

Driving Force of Inverse Electron Demand Diels-Alder Reactions of Diphenyl Tetrazines

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Abstract We explore the inverse electron demand Diels-Alder reactions of tetrazines with various functional groups employing quantum calculations. In general, the rate of inverse electron demand Diels-Alder reaction depends on molecular orbital levels of electron donor and electron acceptor. Likewise, π orbital of the dienophile and π^* orbital of the diene is a key factor. In this work, we discuss the case where the energy of diene's π^* molecular orbital is not the sole governing factor to determine the reaction rate, rather the rate shows strong correlation with the charge density of dienes.

Introduction

The Diels-Alder reaction, one of the most widely used methodology in organic synthesis today,¹ is an organic chemical reaction between a conjugated electron-rich diene and an electron-poor alkene.² Unlike the Diels-Alder reaction, the inverse electron demand Diels-Alder (IEDDA) reaction is reaction between an electron-poor diene and an electron-rich dienophile.³

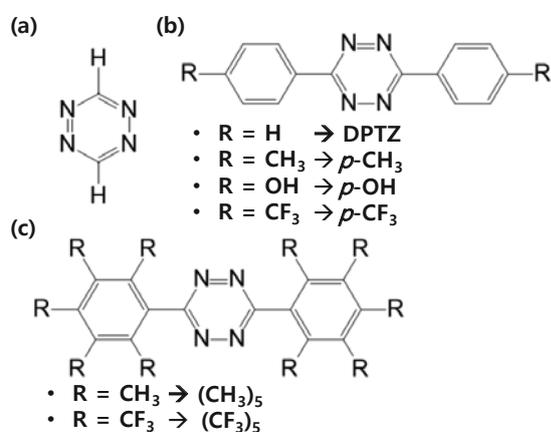
Cycloadditions of tetrazine are one of most important reactions in bioorthogonal chemistry⁴ owing to the application of IEDDA reactions of 1,2,4,5-tetrazines.⁵ Tetrazine has lower activation barrier than benzene and other azobenzenes.⁶ Therefore, tetrazine cycloadditions have been used in various synthesis like natural products,⁷ metal-organic frameworks,⁸ functionalization of carbon

nanotubes,⁹ and microarrays constructions.¹⁰ There has been a number of trials to control the reactivity of IEDDA. Types of dienophile are known to alter the reaction rate. In particular, strained dienophiles with low distortion and activation energy have higher reactivity due to their structural unstability.¹¹ Reaction rate also depends strongly on the functional group of diene. For instance, dipyridyltetrazine has been reported to be more reactive than diphenyltetrazine (DPTZ).¹²

Further theoretical and experimental studies show interesting results of controlling rates by functional groups of dienes. π -electrons occupying frontier molecular orbital play a decisive role in chemical activation.¹⁴ To see the reactivity, Houk's group used LUMO+1 level comparison and activation energy using transition state optimization.¹⁵ Because electron withdrawing functional groups lower the energy

of Lowest Unoccupied Molecular Orbital (LUMO) of tetrazine, it is expected that with more electron withdrawing effects, faster reaction will result.

To better understand the effect of various functional groups, we explored a series of DPTZ derivatives shown in Scheme 1. Density functional theory (DFT) with B3LYP functional was used.¹⁶ Computation details appear later.



Scheme 1. (a) Tetrazine structure, (b) para-substituted diphenyl tetrazine structure, and (c) di(penta substituted)phenyl tetrazine structure.

Results and Discussion

A. LUMO+1 Energy Level

Tetrazine is widely used as diene for IEDDA reactions. In particular, diphenyl functionalized DPTZ undergoes efficient IEDDA reaction due to the low LUMO+1 energy level. Setting DPTZ as a standard, the LUMO+1 energy of DPTZ is further lowered by attaching additional electron withdrawing groups on *para* (*p*-) position of phenyl ring. Likewise, electron donating groups raise LUMO+1 energy. In Figure 1, the energy

levels of LUMO+1 of various DPTZ derivatives follow the general trend that the more electron withdrawing group, the lower LUMO+1 energy.

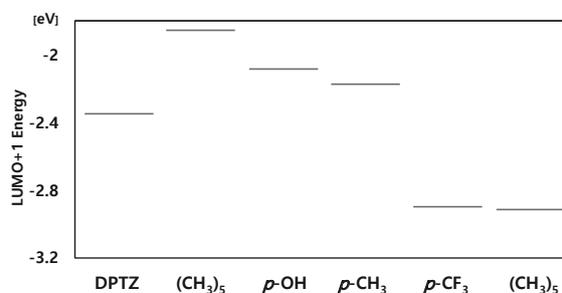


Figure 1. Energy level of LUMO+1 state of DPTZ derivatives in Scheme 1.

According to the frontier molecular orbital theory, the reactivity of compounds can be easily deduced. LUMO+1 energy of *p*-OH is close to that of *p*-CH₃. Thus, the reactivity of the two compounds is expected to be similar. Likewise, *p*-CF₃ is expected to be most reactive. Thus, it is a general trend that electron withdrawing groups increase the reactivity of dienes in IEDDA reactions and it is reasonable to compare reactivity with π^* orbital of diene.

Table 1. Total charge of tetrazine ring with additional functional groups substituted.

| | DPTZ | <i>p</i> -OH | <i>p</i> -CH ₃ | <i>p</i> -CF ₃ | (CH ₃) ₅ | (CF ₃) ₅ |
|---|-------|--------------|---------------------------|---------------------------|---------------------------------|---------------------------------|
| Q | -0.10 | -0.13 | -0.12 | -0.09 | -0.38 | -0.15 |

With different functional groups, the Mulliken charge of center ring could be affected. The trend is that with more donating group, the more negative the charge is. As shown in Table

1, the total charge of tetrazine ring is more negative if there is electron donating group. The result shows that if the charge of the center ring in substituted DPTZ is more positive, the more reactive the compound is. Tetrazine ring charge of Penta CH_3 has negative charge following the trend, while Penta CF_3 doesn't.

In this result, electron withdrawing effect seems small than the electron donating effect. This trend is opposite to the LUMO+1 energy trend.

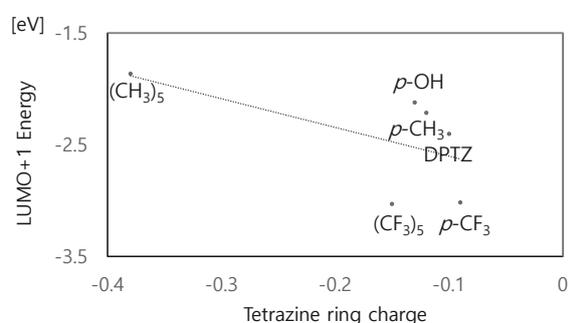


Figure 2. Plot of LUMO+1 energy versus tetrazine ring charge.

In Figure 2, DPTZ and para derivatives show linear correlation. For p -(electron donating group), it is easy to see the correlation between LUMO+1 energy and tetrazine ring charge. However, with penta derivatives, for example for $(\text{CF}_3)_5$, the tetrazine ring charge is more negative than $p\text{-CF}_3$. Despite the low LUMO+1 energy, $(\text{CF}_3)_5$ might have lower reactivity.

B. Charge Density

We compare the effect of the functional groups in the charge density, as shown in Figure 3. For para position, CF_3 derivatives the tetrazine ring are relatively low and for CH_3

derivatives, the density is relatively high. Thus, tetrazine ring charge density of CH_3 derivatives, which is charge donating group, is higher than CF_3 derivatives. We can see the same trend in penta substituted compounds.

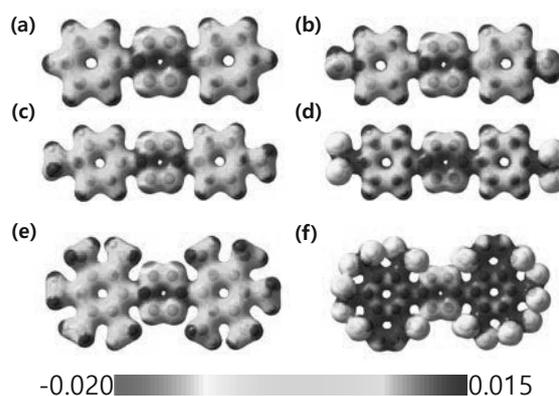


Figure 3. Charge density of DPTZ and derivatives drawn in $4 \times 10^{-2} e^-/\text{Bohr}^3$ isovalue level (a) DPTZ, (b) $p\text{-OH}$, (c) $p\text{-CH}_3$, (d) $p\text{-CF}_3$ (e) $(\text{CH}_3)_5$, and (f) $(\text{CF}_3)_5$.

Conclusion

Using DFT, we have studied several DPTZ derivatives to find the substituent effect on DPTZ. By comparing molecular orbital energy, electron withdrawing substituents on phenyl ring lower the LUMO+1 energy, leading to stronger interaction energy. Same trend was found in the charge of the center ring except $(\text{CF}_3)_5$ case. It showed that the electron donating group has more negative charge on tetrazine ring, thus, the electron rich dienophile hardly reacts with the diene. By examining the charge density, we found that compound with the lower LUMO+1 state has higher electron density on the tetrazine ring atoms.

To reduce computational cost calculating the transition state of molecules, charge density

and ring charge could be a good alternative method.

Computational Details

The DFT calculations were performed with TURBOMOLE and UCHEM in Edison web site (<http://www.edison.re.kr>). To study solely for the substituent effect on electron configuration by density calculation, we fixed the atoms of DPTZ and angle point calculation is done at the B3LYP level with def2-TZVP basis set. The frontier molecular orbitals and their energies were computed at the same level.

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