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Theoretical Study of the Reaction Mechanism and Solvent Effect on the Regioselectivity of 1,3-Dipolar Cycloaddition Reaction Between Azide and Acetylene Derivatives

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ABSTRACT: *The reaction mechanism and solvent-dependant regioselectivity of 1,3-dipolar cycloaddition reactions between azide and acetylene derivatives have been studied using computational methods. The two possible reaction transition states were located. Geometry and NBO analysis found that the reactions take place along a synchronous and concerted mechanism for* **TS1** *and an asynchronous and less concerted mechanism for* **TS2**. *SCRF analysis found that* **TS2** *is more sensitive to the polarity of solvent. In less polar solvent such as CCl_4, the difference of activation barriers of the two transition states is small. However, when the reactions were conducted in water, the activation barriers for* **TS2** *increase which leads to the observed regioselectivity.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:203–207, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20236

INTRODUCTION

Water is one of the least popular solvents in synthetic organic chemistry. However, the use of water has obvious environmental and economic advantages and recent studies have revealed that a number of organic reactions proceed more rapidly and efficiently in aqueous solution than in organic solvents [1–4]. Particularly pericyclic reactions have drawn considerable attention, because these types of reactions were notoriously solvent insensitive.

1,2,3-Triazoles have attracted much attention in recent years because of their biological activity [5,6] and wide applications in organic synthesis [7,8]. Numerous synthetic methods for the preparation of 1,2,3-triazole derivatives have been developed. Amongst them, 1,3-dipolar cycloaddition between acetylene and azide is the traditional and extensively used method [9]. The regioselectivities of these reactions are generally low in organic solvent [10]. Efforts to improve the regioselectivity have so far met varying success [11,12]. The reaction conducted in solvent water is one of them. FMO theory was proposed to explain this phenomenon [11], i.e., in organic solvent, the regioselectivity is controlled by both dipole-HOMO and dipole-LUMO interactions simultaneously, while in water dipole-HOMO and dipolarophile-LUMO interaction predominates. Concerning the regioselectivity of pericyclic reaction, many other methods were used, such as the HSAB theory [13,14], the spin-polarized conceptual DFT method [13], magnetic susceptibility anisotropy χ_{anis} [15], and nucleus-independent chemical shifts (NICS) [15,16], etc. In this paper, the obvious solvent effect has been investigated based on energy

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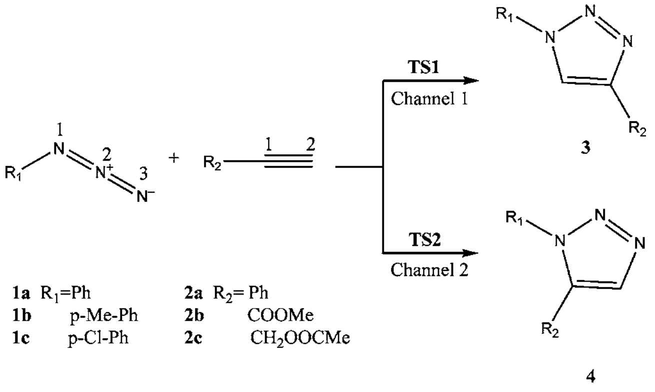

SCHEME 1 1,3-Dipolar cycloaddition reaction between azide and aceylene derivatives.

calculation. Also, the reaction mechanism was investigated using geometrical parameters analysis and natural bond orbital analysis. The studied reactions are shown in Scheme 1. Previous experimental results are listed in Table 1.

COMPUTATIONAL METHODS

All calculations included in this work were performed with the Gaussian 03 program [19] package. The geometries of reactants, transition states, and products were fully optimized. For those molecules that have more than one possible conformation, the conformation with the lowest electronic energy was singled out and used in the ensuing calculations. Density functional theory (DFT) has proven to be a widely applicable method for exploring organic chemistry [13]. It can give results comparable to MP2 and CCSD(T) methods. Here all the geometric parameters of possible stationary points were located at the B3LYP/6-31G level and were characterized by the number of imaginary frequencies. The zero-point vibrational energies (ZPVE) were computed at the same level and were not scaled. To obtain more accurate results, single-point energies were computed at MP2/6-311+G(d,p) level. Polarization continuum model [20] and CCl4 ($\varepsilon = 2.228$), water ($\varepsilon = 78.39$) and sometimes toluene ($\varepsilon = 2.379$) solvents were employed to calculate the solvent effects at 298.15 K.

TABLE 1 Experimental Product Ratios of the Cycloaddition between Azide **1** and Acetylene Derivatives **2** in Different Solvents

	*Organic Solvent (**3**:**4**)*	*Water (**3**:**4**)*
1a + **2a**	0.8:1[a]	**3** only[b]
1a + **2b**	3:1[c,d]	4.5:1[b]
1a + **2c**	–	15:1[e]
1b + **2a**	–	**3** only[b]
1b + **2b**	2.7:1[c]	3:1[b]
1c + **2a**	–	**3** only[b]
1c + **2b**	–	5.2:1[b]
1c + **2c**	2.1:1[c]	2.5:1[b]

[a] Under refluxed toluene [17], obtained 0.3:1–0.7:1 under refluxed ethanol [18].
[b] Under 85°C.
[c] Under refluxed CCl_4.
[d] Obtained **3** only in refluxed ethanol [18].
[e] Under 120°C.

RESULTS AND DISCUSSION

Geometrical Parameters

Selected geometrical parameters of the reactants, transition states, and possible products for the two reaction channels obtained at B3LYP/6-31G level are shown in Fig. 1 and Table 2. The most important geometrical parameters are the lengths of the two forming bonds, which are compared by Δr. This Δr provides an estimate for the synchronicity on the bond-formation process.

From Table 2, it can be seen that for all **TS2**, L_{N1-C1} is always longer than L_{N3-C2}, while for **TS1**, L_{N1-C2} is almost equal to L_{N3-C1} except when **2b** is used, in which L_{N3-C1} is longer than L_{N1-C2}. Overall, these data indicated that a less concerted transition state for channel 2 was formed and there were longer L_{N1-C1} bond than L_{N3-C2} bond formed in the transition state. A more concerted transition state is formed for channel 1. L_{N1-C2} and L_{N3-C1} are almost formed synchronously when **2b** is not used.

Why are there less concerted transition states in channel 2? An analysis of the geometry indicated that there are more steric repulsions between two phenyl groups in **TS2** (Fig. 1). Δr for products **3** and **4** is small.

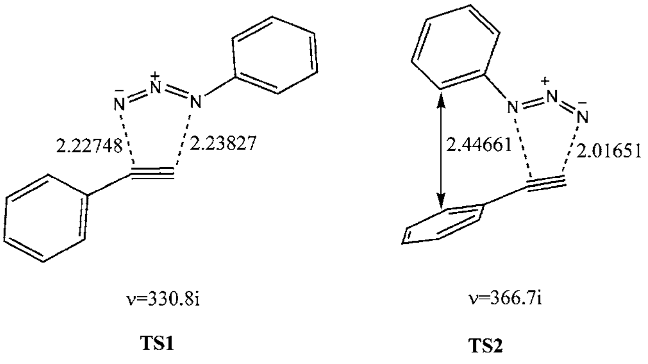

FIGURE 1 Selected geometrical parameters of transition state. Bond lengths are given in angstrom, and imaginary frequencies are given in cm^{-1}.

TABLE 2 B3LYP/6-31G Bond Lengths (in Å) and the Bond Differences Δr

		1a + 2a	1a + 2b	1a + 2c	1b + 2a	1b + 2b	1c + 2a	1c + 2b	1c + 2c
TS1	L_{N1-C2}	2.23827	2.11476	2.22687	2.23297	2.11042	2.25348	2.12787	2.24193
	L_{N3-C1}	2.22748	2.30381	2.20417	2.23461	2.31069	2.21364	2.28704	2.19017
	Δr_1	0.01079	0.18905	0.0227	0.00164	0.20027	0.03984	0.15917	0.05176
TS2	L_{N1-C1}	2.44661	2.31130	2.32409	2.43728	2.31277	2.46484	2.31418	2.33580
	L_{N3-C2}	2.01651	2.07843	2.06582	2.02530	2.07980	2.01003	2.08020	2.05743
	Δr_2	0.4301	0.23287	0.25827	0.41198	0.23297	0.45481	0.23398	0.27837
3	L_{N1-C2}	1.36979	1.35882	1.37210	1.36909	1.35850	1.37071	1.35958	1.37276
	L_{N3-C1}	1.38994	1.38491	1.38201	1.38939	1.38456	1.39090	1.38523	1.38271
	Δr_1	0.02015	0.02609	0.00991	0.0203	0.02606	0.02019	0.02565	0.00995
4	L_{N1-C1}	1.38053	1.38136	1.37641	1.38034	1.38128	1.38120	1.38199	1.37695
	L_{N3-C2}	1.37501	1.36898	1.37866	1.37478	1.36863	1.37561	1.36961	1.37915
	Δr_2	0.00552	0.01238	0.00225	0.00556	0.01265	0.00559	0.01238	0.0022

All the transition states were found to have only one imaginary frequency, which corresponds to the movements in the direction of the reaction coordinate. In this reaction, the mode of the imaginary frequency has contribution from the stretching of two intermolecular distances, the bending of the NNN framework, and the distortion of the CCH framework. The displacement vectors analysis reveals that the magnitude of the N3–C1 movement is greater than that of the corresponding N1–C2 movement for **TS1** and the N3–C2 movement is greater than that of the corresponding N1–C1 movement for **TS2**.

Natural Bond Orbital Analysis

The bond order analysis [21,22] has been used to study the synchronicity on the bond formation along the reaction pathways. To follow the nature of the molecular mechanism of this chemical reaction, the Wiberg bond indices [23] have been computed by using the NBO analysis as implemented in Gaussian 03. The bond order values are given in Fig. 2 and Tables 3 and 4.

It can be seen from Tables 3 and 4 that N1–N2 and N2–N3 of compounds **1** have bond orders around 1.48 and 2.29 which have bond orders between single bond and double bond and between double bond and triple bond, respectively. For compound **2**, the bond order is around 2.8 which is very close to a triple bond. Comparing the bond order of the two forming bonds of **TS1** and **TS2** with those of products **3** and **4**, we can estimate the degree of bond formation. For **TS1**, about 19–24% of N1–C2 and 19–24% of N3–C1 are formed. For **TS2**, about 15–19% of N1–C1 and 25–29% of N3–C2 are formed. This indicates that along reactive channel 1 the reaction progresses via a synchronously transition state, but for reactive channel 2 the reaction proceeds via an asynchronously transition state. This is consistent with geometry analyses that give a small Δr_1 of **TS1** and a big Δr_2 of **TS2**.

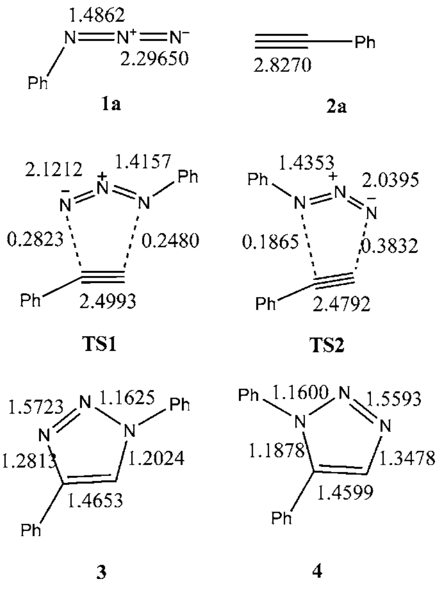

FIGURE 2 Bond orders for **1a** and **1b** and their transition states and products.

TABLE 3 Wiberg Bond Indices (Calculated at B3LYP/6-31G Level) Computed for Reactants

	1a	1b	1c		2a	2b	2c
N2–N3	2.2950	2.2909	2.3032	C1–C2	2.8270	2.8275	2.8774
N1–N2	1.4862	1.4884	1.4783				

TABLE 4 Wiberg Bond Indices (Calculated at B3LYP/6-31G level) Computed for Transition States and Products

		1a + 2a	**1a + 2b**	**1a + 2c**	**1b + 2a**	**1b + 2b**	**1c + 2a**	**1c + 2b**	**1c + 2c**
TS1	N1–C1	0.2480	0.2978	0.2543	0.2490	0.2990	0.2431	0.2923	0.2494
	N3–C2	0.2823	0.2450	0.2843	0.2800	0.2424	0.2869	0.2509	0.2896
	N1–N2	1.4157	1.3989	1.4223	1.4165	1.3990	1.4084	1.3931	1.4156
	N2–N3	2.1212	2.1714	2.1164	2.1215	2.1715	2.1224	2.1714	2.1172
	C1–C2	2.4993	2.5001	2.5447	2.5006	2.5000	2.4967	2.5020	2.5431
TS2	N1–C2	0.1865	0.2208	0.2245	0.1877	0.2188	0.1803	0.2215	0.2209
	N3–C1	0.3832	0.3443	0.3544	0.3782	0.3435	0.3872	0.3422	0.3586
	N1–N2	1.4353	1.4573	1.4201	1.4365	1.4588	1.4255	1.4504	1.4126
	N2–N3	2.0395	2.0770	2.0824	2.0424	2.0750	2.0419	2.0817	2.0836
	C1–C2	2.4792	2.4877	2.5169	2.4827	2.4886	2.4762	2.4881	2.5142
3	N1–C1	1.2024	1.2499	1.3155	1.2061	1.2518	1.1968	1.2445	1.1917
	N3–C2	1.2813	1.2852	1.1963	1.2860	1.2868	1.2782	1.2837	1.3122
	N1–N2	1.1625	1.1326	1.1761	1.1662	1.1340	1.1576	1.1279	1.1700
	N2–N3	1.5723	1.6072	1.5523	1.5661	1.6042	1.5771	1.6111	1.5580
	C1–C2	1.4653	1.4427	1.4995	1.4609	1.4399	1.4686	1.4473	1.5028
4	N1–C2	1.1878	1.1759	1.1943	1.1888	1.1762	1.1838	1.1731	1.1907
	N3–C1	1.3478	1.3798	1.3369	1.3493	1.3819	1.3443	1.3757	1.3335
	N1–N2	1.1600	1.2168	1.1543	1.1624	1.2185	1.1530	1.2092	1.1469
	N2–N3	1.5593	1.5163	1.5677	1.5564	1.5132	1.5652	1.5230	1.5741
	C1–C2	1.4599	1.4325	1.4878	1.4588	1.4305	1.4638	1.4360	1.4908

Energetics

The 1,3-dipolar cycloaddition reaction of the azide **1** and the acetylene **2** can take place along two reactive channels corresponding to **3** and **4**. Transition states for the two reaction channels were calculated in the gas phase. Then, solvent effects were considered by computing single point energies in solvent water and CCl_4 at MP2/6-311 + G(d,p) level. Activation energies are reported in Table 5.

When the solvents change from less polar one to polar one, the activation barriers increased. Comparing the activation energies, it can be seen that the activation energies gained by the assistance of the solvent CCl_4 is around 0.4–0.9 kcal/mol for **TS1** and 0.6–1.7 kcal/mol for **TS2**; for solvent water, it is around 0.5–1.6 kcal/mol for **TS1** and 1.5–3 kcal/mol for **TS2**. Overall, solvent effect on $\Delta E_2^{\neq}$ is significant. This is consistent with dipole moment. In the gas phase, the computed dipole moments of **1a, 1b, 1c, 2a, 2b,** and **2c** are 1.8, 2.4, 0.7, 0.8, 2.1, and 2.0 D, respectively. The significant solvent effect on the **TS2** arises because the polarities of transition state are high. By contrast, the **TS1** dipole moment is similar to the reactants. Consequently, the reactions are unaffected or even slowed down by polar solvents for **TS1** and accelerated to varying degrees by an increase in solvent polarity for **TS2**. $\Delta E_1^{\neq}/\Delta E_2^{\neq}$ decreases when the solvents change from CCl_4 to water, i.e., from less polar solvent to more polar solvent.

For **1a + 2b, 1b + 2b**, and **1c + 2b** reactions, the computed activation barriers for **TS1** are higher than that of **TS2** in less polar solvent CCl_4. When the solvent changes to water, the results reverse. The PCM

TABLE 5 Activation Energies $\Delta E^{\neq}$ (kcal/mol) for Reactions in the Gas Phase, CCl_4, and Water Using a PCM Solvation Model Computed at MP2/6-311+G(d,p) Level

	Gas Phase				*CCl_4*		*Water*	
Reaction	$\Delta E_1^{\neq}$	*Dipole Moment*	$\Delta E_2^{\neq}$	*Dipole Moment*	$\Delta E_1^{\neq}$	$\Delta E_2^{\neq}$	$\Delta E_1^{\neq}$	$\Delta E_2^{\neq}$
1a + 2a	14.2	1.2	14.8	2.4	15.1	15.8	15.8	17.3
1a + 2b	11.6	2.2	9.9	3.4	12.0	11.0	12.1	12.4
1a + 2c	12.8	2.6	13.5	3.6	13.3	14.1	13.8	15.0
1b + 2a	14.2	1.8	14.3	2.6	15.0	15.2	15.7	16.6
1b + 2b	11.6	2.5	9.8	4.0	12.0	10.9	12.2	12.2
1c + 2a	15.1	2.1	15.8	3.5	16.0	16.9	16.8	18.6
1c + 2b	12.2	2.2	10.7	3.1	12.7	12.4	12.8	13.7
1c + 2c	13.7	2.3	14.4	3.2	14.4	15.7	14.8	16.2

model for CCl_4 overestimates the relative destabilization of **3** isomer, predicting that the **4** isomer should be favored by 1.0, 1.1, and 0.3 kcal/mol, respectively, with **2b**, whereas the **3** isomer makes up 67–75% of the mixture of isomers experimentally.

The computed energy barriers are consistent with experimental results in water, i.e., good regioselectivity for **3** (it is worthy to note that R2=COOEt was used in the experiment).

Previous experiments [17,24] showed that the reaction of **1a** with **2a** in toluene under reflux gave two regioisomers in approximately 1:1 ratio. We also considered this reaction in solvent toluene at MP2/6-311+G**//B3LYP/6-31G level, which gave the activation barriers 15.1 and 15.9 kcal/mol, respectively. It shows that **TS1** is slightly stable than **TS2** in agreement with the results of no regioselectivity.

CONCLUSION

In conclusion, we have explained the experiment observed solvent effect on regioselectivity of 1,3-dipolar cycloaddition reaction between azide and acetylene derivatives employing computational methods. The results showed that polarity of solvent has a larger solvent effect on **TS2** than **TS1**. **TS1** is favored when solvent change from less polar CCl_4 to polar water. Also computation found the reaction takes along a synchronous and concerted mechanism for **TS1** and an asynchronous and less concerted mechanism for **TS2**.

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