rates (at 298 K) have been calculated for the reaction $\mathrm{ROC^{\bullet}{=}Z \rightarrow R^{\bullet} + O{=}C{=}Z}$ for Z = S and O and R = $\mathrm{CH_3}$, $\mathrm{CH_2F}$, $\mathrm{CH_2OH}$, $\mathrm{CH_2CF_3}$, and $\mathrm{CH_2CN}$ (see Table 1).[6] To assist in the qualitative rationalization of the results, the corresponding radical stabilization energies (RSEs) of the reactant radicals and leaving groups ($\mathrm{R^{\bullet}}$) are also included in Table 1.[7] The charge distributions within the reactant radicals and transition structures were also calculated; those for the two parent reactions are shown in Scheme 1, and those for all 10 reactions are provided in Table 2.

The results demonstrate that, for a given R group, β-scission of the $\mathrm{ROC^{\bullet}{=}S}$ radicals is considerably faster than $\mathrm{ROC^{\bullet}{=}O}$, a preference that arises in the lower reaction barriers in the former case but which occurs despite the similar reaction

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[6] Calculations were at a high level of theory chosen on the basis of a recent assessment study for radical addition to C=O bonds (see ref 10a). Full details of the calculations, together with geometries of all species (in the form of GAUSSIAN archive entries), are provided in the Supporting Information.

[7] The RSE is defined as the energy change of the reaction $\mathrm{R^{\bullet} + CH_4 \rightarrow RH + CH_3^{\bullet}}$. The RSEs of the leaving radicals, $\mathrm{R^{\bullet}}$, were calculated using the R−H bond dissociation energies reported in: Beare, K. D.; Coote, M. L. *J. Phys. Chem. A* **2004**, *108*, 7211−7221. The RSEs of the reactant radicals were calculated at the G3(MP2)-RAD level of theory as part of the present work.

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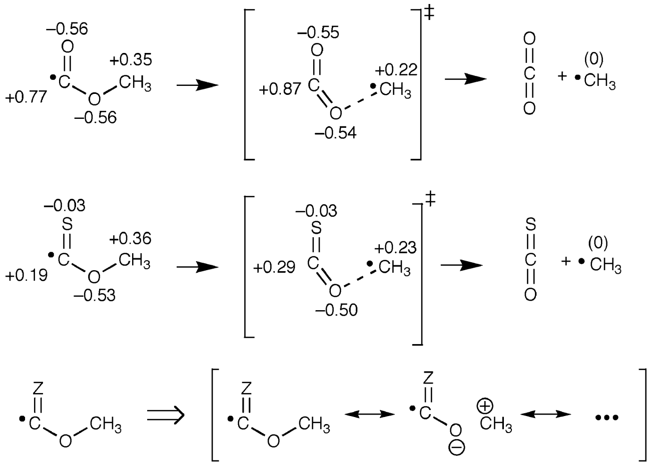
TABLE 1. Calculated Reaction Enthalpies (ΔH_{298}, kJ mol^{-1}), Arrhenius Activation Energies (E_a, kJ mol^{-1}), Frequency Factors (A, s^{-1}) and Reaction Rates (k_{298}, s^{-1}) at 298 K for the β-Scission Reactions, $O{=}C^{\bullet}{-}O{-}R \rightarrow O{=}C{=}O + {\bullet}R$ and $S{=}C^{\bullet}{-}O{-}R \rightarrow S{=}C{=}O + {\bullet}R$, and Corresponding Radical Stabilization Energies (RSEs, 0 K, kJ mol^{-1})[a]

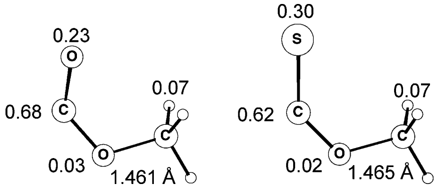
		$O{=}C^{\bullet}{-}O{-}R \rightarrow O{=}C{=}O + {\bullet}R$					$S{=}C^{\bullet}{-}O{-}R \rightarrow S{=}C{=}O + {\bullet}R$				
R	RSE ($R^{\bullet}$)	RSE ($O{=}C^{\bullet}{-}O{-}R$)	ΔH_{298}	E_a	log A	k_{298}	RSE ($S{=}C^{\bullet}{-}O{-}R$)	ΔH_{298}	E_a	log A	k_{298}
CH_3	0.0	15.6	−95.2	60.6	13.9	1.9×10^{3}	29.2	−93.5	43.7	14.4	5.2×10^{6}
CH_2CF_3	−7.1	10.9	−98.4	59.8	13.7	1.5×10^{3}	23.6	−97.2	41.8	13.3	9.8×10^{5}
CH_2CN	33.2	10.5	−146.5	41.5	13.5	1.5×10^{6}	24.9	−144.7	24.1	13.6	2.3×10^{9}
CH_2OH	33.3	14.0	−73.1	64.1	13.8	4.1×10^{2}	28.6	−70.5	38.8	13.6	6.6×10^{6}
CH_2F	13.6	12.3	−73.0	78.8	14.2	2.4	27.2	−74.6	57.1	13.9	7.8×10^{3}

[a] Barriers and enthalpies were calculated at the G3(MP2)-RAD level of theory using B3-LYP/6-31(d)-optimized geometries and include scaled B3-LYP/6-31(d) zero-point vibrational energy corrections. Entropies and thermal corrections to enthalpy were calculated using B3-LYP/6-31G(d)-optimized geometries and scaled B3-LYP/6-31(d) frequencies using standard formulas based on the statistical thermodynamics of an ideal gas under harmonic oscillator/rigid rotor approximation. These quantities were then used to calculate the Arrhenius activation energies, frequency factors, and reaction rates via standard transition-state theory. The RSEs of the reactant radicals were calculated at the G3(MP2)-RAD level of theory, while those of $R^{\bullet}$ were calculated at the G3X(MP2)-RAD//MPW1K/6-31+G(d,p) level of theory, using the R−H bond dissociation energies from a previous study.[7]

SCHEME 1. Charge Distributions in the β-Scission Reactions of $CH_3OC{\bullet}{=}O$ and $CH_3OC{\bullet}{=}S$



SCHEME 2. B3-LYP/6-31G(d)-Optimized Geometries of $O{=}C{\bullet}OCH_3$ and $S{=}C{\bullet}OCH_3$, Showing the $O{-}CH_3$ Bond Lengths (Å) and the Spin Densities



exothermicities. For any of the $R^{\bullet}$ groups considered, the exothermicity difference between corresponding $ROC^{\bullet}{=}S$ and $ROC^{\bullet}{=}O$ β-scission reactions is less than 3 kJ mol^{-1}; the corresponding difference in activation energies ranges from 17 to 25 kJ mol^{-1}, leading to differences in β-scission rates (at 298 K) of 2−4 orders of magnitude. The results also indicate that the β-scission of both types of radical is extremely sensitive to the nature of the R group, the exothermicities varying by over 70 kJ mol^{-1} and the activation energies by over 30 kJ mol^{-1} among the R groups considered in the present work. In the following text, we show that these trends are explicable in terms of polar and radical stabilization effects.

Let us consider first the *absolute* rates of β-scission of corresponding $ROC^{\bullet}{=}S$ and $ROC^{\bullet}{=}O$ radicals. As noted above, in all cases, the β-scission of the $ROC^{\bullet}{=}S$ radicals is considerably faster than that of its carbonyl analogues, $ROC^{\bullet}{=}O$. This is despite the fact that the leaving radical (and hence its radical stabilization energy) is the same and the exothermicity difference is negligible. Although there are minor systematic differences in the radical stabilization energies of the corresponding $ROC^{\bullet}{=}S$ and $ROC^{\bullet}{=}O$ radicals, they indicate that the $ROC^{\bullet}{=}S$ radical is more stabilized and, on this basis, should have been expected to be *less* reactive. Moreover, an examination of the bond lengths and spin densities in the reactant radicals reveals no substantial differences that could explain the observed trends (see Scheme 2). Instead, the difference in reactivity appears to be polar in origin. From Scheme 1 and Table 2, it is seen that there is a systematic difference in the charge distribution within the $ROC^{\bullet}{=}S$ and $ROC^{\bullet}{=}O$ radicals. Although in both systems the oxygen of the alkoxy group is strongly negative and the leaving R group is strongly positive, in the $ROC^{\bullet}{=}O$ radicals (and transition structures), the $C^{\bullet}{=}O$ bond is also highly polarized, with the carbon bearing a large positive charge and the oxygen a large negative charge. In contrast, in the $ROC^{\bullet}{=}S$ radicals, the S atom is much less electronegative and the $C^{\bullet}{=}S$ bond is thus less polarized. This polarization of the $C^{\bullet}{=}O$ bond has important implications for the β-scission kinetics. Since the product $R^{\bullet}$ radical is neutral, during the course of the β-scission reaction the electron-deficient R group must receive electron

TABLE 2. Charge on the Z, C, O, and R Fragments in the Reactant Radical and Transition Structure for the β-Scission Reactions, $Z{=}C^{\bullet}{-}O{\text -}R \rightarrow Z{=}C{=}O + {}^{\bullet}R$[a]

	$Z{=}C^{\bullet}OR$ reactant radical								$[Z{=}CO\cdots R]^{\bullet}$ transition structure							
	Z = O				Z = S				Z = O				Z = S			
R	Z	C	O	R	Z	C	O	R	Z	C	O	R	Z	C	O	R
CH_3	−0.56	0.77	−0.56	0.35	−0.03	0.19	−0.53	0.36	−0.55	0.87	−0.54	0.22	−0.03	0.29	−0.50	0.23
CH_2CF_3	−0.54	0.78	−0.56	0.32	0.00	0.20	−0.53	0.33	−0.52	0.88	−0.54	0.17	0.02	0.28	−0.49	0.19
CH_2CN	−0.54	0.79	−0.55	0.30	0.01	0.20	−0.52	0.31	−0.53	0.87	−0.53	0.19	0.03	0.26	−0.50	0.21
CH_2OH	−0.60	0.78	−0.58	0.39	−0.08	0.22	−0.54	0.41	−0.56	0.84	−0.61	0.33	−0.13	0.29	−0.52	0.36
CH_2F	−0.54	0.78	−0.58	0.34	0.02	0.18	−0.55	0.35	−0.54	0.87	−0.57	0.25	−0.01	0.27	−0.52	0.26

[a] Charges calculated at the B3-LYP/6-311+G(3df,2p)//B3-LYP/6-31G(d) level on the basis of a natural bond orbital (NBO) population analysis.

density. One would expect that this would be principally provided by the unpaired electron on the carbon center of the $\mathrm{ROC^{\bullet}{=}Z}$ radical. However, since in the $\mathrm{ROC^{\bullet}{=}O}$ radicals this carbon center is itself highly electron deficient, this electron density is less available, and the β-scission reaction is thus less favorable. In other words, the unpaired electron is able to interact more strongly with the σ^* orbital of the breaking alkoxy bond, and this is further confirmed when one examines the SOMO−LUMO gaps in the reactant radicals (which are 6.29 and 4.26 eV for $\mathrm{CH_3OC^{\bullet}{=}O}$ and $\mathrm{CH_3OC^{\bullet}{=}S}$, respectively).

On the basis of this polar effect, one might predict that the presence of electron-donating substituents on the R group would interfere with its ability to accept electron density and should thus reduce further the rates of β-scission. This reduction in β-scission rate would be expected in the reactions of both types of radical but would be expected to be stronger in the more polarized $\mathrm{ROC^{\bullet}{=}O}$ radicals and should thus enhance the preference for β-scission of $\mathrm{ROC^{\bullet}{=}S}$ over $\mathrm{ROC^{\bullet}{=}O}$. In support of this hypothesis, we note that the largest differences in β-scission barriers occur when the R group bears the electron-donating substituents OH (25 kJ $\mathrm{mol^{-1}}$) and F (22 kJ $\mathrm{mol^{-1}}$). The other R groups bear substituents that are less effective donors (i.e., H, $\mathrm{CF_3}$, and CN), and in these cases, the barrier differences are smaller (17−18 kJ $\mathrm{mol^{-1}}$).

We are now in a position to explain the large effect of the R group on the *relative* rates of β-scission of the $\mathrm{ROC^{\bullet}{=}S}$ or $\mathrm{ROC^{\bullet}{=}O}$ radicals. As noted above, on one hand, R groups with electron-withdrawing substituents should favor the β-scission reaction and those with electron-donating groups should not. On the other hand, now that the leaving radical $\mathrm{R^{\bullet}}$ is also being varied, one would expect that R groups with substituents that stabilize an unpaired electron should favor the β-scission reaction, when compared with those with less stabilizing substituents. Of course, the R group will also affect the stability of the reactant radical;[8] however, for the present substituents these effects are relatively small, particularly when compared with the corresponding effects on the $\mathrm{R^{\bullet}}$ stabilization energy (see Table 1). To understand the interplay of the (sometimes competing) polar and radical stabilization energy effects, free energy diagrams for the $\mathrm{ROC^{\bullet}{=}S}$ reactions have been plotted in Figure 1. (Those for the $\mathrm{ROC^{\bullet}{=}O}$ systems show similar trends, but have higher reaction barriers.) To assist in the analysis, the R^+ parameters of the R group substituents, as taken from ref 9, are also displayed in Figure 1. These parameters are the resonance constants for substituents that can effectively delocalize a charge from the reaction center and provide a measure of the ability of the R group to stabilize a positive charge.

Taking the parent (R = $\mathrm{CH_3}$) system as our reference point, we first note that R = $\mathrm{CH_2CF_3}$ system shows almost identical behavior, because the leaving radical is only slightly less stable and this is compensated for by the slightly improved ability of the R group to stabilize a positive charge. However, when these systems are compared with the R = $\mathrm{CH_2CN}$ system, the exothermicity increases dramatically and the fragmentation barrier drops accordingly. This reflects the increased stability of the leaving radical and the increased electron-accepting ability of the R group. In contrast, in the R = $\mathrm{CH_2OH}$ system, the stability of the leaving group radical is similar to that of $\mathrm{CH_2CN}$, but this is now countered by a reduced ability to stabilize a positive charge. As a result, the exothermicity is reduced, and the reaction barrier is considerably higher. Finally, the highest reaction barrier occurs for the R = $\mathrm{CH_2F}$ group. In these reactions, the poor electron-accepting ability of the $\mathrm{CH_2F}$ group is not compensated for by the stability of the leaving radical.

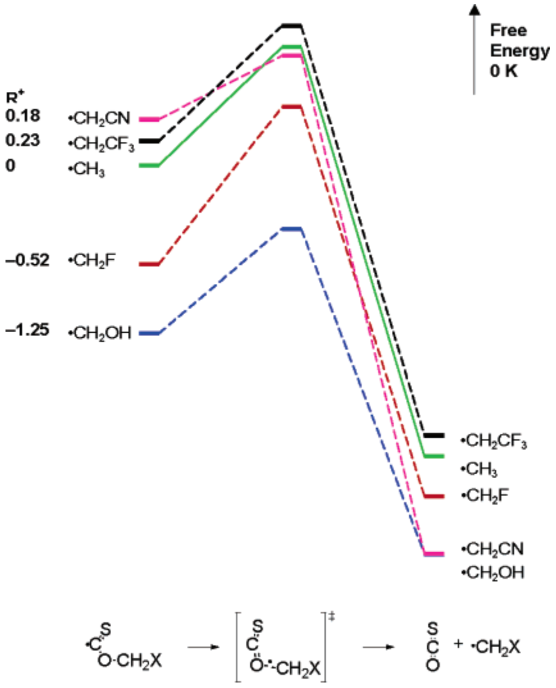


FIGURE 1. Free energy diagram (0 K) for the β-scission of the $\mathrm{S{=}C^{\bullet}OCH_2X}$ radicals for X = CN, $\mathrm{CF_3}$, H, F, and OH. The numbers in bold are the R^+ parameters for the X substituents, as taken from ref 9.

Finally, it is worth noting that the relative *exothermicities* (as well as the barriers) depend not only on the RSE of the leaving group radical but also its polarity. This polar effect on the thermodynamics of the β-scission reaction can be understood in terms of the stabilization of the breaking O−R bond from resonance between the covalent and ionic ($\mathrm{O^{-}R^{+}}$) forms.[10] However, unlike the barrier heights, this polar effect does not lead to a systematic difference in the exothermicities of corresponding $\mathrm{ROC^{\bullet}{=}S}$ and $\mathrm{ROC^{\bullet}{=}O}$ β-scission reactions. Instead, the polarity of the breaking O−R bond itself is relatively consistent between corresponding $\mathrm{ROC^{\bullet}{=}S}$ and $\mathrm{ROC^{\bullet}{=}O}$ (see Table 2) and appears to be unaffected by the polarity of the $\mathrm{C^{\bullet}{=}S}$ or $\mathrm{C^{\bullet}{=}O}$ bonds.

Alkoxythiocarbonyl radicals can thus undergo β-scission significantly faster than alkoxycarbonyl radicals because the thiocarbonyl group can more effectively provide electron density to the departing $\mathrm{R^{\bullet}}$ group. The polarity of the R group (together with its radical stability) has a profound effect on the relative and absolute rates of fragmentation reactions, the latter varying by almost 6 orders of magnitude. This has important synthetic consequences—implying that the use of $\mathrm{ROC^{\bullet}{=}S}$ radicals as a source of alkyl radicals will be significantly more successful when the alkyl radical is highly stabilized and/or bears electron-

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[10] Similar polar effects on alkoxy−oxygen bond strength have been reported previously in: (a) Coote, M. L.; Pross, A.; Radom, L. In *Fundamental World of Quantum Chemistry: A Tribute to the Memory of Per-Olov Löwdin*; Brändas, E. J., Kryachko, E. J., Eds.; Kluwer-Springer: Dordrecht, 2004; Vol. III, pp 581−596. (b) Coote, M. L.; Pross, A.; Radom, L. *Org. Lett.* **2003,** *5*, 4689−4692.

accepting groups (such as CN), rather than electron donating groups (such as OH or F). The work also implies that the rate of β-scission should be further enhanced through the use of polar solvents.

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Supporting Information Available: Details of the ab initio calculations, the B3-LYP/6-31G(d)-optimized geometries, and corresponding thermodynamic quantities. This material is available free of charge via the Internet at http://pubs.acs.org.

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