Understanding the Relative Acyl-Transfer Reactivity of Oxoesters and Thioesters: Computational Analysis of Transition State Delocalization Effects

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Abstract: Computational studies were performed in an effort to understand the relative reactivity of oxoesters and thioesters in nucleophilic acyl transfer reactions. Transition state models were developed for the reactions of methyl acetate and methyl thioacetate with hydroxide, ammonia, and methylcyanoacetate carbanion. Quantum mechanical calculations based on these models reproduced experimental observations that oxoesters and thioesters have similar reactivity toward hydroxide while thioesters are about 100-fold and at least 2000-fold more reactive than oxoesters toward amine and carbanion nucleophiles, respectively. NBO analysis was performed to elucidate the role of electron delocalization in reactant and transition state stabilization. These calculations indicate similar losses of delocalization energy for the oxoester and thioester in going from the reactants to the transition state in reaction with hydroxide while the loss of delocalization energy is significantly greater for the oxoester in reactions with the other nucleophiles. Bond rotational analysis of the transition states for the reactions with hydroxide and ammonia provide support for an important role of the $p_X \rightarrow \sigma^*_{C-Nu}$ interaction (X = O or S of the oxoester or thioester respectively, Nu = nucleophile) in governing the reactivity of oxoesters and thioesters in nucleophilic acyl substitution.

The reactivity of thioesters and comparison to the reactivity of oxoesters has been of longstanding interest, largely because of the importance of thioesters in enzymatic reactions of coenzyme A and cysteine proteases. In a classic study, Connors and Bender demonstrated that the reactivities of an oxoester (ethyl *p*-nitrobenzoate) and the corresponding thioester toward hydrolysis in basic solution were very similar, the reaction of the oxoester being about 20% faster than that of the thioester.[1] In contrast, the reaction of the thioester with *n*-butylamine to form an amide was more than 100-fold faster than the reaction of the corresponding oxoester. Numerous other studies have confirmed these observations with a range of oxoester and thioester structures and have shown that the similar reactivity of oxoesters and thioesters is also observed with alkali metal ethoxides in ethanol.[2−5] Reactions of oxoesters and thioesters with other types of nucleophiles have also been studied. A thioester was shown to be at least 2000-fold more reactive than the equivalent oxoester toward reaction with the ethylcyanoacetate carbanion.[6] Likewise, more than 100-fold greater reactivity of a thioester vs an oxoester has been observed in reaction with a thiolate nucleophile.[7,8]

The greater reactivity of thioesters than oxoesters toward most nucleophiles is consistent with the greater thermodynamic stability of oxoesters. The free energy of hydrolysis of a thioester was reported to be about 2 kcal/mol greater than that of an oxoester in aqueous solution, while computational studies that did not consider solvation effects predict a difference of more than 8 kcal/mol.[9,10] The greater thermodyanamic stability of an oxoester may be attributed to a greater degree of electron delocalization or resonance of a lone electron pair of the bridging oxygen with the carbonyl group relative to the same interaction in a thioester.[4,10,11] This may also rationalize the lower reactivity of oxoesters than thioesters toward most nucleophiles. The near equivalent reactivity of oxoesters and thioesters toward hydroxide and alkoxides is more difficult to rationalize. An early suggestion was that oxoesters and thioesters have similar reactivity toward nucleophiles in which the first step is rate-limiting while thioesters are more reactive in reactions in which the second step is rate-limiting due to the greater leaving group ability of the thiolate relative to an alkoxide.[1,2] While both experimental and computational studies support the greater leaving group ability of a thiolate,[12,13] computational studies indicate that the first step is rate-limiting even with nucleophiles toward which thioesters are much more reactive than oxoesters.[14] Though other efforts have been made to explain the observed reactivities of oxoester and thioesters, Al-Arab and Hamilton noted in 1987 that no satisfactory explanation had been offered.[15]

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Hard−soft acid base theory has more recently been invoked, with the assertion that the ratio of thioester to oxoester reactivity is greatest with soft nucleophiles.[5] While this is perhaps consistent with experimental observations, this matching of nucleophile and leaving group polarizability appears to go beyond standard hard−soft acid−base theory and does not necessarily provide an explanation in fundamental terms. While both experimental and computational studies of acyl transfer reactions continue to be reported,[16] none have provided a general rigorous explanation for relative oxoester and thioester reactivity. Presented here is a detailed computational study directed at understanding the relative reactivity of thioesters and oxoesters in nucleophilic acyl transfer with hydroxide, amine, and carbanion nucleophiles.

Methods

Reactions of methyl acetate and methyl thioacetate with hydroxide ion were modeled by incorporation of four water molecules for transition state stabilization. In the reactants, one of the four water molecules was considered to be associated with the ester/thioester and the other three with hydroxide. A procedure for automated positioning of water molecules was developed as follows. The crude transition state structure clusters generated by arbitrarily orienting water molecules around the reaction core followed by geometry optimization at the HF/6-31++G** level were taken as initial structures. The nucleophilic oxygen and carbonyl carbon and oxygen atoms were frozen and hydrogen bonds between water molecules and the reaction core were taken as real bonds for Monte Carlo analysis in which possible transition state structures with different water molecule orientations were generated by using PM3-SM3.[17−19] Lowest energy structures underwent transition state optimization at the HF/6-31++G** and B3LYP/6-31++G** levels and were verified by frequency and IRC calculations. General solvation effects were calculated by using the continuum models IPCM and SM3.[18−20] Transition state models for reactions with ammonia were developed as recently described by us and others.[14] Transition state models for reactions with the methylcyanoacetate carbanion did not consider solvation effects. Transition state structures were generated at the HF/6-31+G* level, verified by using frequency and IRC calculations, and further optimized at the B3LYP/6-31+G* level.

NBO calculations were performed by using HF/6-31++G** upon reactant and transition state structures generated at the B3LYP level.[21,22] Standard NBO deletion procedures were used to evaluate secondary interactions.

Dependence of transition state energies on rotation of the carbonyl carbon to leaving group bond was analyzed by relaxed energy surface scan techniques with rotation of the C−X bond in 20° increments while freezing the nucleophile and carbonyl carbon and oxygen atoms.[23] Transition state optimization and energy evaluation were performed at the HF/6-31+G*, HF/6-31++G**, and B3LYP/6-31++G** levels.

Results

The reactions of methyl acetate (**1**) and methyl thioacetate (**2**) with three different nucleophiles were chosen as simple models to compare the relative reactivity of oxoesters and thioesters. The nucleophiles were hydroxide ion **3**, ammonia **4**, and methyl cyanoacetate anion **5** (Figure 1). Initially, computational models for each of the reactions were developed. The reaction models developed and employed are shown in Scheme 1, with the transition state structures for each reaction shown in Figure 2. For comparison of reactions with hydroxide to experimental results which have normally been obtained in aqueous or alcohol solution,[1−5] a reaction model similar to that recently reported by Zhan et al. for ester hydrolysis involving four water molecules was employed.[24] A stepwise mechanism for oxoester hydrolysis via a tetrahedral intermediate was modeled, as also reported.[24] The first step has been shown to be rate limiting as was confirmed by our computational studies. A Monte Carlo method for positioning of water molecules was developed, with different positions of water molecules in the transition state and in the solvation of hydroxide ion generated by Monte Carlo methods, and the resulting structures optimized. Specific solvation of the tetrahedral intermediate is not shown in Scheme 1, as only the relative energies of the reactants and transition state are considered. For thioester hydrolysis, an intermediate could not be identified, indicating a concerted pathway. The transition state is similar to that for the first step of oxoester hydrolysis, including similar positioning of water molecules, though there is a small degree of cleavage of the carbon−sulfur bond in the transition state of this concerted reaction. For reactions with ammonia, stepwise mechanisms involving catalysis by a single water molecule were assumed for both the oxoester and thioester based on recently reported studies from this and other groups.[14,25,26] Again, this model

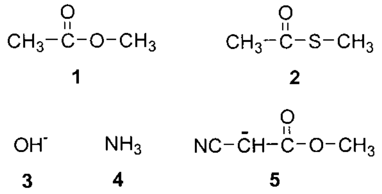
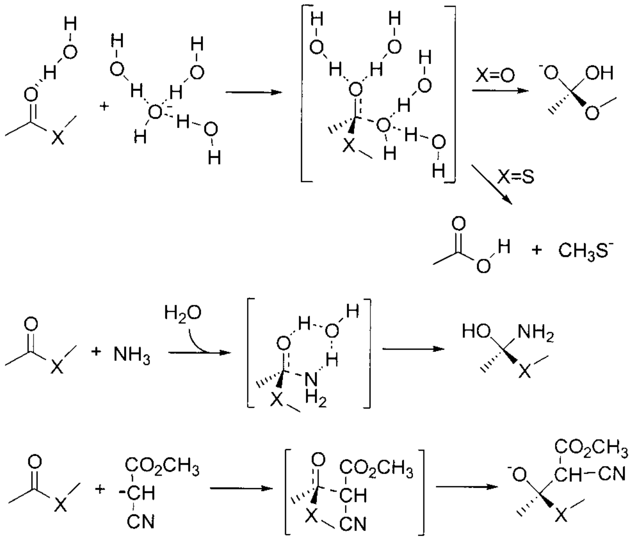


Figure 1. Structures of methyl acetate **1**, methyl thioacetate **2**, and the three nucleophiles considered in this study.

Scheme 1



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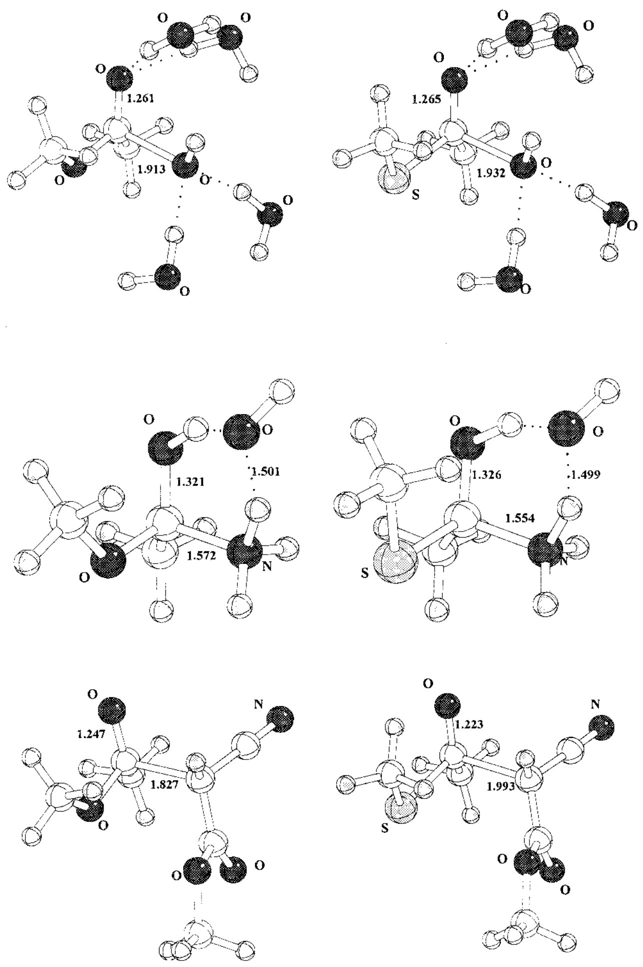

Figure 2. Structures of the transition states of the reactions of methyl acetate (left column) and methyl thioacetate (right column). In descending order rows show reactions with hydroxide, ammonia, and methylcyanoacetate carbanion.

Table 1. Relative Energies (ZPE corrected) with Respect to Reactants (ΔE in kcal/mol) for Reactions of Methyl Acetate and Methyl Thioacetate with Different Nucleophiles

level of theory	X = O	X = S
reaction with hydroxide		
MP2/6-311++G(2d,2p)//B3LYP/6-31++G(d,p)	−9.2	−8.9
MP2/6-311++G(3d,2p)//B3LYP/6-31++G(d,p)	−7.8	−6.9
SM3 solvent correction	22.7	23.2
IPCM solvent correction	20.5	21.2
solvent corrected energy[a]	11.3	12.3
reaction with ammonia		
MP2/6-31G**//HF/6-31+G*	17.1	13.3
SM3 solvent correction	1.6	2.4
solvent corrected energy	15.5	10.9
reaction with carbanion **5**		
B3LYP/6-311+G*//B3LYP/6-31+G*	17.7	9.6
B3LYP/6-311++G(2d,p)//B3LYP/6-31+G*	18.7	11.0

[a] Based on the first listed method and IPCM solvent correction.

Table 2. Contributions of Delocalization Interactions to the Transition State Energies of Nucleophilic Acyl Transfer Reactions of **1** and **2**

	nucleophile					
	OH^-		NH_3		**5**	
contribution	X = O	X = S	X = O	X = S	X = O	X = S
ester/thioester						
$p_X \rightarrow \pi^*_{C-O}$	41.6	25.4				
$sp^2_X \rightarrow \sigma^*_{C-O}$	10.9	6.5				
$n_O \rightarrow \sigma^*_{C-X}$	35.3	28.7				
sum[a]	87.8	60.6				
total[b]	86.1	60.4				
transition state						
$p_X \rightarrow \pi^*_{C-O} +$ $p_X \rightarrow \sigma^*_{C-Nu}$	25.6	15.1	16.3	9.1	12.1	8.0
$sp^2_X \rightarrow \sigma^*_{C-O}$	10.4	5.4	8.0	3.4	6.5	3.1
$n_O \rightarrow \sigma^*_{C-X}$	35.5	29.8	24.7	20.3	38.9	39.5
sum[a]	71.5	50.3	49.0	32.8	57.5	50.6
total[b]	71.5	48.7	49.1	29.4	56.7	49.8
ΔE[c]	14.6	11.7	37.0	31.0	29.4	10.6

[a] Sum of individually determined delocalization interactions. [b] Total of the above-listed delocalization interactions when determined simultaneously. [c] Based on the difference in "total" effects for transition state vs the ester or thioester.

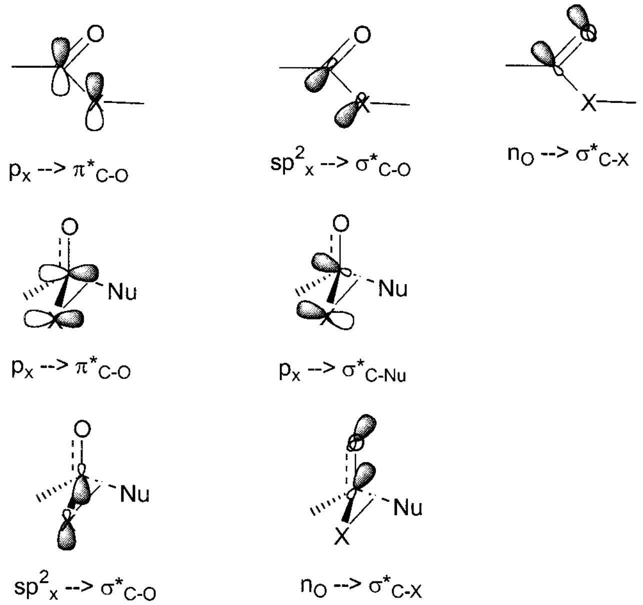

Figure 3. Important delocalization interactions of the ester and thioester (upper) and of the transition states of the reactions of Scheme 1 (lower).

was chosen for comparison to rates of aminolysis reactions studied in aqueous solution.[1,2] For the reaction with the methyl cyanoacetate carbanion, water was not included since the relevant experimental results have been obtained with tetrahydrofuran as solvent.[6] Stepwise mechanisms were identified for both the oxoester and thioester.

Table 1 shows a comparison of calculated activation energies for the reactions of **1** and **2** with nucleophiles **3**−**5** at different levels of theory. Reactant and transition state energies were first calculated considering only specific solvation by water molecules included in the reaction models. ICPM and SM3 methods were used to further account for general solvation effects. The solvent corrections and solvent-corrected transition state energies are included in Table 1. For aminolysis reactions, other levels of theory were previously described.[14] No solvent correction was considered for the reactions of the carbanion **5**.

NBO analysis was performed to quantify and compare the role of electron delocalization in each reaction. The energy of each interaction was calculated as the difference between the total energy and the energy calculated while removing the off-diagonal element in the Fock matrix corresponding to the interaction of interest. Table 2 shows the calculated contributions of delocalization involving the bridging oxygen or sulfur for the ester and thioester and for the transition states of reactions with the three nucleophiles. The important delocalized interactions indicated by this analysis are illustrated in Figure 3. Other delocalized interactions involving the bridging oxygen or sulfur amounted to <0.5 kcal/mol. The $p_X \rightarrow \pi^*_{C-O}$ and $p_X \rightarrow \sigma^*_{C-Nu}$

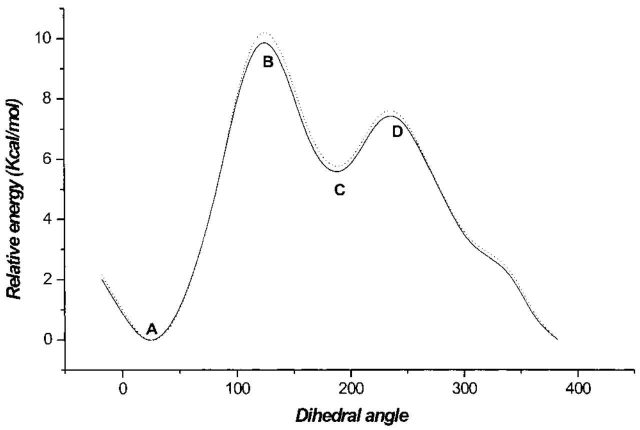

Figure 4. Energy profiles for rotation of the C−S bond of the transition state for reaction of methyl thioacetate with ammonia at the HF/6-31+G* (dotted line) and B3LYP/6-31++G** (solid line) levels. Letters correspond to minimum and maximum energy conformers illustrated in Figure 7.

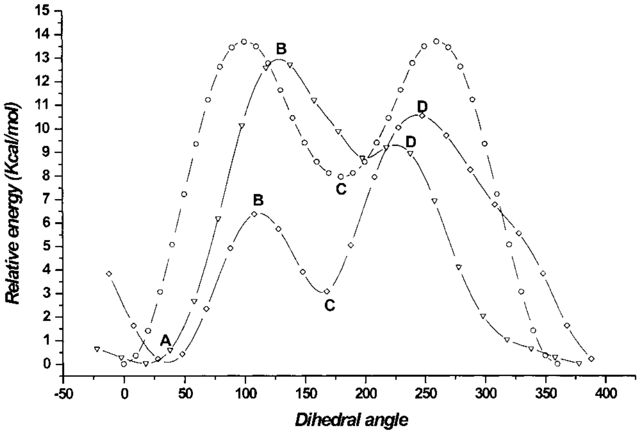

Figure 5. Energy profiles for rotation of the C−O bond of methyl acetate (○) and for the transition states of reactions with hydroxide (◇) and ammonia (▽). Letters correspond to minimum and maximum energy transition state conformers illustrated in Figure 7.

interactions are combined in Table 2 as attempts to compute separate values did not give reasonable results. Also shown in Table 2 are the sums of individually determined effects and the combined effects determined by deleting all of the listed interactions simultaneously. The bottom line gives the delocalization energy for each reaction based on the difference in simultaneously determined delocalization energies of oxoester or thioester vs the transition state of each reaction.

Transition state energies for the reactions of **1** and **2** with hydroxide and ammonia were also computed as a function of rotation of the C−X bond. Figure 4 shows the rotation-dependent energies of the transition state for reaction of the thioester with ammonia at two levels of theory. Figure 5 shows the rotation-dependent energies for the oxoester and for the transition states for reaction of the oxoester with hydroxide and ammonia. Figure 6 shows the equivalent plots for the thioester and for the transition states of its reactions. The letters A−D in Figures 4−6 correspond to approximate minimum and maximum energy conformers in the transition state rotational profiles as illustrated in Figure 7.

Discussion

The transition state models predict a concerted mechanism for thioester hydrolysis while predicting stepwise mechanisms for the other reactions. The feasibility of concerted acyl transfer is supported by isotope effects and other kinetic studies that have indicated concerted mechanisms for acyl transfer reactions of esters having weakly basic leaving groups.[27−30] The calculated activation energy for ester hydrolysis when specific and general solvent effects are considered is fairly close to the reported experimental value of 10.45 kcal/mol.[31] The calculated activation energy for thioester hydrolysis is 1 kcal/mol higher than that for the oxoester. Experimental data indicate almost identical rates for oxoester and thioester hydrolysis though some studies have indicated a higher activation energy for thioester hydrolysis.[1−5,32] The computations indicate much higher activation energies for reactions of the oxoester with ammonia and the carbanion nucleophile relative to the activation energies for the corresponding thioester reactions. This is consistent with the substantially greater observed reaction rates for thioesters relative to oxoesters with these types of nucleophiles.[1,2,6] While

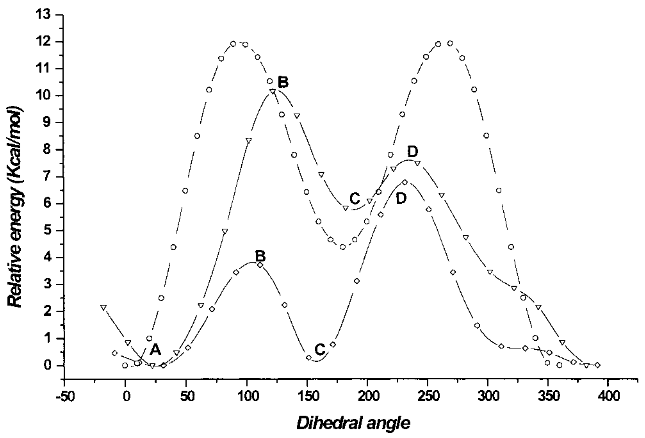

Figure 6. Energy profiles for rotation of the C−S bond of methyl thioacetate (○) and for the transition states of reactions with hydroxide (◇) and ammonia (▽). Letters correspond to minimum and maximum energy transition state conformers illustrated in Figure 7.

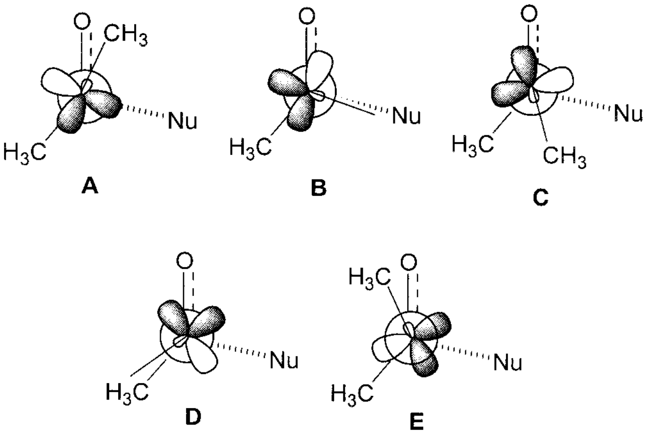

Figure 7. Newman projections of conformers corresponding to energy minima and maxima in Figures 4−6.

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relative reaction rates may not directly correlate with relative activation energies, for reactions with ammonia the calculated difference in activation energies of 4.6 kcal/mol is reasonably consistent with the almost 3 kcal/mol difference in free energy of activation at room temperature.[1] For the carbanion, the reported lower limit of the 2000-fold greater reaction rates for the thioester vs the oxoester results from assignment of an upper limit to the rate of an undetectable reaction with the oxoester.[6] Thus the relative free energy of activation could be substantially larger than the value of about 4.5 kcal/mol based on this minimum and thus may be consistent with the calculated difference in activation energies of almost 8 kcal/mol.

The mechanisms of the reactions in aqueous solution and the role of solvent in these reactions are undoubtedly more complex than indicated by the transition state models developed and used in this work. However, the inclusion of minimal explicit solvent molecules combined with general solvation models gives results consistent with experimental observations, giving support to these models for use in further computational studies of oxoester and thioester reactivity.

Stereoelectronic effects based on electron delocalization have been widely studied in a range of systems in efforts to understand and explain the anomeric effect and related phenomena, including effects on reactivity.[33−41] NBO analysis has been used previously to study delocalization effects in acetals and related heteroatom analogues[38,42] and in the transition state for hydroxyl radical addition to imidazole.[43] In the present study, NBO analysis was performed to investigate the role of electron delocalization in governing the relative reactivity of oxoesters and thioesters with different nucleophiles. As previously reported,[10] delocalization energy is much greater for the oxoester than for the thioester, by about 26 kcal/mol. The magnitude of the $n_O \rightarrow \sigma^*_{C-X}$ interaction is perhaps surprising, though this interaction in esters and its influence on electron densities is well recognized.[44,45] Perhaps the most important observation from Table 2 is that the delocalization energy is much greater in the transition state for reaction of the oxoester with hydroxide compared to the corresponding reaction of the thioester, the difference being about 23 kcal/mol. Thus despite the large degree of electron delocalization in the oxoester, the net loss of delocalization energy in forming the transition state is only about 3 kcal/mol greater for the oxoester than for the thioester. Most of the loss in delocalization energy results from a diminished $p_X \rightarrow \pi^*_{C-O}$ interaction that is not fully compensated for by the additional $p_X \rightarrow \sigma^*_{C-Nu}$ interaction. The net loss of delocalization energy in forming the transition state is about 6 and 19 kcal/mol greater for the oxoester than for the thioester in reactions with ammonia and methyl cyanoacetate ion, respectively. These numbers are again consistent with the observation that the rates of reaction of thioesters are much greater than those of oxoesters in reactions with amine and carbanion nucleophiles. The delocalization effects alone consistently overestimate the calculated relative activation energies for the oxoester and thioester. There are undoubtedly other significant delocalization interactions in addition to those considered in Table 2, including interactions involving electron pairs of the nucleophile. The degree of bond formation to the nucleophile is similar for the oxoester and thioester with all three nucleophiles, which may provide some canceling of these effects in oxoester vs thioester comparisons. The very small degree of proton transfer from nitrogen in the transition states of reactions with ammonia and the absence of a second free electron pair on the carbanion preclude interactions involving unshared electron pairs of the nucleophile as donors in these reactions. Overall, while detailed analysis of individual delocalization effects is difficult, the combined delocalization effects do help to rationalize the differences in relative reactivities of oxoesters and thioesters toward different nucleophiles.

Analysis of bond rotational dependence of energies of ground state molecules has been widely applied in the study of the generalized anomeric effect.[33−41] Similar analysis involving rotation about the C−O or C−S bond was thus performed on the oxoester and thioester and on the transition states of their reactions with hydroxide and ammonia. Figure 4 shows that excellent agreement between two levels of theory was obtained for one of these reactions. The rotational profiles for the oxoester and thioester give rotational barriers that are 1−2 kcal/mol higher and *E* vs *Z* energies that are slightly (<1 kcal/mol) lower than those previously reported.[10] The rotational barrier and *E* vs *Z* energy is somewhat lower for the thioester relative to the oxoester, as expected and as also previously shown.[10] Figure 7 shows the rotational conformers A−D corresponding to the two energy mimina and the two energy maxima in the transition state rotational profiles, along with a view of the p and sp^2 orbitals of oxygen or sulfur, based on assumed sp^2 hybridization. The $p_X \rightarrow \pi^*_{C-O}$, $p_X \rightarrow \sigma^*_{C-Nu}$, and $sp^2_X \rightarrow \sigma^*_{C-O}$ interactions are expected to have large rotational dependence and there is no single rotamer that optimizes all of these interactions. The individual delocalization effects cannot be analyzed unambiguously based on rotational analysis, but some interesting points can be made. The minimum energy transition states for all of the reactions have an O−C−X−C dihedral angle between 18 and 28° (conformer A). This provides near alignment of the p_x orbital with the forming bond to the nucleophile (≤10° away from perfect alignment) thus providing a favorable $p_X \rightarrow \sigma^*_{C-Nu}$ interaction while avoiding severe eclipsing and torsional strain between the C−O and X−CH_3 bonds. This conformer deviates somewhat from the 0° dihedral angle optimal for the $p_x \rightarrow \pi^*_{C-O}$ and $sp^2_X \rightarrow \sigma^*_{C-O}$ interactions, though the data in Table 2 indicate a significant energetic contribution from the latter that is hardly diminished in the transition state for hydrolysis relative to the reactant ester or thioester. The energy maxima (conformers B and D) result from unfavorable steric and torsional (eclipsing) interactions as well as weakened delocalization effects. The second minimum energy rotamer (conformer C) recovers some of the $p_X \rightarrow \sigma^*_{C-Nu}$ interaction lost in B and D while lessening the steric interactions. The higher energy of conformer C relative to A may be largely due to the diminished $sp^2_X \rightarrow \sigma^*_{C-O}$ interaction. The small degree of proton transfer and partial positive charge on nitrogen in the reactions with ammonia may warrant some consideration of the reverse anomeric effect, though recent results suggest that this effect is due to electrostatic effects rather than electron delocalization.[46]

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Table 3. Relative Transition State Delocalization Energies (kcal/mol) Based on Bond Rotation Analysis

	rotamer A vs rotamer D[a]		rotamer A vs rotamer E[b]	
	X = O	X = S	X = O	X = S
hydrolysis	10.8 (28/244°)	6.9 (23/232°)	5.3 (±28°)	0.6 (±23°)
aminolysis	9.4 (18/224°)	7.6 (22/236°)	0.6 (±18°)	2.4 (±22°)

[a] Relative energies of the A vs D rotamers for the transition state of each reaction. Rotations used for each value are shown in parentheses. [b] Relative energies of rotamer A for the transition state of each reaction (+ rotation) vs the energy of rotamer E in which the C−X bond is rotated the same amount in the negative direction.

Table 3 provides a comparison of selected data from Figures 5 and 6. First, this table shows a comparison of the energy of the most stable conformer of the transition state (conformer A) with that of the second (230 to 240°) energy maximum (conformer D) in the rotational analysis for each reaction. Conformer D appears to have minimal $p_X \rightarrow \pi^*_{C-O}$ and $sp^2{}_X \rightarrow \sigma^*_{C-O}$ interactions and diminished $p_X \rightarrow \sigma^*_{C-Nu}$ relative to conformer A in addition to unfavorable steric and torsional interaction between methyl groups. Comparison of the values for oxoester vs thioester hydrolysis indicates the combined effect of loss of delocalization energy and increased steric effects is about 4 kcal/mol greater in the transition state for hydrolysis of the oxoester relative to the thioester. For the aminolysis reactions these effects are less than 2 kcal/mol greater for the oxoester than the thioester. Thus while there is a greater loss of delocalization energy in reactions of the oxoester than reactions of the thioester with both nucleophiles, the difference is 2 kcal/mol greater in the reactions with ammonia compared to the reactions with hydroxide. Since the relative change in steric effects is expected to be about the same, this further supports the role of electron delocalization in the transition states in the different relative reactivities of oxoesters and thioesters toward hydroxide and ammonia. As an alternate view, for the oxoester the barrier of rotamer D is higher for the reaction with hydroxide than ammonia, while for the thioester rotamer D is higher in energy for the reaction with ammonia.

The right column of Table 3 compares the energy of the minimum energy conformation (conformer A) with that of the conformation in which the C−X bond is rotated the same amount in the negative direction from the C−O bond (conformer E, Figure 7). Conformer E is chosen for comparison because it is expected to maintain equivalent steric and torsional strain values as conformer A as well as equivalent $sp^2{}_X \rightarrow \sigma^*_{C-O}$ and $p_X \rightarrow \pi^*_{C-O}$ interactions due to equal though opposite orientations relative to the C−O bond. However, the $p_X \rightarrow \sigma^*_{C-Nu}$ interaction is much less favorable in conformer E, as the Nu−C−X−C dihedral angle has gone from very near the optimal 90° to about 130°. Comparison of the energies of rotamers A and E may thus allow an alternate approximation of the magnitude of the $p_X \rightarrow \sigma^*_{C-Nu}$ interaction, though the different degrees of rotation among the transition states for the different reactions may cause modest differences in the extent of loss of the $p_X \rightarrow \sigma^*_{C-Nu}$ interaction. The energy difference between A and E is quite substantial in the transition state for hydrolysis of the oxoester but is much smaller in the transition state for hydrolysis of the thioester. This is consistent with the early conclusion of Schleyer et al. that anomeric effects are strong with two oxygen atoms bonded to the same carbon atom and are weaker in systems containing a second row element.[47] The apparent strength of the $p_X \rightarrow \sigma^*_{C-Nu}$ interaction in ester hydrolysis may provide a simplistic view of why esters are especially prone to hydrolysis relative to the otherwise more reactive thioesters. The low barrier to rotation of the transition state for thioester hydrolysis through the eclipsing interaction as observed by the curve in Figure 7 is consistent with the observation of low torsional and steric strain in rotation of C−S bonds.[48] In the aminolysis reactions, the observations are somewhat reversed relative to the hydrolysis reactions as the energy difference between rotamers A and E is very small for the oxoester but more significant for the thioester. This may be rationalized based on the conclusion that the $n_X \rightarrow \sigma^*_{C-N}$ orbital interaction energy is more than 2-fold greater when X is sulfur than when X is oxygen, a reversal of the effectiveness of oxygen vs sulfur donor orbitals with a σ^*_{C-O} acceptor orbital.[41]

Electron delocalization has been demonstrated to be a major contributor to the generalized anomeric effect and bond separation energies.[38] Especially important is the $p_X \rightarrow \sigma^*_{C-Y}$ interaction, where X and Y represent the heteroatom substituents on a single carbon atom.[38] The anomeric effect has been most studied in systems containing two oxygen atoms bonded to the same carbon atom but is also well recognized in O−C−N and other systems. The generalized anomeric effect has also been observed in systems containing second row and higher elements, though the group separation energies are much smaller and NBO analysis has indicated that orbital interactions are less effective relative to systems containing only first row elements.[38] However, a study based on bond rotational analysis concluded that sulfur is highly effective in promoting anomeric stabilization, even more effective than oxygen.[39] A recent study of conformational energies in systems containing first and second row elements in several combinations indicates a complex interplay between donor and acceptor atoms in orbital interaction energies.[41] For example, it was concluded that for a σ^*_{C-O} acceptor orbital, an oxygen donor orbital is more effective than sulfur, while for a σ^*_{C-N} acceptor orbital, a sulfur donor orbital is more effective than oxygen.[41] These studies provide some precedence for the observations in this work.

Conclusion

The studies reported here provide evidence that electron delocalization and especially $p_X \rightarrow \sigma^*_{C-Nu}$ interactions play a major role in the reactivity of oxoesters and thioesters in nucleophilic acyl transfer. Especially important is the large role of delocalization energy in stabilizing the transition state for reaction of an oxoester with hydroxide, bringing the reactivity of oxoesters toward hydroxide up to the level of the generally more reactive thioesters. The contribution of electron delocalization may thus help to explain some long-standing mysteries regarding the relative reactivity of oxoesters and thioesters in nucleophilic acyl transfer reactions.

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Supporting Information Available: Complete descriptions of the geometries of all stationary points and the absolute energies for each (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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