Catalysis Mediated by Hydrogen Bonding: A Computational Study of the Aminolysis of 6-Chloropyrimidine

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Received February 22, 2000. Revised Manuscript Received April 13, 2000

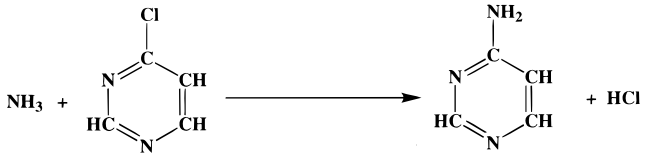
Abstract: Density functional theory has been employed to investigate the effects of hydrogen bonding on the aminolysis of 6-chloropyrimidine, i.e., the reaction of NH_3 with 6-chloropyrimidine to give HCl and 6-aminopyrimidine. The isolated aminolysis of 6-chloropyrimidine requires 138.1 kJ mol^{-1}. If the electron-donating species H_2CO is hydrogen bonded to the NH_3 moiety during aminolysis, the barrier is reduced to 112.2 kJ mol^{-1}. When H_2NCHO is added to NH_3 + 6-chloropyrimidine, the electron-donating −CHO group is able to hydrogen bond to the NH_3 moiety while the electron-accepting $-NH_2$ group hydrogen bonds to the N of the pyrimidine ring that is adjacent to the carbon at which substitution occurs. This results in the barrier to aminolysis of 6-chloropyrimidine being reduced to 95.3 kJ mol^{-1}. Thus, the aminolysis of 6-chloropyrimidine, as mediated by hydrogen bonding, provides a clear and simple example of the catalytic possibilities of well-chosen hydrogen bonding.

Introduction

The use of hydrogen bonds in enzymes and supramolecular chemistry to bind substrates in favorable reaction positions and to stabilize reaction intermediates and transition structures, thus assisting in accelerating reactions, is now well established.[1−9] It has also been suggested that hydrogen bonds may in fact be able to "activate" some species, thus enhancing their reactivity.[10] Recently, Tominaga, Konishi, and Aida[11] reported the catalysis of aminolysis of 6-chloropurine and related species by derivatives of the nucleobase uracil. The reactions were performed in the nonpolar solvent, benzene. This catalytic behavior was proposed to occur as a result of multiple hydrogen-bonding interactions between the uracils and 6-chloropurine derivatives, giving rise to a reactive intermediate and possible stabilization of the transition structure.

In this present study, density functional theory is employed to provide a rationalization for the role of the hydrogen-bonding interactions, by considering the model reaction: aminolysis of 6-chloropyrimidine, Scheme 1. Possible solvent effects have also been considered.

Scheme 1. Schematic Illustration of the Aminolysis of 6-Chloropyrimidine



Computational Methods

Density functional theory calculations were carried out using the Gaussian 98[12] suite of programs. The B3 exchange functional,[13,14] as implemented in GAUSSIAN 98,[15] was used in combination with the correlation functional of Lee, Yang, and Parr (LYP).[16] Optimized geometries[17] were obtained using the B3-LYP functional in conjunction with the 6-31G(d,p) basis set. Harmonic vibrational frequencies and zero-point vibrational energy (ZPVE) corrections were also calculated at this level of theory. Relative energies were calculated by performing single point energy calculations at the B3-LYP/6-311+G(2df,p) level

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(17) Optimized geometries and relative energies, for the species involved in both the "isolated" aminolysis mechanism and that involving H_2CO, were also obtained at the MP2/6-31G(d,p) level of theory. The structures and relative energetics obtained are similar to those obtained at the B3-LYP/6-31G(d,p) level.

10.1021/ja000628+ CCC: $19.00
Published on Web 05/20/2000

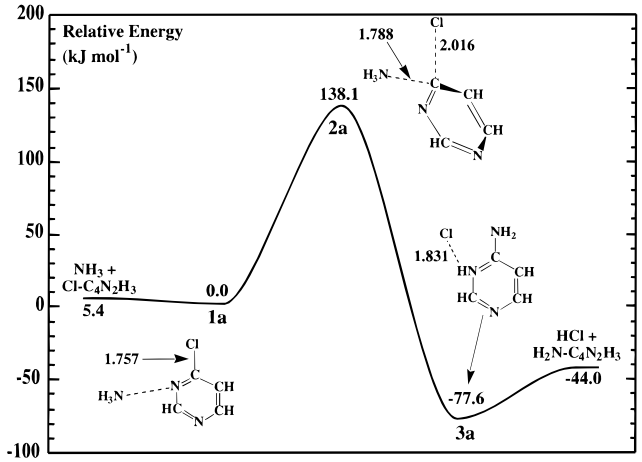

Figure 1. Schematic energy profile for the "isolated" aminolysis of 6-chloropyrimidine (see text).

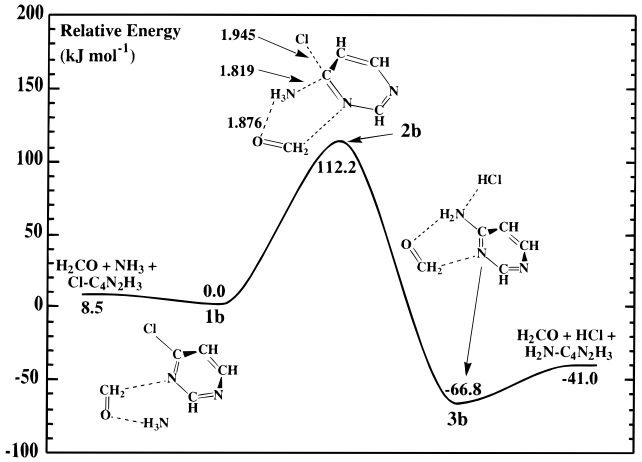

Figure 2. Schematic energy profile for aminolysis of 6-chloropyrimidine, with H_2CO hydrogen bonded to the NH_3 moiety (see text).

using the above geometries and corrected with the appropriate ZPVE, i.e., B3-LYP/6-311+G(2df,p)//B3-LYP/6-31G(d,p) + ZPVE. All bond lengths are in angstroms (Å) unless otherwise specified. Optimized structures and charges on atoms in the various transition structures (from Mulliken population analyses) are given in Table S1 and Figure S1, respectively, of the Supporting Information.

The effects of the solvent on the aminolysis reactions were investigated using the Onsager model.[18] Two solvents were considered: benzene with a dielectric constant of 2.28, and water with a dielectric constant of 78.34. The results are summarized in Figures S2 and S3, respectively, of the Supporting Information.

Results and Discussion

The "isolated" aminolysis of 6-chloropyrimidine (hereafter denoted by $Cl-C_4N_2H_3$) is shown schematically in Figure 1. Initially, the reactants, $NH_3 + Cl-C_4N_2H_3$, can form hydrogen-bonded complex **1a**, lying just 5.4 kJ mol^{-1} lower in energy. Aminolysis can then proceed via **2a** with a sizable barrier of approximately 138.1 kJ mol^{-1}, to eventually give $HCl + H_2N-C_4N_2H_3$. The C···Cl and C···NH_3 distances in **2a** (see Figure 1) are 2.016 and 1.788 Å, respectively.

Based on the hydrogen-bonding motif of uracil, the effect on the above aminolysis reaction (see Scheme 1) of adding H_2CO or H_2N-CHO was considered.

Addition of H_2CO, an electron-donating species, to $NH_3 + Cl-C_4N_2H_3$ (Figure 2) forms complex **1b**, lying approximately 8.5 kJ mol^{-1} lower in energy. If H_2CO remains bound to NH_3 via an O···H−N hydrogen bond, aminolysis of $Cl-C_4N_2H_3$ can proceed via **2b** at a cost of 112.2 kJ mol^{-1}, i.e., the barrier is 25.9 kJ mol^{-1} less than that of the isolated system. From Figure 2 one can see that in **2b** the C···Cl bond (1.945 Å) is shorter, while the C···NH_3 bond (1.819 Å) is longer than that calculated for **2a** (2.016 and 1.788 Å, respectively). The H_2CO···HNH_2 hydrogen bond in **2b** is remarkably strong with a quite short O···H length of approximately 1.876 Å. We also note that in **2b**, the charges on the leaving Cl and incoming N are smaller in magnitude than those found in **2a** (Figure S1). This suggests that if H_2CO is hydrogen bonded to the NH_3 moiety, the transition structure for aminolysis occurs earlier, i.e., the electron-donating ability of N of the NH_3 moiety is enhanced by hydrogen bonding to H_2CO.

The H_2NCHO moiety contains both electron-donating (−CHO) and electron-accepting ($-NH_2$) groups. H_2NCHO interacts with $NH_3 + Cl-C_4N_2H_3$ (Figure 3) to form complex **1c**, which lies

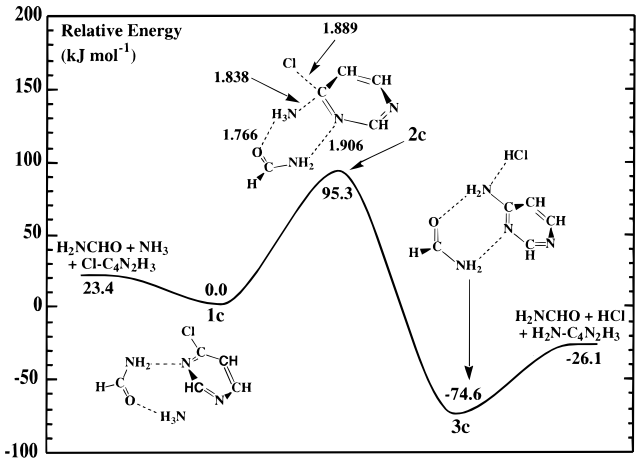

Figure 3. Schematic energy profile for aminolysis of 6-chloropyrimidine, with H_2NCHO hydrogen bonded to both the NH_3 moiety and the pyrimidine ring (see text).

lower by 23.4 kJ mol^{-1}. Aminolysis of $Cl-C_4N_2H_3$ is then able to proceed via **2c** with a substantially reduced barrier of just 95.3 kJ mol^{-1}. In **2c**, H_2NCHO is hydrogen bonded to *both* the incoming NH_3 moiety, via a short and strong O···HN bond (1.766 Å), and to N of the pyrimidine ring, by a short NH···N bond (1.906 Å), see Figure 3. In **2c**, the C···Cl distance is shorter (1.889 Å) while the C···NH_3 bond (1.838 Å) is longer than that found in **2b**, i.e., when H_2NCHO is used the transition structure occurs even earlier than when H_2CO is used (see above). Within **2c** we note that the magnitude of the charges of the leaving Cl and incoming N are smaller than those observed in **2b** and **2a** (Figure S1). Thus, the electron-donating −CHO group promotes the electron-donating ability of N of the incoming NH_3 moiety while, simultaneously, the electron-accepting $-NH_2$ group stabilizes the negative charge of the N in the pyrimidine ring that is adjacent to the carbon at which substitution is occurring.

As previously mentioned, Tominaga and co-workers[11] observed the catalytic behavior of uracils in benzene. Inclusion of the effects of the solvent benzene on the above aminolysis reactions by use of the Onsager model[18] results in only minor decreases in the reaction barriers of less than 1 kJ mol^{-1}, see Figure S2. The reaction barriers are decreased to a larger extent when the polar solvent water is used. However, this decrease is still only of the order of 1 to 2 kJ mol^{-1}, see Figure S3. Thus, the effect of the solvent on the barrier to aminolysis is much

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less than that due to specific hydrogen-bonding interactions between the uracil, 6-chloropyrimidine, and ammonia.

Conclusions

The aminolysis of 6-chloropyrimidine has been investigated by use of the density functional theory method B3-LYP.

The "isolated" aminolysis of 6-chloropyrimidine, i.e., without any additional neutral hydrogen-bonding moiety present, is found to proceed with a barrier of 138.1 kJ mol^{-1}. When the electron-donating moiety H_2CO is included, it is able to form a strong hydrogen bond with the incoming NH_3 moiety. The barrier for aminolysis is calculated to be lowered to 112.2 kJ mol^{-1}. When the H_2NCHO moiety is included, it is able to hdyrogen bond to both the incoming NH_3 moiety and to the pyrimidine ring nitrogen adjacent to the carbon at which substitution occurs. The barrier is found to be lowered further to just 95.3 kJ mol^{-1}.

Solvent effects have also been considered by use of the Onsager model. When the nonpolar solvent benzene is used, the barriers for aminolysis are found to be lowered only marginally by less than 1 kJ mol^{-1}. When the polar solvent water is considered, the barriers for aminolysis are lowered by 1 to 2 kJ mol^{-1}. These effects are much less than those observed due to the specific strong hydrogen-bonding interactions noted above.

Thus, the aminolysis of 6-chloropyrimidine, as catalyzed by the hydrogen-bonding moieties H_2CO and H_2NCHO, provides a simple and clear example by which to illustrate the catalytic possibilites of hydrogen bonds.

Acknowledgment. We gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Killam Trusts for financial support.

Supporting Information Available: Archive entries of the B3-LYP/6-31G(d,p) optimized structures (Table S1), charges on heavy atoms in the various transition structures from Mulliken population analyses (Figure S1), and schematic potential energy surfaces illustrating the effects of the solvents benzene and water on each of the aminolysis reactions considered (Figures S2 and S3, respectively) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000628+