# Hydrogen-Bond Mediated Catalysis: The Aminolysis of 6-Chloropyrimidine as Catalyzed by Derivatives of Uracil

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**Abstract:** The aminolysis of 6-chloropyrimidine and 2-amino-6-chloropyrimidine has been examined by using density functional theory. Relative to the aminolysis of 6-chloropyrimidine, the addition of an electron-donating $NH_2$ group to $C_2$ increases the barrier to aminolysis, indicating that the third hydrogen bond does not play a catalytic role but introduces additional rigidity into the system. However, the computations suggest that there is an interesting correlation between the barrier to aminolysis and the proton affinity of the species that interacts with the incoming $NH_3$. To extend the range of proton affinities, the aminolysis of 6-chloropyrimidine was examined by using fluoro, imine, and thioketo derivatives of the uracil-derived bases. The proton affinity of the moiety that hydrogen bonds with $NH_3$ is decreased by fluoro substitution, and thus the aminolysis barriers are increased. Similarly, imine substitution enhances the PA of the moiety, which is reflected in a decrease in the aminolysis barriers. The same correlation exists for the thioketo-derived bases, whose PAs are intermediate between the fluoro and imine derivatives. Thus, the aminolysis of 6-chloropryimidine and 2-amino-6-chloropyrimidine demonstrates the importance of a well-chosen proton acceptor and the catalytic possibilities associated with the formation of multiple hydrogen bonds.

## Introduction

Hydrogen bonds are an essential feature of the structure and function of biological molecules. Although an individual hydrogen bond is relatively weak compared to a typical covalent bond, the cooperative nature of multiple hydrogen bonds confers stability to a complex,[1,2] an important factor in the self-assembly of molecules.[1,3,4] Due to the specificity of the donor−acceptor units and the inherent weakness of the individual bonds within a multiply hydrogen-bonded complex, molecules capable of forming hydrogen bonds have been employed as potential catalysts in reactions of organic and biological importance.[3,5−8] Recently, nucleotide bases such as uracil have been utilized[9,10] as catalytic agents due to the large variety of hydrogen bond functional groups associated with these molecules.[11]

Tominaga et al.[9] accelerated the aminolysis of 2-amino-6-chloropurine by the addition of derivatives of uracil, which on the basis of $^1$H NMR evidence were assumed to form multiple hydrogen-bonding interactions. The latter were presumed to assist the formation of a reactive intermediate and to stabilize the transition state, giving rise to a catalytic enhancement in the observed rate of aminolysis. Subsequently, the present authors proposed a rationalization for the role of multiple hydrogen-bonding interactions on the basis of density functional theory calculations[12] carried out on a model reaction of the aminolysis of 6-chloropyrimidine. The uncatalyzed aminolysis was found to proceed with a sizable barrier, but through the addition of $OCH_2$, which forms a hydrogen bond to the incoming $NH_3$, the barrier to aminolysis was reduced. A further reduction in the barrier to aminolysis was obtained by enlarging the base to OHC−$NH_2$, which forms hydrogen bonds to both the incoming $NH_3$ and the N adjacent to the carbon at which substitution occurs.

Density functional theory is employed herein to investigate the role of the third hydrogen bond present in the aminolysis of 2-amino-6-chloropyrimidine (Scheme 1a). In addition, recent interest in the proton affinity of the proton donor[13−15] involved in hydrogen bonding has prompted an investigation into the role of the hydrogen bond acceptor and the correlation between the proton affinity of the group that interacts with the incoming $NH_3$ moiety and the barrier to aminolysis. To examine this correlation, fluoro, imine, and thioketo derivatives of the uracil-derived bases ($OCH_2$, OHC−$NH_2$, and OHC−NH−CHO) were utilized in the aminolysis of 6-chloropyrimidine (Scheme 1b).

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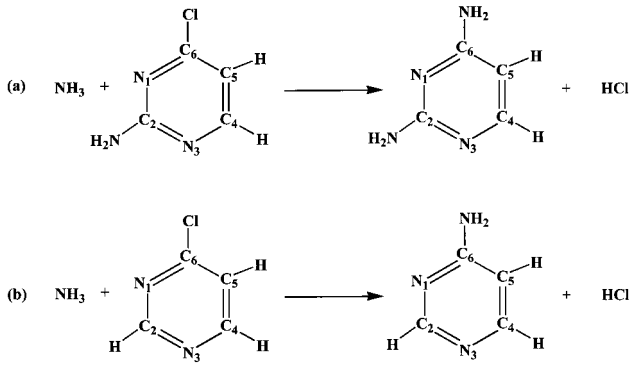
**Scheme 1.** Schematic Illustration of the Aminolysis of (a) 2-Amino-6-chloropyrimidine and (b) 6-Chloropyrimidine



## Computational Methods

Density functional theory calculations were carried out with use of the Gaussian 98[16] suite of programs. Becke's three-parameter exchange functional (B3),[17,18] as implemented[19] in the Gaussian suite of programs, was used in conjunction with the correlation functional of Lee, Yang, and Parr (LYP).[20] Geometry optimizations were performed at the B3-LYP/6-31G(d,p) level. Harmonic vibrational frequencies and zero-point vibrational energy (ZPVE) corrections were calculated at the same level of theory. Relative energies were calculated at the B3-LYP/6-311+G-(2df,p) level by using the B3-LYP/6-31G(d,p) geometries and corrected with the appropriate ZPVE, i.e., B3-LYP/6-311+G(2df,p)//B3-LYP/6-31G(d,p) + ZPVE. The proton affinities for the uracil-derived bases were calculated at the aforementioned level of theory. All relative energies are in kJ $mol^{-1}$ and bond lengths in angstroms (Å). The optimized structures and total energies of all species are summarized in Tables S1 and S2, respectively, of the Supporting Information.

## Results and Discussion

Previous calculations, utilizing $OCH_2$ and $OHC-NH_2$ to mimic the hydrogen-bonding functional groups in uracil alluded to the importance of hydrogen bonding to the incoming $NH_3$ moiety. While the isolated aminolysis was found to proceed with a sizable barrier of 138.1 kJ $mol^{-1}$, the barrier to aminolysis was reduced to 112.2 kJ $mol^{-1}$ by the addition of $OCH_2$ that formed an O···$HNH_2$ bond of 1.876 Å to $NH_3$. A further reduction in the aminolysis barrier to 95.3 kJ $mol^{-1}$ was attained by enlarging the base to $OHC-NH_2$ which formed two hydrogen bonds; a shorter O···$HNH_2$ bond of 1.766 Å to $NH_3$ and a longer NH···N bond of 1.906 Å to the N adjacent to the carbon undergoing substitution. However, in the original study performed by Tominaga et al.,[9] it is possible that the third hydrogen bond was involved in the aminolysis reaction. To assess the importance and function of the third hydrogen bond, an $-NH_2$ group was attached to $C_2$ of $Cl-C_4N_2H_3$ and the aminolysis of 2-amino-6-chloropyrimidine (Scheme 1a) was examined by using $OCH_2$, $OHC-NH_2$, OHC−NH−CHO, and 1-methyluracil as bases.

In the isolated aminolysis of 2-amino-6-chloropyrimdine ($NH_3$ + $Cl-C_4N_3H_4$), the reactants generate the initial complex **1a** (Figure 1a) lying 21.4 kJ $mol^{-1}$ lower in energy. As $NH_3$ remains hydrogen bonded to $Cl-C_4N_3H_4$, aminolysis proceeds via transition structure (TS) **1b** with a sizable barrier of 158.8 kJ $mol^{-1}$. The addition of $OCH_2$ to $NH_3$ + $Cl-C_4N_3H_4$ (Figure 1b) forms complex **2a** lying 5.1 kJ $mol^{-1}$ lower in energy. As $OCH_2$ remains bound to the incoming $NH_3$ moiety by a short O···$HNH_2$ bond of 1.888 Å, aminolysis proceeds via transition structure (TS) **2b** with a barrier of 117.8 kJ $mol^{-1}$. Enlarging the base to $OHC-NH_2$ generates the initial complex **3a** lying 15.3 kJ $mol^{-1}$ lower in energy upon addition to $NH_3$ + $Cl-C_4N_3H_4$ (Figure 1c). Aminolysis of $Cl-C_4N_3H_4$ proceeds via TS **3b**, a barrier of 99.9 kJ $mol^{-1}$, in which $OHC-NH_2$ generates a noticeably shorter O···$HNH_2$ bond of 1.797 Å to the incoming $NH_3$ and forms an N···HN bond (1.930 Å) to $N_1$ of $Cl-C_4N_3H_4$. With OHC−NH−CHO as the base (Figure 1d), complex **4a** is generated lying 34.4 kJ $mol^{-1}$ lower in energy than $NH_3$ + $Cl-C_4N_3H_4$. As OHC−NH−CHO remains bound to $NH_3$ via an elongated O···$HNH_2$ bond (1.869 Å) and bound to $Cl-C_4N_3H_4$ by a shorter N···HN bond (1.725 Å) to $N_1$, aminolysis proceeds via TS **4b** with a noticeable increase in the barrier to 110.3 kJ $mol^{-1}$. Finally, the addition of 1-methyluracil to 2-amino-6-chloropyrimidine (Figure 1e) generates the initial complex **5a** lying 24.7 kJ $mol^{-1}$ lower in energy. Aminolysis proceeds via TS **5b** with a barrier of 103.6 kJ $mol^{-1}$ in which 1-methyluracil forms a short O···$HNH_2$ bond (1.809 Å) to $NH_3$, an elongated N···HN bond (1.792 Å) to $N_1$ of $Cl-C_4N_3H_4$, and an O···HNH bond (2.025 Å) with the amino group at $C_2$ of $Cl-C_4N_3H_4$. For the purpose of comparison, the addition of OCH−NH−HCO (Figure S2a) and 1-methyluracil (Figure S2b) to 6-chloropyrimidine ($NH_3$ + $Cl-C_4N_2H_3$) yields barriers to aminolysis of 100.8 and 95.2 kJ $mol^{-1}$, respectively.

The barriers to aminolysis for 2-amino-6-chloropyrimidine (Scheme 1a) and 6-chloropyrimidine (Scheme 1b) are summarized in Table 1. Relative to the aminolysis of 6-chloropyrimidine, the presence of the amino group in 2-amino-6-chloropyrimidine increases the barriers by 5.6 and 4.6 kJ $mol^{-1}$, for $OCH_2$ and $OHC-NH_2$, respectively. The presence of the electron-donating $NH_2$ group results in $C_6$, the carbon undergoing substitution, being less susceptible to nucleophilic attack by the incoming $NH_3$, and as a consequence, the C···Cl distance in the transition structures is elongated by ~0.02 Å. Enlarging the model base to OHC−NH−CHO, which forms a third hydrogen bond in the aminolysis of 2-amino-6-chloropyrimidine, leads to a barrier 9.5 kJ $mol^{-1}$ larger than that observed in the aminolysis of 6-chloropyrimidine. Due to the formation of the third hydrogen bond, the electron donating ability of $-NH_2$ is further enhanced, resulting in an additional decrease in the electrophilicity of the C undergoing substitution. The addition of 1-methyluracil to 2-amino-6-chloropyrimidine exhibits a similar effect with a barrier to aminolysis that is 8.4 kJ $mol^{-1}$ larger than that observed for 6-chloropyrimidine. Thus, the absence of a decrease in the barrier to aminolysis for 2-amino-6-chloropyrimidine and the minor changes in the transition structure geometry indicate that the third hydrogen bond does not play a catalytic role in the aminolysis reaction. However, the partial double bond character of the $C-NH_2$ bond provides a more rigid framework upon which the aminolysis reactions may proceed.

Closer examination of the aminolysis of 6-chloropyrimidine reveals a correlation between the barriers to aminolysis and the

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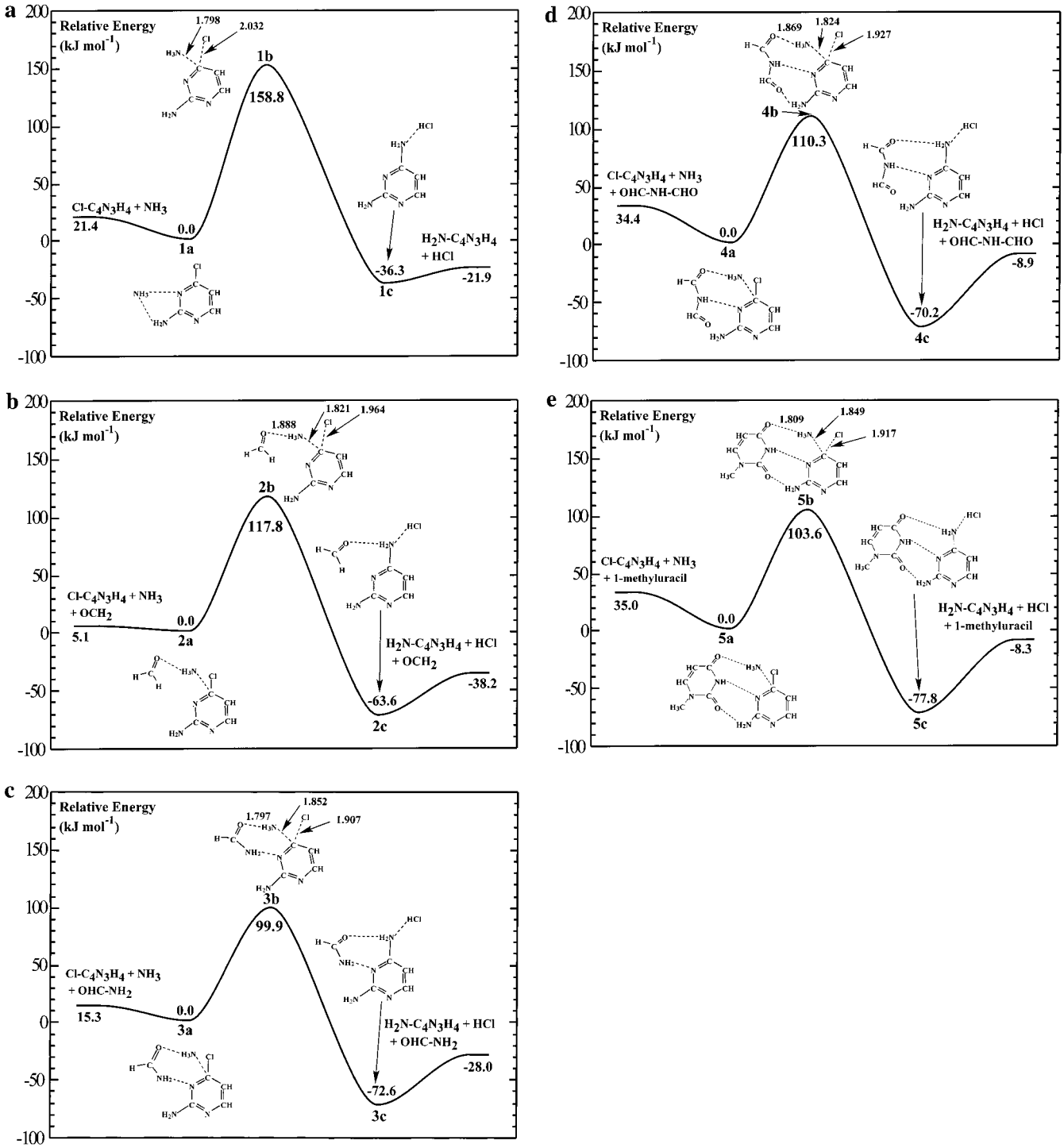


**Figure 1.** (a) Schematic energy profile for the aminolysis of 2-amino-6-chloropyrimidine with (b) $OCH_2$ hydrogen bonded to the incoming $NH_3$ moiety (see text). (c) $OHC-NH_2$ hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text). (d) OHC−NH−CHO hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text). (e) 1-Methyluracil hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text).

$O\cdots HNH_2$ hydrogen bond distance, a consequence of the proton affinity (PA) of the carbonyl group of the base involved in hydrogen bonding to $NH_3$. In Table 2, the proton affinities of the uracil-derived bases are summarized. For the aminolysis of 6-chloropyrimidine, the barrier to aminolysis decreases from 112.2 kJ $mol^{-1}$ for $OCH_2$ to 100.8 and 95.3 kJ $mol^{-1}$ for the addition of OHC−NH−CHO and $OHC-NH_2$, respectively. For these three bases, the decrease in the barrier to aminolysis of 6-chloropyrimidine is correlated with an increase in the PA of the terminal carbonyl group interacting with $NH_3$, as is evident by the decrease in the $O\cdots HNH_2$ distance from 1.876 Å[12] to 1.839 and 1.766 Å.[12] As expected, a further decrease in the barrier to aminolysis is attained by the use of 1-methyluracil, which has the largest PA of the bases examined. However, there is a slight increase in the $O\cdots HNH_2$ distance (1.787 Å), a consequence of the electron-donating influence of the methyl group.

The same qualitative trends are evident for the aminolysis of 2-amino-6-chloropyrimidine. The barrier to aminolysis (and the $O\cdots HNH_2$ distances) decreases from 117.8 kJ $mol^{-1}$ (1.888 Å) for $OCH_2$ to 110.3 kJ $mol^{-1}$ (1.869 Å) and 99.9 kJ $mol^{-1}$ (1.797 Å) for OHC−NH−CHO and $OHC-NH_2$, respectively. The

**Table 1.** Summary of the Barriers to Aminolysis (kJ mol$^{-1}$) Involving the Uracil-Derived Bases

| | $NH_3 + Cl-C_4N_3H_4$ | $NH_3 + Cl-C_4N_2H_3$ | | |
|---|---|---|---|---|
| base | X = O | X = O | X = S | X = NH |
| uncatalyzed | 158.8 | 138.1 | | |
| **X**$CH_2$ | 117.8 | 112.2 | 117.8 | 107.6 |
| **X**HC-$NH_2$ | 99.9 | 95.3 | 102.6 | 90.6 |
| **X**HC-NH-CHHO | 110.3 | 100.8 | 106.9 | 98.3 |
| 1-methyluracil | 103.6 | 95.2 | | |
| **X**CHF | | 117.1 | | |
| **X**FC-$NH_2$ | | 100.9 | | |
| **X**FC-NH-CHO | | 105.3 | | |

**Table 2.** Calculated[a] Proton Affinities (kJ mol$^{-1}$) of the Carbonyl Oxygens in the Uracil-Derived Bases

| | proton affinities | | |
|---|---|---|---|
| base | X = O | X = S | X = NH |
| **X**$CH_2$ | 700.9 | 763.6 | 861.9 |
| **X**HC−NH−CHO | 789.9 | 801.8 | 896.2 |
| **X**HC−$NH_2$ | 808.5 | 850.6 | 945.8 |
| 1-methyluracil[b] | 861.5 | | |
| 1-methyluracil[c] | 831.2 | | |
| **X**CHF | 646.8 | | |
| **X**FC−NH−CHO | 701.1 | | |
| **X**FC−$NH_2$ | 743.7 | | |

[a] See theoretical methods. [b] Carbonyl oxygen that interacts with the incoming $NH_3$. [c] Carbonyl oxygen that interacts with $-NH_2$ on 2-amino-6-chloropyrimidine.

addition of 1-methyluracil to 2-amino-6-chloropyrimidine marginally increases the aminolysis barrier by 3.7 kJ mol$^{-1}$ (103.6 kJ mol$^{-1}$), whereas there is no effect for the corresponding aminolysis of 6-chloropyrimidine. In this instance, the PA of the carbonyl group of 1-methyluracil interacting with $-NH_2$ of 2-amino-6-chloropyrimidine is larger than that associated with the corresponding group in OHC−NH−CHO (Table 2). Thus, utilizing 1-methyluracil as the base in the aminolysis enhances the electron density in the pyrimidine ring to a greater degree than that observed when OHC−NH−CHO acts as the base. While the carbonyl group in 1-methyluracil (which interacts with $NH_3$) has the largest PA of the molecules examined, it is insufficient to compensate for the decreased electrophilicity of the C at which substitution occurs. Thus, while the general trend in barriers to aminolysis is consistent with the PA of the terminal group interacting with $NH_3$, the electronic effect associated with the formation of the third hydrogen bond in the aminolysis of 2-amino-6-chloropyrimidine must also be considered.

Thus, the barriers to aminolysis of 6-chloropyrimidine correlate with the PA of the carbonyl oxygen of the base that hydrogen bonds with the incoming $NH_3$ moiety. This correlation is also prevalent for the aminolysis of 2-amino-6-chloropyrimidine although geometrical factors must be considered. Since the formation of the third hydrogen bond does not catalyze the aminolysis reaction, the model reaction of 6-chloropyrimidine was employed to further examine the correlation between the PA of the portion of the base that hydrogen bonds to the incoming $NH_3$ and the calculated barrier to aminolysis. To provide a range of PAs, derivatives of the carbonyl bases were examined in which the PA of the carbonyl-derived group was modified by fluorine substitution, which decreases the PA of the carbonyl oxygen, and by imine substitution, which leads to a larger PA.

**Fluorine Substitution.** Replacement of the H adjacent to the carbonyl group of the three smallest bases involved in hydrogen bonding to the $NH_3$ moiety by an electron-withdrawing fluorine yields OCHF, OFC−$NH_2$, and OFC−NH−CHO. Addition of

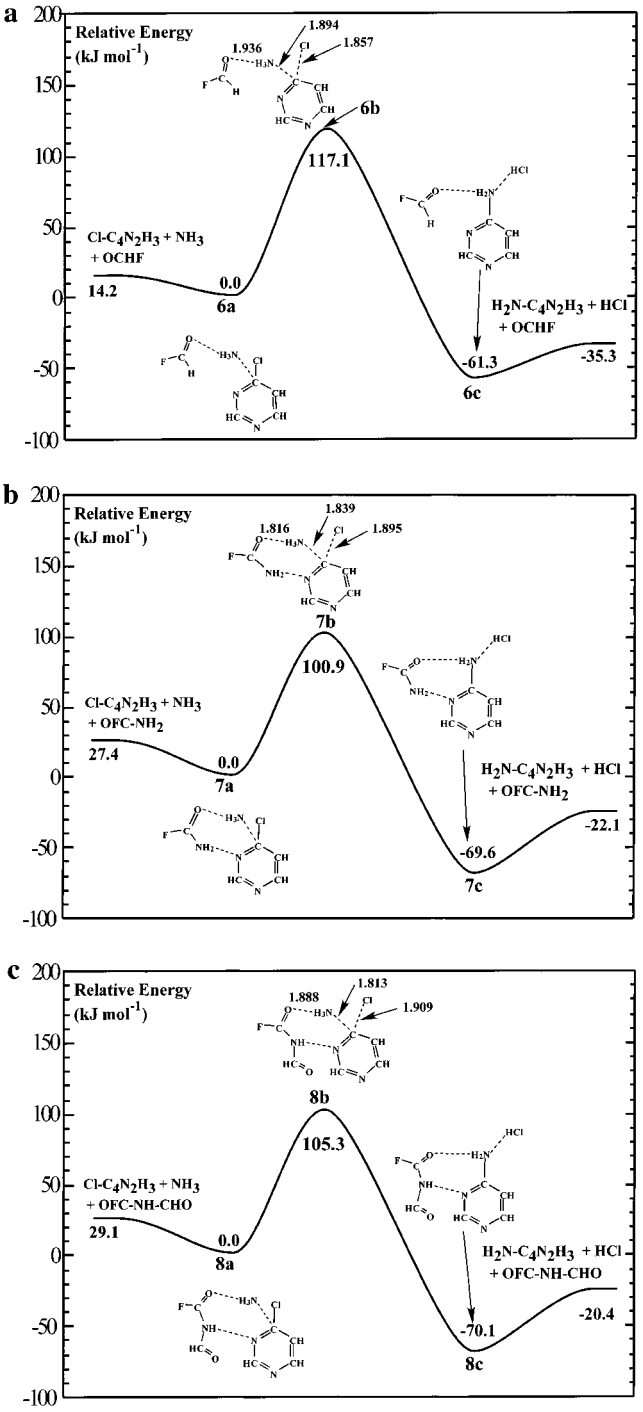


**Figure 2.** Schematic energy profile for the aminolysis of 6-chloropyrimidine with (a) OCHF hydrogen bonded to the incoming $NH_3$ moiety (see text), (b) OFC−$NH_2$ hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text), and (c) OFC−NH−CHO hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text).

OCHF to $NH_3$ + Cl−$C_4N_2H_3$ (Figure 2a) generates complex **6a** lying 14.2 kJ mol$^{-1}$ lower in energy. Aminolysis proceeds via TS **6b** with a barrier of 117.1 kJ mol$^{-1}$ and a long O···$HNH_2$ bond of 1.936 Å. With OFC−$NH_2$ as the base, complex **7a** is generated lying 27.4 kJ mol$^{-1}$ lower in energy upon addition to $NH_3$ + Cl−$C_4N_2H_3$ (Figure 2b). Aminolysis proceeds via TS **7b** with a reduced barrier of 100.9 kJ mol$^{-1}$ and a significantly shorter O···$HNH_2$ bond of 1.816 Å. Addition of OFC−NH−CHO to $NH_3$ + Cl−$C_4N_2H_3$ (Figure 2c) generates complex **8a** lying 29.1 kJ mol$^{-1}$ lower in energy. Ami-

nolysis proceeds via TS **8b** with a barrier of 105.3 kJ mol$^{-1}$ and an O···$HNH_2$ bond of 1.888 Å.

For the fluorine-derived bases, the barrier to aminolysis of 6-chloropyrimidine decreases in the sequence OCHF, OFC−NH−CHO, and OFC−$NH_2$. As summarized in Table 2, this decrease in barrier height is associated with the increase in the PA of the terminal oxygen that interacts with $NH_3$. As observed for the uracil-derived bases, increasing the PA of the terminal oxygen shortens the O···$HNH_2$ distance of the transition structures from 1.936 Å for OCHF to 1.888 Å for OFC−NH−CHO and to 1.816 Å for OFC−$NH_2$. As the PA of the fluoro-substituted uracil bases is lower than that of unsubstituted uracil-derived bases, it follows that the barrier to aminolysis is larger by ∼5 kJ mol$^{-1}$ and the O···$HNH_2$ distances are longer by ∼0.05 Å.

**Imine Substitution.** Due to the abundance of nitrogen-containing species in biological systems and the evidence that the nitrogen in the imine group is a better proton acceptor than the carbonyl oxygen,[21] and hence has a larger PA, the aminolysis of Scheme 1b was reexamined with the carbonyl oxygen replaced by an imine group to produce the bases $HNCH_2$, HNCH−$NH_2$, and HNCH−NH−HCO. The addition of $HNCH_2$ to $NH_3$ + Cl−$C_4N_2H_3$ (Figure 3a) generates complex **9a** lying 10.7 kJ mol$^{-1}$ lower in energy. As $HNCH_2$ remains bound to $NH_3$ by a short N···$HNH_2$ bond of 1.878 Å, aminolysis proceeds via TS **9b** with a barrier of 107.6 kJ mol$^{-1}$. Utilizing HNCH−$NH_2$ as the base in the aminolysis of $NH_3$ + Cl−$C_4N_2H_3$ (Figure 3b) produces complex **10a** lying 21.5 kJ mol$^{-1}$ lower in energy. Aminolysis proceeds via TS **10b** with a barrier of 90.6 kJ mol$^{-1}$ and a shorter N···$HNH_2$ bond of 1.800 Å. Finally, the addition of HNCH−NH−HCO to $NH_3$ + Cl−$C_4N_2H_3$ (Figure 3c) produces complex **11a** lying 22.5 kJ mol$^{-1}$ lower in energy. Aminolysis of $NH_3$ + Cl−$C_4N_2H_3$ proceeds with a barrier of 98.3 kJ mol$^{-1}$ and an N···$HNH_2$ distance of 1.875 Å in TS **11b**.

Thus, the barrier to aminolysis is reduced from 107.6 kJ mol$^{-1}$ when $HNCH_2$ is used as the base in the reaction of 6-chloropyrimidine to 98.3 and 90.6 kJ mol$^{-1}$ with NHCH−NH−HCO and HNCH−$NH_2$, respectively. As the barrier decreases, the N···$HNH_2$ distance shortens from 1.878 Å with $HNCH_2$ as the base to 1.875 and 1.800 Å with NHCH−NH−HCO and HNCH−$NH_2$, respectively. The shortening of the N···$HNH_2$ distances is consistent with a sequential increase in the PA associated with the imine that interacts with $NH_3$ (Table 2). This is the same trend as that observed for the uracil- and fluorine-derived bases examined in the aminolysis of 6-chloropyrimidine and provides a range of behavior between the small PAs associated with the fluorine-derived bases and the high PAs of the imine-derived bases.

**Sulfur Substitution.** Sulfur may act as a hydrogen bond acceptor and is known to replace oxygen in this function. However, due to its larger size, sulfur is expected to act as a weaker hydrogen bond acceptor than oxygen. To determine if the correlation between the PA of the base that interacts with $NH_3$ and the barrier to aminolysis is maintained as the carbonyl-oxygen of the base is replaced by sulfur, the aminolysis of 6-chloropyrimidine (Scheme 1b) was examined with $SCH_2$, SCH−$NH_2$, and SCH−NH−HCO as bases.

The aminolysis of 6-chloropyrimidine with $SCH_2$ as the base proceeds via TS **12b** (Figure S2a) with a barrier of 117.8 kJ mol$^{-1}$ and an S···$HNH_2$ bond of 2.442 Å. The PA of the thioketo group is increased upon enlarging the base to SCH−$NH_2$ (Figure S2b) and the aminolysis proceeds via TS **13b** with a notably reduced barrier of 102.6 kJ mol$^{-1}$ and a shortened S···$HNH_2$ bond (2.335 Å). As the base is enlarged further to SCH−NH−HCO, which has a lower PA than that observed for SCH−$NH_2$, the aminolysis of 6-chloropyrimdine (Figure S2c) proceeds via TS **14b** with a slightly larger barrier of 106.9 kJ mol$^{-1}$ and an elongation of the S···$HNH_2$ bond by 0.053 Å (2.388 Å). While the PAs of the thioketo bases (Table 2) are intermediate between those of the carbonyl- and the imine-

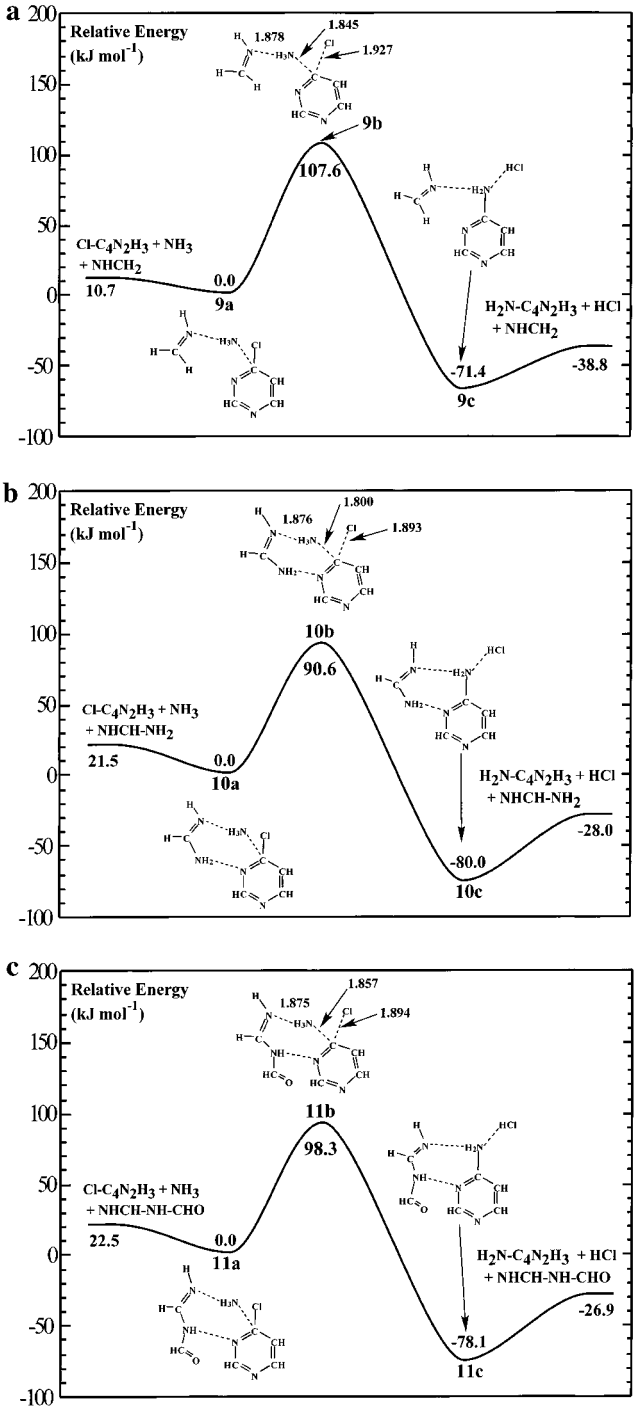


**Figure 3.** Schematic energy profile for the aminolysis of 6-chloropyrimidine with (a) $HNCH_2$ hydrogen bonded to the incoming $NH_3$ moiety (see text), (b) HNCH−$NH_2$ hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text), and (c) HNCH−NH−CHO hydrogen bonded to both the incoming $NH_3$ moiety and the pyrimidine ring (see text).

(21) Scheiner, S. *Hydrogen Bonding: A Theoretical Perspective*; Oxford University Press: New York, 1997.

derived bases, the barriers are slightly larger than those reported for the aminolysis of 6-chloropyrimidine employing $OCH_2$, $OCH-NH_2$, and OCH−NH−HCO as bases. The larger size of the sulfur atom results in an elongation of the $S\cdots HNH_2$ bond to the incoming $NH_3$, and as such, hydrogen bonding does not enhance the electron-donating ability of $NH_3$ to the same degree as was observed for the uracil-derived bases. Nonetheless, the correlation between the PA of the terminal thioketo group that hydrogen bonds to $NH_3$ and the barrier heights is evident.

## Conclusions

The aminolysis of 6-chloropyrimidine and 2-amino-6-chloropyrimdine has been investigated by density functional theory calculations. Comparison of the barriers for aminolysis of 6-chloropyrimidine to those calculated for the aminolysis of 2-amino-6-chloropyrimidine reveals that the presence of the $-NH_2$ group enhances the electron density in the pyrimidine ring which in turn diminishes the electrophilicity associated with the C at which substitution occurs. While the formation of the third hydrogen bond does not act as a catalyst in the reaction, it does provide a more rigid skeleton upon which the aminolysis reaction may proceed.

Closer examination of the aforementioned aminolysis reactions has revealed a correlation between the observed barrier and the proton affinity of the carbonyl group of the base that forms the $O\cdots HNH_2$ hydrogen bond to the incoming $NH_3$ group. To further investigate the correlation between the PA of the base interacting with the $NH_3$ and the barrier to aminolysis, the chemical nature of the proton acceptor, i.e., the base, was altered. Replacement of the H adjacent to the carbonyl group by a fluorine atom decreases the calculated PA of the proton acceptor relative to that observed for the nonsubstituted bases and, hence, increases the barrier to aminolysis of 6-chloropyrimidine. Similarly, the imine derivatives of the carbonyl bases have larger PAs than the carbonyl-derived bases and therefore decrease the barrier to aminolysis. While the results for the fluorine- and imine-derived bases provide evidence for the important role of the proton acceptor, thioketo substitution was also examined to extend the scope of the study. Although the sulfur-derived bases possess a proton affinity intermediate between the carbonyl- and fluoro-derived bases, they generate elongated bonds to $NH_3$ which is reflected in the aminolysis barrier of 6-chloropyrimidine being slightly larger than that observed for the uracil-derived species.

Thus, the aminolysis of 6-chloropyrimidine and 2-amino-6-chloropyrimidine illustrates the ability of the functional groups in uracil to catalyze the reaction by the formation of multiple hydrogen bonds, which stabilize the transition structures. Thus the aminolysis reaction provides a clear example of the catalytic possibilities associated with the formation of multiple hydrogen bonds and illustrates the importance and flexibility associated with a well-chosen hydrogen bond acceptor.

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**Supporting Information Available:** Archive entries of the B3-LYP/6-31G(d,p) optimized structures (Table S1), total electronic energies of all species in the study (Table S2), schematic energy profiles for the aminolysis of 6-chloropyrimidine with OCH−NH−HCO and 1-methyluracil as bases (Figure S1, parts a and b, respectively), schematic energy profiles for the sulfur-derived bases (Figure S2a−c) and charges on the heavy atoms in the various transition structures from Mulliken population analyses (Figure S3) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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