ORGANIC LETTERS
2000
Vol. 2, No. 26
4133−4136

Computational Studies of the Aminolysis of Oxoesters and Thioesters in Aqueous Solution

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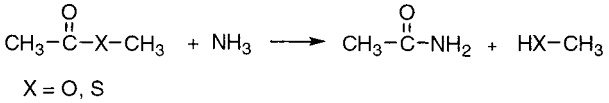
Received October 5, 2000

ABSTRACT



$$CH_3-\overset{O}{\overset{\|}{C}}-X-CH_3 + NH_3 \longrightarrow CH_3-\overset{O}{\overset{\|}{C}}-NH_2 + HX-CH_3$$

$X = O, S$

Transition state structures and energies have been investigated for concerted and stepwise mechanisms for the acyltransfer reactions of ethyl acetate and ethyl thioacetate with ammonia. Specific and general solvent effects have been evaluated. The results predict stepwise mechanisms involving water-catalyzed proton transfer for both reactions and indicate that the thioester is more reactive than the oxoester in both the addition and elimination steps.

The reactivity of thioesters and comparison to the reactivity of oxoesters has attracted recurring interest over the past 40 years, largely due to the biochemical importance of thioesters of coenzyme A. In a classic study, Connors and Bender demonstrated that the acyl transfer reaction of a thioester with an amine in aqueous solution to form an amide and thiol is much faster than the reaction of the corresponding oxoester.[1] In contrast, the reactivities of oxoesters and thioesters toward hydrolysis by hydroxide ion were shown to be virtually equivalent. These general observations have been confirmed in numerous other studies.[2,3] The similar reactivity of oxoesters and thioesters has also been observed toward alkali metal ethoxides in ethanol,[4] while much greater reactivity of thioesters is observed with other non-oxygen nucleophiles including carbanions[5] and thiolates.[6] While a number of explanations have been offered for these observed reactivities, as noted by Al-Arab and Hamilton, none appears to be fully satisfactory.[7]

In an effort to understand these reactivity patterns and to make comparisons between reactions with different nucleophiles, it is first necessary to understand the mechanisms and the transition state structures of rate-determining steps of dominant reaction pathways. Acyl transfer reactions have been the subject of extensive experimental and theoretical studies.[8] Relative to the simple mechanisms with anionic nucleophiles, reactions with neutral amine and ammonia nucleophiles are complicated by the necessary involvement of proton transfer. Aminolysis reactions of oxoesters have been studied experimentally[9,10] and computationally,[11−13] and three reaction pathways or mechanisms have been considered

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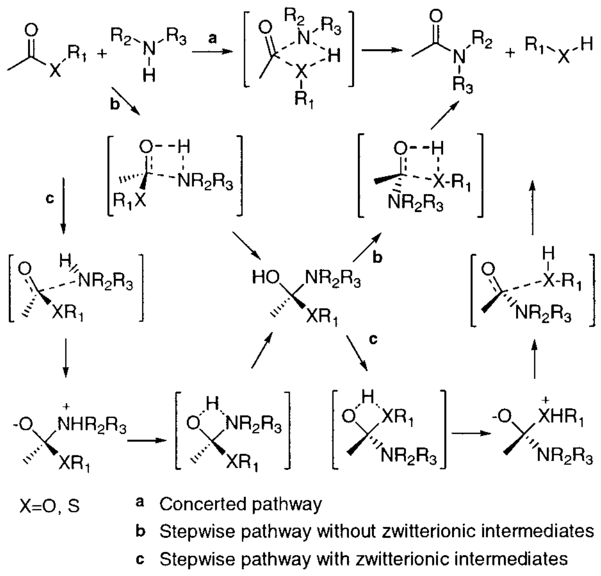

Figure 1. Possible mechanisms for aminolysis reactions of oxoesters and thioesters.

(Figure 1). The first is a fully stepwise pathway involving zwitterionic intermediates in which all bond-forming and -breaking events occur in separate steps. Another one is a stepwise "addition/elimination" pathway without zwitterionic intermediates in which the addition and elimination steps are coupled with proton transfer to maintain neutrality in the tetrahedral intermediate. The final mechanism is a concerted pathway involving direct nucleophilic substitution coupled with proton transfer from nucleophile to leaving group. Early computational studies of Oie et al. failed to identify transition states for the fully stepwise pathway, and this was further confirmed by Zipse et al.[11,12] It was thus concluded that the zwitterionic intermediates and the associated transition states are too high in energy for the fully stepwise pathway to be viable, at least in the gas phase.[12] The potential energy surfaces for the remaining two mechanisms were studied, and transition states for both pathways were found.[13] For the reaction of methylamine with methyl acetate, almost identical activation energies of 35.5 and 36.2 kcal/mol were calculated for the stepwise and concerted mechanisms, respectively.

The present computational study further addresses the two preferred mechanisms for ester aminolysis and the corresponding aminolysis reaction of a thioester, with consideration of both general and specific solvent effects in aqueous solution. Ammonia, methyl acetate, and methyl thioacetate were used to represent amine, oxoester, and thioester, respectively, to simplify the reaction model. Potential energy surfaces for the reaction pathways were searched using the semiempirical method AM1.[14] Transition states located were optimized at the HF/6-31+G* level and were verified by frequency and IRC calculations. All reactants (ammonia, water, methyl acetate, and methyl thioacetate) were optimized at the HF/6-31+G* level. Gas-phase energy calculations were performed at the levels MP2/6-31+G* and MP2/6-31G** with zero point energy correction.

As the tetrahedral intermediates for stepwise reaction pathways have several different conformations, systematic conformational searches were performed using SM3 to investigate conformational space. For each kind of intermediate, 25 conformations were obtained, each of which was optimized at the HF/6-31+G* level and total energies compared on the basis of the combination of gas-phase energy at the MP2/6-31+G* (or MP2/6-31G**) level and solvation energies. The conformations with lowest total energies were identified and assumed to be the true configurations.

Both specific and general solvent effects were evaluated. For specific solvent effects, an associated water molecule was included throughout the pathway of each mechanism. Water molecules were manipulated manually on the basis of conformational analysis and previous related computational studies. As shown in Figure 2, the water molecule was positioned to catalyze N to X proton transfer in the concerted mechanism and to catalyze N to carbonyl O and subsequent O to X proton transfer in the stepwise mechanism for oxoester and thioester aminolysis. These represent the simplest models for specific solvent effects, although mechanisms involving multiple water molecules are possible. These mechanisms represent reactions at low amine concentrations, as kinetic terms second order in amine become dominant at higher concentration. General solvation energies were evaluated using SM3, which is built upon the semiempirical method PM3.[15,16]

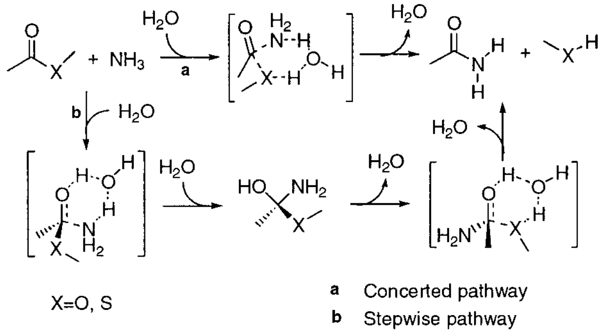

Figure 2. Proposed mechanisms for water catalysis of aminolysis reactions.

Energy profiles for stepwise and concerted pathways for oxoester aminolysis were generated for the mechanisms without specific solvent molecules (Figure 1) and with inclusion of a catalytic water molecule (Figure 2). Figure 3

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(14) All calculations except NBO calculations were carried out using the Gaussian 98 suite of programs: *Gaussian 98, Revision A.7*, Gaussian, Inc., Pittsburgh, PA, 1998.

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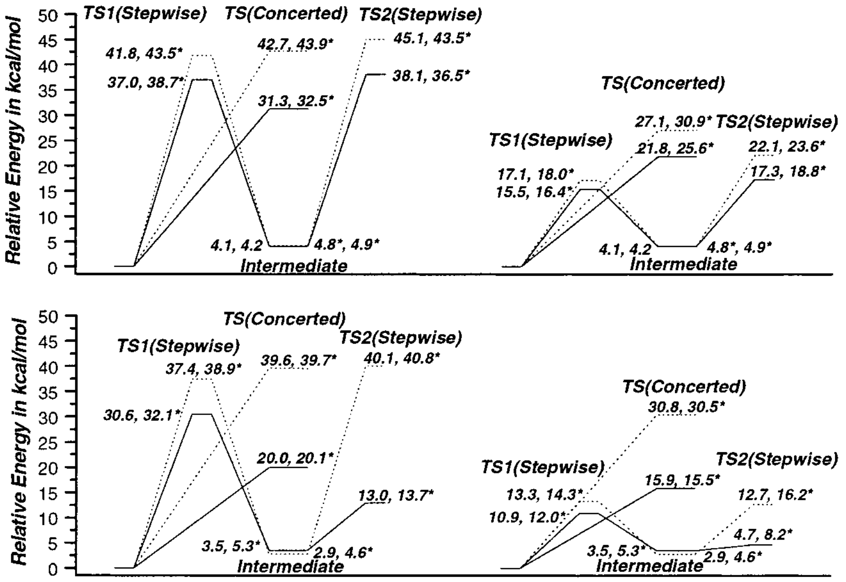

Figure 3. Energy profiles for aminolysis reactions of ethyl acetate (upper) and ethyl thioacetate (lower). Left: the reaction without specific catalysis by water. Right: the reaction with specific catalysis by water. Dotted line: gas phase. Solid line: corrected with SM3 solvation energy. Lines and numbers without asterisk are from MP2/6-31G**. Numbers with asterisk are from MP2/6-31+G*. Energies of reactants with and without SM3 solvent correction are set up as energy standards.

(upper) shows the resulting energy profiles without (left) and with (right) inclusion of specific solvent.[17] If no catalytic water molecule is included, energy barriers in the gas phase for concerted and stepwise mechanisms are very similar. The activation energy for the concerted pathway is lowered substantially (about 11 kcal/mol) when general solvent effects are included, whereas the activation energy for the stepwise pathway is lowered less (step 1 about 5 kcal/mol, step 2 about 7 kcal/mol). The concerted pathway is thus predicted to be the favored pathway in aqueous solution if only general solvent effects are considered. However, the activation energy is too high (about 32 kcal/mol) to explain the observed aminolysis of oxoesters at room temperature. This suggests that the general solvent effect model alone is not sufficient to simulate the role of solvent in the reaction.

Inclusion of one water molecule to catalyze proton transfer lowers the energy barriers for both the concerted and stepwise mechanisms to a range more consistent with experimental observations. As indicated in Figure 3, when the specific solvent effect is included, the stepwise pathway becomes significantly lower in energy than the concerted pathway. The second step is predicted to have a somewhat higher activation energy than the first step, although the difference becomes quite small (about 2 kcal/mol) when the general solvent effect is also included. The calculations thus predict that a stepwise pathway with a water molecule as catalyst is the preferred mechanism for oxoester aminolysis in aqueous solution.

Similar results were obtained in computational analysis of the aminolysis of a thioester (Figure 3, lower). As with the oxoester, the activation energies are very high when solvent effects are not considered. General solvent effects again greatly decrease the activation energy of the concerted pathway and also the activation energy of the second step of the stepwise mechanism. Again, when specific solvent effects are invoked, the activation energy of the stepwise mechanism becomes significantly lower than that of the concerted mechanism. When both specific and general solvent effects are considered, the activation energy for the second step of the stepwise mechanism becomes significantly lower than that of the first step and the activation energy of 10.9 kcal/mol calculated for the stepwise pathway is consistent with experimental data.

The structures of the transition states of the water-catalyzed concerted pathways (Figure 4) indicate late transition states with almost complete formation of the C−N bond and almost complete breaking of the C−X bond. This is consistent with isotope effect studies that indicate that bond fission to the leaving group is well advanced in the transition state of concerted acyl-transfer reactions.[18] There is little proton transfer in the concerted transition states, indicating that the transition states have zwitterionic character. The stepwise pathways show a high degree of H_2O to carbonyl O proton transfer but little N to O transfer in the transition state of the first step, indicating a somewhat cationic transition state.

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(17) Calculations using the 6-31G** basis set, which allow the hydrogen atom to have characteristics of a p orbital predict a lower activation energy than that using 6-31+G* by 1.2−1.7 kcal/mol for oxoester aminolysis as well as for thioester aminolysis (see Figure 4). The small and fairly consistent differences between results using the 6-31G** and 6-31+G* basis sets show that these basis sets are sufficient to describe these systems and diffuse functions are not necessary. Energy levels are reported to a single decimal to reflect calculated energy differences, although 1−3 kcal/mol errors in absolute energies are likely.

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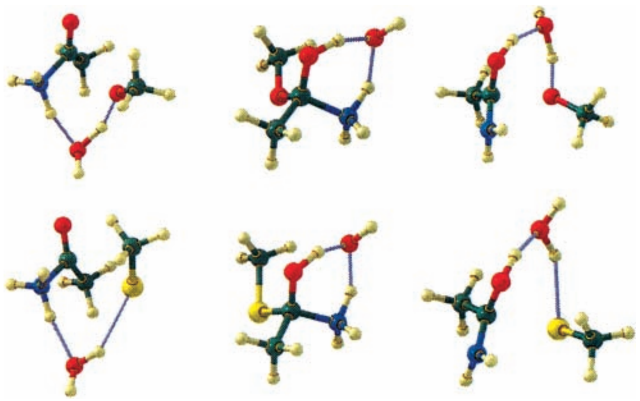

Figure 4. Calculated transition state structures for water-catalyzed aminolysis reactions. Upper: oxoester. Lower: thioester. Left: concerted reaction. Center: first step of stepwise reaction. Right: second step of stepwise reaction.

The proton transfers are also not very advanced in the transition state of the second step.

The results predict stepwise mechanisms for aminolysis of both oxoesters and thioesters in aqueous solution. The first step is clearly rate-limiting in thioester aminolysis, although for oxoester aminolysis, the second step is predicted to have a slightly higher activation energy. Comparison of the energy profiles indicates that the activation energy for formation of the tetrahedral intermediate is higher for the oxoester than for the thioester by about 4.5 kcal/mol. The activation energy for conversion of the tetrahedral intermediate to product is higher for the oxoester by about 12 kcal/mol.

In early efforts to rationalize the relative reactivities of oxoesters and thioesters, it was suggested that oxoesters and thioesters are equally reactive in formation of the tetrahedral intermediate, thus with nucleophiles in which the first step is rate-limiting, the reactivity of oxoesters and thioesters is similar.[1,2] It was suggested that with nucleophiles in which the second step is rate-limiting, thioesters are more reactive due to the greater leaving group ability of the thiolate relative to an alkoxide. The computational studies reported here further support the assumption that the thiolate is a better leaving group than alkoxide in breakdown of the tetrahedral intermediate, as expected on the basis of the weaker basicity of the thiolate and as supported by experimental comparisons of leaving groups in elimination reactions.[19,20] The present studies also predict that the thioester is more reactive in formation of the tetrahedral intermediate, at least with ammonia as nucleophile.

The greater reactivity of thioesters than oxoesters in the nucleophilic addition step is consistent with the smaller degree of hyperconjugation or resonance contribution of the sulfur lone electron pair onto the carbonyl carbon compared to the bridging oxygen of an oxoester.[4,21] NBO calculations were performed at the HF/6-31G* level to evaluate the change of C−X bond order (Lowdin bond order) between reactants and transition states in the first step of the stepwise mechanisms.[22] These calculations show that for the oxoester the bond order is decreased by 0.166, while for the thioester the bond order change is only 0.127.[23] As expected intuitively, this loss of hyperconjugation may explain why the activation energy for the first step is higher for the oxoester relative to the thioester.

The computational studies presented here provide new details for the potential energy surfaces and transition state structures for aminolysis reactions of oxoesters in aqueous solution. These studies also provide comparative information for aminolysis reactions of thioesters. These results will provide the basis for further computational efforts to understand the relative reactivities of oxoesters and thioesters toward nucleophiles.

Acknowledgment. This work was supported by NSF Grant MCB9722936.

Supporting Information Available: Structures of all transition states including bond lengths and atomic charges. This material is available free of charge via the Internet at http://pubs.acs.org.

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