

# Disparate Behavior of Carbonyl and Thiocarbonyl Compounds: Acyl Chlorides vs Thiocarbonyl Chlorides and Isocyanates vs Isothiocyanates

Kenneth B. Wiberg,\* Yi-gui Wang, Scott J. Miller,\* and Angela L. A. Puchlopek

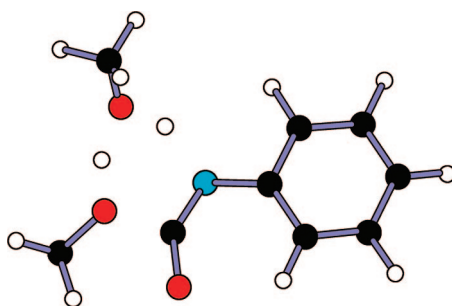
*Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107*

William F. Bailey\* and Justin D. Fair

*Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06269-3060*

*Kenneth.Wiberg@yale.edu; Scott.Miller@yale.edu; William.Bailey@uconn.edu*

*Received February 25, 2009*



The reaction of benzoyl chloride with methanol catalyzed by pyridine is 9 times more rapid than is the same reaction with thiobenzoyl chloride. The difference in reactivity, as well as the dealkylation reactions that occur when the reaction of thiobenzoyl chloride is catalyzed by bases such as  $\text{Et}_3\text{N}$ , can be understood in terms of the charge distributions in the intermediate acylammonium ions. The reaction of  $\text{PhNCO}$  with ethanol occurs at a much higher rate ( $4.8 \times 10^4$ ) than that of  $\text{PhNCS}$ , corresponding to a difference in activation free energies for the additions of 6 kcal/mol. Transition states for each of these reactions were located, and each involves two alcohol molecules in a hydrogen bonded six-membered ring arrangement. Information concerning differences in reactivity was derived from analysis of Hirshfeld atomic charge distributions and calculated hydrogenolysis reaction energies.

## Introduction

The chemistry of acyl chlorides and isocyanates often parallels that of their sulfur analogs, thiocarbonyl chlorides and isothiocyanates.<sup>1</sup> However, as detailed below, some significant differences in the reactivity of carbonyl and thiocarbonyl compounds have been noted in the literature. We have been interested for some time in the effect that replacement of a  $\text{C}=\text{O}$  bond by a  $\text{C}=\text{S}$  bond has on the chemistry of various functional groups.<sup>2,3</sup> Herein we report the results of a coordinated

experimental and computational investigation of the contrasting behavior of acyl chlorides and isocyanates vis-à-vis their sulfur analogs.

## Results and Discussion

The literature indicates that benzoyl chloride<sup>4</sup> is more reactive toward methanol than is thiobenzoyl chloride.<sup>5</sup> In this connection, the reactions of phenoxycarbonyl chloride and phenoxithiocarbonyl chloride with secondary alcohols in the presence of  $\text{Et}_3\text{N}$  has been examined and, whereas the carbonyl chloride reacts normally to give the expected ester (eq 1), the thiocarbonyl chloride reaction occurs by nucleophilic substitution at an ethyl group on N, leading to a thioamide as the product (eq

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(4) Norris, J. F.; Young, H. H., Jr. *J. Am. Chem. Soc.* **1935**, *57*, 1420.

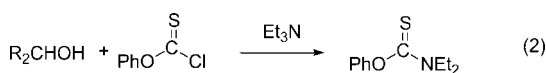
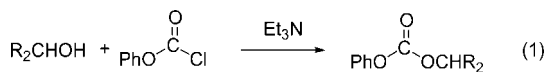
(5) Scheithauer, S.; Mayer, R. *Chem. Ber.* **1965**, *98*, 838.

TABLE 1. B3LYP/6-311+G\* Calculated Energies (Hartrees) of Acyl Derivatives<sup>a</sup>

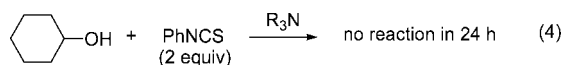
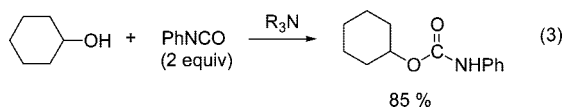
compound	<i>E</i> (0 K)	<i>H</i> (298 K)	<i>G</i> (298 K)	<i>G</i> (soln)
MeCOCl	-613.52101	-613.46816	-613.50163	-613.50716
MeCSCl	-936.46492	-936.41421	-936.44872	-936.45184
PhCOCl	-805.29903	-805.18998	-805.23157	-805.24152
PhCSCl	-1128.24334	-1128.13648	-1128.17989	-1128.18749
PhOCOCl	-880.53796	-880.42400	-880.46898	-880.48028
PhOCSCl	-1203.48011	-1203.36848	-1203.41442	-1203.42384
MeCONMe <sub>3</sub> <sup>+</sup>	-327.55854	-327.37717	-327.41997	-327.49747
MeCSNMe <sub>3</sub> <sup>+</sup>	-650.50352	-650.32399	-650.36697	-650.44125
PhCONMe <sub>3</sub> <sup>+</sup>	-519.33766	-519.09984	-519.15040	-519.22427
PhCSNMe <sub>3</sub> <sup>+</sup>	-842.28157	-842.04607	-842.09709	-842.16925
PhOCONMe <sub>3</sub> <sup>+</sup>	-594.58873	-594.34658	-594.39728	-594.47138
PhOCSNMe <sub>3</sub> <sup>+</sup>	-917.52958	-917.28992	-917.34168	-917.41290
Me <sub>3</sub> N	-174.51680	-174.39007	-174.42379	-174.42601
Cl <sup>-</sup>	-460.30373	-460.30137	-460.31875	-460.43280

<sup>a</sup> The *G*(soln) values were derived from the solvation energies calculated using the PCM model with acetonitrile as the solvent; these were added to the *G*(289K) values.

2).<sup>6</sup> It might be noted that the thioester is formed when a pyridine base is used and dealkylation is not possible. The same type of behavior has recently been documented in reactions of phenoxy-carbonyl chloride and phenoxythiocarbonyl chloride with cyclohexanol.<sup>3</sup>



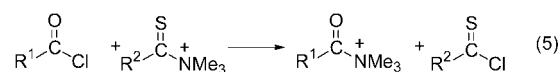
In a related transformation, we have observed, as shown below, that phenyl isocyanate reacts with cyclohexanol in the presence of 20-mol% *N*-methylimidazole as the catalyst to give an 85% yield of cyclohexyl phenylcarbamate in 24 h; (eq 3) however, phenyl isothiocyanate gives no product under these conditions (eq 4). There are other data that relate to this difference in reactivity.<sup>7,8</sup>



We were interested in exploring the reasons for these differences in reactivity, and we have made use of experimental and computational tools to investigate the systems. There are kinetic data reported for the reactions of benzoyl and thiobenzoyl chlorides with methanol that indicate the former to be 12 times more reactive than the latter at 0 °C.<sup>4,5</sup> In order to have a direct comparison at 25 °C, thiobenzoyl chloride was prepared following the procedure of Staudinger and Siegart<sup>9</sup> and its reaction with methanol in pyridine solution was examined. The

reaction proceeded at a modest rate, and it was clearly slower than the corresponding reaction of benzoyl chloride. In order to have a more quantitative comparison, a competition experiment was performed in which a CDCl<sub>3</sub> solution containing one molar equiv each of methanol, pyridine, benzoyl chloride and thiobenzoyl chloride was followed by <sup>1</sup>H NMR. The ratio of products was determined by integration of the methyl singlets of methyl benzoate ( $\delta = 3.85$ ) and *O*-methyl thiobenzoate ( $\delta = 4.18$ )<sup>10</sup> products. The average of three runs indicated that benzoyl chloride was more reactive than thiobenzoyl chloride by a factor of  $9.0 \pm 0.5$  at 25 °C. In order to gain information of potential significance to this rate difference, we carried out a number of geometry optimizations for the relevant species using the B3LYP/6-311+G\* theoretical model. The results are summarized in Table 1.

The reactions of benzoyl and thiobenzoyl chlorides with MeOH in the presence of an amine catalyst presumably involve two steps: a relatively rapid reaction leading to an acylammonium ion and a chloride ion followed by rate determining reaction of a nucleophile to give the product.<sup>11</sup> The energies summarized in Table 1 allow the calculation of energy changes for reactions of the acyl derivatives (the amine catalyst was modeled as Me<sub>3</sub>N in the calculations). The initial reaction will be strongly disfavored in the gas phase because of the high electrostatic energies of ions in the gas phase. This effect may be minimized, but still provide the needed information, by looking at the exchange reactions illustrated below since the electrostatic energies will roughly cancel.



However, to ensure that this approximation is reasonable, the stabilization of the ions in acetonitrile solution (chosen because it has a high dielectric constant)<sup>12</sup> was calculated using the PCM polarized continuum model.<sup>13</sup> The gas phase free energies were corrected for the solvation energies and the results are given in the last column of Table 1. The calculated energy changes in kcal/mol for the exchange reactions, including the effect of solvent, are summarized in Table 2.

(6) (a) Hsu, F.-L.; Zhang, X.; Hong, S.-S.; Berg, F. J.; Miller, D. D. *Heterocycles* **1996**, *39*, 801. (b) Millan, D. S.; Prager, R. H. *Tetrahedron Lett.* **1998**, *39*, 4387. (c) Millan, D. S.; Prager, R. H. *Aust. J. Chem.* **1999**, *52*, 841.

(7) (a) Coseri, S. *High Perform. Polym.* **2007**, *19*, 520. The authors report kinetic data for the reaction of PhNCO with ethanol obtained in dilute benzene solutions. The rate constants (given as L mol<sup>-1</sup> min<sup>-1</sup>) increase linearly with ethanol concentration, suggesting a second order dependence on the alcohol concentration. See, for example: (b) Caraculacu, A. A.; Agherghine, I.; Baron, P.; Timpu, D. *Rev. Roum. Chim.* **1996**, *18*, 725.

(8) Rao, C. N. R.; Venkataraghavan, R. *Tetrahedron* **1962**, *18*, 531.

(9) Staudinger, H.; Siegart, J. *Helv. Chim. Acta* **1920**, *3*, 824.

(10) Kata, S. *Phosphorus, Sulfur, Silicon* **1997**, *120*, 213.

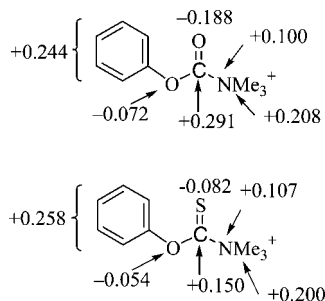
(11) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432; **1970**, *92*, 5442.

**TABLE 2.** Calculated Energy Changes (kcal/mol) for Exchange Reactions (eq 5)

R	$\Delta H(298)$	$\Delta G(298)$	$\Delta G(\text{soln})$
Me	0.5	-0.1	-0.6
Ph	-0.2	-1.0	-0.6
PhO	-0.7	-0.7	-1.3

It can be seen that the energy changes are small, but they do slightly favor the acylammonium ion over the thioacylammonium ion. When R = Ph, the computed  $\Delta G$  values are too small to explain the experimentally observed reactivity difference, but it should be recognized that there are possible small errors in the calculated values resulting from the theoretical level that was used. It does not appear that the initial equilibrium can fully account for the rate difference in the reactions of benzoyl and thiobenzoyl chlorides with methanol.

It is not straightforward to carry out calculations for the transition state for second step in the reaction since the species involved are not well-defined, and nucleophilic attack might involve the alkoxide ion that is in equilibrium with the alcohol and the amine, or it may involve the alcohol itself, perhaps hydrogen-bonded to the amine. In addition, the difference in reaction rate for the formation of the esters is small. However, there is another quantity that should be considered when evaluating the reaction of an intermediate thioacylammonium ion leading to dealkylation at nitrogen. To this end, atomic charges were calculated using the Hirshfeld model<sup>14</sup> that we have found to be particularly useful in comparing similar compounds. These charges are illustrated in Figure 1.

**FIGURE 1.** Hirshfeld charges for the initial product of the reaction of acyl and thioacyl chlorides with trimethylamine.

The replacement of O by S leads to significant changes in charge populations due to the difference in electronegativity of these atoms, and these are especially large at the carbonyl and thiocarbonyl carbons. The reaction of that carbon with a nucleophile would be expected to be more rapid with the more electrophilic (positively charged) carbon. With the reduced carbon charge (and presumably lower reactivity) in the thio-carbonyl derivative it is not surprising that a nucleophile could react with the positively charged carbon at the  $\text{NMe}_3^+$  group (+0.200) relative to  $\text{S}=\text{C}$  (+0.150) leading to dealkylation as observed in such reactions.

The reactions of PhNCO and PhNCS are potentially of greater interest because of the apparently larger difference in reactivity.

(12) In the polarized continuum model, all solvents with a dielectric constant of 20 or greater will give approximately the same solvent effect.

(13) (a) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43. (b) Cammi, R.; Mennucci, B.; Tomasi, J. *J. Phys. Chem. A* **1999**, *103*, 9100.

(14) (a) Hirshfeld, F. L. *Theor. Chim. Acta* **1977**, *44*, 129. (b) Nalewajski, R. F.; Parr, R. G. *Proc. Natl. Acad. Sci.* **2000**, *97*, 8879. (c) Parr, R. G.; Ayers, P. W.; Nalewajski, R. F. *J. Phys. Chem. A*, **2005**, *109*, 3957.

**TABLE 3.** Kinetic Data for the Reactions of PhNCO and PhNCS with Ethanol

compound	medium	T, °C	k, sec <sup>-1</sup>
PhNCS	ethanol-benzene	60.0	$0.55 \times 10^{-5}$
PhNCS	ethanol-THF	60.0	$0.63 \times 10^{-5}$
PhNCS	ethanol	60.0	$1.52 \times 10^{-5}$
PhNCS	ethanol	40.0	$2.47 \times 10^{-6}$
PhNCS <sup>a</sup>	ethanol	0.0	$2.9 \times 10^{-8}$
PhNCO	ethanol	0.0	$1.38 \times 10^{-3}$

<sup>a</sup> Extrapolated from the 60 and 40 °C rate constants.

There are some kinetic data available for the reactions of PhNCO and PhNCS with ethanol. The rate of reaction between phenyl isocyanate and ethanol was determined at 60 °C in dilute benzene solutions.<sup>7</sup> The rate constants were reported as second order, but they increased linearly with ethanol concentration suggesting a second order dependence on the ethanol concentration:

$$v = k[\text{PhNCO}][\text{EtOH}]^2$$

The rate of reaction between phenyl isothiocyanate and ethanol has been determined in pure ethanol solution at 43 and 53 °C: the pseudofirst order rate constant at 53 °C was  $0.95 \times 10^{-5} \text{ sec}^{-1}$ .<sup>8</sup> Second order behavior was noted when equal concentrations of PhNCS and ethanol were used in benzene solution:<sup>8</sup> however, the concentration dependence was not further investigated and, therefore, the order with respect to ethanol is ambiguous. First order catalysis by triethylamine was also observed and a study of substituent effects led to  $\rho = 1.70$ .<sup>8</sup>

To determine the relative rates of reaction of the two isocyanates under the same conditions, and to study the kinetic order in ethanol, the following studies were carried out. The rate of reaction of phenyl isothiocyanate with pure ethanol was determined at 40.0 °C and at 60.0 °C, and the rate was also determined using a 1:1 mixture of ethanol and benzene as well as a 1:1 mixture ethanol and THF at 60.0 °C. Additionally, the rate of reaction of PhNCO with pure ethanol was determined at 0.0 °C. The pseudofirst order rate constants, summarized in Table 3, include the extrapolated rate of reaction of PhNCS with pure ethanol at 0.0 °C. These data indicate that the reaction of PhNCO with ethanol is  $\sim 48\,000$  times more rapid than the analogous reaction with PhNCS. This corresponds to a difference in activation free energy ( $\Delta\Delta G^\ddagger$ ) for the addition of ethanol to PhNCO and PhNCS of about 6 kcal/mol.

If the reaction of PhNCS were second order in ethanol in pure ethanol solution, in the absence of a solvent effect, the rate of reaction would decrease by a factor of 4 in the 1:1 mixed solvents. Since the rate of reaction was similar in the two quite different mixed solvents, the solvent effect appears to be relatively small. The decrease in rate by a factor of 2.4 to 2.8 suggests that much of the reagent is hydrogen bonded to ethanol (that would lead to a rate factor of 2 rather than four) and that the reaction involves both free and hydrogen-bonded PhNCS in pure ethanol. Evidence for hydrogen bonding between PhNCS and ethanol has been noted in a previous study.<sup>8</sup>

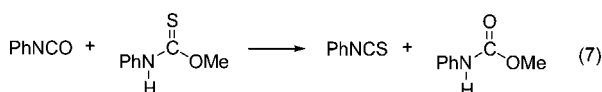
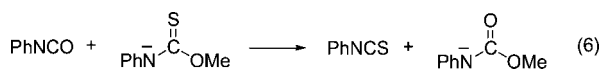
In an effort to understand the sizable difference in reactivity of PhNCO and PhNCS with ethanol, we explored the reactions computationally. The results of these studies are summarized in Table 4. Methanol rather than ethanol was used as the reactant in these computations so as to avoid conformational problems associated with the intermediate species.

In examining these energies, it is useful to again use exchange reactions. The relevant reactions are illustrated below. The

**TABLE 4.** B3LYP/6-311+G\* Calculated Energies (Hartrees) of Isocyanates, Isothiocyanates, and their Reaction Products

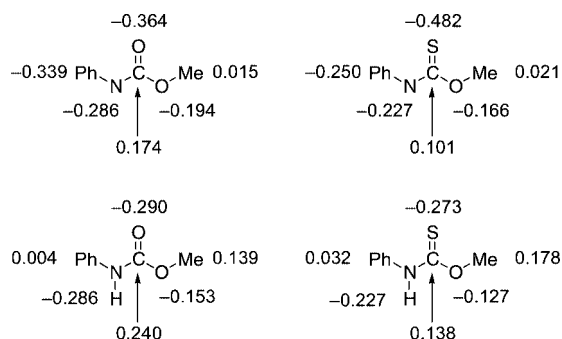
compound	$E(0\text{ K})$	$H(298\text{ K})$	$G(298\text{ K})$	$G(\text{soln})$
PhNCO	-399.83490	-399.72337	-399.76393	-399.77294
PhNCS	-722.79444	-722.68500	-722.72720	-722.73536
PhNC(=O)OMe	-515.06059	-514.90458	-514.95148	-515.04127
PhNC(=S)OMe	-838.02061	-837.86728	-837.91235	-838.99880
PhNHC(=O)OMe	-515.62480	-515.45348	-515.50091	-515.51722
PhNHC(=S)OMe	-838.56853	-838.39935	-838.44783	-838.46290
MeOH	-115.75387	-115.69845	-115.72548	-115.73624
MeO <sup>-</sup>	-115.14208	-115.10331	-115.1237	-115.24380

reaction shown in eq 6 is concerned with the exchange of methoxide ion; eq 7 shows the exchange of methanol. The calculated energies (kcal/mol) for these exchange reactions are given in Table 5.

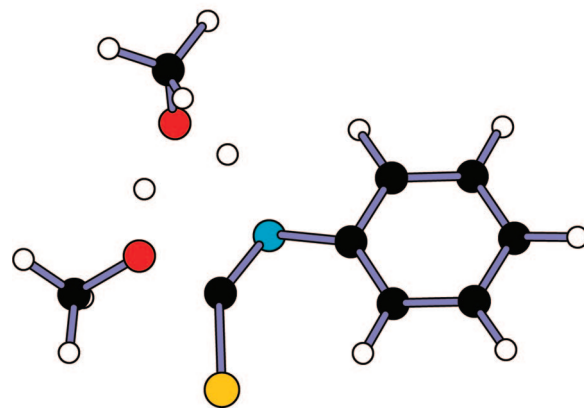
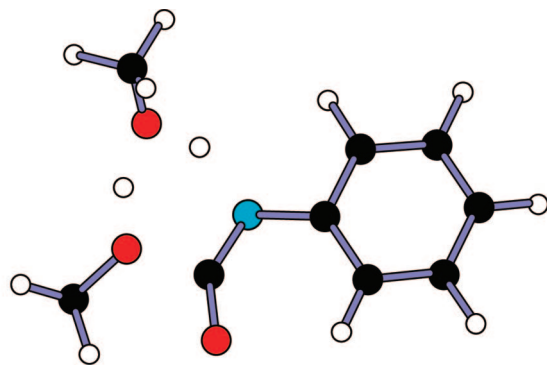
**TABLE 5.** Energies (kcal/mol) of Exchange Reactions 6 and 7

reaction	$\Delta H$	$\Delta G$	$\Delta G(\text{soln})$
1	0.7	-1.5	-3.1
2	-9.9	-10.3	-10.5

The computed energy change for reaction 6 demonstrates that methoxide ion has a small preference for addition to PhNCO vis-à-vis PhNCS. However, the results for reaction 7 show that methanol has a large preference for addition to PhNCO vs PhNCS. In addition, there is only a small solvent effect on these reactions. The calculated  $\Delta G$  for exchange of methanol (reaction 2, Table 5) is, as might be expected, somewhat larger than the experimental  $\Delta\Delta G^\ddagger$  (6 kcal/mol) for additions of ethanol to PhNCO and PhNCS. These results beg the question: why is there such a large change on going from methoxide ion to methanol? A clue is provided by the Hirshfeld charges for these compounds illustrated in Figure 2.

**FIGURE 2.** Hirshfeld charges for isocyanate and isothiocyanate derivatives in exchange reactions 6 and 7.

The product of addition of methoxide to PhNCS leads to a considerably larger negative charge at sulfur than is found at the carbonyl oxygen for addition of methoxide to PhNCO (Figure 2, top row). Clearly, sulfur is better able to bear a negative charge than is oxygen (cf. the greater acidity of H<sub>2</sub>S as compared to H<sub>2</sub>O). This benefit is lost in the neutral products generated by addition of methanol (Figure 2, bottom row), and now the difference in exchange reactions increases. All of this,

**FIGURE 3****TABLE 6.** B3LYP/6-31+G\* Calculated Energy Changes in kcal/mol for Conversion of Reactants to Products for the Reactions of PhNCO and PhNCS with 2 Equiv of Methanol

reactant	$\Delta E^\ddagger(0\text{ K})$	$\Delta H^\ddagger(298\text{ K})$	$\Delta G^\ddagger(298\text{ K})$	$\Delta G^\ddagger(\text{soln})$
PhNCO	5.7	5.1	29.5	39.3
PhNCS	15.1	14.4	38.8	46.6

of course, refers to the thermodynamics of the reactions. However, given the large differences in rates that have been found in the reactions of PhNCO and PhNCS with ethanol, it is likely that the kinetics of the reactions will be related to the overall thermodynamic changes.

Since it has been found that the addition of an alcohol to PhNCO and PhNCS is second order in the alcohol, it is reasonable to propose that one alcohol forms a hydrogen bond with the nitrogen of the reactant, and the second alcohol is involved with nucleophilic attack on the carbon. Transition states were located for this type of reaction using methanol as the reactant in which the two methanol molecules are bridged via a hydrogen bond, leading to a six-membered ring transition state (Figure 3). The calculated energy changes are given in Table 6 and they include the effect of methanol as the solvent.

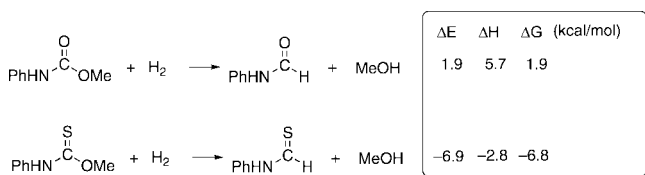
In reviewing the results summarized in Table 6, it should be noted that there is a small change in energy on going from  $E(0\text{ K})$  to  $\Delta H^\ddagger(298\text{ K})$  due to differences in zero-point energies and thermal excitation of low frequency vibrations. The large difference between the  $\Delta H^\ddagger(298\text{ K})$  and  $\Delta G^\ddagger(298\text{ K})$  values is mainly due to the unfavorable entropy change on going from three molecules to one in the gas phase as the reaction proceeds. The further change on going to  $\Delta G^\ddagger(\text{soln})$  is a result of the difference in solvation energies between reactants and products. What is not included in this analysis is the significant change



in reaction entropy on going from the gas phase to solution resulting from translation being converted to diffusion. There is no simple way of calculating this change, and it will lead to exaggerated values of  $\Delta G^\ddagger(\text{soln})$ . This effect will approximately cancel in comparing the energy changes for the two reactions in Table 6. The difference in the computed  $\Delta\Delta G^\ddagger$  values of 7 kcal/mol, favoring more rapid addition of methanol to PhNCO vis-à-vis PhNCS, is in very good agreement with the experimentally determined difference in activation free energy (6 kcal/mol) derived from kinetic data for the addition of ethanol to PhNCO and PhNCS (Table 3).

How can one account for the considerable difference in reactivity of an alcohol with PhNCO and PhNCS? A suggestion may be found in the Hirshfeld charges illustrated in Figure 2: the calculations indicate that the O–C–O charges in the PhNCO product are significantly larger than are the O–C–S charges in the PhNCS product because of the greater electronegativity of O vs S. In an earlier study of substituent effects on a carbonyl group, it was found that internal Coulombic attraction was important in stabilizing the compounds.<sup>2,15</sup> This is, for example, a reason why methyl fluoride has a larger bond dissociation energy than methyl chloride despite its lower covalent bond order. Therefore, we suggest that the greater stability of methyl phenylcarbamate relative to phenyl isocyanate (in comparison to their sulfur analogs) is due to the increased internal Coulombic attraction.

One might wonder if the difference in charge distribution is sufficient to give the calculated energy difference. It is possible to provide evidence in favor of this proposal by examining the hydrogenolysis reactions shown below. The energies were calculated at the B3LYP/6-31+G\* level and the details are given in the Supporting Information.



There are differences between the calculated quantities  $\Delta E$ ,  $\Delta H$ , and  $\Delta G$  because of differences in vibrational frequencies between reactants and products. However, in each case, the reaction of the carbonyl compound is endothermic and that of the thiocarbonyl compound is exothermic. The difference in calculated energies is about 8.5 kcal/mol in all cases. Clearly, there is an energetic preference for the carbonyl group to be attached to oxygen, whereas there is a disadvantage for a thiocarbonyl group to be attached to oxygen.

## Summary

In conclusion, we have performed experiments and calculations to explore the marked difference in reactivity between acyl chlorides and thiocarbonyl chlorides on the one hand, and between isocyanates and isothiocyanates on the other. The general reactivity trends are similar in these two compound classes (*O*-substituted compounds react more rapidly with alcohols than their *S*-homologues). In both cases, the experimental and computational data point to differential charge

distributions, albeit within quite different intermediates en route to quite different transition states, as consistent with the observed reactivity trends. In the chemistry of the acyl/thiocarbonyl chlorides, the corresponding acyl/thioacyl ammonium ions possess substantial differences in positive charge at the reacting carbon center, suggesting substantial Coulombic differentials in the transition states leading to products; the more positively charged acylammonium ion reacts more rapidly with electron-rich nucleophiles than the corresponding thioacylammonium ion.

The experiments and calculations involving the reactions of isocyanates and isothiocyanates reveal a more complicated story. In the reactions of these compounds with alcohols, a second order dependence of the rate of reaction in alcohol concentration unveils a substantial role for hydrogen bonding throughout the reaction coordinate for these processes. In the rate-determining transition states, it may be that the internal charge distributions start to reflect those observed in the products as multivalent hydrogen bond-stabilized ensembles are no longer present. In this limit, the internal charge distributions emerge as rather different in comparing the carbonyl- and thiocarbonyl-containing products. For the isocyanate-derived product, the internal Coulombic stabilization substantially exceeds that available in the corresponding thiocarbamate product. To the extent that these effects are mirrored in the final, rate-determining transition state, Coulombic effects once again, appear to account for the phenomenological rate differentials rather well.

## Experimental Section

**Kinetic Experiments.** The reaction of phenyl isothiocyanate with ethanol was studied by preparing a 1.0 M solution of the reagent plus tetradecane as an internal standard in 40 mL of the solvent (ethanol, 1:1 ethanol–benzene or 1:1 ethanol–THF). The solvent was prewarmed to the reaction temperature before the addition of the isothiocyanate. The reaction solutions were kept at  $60 \pm 0.1$  or  $40.0 \pm 0.1$  °C; 1.2 mL samples were removed at appropriate times and were cooled to  $-25$  °C prior to GC analysis.

The reaction of phenyl isocyanate with ethanol was studied by weighing an appropriate amount of the reactant along with undecane as an internal standard, and cooling the solutions to 0 °C. Ethanol (20 mL) was similarly cooled, and at the initial time it was added to the reactant, maintaining it at 0 °C. At 1 min intervals, 0.25 mL samples were removed and added to 1 mL of THF in a GC vial that had been cooled to 0 °C. It was quickly shaken to mix the contents, immediately placed in Dry-Ice, and stored at  $-75$  °C until GC analysis using a FID detector. In both cases, the isocyanate or isothiocyanate was well separated from the reaction product. The rate of appearance of the product corresponded to the rate of appearance of the reactant.

**Relative Rates of Reaction of Benzoyl and Thiobenzoyl Chlorides with Methanol.** A solution consisting of one mmol each of benzoyl chloride, thiobenzoyl chloride,<sup>9</sup> pyridine and methanol in 5 mL of  $\text{CDCl}_3$  was monitored at 25 °C by  $^1\text{H}$  NMR over a period of 90 min. The product ratio was determined by integration of the  $\text{CH}_3$  singlets for methyl benzoate at  $\delta = 3.85$  and *O*-methyl thiobenzoate at  $\delta = 4.18$ .<sup>10</sup> The product ratio (methyl benzoate/*O*-methyl thiobenzoate) from three replicate runs was  $9.0 \pm 0.5$ .

**Reaction of Cyclohexanol with Phenyl Isocyanate.** To a solution of cyclohexanol (15.0  $\mu\text{L}$ , 0.142 mmol) in dichloromethane (1.4 mL) was added *N*-methylimidazole (2.3  $\mu\text{L}$ , 0.028 mmol) and phenyl isocyanate (31.0  $\mu\text{L}$ , 0.284 mmol). The orange solution was allowed to stir at room temperature for 24 h and then the excess isocyanate was quenched with diethylamine. The product ratio was determined by  $^1\text{H}$  NMR integration of the carbinol C–H proton for cyclohexanol at  $\delta = 3.58$  and cyclohexyl phenylcarbamate C–H at  $\delta = 4.76$  (1:17.2 or 94% conv.). The orange solution was

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concentrated and purified by silica gel flash chromatography to yield 26.5 mg (85%) of cyclohexyl phenylcarbamate, mp 80 °C (lit 82–82.5 °C<sup>16</sup>).

**Reaction of Cyclohexanol with Phenyl Isothiocyanate.** To a solution of cyclohexanol (15.0  $\mu$ L, 0.142 mmol) in dichloromethane (1.4 mL), was added *N*-methylimidazole (2.3  $\mu$ L, 0.028 mmol) and phenyl isothiocyanate (33.9  $\mu$ L, 0.284 mmol). The solution was allowed to stir at room temperature for 24 h and then the excess isocyanate was quenched with diethylamine. No product formation was observed by <sup>1</sup>H NMR and TLC analysis.

**Calculations.** All of the ab initio calculations were carried out using a development version of Gaussian.<sup>17</sup> The Hirshfeld charges were obtained using a local program<sup>18</sup> that makes use of the wave function file derived from Gaussian.

**Acknowledgment.** Research at Yale was carried out with support from the National Science Foundation (KBW, CHE-0445847) and the NIH (S.J.M. and A.L.A.P., NIGMS068649); the work at UCONN was supported by a grant from Procter & Gamble Pharmaceuticals, Mason, Ohio. We thank Prof. Paul Carlier (VA Tech) for a helpful suggestion.

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**Supporting Information Available:** Calculated energies for the formation of transition states for the reactions of PhNCO and PhNCS with methanol and for the hydrogenolysis reactions of methyl *N*-phenylcarbamate and methyl *N*-phenylthiocarbamate. Calculated structural data in Cartesian coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO9004316

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