External Electric Field Will Control the Selectivity of Enzymatic-Like Bond Activations

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Abstract: Controlling the selectivity of a chemical reaction is a Holy Grail in chemistry. This paper reports theoretical results of unprecedented effects induced by moderately strong electric fields on the selectivity of two competing nonpolar bond activation processes, C−H hydroxylation vs C=C epoxidation, promoted by an active species that is common to heme-enzymes and to metallo-organic catalysts. The molecular system by itself shows no selectivity whatsoever. However, the presence of an electric field induces absolute selectivity that can be controlled at will. Thus, the choice of the orientation and direction of the field vis-à-vis the molecular axes drives the reaction in the direction of complete C−H hydroxylation or complete C=C epoxidation.

Introduction

The high-valent iron-oxo porphyrin species, referred to as Compound I (Cpd I),[1,2] is the active species of heme enzymes, such as Cytochrome P450 (P450). This reagent and its artificial analogs[3−5] carry C−H hydroxylation and C=C epoxidation; two important functionalizations of hydrocarbons.[3−11] A typical Cpd I species is the triradicaloid species, shown in Figure 1, with three singly occupied molecular orbitals, two in orthogonal π^* orbitals of the Fe−O moiety and one in a porphyrin-type orbital mixed with the axial ligand, e.g., a thiolate in the case of P450. The spin distribution on the main fragments of the species is shown in Figure 1. It is seen that the species carries net two unpaired electrons on the FeO moiety (one on each atom) and single spin distributed partly on the porphine and partly on the axial sulfur ligand. The three unpaired electrons generate two spin-states, one ferromagnetic (quartet spin, $2S + 1 = 4$) and one antiferromagnetic (doublet spin, $2S + 1 = 2$), which are almost degenerate.[1,2,12] As such, Cpd I is a two-state reagent.[13,14]
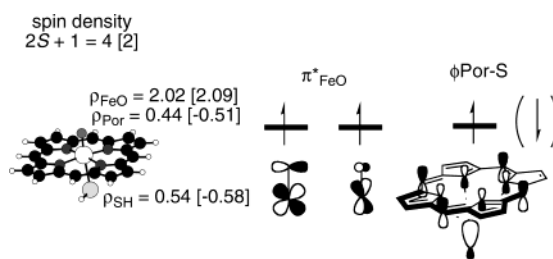

Figure 1. Electronic structure of Compound I (Cpd I). Group spin densities (ρ) and singly occupied orbitals of Cpd I in a vacuum, zero electric field ($F = 0$). Spin density values out of brackets correspond to the quartet state ($2S + 1 = 4$) and in brackets to the doublet state ($2S + 1 = 2$).

Can electric fields affect these electronic structural features and control the reactivity of Cpd I species in a desired fashion? This is the central question of this article. To answer it, we selected the reactions of Cpd I with propene that can undergo either C=C epoxidation or allylic C−H hydroxylation, shown in Scheme 1. The specific reaction has been studied enzymatically (using P450$_{LM2}$),[15] where it gave only C=C epoxidation. Notably, the epoxidation process of propene has considerable commercial value.[16] Furthermore, the high-valent iron-oxo species is common to heme enzymes[8−11,17] and to organometallic catalysts,[3−5] so that the competition has a general appeal.

(1) Loew, G. H.; Harris, D. L. *Chem. Rev.* **2000**, *100*, 407−419.
(2) (a) Harris, D. L. *Curr. Opin. Chem. Biol.* **2001**, *5*, 724−735. (b) Green, M. T. *J. Am. Chem. Soc.* **1999**, *121*, 7939−7340. (c) Ogliaro, F.; de Visser, S. P.; Cohen, S.; Kaneti, J.; Shaik, S. *ChemBioChem.* **2001**, 848−851.
(3) Kaizer, J.; Klinker, E. J.; Oh, N. Y.; Rohde, J.-U.; Song, W. J.; Stubna, A.; Kim, J.; Münck, E.; Nam, W.; Que, L., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 472−473.
(4) Rohde, J.-U.; In, J.-H.; Lim, M. H.; Brennessel, W. W.; Bukowski, M. R.; Stubna, A.; Münck, E.; Nam, W.; Que, L., Jr. *Science* **2003**, *299*, 1037−1039.
(5) Groves, J. T.; Shalyaev, K.; Lee, J. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Chapter 27, pp 17−40.
(6) Neuman, R.; Dahan, M. *Nature* **1997**, *388*, 353−355.
(7) Mayer, J. M. *Acc. Chem. Res.* **1998**, *31*, 441−450.
(8) Ortiz de Montellano, P. R.; De Voss, J. J. *Nat. Prod. Rep.* **2002**, *19*, 1−18.
(9) Groves, J. T.; Han, Y.-Z. in *Cytochrome P450: Structure, Mechanism and Biochemistry*, 2nd ed.; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1995; Chapter 1, pp 3−48.
(10) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411−1456.
(11) Woggon, W.-D. *Top. Curr. Chem.* **1996**, *184*, 40−96.

(12) Schöneboom, J. C.; Lin, H.; Reuter, N.; Thiel, W.; Cohen, S.; Ogliaro, F.; Shaik, S. *J. Am. Chem. Soc.* **2002**, *124*, 8142−8151.
(13) (a) Shaik, S.; de Visser, S. P.; Ogliaro, F.; Schwarz, H.; Schröder, D. *Curr. Opin. Chem. Biol.* **2002**, *6*, 556−567. (b) Shaik, S.; Cohen, S.; de Visser, S. P.; Sharma, P. K.; Kumar, D.; Kozuch, S.; Ogliaro, F.; Danovich, D. *Eur. J. Inorg. Chem.* **2004**, 207−226.
(14) (a) de Visser, S. P.; Ogliaro, F.; Sharma, P. K.; Shaik, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1947−1951. (b) de Visser, S. P.; Ogliaro, F.; Sharma, P. K.; Shaik, S. *J. Am. Chem. Soc.* **2002**, *124*, 11 809−11 826.
(15) Groves, J. T.; Avaria-Neisser, G. E.; Fish, K. M.; Imachi, M.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 3837−3838.
(16) Danciu, T.; Beckman, E. J.; Hancu, D.; Cochran, R. N.; Grey, R.; Hajnik, D. M.; Jewson, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1140−1142.
(17) Sono, M.; Roach, M. P.; Coulter, E. D.; Dawson, J. H. *Chem. Rev.* **1996**, *96*, 2841−2887.

Scheme 1. Epoxidation and Hydroxylation Reactions of Propene, Potentially Effected by Cpd I
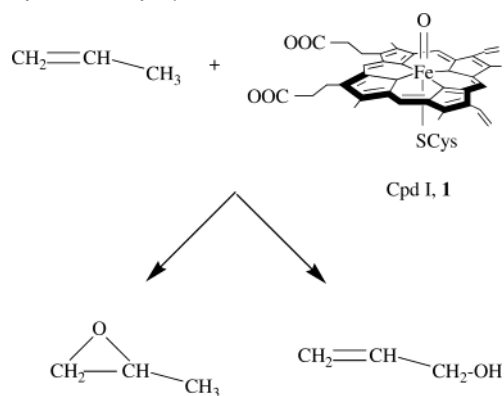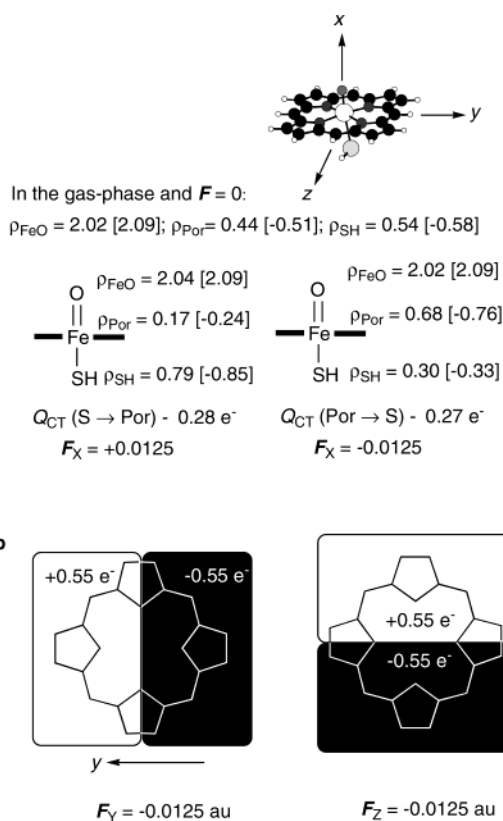
Electric fields are known to affect the spectroscopy of atoms (Stark Effect[18]) and molecules. Intense laser fields ($F = 0.1-100$ au; $I = 10^{14} - 10^{18}$ W/cm^2) can even induce severe geometry changes, tunneling ionization, and other phenomenon associated with state crossing and avoided crossing.[19,20] Here, we use density functional theory (DFT) to report unprecedented effects induced by moderately strong electric fields ($F = 0.001-0.01$ au) on the selectivity of Cpd I toward the above two competing bond activation processes, which are considered to be essentially nonpolar. It shall be seen that the electric field changes the electronic structure of the catalyst and affects its transition states in a selective anisotropic manner, *thereby leading to controlled selectivity* that depends on the field orientation, polarity, and strength.

Methods

Following common computational practices,[14] we used the hybrid UB3LYP[21,22] density functional in combination with an LACVP basis set[23] on iron and a 6-31G basis set[24] on all other atoms. All calculations were performed with the Gaussian-98 program package,[25] where the facility of electric field calculations is implemented. The field was oriented along the three molecular axes of Cpd I, as depicted in Scheme 2, and its strength was varied from zero to 0.015 au. Subsequently, the field direction was reversed and varied again between the two extreme values zero and −0.015 au. These calculations were done for the two spin states and for the transition states of both epoxidation and hydroxylation. This generated a wealth of data, which are collected in a Supporting Information; the following sections describe the key results.

Results and Discussion

Figure 2 shows the spin distribution of Cpd I under different conditions. The upper information line repeats the spin density distribution of the species in the absence of an external field, while underneath we show these quantities under the influence of an electric field with strength $F = 0.0125$ au, oriented along the molecular axes. The stabilization energies in this field strength, are 7−20 kcal/mol depending on strength and directionality (See Supporting Information), comparable with the

(18) Treynor, T. P.; Boxer, S. G. *J. Phys. Chem. A* **2004**, *108*, 1764−1778.
(19) Yamanouchi, K. *Science* **2002**, *295*, 1659−1660.
(20) Kono, H.; Koseki, S.; Fujimura, Y. *J. Phys. Chem. A* **2001**, *105*, 5627−5636.
(21) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(22) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(23) Hay, J. P.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270−283.
(24) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257−2261.

In the gas-phase and $F = 0$:
$\rho_{FeO} = 2.02$ [2.09]; $\rho_{Por} = 0.44$ [-0.51]; $\rho_{SH} = 0.54$ [-0.58]

a

$\rho_{FeO} = 2.04$ [2.09] $\rho_{FeO} = 2.02$ [2.09]
$\rho_{Por} = 0.17$ [-0.24] $\rho_{Por} = 0.68$ [-0.76]
$\rho_{SH} = 0.79$ [-0.85] $\rho_{SH} = 0.30$ [-0.33]

Q_{CT} (S → Por) - 0.28 e$^-$ Q_{CT} (Por → S) - 0.27 e$^-$
$F_X = +0.0125$ $F_X = -0.0125$

b

+0.55 e$^-$ -0.55 e$^-$ +0.55 e$^-$ -0.55 e$^-$

$F_Y = -0.0125$ au $F_Z = -0.0125$ au

Figure 2. Cartesian axes vis-à-vis Cpd I, and spin densities in a zero electric field; data out of brackets refer to the quartet spin-state, while in brackets to the doublet spin-state. The field effects are shown in parts **a** and **b**. (**a**) Group spin densities (ρ) of a Cpd I in an external electric field of 0.0125 au in the $+x$ and $-x$ directions. Also shown are the amounts of charge transfer Q_{CT} from sulfur to the porphine and vice versa. The porphine ring is schematized as two bold lines flanking iron. (**b**) Charge polarization in the porphine plane, in the presence of electric fields of 0.0125 au in the y and z directions.

Scheme 2. Cpd I in a Coordinate Axes System, along with Indications of the Directions of the Positive and Negative Fields
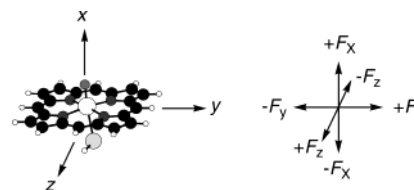
stabilization in a nonpolar solvent with a dielectric constant, $\epsilon = 5.7$ (14−15 kcal/mol). From part (**a**) of the figure, it is seen that an electric field oriented along the positive x-axis (the S−Fe−O axis) converts Cpd I to a thiolate radical species; the porphine ring becomes virtually closed-shell. Reversing the direction of this field achieves exactly the opposite effect; now the majority of the spin density is located on the porphine that becomes radical cationic, and is depleted away from the sulfur.

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Gaussian, Inc.: Pittsburgh, PA, 1998.
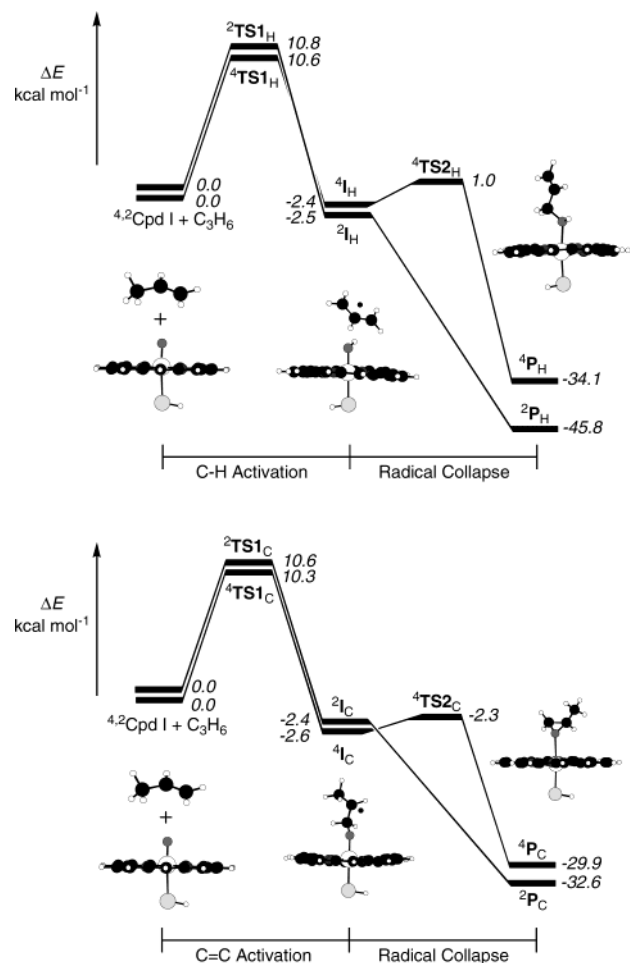
Figure 3. Two-states energy profiles for propene hydroxylation (top) and epoxidation (bottom) in a vacuum; the quartet and doublet spin states are indicated by the superscripts near the species. In both cases, the initial phase involves bond activation, via corresponding transition states, $^{2,4}\mathbf{TS1_H}$ (for H-abstraction) and $^{2,4}\mathbf{TS1_C}$ (for attack on C=C). These transition state species generate an alkyl radical coordinated to iron-oxo porphine moiety. The radical is indicated by the heavy dot near the alkyl moiety. Subsequently, the radicals collapse to form either ferric alcohol complex (top) or a ferric-epoxide (bottom). All relative energies contain zero-point energy corrections.

Furthermore, these changes are attended by significant amount of charge transfer ($\sim 0.3e^-$) from the sulfur to the porphine, when the field is oriented in $+x$ direction, and vice versa in the $-x$ direction. By contrast, as shown in Figure 2**b**, an electric field in the y, z directions, in the plane of the porphine, causes a strong charge polarization of the macrocycle, but has no effect on the electronic properties of Cpd I along the S–Fe–O axis. Clearly, an electric field induces qualitative changes in the electronic structure of Cpd I, which are more apparent in the $\pm x$-directions since the species has a mixed valent character (sulfur radical or porphyrin radical cation) that can be manipulated by perturbations along this axis.[2,12]
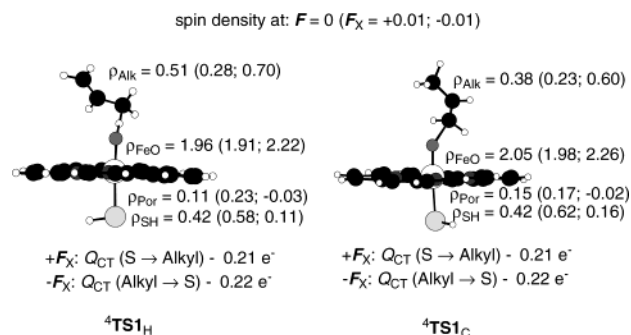
Can one hope to use external electric fields to direct the selectivity of a Cpd I reagent to carry at will C–H hydroxylation or C=C epoxidation in a substrate that contains the two functionalities? To answer this question, we turned to investigate the effect of an external electric field on the selectivity of Cpd I toward the allylic C–H hydroxylation vs the double bond epoxidation of propene (Scheme 1). Figure 3 shows the situation for the reaction in a vacuum and in a zero electric field ($F =$
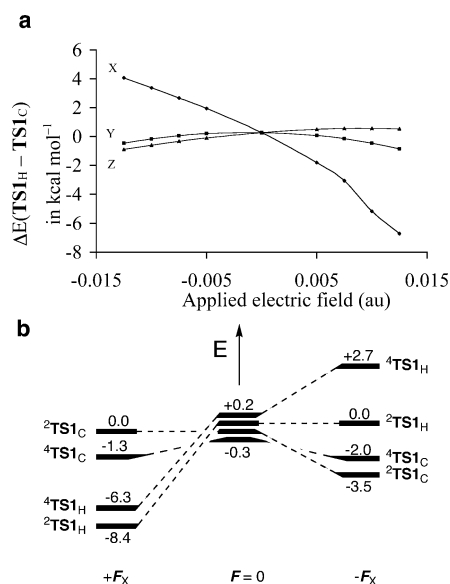
Figure 4. (a) Relative energies (with zero-point energy correction) of the bond activation transition states ($\mathbf{TS1_H}$ and $\mathbf{TS1_C}$; these are average energies of the spin states) under the influence of applied electric fields of different strengths, x, y, z-orientations and directionality; x is the S–Fe–O axis, perpendicular to the porphine plane. (b) The relative energies of the four transition states, $^{2,4}\mathbf{TS1_H}$ and $^{2,4}\mathbf{TS1_C}$, in a zero field (in the center), and in x-directed fields of $F_x = +0.01$ au and $F_x = -0.01$ au. Note that positive and negatively directed fields induce opposite regioselectivity. $F_x = +0.01$ au prefers C–H hydroxylation, whereas $F_x = -0.01$ au prefers C=C epoxidation.

0). This figure is typical of the two-state reactivity espoused by Cpd I, due to its closely lying quartet and doublet state.[12–14] The reaction pathway of each process involves a bond activation phase wherein the oxo-end of Cpd I activates either the C–H and C=C bonds (either H-abstraction or radical attack on the double bond), followed by a radical-collapse step to form either an alcohol complex or an epoxide complex. However, only the quartet-spin pathways exhibit significant barriers for radical-collapse, whereas the doublet-spin pathways have no such barriers and are effectively concerted. Consideration of the bond-activation barriers for epoxidation vs hydroxylation reveals that all the four transition states are condensed within 0.5 kcal/mol, with a tiny preference for the epoxidation pathways.[14] As such, bare Cpd I is a nonregioselective reagent, with hardly any preference for C=C or C–H activation, and furthermore, for other substrates with stereochemical labels in the organic molecule, it is unlikely to be stereoselective, due to scrambling of the stepwise and effectively concerted spin pathways.

What happens to these reactivity features when an external electric field is applied on the reactions? Since the bond activation steps are rate limiting, it is sufficient to look at the field effect on the respective transition states (TSs), $\mathbf{TS1_C}$ and $\mathbf{TS1_H}$. Figure 4**a** shows the spin-states averaged relative energy of the TSs for hydroxylation vs epoxidation ($\Delta E(\mathbf{TS1_H}-\mathbf{TS1_C})$) as a function of the field strength along the x, y, and z directions, where positive x is along the S–Fe–O axis and perpendicular to the porphine ring. It is seen that the y, z-oriented fields (in the plane of the porphine) exert relatively small effects on the energy difference, i.e., they do not induce significant regioselectivity relative to the system in a vacuum. By contrast, an x-oriented field *of whatever strength* induces significant regioselectivity that depends on the direction of the field. Thus, in

spin density at: $F = 0$ ($F_X = +0.01; -0.01$)

$\rho_{Alk} = 0.51 \ (0.28; 0.70)$

$\rho_{FeO} = 1.96 \ (1.91; 2.22)$

$\rho_{Por} = 0.11 \ (0.23; -0.03)$

$\rho_{SH} = 0.42 \ (0.58; 0.11)$

$+F_X$: Q_{CT} (S → Alkyl) - 0.21 e⁻

$-F_X$: Q_{CT} (Alkyl → S) - 0.22 e⁻

$^4\mathbf{TS1}_H$

$\rho_{Alk} = 0.38 \ (0.23; 0.60)$

$\rho_{FeO} = 2.05 \ (1.98; 2.26)$

$\rho_{Por} = 0.15 \ (0.17; -0.02)$

$\rho_{SH} = 0.42 \ (0.62; 0.16)$

$+F_X$: Q_{CT} (S → Alkyl) - 0.21 e⁻

$-F_X$: Q_{CT} (Alkyl → S) - 0.22 e⁻

$^4\mathbf{TS1}_C$

Figure 5. Group spin densities (ρ) in the quartet-state transition states for hydroxylation ($^4\mathbf{TS1}_H$) and epoxidation ($^4\mathbf{TS1}_C$), in a vacuum ($F = 0$) and in applied external fields oriented along the *x*-axis (the S−Fe−O axis) in the positive and negative directions. Also shown are the corresponding charge-transfer quantities (Q_{CT}) and their direction, which are induced by the electric fields.

the positive *x*-direction one finds $\Delta E(\mathbf{TS1}_H - \mathbf{TS1}_C) < 0$, namely, the applied field causes preference of hydroxylation over the epoxidation, while in the negative *x*-direction we have throughout $\Delta E(\mathbf{TS1}_H - \mathbf{TS1}_C) > 0$, and the field prefers epoxidation throughout. Figure 4**b** shows the situation of the four TSs in a field of $F_x = \pm 0.01$ au relative to the zero field situation, in which nonselectivity nests since the four TSs are condensed to within 0.5 kcal/mol. It is seen that the positively *x*-oriented field, for which Cpd I acquires mostly a thiolate radical character, prefers the hydroxylation processes by as much as 6−10 kcal/mol. On the contrary, a negatively *x*-oriented field, which renders Cpd I into a porphine radical cationic species, prefers the epoxidation process by as much as 2−6 kcal/mol. Moreover, for each process, the field prefers the effectively concerted doublet-state over the stepwise quartet-state reaction. *Clearly, an x-electric field leads to the emergence of absolute regioselectivity and stereoselectivity, and the switch in the direction of the field causes a complete reversal in the selectivity of the reaction.*

Figure 5 compares the spin density distribution of $^4\mathbf{TS1}_H$ and $^4\mathbf{TS1}_C$ in a zero field and in *x*-oriented field with strengths $F_x = \pm 0.01$ au. As for Cpd I above (Figure 2**b**), here too the *y*, *z*-oriented fields exert changes mainly in the porphine plane and hence, are skipped (see Supporting Information). Inspection of the spin densities on the alkyl and sulfur moieties one observes the following trends: For both TSs, a positive *x*-field reduces the spin density development on the alkyl moiety and increases the spin on the sulfur, whereas a negatively directed *x*-field induces the opposite change; the alkyl spin density increases, whereas that of the sulfur almost vanishes. Since the spin development of the alkyl is a measure of the progress of the TS along the respective bond activation coordinate, it is apparent that a positively directed *x*-electric field shifts the TSs to an 'earlier' position, whereas a negatively directed *x*-field changes them to a 'later' position. These changes are attended by significant charge transfer of $0.26-0.27 e^-$; for a positively

directed *x*-field the charge transfer occurs from the sulfur to the alkyl group, whereas for the negatively directed field, the alkyl moiety donates electron density to the sulfur. All of these changes are common also to the doublet-spin species, $^2\mathbf{TS1}_H$ and $^2\mathbf{TS1}_C$ (Supporting Information). We can see therefore that the regioselectivity switches of C−H vs C=C activation, transpires because the hydrogen abstraction TSs ($^{4,2}\mathbf{TS1}_H$) benefit relatively more, compared with the epoxidation species ($^{4,2}\mathbf{TS1}_C$), from changes that shift the electronic structure to an "earlier" position. And on the contrary, the epoxidation TSs, $^{4,2}\mathbf{TS1}_C$, benefit relatively more from those changes that shift the electronic structure to a 'later' position. *As such, external electric fields oriented in the ±x-direction, along which the electrons and bonds are reorganized during the chemical reaction, are capable of inducing perfect selectivity in a desired direction.*

Summary and Conclusions

At this stage, we cannot offer a straightforward explanation for the opposite response of the TSs to the electric field. However, it is clear that this effect originates in state mixing in the presence of the electric field,[12,20,26] and further study of the state spacing and their mixing patterns will be required to establish a cause and effect relationship. Nevertheless, at present, the effect itself of controlled selectivity is remarkable enough to be submitted as subject of experimental scrutiny. For example, the orientation of the molecules can be achieved by means of Langmuir−Blodgett techniques while the reaction is carried out in the presence of an electric field. Furthermore, catalyst engineering can be used to create environments that lead to controlled selectivity due to the pre-designed electric fields. It also did not escape us that, since proteins possess anisotropic electric fields,[27,28] part of the selectivity of P450 enzyme ascribed to substrate fit may result from the electric field effects, such as the ones shown in this paper. The selectivity of P450 enzymes toward C−H and C=C oxidation is currently being studied in our group by means of QM/MM calculations.

Supporting Information Available: Nineteen Figures and 19 Tables with absolute and relative energies, group charges, group spin densities, and dipole moments of all systems discussed here under various external electric fields. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) (a) Ogliaro, F.; Cohen, S.; de Visser, S. P.; Shaik, S. *J. Am. Chem. Soc.* **2000**, *122*, 12 892−12 893. (b) Ogliaro, F.; de Visser, S. P.; Groves, J. T.; Shaik, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2874−2878.
(27) Poulos, T. L. *J. Biol. Inorg. Chem.* **1996**, *1*, 356−359.
(28) Poulos, T. L. In *The Porphyrin Handbook*; Kadish, K. M.; Smith, K. M.; Guillard, R., Eds.; Academic Press: San Diego, 2000; Volume 4, pp 189−218.