

Substituent Effects on the Diimide Reduction of Dienes: Relative Reactivity of two Olefin Centers with a Differently Substituted Derivative

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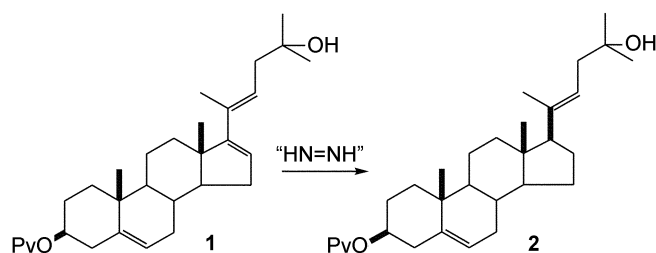
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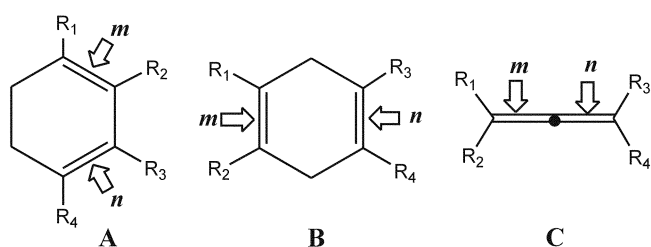
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Diimide, HN=NH, an unstable hydrogen donor that can only be generated *in situ*, finds broad application in the reduction of C=C bonds.¹ One of the advantages of diimide reduction is not undergoing hydrogenolysis as is often the case with catalytic hydrogenations. The mechanism of the reaction is known to involve hydrogen transfer of (*Z*)-diimide *via* a nonpolar cyclic transition state and the stereochemistry of addition is *syn*.² A number of relative reactivity studies have been carried out on alkyl-substituted alkenes and dienes. Generally, as alkenes or dienes are more substituted with alkyl groups on the double bonds, the reactions proceed slower. The relative reactivities of alkenes often have been theoretically interpreted in terms of torsional/angle strain and α -alkyl substituent effects.³ Most theoretical researches on the diimide reduction of olefins and polyenes were limited to the studies of the relative rates based on experimental data, but systematic accounts on the regio-selectivity of the diimide reduction are scarce. We were interested in understanding the regio-selective diimide reduction of dienes and polyenes including a specialized example as in the stereoselective conversion for constructing the steroidal side chain (from **1** to **2**).⁴



We investigated the regio-selectivity of the diimide reduction in various dienes by analyzing the energies of the transition states (TSs) of the reaction for each of two the differently substituted center ('*m*' vs. '*n*'). Here the '*n*' indicates



less substituted olefinic center than '*m*'. In case of tetra-substituted dienes, the '*TS_m*' corresponds to a system lower in calculated energy than the '*TS_n*'. The relative reactivity was analyzed by comparing two TSs energies,⁵ and interpreted in terms of substituent effects (steric and/or electronic).

All *ab initio* calculations were carried out using GAUSSIAN-98 programs.⁶ The electronic energies of TSs were calculated using DFT (B3LYP/6-311+G(d,p)) method.⁵ The optimized TSs were further confirmed by calculating vibrational frequencies, which was obtained as only one negative frequency, indicating the computed TSs were true ones. According to the Curtin-Hammett principle,⁷ the compound ratio, P_m/P_n depends on the relative energies of the transition states, $E_{TS_m}^\ddagger$ and $E_{TS_n}^\ddagger$, then $P_m/P_n = \exp[\Delta E^\ddagger/RT]$, here $\Delta E^\ddagger = (E_{TS_m}^\ddagger - E_{TS_n}^\ddagger)$. The calculation results are shown in Table 1.

Regarding to regio-selectivity on dienes, the diimide reduction is predicted to prefer less substituted C-C bonds ('*n*' center) in general. In other words, the total TS energies of '*n*' center ($E_{TS_n}^\ddagger$) are shown to be lower than the energies

Table 1. The calculation results from B3LYP/6-311+G(d,p)

no.	type	R ₁	R ₂	R ₃	R ₄	$E_{TS_m}^\ddagger$ ^a	$E_{TS_n}^\ddagger$ ^b	ΔE^\ddagger ^{c,d}
1	A	Me	H	H	H	-383.47648	-383.47961	1.961(96.4)
2	A	H	Me	H	H	-383.47281	-383.47838	3.490(99.7)
3	A	Me	Me	H	H	-422.79966	-422.80449	3.029(99.4)
4	A	Me	Me	Me	H	-462.12511	-462.12691	1.127(86.9)
5	A	Me	Me	H	Me	-462.12975	-462.13142	1.046(85.3)
6	B	Me	H	H	H	-383.47148	-383.47444	1.857(95.8)
7	B	Me	Me	H	H	-422.79485	-422.79958	2.972(99.3)
8	B	Me	Me	Me	H	-462.12465	-462.12642	1.110(86.6)
9	B	F	H	H	H	-443.41141	-443.41592	2.831(99.1)
10	B	F	F	H	H	-542.66891	-542.67835	5.923(100)
11	B	F	F	F	H	-641.93735	-641.94227	3.090(99.4)
12	B	F	F	Me	Me	-621.32436	-621.32849	2.593(98.7)
13	B	Cl	Cl	Me	Me	-1342.03917	-1342.04097	1.135(87.0)
14	B	F	F	Cl	Cl	-1461.90975	-1461.91188	1.334(90.4)
15	C	Me	Me	H	H	-306.01059	-306.01476	2.614(98.8)
16	C	CH ₂ -CH ₂	H	H	H	-304.75017	-304.75213	1.227(88.7)
17	C	Me	Me	CH ₂ -CH ₂	H	-383.40438	-383.40595	0.985(83.9)
18	B	CF ₃	CF ₃	H	H	-1018.42795	-1018.42940	0.910(82.2)
19	B	Cl	Cl	H	H	-1263.38320	-1263.39031	4.460(99.9)
20	B	CN	CN	H	H	-528.66772	-528.67247	2.980(99.3)

^aTotal energies (hartree) for TSs of diimide reduction to '*m*' center in olefin. ^bTotal energies (hartree) for TSs of diimide reduction to '*n*' center in olefin. ^c $\Delta E^\ddagger = E_{TS_m}^\ddagger - E_{TS_n}^\ddagger$, kcal/mol. ^dThe number in parenthesis is calculated % product *via* '*TS_n*' at 300°K.

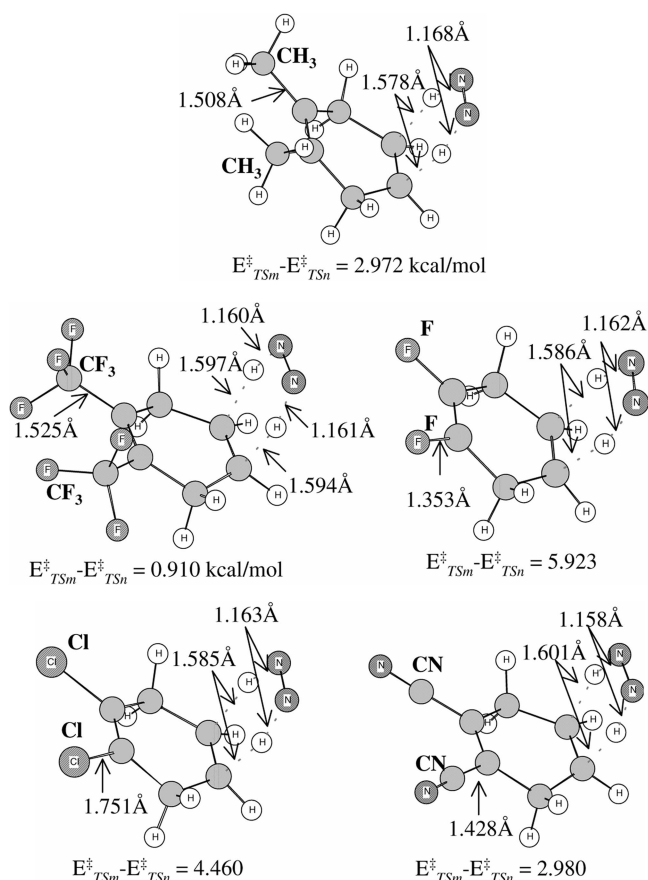


Figure 1. Transition structures for diimide reduction of unsubstituted 'n' center in 1,2-disubstituted-1,4-cyclohexadienes (B type), optimized at the B3LYP/6-311+G(d,p) level of theory. The value of ($E_{Tsm}^{\ddagger} - E_{Tsn}^{\ddagger}$) indicates the relative stability from the disubstituted 'm' center (kcal/mol).

of 'm' center (E_{Tsm}^{\ddagger}). The steric effect dominates in controlling the selectivities. For an example of 1-methyl-1,3-cyclohexadiene,⁸ the value E_{Tsm}^{\ddagger} is lower than E_{Tsn}^{\ddagger} by 1.96 kcal/mol (entry 1), and the 'n' reduction is predicted by 96% at 300°K based on the Curtin-Hammett principle. For 2-methyl-1,3-cyclohexadiene, the value ΔE^{\ddagger} increased to 3.49 kcal/mol (entry 2), which may be ascribed to the proximal methyl substituent. The similar trend is observed in Me-substituted-1,4-cyclohexadienes (entry 6-8, system B).

With introducing F substituent in system B (entry 9-11), the similar trend as in Me-substituted derivatives with higher ΔE^{\ddagger} is observed. The value ΔE^{\ddagger} is 2.83 kcal/mol for 1-fluoro-1,4-cyclohexadienes (cf. 1.86 kcal/mol for 1-methyl-1,4-cyclohexadienes in entry 6). For tetra-substituted-1,4-cyclohexadienes (entry 12-14), the selectivity of reduction on double bonds increases with order of substituents Me > Cl > F. This trend, however, cannot be interpreted simply by a correlation between the relative reactivity and the steric factor. This suggests a special electronic effect is present in this example.

With introducing trifluoromethyl group, more electron-withdrawing than methyl, in system B (entry 18), the value ΔE^{\ddagger} is decreased to 0.91 kcal/mol (cf. 2.97 kcal/mol for 1,2-dimethyl-1,4-cyclohexadiene). Considering the CF₃ may be a sterically bulkier group than CH₃, it apparently indicates

that the diimide reduction can be accelerated by the presence of an electron-withdrawing substituent.⁹ For 1,2-difluoro-1,4-cyclohexadiene, ΔE^{\ddagger} is predicted by 5.92 kcal/mol (cf. 4.46 kcal/mol for 1,2-dichloro derivative), which seems an opposing result based on the electronic effect. It is ascribed to an extra steric effect by the proximal substituent groups (1.353 for C-F bond-length, and 1.751 Å for C-Cl bond-length, see Figure 1).

In allene derivatives (system C), less substituted center is reduced as shown in other dienes (entry 15-16). A strain effect may involve in this example as explained in previous experimental results.¹⁰ This result shows the diimide reduction prefers the cyclopropylic double bond side ('n' center) which may result in a possible relief of the strain energy through the TS (entry 17).

In summary, our predictions show diimide reduction prefers the less substituted and the more strained double bond. These results are in good agreement with conventional investigations. While the regio-selectivity of the diimide reduction on dienes is mainly controlled by steric effects of the substituents, the selectivity is shown to depend on the electronic effects of the substituents (particularly, CH₃ vs. CF₃, for entry 7 and 18). This provides an evidence that the diimide reduction may be facilitated by the electron-withdrawing group.

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References and Notes

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