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Computational Study of the Aminolysis of 2-Benzoxazolinone

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Three possible mechanisms (zwitterionic, neutral stepwise, and neutral concerted) of the ring-opening reaction of 2-benzoxazolinone (BO) upon aminolysis with methylamine were studied at the B3LYP/6-31G* level. In the gas phase, the neutral concerted mechanism is shown to be most favorable, which proceeds via a rate-determining barrier of 28−29 kcal/mol. The transition state, **CTS**, associated with this barrier is a four-centered one, where 1,2-addition of the N−H bond of methylamine to the C−O single bond of BO ring occurs. The rate-determining barrier of the neutral stepwise pathway is found to be ca. 42 kcal/mol. The inclusion of solvent effects by a polarizable continuum model (PCM) does not change the conclusions based on the gas-phase study; the barrier at **CTS** is reduced to 20, 20, and 22 kcal/mol in water, ethanol, and acetonitrile, respectively.

1. Introduction

The reaction of aminolysis of esters has been a subject of numerous theoretical studies as a model for the formation of peptide bonds. Conceptually, there are three possible reaction mechanisms, as shown in Figure 1. The first possibility is the concerted mechanism in which the formation of two new bonds and breaking of two old bonds take place in one activation step. The other two considered reaction schemes are stepwise mechanisms that take place via an intermediate or intermediates. The stepwise mechanism can involve neutral intermediates (neutral stepwise mechanism) or zwitterionic intermediates (zwitterionic mechanism). In the zwitterionic mechanism, a nucleophilic attack of the amine lone pair at the carbonyl carbon gives a zwitterionic intermediate **Z1** with NH_2^+ and CO^- ionic centers. At the next step, the cleavage of the C−O single bond occurs with simultaneous recovery of the carbonyl bond, leading to a second zwitterionic intermediate structure **Z2**. The second intermediate converts to the final product *o*-hydroxyphenylmethyl urea **P** via a proton transfer from the electropositive nitrogen atom to the electronegative oxygen. All of the three possible reaction pathways conform with the available experimental kinetic data.[1,2] Since the structures of the reaction intermediates and transition states have not been determined experimentally, the mechanistic pathway of the ester aminolysis was studied by applying computational methods.[3−9] Yang and Drueckhammer[3] have investigated transition-state structures and energies for concerted and stepwise mechanisms for the aminolysis of oxoesters and thioesters in aqueous solution. The stepwise mechanism involving water-catalyzed proton transfer for the acyl-transfer reaction of ethyl acetate and ethyl thioacetate with ammonia was

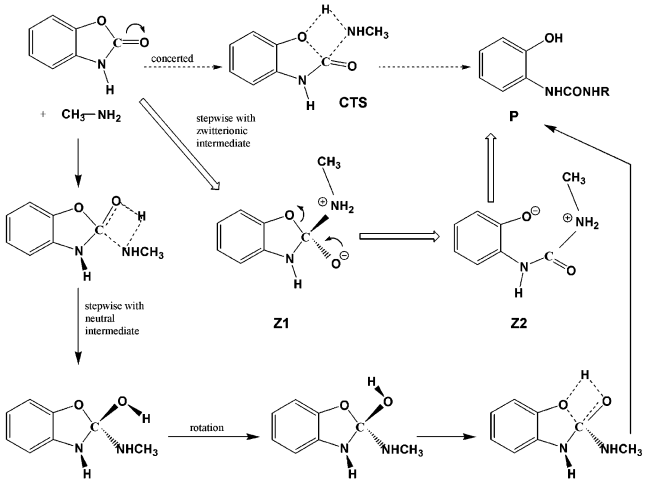

FIGURE 1. Possible mechanisms for the aminolysis of 2-benzoxazolinone: concerted, stepwise with zwitterionic intermediates, and neutral stepwise.

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predicted to be more favorable. O'Hair and Androutsopoulous[4] studied the occurrence of transacylation reactions via S_N2 pathways in the gas phase and found an excellent agreement with experimental results. For a common acyl-transfer reaction $X^- + RCOY \leftrightarrow RCOX + Y^-$, Kim et al.[5] predicted a stepwise mechanism in the gas and solution phases. Model systems for the reaction of amines with esters have been investigated by Zipse and others.[6,7] Neutral and catalyzed aminolysis of β-lactams have been studied theoretically in a series of papers of Sordo and co-workers.[10−14] Adalstensson and Bruice[8] have compared experimental and theoretical results for the aminolysis of substituted phenyl esters of quinoline-6- and -8-carboxylic acids. The authors proposed a stepwise mechanism involving zwitterionic intermediates.

The published computational studies failed to identify zwitterionic transition states for the reaction of ester aminolysis.[6,15] In the case of aminolysis of lactams Sordo and co-workers[12] concluded that the zwitterionic intermediates formed during the reaction of 2-azetidinone with methylamine are expected to be very unstable even in strongly polar media.

In a recent study,[9] the ester aminolysis was reinvestigated by applying a higher level of electronic structure theory, examining the general base catalysis by the nucleophile, and a more comprehensive study of the solvent effect. Ab initio QCISD/6-31G(d,p) and B3LYP/6-31G(d) density functional theory computations were applied. The results showed that in the case of uncatalyzed aminolysis the neutral 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 distinctly lower energy. No transition state involving zwitterionic intermediates could be detected. The changing pattern of the reaction pathway depending on the conditions reveals that none of the discussed mechanistic schemes for the ester aminolysis can be discarded except, possibly, the zwitterionic stepwise mechanism. It was of interest to extend the theoretical studies on ester aminolysis to other systems having different molecular environments for the ester grouping in order to assess the applicability of the established mechanistic schemes to more complex systems.

In the present work, we study the ring opening of 2-benzoxazolinone (BO) in the process of aminolysis by quantum mechanical methods. The aminolysis of 2-benzoxazolinone, considered to be one of the convenient ways of synthesis of substituted ureas, is expected to follow through a similar pathway to the ester aminolysis via the cleavage of O−CO bond. Kinetic data for the aminolysis of 2-benzoxazolinone are available.[16] 2-Benzoxazolinone and its derivatives are widely studied for biological activity properties. BO and its 6-methoxy derivative are found in corn, wheat, and rye.[17] Derivatives of BO have found practical applications as pesticides.[17] Other compounds from this group possess anticonvulsant, hypnotic, and analgetic activities.[18] Chlorzoxazon (6-chloro-2-benzoxazolinone) is an established muscle relaxant. Solvolysis reactions are included in the metabolitic pathways of these derivatives.[18d]

2. Computational Methods

The calculations were carried out with the Gaussian 98 program package.[19] In these calculations, we used the Becke 3-parameter density functional with the Lee−Yang−Parr correlation functional (B3LYP)[20−22] in conjunction with the 6-31G* basis set. All reactants, intermediates, transition states, and products were fully optimized at the B3LYP/6-31G* level of theory. Analytic harmonic frequencies at the same level were used to characterize the nature of the structures and to evaluate vibrational energy and zero-point energy correction (ZPEC).

Solvent effects were taken into account using the integral equation formulation of the polarizable continuum model (IEFPCM).[23] In this approach, the solvent is represented by a homogeneous continuum medium which is polarized by the solute placed in cavity. The solute−solvent interactions are described in terms of a solvent reaction field, which can be partitioned into dispersion, repulsive and electrostatic forces between solute and solvent molecules.[24] Single-point IEFPCM B3LYP/6-31G* calculations were performed for estimating the influence of water, ethanol, and acetonitrile on the energies of all structures along the reaction pathways, unless full optimization in IEFPCM is explicitly noted. For all solvents we applied the standard dielectric constants implemented in Gaussian 98.

3. Results and Discussion

A. Zwitterionic Mechanism. As discussed above, the first step of this pathway is a direct attack of nucleophilic nitrogen of the methylamine group at the electrophilic

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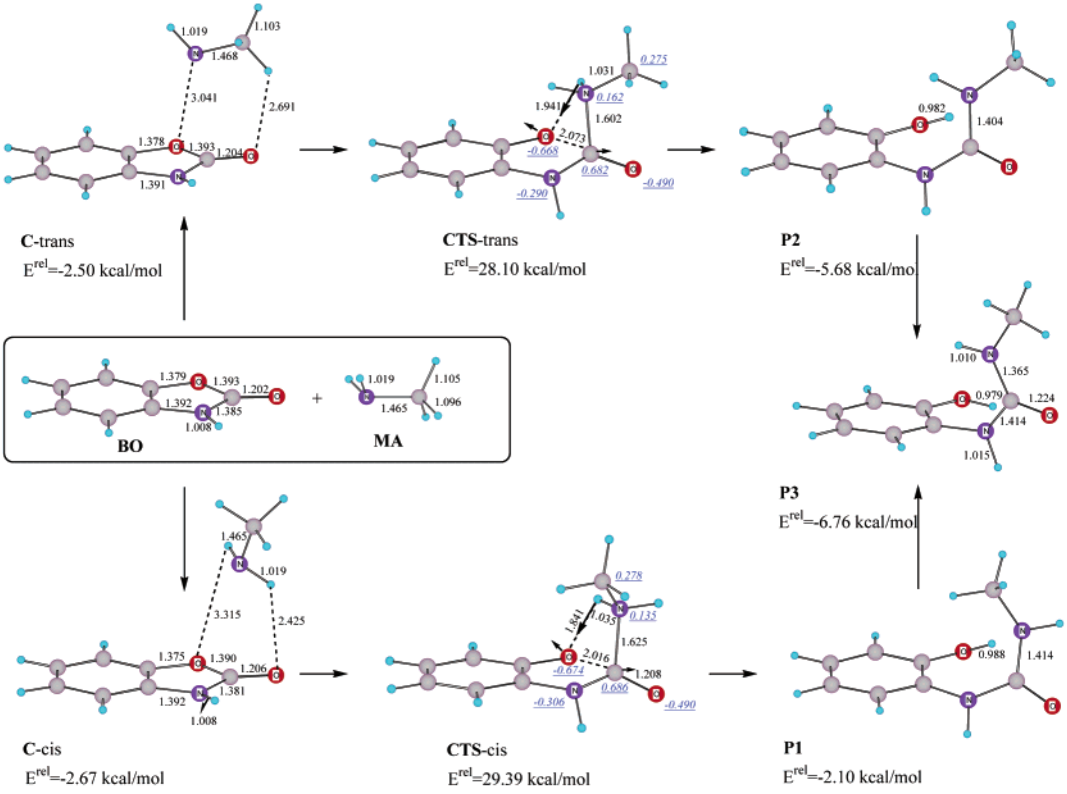

FIGURE 2. B3LYP/6-31G*-optimized structures (bond distances in Å) and the Mulliken atomic population (underlined) along the concerted pathway for the aminolysis of 2-benzoxazolinone. The arrows on the transition-state structures indicate the reaction coordinate or the normal coordinate with an imaginary frequency.

carbon center of the carbonyl group of BO. The resulting complex is expected to be the tetrahedral zwitterionic **Z1** intermediate (see Figure 1). However, our calculations of the potential energy surface of the reaction BO + $NH_2CH_3 \rightarrow$ **Z1** in the gas-phase using the C−N distance as a reaction coordinate (fixing C−N bond and fully optimizing all other geometric parameters) show no minimum corresponding to the structure **Z1**. The inclusion of solvent effects (water is chosen to be as solvent) by performing single-point IEFPCM calculations at each gas-phase optimized structures lead to the appearance of a shallow well in the energy profile. However, optimization of all geometric parameters (without any constraint) at the IEFPCM level in the water and ethanol solvents gave no minimum; optimizations led to dissociation of BO and NH_2CH_3 fragments.

The attempt to optimize the second zwitterionic intermediate **Z2** in water led to a neutral structure following an immediate proton transfer from the nitrogen atom to the negatively charged oxygen bonded to the aromatic ring. Thus, the above given results clearly indicate that the zwitterionic mechanism is unlikely pathway for reaction even in water.

B. Neutral Concerted Mechanism. Now, let us discuss one of the neutral mechanisms, the concerted pathway, which is a one-step reaction where all the bond-forming and bond-breaking processes occur simultaneously (Figure 1). The transition state **CTS** corresponding to this step should involve simultaneous creation of the C−N bond, cleavage of the C−O single bond in BO, and hydrogen transfer from the N atom of amine group to the oxygen atom bonded to the aromatic ring.

Here there could be two different transition states, **CTS**-trans and **CTS**-cis, corresponding to the trans and cis orientation of the methyl group of methylamine with respect to the NH group of 2-benzoxazolinone, respectively. Therefore, below we have studied both trans and cis pathways. Fully optimized structures of the reactants, pre-reaction complexes (**C**-trans and **C**-cis), transition states (**CTS**-trans and **CTS**-cis), and products (**P1**, **P2**, **P3**) of the reaction for trans and cis pathways are shown in Figure 2. According to the intrinsic reaction coordinate (IRC)[25] calculations (starting from the transition states **CTS**-trans and **CTS**-cis), the complexes **C**-trans and **C**-cis are the first intermediates on the potential energy surface of the reaction for the trans and cis-concerted mechanisms, respectively, and nascent products are **P1** and **P2**, respectively. The calculated bond distances suggest that the **C**-trans and **C**-cis complexes have van der Waals interactions with possibly a weak hydrogen bond between the N−H hydrogen (from the NH_2-group) and the carbonyl oxygen for **C**-cis (R(N−H···O) = 2.425 Å). The binding energy is similar for trans and cis pathways: 2.50 and 2.67 kcal/mol, respectively, relative to the reactants.

As mentioned above, the transition states for the concerted aminolysis (**CTS**-trans and **CTS**-cis) are four-centered structures corresponding to the 1,2-addition of H−$NHCH_3$ to the C−O single bond of the BO ring. In these structures, the attacking amine is syn periplanar with respect to the lone pair of the nitrogen atom of BO ring. Calculations show that the reaction coordinate for

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TABLE 1. B3LYP/6-31G* Calculated Relative Energies (without and with ZPEC) and Free Energies (at 1 atm, 298.15K) (All Relative to the Reactants, in kcal/mol) of All the Optimized Intermediates, Transition States, and Products of the Concerted and Stepwise Mechanisms of Aminolysis of 2-Benzoxazolinone (BO)

structure[a]	ΔE	ΔE + ZPEC	ΔG
BO + MA	0.0	0.0	0.0
C-trans	−3.27	−2.50	5.96
CTS-trans	26.20	28.10	39.85
P2	−7.57	−5.68	5.28
C-cis	−3.39	−2.67	5.00
CTS-cis	27.73	29.40	41.09
P1	−4.37	−2.10	9.09
P3	−8.26	−6.76	2.81
C-syn/trans	−3.48	−2.66	5.37
C-syn/cis	−3.38	−2.64	5.17
TS1-syn/trans	43.01	42.03	53.79
TS1-syn/cis	42.80	41.78	53.50
I1-syn/trans	12.71	14.74	26.56
I1-syn/cis	11.65	13.83	25.74
TSR	14.07	15.59	27.68
I2	11.48	13.30	25.06
TSI	12.66	13.96	25.91
I3	11.46	13.41	25.12
TS2	24.91	25.73	37.51
P4	−10.69	−9.14	1.27
tsr13	6.43	7.73	18.47
tsr25	−0.56	1.64	10.61
P5	−6.02	−4.46	5.83
P6	−7.32	−6.05	3.98

[a] For structures, see Figures 2 and 5.

both cis and trans **CTS**-cis and **CTS**-trans transition states (shown by arrows in Figure 2) consists of the motion of the four atoms, H, N, C, and O, involved to the cleavage breaking of N−H bond in methylamine and the C−O single bond in the ring, and the formation of O−H and C−N bonds. As seen in Figure 2, in these transition states the N−H bonds are only slightly elongated (1.035 and 1.031 Å in **CTS**-cis and **CTS**-trans, respectively, vs 1.019 Å in the reactant or reactant complexes), while the C−O bond is nearly broken (2.016 and 2.073 Å in **CTS**-cis and **CTS**-trans, respectively vs 1.393 Å in the reactant). The forming O−H bond is still unformed (1.841 and 1.941 Å in **CTS**-cis and **CTS**-trans, respectively vs 0.988 Å and 0.982 Å in the product **P1** and **P2**, respectively), while the formation of the C−N bond is much advanced (1.625 and 1.602 Å in **CTS**-cis and **CTS**-trans, respectively vs 1.414 Å and 1.404 Å in the product **P1** and **P2**, respectively).

The B3LYP/6-31G*-calculated relative energies and free energies of all the optimized structures of the concerted mechanisms of aminolysis of 2-benzoxazolinone (BO) are given in Table 1. It can be seen from the relative energies of the structures depicted in Figure 3 that the energy barriers of the reaction along the concerted pathway in both trans and cis pathways are very similar, 28.10 and 29.39 kcal/mol, respectively, relative to the reactants.

The energy barriers of the reaction for the trans and cis pathways taken with respect to the pre-reaction complexes are also very close, 30.60 and 32.06 kcal/mol, respectively. Additional transformations of the primary products of the reaction **P1** and **P2** are also represented on the energy diagram in Figure 3. The conversion between different conformational isomers of *o*-hydroxyphenylmethyl urea, which is the product of the aminolysis of BO, may take place by internal rotation around the skeletal C−N bond in the molecule. These conformers (**P1**−**P6**) can be characterized by the position of N−H bond with respect to the C=O double bond. The conformation of Ar-NH-CO-NH-Me (ureido) group is as follows: cis−cis for **P1**, cis−trans for **P2**, **P3** and **P5**, and trans−trans for **P6**. The relative energies of these conformers are quite close, ranging from −2.10 to −6.76 kcal/mol with respect to the reactants. Relative energies of the transition states for the respective rotational processes, **tsr13** and **tsr25**, are shown in Figure 3. The barriers range from 7.32 to 9.83 kcal/mol, suggesting that the isomerization between different rotameric forms can take place at moderate condition.

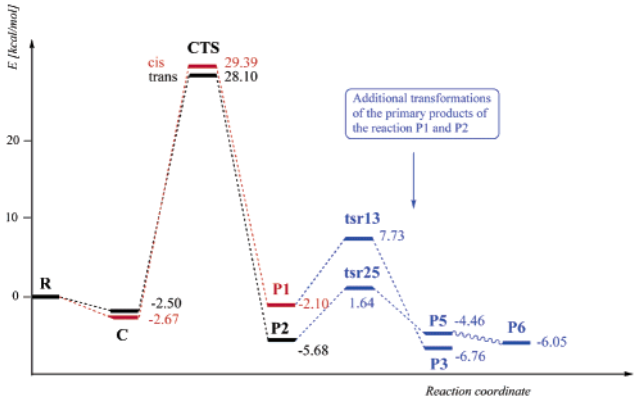

FIGURE 3. Potential energy profile (with ZPEC) for the concerted pathway for the aminolysis of 2-benzoxazolinone. Structures correspond to those in Figure 2.

The comparison with the energetic characteristics of a typical ester aminolysis reaction is of interest. Computational data for the reaction of methylformate and ammonia at the same level/basis set are available.[9] The theoretically estimated activation energy for the reaction of methylformate with ammonia along a concerted pathway from B3LYP/6-31G(d) computations is 40.1 kcal/mol for the gas-phase reaction. The much lower activation energy in the case of BO aminolysis can be attributed to the relative stabilization of **CTS** via electron delocalizations in the conjugated system of heterocycle and aromatic ring. The effect may also be partly due to the higher nucleophilicity of CH_3NH_2 as compared to NH_3.

C. Neutral Stepwise Mechanism. The third possibility for the reaction is a stepwise pathway through neutral intermediates (Figure 1). In fact, this is an addition/elimination mechanism in which the addition and elimination steps are coupled with hydrogen atom transfer maintaining neutrality of the tetrahedral intermediates.

As in the case of the concerted mechanism, two ways of attack by the amine molecule are possible: cis and trans orientation of the methyl group in CH_3NH_2 with respect to the N−H bond in BO. These two attacks give rise to two different pathways with distinct sets of transition states and intermediates. Furthermore, in course of the reaction the BO molecule becomes nonplanar and the N−H bond deviates from the plane of the heterocycle, and several other transition states and intermediates are possible. These reflect the orientation

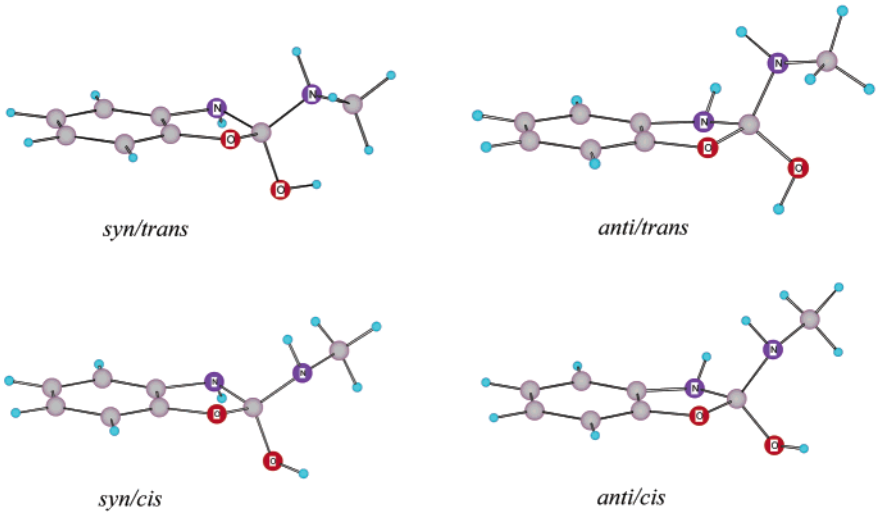

FIGURE 4. Four different isomeric intermediate species expected for the neutral stepwise mechanism: syn/cis, syn/trans, anti/cis, and anti/trans.

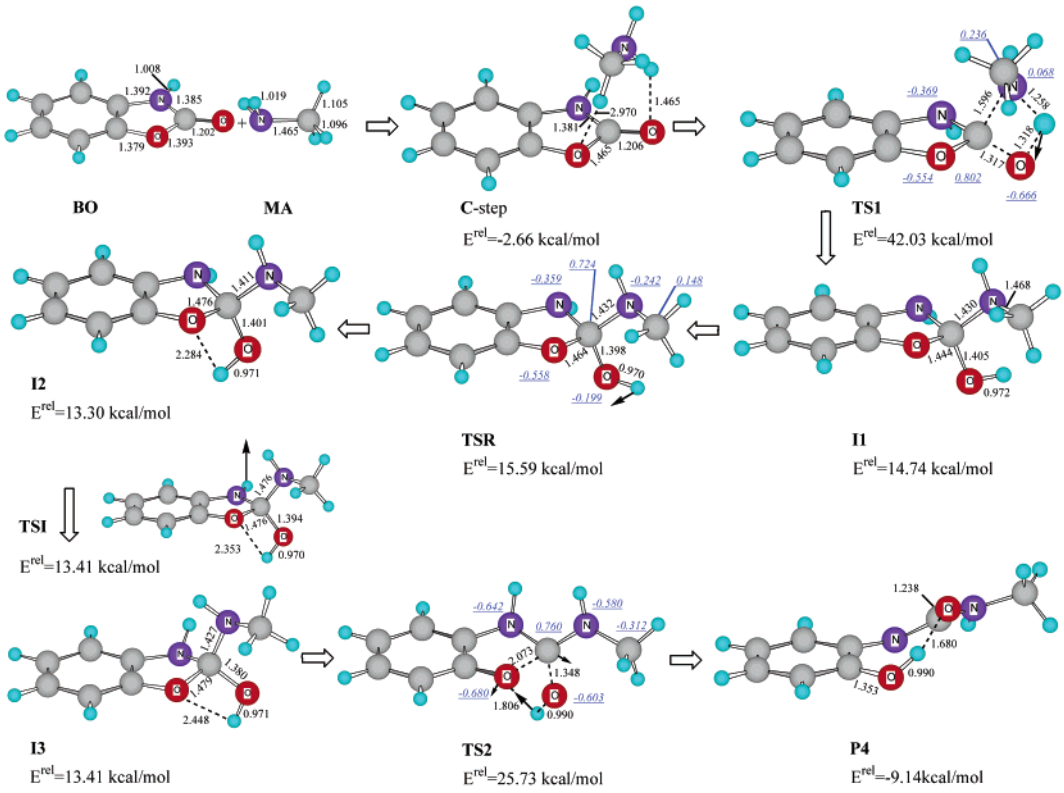

FIGURE 5. B3LYP/6-31G*-optimized structures (bond distances in Å) and the Mulliken atomic population (underlined) along the syn/trans stepwise pathway through neutral intermediates for the aminolysis of 2-benzoxazolinone.

of the amine with respect to the nitrogen lone pair as syn or anti. Therefore, combined with the cisoid and transoid attacks four different isomeric species can be expected: syn/cis, syn/trans, anti/cis, and anti/trans, as illustrated in Figure 4.

We were able to find only two pathways, syn/cis and syn/trans. All attempts to locate **TS1** for the other two pathways, anti/cis and anti/trans, led to corresponding syn structures. The syn structures, as will discussed later, are converted to anti structures through a series of conformational changes. We found the anti transition state **TS2** for the next step of reaction. Our attempts to locate a syn-oriented **TS2** gave the corresponding anti-oriented structure. The optimized structures only along the trans pathway are shown in Figure 5. The relative energies for all the optimized structures for both syn/cis and syn/trans pathways are shown in Figure 6. The complex rearrangements between **I1** and **TS2** are shown in the figure for the trans pathway.

As expected,as seen in Figure 6, the reaction begins with the formation of pre-reaction complex corresponding to a stacking orientation of the H−N−H group from the

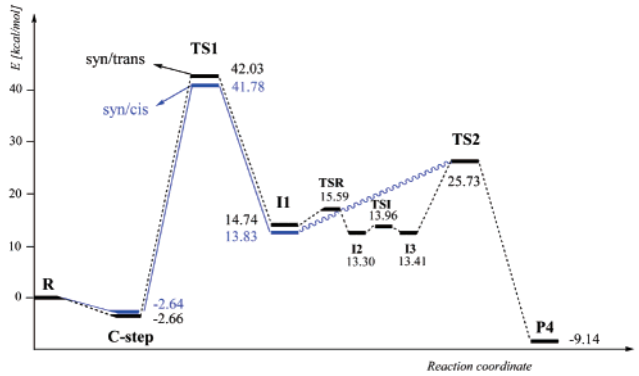

FIGURE 6. Potential energy profile (with ZPEC) for the stepwise pathway through neutral intermediates for the aminolysis of 2-benzoxazolinone. Structures correspond to those in Figure 5.

methylamine with respect to the O−C═O fragment of the BO ring. This weakly bonded complex **C-step**-syn/trans has a stabilization energy of only 2.66 kcal/mol with the long (1.465 Å and 2.970 Å, respectively) H···O(O═C) and H···O(O−C) distances.

The first transition state along the reaction coordinate is **TS1**-syn/trans (Figure 5), which corresponds to the N−H and C═O π-bond cleavage, and the C−N and O−H bond formation processes, and possesses a tetrahedral carbon atom. At the transition state the C−N bond is nearly formed (1.596 Å), while the C═O bond has a length intermediary between double and single bond (1.317 Å). The calculated reaction coordinate at this transition state consists mainly of the hydrogen atom transfer from the nitrogen atom of the amine to the oxygen atom of the carbonyl group. Overcoming this transition state, one is led to the stable intermediate **I1**-syn/trans, in which the C−N bond is formed, the carbonyl carbon atom became a tetrahedral center and the H atom is already transferred to form a hydroxyl group.

The intermediate **I1** converts to intermediate **I2** through the transition state **TSR** corresponding to rotation around the C−O(H) bond. The resulted intermediate **I2** has a syn/trans structure (Figure 5). The barrier associated with this transition state is calculated to be only 0.85 kcal/mol. The **I1** → **I2** isomerization process is found to be 1.44 kcal/mol exothermic. The intermediate **I2** rearranges to another intermediate, **I3**, which is different from the **I2** by inversion of NH bond of BO ring. Energy difference between the **I2** and **I3** intermediates is very small, 0.11 kcal/mol. These intermediates are separated by a barrier of only 0.66 kcal/mol at the transition state **TSI**, calculated from the **I2**.

In the next step, the intermediate **I3** converts to the product **P4** through the transition state **TS2**, which has anti/trans conformation. IRC calculations confirmed that **TS2** connects **I3** with **P4**. The calculated transition state vector for **TS2** basically includes the cleavage of the C−O single bond of BO ring, the H-transfer from the OH-group to the O-atom of the broken C−O bond, and formation of C═O double bond between the O and C atoms of the broken OH-group and C−O bonds. The barrier associated with these transformations at the **TS2** is 12.32 kcal/mol.

It can be seen from Figure 6 that the first step of the reaction at the **TS1** is the rate-determining stage of the entire process with a barrier of about 42 kcal/mol. The comparison of above presented results for the possible reaction pathways of the aminolysis of benzoxazolone shows the concerted mechanism to be most favorable one.

The conclusion is in accord with kinetic results of Hengge et al.[26,27] that provide experimental evidence for preference of concerted acyl transfer reactions for the interaction of *p*-nitrophenyl acetate with a number of different nucleophiles, including methoxyethylamine.

The comparison of the energetics of the neutral stepwise aminolysis of BO with the analogous mechanistic pathway for the interaction of methylformate with ammonia[19] reveals distinct differences in the two reactions. The energy of **TS1** transition state in the case of BO is about 42 kcal/mol while a lower energy with $E_{TS1} = 31.1$ kcal/mol is theoretically predicted in the case of the simple aminolysis reaction. Inversely, the energy of the TS2 transition state has distinctly lower energy in the aminolysis of BO ($E_{TS2} = 25.7$ kcal/mol) than in the case of methylformate, where $E_{TS2} = 38.1$ kcal/mol. The overall energy profiles of the reaction paths for the aminolysis of BO and methylformate are also quite different. In the case of aminolysis of 2-benzoxazolinone the thermodynamically favored pathway appears to be the concerted mechanism. In the case of the model aminolysis reaction, however, the concerted and stepwise mechanisms have quite similar activation energies. The effect of solvents on the energy profile is also different for the two studied reactions. It does, therefore, appear that there is no uniform mechanism for the aminolysis reaction. Depending on the nature of reactants and the medium, the reaction can proceed either through concerted or neutral stepwise mechanistic pathways.

D. Solvent Effect. Experimentally, the aminolysis of 2-benzoxazolinone takes place in the liquid phase: in ethanol solution or in medium of the amine itself.[16] Therefore, below we discuss the influence of the solvent effects on the energy profile of the reaction.

The energies of reactants, transition states, intermediates, and products of the both concerted and neutral stepwise mechanisms presented above were recalculated at the IEFPCM SCRF/B3LYP/6-31G* level in the presence of polar and aprotic solvents. Computed single-point energies (relative to the reactants) for all the critical structures inmedium of water, ethanol, and acetonitrile are presented in Table 2 and are compared with the corresponding gas-phase values. It can be seen from this table that the including solvent effects decreases the energy barrier at the concerted transition state, **CTS**, in both trans and cis pathways. The presence of solvent increases the rate-determining energy barrier at the transition state **TS1** along the neutral stepwise pathway.

Thus, the data given in Table 2 unambiguously show that the concerted mechanism for aminolysis of 2-benzoxazolinone becomes even more favorable than the neutral stepwise pathway in polar (water, ethanol) and aprotic (acetonitrile) solvents. From these data one can conclude that the concerted pathway for the aminolysis of 2-benzoxazolinone is the most favorable mechanism. The available experimental data showing first-order

(26) Hengge, A. C.; Hess, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 11256.
(27) Hess, R. A.; Hengge, A. C.; Cleland, W. W. *J. Am. Chem. Soc.* **1998**, *120*, 2703.

TABLE 2. PCM Relative Energies, Compared to Reactants, for Selected Structures along the Concerted and Neutral Stepwise Mechanisms of Aminolysis of 2-Benzoxazolinone in the Gas and in Solvents

	E_{rel} (kcal/mol)			
structure	gas phase[a]	water[b]	ethanol[b]	acetonitrile[b]
C-trans	−2.50	1.78	1.02	0.49
CTS-trans	28.10	20.10	20.32	22.40
P2	−5.68	−3.54	−4.03	−4.82
C-cis	−2.67	1.43	0.77	0.31
CTS-cis	29.39	22.20	22.31	24.36
P1	−2.10	0.28	−0.38	−1.21
C-syn/trans	−2.64	1.69	0.96	0.25
C-syn/cis	−2.66	1.38	0.78	0.23
TS1-syn/trans	42.03	46.05	45.71	44.88
TS1-syn/cis	41.78	45.90	45.59	44.54
I1-syn/trans	14.74	14.50	14.40	14.49
I1-syn/cis	13.83	15.00	13.91	14.01
TS2	25.73	22.17	22.30	23.80

[a] B3LYP/6-31G*-optimized values. [b] The influence of the solvent is simulated by single-point B3LYP/6-31G* IEFPCM calculations at the B3LYP/6-31G*-optimized geometry.

kinetics toward both BO and amine for this reaction agree with both stepwise and concerted mechanisms.[16] The experimentally determined activation energy for a reaction taking place in the medium of triethylamine is 12.8 kcal/mol. The disparity between experimental and theoretical values (20.1 kcal/mol in water, 20.32 kcal/mol in ethanol and 22.40 kcal/mol in acetonitrile) can be attributed to the possible role of general base catalysis by a free molecule of amine.

E. General Base Catalysis. It was shown for the reaction of methylformate with ammonia that a general base catalysis by a free molecule of amine substantially alters the energy profile of the reaction. Under the condition of general base catalysis the most preferred mechanism becomes the neutral stepwise pathway with distinctly lower activation energy than the concerted pathway. Similar computations are currently in progress for the methylaminolysis of BO.[28] Preliminary results reveal that the general base catalysis lowers substantially the energies of transition state structures. However, the concerted mechanism remains the preferred pathway of the reaction.

4. Conclusions

From the above-presented discussions of the three (zwitterionic, neutral stepwise, and neutral concerted) possible mechanisms of the ring-opening reaction of 2-benzoxazolinone (BO) upon aminolysis one may draw the following conclusions:

1. Among the three different mechanisms of this reaction, the neutral concerted mechanism is shown to be the most favorable. This mechanism proceeds via formation of a weakly bound pre-reaction molecular complex, **C**, followed by the rate-determining four-centered transition state **CTS**. At this transition state the 1,2-addition of the H−N bond of methylamine to the C−O single bond of BO ring occurs. The calculated barrier (relative to the reactants) is about 28−29 kcal/mol. The rate-determining barrier of the neutral stepwise pathway, ca. 42 kcal/mol, is a significantly higher than that for the neutral concerted one.

2. The inclusion of solvent effects from the water, ethanol and acetonitrile does not change the conclusion based on gas-phase studies. It only slightly reduced the rate-determining barrier at the transition state **CTS**, from 28 to 29 kcal/mol in gas phase to 20, 20, and 22 kcal/mol in water, ethanol and acetonitrile, respectively.

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Supporting Information Available: Cartesian coordinates and energies in hartrees for B3LYP/6-31G(d)-optimized and IEFPCM/B3LYP/6-31G(d) single-point calculations for reactants, transition states, intermediates, and products along the concerted and neutral stepwise mechanism of aminolysis of 2-benzoxazolinone. This material is available free of charge via the Internet at http://pubs.acs.org.

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