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Substituent Effects, Reactant Preorganization, and Ligand Exchange Control the Reactivity in Rh^I-Catalyzed (5+2) Cycloadditions between Vinylcyclopropanes and Alkynes**

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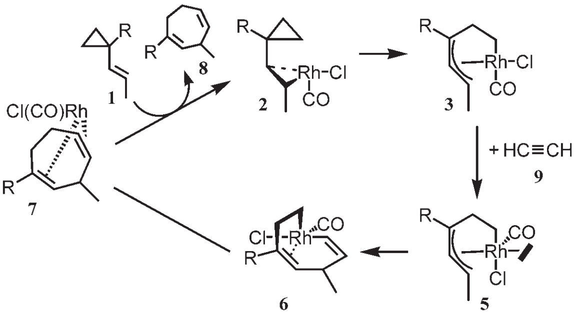
Transition-metal-catalyzed cycloadditions have become powerful reactions for the construction of carbocycles.[1] $[\{Rh(CO)_2Cl\}_2]$-catalyzed (5+2) reactions between vinylcyclopropanes (VCPs) and alkynes are an effective way to construct seven-membered rings.[2,3] Experimental studies have shown that siloxy, alkoxy, or alkyl group substitution at the C^1 position of the cyclopropane is required to confer adequate reactivity of the VCPs in these reactions.[3] The cycloaddition of 1-siloxy-, 1-alkoxy-, or 1-isopropyl-substituted VCPs with methyl propiolate provides the (5+2) cycloadducts in high yields (84–93 %) in 10 min to 2 h at 40–80 °C.[3] Cycloaddition with the 1-methyl-substituted VCP is slower, giving 83 % yield in 8 h at 80 °C.[3c] The unsubstituted VCP (R = H) is the slowest-reacting compound, giving only 23 % yield in 30 h at 80 °C. We have investigated the origins of these effects using density functional theory and show that substituent effects both on transition state energetics and on reactant preorganization influence the reaction rates.[4]



Scheme 1. Catalytic cycle for Rh^I-catalyzed (5+2) cycloadditions.

Previous theoretical and mechanistic studies have shown that the (5+2) reactions occur by the catalytic cycle shown in Scheme 1.[5] The reactions of acetylene with four VCPs (**1a**, R = H; **1b**, R = Me; **1c**, R = *i*Pr; and **1d**, R = OMe) were investigated using B3LYP/SDD-6-31G* with CPCM solvation energy corrections for CH_2Cl_2. The free energy surface for the reaction with **1a** is shown in Figure 1. Such diagrams conventionally start with **2a**, but we show the catalytic cycle beginning from the product complex **7a**, which is the most stable intermediate in the catalytic cycle, and the most stable conformer of the VCP complex is s-*trans*-**1a**. The surfaces computed for other VCPs are included in the Supporting Information. The transition state for the alkyne insertion (**TS3**) has the highest free energy. The free energy span from complex **7** plus VCP and alkyne reactants to **TS3** plus product **8** determines the rate of these cycloadditions.[6] The VCPs **1a**, **1b**, and **1d** adopt the s-*trans* conformation, while only the s-*cis* conformer of the Rh–VCP complex **2** can lead to the allyl intermediate **3** from which cycloadduct **8** is derived. Thus, the ground state of the VCP, the s-*trans* conformer, needs to be preorganized to s-*cis* before binding with the rhodium catalyst. Since the ground state of bulky **1c** is s-*cis*, there is no need for a preorganization.

The overall activation barrier could be broken down to three parts: the preorganization energy (ΔG_{po}) to form the s-*cis*-VCP, the free energy of exchange (ΔG_{ex}) to transfer the catalyst from the product complex **7** to the s-*cis*-VCP to form the VCP–catalyst complex **2** and liberate product **8**, and the free energy of **TS3** relative to reactant complex **2** (ΔG(**TS3**−**2**)). Thus, the observed accelerations upon substituting the C^1 position might arise from the electronic stabilization of **TS3** and the factors influencing the preorganization energy (ΔG_{po}) or ligand exchange energy (ΔG_{ex}). The contributions of these energies to the activation barrier are shown in Figure 2.

The transition state of the alkyne insertion (**TS3**; ΔG(**TS3**−**2**)) is stabilized by the conjugation or hyperconjugation of the C^1 substituent with the allyl π system. **TS3d** with its strongly conjugating methoxy group is 9.2 $kcal\,mol^{-1}$ more stable relative to **2d** than the unsubstituted **TS3a** relative to

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

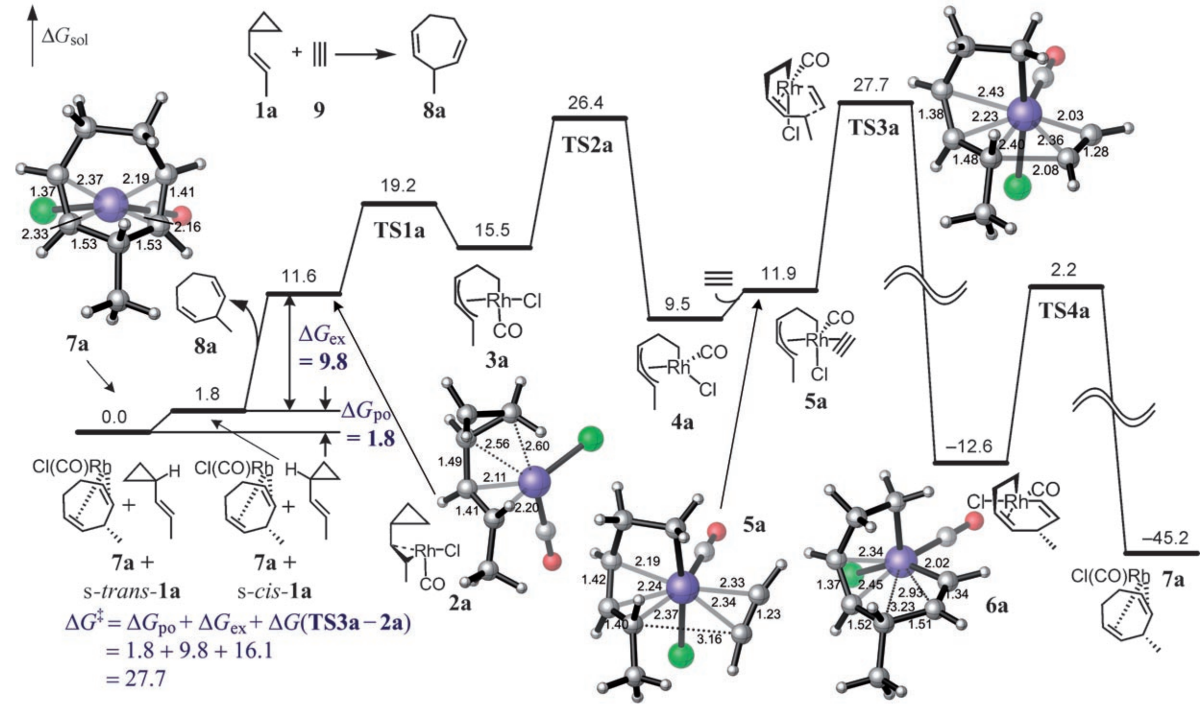

Figure 1. The energy surface of the (5+2) cycloaddition between 1-(1-propenyl)cyclopropane (**1a**) and acetylene. Bond lengths are in Å, energies in kcal mol^{-1}.

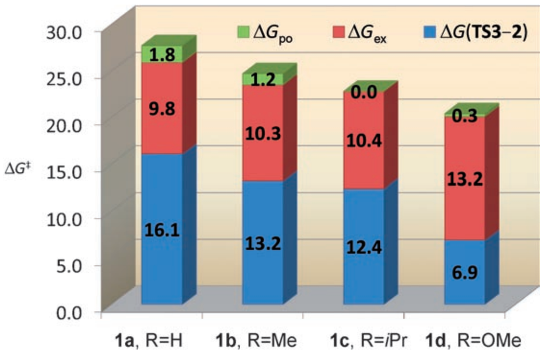

Figure 2. Activation barriers in kcal mol^{-1} of the (5+2) cycloaddition between VCPs **1a–d** and acetylene **9**.

Table 1: C^1−R bond lengths in reactants **1**, complexes **2**, and transition states **TS3** (in Å).

R	Reactant 1		Complex 2	2−1 (s-*cis*)	TS3	TS3−1 (s-*cis*)
	s-trans	*s-cis*				
H	1.088	1.091	1.086	−0.005	1.088	−0.003
Me	1.517	1.524	1.521	−0.003	1.505	−0.019
*i*Pr	1.539	1.545	1.538	−0.007	1.519	−0.026
OMe	1.405	1.412	1.381	−0.031	1.338	−0.074

2a. The corresponding stabilization energies for the methyl- and isopropyl-substituted **TS3b** and **TS3c** are 2.9 and 3.7 kcal mol^{-1}, respectively (Figure 2).

Conjugation can be detected in the changes of C^1−R bond lengths in VCPs **1a–d**, pre-reaction complexes **2a–d**, and **TS3a–d** (Table 1). In **TS3d**, the methoxy lone pair conjugates with the allyl π system, and the C^1−O bond is shortened by 0.07 Å compared to that in s-*cis*-**1d**. As expected, the conjugation is weaker in the pre-reaction complex **2d**, and the C^1−O bond is only shortened by 0.03 Å. For methyl- and isopropyl-substituted VCPs (**1b** and **1c**), the hyperconjugation between the alkyl group and the allyl π system shortens the C^1−R bond by 0.02 (**TS3b**) and 0.03 Å (**TS3c**), respectively. As in the alkyl-substituted system, the C^1−R bond in the pre-reaction complex is only slightly shortened (0.003 Å for **2b** and 0.01 Å for **2c**).

Substituents on the VCP also affect its reactivity by steric effects on ΔG_{po} and ΔG_{ex}. Substituents at the C^1 position could accelerate the cycloaddition by decreasing the preorganization energy (ΔG_{po}) to form the s-*cis*-VCP. ΔG_{po} for **1a**, **1b**, and **1d** is 1.8, 1.2, and 0.3 kcal mol^{-1}, respectively (Figure 2). For **1c**, s-*cis* is the most stable conformer, and no energy is needed for preorganization. From the data it can be concluded that bulky substituents decrease the VCP preorganization energy and thus accelerate the reaction.

The free energies of transfer (ΔG_{ex}) of the Rh catalyst from the product complex **7** to form the VCP–catalyst complex **2** are similar for **1a–c** (9.8, 10.3, and 10.4 kcal mol^{-1}). This suggests that ligand exchange energies have small effects on the overall reaction barrier of cycloadditions with alkyl-substituted VCPs. The corresponding process for the methoxy-substituted **1d** is more difficult (13.2 kcal mol^{-1}), due to stabilization of **7** by the methoxy group.

The computed reaction free energy barriers are 27.7, 24.7, 22.8, and 20.4 kcal mol^{-1} for **1a**, **1b**, **1c**, and **1d**, respectively (Figure 2). This trend is in agreement with the experimental reactivities discussed in the introduction. Methyl-substituted

VCP reacts slower than methoxy- and isopropyl-substituted VCPs, while un unsubstituted VCP reacts most slowly.[3]

These theoretical studies of $[\{Rh(CO)_2Cl\}_2]$-catalyzed (5+2) cycloadditions between C^1-substituted VCPs and alkynes show why both bulky substituents and heteroatom substituents on the 1-position of the cyclopropane ring accelerate the reaction. The C^1 substituents promote the reaction by stabilizing the intermediates involving an electron-deficient allyl group, including the rate-determining alkyne insertion transition state structure **TS3**, and by destabilizing the reactant ground state relative to the transition state, easing the preorganization of the VCP reactant.

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