

Comparative Studies on the Reactions of Carbamyl and Thiocarbamyl Halides with NH₃ in the Gas Phase and in Aqueous Solution: A Theoretical Study

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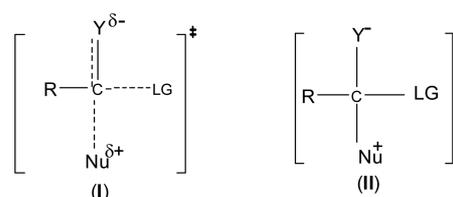
In this work, the reactions of carbamyl and thiocarbamyl halides with NH₃ were studied in the gas phase at the MP2(FC)/6-31+G(d) level of theory. Single point calculations were performed at the QCISD/6-311+G(3df,2p) to refine the energetics. The reaction mechanisms were also studied in aqueous solution. The structures were fully optimized at the CPCM-MP2(FC)/6-31+G(d) and refined by a single point CPCM-QCISD/6-311+G(3df,2p) calculations. The reaction mechanisms for the title compounds were compared with those for the acetyl and thioacetyl halides. The lower reactivity of carbamyl (and thiocarbamyl) groups was explained by comparing the C=O and C=S π-bond strengths as well as resonance contributions in the ground state.

Key Words : Aminolyses of carbamyl and thiocarbamyl halides, Stability of tetrahedral structures, Deformation energy, Double bond strength

Introduction

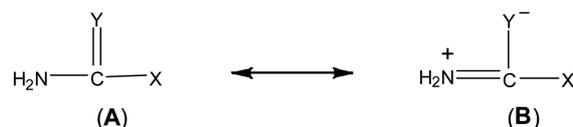
The nature of a zwitterionic tetrahedral structure (T[±]) plays an important role in determining the reaction mechanism for substitution reactions of carbonyl and their related derivatives.¹ The reaction will proceed *via* the concerted process if the T[±] corresponds to a saddle point, (I).² On the contrary, the reaction will occur through the stepwise process if the T[±] structure corresponds to an energy minimum, (II).³ Numerous theoretical⁴ and experimental⁵ works for the reactions of carbonyl and their related derivatives have been carried out in order to elucidate the reaction mechanisms and the nature of T[±]-species, but some controversies have not been completely solved.

In our previous work, the substitution reactions of acetyl and thioacetyl halides, CH₃C(=Y)X where Y = O or S and X = F or Cl, with NH₃ as a neutral nucleophile have been examined theoretically in the gas phase and in aqueous solution.⁶ We have shown that the reaction of acetyl chloride, CH₃C(=O)Cl, occurs *via* a concerted process, but the reaction of thioacetyl chlorides, CH₃C(=S)Cl, proceeds through a stepwise process both in the gas phase and in aqueous solution. This result suggested that the mechanistic changeover could be caused from the fact that the C=S π-bond is weaker than the C=O π-bond, *i.e.*, in forming the T[±]



Nu: nucleophile, LG: leaving group

Scheme 1



Scheme 2

species, the energy required to break the C=S π-bond could be easily compensated by the C---NH₃⁺ bond formation, but the energy required to break the C=O π-bond might not be sufficiently replenished.

As a continuing work, the reaction of carbamyl, NH₂C(=O)X, and thiocarbamyl halides, NH₂C(=S)X where X = F and Cl, with NH₃ was investigated theoretically in this work. The C=Y π-bond strengths in carbamyl and thiocarbamyl halides could be weakened by the amine substituent, -NH₂, due to possible resonance contribution shown in Scheme 2 compared to the corresponding C=Y π-bond strengths in acetyl and thioacetyl halides.⁷

Computational Details

In this work, all the gas-phase structures were optimized at the MP2(FC)/6-31+G(d)⁸ level of theory. For reactions in aqueous solution, the structures were optimized by use of the self-consistent reaction field (SCRf) method of the conductor-like polarizable continuum model (CPCM)⁹ with the Universal Force Field (UFF)¹⁰ cavity model at CPCM-MP2/6-31+G(d) level of theory. The levels of theory were the same as those employed in the previous work⁶ to allow direct comparisons.

In order to obtain more accurate energetics, the single-point calculations were performed at the QCISD and CPCM-QCISD levels with 6-311+G(3df,2p) basis set on the geometries optimized at the MP2 level in the gas phase and

in aqueous solution, respectively. The activation (ΔG^\ddagger) and reaction (ΔG_R) Gibbs energies in aqueous solution were obtained at 298 K by use of Eq. (1), where ΔG_{sol} is the Gibbs free energy of solvation. In Eq. (1), E_{el} is the gas-phase electronic energy optimized at the CPCM-QCISD level and E_{ZPVE} , E_{Th} , and S are zero-point vibration energy, thermal energy and entropy terms, respectively. All calculations were performed with the *Gaussian 03* programs.¹¹ The potential energy diagrams shown in this work were drawn by positioning the energy levels of the reactants to zero energy. This could allow comparison for the mechanisms in the gas phase and in aqueous phase.

$$G(\text{at } 298 \text{ K}) = E_{\text{el}} + E_{\text{ZPVE}} + E_{\text{Th}} + PV - TS + \Delta G_{\text{sol}} \quad (1)$$

Results and Discussion

Reactivities and Reaction Mechanisms in the Gas Phase. In this work, three reaction paths were examined as shown in Scheme 3: (1a) one-step concerted mechanism *via* a tetrahedral TS, (1b) stepwise mechanism *via* a stable tetrahedral zwitterionic intermediate, and (1c) nucleophilic attack at carbonyl carbon concurrent with the proton transfer mechanism *via* a neutral tetrahedral intermediate. In the previous work,⁶ we have examined similar pathways and found that the reaction path (1c) was the most unfavorable both in the gas phase and in aqueous solution.

In the gas-phase substitution reactions of carbamyl fluoride, the T^\ddagger structure could not be located either as a saddle point or a stable intermediate indicating that the reaction could not proceed *via* the reaction path (1a) and/or (1b). Therefore, if the substitution reaction of carbamyl fluoride with NH_3 could occur in the gas phase, the reaction would proceed exclusively *via* the path (1c). However the reaction *via* the path (1c) seemed to be very difficult to occur in general reaction conditions because of higher activation energy barrier (ΔG^\ddagger) of 64.1 kcal mol⁻¹ at the QCISD/6-311+G(3df, 2p)/MP2/6-31+G(d) level. On the contrary, the

T^\ddagger structure was located as a saddle point in the reaction of carbamyl chloride. This mechanistic difference between carbamyl fluoride and carbamyl chloride could be clearly caused from the leaving group abilities. The potential energy diagrams are represented in Figures 1 and 2 for the reactions of carbamyl fluoride and chloride, respectively.

For the gas-phase substitution reactions of thiocarbamyl halides, the T^\ddagger structures were located as stable intermediates indicating that the reactions could proceed *via* the reaction path (1b) with zwitterionic T^\ddagger intermediates. For the reaction of thiocarbamyl fluoride, the second step was clearly rate-limiting, because the ΔG^\ddagger value for the second step was 13.2 kcal mol⁻¹ higher than that for the first step. For the reaction of thiocarbamyl chloride, however, the difference in the ΔG^\ddagger values between the first and the second

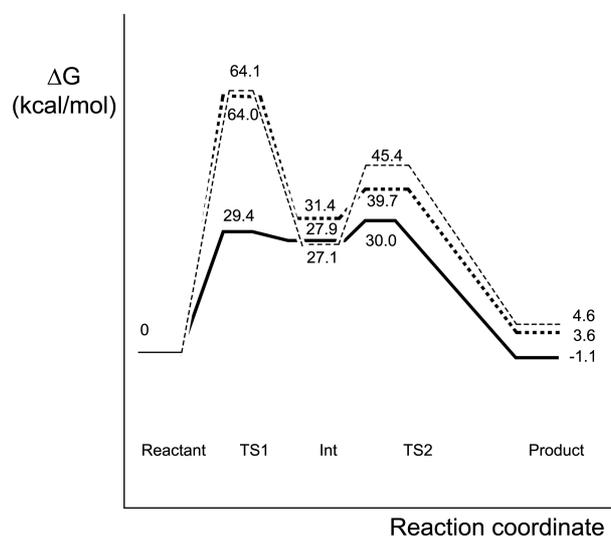
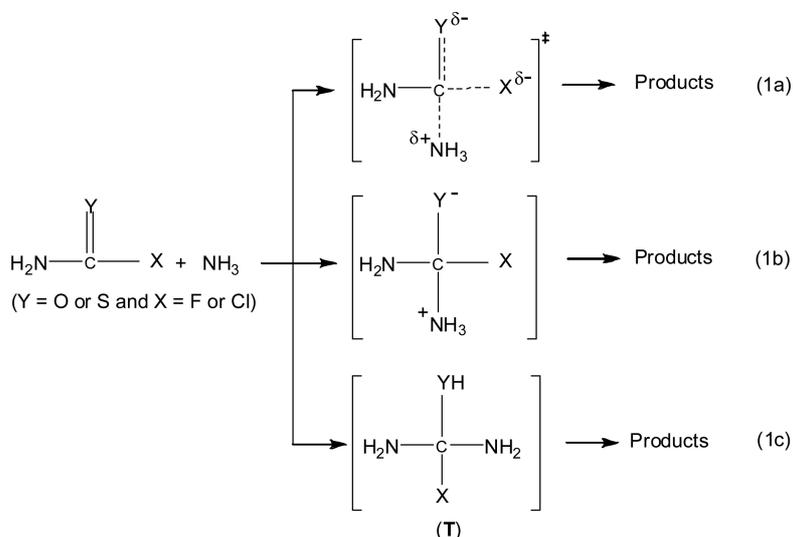


Figure 1. Potential energy diagrams for reactions of carbamyl fluoride at QCISD/6-311+G(3df,2p)/MP2/6-31+G(d) level of theory. Dashed lines represent the reaction path (1c) in the gas phase, and bold solid and dashed lines represent the reaction paths (1b) and (1c), respectively, in aqueous solution.



Scheme 3

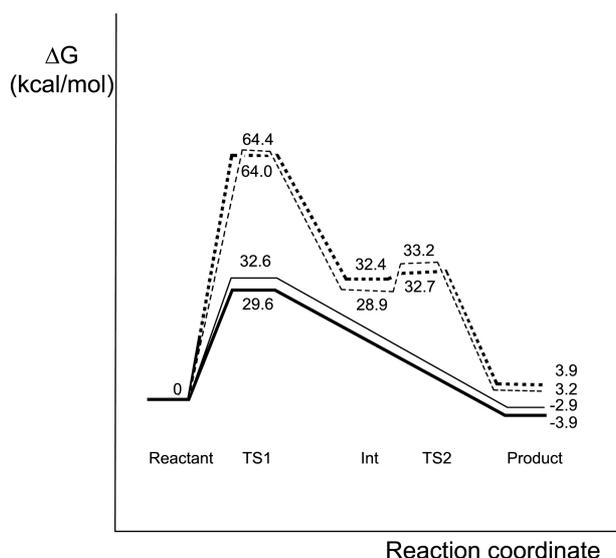


Figure 2. Potential energy diagrams for reactions of carbamyl chloride at QCISD/6-311+G(3df,2p)/MP2/6-31+G(d) level of theory. Dashed and solid lines represent the reaction paths (1c) and (1a), respectively, in the gas phase, and bold solid and dashed lines represent in aqueous solution.

steps was very small (only 0.8 kcal mol⁻¹), even though the second step was still rate-limiting. This difference could be also resulted from the leaving group abilities as observed in the reactions of carbamyl halides. Anyway, the reaction mechanisms for thiocarbamyl halides were definitely different from those for carbamyl halides, and the mechanistic changeovers could be caused from the differences in the π -bond strengths: the C=S bond is weaker than the C=O bond.¹²

For thiocarbamyl halides, the path (1c) could proceed through the stepwise process with the rate-limiting first step similar to the reactions of carbamyl halides, but the ΔG^\ddagger values for thiocarbamyl halides were about 10 kcal mol⁻¹ lower than the corresponding carbamyl halides. The potential energy diagrams for the reaction paths are shown in Figures 3 and 4 for the reactions of thiocarbamyl fluoride and chloride, respectively. These figures showed that the reaction path (1c) should be ruled out from consideration because the ΔG^\ddagger values for the rate-limiting step of the path (1c) were much higher than those for the rate-limiting step of the path (1b).

Reactivities and Reaction Mechanisms in Aqueous Solution. In aqueous solution, all the T[±] structures were located as stable intermediates due to the strong stabilization by solvation. This means that the reaction of carbamyl fluoride in aqueous solution is different from the reaction in the gas phase: The reaction could proceed through stepwise mechanism of either path (1b) or path (1c). However, the ΔG^\ddagger value for the rate-limiting step in the path (1c) was not affected by the solvation due to neutral nature of the intermediate. Therefore, the substitution reaction of carbamyl fluoride in aqueous solution should proceed exclusively *via* the reaction path (1b) (see Figure 1).

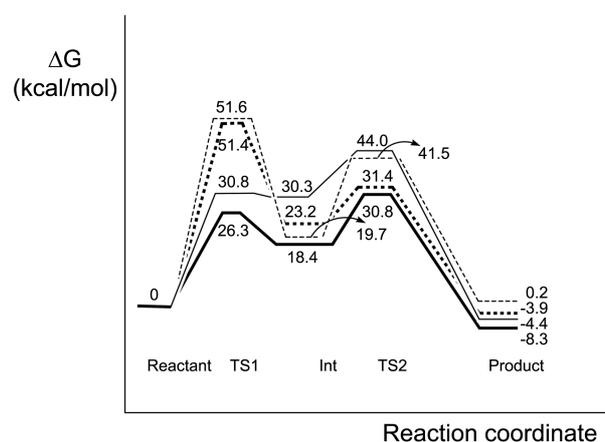


Figure 3. Potential energy diagrams for reactions of thiocarbamyl fluoride at QCISD/6-311+G(3df,2p)/MP2/6-31+G(d) level of theory. Dashed and solid lines represent the reaction paths (1c) and (1b), respectively, in the gas phase, and bold solid and dashed lines represent in aqueous solution.

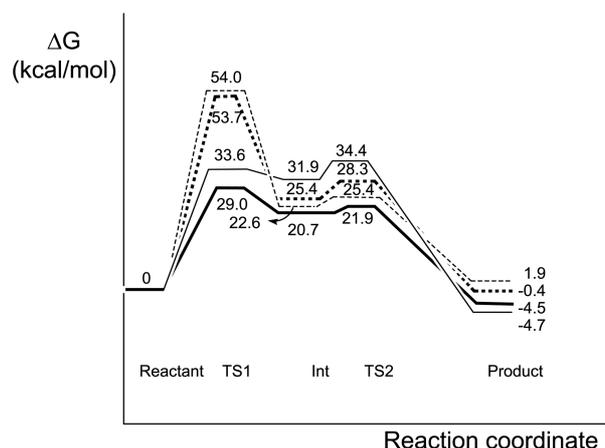


Figure 4. Potential energy diagrams for reactions of thiocarbamyl chloride at QCISD/6-311+G(3df,2p)/MP2/6-31+G(d) level of theory. Dashed and solid lines represent the reaction paths (1c) and (1b), respectively, in the gas phase, and bold solid and dashed lines represent in aqueous solution.

It is obvious that solvent plays an important role on the stability of the tetrahedral T[±] species in aqueous solution. To study the solvent effects in detail, we examined the tetrahedral structure in the reaction of carbamyl fluoride with NH₃ in several solvent media, and the results are summarized in Table 1. As mentioned above, the T[±] structure was neither a saddle point nor a stable intermediate in the gas phase. However, this structure could exist as a stable intermediate even in carbon tetrachloride with the low dielectric constant (ϵ) of 2.228. Moreover, Table 1 shows that the d_{C-N} bond lengths become shorter, but the d_{C-F} bond lengths become longer as the dielectric constant increases. The change in d_{C-N} , however, is relatively large, since the d_{C-N} is shortened by 0.064 Å, but the d_{C-F} is lengthened by 0.035 Å when the solvent changes from carbon tetrachloride to water. This implies that structural variation in the tetrahedral T[±] species is more pronounced in the bond formation than in

Table 1. The nature of T^\ddagger species in several solvent media for the reaction of carbamyl fluoride with NH_3 at CPCM-MP2/6-31+G(d) level

Solvent Media	ϵ^a	The nature	d_{C-N}^b	d_{C-F}^c
Gas Phase	1	Non-existence	-	-
Carbon Tetrachloride	2.228	Intermediate	1.626	1.521
Diethyl Ether	4.335	Intermediate	1.584	1.550
Tetrahydrofuran	7.58	Intermediate	1.576	1.549
Acetone	20.7	Intermediate	1.566	1.555
Acetonitrile	36.64	Intermediate	1.563	1.555
Water	78.39	Intermediate	1.562	1.556

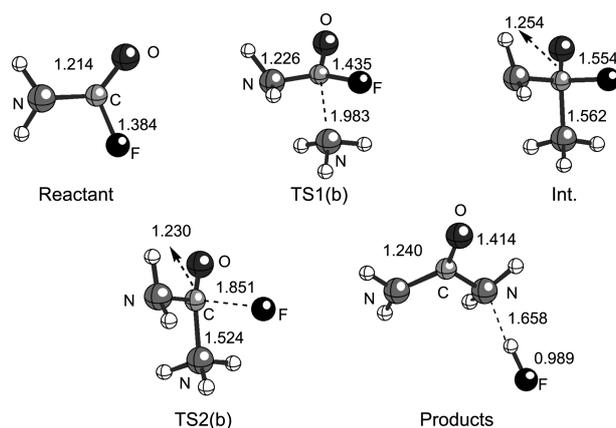
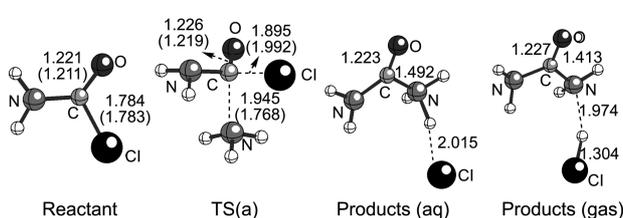
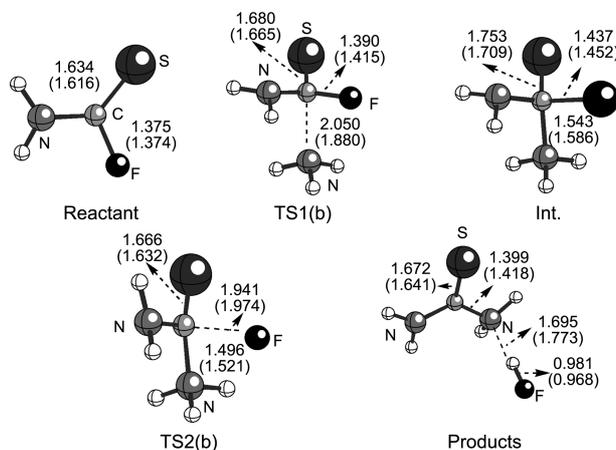
Dielectric constants taken from Frisch, A.; Frisch, M. J.; Trucks, G. W. *Gaussian 03 User's Reference*; Gaussian Inc.: Carnegie, PA, 2003. Bond length between carbonyl carbon and nitrogen on NH_3 in Å. Bond length between carbonyl carbon and fluorine atom in Å.

the bond cleavage as the solvent polarity increases.¹³

For the reaction of carbamyl chloride in aqueous solution, the reaction mechanism is the same as that in the gas phase, *i.e.*, the reaction proceeds through the path (1a). However, the ΔG^\ddagger in aqueous solution was 3.0 kcal mol⁻¹ lower than that in the gas phase as shown in Figure 2. As we discovered in the reactions of acetyl and thioacetyl halides,⁶ the lowering of ΔG^\ddagger in aqueous solution was not caused from the solvent stabilization effects but was the result of shift of TS to an earlier one, which can alleviate the unfavorable geometrical deformation energy (ΔE_{def}) on going from reactants to TS. As an example, in the reaction of carbamyl chloride, the ΔE_{def} in aqueous solution was lowered by 10.9 kcal mol⁻¹ compared to that in the gas phase.¹⁴ In contrast, the differential solvation free energies ($\delta\Delta G_{sol}$) between the reactants and TS, $\delta\Delta G_{sol} = \Delta G_{sol}(TS) - \Delta G_{sol}(Reactants)$, was only -2.8 kcal mol⁻¹, since the ΔG_{sol} values were -14.4 and -17.2 kcal mol⁻¹ for the reactants and TS, respectively, at CPCM-MP2/6-31+G(d) level.¹⁵ This indicates that the contribution of structural deformation is more important than the solvent effects.

The releasing effects of ΔE_{def} ¹⁶ in aqueous solution compared to the gas phase could be clearly resulted from the shift of the TS structures to an earlier position, and such a structural variation could be confirmed by analyzing the optimized structures. The optimized structures of the stationary points are represented in Figures 5-8. Figure 6 showed that both the C--- NH_3 bond formation and C---Cl bond breaking at TS(a) were less advanced in aqueous solution; the C--- NH_3 bond lengths (d_{C-N}) at the TS(a) were 1.945 and 1.768 Å in aqueous solution and in the gas phase, respectively, indicating that the bond formation was less advanced by 0.177 Å in the aqueous solution, and the C---Cl bond breaking (d_{C-Cl}) was also less advanced by 0.097 Å in aqueous solution. This implies that the TS(a) in aqueous solution was moved to an earlier position on the reaction coordinate.

For the reactions of thiocarbamyl halides in aqueous solution, all the reaction mechanisms were very similar to those in the gas phase, *i.e.*, both the thiocarbamyl fluoride

**Figure 5.** Optimized structures of the stationary point species at MP2/6-31+G(d) level of theory for the reaction path (1b) of carbamyl fluoride in aqueous solution. Bond lengths are in Å.**Figure 6.** Optimized structures of the stationary point species at MP2/6-31+G(d) level of theory for the reaction path (1a) of carbamyl chloride in aqueous solution. Bond lengths are in Å and parentheses values are in the gas phase.**Figure 7.** Optimized structures of the stationary point species at MP2/6-31+G(d) level of theory for the reaction path (1b) of thiocarbamyl fluoride in aqueous solution. Bond lengths are in Å and parentheses values are in the gas phase.

and chloride might expect to proceed competitively through the stepwise path (1b) or (1c), but path (1c) could be ruled out due to considerably higher ΔG^\ddagger . Therefore the substitution reactions of thiocarbamyl halides with NH_3 proceed exclusively through the reaction path (1b) with the T^\ddagger intermediate. However, as shown in Figure 4, for the reaction of thiocarbamyl chloride, the rate-limiting step was changed from the second step in the gas phase to the first step in aqueous solution. This mechanistic changeover could be

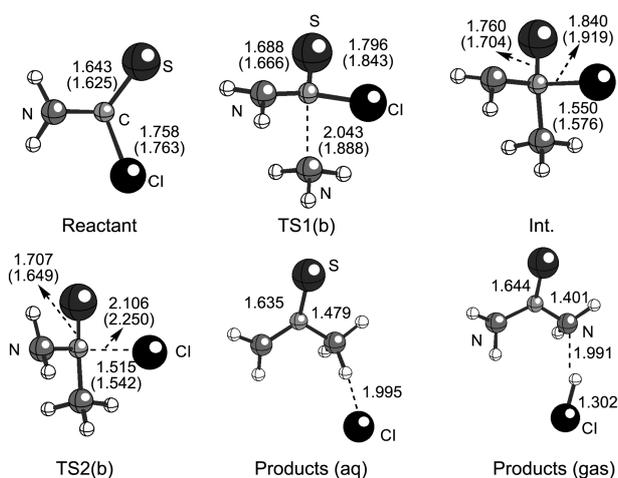


Figure 8. Optimized structures of the stationary point species at MP2/6-31+G(d) level of theory for the reaction path (1b) of thiocarbamyl chloride in aqueous solution. Bond lengths are in Å and parentheses values are in the gas phase.

caused by the solvent stabilizing effects on the T^{\pm} intermediate. Since the T^{\pm} intermediate corresponds to a kind of ylide, it can be stabilized effectively by solvation effects. As expected, the T^{\pm} intermediate was stabilized by above 10 kcal mol⁻¹ by solvation, but the preceding TS1(b) was stabilized only by about 5 kcal mol⁻¹ (see Figures 3 and 4). On the other hand, the following TS2(b) was stabilized in a greater extent by solvation because this structure became loose due to the release of the leaving group. Anyway, TS1(b) became rate-limiting in aqueous solution for the reaction of thiocarbamyl chloride. However, in the aqueous reaction of thiocarbamyl fluoride, TS2(b) remained as the rate-limiting albeit the lowering effect of TS2(b), because the difference in ΔG value between TS1(b) and TS2(b) was over 10 kcal mol⁻¹ in the gas phase.

The final products for the reaction of carbamyl (and/or thiocarbamyl) chloride was an ion-pair complex of *N*-protonated urea (and/or *N*-protonated thiourea) and chloride ion in aqueous solution but was a molecular complex of urea and hydrogen chloride in the gas phase. These results could be easily understandable; (i) in the gas phase, a charge-separated ion-pair product is highly unstable. (ii) The hydrogen chloride, HCl, could fully ionize in aqueous solution to form the ion-pair complex. This also implies that in the reaction of carbamyl (and/or thiocarbamyl) fluoride, the final product was a molecular complex of urea and hydrogen fluoride, HF, in both phases, since HF is a weak acid in aqueous solution.

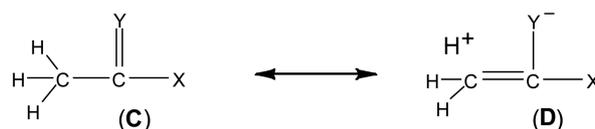
The Effects on the Stabilities of T^{\pm} -Structures. Carbamyl and thiocarbamyl halides were structurally similar to acetyl and thioacetyl halides, respectively. But the C=Y π -bond strengths in carbamyl and thiocarbamyl halides could be weaker than the corresponding analogues because of the resonance delocalization as shown in Scheme 2. Indeed, the effects of resonance delocalization were confirmed by using the Natural Resonance Theory (NRT) analyses developed by

Table 2. The percentage weightings (%wt's) of resonance structures calculated at RHF/6-31+G(d)//MP2/6-31+G(d) level of theory

Y/X	NH ₂ -C(=Y)-X		CH ₃ -C(=Y)-X	
	(A)	(B)	(C)	(D)
O/F	76.6%	9.2%	84.8%	0.3%
O/Cl	75.5%	10.0%	84.1%	0.3%
S/F	73.7%	12.8%	84.7%	0.7%
S/Cl	72.6%	13.4%	84.2%	0.6%

Weinhold and coworkers and the results are summarized in Table 2.

Examination of Table 2 showed that, in carbamyl and thiocarbamyl halides, the major contribution came from the resonance structure (A), and the percentage weighting (wt %) of (B) was in the range of 9-13%. Therefore the C=Y π -bond could be weakened by taking into account of contribution (B). In principle, some similar resonance delocalization might be also possible in acetyl or thioacetyl halide as shown in Scheme 4. However, the contribution of the resonance structure (D) was relatively small due to hyperconjugation-type resonance: In acetyl fluoride, for example, the wt % of (C) was 84.8% but the wt % of (D) was only 0.3%. The NRT analyses, therefore, suggest that the T^{\pm} structure corresponding to a TS or a stable intermediate can be easily formed (or more stable) in the reactions of carbamyl (and thiocarbamyl) halides compared to the corresponding acetyl (and thioacetyl) analogues. This prediction seemed to be well applied in a measure: the T^{\pm} structure was a stable species for carbamyl fluoride but was non-existent for acetyl fluoride in carbon tetrachloride.



Scheme 4

At this point, it would be interesting to compare the relative reactivities of carbamyl (and/or thiocarbamyl) halides and corresponding acetyl (and/or thioacetyl) halides. As mentioned above, the reaction mechanisms were similar for both substrates. To compare the reactivities, the relative positions of T^{\pm} structures in the potential energy profiles were examined. In aqueous solution, the Gibbs free energy difference between reactants (set to zero) and T^{\pm} intermediate, $\Delta G(R \rightarrow T^{\pm})$, was 20.8 kcal mol⁻¹ for acetyl fluoride, but increased to 27.9 kcal mol⁻¹ for carbamyl fluoride at CPCM-QCISD/6-311+G(3df,2p)/CPCM-MP2/6-31+G(d) level. Similarly, the activation free energy, $\Delta G^{\ddagger}(R \rightarrow T^{\pm})$, on going from reactants to T^{\pm} -type TS was 20.5 and 29.4 kcal mol⁻¹ for acetyl and carbamyl chlorides, respectively. To understand the results, we estimated the C=Y π -bond strengths, $D_{C=Y}$, by using the partial-substituted divalent state stabilization energy (PSub-DSSE) method developed by us¹⁷ at the QCISD(T)/6-311++G(3df,2p)//MP2/6-31+G(d) level

Table 3. The estimated π -bond strengths, $D_{C=Y}$,^a the hydrogenation energies, ΔE_{Hyd} in eq. (2), and the $\Delta G(\text{R} \rightarrow \text{T}^\ddagger)$ values^b in kcal mol⁻¹ for R-C(=Y)-F species

Species	$D_{C=Y}$	ΔE_{Hyd}	$\Delta G(\text{R} \rightarrow \text{T}^\ddagger)$
CH ₃ -C(=O)-F	68.6	-4.9	-
CH ₃ -C(=S)-F	33.9	-18.9	8.0
NH ₂ -C(=O)-F	52.7	2.0	-
NH ₂ -C(=S)-F	10.7	-5.7	13.5

^aEstimated at the QCISD(T)/6-311++G(3df,2p)/MP2(Full)/6-31+G(d) level of theory. ^bDifferences in the Gibbs free energies between reactants and T[‡] intermediate at the QCISD/6-311+G(3df,2p)/MP2(FC)/6-311+G(d,p) level of theory for reactions of R-C(=S)-F with NH₃ in the gas phase.

of theory and the results are summarized in Table 3. Table 3 shows that the estimated $D_{C=Y}$ value for carbamyl (or thiocarbamyl) fluoride is smaller than the corresponding acetyl (or thioacetyl) fluoride. For example, the $D_{C=Y}$ value for carbamyl fluoride was 15.9 kcal mol⁻¹ smaller than that for acetyl fluoride. This indicates that the C=Y π -bonds of carbamyl and thiocarbamyl groups are indeed weakened by resonance as predicted by NRT analyses. If so, it would be much easier to form T[‡] structures from carbamyl (or thiocarbamyl) halides than acetyl (or thioacetyl) halides. The results shown above, however, were contrary to what expected from the C=Y π -bond strength. To rationalize this phenomenon, hydrogenation reactions of C=Y π -bonds, eq (2), were studied. If we assume that the C-H and Y-H bond strengths in the product are the same for carbamyl (thiocarbamyl) and the corresponding acetyl (thioacetyl) analogues, the difference in ΔE_{Hyd} indicates relative stability of the substrates in the ground states. The computational results are summarized in Table 3. Interestingly, the ΔE_{Hyd} value for acetyl (thioacetyl) fluoride was much lower than the corresponding value for carbamyl (thiocarbamyl) analogue. For example, the ΔE_{Hyd} for thioacetyl fluoride was more favorable by 13.2 kcal mol⁻¹ than that for thiocarbamyl fluoride. This result could only be explained based on the destruction of the resonance stabilization in the substrates, since the degree of resonance delocalization was much larger for carbamyl and thiocarbamyl fluorides. Our result is also supported by the well-known fact that the amide bond is less reactive than the carbonyl bond.



Conclusions

From the studies on the nucleophilic substitution reactions on carbamyl and thiocarbamyl halides in the gas phase and in solution phase, we can derive the following conclusions.

1) The reaction mechanisms of title compounds were similar to those of acetyl and thioacetyl halides.

2) Solvent plays an important in stabilizing the tetrahedral structures. However, shift in TS to an earlier position contributes to the lowering of the activation free energy by reducing unfavorable deformation energies.

3) Resonance stabilization of carbamyl and thiocarbamyl groups in the ground state is the major factor of lower reactivity of these groups compared to the corresponding acetyl and thioacetyl groups.

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15. The ΔG_{sol} values are obtained from differences between the energies obtained at the CPCM calculation and the gas-phase calculation on geometries optimized at CPCM-MP2(FC)/6-31+G(d) level, *i.e.*, $\Delta G_{\text{sol}} = E(\text{CPCM-MP2}/\text{CPCM-MP2}) - E(\text{MP2}/\text{CPCM-MP2})$.
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