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Abnormally High Reactivity of the Vinyl Hydrogen Toward Singlet Oxygen in a Twisted 1,3-Diene

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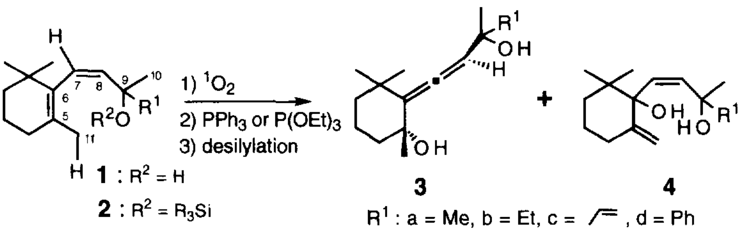
Abstract: In a significantly twisted 1,3-diene, a regio-selective ene-reaction of the vinyl hydrogen rather than the allyl hydrogen with singlet oxygen was observed, and this phenomena is rationalized by considering large $\sigma^*-\pi$ orbital interactions between the vinyl C-H bond and another double bond.

Although synthetic utility of normal 1,3-dienes represented by Diles-Alder reaction has been well studied,[1] chemistry of significantly twisted 1,3-dienes has not been paid attention. These compounds are unusual, and their characters and method of synthesis have not been well known.

In 1968, allene formations by an ene-reaction of vinyl hydrogens of *trans*-β-ionone derivatives with singlet oxygen were independently reported by three groups,[2] however the yields of the allenes were very poor in all reported compounds. This unique ene-reaction should be attributable to the characteristic nature of slightly twisted 1,3-diene of β-ionone derivatives,[3] although in those papers there was no apparent description concerning to these characteristic nature of β-ionone derivatives. Now, we have found the abnormally more reactive vinyl hydrogen toward singlet oxygen than the allyl hydrogen in significantly twisted *cis*-β-ionol derivatives. Herein, we report the first example that has proposed the large interaction between the σ*orbital of the vinyl C-H bond and the π orbital of another double bond.

The requisite substrates **1** and **2** for the photosensitized oxygenation were prepared by the reaction of *cis*-β-ionone with Grignard reagents[4] followed by silylation.[5] Both compounds **1** and **2** were present as a mixture of rotational isomers of almost one to one ratio, and these isomers were detectable by NMR.[3a,3b] The photosensitized oxygenations were carried out in dichloromethane by irradiation using a halogen lamp under an oxygen atmosphere in the presence of catalytic amount of tetraphenylporphine and 1 molar equivalent of triethylphosphite or triphenylphosphine at 0 °C.[6] The results of the photosensitized oxygenation are listed in Table 1. In every R^1 substituent, triethylsilyl group of R^2 gave the best selectivity for the allene formation, and the bulkiness of the substituents at the C-9 position clearly affected the selective ene-reaction of the C-7 vinyl hydrogen against that of the C-11 allyl methyl hydrogen. Thus, for entries 7 and 9 in Table 1, the allenes **3c** and **3d** were obtained in 63 and 67% yield from compounds **1c** and **1d** as a mixture of diastereoisomers of almost one to one ratio, which would result from rotational isomers, respectively.[7]

We then explored the reason why the selective ene-reaction of the C-7 vinyl hydrogen rather than the C-11 allyl hydrogen remarkably proceeded in **2c-2** and **2d**. The conformation of one of the rotational isomers of **1d** was successfully determined by X-ray analysis,[8] and it was revealed that this molecule entirely exists in a *s-cis* conformer, and that the double bond in the cyclohexene ring makes a torsion angle of about 70



1 : $R^2 = H$
2 : $R^2 = R_3Si$

3
4

R^1 : a = Me, b = Et, c = /=, d = Ph

Table 1. Ene-Reaction of β-Ionone Derivatives with Singlet Oxygen

Enrty	Substrates	R^1	R^2	Yield of 3^a (%)	Yield of 4^a (%)	Products 3 or 4
1	**1a**	Me	H	40	54	**3a, 4a**
2	**2a**	Me	$SiEt_3$	51^b	29^b	**3a, 4a**
3	**1b**	Et	H	40	44	**3b, 4b**
4	**2b**	Et	$SiEt_3$	52^b	15^b	**3b, 4b**
5	**1c**		H	37	55	**3c, 4c**
6	**2c-1**		$SiMe_3$	40^b	40^b	**3c, 4c**
7	**2c-2**		$SiEt_3$	63^b	32^b	**3c, 4c**
8	**1d**	Ph	H	39	51	**3d, 4d**
9	**2d**	Ph	$SiEt_3$	67^b	24^b	**3d, 4d**

[a] Isolated yield. [b] The yields were for three steps; silylation of the corresponding alcohols followed by photosensitized oxygenation and then desilylation.

degrees toward the Z-olefin plane. Thus, this molecule is largely twisted around the C6-C7 single bond. Based on the results obtained by X-ray analysis, the most stable conformation of the another rotational isomer of **1d** and two rotational isomers of the vinyl derivative **2c-2** were obtained by molecular mechanics calculations and molecular orbital calculations. Their conformations were almost same one another, and are represented by that of one isomer of **2c-2** as shown in Fig. 1.[9] In its pictorial representation, the vinyl hydrogen at C-7 of **2c-2** is exactly located at the β-face, and hence the attack of singlet oxygen from the α-face only gives the exo-methylene compound **4c**. However, the α-face is entirely covered over by the bulky substituents at the C-9 position. The results of entries 5, 6, and 7 in Table 1 clearly demonstrate the remarkable effect of the bulky substituents at the C-9 position of **2**. Thus, singlet oxygen attacks **2c-2** selectively from its β-face, and abstracts the C-7 vinyl hydrogen to give the allene **3c**, or abstracts the C-11 allyl hydrogen to give the exo-methylene **4c**, respectively. Comparison of the relative reactivity of the C-7 vinyl hydrogen and the C-11 allyl hydrogen toward singlet oxygen was then made possible by the above conformational analysis for **2c-2**.

It has been well known that an ene-reaction of singlet oxygen with olefins proceeds by interactions of LUMO of singlet oxygen with HOMO of olefins.[10] In order to investigate the relative reactivity of the reactive C-7 and C-11 hydrogens, we focused our attention on the relative electron densities of the frontier orbitals around these hydrogens obtained by molecular orbital calculations, although polarized intermediates with perepoxide geometry has been accepted and their characters may be important to understand the regioselectivity of an ene-reaction of singlet oxygen.[11] The calculated results[12] have shown that the frontier electron density around the C-7 vinyl hydrogen is slightly richer than that around the C-11 allyl hydrogen.

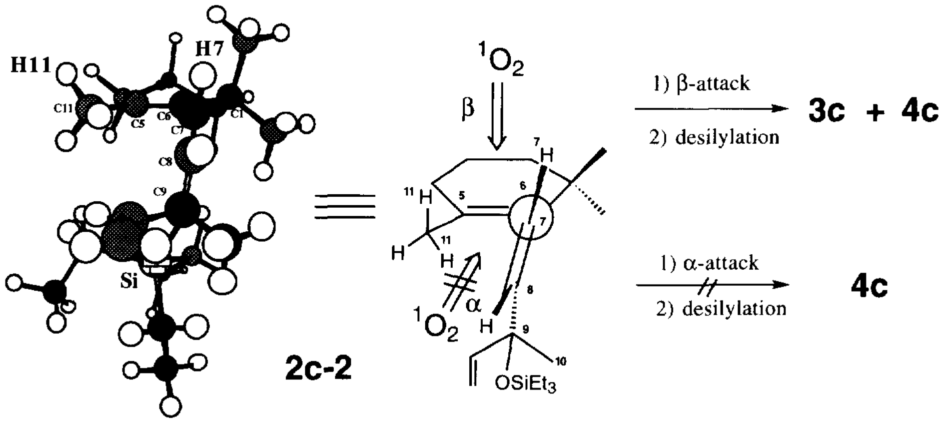


Fig. 1. Chem 3D representation of optimized structure of **2c-2** and its pictorial representation.

Thus, the relative frontier electron densities around these hydrogens have evidently reflected their reactivity toward singlet oxygen. Furthermore, we compared the calculated electron densities of the frontier orbitals around both the C-7 vinyl hydrogen and the C-11 allyl hydrogen of various rotational isomers of **2c-2**. The electron densities of the frontier orbitals gradually increased with enlargement of the torsion angle between the two double bonds, and they are largest at 90 degrees. These calculated results are rationalized by considering that the σ* orbital of the C-7 vinyl C-H bond interacts with the π orbital of the C5-C6 double bond in significantly twisted **2c-2**, as shown in Fig. 2.[13]

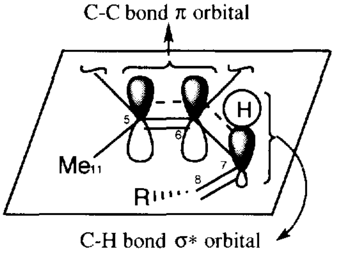


Fig. 2. Orbital interactions between the π orbital and the σ* orbital in a twisted Z-1,3-diene system.

Thus, we have found that the vinyl hydrogen in a significantly twisted 1,3-diene is highly activated by the large σ*-π orbital interactions between the vinyl C-H bond and another double bond,[14] and to the best of our knowledge, this is the first observation of these interactions in 1,3-dienes.

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5. The triethylsilylation of **1a**-**1d** quantitatively proceeded (Et_3SiCl / DMAP / Et_3N / CH_2Cl_2 or DMF), while treatment of **1c** with a more bulky silyl reagent (TBDMSCl) completely recovered the starting material.
6. In the absence of the phosphine reducing agents, the yields of **3** and **4** were very poor. Oxygenation of these reducing reagents with singlet oxygen would be slower than that of the substrates; Turner, J. A.; Herz, W. *J. Org. Chem.*, **1977**, *42*, 1657.
7. Compound **3c** : IR (KBr disk, cm^{-1}) 3424, 1966, 1454, 1364, 1092; ^{1}HNMR (400MHz, $CDCl_3$) δ 5.98 (1H, dd, *J* = 17.1, 10.5Hz), 5.42 (1H, s), 5.28 (1H, dd, *J* = 17.1, 1.2Hz), 5.05 (1H, dd, *J* = 10.5, 1.2Hz), 1.78-1.88 (2H, m), 1.26-1.55 (4H, m), 1.39 (3H, s), 1.34 (3H, s), 1.24 (3H, s), 1.07 (3H,s); ^{13}CNMR (400MHz, $CDCl_3$) δ 196.21, 143.94, 120.99, 111.75, 102.35, 72.13, 70.71, 40.52, 40.41, 34.26, 31.32, 30.93, 29.41, 27.87, 18.43.; HRMS calcd for $C_{15}H_{24}O_2$ 236.1770, found 236.1770. **Diasteroisomer** : IR (KBr disk, cm^{-1}) 3372, 1962, 1450, 1386, 1148, 1102 ; ^{1}HNMR (400MHz, $CDCl_3$) δ 5.97 (1H, dd, *J* = 17.30, 10.5Hz), 5.42 (3H, s), 5.28 (1H, dd, *J* = 17.3, 1.2Hz), 5.06 (1H, dd, *J* = 10.5, 1.2Hz), 1.78-1.88 (2H, m), 1.26-1.55 (4H, m), 1.39 (3H,s), 1.36 (3H, s), 1.24 (3H, s), 1.05 (3H, s) ; ^{13}CNMR (400MHz, $CDCl_3$) δ 196.17, 144.01, 121.17, 111.81, 102.30, 72.15, 70.71, 40.55, 40.42, 34.32, 31.31, 31.05, 29.38, 27.78, 18.4.; HRMS calcd for $C_{15}H_{24}O_2$ 236.1770, found 236.1770.

   Compound **4c** : IR (KBr disk, cm^{-1}) 3352, 1640, 1464, 1366, 1120; ^{1}HNMR (400MHz, $CDCl_3$) δ 6.03 (1H, dd, *J* = 17.3, 10.5Hz), 5.81 (1H, d, *J* = 13.4Hz), 5.64 (1H, d, *J* = 13.4Hz), 5.20 (1H, dd, *J* = 17.3, 1.2Hz), 5.02 (1H, dd, *J* = 10.5, 1.2Hz), 4.89 (1H, d, *J* = 1.7Hz), 4.86 (1H, m), 2.46 (1H, brdt, *J* = 13.4, 6.6Hz), 2.16 (1H, brdt, *J* = 12.9, 6.4Hz), 1.58-1.71 (4H, m), 1.42 (3H, s), 0.97 (3H, s), 0.96 (3H, s); ^{13}CNMR (400MHz, $CDCl_3$) δ 153.30, 145.69, 135.31, 131.94, 111.67, 108.81, 80.01, 73.26, 39.53, 36.63, 32.58, 29.35, 24.04, 23.54, 22.91.; HRMS calcd for $C_{15}H_{24}O_2$ 236.1770, found 236.1775. **Diasteroisomer** : IR (KBr disk, cm^{-1}) 3288, 1642, 1388, 1358, 1116, 1098; ^{1}HNMR (400MHz, $CDCl_3$) δ 6.10 (1H, dd, *J* = 17.3, 10.5Hz), 5.84 (1H, d, *J* = 13.2Hz), 5.61 (1H, d, *J* = 13.2Hz), 5.26 (1H, dd, *J* = 17.3, 1.2Hz), 5.05 (1H, dd, *J* = 10.5, 1.2Hz), 4.97 (1H, brd, *J* = 2.0Hz), 4.88 (1H, m), 4.00 (2H, brs), 2.43 (1H, brdt, *J* = 13.6, 6.1Hz), 2.18 (1H, brdt, *J* = 13.6, 6.4Hz), 1.58-1.62 (4H, m), 1.39 (3H, s), 0.95 (3H, s), 0.93 (3H, s); ^{13}CNMR (400MHz, $CDCl_3$) δ 153.25, 145.67, 135.28, 131.92, 111.67, 108.81, 80.00, 73.22, 39.52, 36.61, 29.33, 24.04, 23.53, 22.90.; HRMS calcd for $C_{15}H_{24}O_2$ 236.1770, found 236.1775.
8. Full details of the crystallographic structure analysis of **1d** will be described in the full paper.
9. The geometries were optimized with CFF91 forcefield by use of software packages Insight II 2.1.0 Program. Biosym Technol. Inc. San Diego, U. S. A., and with semiempirical method (PM3) by use of SPARTAN version 3.1, 4.0 Wavefunction, Inc., Irvine, CA.
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12. The relative electron densities of frontier orbitals were calculated with HF/3-21G level by use of software packages SPARTAN version 3.1, 4.0 Wavefunction., Inc., Irvine, CA.
13. Full details of the frontier electron densities of **2c-2** and the related compound will be described in the full paper.
14. Further study on the reactivity of significantly twisted 1,3-dienes is under investigation from the view point of σ-π orbital interactions.

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