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Effect of electron-withdrawing group on the [3,3]-sigmatropic rearrangements of 1,5-enynes, 1,5-diynes and 1,2-diene-5-ynes: A theoretical study

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ABSTRACT

The electronic effects of an electron-withdrawing group (exemplified by formyl group) on the kinetic and thermodynamic aspects of substituted 1,5-enyne, 1,5-diyne, and 1,2-diene-5-yne Cope rearrangements were investigated by means of DFT and CBS-QB3 calculations. The energy barriers of the formyl substituted reactions are lower than those of the unsubstituted ones almost in all cases, and the barriers will be further lowered when catalyzed by $AlCl_3$. The most obvious electronic effect was calculated for the C-2 formyl substituted 1,5-enyne rearrangements, which have activation barriers of 27.1 and 18.1 kcal/mol, respectively, for the uncatalyzed and catalyzed reactions. The charge transfer induced by the electron-withdrawing group and stabilization of the charge by Lewis acid are responsible for the different energetic profiles. The formyl substitution will change the thermodynamic profiles of the transformations, notablely, increase the reaction enthalpies of the 1,5-diyne and 1,2-diene-5-yne rearrangements by over 5.0 kcal/mol, as result of the stabilization effect of a formyl substitution attached directly to the unsaturated moieties of the products.

1. Introduction

As part of the [3,3]-sigmatropic rearrangement family, the Cope rearrangement of 1,5-diene is a powerful tool in organic synthesis, and many variants have been developed up to date [1]. The parent reaction needs to be heated over 150 °C, and the activation barrier was determined to be about 34 kcal/mol [2,3]. To expand the scope of this useful transformation, many methods have been carried out to accelerate the reaction rate and lower the operational temperature. Introduction of functional groups to the all-carbon framework for activation of the reactants or stabilization of the transition state has been proved to be quite practical [4–6]. Among the methods used, the introduction of a hydroxyl substituent at C-3 of the 1,5-dienes, known as the oxy-Cope and anionic oxy-Cope rearrangements, has been found to be a practical protocol for ring formation and stereoselective synthesis [7]. The catalytic Cope rearrangements are also widely studied, and remarkable effect of acids on the reaction rate has been found, as results of charge delocalization [8]. The Cope rearrangement is also a hot topic in theoretical studies [9]. The detailed reaction pathway has been investigated at various levels of theory and a concerted process with an aromatic transition state has been defined [10]. Substituent effects on the kinetic, thermodynamic as well as variation of the mechanism were better understood with the theoretical results [11,12].

The thermal rearrangements of 1,5-enyne and 1,5-diyne were first reported by Huntsman and co-workers more than 40 years ago [13], and later the rearrangement of 1,2-diene-5-yne was reported by the Hopf group in 1972 (Fig. 1) [14]. These rearrangements expand the Cope rearrangement to alkyne and allene containing substrates, which may be of great theoretical and synthetic interests [15]. However, the demanding conditions for such kind of rearrangement hindered the possible applications, as relative high temperatures are needed for the occurrence of the reactions [16]. To understand the essence of these new transformations, theoretical investigation on the nature of the transition state, activation barrier and reaction energy has been conducted by the Houk group [17]. By means of DFT and ab initio calculations, it's found that these Cope rearrangements of divergent substrates are similar to the parent 1,5-diene rearrangement and belonged to the family of pericyclic reactions [17].

While the variants of the 1,5-diene rearrangement were widely pursued and used in organic synthesis, applications of the 1,5-enyne, 1,5-diyne, and 1,2-diene-5-yne Cope rearrangements are still quite limited [18,19]. Inspired by the remarkable effect of the substituents in the 1,5-diene rearrangements, we wonder whether such effect can also be applicable to the 1,5-enyne, 1,5-diyne, and 1,2-diene-5-yne rearrangements shown in Fig. 1. Encouraged

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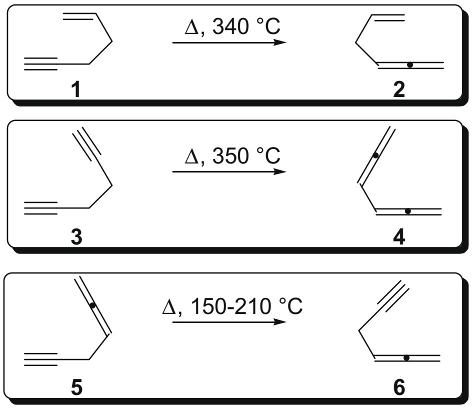

Fig. 1. Thermal rearrangements of 1,5-enyne, 1,5-diyne and 1,2-diene-5-yne.

by the reliable results of previous theoretical studies, we carried out our attempts by computation of the reaction pathways of substituted 1,5-enyne, 1,5-diyne, and 1,2-diene-5-yne substrates. The electronic effect of a CHO substituent and the influence of a Lewis acid catalyst on the energetics of the reactions were studied and reported herein [1b,20]. The results showed that dramatic electronic effect was found when formyl is substituted to C-2 of the 1,5-enyne, and the activation barrier of this reaction could be lowered to about 18 kcal/mol with $AlCl_3$ used as the Lewis acid catalyst.

2. Computational details

All calculations were done by using the GAUSSIAN 03 software package [21]. The B3LYP/6-31G* method was used to obtain the transition state structures and activation barriers [22,23]. Previous studies showed that this level of theory could predict activation energies of Cope rearrangements in excellent agreements with the experiments [9a,10d,f]. While the stability of allene would be overestimated by the B3LYP/6-31G* method, the CBS-QB3 method was used for the calculations of the reaction energies according to literature [24]. All the stationary points were optimized with B3LYP/6-31G* method in the gas phase, and the reactants and products were recalculated with CBS-QB3 method. Frequency calculations were used to characterize the stationary points as minima or first-order saddle points. All reactions and activation enthalpies reported were zero-point (ZPE) corrected with unscaled frequencies. All the deviations of these energy values were within 1 kcal/mol compared with those in which the frequencies were scaled by 0.96 according to the recommendation of Radom [25] and Houk [17], which are given in Table S2 of the Supplementary Material.

All the activation enthalpies discussed were calculated at B3LYP/6-31G* level of theory. As expected, the allene stabilities were overeatimated by the DFT method (Table 1), and all the reaction enthalpies reported in the text were from CBS-QB3 calculations. The formyl substituted reactions are depicted in Fig. 2. Only the concerted transition states were located for the reactions, and calculations by using the UB3LYP/6-31G* method would give the same results as the B3LYP/6-31G* calculations [26]. The nomination of the transition states is corresponding to the reactants, for example, **TS1a** refers to the transition state of the Cope rearrangement of **1a** and **2a**, while **TS1a-LA** is the transition state of the $AlCl_3$-catalyzed **1a** to **2a** transformation. The activation barrier of the $AlCl_3$-catalyzed reaction was the energy gap between the transition state and the complex of $AlCl_3$ and formyl substituted substrate [27]. The geometries of the most stable conformers of the reactants and products are given in the Supplementary Material.

Table 1
Activation enthalpies and reaction enthalpies (kcal/mol).

Transformation	$\Delta H^{\neq}$[a]	$\Delta H^{\neq}$(LA)[a]	ΔH_{rxn}(DFT)[b]	ΔH_{rxn}(CBS-QB3)[b]
1 → **2**	32.2		−5.3	−4.1
1a → **2a**	35.9	33.9	1.9	3.6
1b → **2b**	27.1	18.1	−5.7	−0.6
1c → **2c**	28.0	22.8	−13.6	−5.6
1d → **2d**	28.7	19.0	−13.1	−5.6
1e → **2e**	31.9	24.7	−8.4	−7.4
3 → **4**	32.0		−14.0	−3.9
3a → **4a**	26.5	24.8	−16.5	−9.5
3b → **4b**	28.9	24.7	−21.5	−10.7
5 → **6**	32.8		0.0	0.0
5a → **6a**	29.6	26.1	−7.7	−4.9
5b → **6b**	28.3	26.2	−2.0	−5.1

[a] Activation enthalpies for the uncatalyzed and $AlCl_3$-catalyzed transformations.
[b] Reaction enthalpies calculated at B3LYP/6-31G* and CBS-QB3 levels.

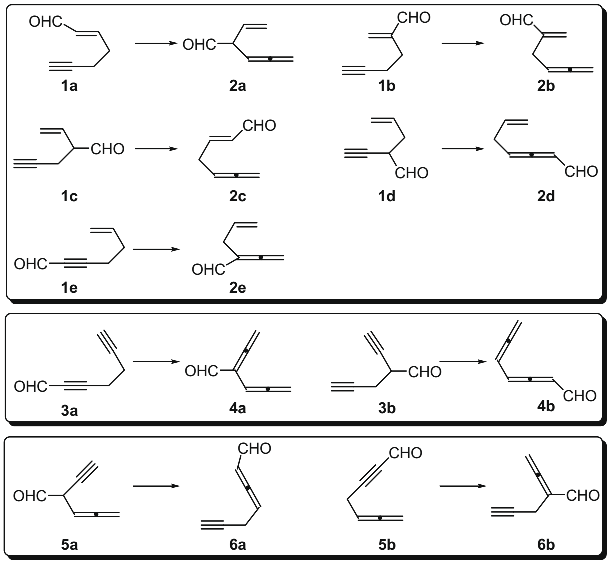

Fig. 2. Cope rearrangements of formyl substituted 1,5-enynes, 1,5-diynes and 1,2-diene-5-ynes.

3. Results and discussion

The computed reaction barriers and reaction energies of the formyl-substituted and $AlCl_3$-catalyzed reactions are given in Table 1, and the geometrical structures of the transition states are depicted in Figs. 3–5.

3.1. Rearrangements of the formyl substituted 1,5-enynes

As $\Delta H^{\neq}$ values in Table 1 show, the reaction barriers for **1c** and **1d** rearrangements will be lowered by 4–5 kcal/mol compared with that of the unsubstituted substrate **1**, and a lowest barrier of 27.1 kcal/mol was calculated for converting of **1b** to **2b** through **TS1b**. However, the substitution at C-1 (**1a**) will increase the activation barrier to 35.9 kcal/mol, and only quite limited effect of the C-6 substitution was found in the **1e** to **2e** transformation.

Mulliken charge population shows charge transfer will be enhanced in all the formyl substituted reactions [28]. The electron-withdrawing group influences the charge transfer most in **TS1b** and the formyl moiety in this transition state holds greater negative charge than in **TS1a**, **TS1c**, **TS1d** and **TS1e**, which result a more stable **TS1b** among the transition states in the uncatalyzed reactions.

The reaction enthalpies of the substituted reactions will also be changed by the formyl substituent. Compared with the reaction