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# How to Promote Sluggish Electrocyclization of 1,3,5-Hexatrienes by Captodative Substitution

Tang-Qing Yu, Yao Fu,* Lei Liu,* and Qing-Xiang Guo

*Department of Chemistry, University of Science and Technology of China, Hefei 230026, China*

*fuyao@ustc.edu.cn; leiliu@ustc.edu*

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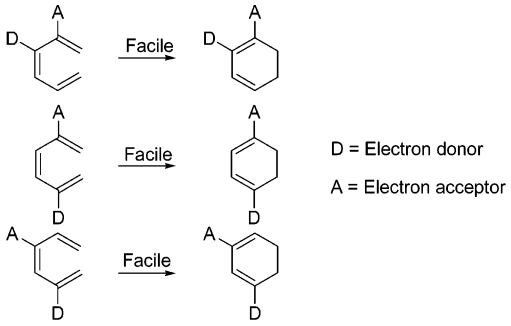


Extraordinarily rapid 6π-electrocyclization

Hexatriene electrocyclization, if not disfavored by its harsh reaction conditions, can be highly useful for the synthesis of complex organic molecules. Herein we developed a two-layer ONIOM method which could predict the activation free energy of hexatriene electrocyclization with an accuracy of about 1.0 kcal/mol. Using this carefully benchmarked method, we calculated the activation free energies for a variety of substituted hexatrienes. It was found that extraordinarily rapid electrocyclization could occur for certain patterns of captodative substituted hexatrienes, including 2-acceptor−3-donor hexatrienes, 2-acceptor−5-donor hexatrienes, and 3-acceptor−5-donor hexatrienes. The activation free energies for these systems could be up to 10 kcal/mol lower than that of the unsubstituted hexatriene, and therefore, their electrocyclization could proceed smoothly even at room temperature. The mechanism for the captodative effect on hexatriene electrocyclization could be understood by calculating the affinity between the donor and acceptor group in the reactant state and transition state of the reaction. If the affinity was stronger in the transition state, captodative substitution would produce an extra acceleration effect. It was shown that our theoretical results were in excellent agreement with the experimental data from the recent synthetic studies of hexatriene electrocyclizations. Thus, the theoretical tools developed in the present study could be used to predict not only how to accelerate the hexatriene electrocyclization via substituent manipulation but also under what conditions each particular electrocyclization could be accomplished in the real experiment.

## 1. Introduction

The interconversion of 1,3,5-hexatriene to 1,3-cyclohexadiene (Figure 1) is the most simple example of a thermal, disrotatory, six-electron electrocyclization allowed for by the Woodward−Hoffmann rules.[1] This type of reaction has been proposed to be involved in the biosynthesis of vitamin D,[2] certain polycyclic endiandric acids,[3] and eudesmane sesquiterpene (+)-occidentalol from plants,[4] polypropionate-derived 9,10-deoxytridachione produced by a marine mollusc,[5] a small number of pheromones isolated from a brown alga,[6] and certain *o*-dialkyl-substituted benzenoid natural products.[7] The elegance and efficiency of

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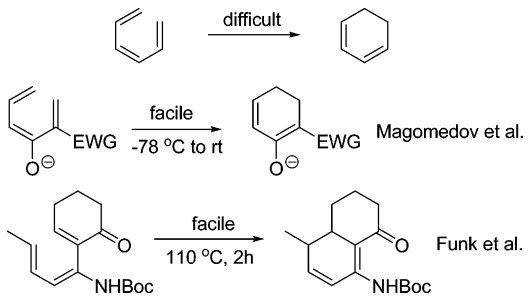


**FIGURE 1.** Some unusually facile hexatriene electrocyclizations.

these biological transformations have prompted chemists to find applications of hexatriene electrocyclization in the synthesis of complex molecules, including natural products. It has been demonstrated in many cases that thermal hexatriene electrocyclization is indeed an enabling approach for the construction of carbocyclic six-membered rings in suitably substituted or functionalized forms.[8]

Despite the previous successes, there remain a few serious problems with the utilization of hexatriene electrocyclization in target-oriented synthesis.[9] First, the preparation of trienes with the required *cis* configuration of the central double bond has not been straightforward. This problem can sometimes be solved or avoided by placing the central double bond in a ring system. Second, and perhaps even more limiting, hexatriene electrocyclization normally has a huge energy barrier to overcome. Thus, a reaction temperature as high as 150−200 °C is often necessary to trigger hexatriene electrocyclization. Such high temperatures may cause tremendous problems in the synthesis of delicate compounds. It is, therefore, highly important to find solutions to effectively decrease the energy barrier of hexatriene electrocyclization. In this regard, Magomedov et al. recently reported a very interesting finding that the presence of electron-withdrawing groups at the C2 of the 3-oxido hexatrienes enormously lowers the activation energy of the 6$\pi$-electrocyclizations (see Figure 1).[10] More recently, Funk et al. reported novel indole annulations that involved fairly facile electrocyclic ring closures of amidotrienes (also see Figure 1).[11] It was proposed that the coexistence of amido and carbonyl groups "electronically activated" the thermal 6$\pi$-cyclization.

Both Magomedov's and Funk's studies intimate that tactical incorporation of electron-donating and -withdrawing groups in a hexatriene may effectively lower the activation energy of its electrocyclization. This hypothesis, if true, would have significant implications for the utilization of hexatriene electrocyclization in target-oriented organic synthesis. It would allow one to design captodative[12] substituted hexatrienes from which novel carbocycles could be obtained via facile 6$\pi$-electrocyclization. Furthermore, by strategic substituent manipulations, in particular, protecting group introductions and removals, one could be able to achieve thermal 6$\pi$-electrocyclization of fragile molecules under tolerable conditions. Nonetheless, a few questions have to be answered first: (1) to what extent the captodative substitution can reduce the activation energy of thermal 6$\pi$-electrocyclization? (2) whether all the captodative substituted hexatrienes can undergo facile 6$\pi$-electrocyclization? and (3) what is the mechanism responsible for the acceleration of 6$\pi$-electrocyclization by captodative substitution? Since none of these important questions have been answered before, we recently carried out a systematic study on the electrocyclization of captodative substituted 1,3,5-hexatrienes using the state-of-art computational methods.

It is worth mentioning that some other theoretical studies have also been conducted concerning the electrocyclization of certain special groups of hexatrienes.[13] For instance, Houk et al. once studied the electrocyclization reaction of 1-substituted 1,3,5-hexatrienes (F, $CH_3$, CN, CHO, NO, $BH_2$) using the MP2/6-31G* method, with an emphasis on the inward or outward rotation of the substituent in the transition state.[13a] More recently, Guner et al. investigated the electrocyclizations of 1,3,5-hexatrienes having a 1-dimethylamino latent leaving group using the B3LYP/6-31G* method.[13i] It was found that introducing $CO_2Me$ at C4 further decreases the activation energy by 7 kcal/mol. Electron-withdrawing groups ($NO_2$, $SO_2Ph$, and $C{=}N^+Me_2$) at C2 have a profound effect of 17−25 kcal/mol on the activation energy. Furthermore, Jiao and Schleyer predicted appreciable electrostatic acceleration (10.9 kcal/mol, B3LYP/6-311+G*) of the cyclization of 1,3-*cis*-5-hexatriene to 1,3-cyclohexadiene by $Li^+$ complexation.[13b]

## 2. Methods

Ab initio calculations were performed with the Gaussian 03 suite of programs.[14] Geometry optimizations were performed using the B3LYP/6-31G(d) method without any constraint. For compounds

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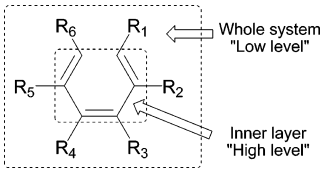
**CHART 1**




that have multiple conformations, the conformation with the lowest energy was chosen for the present study. Frequency calculations were carried out at the B3LYP/6-31G(d) level of theory and performed on all of the species to confirm convergence to appropriate local minima or saddle points on the energy surface. In all instances, transition-state structures gave one significant imaginary frequency, while no imaginary frequencies were observed for the minimum-energy species.

Single-point energies were determined using the ONIOM method,[15] as pure QCISD(T) calculations for the substituted hexatrienes were impractical for our computational resources. A two-layer ONIOM method was utilized, that is, ONIOM(QCISD-(T)/6-31+G(d,p)):B3LYP/6-311+G(2df,2p)). The inner layer treated at the "high" level (i.e., QCISD(T)/6-31+G(d,p)) was comprised of six carbon atoms and their hydrogens, while the whole system was treated at the "low" level (i.e., B3LYP/6-311+G(2df,2p)) (see Chart 1). Corrections of the energy to 298 K were made from the frequency calculations, including zero point energy corrections.

The integral equation formalism version of PCM (IEF-PCM) as implemented in Gaussian 03 was used to calculate the solvation free energies in benzene.[16] In the calculation, the solute was modeled as a cavity made up of a set of interlocking spheres by using the United Atom model (UA0). Hydrogen atoms were included in the sphere of the atom to which they were bonded. All the IEF-PCM calculations were performed at the B3LYP/6-31+G(d,p) level. Both the electrostatic and nonelectrostatic contributions were considered for the total solvation energies.

## 3. Results and Discussion

**3.1. Systems with Known Experimental Data.** In Table 1, we show the experimental rate constants and corresponding activation free energies for the thermal 6$\pi$-electrocyclization of several hexatrienes (note: these experiments were performed in neat conditions). Compared to the experimental data,[17−19] our theoretical activation free energies in the gas phase have a root of mean square error (RMS) of 1.0 kcal/mol. This manifests that the ONIOM(QCISD(T)/6-31+G(d,p)):B3LYP/6-311+G(2df,2p) method can provide reliable predictions for the 6$\pi$-electrocyclization of substituted hexatrienes. To take the solvent effects into consideration, we have chosen benzene as a solvent whose polarity is close to hexatrienes. It is found that the theoretical activation free energies in benzene have a RMS error of 0.9 kcal/mol, which represents a marginal improvement over the calculations in the gas phase. Thus, we conclude that the solvation effects on the thermal 6$\pi$-electrocyclization are usually negligible. In the subsequent studies, we will focus on the gas phase free energies only.

**3.2. Electrocyclization of Monosubstituted Hexatrienes.** Before studying captodative substituted hexatrienes, we need to know the effect of monosubstitution on the thermal 6$\pi$-electrocyclization of hexatrienes. Previously, Houk et al. reported that most of the substituents at C1 would slightly increase the activation barrier of hexatriene electrocyclization, as expected due to the steric crowding.[13a] In agreement with this finding, our own calculations for seven representative substituents (i.e., an alkyl group $CH_3$, two typical electron donors $NH_2$ and OH, a halogen F, and three typical electron acceptors CHO, CN, and $NO_2$) show that four of them increase the activation free energy slightly by 0.3−2.4 kcal/mol (see Table 2). Although the remaining three C1 substituents (i.e., OH, F, and $NO_2$) reduce the activation free energy, the decrease is insignificant (0.7−2.4 kcal/mol). Thus, it is concluded that monosubstitution at C1 does not exert any significant effect on the rate of thermal 6$\pi$-electrocyclization.

Compared to the case of C1 substitution, our calculations suggest that monosubstituent at C2 or C3 will decrease the activation free energy of hexatriene electrocyclization, regardless of whether the substituent is an electron donor or acceptor. The mechanism for the energy decrease is probably attributable to the anchimeric assistance effect exerted by the substituent on the transition state.[18] It is interesting to note that an electron acceptor tends to bring about more significant decrease in the activation free energy. Furthermore, for each particular substituent, the C2-substituted hexatriene always exhibits an activation free energy lower than that in the C3 case. Combining these two effects, the lowest activation free energy is seen for 2-$NO_2$-hexatriene (24.8 kcal/mol). Its cyclization rate is predicted to be about $2 \times 10^4$ times faster than that of the nonsubstituted hexatriene.

**3.3. Electrocyclization of Disubstituted Hexatrienes.** Having learned the effect of monosubstitution on the activation free energy of hexatriene electrocyclization, we next carried out extensive calculations to explore the disubstitution effects. Because very little has been known in the past about such effects, our calculations have to be exhaustive, covering all the possible combination of substituents (see Table 3). Preliminary analysis of the bulky data in Table 2 provides the following summary conclusions:

1. In most cases, the activation free energy of electrocyclization differs from that of the unsubstituted hexatriene by less than 5 kcal/mol. This is consistent with the past experience that thermal electrocyclization of hexatriene is a difficult reaction under most conditions.

2. Extraordinarily low activation free energies are observed for some captodative substituted cases, including 2-$NO_2$-3-$NH_2$ (20.4 kcal/mol), 2-$NO_2$-3-OH (19.8 kcal/mol), 2-CHO-3-$NH_2$

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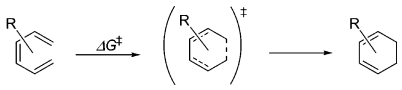
**TABLE 1. Comparison between the Computational and Experimental Activation Free Energies for Seven Hexatrienes (unit for $\Delta G^{\ddagger}$: kcal/mol)**

| R | $T$ | solvent (exp) | log$k$ (exp) | $\Delta G^{\neq}$ (exp)[a] | $\Delta G^{\neq}$ (theor) (gas phase) | $\Delta G^{\neq}$ (theor) (in benzene) | ref. |
|---|---|---|---|---|---|---|---|
|  | 423.2 | Neat | -3.62 | 32.1 | 31.4 | 31.5 | 17 |
|  | 423.2 | Neat | -3.05 | 31.0 | 30.9 | 30.9 | 17 |
|  | 423.2 | Neat | -3.03 | 30.9 | 29.6 | 29.6 | 17 |
|  | 395.2 | Neat | -2.34 | 27.6 | 28.0 | 28.1 | 18 |
|  | 418.2 | Neat | -3.43 | 30.7 | 29.4 | 29.4 | 19 |
|  | 418.2 | Neat | -3.43 | 30.7 | 29.2 | 29.4 | 19 |
|  | 398.6 | Neat | -3.07 | 29.2 | 29.4 | 29.7 | 17 |

[a] Calculated by using the equation: $\Delta G^{\ddagger} = -2.303RT \times \log(kh/k_bT)$.

**TABLE 2. Activation Free Energies (kcal/mol) for Electrocyclization of Monosubstituted Hexatrienes at 298 K**




|  | $\Delta G^{\neq}$ |  | $\Delta G^{\neq}$ |  | $\Delta G^{\neq}$ |
|---|---|---|---|---|---|
| $R_1$ = H | 30.7 | $R_2$ = H | 30.7 | $R_3$ = H | 30.7 |
| $R_1$ = $CH_3$ | 32.2 | $R_2$ = $CH_3$ | 27.7 | $R_3$ = $CH_3$ | 30.4 |
| $R_1$ = $NH_2$ | 31.0 | $R_2$ = $NH_2$ | 27.1 | $R_3$ = $NH_2$ | 30.4 |
| $R_1$ = OH | 30.0 | $R_2$ = OH | 29.8 | $R_3$ = OH | 30.4 |
| $R_1$ = F | 28.3 | $R_2$ = F | 30.0 | $R_3$ = F | 30.0 |
| $R_1$ = CHO | 33.1 | $R_2$ = CHO | 25.3 | $R_3$ = CHO | 27.9 |
| $R_1$ = CN | 31.9 | $R_2$ = CN | 24.9 | $R_3$ = CN | 29.1 |
| $R_1$ = $NO_2$ | 30.2 | $R_2$ = $NO_2$ | 24.8 | $R_3$ = $NO_2$ | 25.4 |

(20.3 kcal/mol), 2-CHO-3-OH (20.0 kcal/mol), 2-$NH_2$-4-$NO_2$ (20.8 kcal/mol), 2-CHO-5-$NH_2$ (17.9 kcal/mol), 2-CN-5-$NH_2$ (18.7 kcal/mol), 2-$NO_2$-5-$NH_2$ (16.7 kcal/mol), 2-CHO-5-OH (20.8 kcal/mol), and 2-$NO_2$-5-OH (20.9 kcal/mol). The activation free energies for these molecules are about 10 kcal/mol lower than that of the unsubstituted hexatriene. Their electrocyclization rates are expected to be more than $2 \times 10^8$ times faster than that of the unsubstituted hexatriene.

3. Not all the captodative substituted hexatrienes have significantly low activation free energies. Sometimes a captodative substituted hexatriene, for example, 3-$NO_2$-4-$NH_2$ (31.9 kcal/mol) or 3-CHO-4-OH (31.5 kcal/mol), may even have a higher activation free energy than the unsubstituted hexatriene (30.7 kcal/mol).

4. Proper location of the electron donor and acceptor is also important in order to produce a dramatic acceleration effect. For instance, 2-$NO_2$-3-OH-hexatriene has an activation free energy of 19.8 kcal/mol, which is considerably lower than that of 2-OH-3-$NO_2$-hexatriene (24.3 kcal/mol) by 4.5 kcal/mol.

5. Some hexatrienes with two electron acceptors also have extraordinarily low activation free energies. The followings are the most outstanding cases: 1-CN-2-CHO (19.0 kcal/mol), 1-CN-2-CN (19.7 kcal/mol), 1-CN-2-$NO_2$ (18.3 kcal/mol), 2-CN-4-$NO_2$ (20.3 kcal/mol), and 2-$NO_2$-4-$NO_2$ (20.8 kcal/mol).

**3.4. Origin of the Captodative Acceleration Effect.** From exhaustive examinations, it is found that captodative substituted hexatrienes indeed tend to have low activation free energies in the thermal 6$\pi$-electrocyclization. In the most pronounced case (2-NO2-5-NH2-hexatriene), the activation free energy is as low as 16.7 kcal/mol. Such a magnitude of activation free energy can be translated to a rate constant of about 4 $s^{-1}$ at 298 K, meaning that the corresponding electrocyclization can be completed in less than a second (!) at room temperature. This finding is remarkable considering that electrocyclization of most hexatrienes requires hours, if not days, to manifest at about 150 °C.

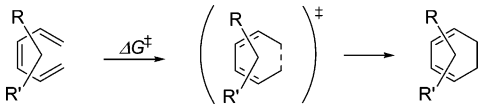
Given the significance of the above results, it becomes obvious that a mechanistic understanding of the captodative substitution effect is highly warranted. At least two questions need to be answered ambiguously: (1) Does captodative substitution produce any extra energetic effect over the sum of the effects produced individually by the electron donor and acceptor in monosubstitution? (2) If such an extra energetic effect exists, why is it not seen for all the captodative substituted cases? To answer these questions, we focus on the captodative substitution of $NH_2$ and $NO_2$ and carry out a series of energetic analyses (see Table 4). These include the calculation of "extra" energetic effect ($E_{extra}$) by using the following equation:

$$E_{extra} = \Delta G^{\ddagger}_{NH_2,NO_2} + \Delta G^{\ddagger}_{H,H} - \Delta G^{\ddagger}_{NH_2,H} - \Delta G^{\ddagger}_{NO_2,H} \quad (1)$$

where the subscripts describe whether the activation free energy corresponds to a disubstituted or monosubstituted case. If $E_{extra}$ is negative, the two substituents (i.e., $NO_2$ and $NH_2$) together produce a more pronounced acceleration effect than that expected from their individual capability of acceleration. Conversely, if $E_{extra}$ is positive, the two substituents together cause a less pronounced acceleration effect than that expected from their individual capability of acceleration.

From Table 4, it can be seen that in five cases (i.e., 1-$NO_2$-3-$NH_2$, 1-$NO_2$-6-$NH_2$, 2-$NO_2$-3-$NH_2$, 2-$NO_2$-5-$NH_2$, and 3-$NO_2$-5-$NH_2$), the $E_{extra}$ values are negative (note: $E_{extra}$ for 1-$NO_2$-5-$NH_2$ is $-0.3$ kcal/mol, a value that is technically considered to be zero due to the inaccuracy of the calculation). Consequently, these substitution patterns (see Figure 2) produce an extra acceleration effect on the electrocyclization reaction compared to the sum of the individual substituent effects. Due to this extra acceleration effect, three of the five cases (i.e., 2-$NO_2$-3-$NH_2$, 2-$NO_2$-5-$NH_2$, and 3-$NO_2$-5-$NH_2$) exhibit the lowest energy barriers (i.e., 20.4, 16.7, and 20.8 kcal/mol) among all the electrocyclization reactions shown in Table 4. The other

**TABLE 3. Activation Free Energies (kcal/mol) for Electrocyclization of Various Disubstituted Hexatrienes at 298 K**




| | | $R_2 = CH_3$ | $R_2 = NH_2$ | $R_2 = OH$ | $R_2 = F$ | $R_2 = CHO$ | $R_2 = CN$ | $R_2 = NO_2$ |
|---|---|---|---|---|---|---|---|---|
| 1,2-disubstitution | $R_1 = CH_3$ | 28.8 | 26.5 | 30.2 | 31.6 | 25.5 | 27.3 | 27.9 |
| | $R_1 = NH_2$ | 29.8 | 26.3 | 26.6 | 31.0 | 31.5 | 29.7 | 34.5 |
| | $R_1 = OH$ | 28.4 | 25.3 | 27.7 | 29.0 | 28.1 | 26.8 | 30.4 |
| | $R_1 = F$ | 26.4 | 24.9 | 27.2 | 26.6 | 24.1 | 24.0 | 25.0 |
| | $R_1 = CHO$ | 28.8 | 35.5 | 38.7 | 32.3 | 21.7 | 26.4 | 23.6 |
| | $R_1 = CN$ | 22.9 | 23.2 | 25.3 | 25.1 | 19.0 | 19.7 | 18.3 |
| | $R_1 = NO_2$ | 28.3 | 36.4 | 39.3 | 30.4 | 22.9 | 25.5 | 25.1 |
| | | $R_3 = CH_3$ | $R_3 = NH_2$ | $R_3 = OH$ | $R_3 = F$ | $R_3 = CHO$ | $R_3 = CN$ | $R_3 = NO_2$ |
| 1,3-disubstitution | $R_1 = CH_3$ | 31.6 | 31.7 | 32.1 | 31.6 | 29.5 | 30.7 | 26.8 |
| | $R_1 = NH_2$ | 30.3 | 30.6 | 31.3 | 30.5 | 30.2 | 30.6 | 27.5 |
| | $R_1 = OH$ | 29.2 | 28.9 | 29.9 | 29.3 | 29.5 | 29.8 | 27.0 |
| | $R_1 = F$ | 27.8 | 27.0 | 28.1 | 27.6 | 28.4 | 28.1 | 25.7 |
| | $R_1 = CHO$ | 32.5 | 31.8 | 32.2 | 31.9 | 30.0 | 31.1 | 27.6 |
| | $R_1 = CN$ | 31.3 | 30.1 | 31.2 | 31.0 | 30.2 | 31.1 | 28.4 |
| | $R_1 = NO_2$ | 29.7 | 28.0 | 29.2 | 29.1 | 29.0 | 29.5 | 26.8 |
| | | $R_4 = CH_3$ | $R_4 = NH_2$ | $R_4 = OH$ | $R_4 = F$ | $R_4 = CHO$ | $R_4 = CN$ | $R_4 = NO_2$ |
| 1,4-disubstitution | $R_1 = CH_3$ | 32.0 | 31.4 | 31.7 | 31.6 | 29.8 | 31.0 | 27.9 |
| | $R_1 = NH_2$ | 30.9 | 30.2 | 30.4 | 31.0 | 29.1 | 30.3 | 27.6 |
| | $R_1 = OH$ | 29.7 | 29.2 | 29.5 | 29.9 | 27.8 | 29.1 | 25.9 |
| | $R_1 = F$ | 28.0 | 27.6 | 28.2 | 28.5 | 26.1 | 27.6 | 24.4 |
| | $R_1 = CHO$ | 33.0 | 33.9 | 33.7 | 32.7 | 29.8 | 31.4 | 27.2 |
| | $R_1 = CN$ | 31.7 | 32.2 | 32.4 | 31.8 | 28.8 | 30.7 | 26.6 |
| | $R_1 = NO_2$ | 29.9 | 30.6 | 30.9 | 30.4 | 27.0 | 29.0 | 24.9 |
| | | $R_5 = CH_3$ | $R_5 = NH_2$ | $R_5 = OH$ | $R_5 = F$ | $R_5 = CHO$ | $R_5 = CN$ | $R_5 = NO_2$ |
| 1,5-disubstitution | $R_1 = CH_3$ | 28.8 | 28.4 | 31.0 | 31.4 | 26.4 | 26.5 | 26.2 |
| | $R_1 = NH_2$ | 27.3 | 26.4 | 28.9 | 29.8 | 25.7 | 26.1 | 25.4 |
| | $R_1 = OH$ | 26.1 | 25.7 | 28.5 | 29.5 | 25.6 | 25.3 | 24.9 |
| | $R_1 = F$ | 24.7 | 24.1 | 27.3 | 28.3 | 24.4 | 24.0 | 24.2 |
| | $R_1 = CHO$ | 30.2 | 29.4 | 32.9 | 33.3 | 28.6 | 28.3 | 28.3 |
| | $R_1 = CN$ | 28.9 | 27.9 | 31.9 | 32.5 | 27.9 | 27.5 | 27.9 |
| | $R_1 = NO_2$ | 27.3 | 26.3 | 30.5 | 31.0 | 26.6 | 26.0 | 26.8 |
| | | $R_6 = CH_3$ | $R_6 = NH_2$ | $R_6 = OH$ | $R_6 = F$ | $R_6 = CHO$ | $R_6 = CN$ | $R_6 = NO_2$ |
| 1,6-disubstitution | $R_1 = CH_3$ | 33.3 | | | | | | |
| | $R_1 = NH_2$ | 32.0 | 33.1 | | | | | |
| | $R_1 = OH$ | 31.1 | 31.2 | 30.5 | | | | |
| | $R_1 = F$ | 29.6 | 29.6 | 29.1 | 28.2 | | | |
| | $R_1 = CHO$ | 34.5 | 32.6 | 32.7 | 31.5 | 36.8 | | |
| | $R_1 = CN$ | 33.1 | 30.8 | 31.4 | 30.7 | 35.7 | 35.1 | |
| | $R_1 = NO_2$ | 31.3 | 29.4 | 30.3 | 30.0 | 34.6 | 34.0 | 33.2 |
| | | $R_3 = CH_3$ | $R_3 = NH_2$ | $R_3 = OH$ | $R_3 = F$ | $R_3 = CHO$ | $R_3 = CN$ | $R_3 = NO_2$ |
| 2,3-disubstitution | $R_2 = CH_3$ | 30.3 | 30.9 | 30.8 | 26.9 | 29.8 | 28.0 | 29.0 |
| | $R_2 = NH_2$ | 29.7 | 29.4 | 29.3 | 26.0 | 24.4 | 22.9 | 23.6 |
| | $R_2 = OH$ | 29.3 | 30.7 | 29.6 | 29.2 | 25.3 | 27.5 | 24.3 |
| | $R_2 = F$ | 29.8 | 29.9 | 30.2 | 30.4 | 28.7 | 28.9 | 24.5 |
| | $R_2 = CHO$ | 26.1 | 20.3 | 20.0 | 22.5 | 27.9 | 25.4 | 26.9 |
| | $R_2 = CN$ | 25.6 | 21.5 | 23.9 | 24.9 | 23.3 | 25.7 | 27.7 |
| | $R_2 = NO_2$ | 26.4 | 20.4 | 19.8 | 25.3 | 27.2 | 27.0 | 30.2 |
| | | $R_4 = CH_3$ | $R_4 = NH_2$ | $R_4 = OH$ | $R_4 = F$ | $R_4 = CHO$ | $R_4 = CN$ | $R_4 = NO_2$ |
| 2,4-disubstitution | $R_2 = CH_3$ | 26.6 | 26.1 | 26.8 | 27.1 | 24.8 | 26.2 | 22.1 |
| | $R_2 = NH_2$ | 26.0 | 25.1 | 25.0 | 25.4 | 24.0 | 24.7 | 20.8 |
| | $R_2 = OH$ | 28.5 | 27.5 | 28.1 | 29.0 | 26.4 | 28.3 | 24.3 |
| | $R_2 = F$ | 28.7 | 27.6 | 28.6 | 29.5 | 26.9 | 28.9 | 24.9 |
| | $R_2 = CHO$ | 25.0 | 25.2 | 25.7 | 25.6 | 23.2 | 24.8 | 21.2 |
| | $R_2 = CN$ | 24.0 | 24.2 | 25.0 | 25.5 | 22.3 | 24.5 | 20.3 |
| | $R_2 = NO_2$ | 24.3 | 24.2 | 25.1 | 25.3 | 22.7 | 24.4 | 20.8 |
| | | $R_5 = CH_3$ | $R_5 = NH_2$ | $R_5 = OH$ | $R_5 = F$ | $R_5 = CHO$ | $R_5 = CN$ | $R_5 = NO_2$ |
| 2,5-disubstitution | $R_2 = CH_3$ | 26.8 | | | | | | |
| | $R_2 = NH_2$ | 26.3 | 25.5 | | | | | |
| | $R_2 = OH$ | 25.1 | 28.0 | 31.9 | | | | |
| | $R_2 = F$ | 25.5 | 26.8 | 27.7 | 28.5 | | | |
| | $R_2 = CHO$ | 21.9 | 17.9 | 20.8 | 23.2 | 21.8 | | |
| | $R_2 = CN$ | 22.5 | 18.7 | 21.9 | 23.9 | 21.9 | 21.7 | |
| | $R_2 = NO_2$ | 21.1 | 16.7 | 20.9 | 23.6 | 22.0 | 21.8 | 22.7 |
| | | $R_4 = CH_3$ | $R_4 = NH_2$ | $R_4 = OH$ | $R_4 = F$ | $R_4 = CHO$ | $R_4 = CN$ | $R_4 = NO_2$ |
| 3,4-disubstitution | $R_3 = CH_3$ | 29.4 | | | | | | |
| | $R_3 = NH_2$ | 30.1 | 29.4 | | | | | |
| | $R_3 = OH$ | 28.7 | 31.2 | 29.1 | | | | |
| | $R_3 = F$ | 30.0 | 29.9 | 30.6 | 30.0 | | | |
| | $R_3 = CHO$ | 26.5 | 31.5 | 31.5 | 27.5 | 23.1 | | |
| | $R_3 = CN$ | 28.8 | 31.1 | 31.1 | 29.4 | 26.5 | 27.7 | |
| | $R_3 = NO_2$ | 26.2 | 31.9 | 31.0 | 26.6 | 23.6 | 24.1 | 22.7 |

**TABLE 4. Energetic Analyses of the Captodative Effects in Hexatriene Electrocyclization (the unit for all the energies is kcal/mol)**

| hexatriene | $\Delta G^{\ddagger}$ | $E_{extra}$ | $\Delta G_{reactant}$ | $\Delta G_{transition}$ | C1−C6 distance (au) | NICS[a] |
|---|---|---|---|---|---|---|
| 1-$NO_2$-2-$NH_2$ | 36.4 | 9.8 | 10.1 | 0.3 | 2.204 | −10.56 |
| 1-$NO_2$-3-$NH_2$ | 28.0 | −1.9 | −0.5 | 1.5 | 2.264 | −14.67 |
| 1-$NO_2$-4-$NH_2$ | 30.6 | 0.7 | 5.1 | 4.5 | 2.234 | −12.48 |
| 1-$NO_2$-5-$NH_2$ | 26.3 | −0.3 | 0.3 | 0.6 | 2.263 | −13.11 |
| 1-$NO_2$-6-$NH_2$ | 29.4 | −1.1 | 5.0 | 6.2 | 2.331 | −10.72 |
| 2-$NO_2$-1-$NH_2$ | 34.5 | 9.4 | 9.1 | −0.3 | 2.200 | −11.73 |
| 2-$NO_2$-3-$NH_2$ | 20.4 | −4.1 | −1.1 | 3.0 | 2.324 | −13.28 |
| 2-$NO_2$-4-$NH_2$ | 24.2 | −0.3 | 2.0 | 2.3 | 2.261 | −14.59 |
| 2-$NO_2$-5-$NH_2$ | 16.7 | −4.5 | 0.1 | 4.5 | 2.318 | −11.46 |
| 2-$NO_2$-6-$NH_2$ | 25.4 | 0.3 | 2.1 | 1.8 | 2.307 | −12.48 |
| 3-$NO_2$-1-$NH_2$ | 27.5 | 1.8 | 2.1 | 0.4 | 2.280 | −13.51 |
| 3-$NO_2$-2-$NH_2$ | 23.6 | 1.8 | 3.6 | 1.8 | 2.369 | −12.93 |
| 3-$NO_2$-4-$NH_2$ | 31.9 | 6.8 | 6.6 | −0.2 | 2.173 | −13.86 |
| 3-$NO_2$-5-$NH_2$ | 20.8 | −1.0 | −0.4 | 0.6 | 2.302 | −13.66 |
| 3-$NO_2$-6-$NH_2$ | 27.6 | 1.9 | 7.2 | 5.4 | 2.282 | −11.96 |

[a] NICS value of the transition state.

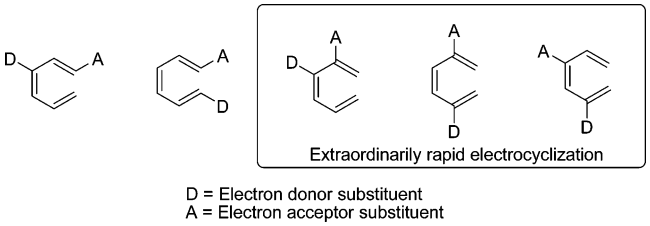
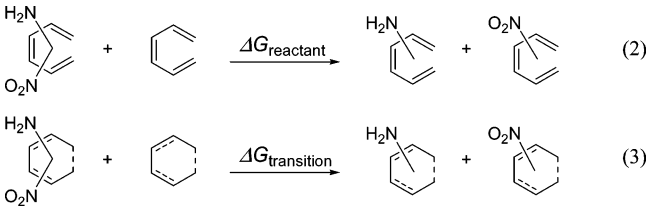



**FIGURE 2.** The substitution patterns that produce captodative acceleration effect on the electrocyclization.

two captodative cases (i.e., 1-$NO_2$-3-$NH_2$ and 1-$NO_2$-6-$NH_2$) have relatively higher energy barriers because substituents at the 1-position tend to decelerate the cyclization reaction due to the steric effects.

Nonetheless, it is clear from Table 4 that not all the captodative substitution patterns would provide a negative $E_{extra}$ value. This means that captodative substitution does not always promise an extra acceleration effect on electrocyclization. To understand this behavior, we decide to calculate the free energy changes for the following two isodesmic reactions (data shown in Table 4):[20]




The free energies describe how the two substituents interact with each other in the starting material and transition state of hexatriene electrocyclization. If the value is negative, it is an energetically favorable process to separate the two substituents. Conversely, if the value is positive, it is energetically unfavorable to separate the two substituents.

According to Table 4, in almost all the cases, the $\Delta G_{reactant}$ and $\Delta G_{transition}$ values are positive (note: $\Delta G_{reactant}$ for 2-$NO_2$-3-$NH_2$ is negative probably because of the steric repulsion between the two adjacent substituents). This means that the donor and acceptor have affinity with each other, and it is energetically unfavorable to separate them. More importantly, due to the change of the way that electrons are conjugated, the affinity between the donor and acceptor changes from the reactant state to the transition state. In some cases, the affinity becomes stronger in the transition state, such as the case of 2-$NO_2$-5-$NH_2$ ($\Delta G_{reactant}$ = 0.1 kcal/mol, $\Delta G_{transition}$ = 4.5 kcal/mol). This is when the captodative substitution produces an extra acceleration effect on electrocyclization. On the other hand, in some cases, the affinity becomes weaker in the transition state, such as the case of 1-$NO_2$-2-$NH_2$ ($\Delta G_{reactant}$ = 10.1 kcal/mol, $\Delta G_{transition}$ = 0.3 kcal/mol). This is when the captodative substitution produces an extra deceleration effect on electrocyclization. Thus, although it is almost always energetically unfavorable to separate a donor substituent from an acceptor

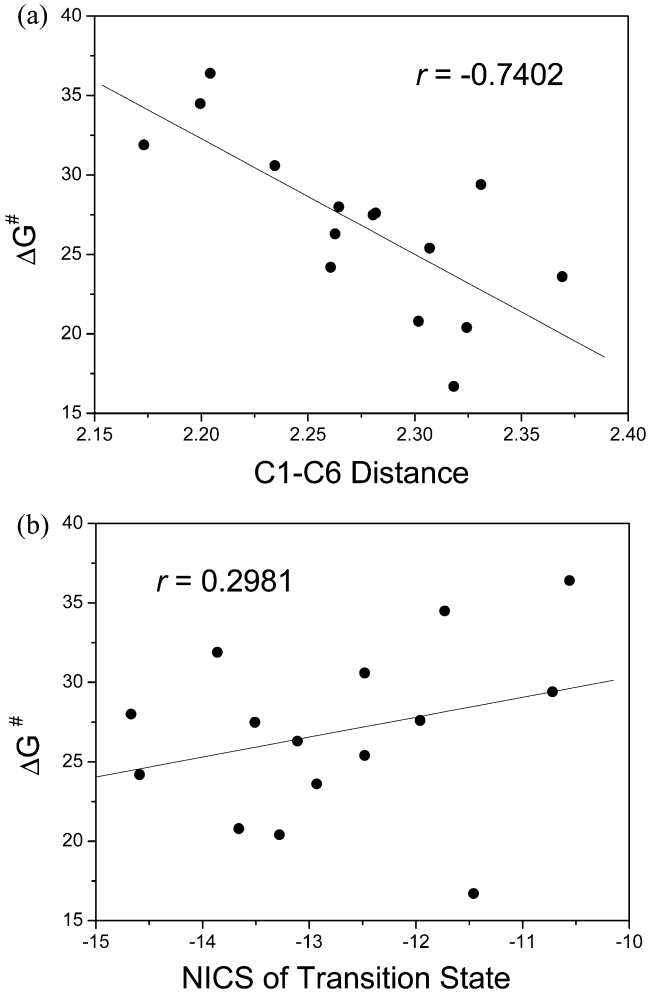



**FIGURE 3.** The correlations between the free energy barriers of the reactions and the C1−C6 distances (a) or the NICS values (b) of the transition state.

**TABLE 5. Energetic Analyses of the Effects of Two Electron Acceptors in Hexatriene Electrocyclization (the unit for all the energies is kcal/mol)**

| hexatriene | $\Delta G^{\ddagger}$ | $E_{extra}$ | $\Delta G_{reactant}$ | $\Delta G_{transition}$ |
|---|---|---|---|---|
| 2-$NO_2$-3-$NO_2$ | 30.2 | 10.7 | −0.3 | −11.1 |
| 2-$NO_2$-4-$NO_2$ | 20.8 | 1.3 | −3.9 | −5.2 |
| 2-$NO_2$-5-$NO_2$ | 22.7 | 3.8 | −1.8 | −5.6 |
| 3-$NO_2$-4-$NO_2$ | 22.7 | 2.6 | −12.2 | −14.9 |

(20) Hoffmann, R.; Stohrer, W. D. *J. Am. Chem. Soc.* **1971**, *93*, 6941.

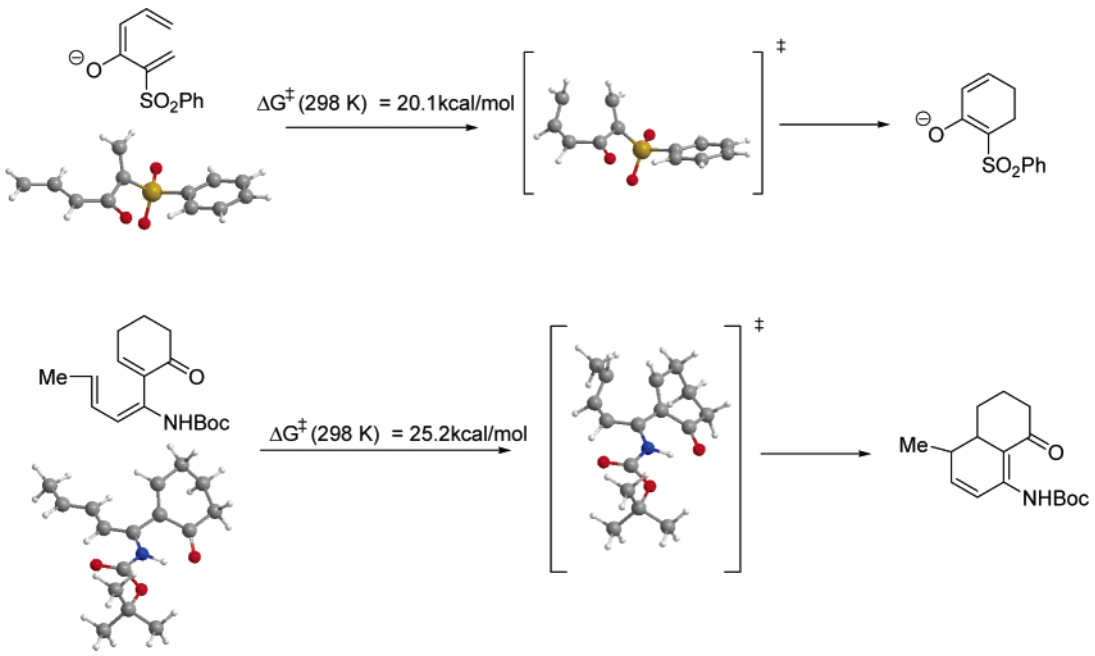



**FIGURE 4.** Activation free energies for the facile electrocyclizations that have been accomplished experimentally.

substituent in a molecular system, whether captodative substitution produces an extra acceleration effect on the overall reaction depends the change of affinity between donor and acceptor from the reactant state to the transition state.

In addition to the energetic analyses, we have also examined some other possible explanation for the captodative effects. These include (1) the relationship between the energetic and geometric properties, and (2) the relationship between the energetic and magnetic properties. Thus, we have calculated the C1−C6 distances in the transition state for all the compounds listed in Table 4. We have also calculated the NICS (Nucleus Independent Chemical Shifts) values[21] for the transition state in order to learn their aromaticity. The correlations between the free energy barriers of the reactions and the C1−C6 distances or the NICS values of the transition state are shown in Figure 3. From the correlations, it can be seen that the free energy barriers exhibit a negative correlation with the C1−C6 distance. This indicates that a lower barrier corresponds to an earlier transition state, while a higher barrier corresponds to a later transition state. Nevertheless, because the correlation coefficient ($r$ value) is only −0.7402, the relationship between the energetic and geometric properties is only modest. From Figure 3, it can also been seen that the energy barrier of the electrocyclization reaction has a positive correlation with the NICS value of the transition state. This is easily understandable because a more negative NICS value suggests a higher degree of electron delocalization. Nonetheless, because the correlation coefficient is only 0.2981, we have to conclude that the relationship between the energetic and magnetic properties is very weak.

**3.5. Concerning Hexatrienes with Two Electron Acceptors.** As aforementioned, some hexatrienes with two electron acceptors also exhibit extraordinarily low activation free energies. To understand why this occurs, we have calculated the $E_{extra}$, $\Delta G_{reactant}$, and $\Delta G_{transition}$ values for representative bis-acceptor systems (see Table 5). As seen from Table 5, the $E_{extra}$ values are always positive. This means that the acceleration effect of two acceptor groups together is lower than the sum of their individual acceleration effects. Nonetheless, because in some cases the $E_{extra}$ value is close to zero (such as in the case of 2-$NO_2$-4-$NO_2$), the overall acceleration effect by two acceptor groups (which individually can lower the electrocyclization energy barrier by up to 6 kcal/mol) is still pronounced.

Furthermore, it is interesting to note that the $\Delta G_{reactant}$ and $\Delta G_{transition}$ values in Table 5 are all negative. Consequently, it is always an energetically favorable process to separate two acceptor groups in a molecular system. For the electrocyclization of hexatrienes, the $\Delta G_{transition}$ values for two acceptor substituents are more negative than $\Delta G_{reactant}$. Thus, the two acceptor substituents repel each other more strongly in the transition state than in the starting material. This explains why the acceleration effect of two acceptor groups together is lower than the sum of the acceleration effects produced by them individually.

**3.6. Experimental Implications.** From the above calculations, it can be envisaged that extremely rapid 6$\pi$-electrocyclization under mild conditions is easily attainable by strategic captodative substitution. To further illustrate the concept, the activation free energies of the facile electrocyclization reactions reported by Magomedov et al.[10] and Funk et al.[11] are calculated (see Figure 4). Assuming that these free energies do not change with temperature significantly and hoping that the reaction can be almost completed (i.e., >80% conversion) in about an hour, we estimate that the desirable reaction temperatures should be 0 and 61 °C for the two electrocyclization reactions, respectively. The first prediction is in excellent agreement with the experiment because the electrocyclization by Magomedov et al. was accomplished at about 0 °C.[10] The second predicted temperature (i.e., 61 °C) is relatively lower than the experimental temperature (i.e., 110 °C) reported by Funk et al.[11]

It is worth noting that, in both Magomedov's and Funk's experiments, an electron acceptor was placed at the 2-position while an electron donor was placed at the 3-position. This pattern of captodative substitution is in excellent agreement with our

(21) Schleyer, P. v. R.; Maercker, C.; Dransfield, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.

predictions shown in Figure 2. Thus, using the theoretical tools developed in the present study, we can predict not only how to accelerate the hexatriene electrocyclization via substituent manipulation but also under what conditions each particular electrocyclization can be accomplished in the real experiment.

## 4. Conclusions

In the present study, we try to learn how to use captodative substitution to promote the sluggish hexatriene electrocyclization. A two-layer ONIOM method is developed, and its accuracy in predicting the activation free energy of electrocyclization for substituted hexatrienes is determined to be around 1.0 kcal/mol by comparison to the known experimental data. Using this carefully benchmarked method, we have calculated the activation free energies for a huge variety of mono- and disubstituted hexatrienes. Our new findings are summarized as follows:

1. For the monosubstituted hexatrienes, monosubstitution at C1 does not exert a significant effect on the rate of thermal 6$\pi$-electrocyclization, whereas monosubstitution at C2 or C3 may significantly decrease the activation free energy of hexatriene electrocyclization by up to 6 kcal/mol.

2. Extraordinarily rapid electrocyclization can be observed for certain captodative disubstituted hexatrienes, including 2-acceptor−3-donor hexatrienes, 2-acceptor−5-donor hexatrienes, and 3-acceptor−5-donor hexatrienes. The activation free energies for these systems are up to 10 kcal/mol lower than that of unsubstituted hexatriene. Therefore, their electrocyclization can be accomplished readily even at room temperature.

3. However, not all the captodative disubstituted hexatrienes have low activation free energies in electrocyclization. In fact, electrocyclization of some captodative disubstituted hexatrienes may be even slower than that of the unsubstituted hexatriene. On the other hand, some hexatrienes with two electron acceptors may be electrocyclized extraordinarily rapidly.

4. The mechanism for the captodative effect on hexatriene electrocyclization can be understood by calculating the affinity between the donor and acceptor group in the reactant state and transition state of the reaction. If the affinity is stronger in the transition state, captodative substitution will produce an extra acceleration effect.

5. By comparing with the experimental results from the recent synthetic applications of hexatriene electrocyclizations, we demonstrate that the theoretical tools developed in the present study can be used to predict not only how to accelerate the hexatriene electrocyclization via substituent manipulation but also under what conditions each particular electrocyclization can be accomplished in the real experiment.

Finally, after demonstrating that extremely facile electrocyclization is not something nature forbids, we wish to note an interesting and important problem that has not been discussed above. That is, how can a hexatriene ever be synthesized in reality if it can undergo very rapid electrocyclization? Clearly, the elegant work by Magomedov et al. has already provided an answer, where an unstable hexatriene could be produced in situ and subsequently utilized to accomplish the predesigned reaction. In Magomedov's study, the unstable hexatriene was produced through the addition of a vinyl anion to cyclobutenone, followed by a charge-accelerated four-electron ring opening. Other possible approaches, especially the recently popularized transition-metal-catalyzed cross-couplings, can also be utilized to construct an unstable hexatriene in situ from stable building blocks. Furthermore, we envisage that, by using protection groups to convert a less electron-donating group (e.g., −OCOR) to a more powerful electron donor (e.g., $-O^-$) or by using Lewis acid to convert a modest electron acceptor (in particular, a carbonyl) to a stronger one, one may also be able to trigger the electrocyclization of an otherwise unreactive hexatriene. Since most of these have not been examined in the past, it appears that more efforts are needed to appreciate the full potential of hexatriene electrocyclization in organic synthesis.

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**Supporting Information Available:** Detailed optimized geometries and detailed energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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