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THEORETICAL STUDIES OF 5-*EXO* SELECTIVE INTRAMOLECULAR CYCLIZATION OF *O*-ALKYNYLBENZOIC ACID CATALYZED BY ORGANIC BASE

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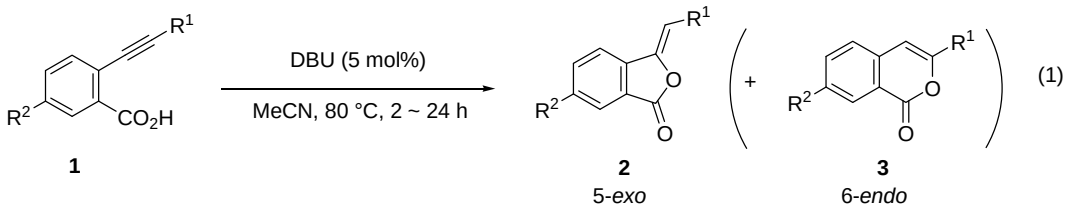
Abstract – Theoretical studies of the organic base-catalyzed 5-*exo* intramolecular cyclization of *o*-alkynylbenzoic acid were documented. The acidic fragment participating in the transition states was shown to reduce the activation energy significantly on the basis of hybrid DFT (BHandHLYP) calculation of 5-*exo* and 6-*endo* transition states. Furthermore, preference for the 5-*exo* cyclization mode was rationalized by natural population analysis of optimized structures of the transition states and the reactants.

INTRODUCTION

The intramolecular cyclization of *o*-alkynylbenzoic acid derivatives (**1**) is one of the most efficient approaches to the synthesis of phthalides (**2**), an important class of oxygen-containing heterocycles often seen in naturally occurring and biologically active compounds.[1] However, in most cases, the intramolecular cyclization of **1** catalyzed by metal complexes provides a mixture of phthalides (**2**) and isocoumarin (**3**) *via* 5-*exo* and 6-*endo* cyclization, respectively.[2-5] Recently, we successfully developed the 5-*exo* selective cyclization of a series of *o*-alkynylbenzoic acid derivatives (**1**) using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as an organic base catalyst (eq. 1).[6] The method enables efficient access to phthalides (**2**) under mild reaction conditions without having to use a metal catalyst.[7,8]



1 **2** 5-*exo* **3** 6-*endo*

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

In our preliminary communication, we proposed that the 5-*exo* cyclization of the carboxylate anion to the triple bond would be assisted by a conjugate acid (**4**) of the organic base catalyst or a carboxylic acid of substrate **1** on its own (Figure 1).[6] The 5-*exo* selective cyclization needs to be thoroughly understood, because this simple method would be applicable to the construction of a variety of heterocyclic ring systems *via* the activation of other functionalities,[9] such as amide, alcohol, and amine, instead of carboxylic acid. Herein we report theoretical studies of the intramolecular cyclization of **1** to clarify the selective formation of phthalides (**2**) *via* the 5-*exo* transition state and the participation of the acidic fragment in the transition state assembly.

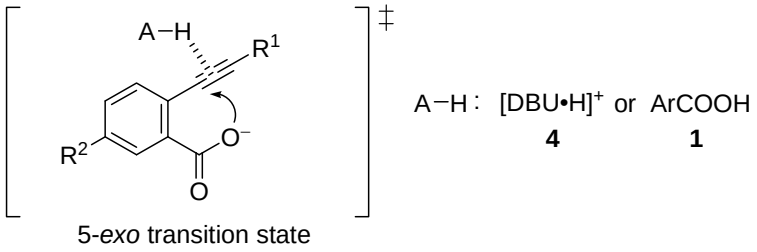
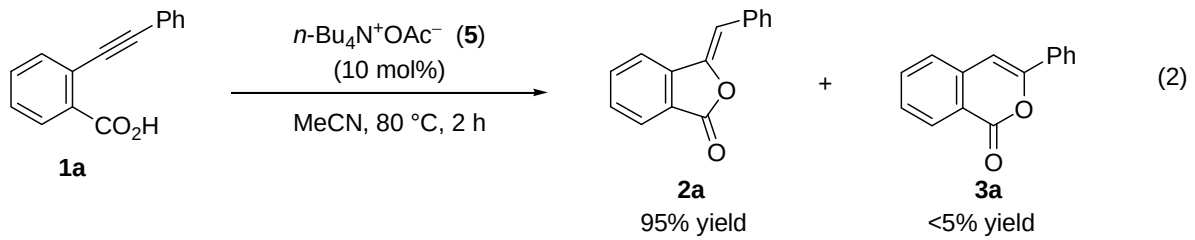


Figure 1. Proposed reaction mechanism for the organic base-catalyzed intramolecular cyclization of *o*-alkynylbenzoic acids (**1**).

RESULTS AND DISCUSSION

In our proposed mechanism, conjugate acid (**4**) or the carboxylic acid of substrate (**1**) participates in the transition states. It is considered that the carboxylic acid of **1** would be suitable for assisting the intramolecular cyclization rather than conjugate acid (**4**), because its parent benzoic acid exhibits higher acidity (benzoic acid: pK_a 21.51 in acetonitrile)[10] than conjugate acid (**4**) ([DBU·H]$^+$: pK_a 24.34 in acetonitrile).[11] In order to confirm whether the reaction would proceed without conjugate acid (**4**), we performed the cyclization reaction using a catalytic amount of tetrabutylammonium acetate (**5**) instead of the organic base catalyst, DBU (eq. 2). The reaction of **1a** (R^1 = Ph, R^2 = H) proceeded smoothly in the presence of **5** (10 mol%) in acetonitrile at 80 °C for 2 h to give the corresponding 5-*exo* cyclized product (**2a**) exclusively in excellent chemical yield. This clearly indicates that the reaction proceeds without an ionic conjugate acid, thus the protonated onium salt of a nitrogen-containing organic base.



With the above experimental evidence in hand, transition state analysis of the present cyclization system was performed taking into account the participation of the carboxylic acid in the cyclization. In our model system, acetic acid (acetic acid: pK_a 23.51 in acetonitrile)[10] was employed instead of benzoic acid derivatives (**1**) to simplify calculations and reduce computational cost. In addition, it is likely that counter cations, $[DBU{\cdot}H]^+$ (**4**) in eq. 1 and Bu_4N^+ in eq. 2, can be neglected in the geometry optimization of stationary points, thus transition states and reactants, because the effect of the counter cations in each model would be cancelled out. Either 5-*exo* or 6-*endo* transition states were explored to clarify the exclusive formation of phthalides (**2**) (Figure 2a). We also evaluated acid-free models (Figure 2b) to confirm the participation of the acidic fragment in the transition states. Geometries of the stationary points were fully optimized and characterized using hybrid density functional theory (BHandHLYP)[12] at the 6-31G* level. All activation energies were computed as the continuum solvation model from the single-point energy calculations of the optimized structures on the basis of the polarizable continuum model (PCM,[13] $\varepsilon = 36.64$ for acetonitrile).

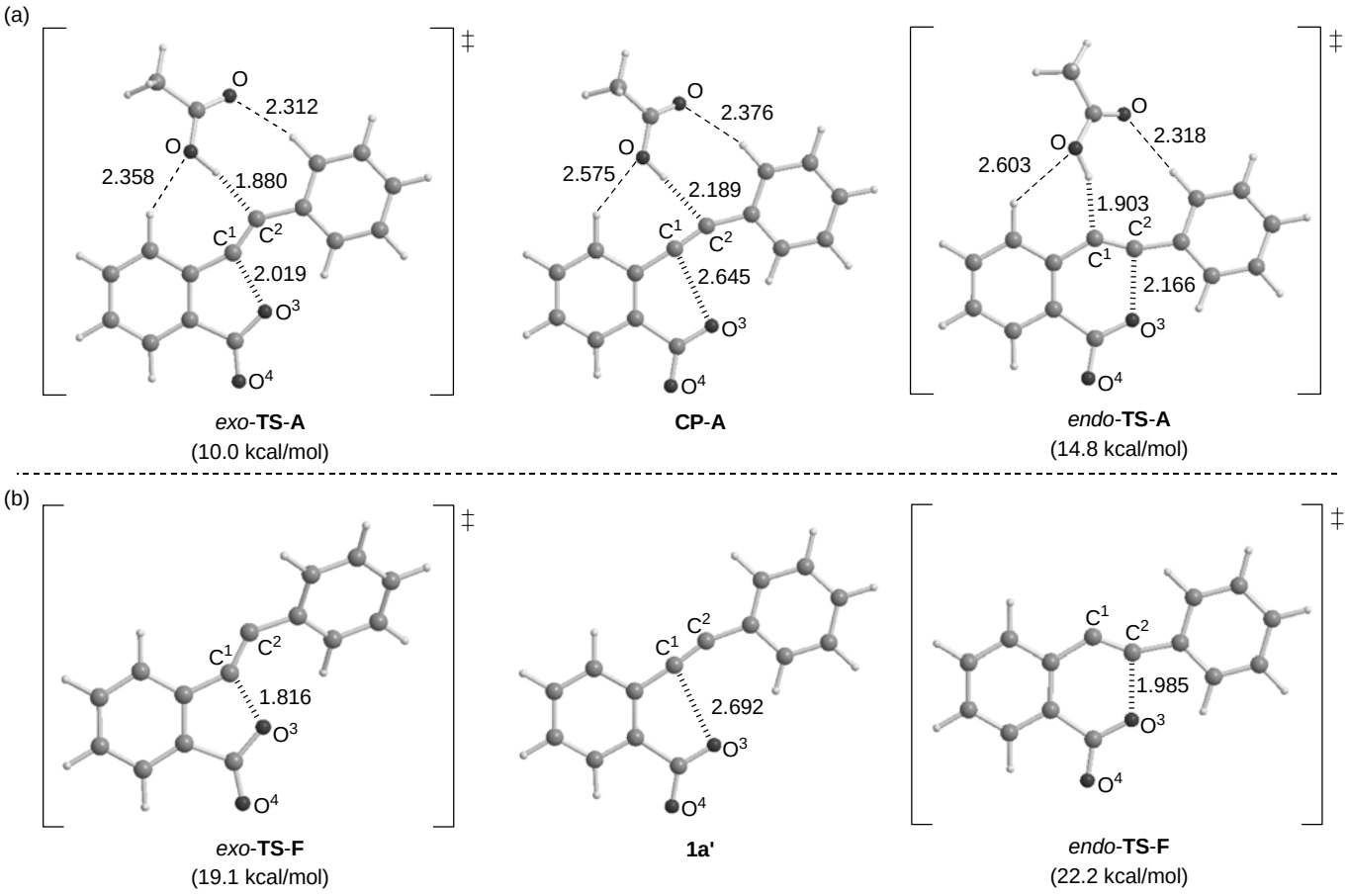


Figure 2. Activation energies of continuum solvation models (in acetonitrile) and 3D structures of initial complex (**CP-A**), anionic intermediate (**1a'**), and transition states (**TS**) of *exo*/*endo* cyclization modes at the BHandHLYP/6-31G* level. Activation energies are in parentheses. Bond lengths are in Å. (a) Intramolecular cyclization assisted by carboxylic acid. (b) Acid-free models of intramolecular cyclization.

As illustrated in Figure 2, it is obvious that the acidic fragment, acetic acid in the model system, markedly reduced the activation energy in both 5-*exo* and 6-*endo* cyclization (Figure 2a *vs.* 2b). The participation of the acidic fragment in the transition states is crucial for the smooth cyclization. The exclusive formation of *Z*-geometry observed in the *exo*-double bond of phthalide (**2**) is well accepted as shown in the transition structure of *exo*-**TS-F** (Figure 2b), in which anion readily generates *trans* to the attacking oxygen atom (O^3) of the carboxylate anion. Hence, in *exo*-**TS-A** (Figure 2a), the acid approaches from the backside of the bond formed between oxygen atom (O^3) and carbon atom (C^1) of the triple bond to stabilize the generating anion on C^1. The significant decrease in the activation energies observed in the acid-assisted transition state (*exo*-**TS-A**) can be rationalized by formation of a hydrogen bond between the generating anion and the acidic proton. This stabilization effect of the acid in *exo*-**TS** is also applicable to *endo*-**TS**. Most importantly, the activation energy of the 5-*exo* cyclization was smaller than that of the 6-*endo* one, regardless of the presence or absence of the acidic fragment (Figure 2a and 2b). In order to elucidate the preference for the 5-*exo* mode, we calculated natural charges of acid-assisted models (**CP-A** and **TS-A**) from natural population analysis. As shown in Figure 3 for the natural population of carbon atoms (C^1 and C^2) and oxygen atoms (O^3 and O^4), the polarity of the charge distribution in the initial complex (**CP-A**) of **1a'** with acetic acid did not change in *exo*-**TS-A** in both carbon atoms and oxygen atoms.[7] In contrast, 6-*endo* cyclization switched the polarity of both carbon atoms, C^1 and C^2, between **CP-A** and the 6-*endo* transition state (*endo*-**TS-A**), although oxygen atoms maintained a negative charge. The relative stability of the 5-*exo* transition state (*exo*-**TS-A**) would be attributed to the small change in charge distribution, avoiding the switching of polarity of carbon atoms (C^1 and C^2) between **CP-A** and **TS-A**.

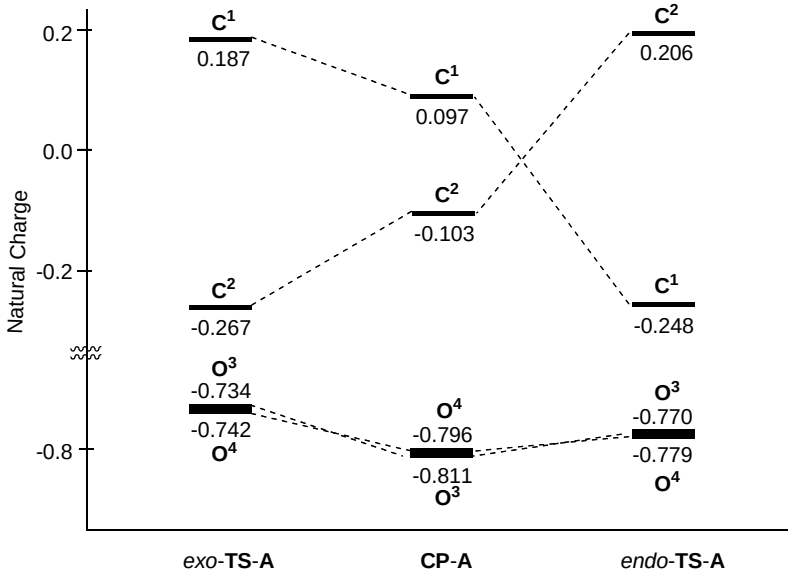


Figure 3. Natural population analysis of carbon atoms (C^1 and C^2) and oxygen atoms (O^3 and O^4) in initial complex (**CP-A**) of **1a'** with acetic acid and acid-assisted transition states (**TS-A**).

In conclusion, we demonstrated theoretical studies of the organic base-catalyzed intramolecular cyclization of *o*-alkynylbenzoic acid derivatives. The participation of acidic fragments in the transition states is the key to the present cyclization, reducing the activation energy significantly. Furthermore, the 5-*exo* selective cyclization was rationalized on the basis of the natural population analysis of the transition states and the initial complex of the reactive intermediates with the acidic fragment.

EXPERIMENTAL

Experimental procedure for intramolecular cyclization of **1a** catalyzed by tetrabutylammonium acetate leading to phthalide **2a**: To a MeCN solution (0.6 mL) of 2-(2-phenylethynyl)benzoic acid (**1a**) (66.7 mg, 0.3 mmol) was added tetrabutylammonium acetate (9.0 mg, 0.03 mol) under Ar atmosphere. The solution was stirred at 80 °C for 2 h. After the consumption of **1a**, the reaction mixture was cooled to room temperature, filtered through a short Florisil pad, and concentrated. The residue was purified by column chromatography (silica gel, *n*-hexane/AcOEt 50:1 - 5:1) to afford (*Z*)-3-(1-benzylidene)phthalide (**2a**) in 95% yield as a white solid (63 mg). ^{1}H NMR (400 MHz, $CDCl_3$): σ 6.41 (1H, s), 7.32 (1H, tt, *J* = 7.5, 1.2), 7.40-7.44 (2H, m), 7.53-7.57 (1H, m), 7.71-7.79 (2H, m), 7.84-7.86 (2H, m), 7.94-7.96 (1H, dt, *J* = 7.5, 1.0); ^{13}C NMR (100 MHz, $CDCl_3$): σ 106.99, 119.73, 123.35, 125.48, 128.32, 128.67, 129.67, 130.03, 133.01, 134.37, 140.51, 144.47, 166.88. These spectral data are consistent with previous reports.

Hybrid DFT calculation studies: All calculations were performed with the Gaussian 98 package.[14] Geometries were fully optimized and characterized by frequency calculation using hybrid density functional theory (BHandHLYP) at the 6-31G* level.[12] Natural charges from natural population analysis were also computed for the gas phase. In the continuum solvation model, single-point energy calculations with the self-consistent reaction field (SCRF) calculation based on the polarizable continuum model (PCM,[13] ε = 36.64 for acetonitrile) were carried out at the same level as that used for geometry optimization.

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