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Computational Study of the Aminolysis of Esters. The Reaction of Methylformate with Ammonia

Sonia Ilieva,[†] Boris Galabov,[†] Djamaladdin G. Musaev,[‡] Keiji Morokuma,[‡] and Henry F. Schaefer III*,[§]

Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria, Emerson Center for Scientific Computations and Department of Chemistry, Emory University, Atlanta, Georgia 30322, and Center for Computational Quantum Chemistry, University of Georgia, Athens, Georgia 30602

hfsiii@uga.edu

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The aminolysis of esters is a basic organic reaction considered as a model for the interaction of carbonyl group with nucleophiles. In the present computational study the different possible mechanistic pathways of the reaction are reinvestigated by applying higher level electronic structure theory, examining the general base catalysis by the nucleophile, and a more comprehensive study the solvent effect. Both the ab initio QCISD/6-31(d,p) method and density functional theory at the B3LYP/6-31G(d) level were employed to calculate the reaction pathways for the simplest model aminolysis reaction between methylformate and ammonia. Solvent effects were assessed by the PCM method. The results show that in the case of noncatalyzed aminolysis the addition/elimination stepwise mechanism involving two transition states and the concerted mechanism have very similar activation energies. However, in the case of catalyzed aminolysis by a second ammonia molecule the stepwise mechanism has a distinctly lower activation energy. All transition states in the catalyzed aminolysis are 10−17 kcal/mol lower than those for the uncatalyzed process.

Introduction

The aminolysis of esters is a basic organic reaction considered as a model for the interaction of carbonyl group with nucleophiles. The process can be studied easily by kinetic methods since for many pairs of reagents it can take place with sufficient rate at ambient temperature. The reaction can also be viewed as a model process for the formation of peptide bonds. There are numerous kinetic and mechanistic studies on the ester aminolysis.[1−11] The rich kinetic data form a solid basis for studying the mechanism of this reaction. In the absence of experimental data concerning the structure of reaction intermediates and transition states, several possible reaction paths have been discussed, all of which conform to the available kinetic results. Three principle schemes have been considered:[12] (a) a stepwise mechanism through zwitterionic intermediates; (b) a stepwise path through neutral intermediates; and (c) a concerted pathway involving simultaneous cleavage of the C−O single bond and formation of a C−N bond. The catalytic influences of solvents such as water and general base catalysis by the amine as well as the overall influence of the media have also been studied.[2,5] It has been shown that in aqueous solution the ester aminolysis proceeds predominantly by a general base-catalyzed attack of free amine.[2,4]

The selection between the different possibilities for the mechanism of the reaction became possible only after theoretical studies of the reaction by applying semiempirical and ab initio electronic structure theory.[12−16] Yang and Drueckhammer studied[12] the aminolysis of ethyl thioacetate by applying molecular orbital calculations. Their results support a stepwise mechanism through neutral intermediates involving water-catalyzed proton transfer. Transition states initially found through AM1 computations were reoptimized by HF/6-31+G(d) computations. The energy profiles for aminolysis reactions of ethyl acetate and ethyl thioacetate have been obtained at MP2/6-31+G(d) and MP2/6-31G(d,p) levels of theory. Notably, the theoretical results showed similar values for the energy of the transition states for the stepwise and the concerted pathways. More pronounced differences in TS energies for the two schemes were obtained after considering a specific catalytic role for the water solvent.

[†] University of Sofia.
[‡] Emory University.
[§] University of Georgia.

(1) Bunnett, J. F.; Davis, G. T. *J. Am. Chem. Soc.* **1960**, *82*, 665.
(2) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 675.
(3) Bruice, T. C.; Mayahi, M. F. *J. Am. Chem. Soc.* **1960**, *82*, 3067.
(4) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638.
(5) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1966**, *88*, 104.
(6) Bruice, T. C.; Donzel, A.; Huffman, R. W.; Butler, A. R. *J. Am. Chem. Soc.* **1967**, *89*, 2106.
(7) Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1973**, *95*, 4452.
(8) Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 2473.
(9) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin Inc.: New York, 1966; Vol. 1.
(10) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.
(11) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387.
(12) Yang, W.; Drueckhammer, D. G. *Org. Lett.* **2000**, *2*, 4133.
(13) O'Hair, R. A. J.; Androutsopoulos, N. K. *Org. Lett.* **2000**, *2*, 2567.
(14) Kim, C. K.; Li, H. G.; Lee, H. W.; Sohn, C. K.; Chun, Y. I.; Lee, I. *J. Phys. Chem. A* **2000**, *104*, 104.
(15) Zipse, H.; Wang, L.; Houk, K. N. *Liebigs Ann.* **1996**, 1511.
(16) Wang, L.; Zipse, H. *Liebigs Ann.* **1996**, 1501.

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In earlier works Zipse, Wang, and Houk[15,16] studied the mechanism of the reaction of methyl acetate with methylamine by applying HF/3-21G and HF/6-31G(d,p) computations. Single point MP2/6-31G(d,p) energies were obtained for the established transition states and intermediates. The results favor a stepwise addition/elimination pathway over the direct substitution mechanism.[17]

Houk and co-workers[15] also evaluated the effects of catalysts on the energy profile of the reaction. The authors found that the difference in energies for the transition states along the two alternative pathways considered is minimal. The predicted energy for the transition state of the concerted mechanism was 42.1 kcal/mol at the HF/6-31G(d,p) level of computations and 41.8 kcal/mol for the stepwise mechanism. Results for several other model esters were also reported.

A fully stepwise pathway through zwitterionic intermediates has also been studied theoretically. Oie et al.[17] and Zipse at al.[15] did not find transition states associated with zwitterionic intermediates. MP2/6-31G(d,p) ab initio computations carried out by some of the present authors for the reaction of methylformate and methylamine also failed to identify zwitterionic transition states and intermediates.[18] A very shallow minimum is obtained if two explicit water molecules are added to stabilize the zwitterionic intermediate. Singleton and Merrigan[19] studied in detail the formation of a zwitterion between methylformate and ammonia and hydrazine in water medium applying density functional theory at the B3LYP/6-31G(d,p) level. They calculated various solvated structures involving from four to eleven explicit water molecules. No effort was made to find global minima for these structures. The focus of the study of Singleton and Merrigan[19] was explaining the kinetic isotope effect data for the aminolysis reaction, obtained earlier by Marlier et al.[20]

Thus the literature survey shows that the reaction pathways treated in most details—the stepwise addition/elimination and the concerted mechanisms—have quite similar energetic characteristics. The present computational study aims at reinvestigating the possible mechanistic pathways for the ester aminolysis reaction by applying higher levels of electronic structure theory and a more comprehensive study of the solvent effects. The general base catalysis of the reaction by the amine is also considered. The model reaction of methylformate and ammonia is studied in the gas phase and the influence of the aprotic organic solvent acetonitrile on the energy of all critical structures is assessed.

Computational Methods

The computations were carried out with the Gaussian 98 program package.[21] The theoretical calculations were performed at the B3LYP/6-31G(d) and QCISD/6-31G(d,p) levels of theory. Stable structures and transition states were fully optimized at the B3LYP/6-31G(d) level of theory. All critical points were further characterized by analytic computations of harmonic vibrational frequencies at the same level/basis set. Transition states were located by using the Synchronous Transit-guided Quasi-Newton (STQN) methods, implemented in the Gaussian program by Schlegel et al.[22,23] Following this stage the structures were fully optimized at the B3LYP/6-31G(d) level by traditional transition state optimization, using the Berny algorithm[22] with the application of the read FC option for specifying curvature information. All transition structures were checked by intrinsic reaction coordinate (IRC) computations[24] at the same level of theory.

A full optimization of all stable structures and transition states was also performed at a higher level of electronic structure theory—QCISD/6-31G(d,p)—for a more accurate estimation of the energies of the structures along the reaction paths studied.

The effects of solvent were predicted by using the Polarized Continuum Model (PCM) incorporated in the Gaussian 98 package.[25,26] PCM B3LYP/6-31G(d) optimization calculations were performed for estimating the change in energetics of the reaction in the presence of the neutral aprotic solvent acetonitrile. The standard dielectric constant of acetonitrile implemented in the Gaussian program was employed.

Results and Discussion

Uncatalyzed Aminolysis. As already discussed the experimental and theoretical results accumulated so far establish the two most likely schemes for the aminolysis reaction: the concerted and neutral stepwise mechanisms. These two possibilities were explored here for the reaction of methylformate with ammonia. The manner of the attack is different in these two cases. For the concerted pathway the reaction consists of one step, in which all bond-forming and -breaking processes occur in concert. The nucleophilic ammonia molecule attaches to the eletrophilic carbon atom from the ester, and a proton transfer from the ammonia molecule toward the ester oxygen atom takes place. Thus, the transition state for the concerted mechanism (designated **CTS)** involves simultaneous creation of a C−N bond, destruction of the single ester C−O bond, and a proton transfer from the ammonia toward the oxygen. The changes (compared to reactants and products) of bond lengths in the **CTS** structure are presented in Figure 1. As can be seen from the figure, the transition vector for the concerted transition state consists basically of motion of the hydrogen atom from the nitrogen to the oxygen atom, partial creation of a C−N bond (1.59 Å in **CTS** compared with 1.36 Å in the product $HCONH_2$ at B3LYP/6-31G(d) level of computations), and considerable extension of the C−O single bond (1.85 Å in **CTS** and 1.34 Å in the reactant

(17) Oie, T.; Loew, G. H.; Burt, S. K.; Binkley, J. S.; McElroy, R. D. *J. Am. Chem. Soc.* **1982**, *104*, 6169.
(18) Ilieva, S.; Galabov, B.; Schaefer, H. F. Unpublished data.
(19) Singleton, D. A.; Merrigan, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 11035.
(20) Marlier, J. F.; Haptonsall, B. A.; Johnson, A. J.; Sacksteder, K. A. *J. Am. Chem. Soc.* **1997**, *119*, 8838.
(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
(22) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49.
(23) Peng, C.; Schlegel, H. B. *Isr. J. Chem.* **1994**, *33*, 449.
(24) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
(25) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.
(26) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.

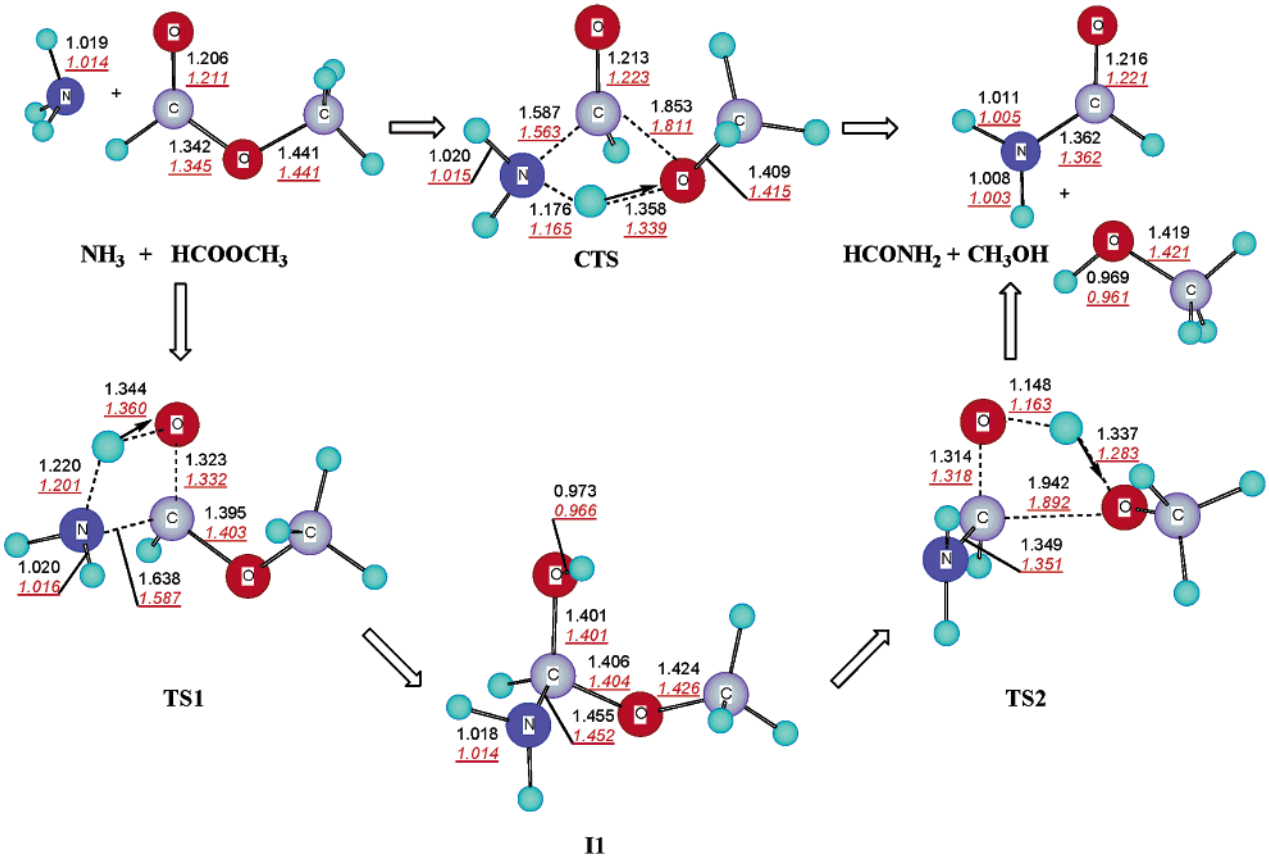

FIGURE 1. B3LYP/6-31G(d) and *QCISD/6-31G(d,p)* optimized structures along the concerted and stepwise pathways for the uncatalyzed aminolysis of methylformate. The arrows on the transition state structures indicate the reaction coordinate, or the normal coordinate with an imaginary frequency.

methylformate). IRC calculations in the two directions from the transition state the reaction showed that the **CTS** structure converts to prereactive and postreactive complexes between the reactants and the products, respectively.

The stepwise pathway for the aminolysis of methylformate is an addition/elimination mechanism, in which the addition and elimination steps are coupled with proton transfer to maintain neutrality in the tetrahedral intermediates formed. In the stepwise case the reaction begins with the addition of the N−H bond from ammonia to the C═O double bond in the ester molecule. The first transition state (**TS1**) along the reaction coordinate (Figure 1) possesses a tetrahedral carbon atom. The C−N bond is almost formed (1.64 Å), while the C═O bond has a length intermediary between double and single bond (1.32 Å). The imaginary vibrational frequency for the first transition state **TS1** is linked mostly to a proton transfer from the nitrogen atom of ammonia toward the carbonyl oxygen atom. Structure **TS1** leads to the stable intermediate **I1**, in which the C−N bond is created (1.45 Å), the carbonyl carbon atom becomes a tetrahedral center, and the proton is already transferred to form a hydroxyl group. The second stage of the process is connected with the breaking of the C−O ester single bond and simultaneous restoration of the C═O bond after proton transfer between the two oxygen atoms. At the second transition state **TS2** (Figure 1) the transition vector corresponds basically to the respective proton transfer yielding the recovery of the C═O double bond. In structure **TS2** the C−O single bond is almost broken (1.94 Å at B3LYP/6-31G(d)). **TS2** leads toward the product complex of the reaction.

TABLE 1. Relative Energies (kcal/mol) for the Optimized Structures along the Concerted and Stepwise Mechanism of Uncatalyzed Aminolysis of Methylformate.

	B3LYP/6-31G(d)		QCISD/ 6-31G(d,p)	PCM/B3LYP/ 6-31G(d)
structure	E_{rel}^{corra} [b]	G_{rel} [a]	E_{rel} [a]	E_{rel} [a]
CTS	40.1	50.5	46.7	36.5
TS1	31.1	41.5	44.8	39.2
I1	10.5	21.1	3.9	5.4
TS2	38.1	48.2	43.2	36.5
products	4.6	3.3	5.0	1.2

[a] All energies are relative to the reactants; [b] Corrected with the zero-point vibrational energy.

The computed energies for the fully optimized critical structures along both concerted and stepwise pathways are given in Table 1. The relative energies of the structures with respect to reactants are schematically represented in Figure 2. It can be seen that B3LYP/6-31G(d) calculations predict the stepwise mechanism to be more favorable than the concerted pathway.

It is of considerable interest to study the influence of a solvent on the energetics of aminolysis, since experimentally the reaction takes place in solution. As a solvent we chose acetonitrile, a neutral, aprotic solvent, which is not expected to have a catalytic effect. The transition

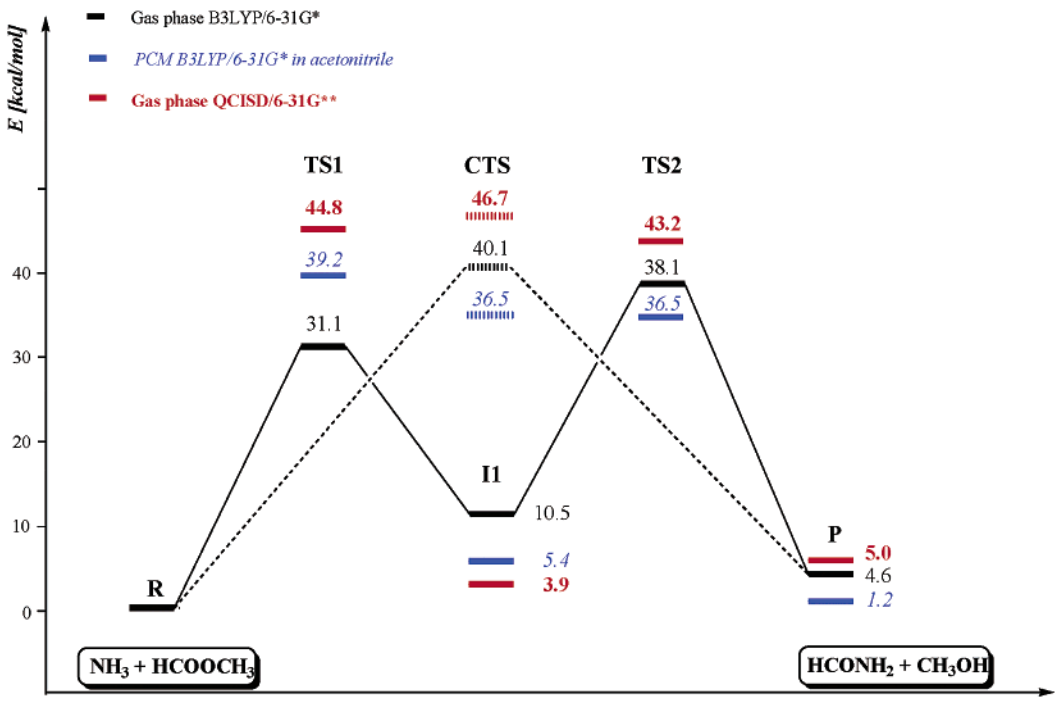

FIGURE 2. Energy diagram for concerted and stepwise mechanisms for the uncatalyzed aminolysis of methylformate.

state and intermediate structures along the two mechanisms were fully optimized in the field of acetonitrile applying PCM B3LYP/6-31G(d) calculations. Theoretical results for the relative total free energies in solution are also represented in Figure 2. On the basis of these results it can be concluded that the presence of the solvent changes substantially the activation energy for the aminolysis of methylformate. In the gas phase, the activation energy for the stepwise mechanism is lower than the activation energy for the concerted mechanism by 2.0 kcal/mol, while in acetonitrile it is higher by 2.7 kcal/mol.

Full geometry optimizations were carried out at the QCISD level of theory combined with the 6-31G(d,p) basis set to obtain an independent picture of the energies of the structures along the reaction path. These computational results are given in Table 1. The theoretically obtained relative energies of the structures are presented in Figure 2. The higher level quantum mechanical computations bring closer the energy barriers for the concerted and stepwise mechanisms of aminolysis studied to 46.7 and 44.8 kcal/mol, respectively.

These theoretical findings are in qualitative accord with the findings of Yang and Drueckhammer for the aminolysis of methylthioacetate.[12] The latter authors showed that the gas-phase energies of the transition states for stepwise and concerted pathways are very close. More definite conclusions for the preferred mechanism may be made if the general base-catalyzed aminolysis process is considered.

General Base-Catalyzed Aminolysis. The experimental aminolysis of esters is usually carried out in the liquid phase. The reaction can take place as a catalyzed process with a catalytic role for a second amine molecule.[2] The present computational study examines the two mechanisms for ester aminolysis with consideration of the general solvent effect of acetonitrile and the catalytic effect of ammonia. Potential energy surfaces for the reaction pathways were searched by applying B3LYP/6-31G(d) and QCISD/6-31G(d,p) quantum mechanical methods. In the case of ester aminolysis, the barrier was earlier found to result mainly from unfavorable proton-transfer geometries.[16] This deduction is also supported by the present computational results for the directions of the transition vectors, characterizing the **CTS**^{catal} and **TS1**^{catal} structures (Figures 3 and 4). The results reveal that the rate-determining steps along the concerted and stepwise pathways involve proton transfers. In fact, the role of the catalyst in the process is to facilitate the proton transfer, thus lowering the proton-transfer energy barrier. The structures of the transition states and intermediates along the concerted and stepwise-catalyzed aminolysis of methylformate are presented in Figure 3. The optimized geometries from the B3LYP/6-31G(d) and QCISD/6-31G(d,p) methods for the located structures are also given in Figure 3. The optimized total and relative energies, zero-point vibrational corrections (ZPVC), and Gibbs free energies along the reaction profiles are collected in Table 2. The structure of the concerted transition state **CTS**^{catal} (Figure 3) reveals the catalytic role of the second ammonia molecule in the proton-transfer process. Formally one of the ammonia molecules could be designated as the nucleophilic agent in the process while the second ammonia serves as the catalyst. The transition vector at **CTS**^{catal} consists basically of the transfer of a hydrogen atom from the nucleophilic NH_3 molecule to the catalytic NH_3 molecule and a simultaneous transfer of another hydrogen atom from the catalyst to the ester oxygen. An examination of the IRC reaction coordinate along both reactants and products shows the existence of prereactive and preproduct complexes, respectively. Their structures and the existing

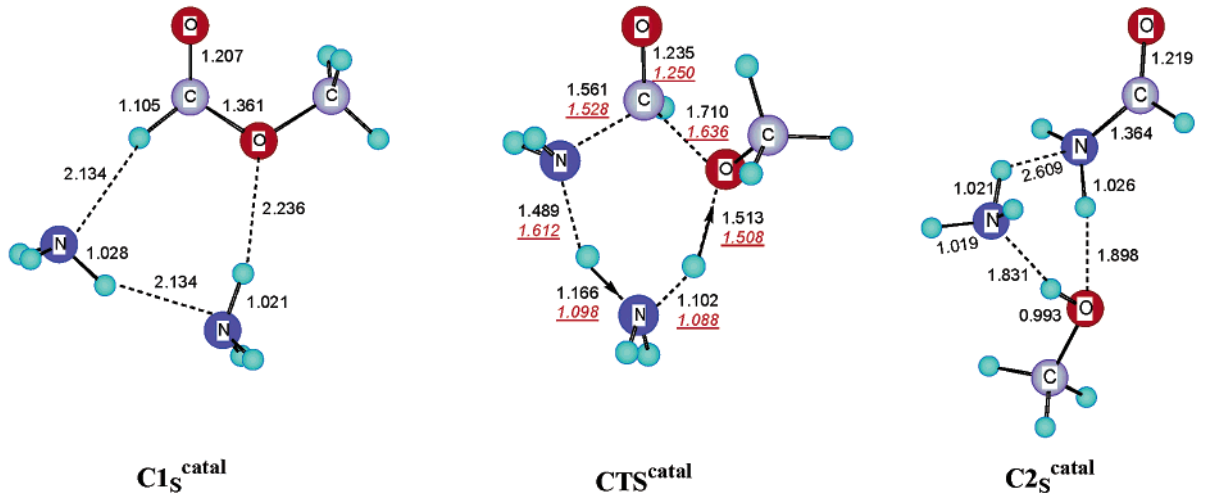

FIGURE 3. B3LYP/6-31G(d) and *QCISD/6-31G(d,p)* optimized structures along the concerted pathway for the self-catalyzed aminolysis of methylformate. The arrows on the transition state structures indicate the reaction coordinate, or the normal coordinate with an imaginary frequency.

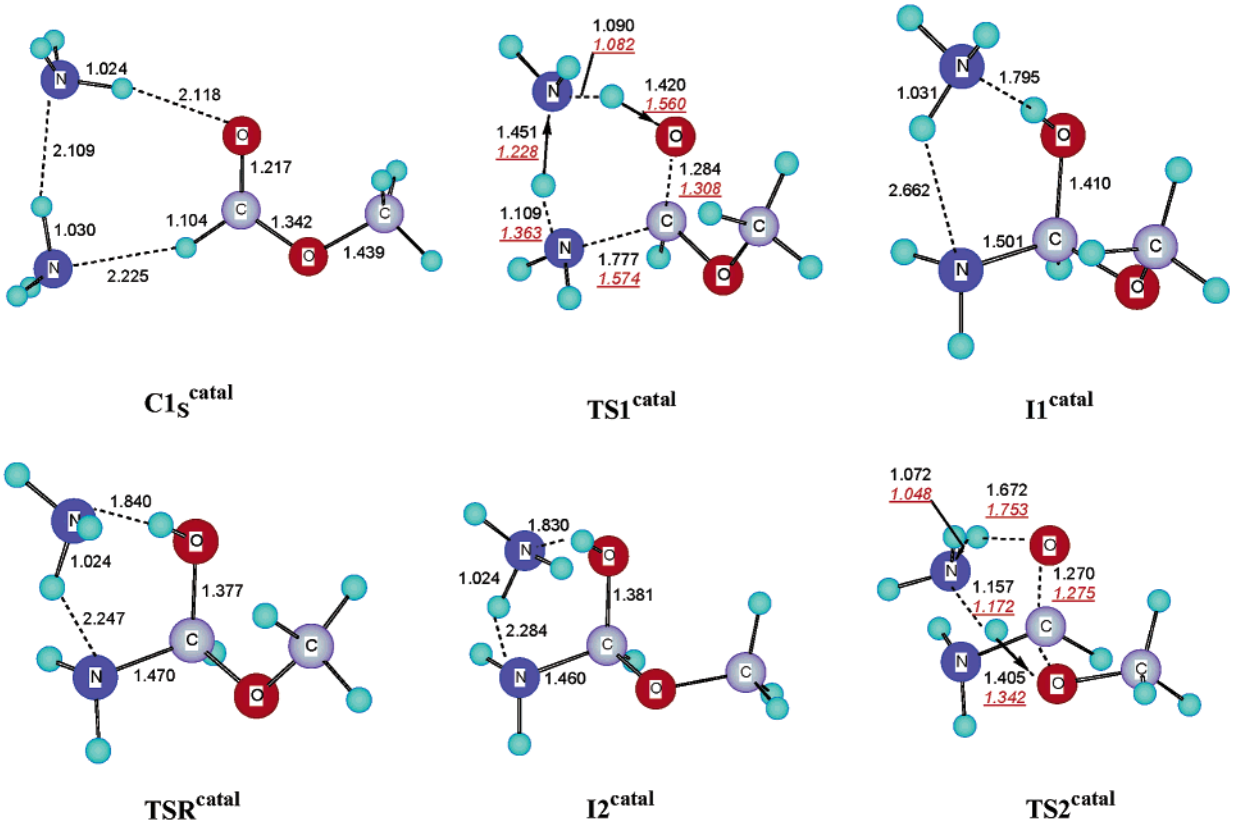

FIGURE 4. B3LYP/6-31G(d) and *QCISD/6-31G(d,p)* optimized structures along the stepwise pathway for the self-catalyzed aminolysis of methylformate. The arrows on the transition state structures indicate the reaction coordinate, or the normal coordinate with an imaginary frequency.

intermolecular hydrogen bonds are shown in Figure 3. Both complexes are more stable than the separate reactants and products, by 8.1 and 11.4 kcal/mol, respectively.

All optimized structures along the catalyzed stepwise aminolysis of methylformate are represented in Figure 4. As in the case of the uncatalyzed process, the attack is along the C=O carbonyl bond. The first critical structure located along the reaction path is the transition state **TS1**^{catal}. The formation of a C−N bond is quite advanced at **TS1**^{catal} and the transition vector clearly reveals the proton-transfer processes taking place. The IRC calculations in the direction of reactants show the existence of a prereactive complex **C1S**^{catal}. The catalytic NH_3 molecule forms a typical O···HN bond with the carbonyl oxygen atom from the ester molecule, having an equilibrium distance of 2.12 Å, and a N···HN hydrogen bond (2.22 Å) with the nucleophilic ammonia molecule.

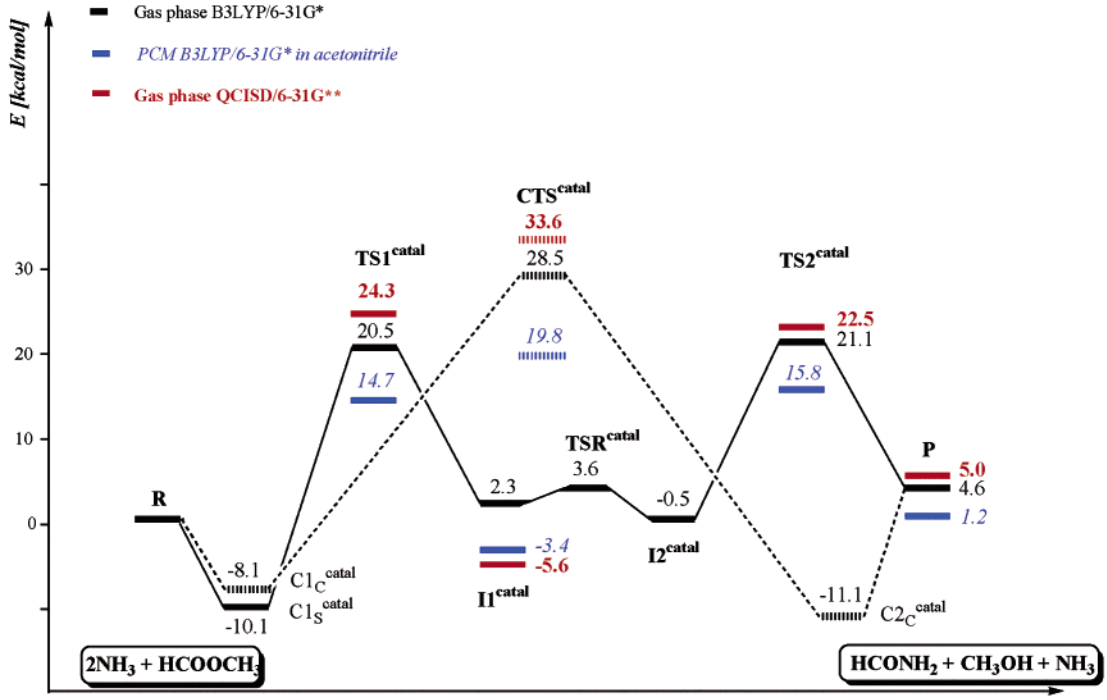

FIGURE 5. Energy diagram for concerted and stepwise mechanisms for the self-catalyzed aminolysis of methylformate.

TABLE 2. Relative Energies in Kcal/Mol for the Optimized Structures along the Concerted and Stepwise Mechanism of Catalyzed Aminolysis of Methylformate.

	B3LYP/6-31G(d)		QCISD/ 6-31G(d,p)	PCM/B3LYP/ 6-31G(d)
structure	E_{rel}[corra] [b]	G_{rel}[a]	E_{rel} [a]	E_{rel} [a]
C1C^{catal}	−8.1	8.2		
CTS^{catal}	28.5	48.9	33.6	19.8
C2C^{catal}	−11.1	5.5		
C1S^{catal}	−10.1	7.0		
TS1^{catal}	20.5	41.2	24.3	14.7
I1^{catal}	2.3	22.2	−5.6	−3.4
TSR^{catal}	3.6	24.1		
I2^{catal}	−0.5	19.3		
TS2^{catal}	21.1	42.0	22.5	15.8
products	4.6	3.3	5.0	1.2

[a] All energies are relative to the reactants; [b] Corrected with the zero-point vibrational energy.

C1S^{catal} evolves through **TS1^{catal}** to a stable intermediate **I1^{catal}**. Its structure is shown in Figure 4. The catalytic NH_3 molecule is linked to this intermediate by an OH···N hydrogen bond (1.79 Å). The subsequent breaking of the C−O single bond and simultaneous restoration of the double C=O bond take place after a proper space orientation of the C−O oxygen atom to facilitate the proton-transfer process. This involves a low-energy barrier of rotation (1.3 kcal/mol) through **TSR^{catal}** resulting in **I2^{catal}** (see Figure 4). The process of breaking/restoring occurs through the **TS2^{catal}** transition state. It is accompanied by a catalyzed transfer of hydrogen atoms, which is the main component of the vibrational transition vector of **TS2^{catal}**.

The energies of all structures along both concerted and stepwise pathways are given in Table 2, and the energetics of the reaction are schematically presented in Figure 5. B3LYP/6-31G(d) calculations reveal the stepwise mechanism to be more favorable by 7.4 kcal/mol. The two main steps of the aminolysis, involving **TS1^{catal}** and **TS2^{catal}**, have very similar activation energies relative to the reactants: 20.5 and 21.1 kcal/mol, respectively.

As already mentioned a full optimization at the QCISD/6-31G(d,p) level was also carried out to evaluate the effect of the method/basis set on the energetics of the reaction. The relative energies for the structures along the concerted and stepwise general base-catalyzed aminolysis at this level of theory are shown in Table 2 and Figure 5. The results confirm that the stepwise mechanism remains more favorable than the concerted pathway by 9.3 kcal/mol.

Transition states and intermediate structures along the two competitive pathways for the catalyzed aminolysis were fully optimized in the presence of the aprotic solvent acetonitrile via PCM B3LYP/6-31G(d) computations. The theoretical predictions are reported in Table 2 and visualized in Figure 5. The theoretical results confirm the conclusion made on the basis of calculations for the gas-phase process. The stepwise pathway has a lower energy barrier (15.8 kcal/mol) than the concerted mechanism (19.8 kcal/mol). The presence of acetonitrile substantially lowers all barriers.

The thermochemistry of the reaction is not correctly predicted at the levels of theory employed. This may be attributed to the abilities of these methods to correctly estimate the heats of formation of the molecules involved. The accuracies of several levels of electronic structure theory in predicting the heats of formation of organic molecules were recently studied.[27,28]

The comparison of the activation energies of uncatalyzed and catalyzed aminolysis is of interest. The cata-

(27) Peterson, G. A.; Malick, D. K.; Wilson, W. G.; Ochterski, J.; Montgomery, J. A.; Frisch, M. J. *J. Chem. Phys.* **1998**, *109*, 10570.
(28) Notario, R.; Castano, O.; Frutos, L. M.; Palmeiro, R. *J. Org. Chem.* **2000**, *14*, 4298.

lytic role of the second ammonia molecule affects mostly the proton-transfer processes. Thus six-membered rings formed in the transition state structures for the catalyzed process are more stable than four-membered rings in the case of the uncatalyzed aminolysis. This explains the lower energy barriers along the reaction path of the catalyzed process in the gas phase, as well as in the presence of aprotic solvent.

Conclusions

B3LYP/6-31G(d) density functional theory and the QCISD/6-31G(d,p) ab initio method were applied to assess the energy profile of the aminolysis of methylformate. The general base catalysis role of the nuclephile and the influence of the aprotic solvent acetonitrile were studied in detail. The results show that the most favorable pathway of the reaction is through the general base catalyzed neutral stepwise mechanism. The structure and transition vectors of the transition states indicate that the catalytic role of ammonia is realized by facilitating the proton transfer processes. The presence of the aprotic solvent acetonitrile substantially lowers all energy barriers.

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Supporting Information Available: Cartesian coordinates and energies in hartrees for B3LYP/6-31G(d), PCM/B3LYP/6-31G(d) (solvent acetonitrile), and QCISD/6-31G(d,p) fully optimized geometries of the transition states and intermediates along the concerted and neutral stepwise mechanism of uncatalized and catalized ammonolysis of methylformate. This material is available free of charge via the Internet at http://pubs.acs.org.

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