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Supplementary Material Available: Fractional coordinates, temperature factors, interatomic distances, and interatomic angles for clavepictine B (**2**) (4 pages). Ordering information is given on any current masthead page.

Do Rotational Barriers Dictate the Regioselectivity in the Ene Reactions of Singlet Oxygen and Triazolinedione with Alkenes?

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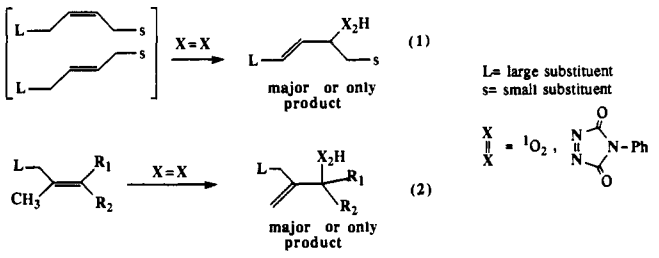
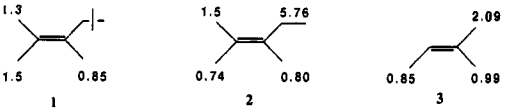
Recently the regioselective ene reactions of singlet oxygen and triazolinedione (TAD) with alkyl-substituted ethylenes have attracted considerable attention. For example, it has been shown that singlet oxygen and TAD react with unsymmetrical *cis*-alkenes with regioselective double-bond formation at the larger group (eq 1).[1] Furthermore, the reaction with tetrasubstituted alkenes was found to favor hydrogen abstraction from the alkyl group that is geminal to the larger substituent of the double bond (eq 2).[2] This remarkable geminal selectivity was recently rationalized[2a] in terms of rotational-barrier differences within the alkyl groups of the double bond.



These arguments, which previously have been utilized by Houk and co-workers[3] in order to explain the singlet oxygen side-selectivity in trisubstituted olefins, have been shown to correctly predict ene regiochemistry in a number of tetrasubstituted olefins. The lower the calculated rotational barrier, the higher the reactivity of the alkyl group.[2a,3] For example, molecular mechanics calculations showed[2a] that the methyl group geminal to the neopentyl group in 2,3,5,5-tetramethyl-2-hexene (**1**) has the lowest rotational barrier and is the most reactive. Furthermore, the ethyl group in 2,3-dimethyl-2-pentene (**2**) has a much higher rotational barrier (5.76 kcal/mol) than the methyl groups and is totally inactive. Similar trends hold with 2-methyl-2-butene (**3**). The numbers shown with structures **1**-**3** are rotational barriers calculated by MM2.



These interesting results prompt us to report here our own findings, which demonstrate that barriers to rotation do not always predict the regioselectivity in the ene reaction of $^1O_2$ or TAD with alkenes. We will show, as we have already pointed out,[2b] that it is the nonbonded interactions in the isomeric transition states that control product formation and that barriers to rotation are irrelevant.

The results are summarized in Table I. In alkenes **4** the methyl groups occupy different stereochemical environments and are expected to show different rotational barriers and reactivities. It is therefore ideally suited for this purpose. Deuterium labeling allows us to distinguish the ene product distribution, and isomers (*E*)- and (*Z*)-**4** can be prepared in high stereochemical purity.[4]

Table I. Relative Yields of Ene Products and Rotational Barriers of Methyl Groups

	% Ene Product		Rotational Barriers (Kcal/mol)	
	With $^1O_2$	With PTAD	HF/STO-3G	HF/3-21G
CD_3 ← 76 CH_3 ← 24 (E)-4	76 24	53 47	1.63 1.11	2.27 1.64
CH_3 ← 74 CD_3 ← 26 (Z)-4	74 26	58 42	1.63 1.11	2.27 1.64
CD_3 ← 14 CH_3 ← 86 5	14 86	18 82	1.64 0.40	2.26 1.03
← 73 ← 27 cis-6	73 27	100 0	0.56	
← 0 ← 100 gem-6	0 100	0 100	0.91	
← 69 ← 31 trans-6	69 31	100 0	1.51	
← 36 Ph ← 64 7	36 64		1.22 1.45	

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(4) Alkenes (*E*)-**4** and **5** were prepared by the following method: Wittig coupling of the stabilized ylide methyl(triphenylphosphoranylidene)propionate with 2,2-dimethylpropanal and 2-methylpropanal respectively gave the *E* configuration of the corresponding esters as the only isomer (GC analysis on an SE-30 10 ft × 1/8 in. column). Complete reduction of these esters with a $LiAlD_4/AlCl_3$ mixture gave in two steps compound (*E*)-**4**: ^1H NMR ($CDCl_3$) δ 5.17 (m, 1 H), 1.71 (d, J = 1.6 Hz, 3 H), 1.08 (s, 9 H). Reaction of methyl(triphenylphosphoranylidene)propionate-*3,3,3-d*$_3$ with 2,2-dimethylpropanal gave the *E* d_3 ester as the only isomer. Reduction of this ester with a $LiAlH_4/AlCl_3$ mixture gave in two steps compound (*Z*)-**4**: ^1H NMR (acetone-d_6) δ 5.16 (m, 1 H), 1.63 (d, J = 1.6 Hz, 3 H), 1.07 (s, 9 H). **5**: ^1H NMR ($CDCl_3$) δ 4.93 (br d, J = 8.8 Hz, 1 H), 2.5 (m, 1 H), 1.60 (br s, 3 H), 0.91 (d, J = 6.4 Hz, 6 H).

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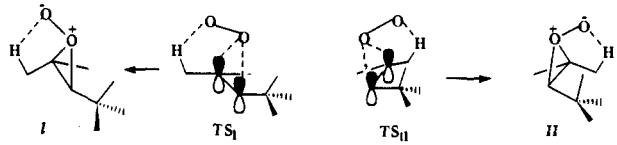
Both compounds **4** were photooxidized at 0 °C in CCl_4 with tetraphenylporphine (TPP) as sensitizer. In the ene reaction, hydrogen abstraction occurs preferentially from the trans methyl group (the less crowded side of the double bond), and the results for the *E* and *Z* isomers were the same within experimental error. This result requires that the perepoxide intermediates I and II be formed in the rate-determining step of this reaction. Similar observations, where the geminal methyl groups of the double bond do not show any significant isotope effect, have been reported earlier.[5]

Ab initio HF/STO-3G calculations[6] using full optimization showed that the cis methyl group in compound **4** has a lower rotational barrier (1.11 kcal/mol) than the trans methyl group (1.63 kcal/mol). Similar results were obtained by using the 3-21G basis.[6] In both calculations the trans methyl group in **4** has an approximately 0.5 kcal/mol higher rotational barrier than the cis methyl group. Although the "rotational barrier postulate" proposed earlier by Houk and recently by Clennan requires lower reactivity of the trans methyl than the cis methyl in compound **4**, the experimental results show the opposite. When the *tert*-butyl substituent in olefin (*E*)-**4** is replaced by an isopropyl group, producing compound **5**, the reactivity of the methyl groups has been reversed, while the rotational barriers are in the same direction as in substrate **4**. These results indicate that rotational barriers do not consistently predict the regiochemistry of this reaction.

We emphasize that in the acyclic olefins **4** the more crowded side of the olefin is the less reactive. As far as we know this is the first example in the literature where the ene reaction of an acyclic trisubstituted olefin does not obey the "cis effect". This can be attributed to the fact that in transition state TS_{II}, leading to the less stable perepoxide II, the severe nonbonded interactions involving the large *tert*-butyl group and the incoming oxygen are much larger than those in transition state TS_I, where these interactions are absent. Furthermore, unlike the "cis effect" where two allylic C–H bonds are available on the same side of the double bond, there is only one allylic C–H bond on each side of the olefinic double bond for "positive interaction" with the incoming oxygen in the transition state. Therefore no further "hydrogen stabilization" is expected in TS_{II} over TS_I. However, the more substituted side of olefin **5**, which is less hindered than in **4**, provides two C–H interactions and thus accounts for syn selectivity. Similar arguments based either on secondary orbital[7] and hydrogen-bonding interactions[8] or on activation parameters[9] have been used previously to rationalize the syn addition of singlet oxygen in trisubstituted alkenes.



Rotational barriers of the methyl groups in *cis*-, *gem*-, and *trans*-**6** compounds have also been calculated. Although the rotational barrier of the methyl group in *trans*-**6** (1.51 kcal/mol) is 3 times larger than in *cis*-**6** (0.56 kcal/mol), the reactivity of both methyl groups and consequently the regiochemistry for both substrates remain practically unchanged with both $^1O_2$ and TAD. Unlike the low reactivity of the methyl group in *cis*- and *trans*-**6** compounds, the reactivity of the methyl group in the isomer *gem*-**6** increases dramatically, while its rotational barrier has an intermediate value of 0.91 kcal/mol. These results again indicate that methyl rotations and reactivity do not correlate. Clennan and co-workers suggested that partial rotation of the neopentyl group in *cis*-**6** is sufficient to place the C–H bond in the proper orientation for abstraction.[10] According to Houk's postulate,[3] the partially rotating neopentyl group must have a lower energy barrier than 0.56 kcal/mol (the rotational barrier of the cis methyl group), in order to account for the high regioselectivity of this reaction. However, we point out that the values of the free energy of activation of ene reactions are between 6 and 13 kcal/mol for singlet oxygen[9] and >10 kcal/mol for PTAD.[5b] Since the rotational barriers of alkyl groups are much lower, the Curtin–Hammett principle[11] requires that the product ratio depend solely on the free energy difference of the transition states. The barriers to rotation are irrelevant.

A similar discrepancy between barriers to rotation and ene reactivity holds for substrate **7**. Again the cis methyl group has a lower rotational barrier than the trans although its reactivity is lower. This result again is not consonant with the interpretation that barriers to rotation dictate the regioselectivity.

The present results show that rotational barriers do not control the selectivity of the ene reaction of singlet oxygen and TAD with alkenes. We have pointed out that the regioselective ene product distribution depends on the free energy difference of the isomeric transition states. Successful prediction of product regioselectivity, therefore, requires knowledge of the structures of the pertinent isomeric transition states with alkenes.

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Synthetic Models for Catechol 1,2-Dioxygenases. Interception of a Metal Catecholate–Dioxygen Adduct

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It is generally agreed that the oxidative cleavage of catechols to *cis,cis*-muconic acids, catalyzed by non-heme iron dioxygenases, involves initial substrate binding to iron, followed by dioxygen attack at an iron(III)–catecholate complex.[1] Both the manner by which O_2 attacks the active site of the enzyme and the structural nature of the intermediate O_2 adduct are questions that may be addressed by the isolation and characterization of model compounds such as those described in this paper.

The reaction of dioxygen with the Ir(III) catecholate complexes [(triphos)Ir(Cat)]BPh_4 [Cat = 9,10-phenanthrenecatecholate (phenCat), **1**;[2] Cat = 3,5-di-*tert*-butylcatecholate (3,5-DTBCat),

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(2) Details on the synthesis and characterization of **1** and **2** together with elemental analytical data for all of the new compounds reported in the paper are given as supplementary material.

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