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Application of Pertubation Theory to Free-radical Benzylic and Allylic Oxidation of Unconjugated π-Systems

Gadi Rothenberg and Yoel Sasson*[†]

Casali Institute of Applied Chemistry, Hebrew University of Jerusalem, Jerusalem 91904, Israel.

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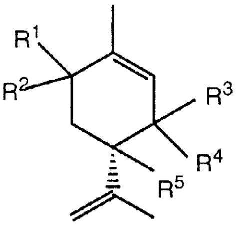
Abstract: Pertubation interactions between Frontier Molecular Orbitals are utilized to predetermine the regioselectivity of allylic and benzylic oxidation reactions. Thus, it is shown that in unsaturated compounds containing two nonconjugated and nonequivalent π-systems, one system contributes mainly to the HOMO and the other to the HOMO-1. Analysis of four representative examples corroborates empirical evidence with previously published studies. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Selective oxidation is still one of the most sought after goals in organic and bioorganic synthesis. Many common organic compounds contain more than one oxidizable site, a situation which often leads to non-selective reactions. Part of this product diversity results from different reaction paths (*e. g.* epoxidation vs. allylic oxidation), and can be circumvented by altering the reaction conditions.[1] The problem is more serious when the same substrate has several available sites for the same type of reaction. (R)-Limonene **1a**, for example, has more than one reactive site for allylic oxidation. In this case, regioselective oxidation carries much industrial benefit. Enone **1b** is an important precursor for the synthesis of food and aroma chemicals, while alcohol **1d** is practically worthless.[2] The low product selectivity normally obtained in autoxidations of such substrates forces the use of expensive, and often environmentally unacceptable, reagents.

1a R^1=R^2=R^3=R^4=R^5=H
1b R^1,R^2=O; R^3=R^4=R^5=H
1c R^1=OH; R^2=R^3=R^4=R^5=H
1d R^1=R^2=R^3=R^4=H; R^5=OH



This example demonstrates the importance of free-radical hydrogen abstraction (HA) processes. HA is a key step in autoxidations that controls (barring allylic rearrangements) the oxygenation site on the substrate, due to the fast subsequent reaction between the alkyl radical and molecular oxygen (k=10^8-10^9).[3] Accumulated experimental findings indicate the following order of reactivity: acyclic position activated by a single π-system < cyclic activated by a single π-system < acyclic activated by two π-systems < cyclic activated by two π-systems.[4] However, extrapolation of these rules to substrates combining two inequivalent and unconjugated π-systems is problematic.[5]

[†] E-mail: ysasson@vms.huji.ac.il

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Today, low-cost molecular orbital modeling at semiempirical and *ab initio* levels of theory can provide good predictions regarding the behavior of ionic species and nucleophile-nucleofuge pairs.[6] It can be rationalized that in a chemical reaction involving two-electron changes, the HOMO of the nucleophile would provide a pair of electrons, which would interact with the LUMO of the nucleofuge (Figure 1a). Thus, if the LUMO of the nucleofuge is located on specific sites of the molecule, a prediction of the regioselectivity of the nucleophilic attack can be made.

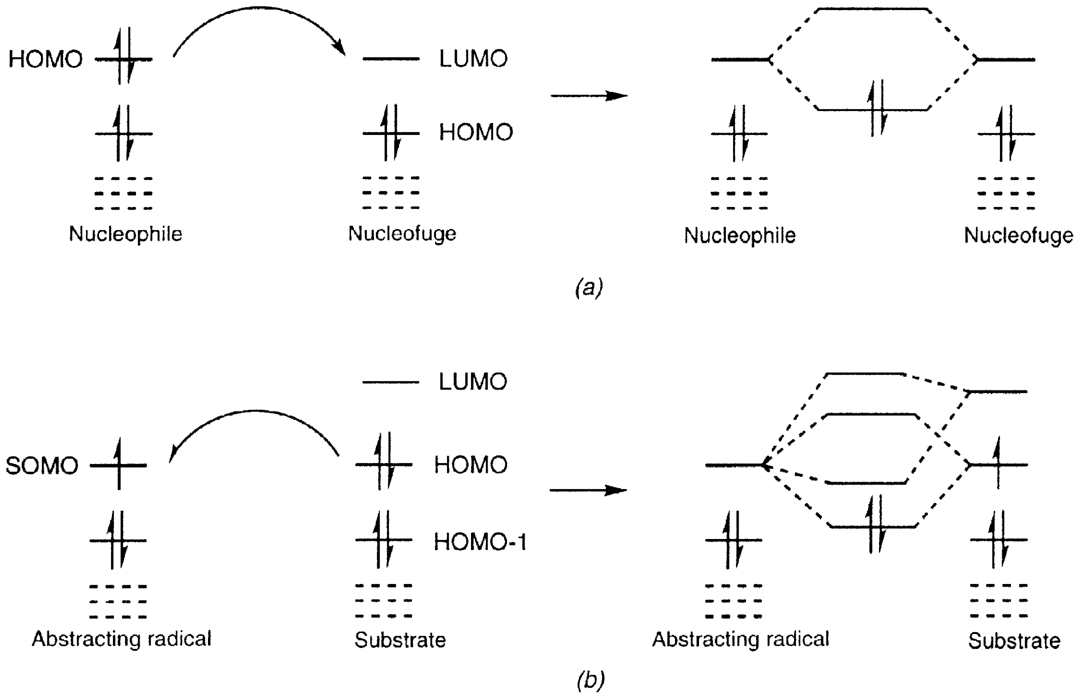


Figure 1. Schematic representation of the electron transfers and the molecular orbitals involved in a nucleophilic process *(a)* and a free-radical process *(b)*.

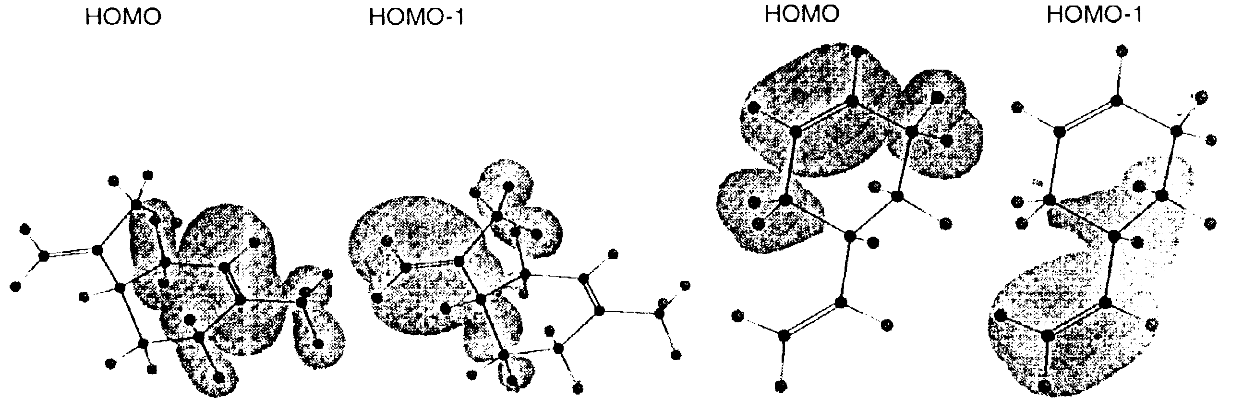
This kind of prediction is based on the well-known pertubation theory of frontier molecular orbitals.[7] When free-radical species are involved, the location of intermediates and transition structures is more difficult. However, the following reasoning can be applied: *(a)* Free-radical HA involves (by definition) the breaking of a C-H σ bond in the substrate and the transfer of a hydrogen atom to the attacking free-radical; *(b)* the electron that is transferred goes from the HOMO of the substrate to the SOMO of the abstracting radical (Figure 1b; in the general case of HA, contributions from HOMO-SOMO mixing would be more substantial than those arising from LUMO-SOMO mixing, but the specific contributions would depend on the relative energies of the HOMO, SOMO, and LUMO, *vide infra*). Consequently, overlap between the SOMO of the abstracting radical and the HOMO of the substrate would then be a prerequisite for HA. Therefore, in chemical transformations where the rate-determining step is HA, a model of the HOMO of the substrate can perhaps enable a prediction of the regioselectivity.

Herein we demonstrate, by combining experimental and computational results, that this technique can be applied to explain the outcome of some free-radical benzylic and allylic oxidations, including cases that involve two unequivalent and unconjugated π-systems. Four representative examples are analyzed, and results are compatible with the literature empirical data.

RESULTS AND DISCUSSION

Example 1: Reactivity of cyclic vs. acyclic allylic positions

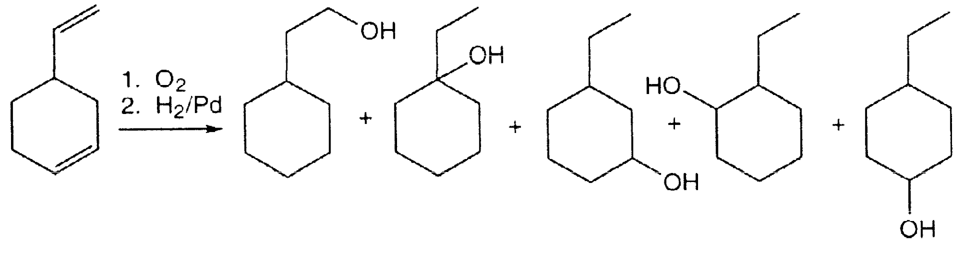
Catalytic allylic autoxidation of **1a** occurs selectively on the ring allylic positions (*cf.* experimental section). Assuming HOMO-SOMO interactions in the free-radical HA step, we would expect the HOMO of **1a** to reflect its reactivity. Indeed, molecular orbitals calculated at semiempirical and *ab initio* levels of theory show (Figure 2, left) that the endocyclic double bond is the exclusive contributor[8] to the HOMO, while the exocyclic double bond is evidenced only an orbital lower (HOMO-1).



1a **2a**

Figure 2. Graphical representations of the HOMO (left) and HOMO-1 (right) of **1a** and **2a**.

Further evidence can be obtained from Farrissey's work on the autoxidation of 4-vinyl-cyclohexene **2a**, a simple analogue of **1a**.[9] By reduction of the allylic hydroperoxides, Farrissey obtained all 5 possible alcoholic isomers (**2b-f**, eq 1), but the fraction of allylic oxidation products resulting from activation by the *exo*cyclic π-system were extremely low (**2d+2e+2f** accounted for over 90% of the products, independent of temperature and solvent changes). Again, these results can be explained by pertubative interactions, which would depend on different contributions from the *exo-* and *endo*cyclic double bonds to the HOMO of **2a** (Figure 2, right).



(1)

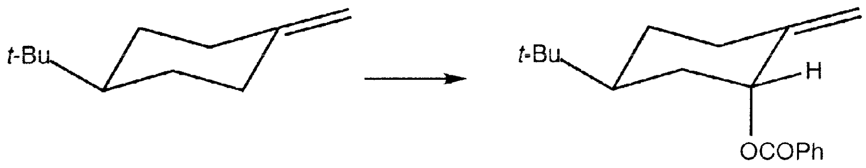
2a **2b** **2c** **2d** **2e** **2f**

The above results corroborate the empirical observations of Ingold *et al*,[4] according to which HA would be more facile from cyclic positions.

Example 2: support for axial HA in the oxidation of 1-methylene-4-t-butyl cyclohexane 3

In the stereoselective formation of 1-methylene-4-*t*-butyl-cyclohexyl-*trans*-2-benzoate **4** *via* perester oxidation of **3**, a favorable loss of the axial hydrogen atom was attributed to better overlap of the π-orbitals with the emerging p-orbital.[10]

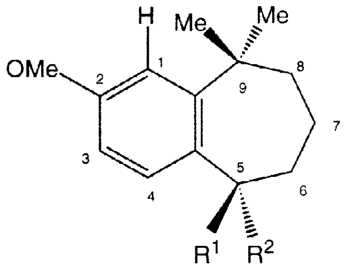
It was later recognized[11] that this experiment cannot clarify unambiguously whether the HA is really from the axial position, as the same allylic radical will form regardless of which allylic hydrogen was abstracted, and a favored axial approach of the carboxylate ligand could also be the reason for the observed stereoselectivity. However, our results show that the atomic orbital contribution coefficient to the HOMO of the axial allylic hydrogen is 0.195, compared with -0.0421 for the equatorial hydrogen. This finding supports the preferred HA from the axial position of **3**.



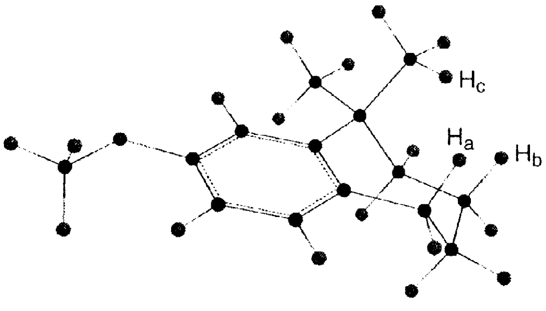
3 **4**

Example 3: benzylic oxidation of 9,9-dimethyl-2-methoxy-benzosuberane 5a

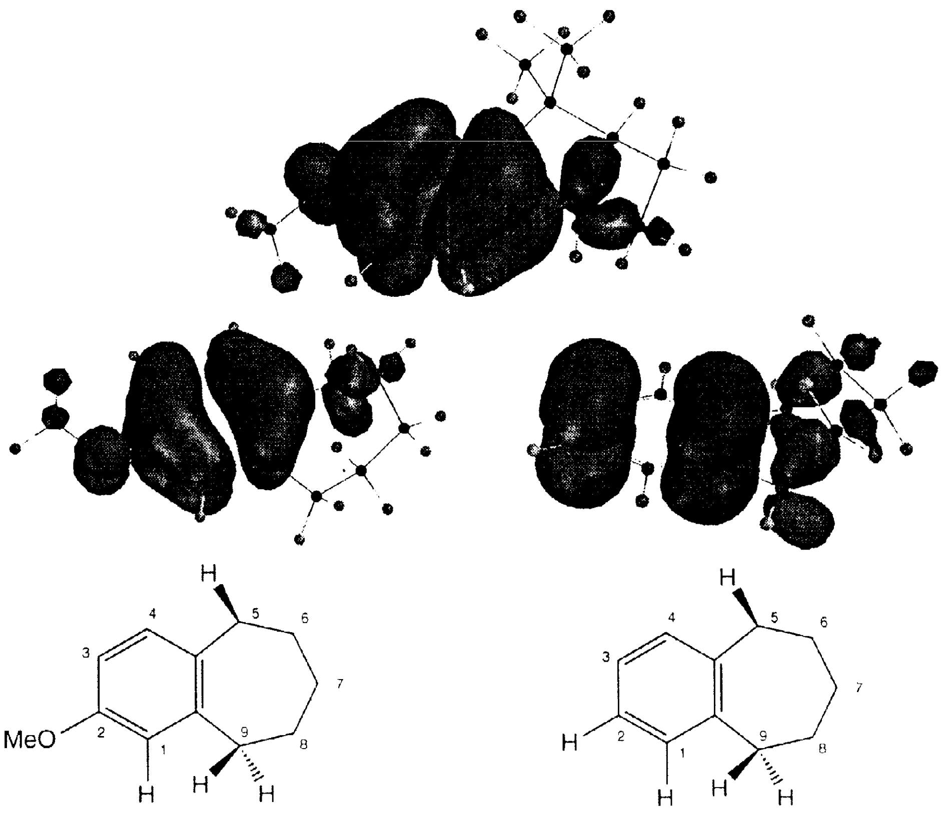
A failure of benzylic oxidation has been reported in the case of **5a**, where the typical stoichiometric reagent for benzylic oxidation, $CrO_3/AcOH\text{-}H_2O$, produced less than 10% of the desired suberone **5b**.[12] Miller *et al* have attributed this failure to a severe peri interaction between the C_9 methyl and the C_1 hydrogen. However, examination of the HOMO of **5a**, of 2-methoxy-benzosuberane **6**, and of plain benzosuberane **7** reveals (Figure 3) that the MeO substitution at C_2 dramatically alters the HOMO so that atomic orbital contributions from C_9 are negligible.[8] Furthermore, the axial benzylic hydrogen should be more active towards HA, as the ratio between the contribution coefficients of the atomic orbitals of the axial and equatorial hydrogens to the HOMO is 15:1 (*cf.* the reactivity of axial and equatorial positions in **3**, where the ratio is 5:1). In the case of **5a**, however, the approach of any abstracting radical to H_a is strongly hindered by the C_9 methyl group. Indeed, the distance from H_a to H_c is a mere 1.881 Å, which is considerably shorter than the distance between H_a and H_b (2.42 Å).



5a $R^1=R^2=H$
5b $R^1,R^2=O$



5a 3-D representation

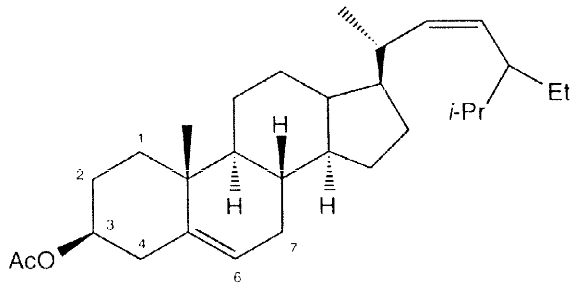


6 **7**

Figure 3. Graphical representations of the HOMO of**5a** (top), **6** (bottom left) and **7** (bottom right) showing the change affected by the presence of the methoxy substituent.

Example 4: catalytic oxidation of stigmasterol acetate

The growing interest in the oxidation products of biomolecules and especially steroids has stimulated several recent investigations.[13, 14] Some of these steroidal substrates contain two double bonds which are separated by a distance of several angstroms. It has been recently shown that the Ru-catalyzed oxidation of stigmasterol acetate[15] **8**, an anti-stiffness factor, probably proceeds *via* a free-radical mechanism. While metal-catalyzed oxidations usually differ from autoxidations, allylic HA would still be an important step here. Experimental results show that only 7-allylic oxidation occurred,[14] which can be explained by examining the contributions of the different π-systems to the HOMO and HOMO-1 (Figure 4).



8

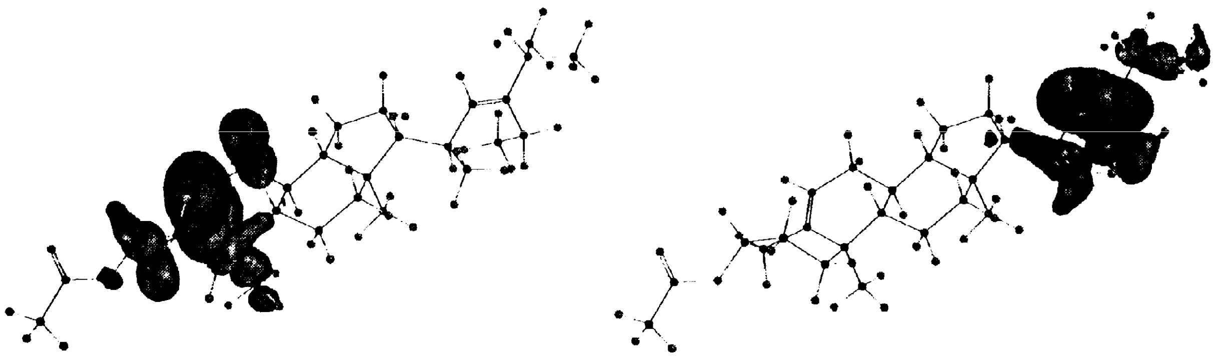
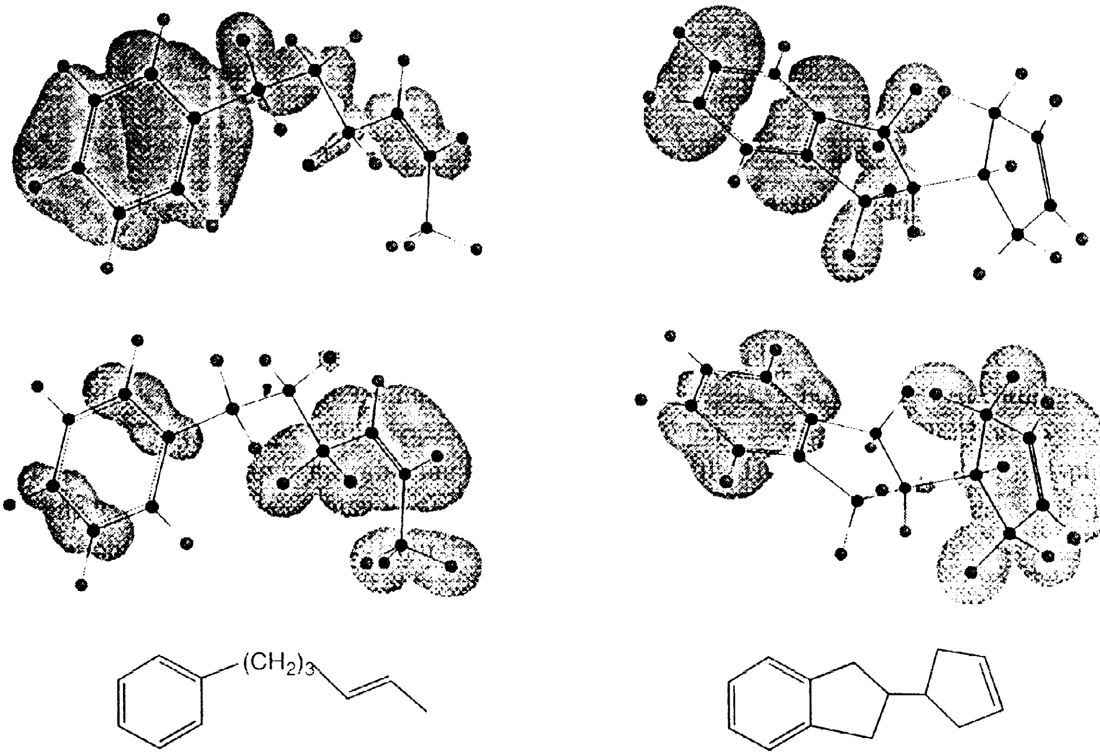


Figure 4. Graphical representations of the HOMO (left) and HOMO-1 (right) of **8**.

The reactivity of substrates that contain both allylic and benzylic positions

When a molecule contains two nonconjugated and nonequivalent π-systems, it is difficult to predict which positions would be more active towards free-radical HA. Benzylic and allylic positions, for example, are often simply grouped together as "active positions". According to our calculations, 2° benzylic positions appear to be more active than 2° allylic ones, for both cyclic and acyclic systems. Thus, when comparing the contributions to the HOMO and HOMO-1 in 1-phenyl-4-hexene **9** and 4-(2-indanyl)cyclopentene **10** (Figure 5) it can be seen that in both cases, the main contribution to the HOMO arises from the aromatic group.



9 **10**

Figure 5. Graphical representations of the HOMO (top) and HOMO-1 (bottom) of **9** and **10**.

The relative magnitudes of SOMO-HOMO and SOMO-LUMO interactions in HA reactions

The magnitude of interaction between two orbitals depends on their relative energies: the closer the energies, the bigger the interaction. It can be generally stated that, for free-radical HA, the important interaction would be a SOMO-HOMO one, rather than a SOMO-LUMO one.[16] This is evidenced when the SOMO energy values of some common abstracting radicals (Table 1) are compared with the energies of the LUMO and HOMO of the substrates discussed in this paper (Table 2).

Table 1: SOMO energy values (eV) for some free-radicals.

	Calculated SOMO energy				Experimental
	Semiempirical		*Ab initio*		(-Ionization
Radical	AM1	PM3	3-21G	6-31G*	potential)[a]
methyl	-9.89	-10.00	-8.21	-8.15	-9.80
ethyl	-9.21	-9.35	-7.49	-7.48	n/a[b]
i- propyl	-8.76	-8.91	-7.01	-7.02	n/a
t- butyl	-8.49	-8.65	-6.73	n/a	-6.90
phenyl	-9.99	-10.03	-7.76	n/a	-9.20
t- butoxy	-11.17	-11.49	n/a	n/a	-12.00
t- butylperoxy	-10.89	-11.16	-9.53	n/a	-11.50

[a] Ref. 17. [b] not available.

Table 2: LUMO and HOMO energy values (eV) for optimized geometries of example substrates.

MO	**1a**[a]	**2a**[b]	**3**[b]	**5**[a]	**6**[b]	**7**[a]	**8**[c]	**9**[a]	**10**[a]
LUMO	5.07	5.20	4.97	0.53	0.57	0.55	1.13	0.54	4.04
HOMO	-9.05	-9.36	-9.22	-8.71	-9.17	-9.18	-9.30	-9.11	-8.80

[a] 3-21G *ab initio* level. [b] 6-31G* *ab initio* level. [c] AM1 semiempirical level.

CONCLUSION

The degree of hyperconjugation between the C-H σ bond and the adjacent π-system is one of the factors that determines the lability of the allylic/benzylic hydrogens towards HA. The important FMO interaction in these free-radical HA processes is SOMO-HOMO. Although the FMO approach does not take into account steric effects and conformational constraints, some insight into the regioselectivity of free-radical HA reactions can be gained by examination of the HOMO and HOMO-1 of the substrates.

EXPERIMENTAL SECTION

Autoxidation of 1a. We have recently published a detailed procedure for the autoxidation of 3-carene and α-pinene.[18] **1a** was oxidized similarly. **1b-d**, and limonene-1,2-oxide were isolated and identified by their spectral properties, compared with those of commercial samples (Aldrich). **1b** and **1c** accounted for over 85% of the allylic oxidation products.

Programs and methods. All computations were carried out using MACSPARTAN *PLUS*[TM,19] on Power Macintosh 6400/180 and G3/266 computers. No extra keywords were used. All computations pertain to the gas phase. Structures for substrates and free-radicals were first optimized by molecular mechanics (SYBYL) methods. The MM results were used as starting guesses for semiempirical (AM1 and PM3) geometry optimizations, which were in turn used as starting guesses for *ab initio* geometry optimizations using the 3-21G split-valence basis set. In 6 cases (Me, Et, and *i*-Pr radicals, and substrates **2a**, **3**, and **6**), comparative optimizations were carried out using the 6-31G* polarization basis set, but significant differences in the constructions of the MO's were not observed. Indeed, most of the orbital representations calculated at the semiempirical theory levels were good enough for the purpose of demonstrating the model. Due to computation costs, geometry optimization of **8** was performed at SYBYL and AM1 levels only. No appreciable qualitative conclusion could be drawn from MO surfaces other than the HOMO and HOMO-1. A normal coordinate analysis was carried out to establish that all structures were energy minima (no negative frequencies).

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