Mechanism of the Aminolysis of Methyl Benzoate: A Computational Study†

Boris Galabov,‡ Yasen Atanasov,‡ Sonia Ilieva,‡ and Henry F. Schaefer, III*,§

Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria, and Center for Computational Chemistry, University of Georgia, Athens, Georgia 30602

Received: July 4, 2005; In Final Form: October 9, 2005

Density functional and ab initio methods were applied in examining the possible mechanistic pathways for the reaction of methyl benzoate with ammonia. Transition state structures and energies were determined for concerted and neutral stepwise mechanisms. The theoretical results show that the two possible pathways have similar activation energies. The general base catalysis of the process was also examined. The predictions reveal that the catalytic process results in considerable energy savings and the most favorable pathway of the reaction is through a 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. Comparison of the energetics of the aminolysis for methyl benzoate and methyl formate shows the more favorable process to be that for the aliphatic ester. The differing reactivity of the two esters is explained in terms of the electrostatic potential values at the atoms of the ester functionality.

Introduction

The aminolysis of carboxylic acids and their esters is the main pathway in the generation of amide functional groups in proteins, peptides, and other biomolecules. The role of the RNA fragments and protein enzymes for the peptide bond synthesis has received considerable attention in experimental studies.[1−6] Theoretical work[7,8] has also examined the nature of the ester aminolysis reaction involved in peptide synthesis. Recently Alfonso and Gotor[9] reviewed advances in the development of biomimetic de novo designed synthetic catalysts and the use of natural enzymes for the ester aminolysis process.

The basic ester aminolysis reaction has been the subject of numerous experimental kinetic[10−19] and theoretical studies.[20−29] The understanding of the mechanism of the reaction under different conditions is crucial in the search and design of novel catalysts for the process.

Because of the importance of this process for chemistry and biochemistry, there is a continuing recent interest in experimental kinetic studies aimed at establishing the influence of various structural factors, solvent effects, and catalysts on the reaction rate and the mechanism of the process.[11−16] It has been demonstrated that variations in the ester structure,[15,16] amine basicity and nature,[12b,c,14b,d,16] as well as the reaction medium[13a,b] can induce changes in the rate-determining stage of the reaction.[11,16]

In a previous study[29a] we applied ab initio QCISD/6-31G(d,p) and density functional (DFT) B3LYP/6-31G(d) theoretical methods in studying the mechanism of the simplest model ester aminolysis process: the reaction of methyl formate with ammonia. The results revealed 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. In the case of catalyzed aminolysis by a second ammonia molecule, the stepwise mechanism has a distinctly lower activation energy. The influence of solvent was also assessed.

In the present study we examine the mechanism of the aminolysis of methyl benzoate with ammonia by applying several levels of electronic structure theory. The principal aim of this research is to establish the influence of the aromatic ring, directly bound to the carbonyl functionality, on the mechanism and energetics of the reaction. Solvent effects and general base catalysis are also considered.

Computational Methods

The computations were carried out with the Gaussian 94[30a] and Gaussian 98[30b] program packages. Stable structures and transition states along the reaction pathway were fully optimized by applying the following methods/basis sets: RHF/6-31+G(d,p),[31−33] B3LYP/6-31G(d),[32,34] B3LYP/6-31G+(d,p),[32−34] and B3LYP/cc-pVTZ.[34,35] The stationary points were further characterized by analytic computations of harmonic vibrational frequencies at the same levels/basis sets. Transition state structures were located by the traditional transition state optimization using the Berny algorithm[36] and then checked by intrinsic reaction coordinate (IRC) computations[37] at the same level of theory. Single point computations at the MP2/6-31+G(d,p)[32,33,38] level were performed for more precise energy predictions.

The effects of solvent were predicted by using the polarized continuum model (PCM)[39] incorporated in the Gaussian packages. Single point PCM//B3LYP/6-31G(d) computations were performed for estimating the change in energy profile of the reaction in the presence of water and the aprotic solvent acetonitrile. The standard dielectric constants for water and acetonitrile implemented in the Gaussian programs were employed.

Results and Discussion

As already emphasized in the introductory section, the experimental and theoretical results accumulated so far showed

† Part of the special issue "Jack Simons Festschrift".
‡ University of Sofia.
§ University of Georgia.

10.1021/jp0536403 CCC: $30.25
Published on Web 11/09/2005

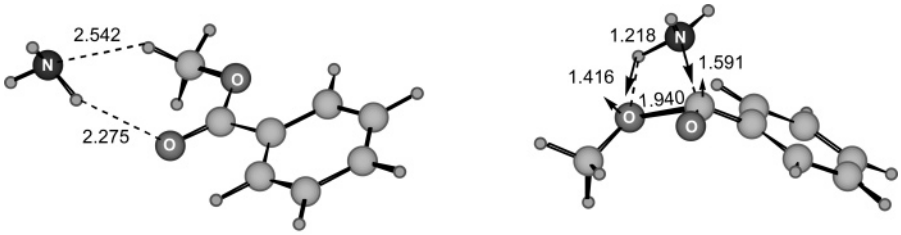

Figure 1. B3LYP/6-31+G(d,p) optimized structures along the concerted pathway for the uncatalyzed aminolysis of methyl benzoate. The arrows in the transition state structure **CTS** indicate the normal coordinate with an imaginary frequency.

the two most likely pathways for the ester aminolysis reaction: the concerted and neutral stepwise mechanisms. Theoretical computations have revealed that a stepwise mechanism involving the formation of zwiterionic intermediates is unlikely.[29b] These two possibilities are explored here in studying the reaction of methyl benzoate with ammonia. The manner of attack by the nucleophile differs in the two mechanisms. For the concerted pathway, the initial nucleophilic attack is along the C−O ester bond, while for the stepwise route the reaction begins with an orientation of an N−H bond from NH_3 along the carbonyl C═O bond.

A. Concerted Mechanism. In the case of 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 electrophilic carbonyl carbon atom from the ester, accompanied by a proton transfer from the ammonia molecule to the oxygen atom of the ester C−O single bond. Thus, the transition state for the concerted mechanism (designated **CTS**) involves simultaneous creation of a C−N bond, cleavage of the C−O bond, and a proton transfer from the ammonia to the oxygen atom. The transition structure involved in the concerted pathway of the aminolysis of methyl benzoate is presented in Figure 1. The main vectors of the imaginary vibrational frequency of the transition state **CTS** are also shown in Figure 1 and correspond mainly to a proton transfer between the nitrogen and the oxygen atoms. There are small contributions corresponding to the cleavage of the C−O ester bond and the formation of the C−N bond. **CTS** is a product-like transition state. The distance between the carbonyl carbon and the ester oxygen in the transition state structure is much longer, 1.940 Å, than that in the reactant methyl benzoate, 1.353 Å, at the B3LYP/6-31+G(d,p) level of computations. The nitrogen−carbon bond is close to formation with a distance of 1.591 Å in **CTS** compared with 1.373 Å in the product benzamide. IRC calculations toward reactants lead to a prereaction complex **Cr** stabilized by a NH···O hydrogen bond with a length of 2.275 Å as well as by a weak CH···N hydrogen bond with a length of 2.542 Å (Figure 1). Forward IRC computations lead to the reaction products benzamide and methanol through a product complex **Cp**.

B. Stepwise Mechanism. The stepwise pathway for the aminolysis of methyl benzoate is an addition−elimination process accompanied with proton-transfer processes that maintain the neutrality of the structures. The transition state structures along the stepwise pathway of methyl benzoate aminolysis are presented in Figure 2.

The first step of the reaction is the addition of an N−H bond from the ammonia molecule to the carbonyl double bond in methyl benzoate. This addition takes place through a transition state **TS1**. The main vectors of the imaginary vibrational frequency for **TS1** are shown in Figure 2 and correspond mainly to a proton transfer from the nucleophile NH_3 to the carbonyl

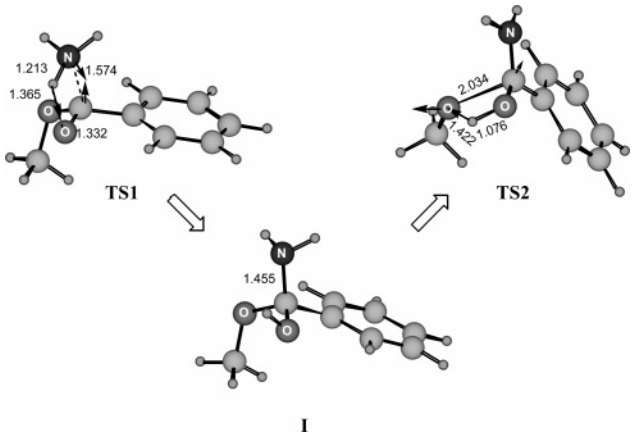

Figure 2. B3LYP/6-31+G(d,p) optimized structures of the transition states for the stepwise pathway of the uncatalyzed aminolysis of methyl benzoate. The arrows associated with the transition state structures **TS1** and **TS2** indicate the respective normal coordinates with imaginary frequency.

oxygen. The hybridization of the electrophilic carbonyl carbon atom converts from sp^2 to sp^3 for the intermediate **I** during the process. The C═O double bond becomes longer (1.332 Å for **TS1**), and an alcohol amine is obtained as an intermediate structure **I**. A new C−N bond is created with a length of 1.574 Å in **TS1** and 1.455 Å for the intermediate **I**. The discussed bond distance values are from B3LYP/6-31+G(d,p) computations. IRC calculations backward from **TS1** show the existence of a stable pre-reaction complex. Its structure is similar to the respective structure **Cr** for the concerted mechanism.

The second step of the reaction is the conversion of the almost tetrahedral intermediate into the products of the aminolysis. The intermediate **I** converts to the products benzamide and methanol through the transition state **TS2**. This stage of the process involves the breaking of the C−O ester single bond and simultaneous restoration of the C═O bond following a proton transfer between the two oxygen atoms. The main component of the transition vector for the second transition state (**TS2)** corresponds to the proton-transfer process (Figure 2).

The relative energies of the structures along the concerted and the stepwise pathways computed at different levels of theory are summarized in Table 1. It can be seen that the DFT computations with the B3LYP functional and several different basis sets predict the concerted mechanism to be slightly more favorable than the stepwise pathway. The higher-level MP2/6-31+G(d,p)//B3LYP/6-31+G(d,p) quantum mechanical computations lead to even closer energy barriers for the concerted and stepwise mechanisms of aminolysis, namely, 40.85 (42.57 kcal/mol relative to **Cr**) and 40.4 kcal/mol, respectively. The theoretical estimations of the solvent effects for CH_3CN and H_2O do not change the established gas-phase dependences for the aminolysis of methyl benzoate (Table 1).

TABLE 1: Relative Energies in kcal/mol for the Stationary Point Structures along the Concerted and Stepwise Mechanisms for the Uncatalyzed and Catalyzed Aminolysis of Methyl Benzoate

	uncatalyzed in gas phase					uncatalyzed in solvent PCM B3LYP/6-31+G(d,p)		B3LYP/ 6-31G(d)
structure[a]	HF/6-31 +G(d,p)	B3LYP/ 6-31G(d)	B3LYP/ 6-31+G(d,p)	B3LYP/ cc-pVTZ	MP2/6-31+G(d,p)// B3LYP/6-31+G(d,p)	CH_3CN	H_2O	catalyzed in gas phase
Cr		−5.01	−3.46	−3.70	−1.72	−0.27	1.57	
CTS	67.50	43.63	44.92	45.74	40.85	43.32	42.90	32.88
Cp		0.06	−1.84	−1.60	1.53	−2.77	−2.93	
TS1	60.83	46.56	47.07	49.14	40.38	46.45	46.23	23.08
I	13.60	12.77	13.03	14.34	4.46	14.05	13.84	0.95
TS2	58.11	43.14	41.55	42.84	40.27	40.98	40.67	23.34
P	4.41	7.04	3.75	4.25	5.32			7.04

[a] See text for symbols; **Cr** and **Cp** are the reactant and product complexes for the concerted mechanism.

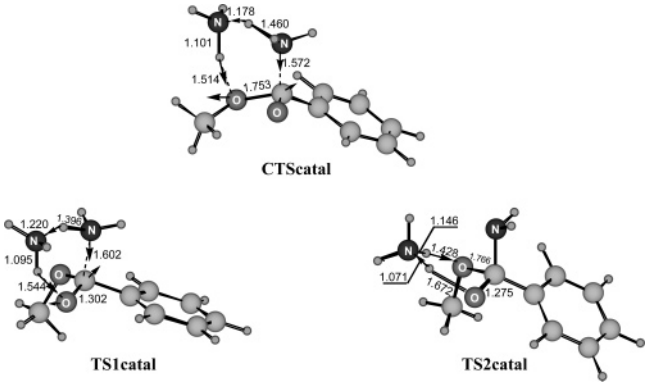

Figure 3. B3LYP/6-31G(d) optimized structures of the transition states for the catalyzed aminolysis of methyl benzoate. The arrows in the transition state structures **CTScatal**, **TS1catal**, and **TS2catal** indicate the respective normal coordinates with one imaginary vibrational frequency.

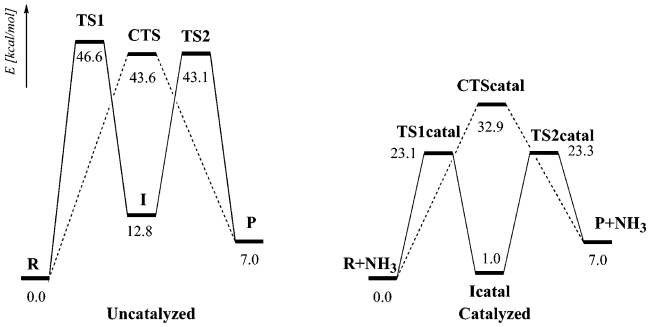

Figure 4. Energy diagram for the uncatalyzed and catalyzed aminolysis of methyl benzoate from B3LYP/6-31G(d) computations.

These theoretical findings are in qualitative agreement with earlier results for the aminolyses of methyl thioacetate[25] and methyl formate.[29a] The latter studies showed that the gas-phase energies of the transition states for the stepwise and concerted pathways are quite close. The inclusion of a dielectric medium, simulated here by PCM//B3LYP/6-31+G(d,p) computations (Table 1), does not significantly affect the energetics of the process.

C. General Base Catalysis. The catalytic effects of a second ammonia molecule on the concerted and stepwise mechanisms of the aminolysis of methyl benzoate were next examined. The potential energy surfaces for the two reaction pathways were searched by applying the B3LYP/6-31G(d) method. This particular method/basis set was selected in order to have a common ground for comparisons with the theoretical results for the aminolysis of the aliphatic methyl formate.[29a] The theoretically estimated energies of the transition states for the concerted and stepwise pathways for the catalyzed aminolysis of methyl benzoate are given in the last column of Table 1. In the case of ester aminolysis, the activation barriers were earlier found to result mainly from unfavorable proton-transfer geometries.[21] This deduction is also supported by the present computational results for the directions of the transition vectors, characterizing the **CTScatal**, **TS1catal**, and **TS2catal** structures. These structures are shown in Figure 3 and reveal that all steps along the concerted and stepwise pathways involve proton transfers. The role of the catalyst in the process is to facilitate the proton transfer, thus lowering the energy barrier. In the case of the general base catalyzed aminolysis, the stepwise mechanism has distinctly lower activation barrier (23 kcal/mol) than the concerted pathway (33 kcal/mol).

TABLE 2: Energies (kcal/mol) Relative to Reactants for the Critical Structures along the Concerted and Stepwise Pathways for the Aminolysis of Methyl Formate[a] (MF) and Methyl Benzoate (MB) from B3LYP/6-31G(d) Computations

	uncatalyzed				catalyzed			
structure	MF E	MB E	MF E_{corr}[b]	MB E_{corr}[b]	MF E	MB E	MF E_{corr}[b]	MB E_{corr}[b]
CTS	40.31	43.63	40.12	43.22	26.03	32.88	28.48	34.38
TS1	42.35	46.56	42.33	46.41	17.94	23.08	20.54	25.30
I	6.64	12.77	10.48	15.90	−3.68	0.95	2.34	6.22
TS2	38.53	43.14	38.05	42.11	17.69	23.34	21.13	26.52
P	4.83	7.04	4.64	7.63	4.83	7.04	4.64	7.63

[a] From ref 29a. [b] Corrected for ZPVE contributions.

The energies of the critical structures along the reaction pathways for the uncatalyzed and catalyzed aminolysis of methyl benzoate are illustrated in Figure 4.

D. Comparison with the Aminolysis of Methyl Formate. As mentioned earlier, one of the aims of this study is to analyze the factors that determine the different energetics of the aminolysis reactions of aliphatic and aromatic esters. In the latter, the phenyl ring is directly bonded to the carbonyl functionality and thus able to influence significantly the process. In the present study we compare the estimated activation barriers for the aminolysis of methyl benzoate with the analogous theoretical results for the reaction of methyl formate with ammonia.[29a] The theoretical predictions for the uncatalyzed process in the gas phase for the reactions of methyl formate and methyl benzoate with ammonia are compared in the first four columns of Table 2. In general, the data reveal that the reaction follows similar energy profiles for both esters considered. The energy differences between the concerted and stepwise mechanisms are relatively small, approximately 2 kcal/mol in the case of methyl formate and 3 kcal/mol for the methyl benzoate aminolysis. In both cases the concerted mechanism is energetically favored. The small energy differences between the

TABLE 3: Electrostatic Potential at Nuclei (V_X) for Methyl Formate and Methyl Benzoate and Transition State Energies (Relative to Reactants) for the Aminolysis Reaction with Ammonia for the Concerted and Stepwise Reaction Pathways[a]

	EPN (au)	transition state energies (kcal/mol)		
	V_C	CTS	TS1	TS2
MF	−14.6088	40.31	42.35	38.53
MB	−14.6135	43.63	46.56	43.14

[a] From B3LYP/6-31G(d) computations.

concerted and the stepwise process support the experimentally established shifts upon substitution between the two mechanistic pathways in certain ester systems.[16]

Table 2 shows also higher activation barriers for both mechanisms in the case of the aromatic ester. The respective energy differences are 3.1 kcal/mol for the concerted mechanism and 4.1 kcal/mol for the stepwise mechanism, respectively. The rationalization of these results can be made considering the variations in the electronic structures of the reactants.

In a recent study[40] the reactivity of a series of 15 *N*-phenylacetamides substituted in the aromatic ring in the alkaline hydrolysis reaction was analyzed by testing a number of reactivity indexes. The results revealed that the most accurate description of the reactivity of the compounds studied is provided by the electrostatic potentials at the nuclei (EPN) estimated for the atoms of the carbonyl group of the reactants. On the basis of these results we conducted a similar analysis of the reactivity of methyl benzoate and methyl formate for the aminolysis reaction. The computed EPN values for the atoms of the −COO− functionality are presented in Table 3. In the case of the stepwise mechanism the attack of the ammonia nucleophile is along the C═O double bond, where the nitrogen approaches the carbonyl carbon with simultaneous interaction between the carbonyl oxygen and a hydrogen atom from NH_3. The higher electrostatic potential at the carbon atom in methyl formate reflects a lower electron density at the site, thus favoring the nucleophilic attack.

In the case of the concerted mechanism, the initial attack is along the ester C−O single bond. For this mechanism, very similar correlations for the EPN shifts are found, indicating more favorable nucleophilic attack at the ester group in methyl formate compared to methyl benzoate. As result the respective activation barriers for both mechanisms are lower for the aminolysis of the aliphatic ester. These results underline once more the power of EPN as a local reactivity index that can successfully be used in rationalizing and predicting the reactivity of carbonyl compounds.

Conclusions

B3LYP/6-31G(d), B3LYP/6-31+G(d,p), and B3LYP/cc-pVTZ density functional methods as well as the RHF/6-31+G-(d,p) and MP2/6-31+G(d,p) ab initio methods were applied in studying the mechanism and the energy profile for the aminolysis of methyl benzoate. The general base catalysis of the process and solvent influence were also examined. The data clearly show that the catalytic process results in considerable energy savings, and 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 comparison of the energetics of the aminolysis for typical aromatic and aliphatic esters, methyl benzoate and methyl formate, respectively, shows the more favorable process to involve methyl formate. The different reactivity of the two esters is explained in terms of the electrostatic potential values at the atoms (EPN) of the ester functionality.

Acknowledgment. B.G. acknowledges the invitation and financial support from the Center for Computational Chemistry, University of Georgia, where some of the present computations were carried out. The research in Georgia was supported by the National Science Foundation, Grant CHE-0451445.

Supporting Information Available: Listings of Cartesian coordinates and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Ban, N.; Nissen, P.; Hanssen, J.; Moore, P. B.; Steitz, T. *Science* **2000**, *289*, 905.

(2) Nissen, P.; Hanssen, J.; Ban, N.; Moore, P. B.; Steitz, T. *Science* **2000**, *289*, 920.

(3) Muth, G. W.; Ortoleva-Donnely, L.; Strobel, S. A. *Science* **2000**, *289*, 947.

(4) Nakano, S.; Chadalavada, D. M.; Bavilacqua, P. C. *Science* **2000**, *287*, 1493.

(5) Barta A.; Dorner, S.; Polacek, N. *Science* **2001**, *291*, 203a.

(6) Fersht, A. *Structure and Mechanism in Protein Science*; W. H. Freeman and Company: New York, 1999.

(7) Suárez, D.; Merz, K. M. *J. Am. Chem. Soc*. **2001**, *123*, 7687.

(8) Rangelov, M. A.; Vayssilov, G. N.; Petkov, D. D. *Org. Biomol. Chem.* **2005**, *3*, 737.

(9) Alfonso, I.; Gotor, V. *Chem. Soc. Rev*. **2004**, *33*, 201.

(10) (a) Bunnett, J. F.; Davis, G. T. *J. Am. Chem. Soc.* **1960**, *82*, 665. (b) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 675. (c) Bruice, T. C.; Mayahi, M. F. *J. Am. Chem. Soc*. **1960**, *82*, 3067. (d) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc*. **1966**, *88*, 104. (e) Bruice, T. C.; Donzel, A.; Huffman, R. W.; Butler, A. R. *J. Am. Chem. Soc*. **1967**, *89*, 2106. (f) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638. (g) Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1973**, *95*, 4452. (h) Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 2473. (i) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387.

(11) Arcelli, A.; Concilio, C. *J. Org. Chem*. **1996**, *61*, 1682.

(12) (a) Castro, E. A. *Chem. Rev*. **1999**, *99*, 3505. (b) Castro, E. A.; Leandro, L.; Quesieh, N.; Santos, J. G. *J. Org. Chem.* **2001**, *66*, 6130. (c) Castro, E. A.; Galvez, A.; Leandro, L.; Santos, J. G. *J. Org. Chem*. **2002**, *67*, 4309. (d) Castro, E. A.; Andujar, M.; Campodonico, P.; Santos, J. G. *Int. J. Chem. Kinet*. **2002**, *34*, 309. (e) Castro, E. A.; Campodonico, P.; Toro, A.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 5930. (f) Castro, E. A.; Andujar, M.; Toro, A.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 3608.

(13) (a) Oh, H. K.; Kim, S. K.; Cho, I. H.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2306. (b) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 8995. (c) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 3874. (d) Lee, H. W.; Guha, A. K.; Kim, C. K.; Lee, I. *J. Org. Chem*. **2002**, *67*, 2215. (e) Oh, H. K.; Lee, J. Y.; Lee, H. W.; Lee, I. *New J. Chem*. **2002**, *26*, 473. (f) Koh, H. J.; Kang, S. J.; Kim, C. J.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc*. **2003**, *24*, 925. (g) Song, H. B.; Choi, M. H.; Koo, I. S.; Oh, H. K.; Lee, I. *Bull. Korean Chem. Soc*. **2003**, *24*, 91.

(14) (a) Um, I. H.; Min, J. S.; Ahn, J. A.; Hahn, H. J. *J. Org. Chem*. **2000**, *65*, 5659. (b) Um, I. H.; Lee, S. E.; Kwon, H. J. *J. Org. Chem*. **2002**, *67*, 8999. (c) Um, I. H.; Lee, E. J.; Lee, J. P. *Bull. Korean Chem. Soc.* **2002**, *23*, 381. (d) Um, I. H.; Seok, J. A.; Kim, H. T.; Bae, S. K. *J. Org. Chem*. **2003**, *68*, 7742. (e) Um, I. H.; Hong, J. Y.; Kim, J. J.; Chae, O. M.; Bae, S. K. *J. Org. Chem*. **2003**, *68*, 5180. (f) Um, I. H.; Park, H. R.; Kim, E. Y. *Bull. Korean Chem. Soc*. **2003**, *24*, 1251.

(15) (a) Castro, E. A.; Santander, C. L. *J. Org. Chem*. **1985**, *50*, 3595. (b) Castro, E. A.; Valdivia, J. L. *J. Org. Chem*. **1986**, *51*, 1668. (c) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453. (d) Castro, E. A.; Bessolo, J.; Aguayo, R.; Santos, J. G. *J. Org. Chem*. **2003**, *68*, 8157.

(16) Um, I. H.; Kim, K. H.; Park, H. R.; Fujio, M.; Tsuno, Y. *J. Org. Chem*. **2004**, *69*, 3937.

(17) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin, Inc.: New York, 1966; Vol. 1.

(18) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969.

(19) Page, M.; Williams, A. *Organic and Bioorganic Mechanisms*; Longman: Harlow, 1997.

(20) Oie, T.; Loew, G. H.; Burt, S. K.; Binkley, J. S.; McElroy, R. D. *J. Am. Chem. Soc*. **1982**, *104*, 6169.

(21) Wang, L.; Zipse, H. *Liebigs Ann.* **1996**, 1501.
(22) Zipse, H.; Wang, L.; Houk, K. N. *Liebigs Ann.* **1996**, 1511.
(23) Marlier, J. F.; Haptonsall, B. A.; Johnson, A. J.; Sacksteder, K. A. *J. Am. Chem. Soc.* **1997**, *119*, 8838.
(24) Adalstensson, H.; Bruice, T. C. *J. Am. Chem. Soc.* **1998**, *120*, 3440.
(25) Yang, W.; Drueckhammer, D. G. *Org. Lett.* **2000**, *2*, 4133.
(26) O'Hair, R. A. J.; Androutsopoulos, N. K. *Org. Lett.* **2000**, *2*, 2567.
(27) Kim, C. K.; Li, H. G.; Lee, H. W.; Sohn, C. K.; Chun, Y. I.; Lee, I. *J. Phys. Chem. A* **2000**, *104*, 104.
(28) Singleton, D. A.; Merrigan, S. R. *J. Am. Chem. Soc.* **2000**, *122*, 11035.
(29) (a) Ilieva, S.; Galabov, B.; Musaev, D. G.; Morokuma, K.; Schaefer, H. F. *J. Org. Chem.* **2003**, *68*, 1496. (b) Ilieva, S.; Galabov, B.; Musaev, D. G.; Morokuma, K. *J. Org. Chem.* **2003**, *68*, 3406. (c) Ilieva, S.; Atanasov, Y.; Kalcheva, V.; Galabov, B. *J. Mol. Struct. Theochem* **2003**, *633*, 49.
(30) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; 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.
(31) Roothan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69.
(32) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (b) Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, *94*, 6081.
(33) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294.
(34) (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864. (b) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(35) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
(36) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49.
(37) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
(38) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 281.
(39) (a) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.
(40) Galabov, B.; Cheshmedzieva, D.; Ilieva, S.; Hadjieva, B. *J. Phys. Chem. A* **2004**, *108*, 11457.