

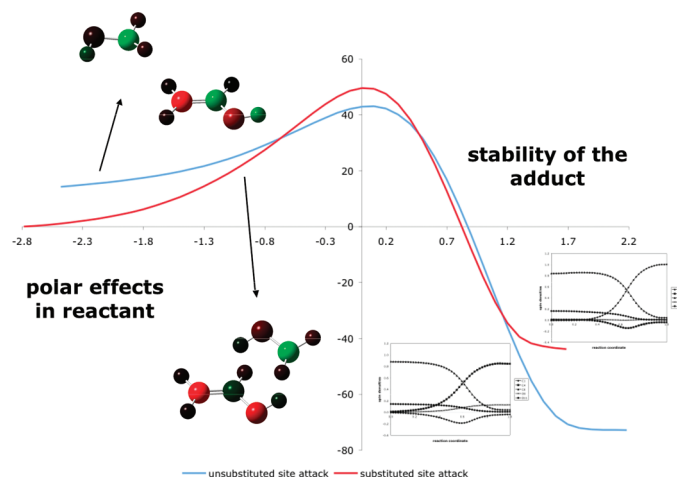
## Regioselectivity of Radical Additions to Substituted Alkenes: Insight from Conceptual Density Functional Theory

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Radical additions to substituted alkenes are among the most important reactions in radical chemistry. Nonetheless, there is still some controversy in the literature about the factors that affect the rate and regioselectivity in these addition reactions. In this paper, the orientation of (nucleophilic) radical additions to electron-rich, -neutral, and -poor monosubstituted substrates (11 reactions in total) is investigated through the use of chemical concepts and reactivity descriptors. The regioselectivity of the addition of nucleophilic radicals on electron-rich and -neutral alkenes is thermodynamically controlled. An excellent correlation of 94% is found between the differences in activation barriers and in product stabilities (unsubstituted versus substituted site attack). Polar effects at the initial stage of the reaction play a significant role when electron-poor substrates are considered, lowering the extent of regioselectivity toward the unsubstituted sites, as predicted from the stability differences. This is nicely confirmed through an analysis for each of the 11 reactions using the spin-polarized dual descriptor, matching electrophilic and nucleophilic regions.

### 1. Introduction

Radical additions to substituted alkenes are among the most important reactions in radical chemistry as they are central in many free-radical chain polymerizations in industry. Nonetheless, there is still some debate about the factors that affect the rate and regioselectivity in these addition reactions. As Tedder et al. already put forward in 1979, no simple property can be used to determine the orientation of

free radical addition, and the rate and orientation of free radical addition to olefins depend on the complex interplay of polar, steric, and bond-strength terms.<sup>1,2</sup> It is commonly known and experimentally seen that in almost all cases radicals add preferentially to the unsubstituted (or less substituted) carbon atom of the double bond, especially for

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monosubstituted alkenes, not because this site is activated but because the “substituted site is very deactivated”.<sup>2,3</sup> Tedder et al. state that although polarity controls the overall rate of addition and has a small influence on the regioselectivity, steric effects play the predominant part in determining the orientation. Moreover, the steric hindrance is principally an enthalpy effect, increasing the activation energy and only having a small effect on the pre-exponential factor.<sup>2</sup> Fischer et al., in their experimental work concerning the reaction of *tert*-butyl and hydroxymethyl radicals with alkenes, confirm that the latter does not change much when changing the alkene substituents and that the variation in the rates is due to changes in the activation energies.<sup>4,5</sup> They found that the electron affinity of the alkenes is suited to describe the polar effects in the addition of the nucleophilic *tert*-butyl radical on the alkenes. Their findings concerning the regioselectivity agree with Tedder et al.,<sup>2</sup> namely that the orientation is caused by steric effects, while polar effects determine the rate of addition.

Ponec et al.<sup>6</sup> concluded that the regioselectivity of CF<sub>3</sub> radical additions is governed mostly by charge-transfer contributions, while the additions of CH<sub>3</sub> radicals are determined predominantly by steric effects. Delbecq et al.<sup>7</sup> state that the preferential site of attack is not necessarily the one with the smaller steric hindrance, although steric effects are important. Later, the addition of the dicyanomethyl (DCM) and trifluoromethyl radicals toward a set of substituted alkenes was investigated in detail by Riemenschneider et al.<sup>8</sup> They found a linear correlation between the logarithm of the addition rates or the activation energies and the superdelocalizability, a reactivity index that measures binding MO interactions between the alkenes and the incoming radical. They concluded that the overall addition rate is governed by polar effects and that a steric  $\alpha$ -effect can be neglected for all alkyl substituents, except for the cases of two alkyl substituents or a branched alkyl group at the attacked C-atom. The regioselectivity for the CF<sub>3</sub> and DCM radical attack is in their view not governed by steric but by polar effects.

Radom et al.<sup>9</sup> looked into the addition of the methyl radicals to alkenes using computational data and investigated the importance of polar effects. They found an excellent correlation between the reaction barrier and the reaction energy, suggesting that reaction thermodynamics is the factor that dominates the rate of methyl radical addition to alkenes and that polar contributions to the reactivity of the methyl radical toward alkenes are generally insignificant.<sup>9</sup> The observation that lower reaction barriers are encountered for alkenes with electron-withdrawing substituents was attributed to the fact that these substituents increase the reaction exothermicity and, therefore, reactivity and not because of induced polar character in the transition state.

Héberger et al. countered some of these conclusions in their experimental work on the addition of the very nucleophilic 2-hydroxy-2-propyl radical to alkenes in solution.<sup>10</sup>

They found that the addition of this nucleophilic radical is dominated by polar effects and that the rates of addition correlate well with the electron affinity of the alkenes. Another experimental work by Fischer et al.<sup>5</sup> on the addition of the hydroxymethyl radical to alkenes in solution showed a dominance of polar effects over the enthalpy effects, in the sense of partial electron transfer from the radical to the alkenes, at least for alkenes with strong electron-withdrawing substituents, like COOR, CHO, and CN. Finally, Héberger et al.<sup>11</sup> investigated experimental as well as theoretical reaction data on the addition of a set of radicals toward a set of substituted alkenes and concluded that polar and enthalpy effects are the dominant factors influencing radical addition reactions and that steric and solvent effects are of lesser importance. More specifically, the dominant factors are: polar effects for strongly electrophilic/nucleophilic radicals, polar and enthalpy effects for moderately electrophilic/nucleophilic radicals and enthalpy effects alone for weak electrophilic/nucleophilic radicals. They also state that the theoretical calculations seem to overemphasize the role of enthalpy effects.<sup>11</sup>

This small overview of studies concerning the issues of rate and regioselectivity in radical addition reactions during the last decades shows that there is still a considerable amount of debate. In this contribution we will investigate the effect of the degree of nucleophilic or electrophilic character of free radicals on the orientation of their addition on electron-rich and electron-poor alkenes. However, in the literature there is little information on reaction data concerning *electrophilic* addition reactions. In several contributions, the CF<sub>3</sub> radical is designated electrophilic<sup>2,8,12</sup> because of the electron-withdrawing fluorine atoms attached to the carbon radical center and because of the radical's accelerated rate of addition on substituted alkenes with electron-donating groups. However, according to the electrophilicity index, as defined by Parr et al.,<sup>13</sup> which led to an (absolute) classification of radicals into electrophiles and nucleophiles<sup>14</sup> and which has proven its usefulness to experimentalists,<sup>15</sup> the trifluoromethyl radical is weakly nucleophilic of nature, though more electrophilic relative to the methyl radical. Aside from this, in the contribution of Héberger et al.,<sup>11</sup> experimental and theoretical reaction data<sup>16–18</sup> are available for the radical additions of the electrophilic<sup>14</sup> phenylsulfonyl, tosyl, and cyclic malonyl radicals. For this contribution, we tried to compute activation barriers and reaction energies for the addition reactions of the electrophilic hydroxyl and chlorine radicals on the unsubstituted and substituted site of the alkene double bond, but most DFT calculations (using the B3LYP functional) failed to locate the transition states, suggesting that these reactions are barrierless.<sup>19</sup>

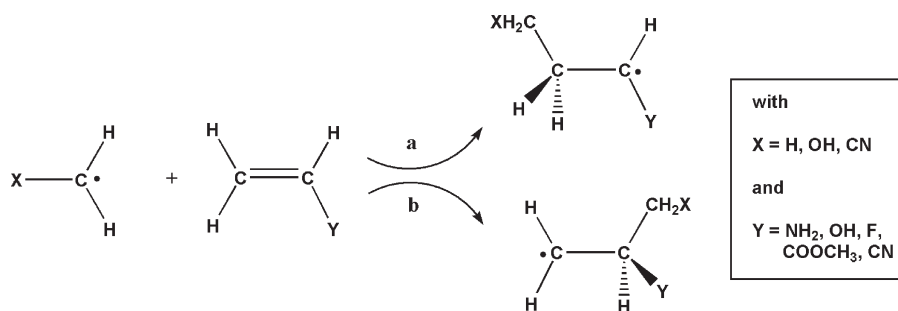
Therefore, we concentrated on addition reactions on some electron-rich and electron-poor alkenes of radicals that

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**TABLE 1.** Activation Barriers  $E_a$  (0 K), Reaction Energies  $E_r$  (0 K), and Works  $W_1$ ,  $W_2$ ,  $W_3$ , and  $W_4$  (As Defined by the Reaction Force Profile) in  $\text{kJ mol}^{-1}$  ((a) Attack on Unsubstituted Site; (b) Attack on Substituted Site), Computed Using the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) Method

radical	alkene	a/b	$E_a$	$E_r$	$W_1$	$W_2$	$W_3$	$W_4$
methyl	ethenamine	a	27.1	-87.8	13.8 69%	6.1 31%	-68.6 53%	-61.9 47%
		b	53.8	-52.5	36.9 75%	12.5 25%	-58.0 49%	-59.9 51%
	ethenol	a	29.0	-87.0	15.0 70%	6.5 30%	-66.0 50%	-65.9 50%
		b	47.7	-62.5	33.1 75%	10.8 25%	-61.5 51%	-58.1 49%
hydroxymethyl	ethenol	a	32.4	-70.9	20.7 72%	8.0 28%	-62.3 54%	-53.5 46%
		b	47.8	-39.5	37.3 75%	12.3 25%	-47.2 50%	-46.3 50%
	fluoroethene	a	31.6	-65.9	19.9 72%	7.9 28%	-56.3 52%	-52.4 48%
		b	36.1	-60.9	25.9 74%	9.3 26%	-55.3 53%	-48.8 47%
cyanomethyl	ethenol	a	27.4	-52.1	14.8 66%	7.5 34%	-45.7 50%	-44.8 50%
		b	49.7	-24.2	32.4 72%	12.6 28%	-42.6 54%	-36.4 46%
	methyl prop-2-enoate	a	31.2	-61.9	19.2 70%	8.2 30%	-41.7 40%	-62.1 60%
		b	58.2	-10.0	44.0 79%	12.0 21%	-37.9 51%	-36.2 49%



**FIGURE 1.** Scheme of radical addition to monosubstituted alkenes: (a) unsubstituted site attack and (b) substituted site attack.

range from a strongly nucleophilic to a neutral character. In accordance with many previous contributions from the literature,<sup>5,11,20,22</sup> hydroxymethyl was taken as a representative for strongly nucleophilic radicals, methyl as a moderately nucleophilic radical, and the cyanomethyl as a neutral radical.<sup>14</sup> As Héberger et al.<sup>11</sup> already concluded for the addition rates of radical additions, a difference in degree of nucleophilicity implies a difference in the kind of effects (polar versus enthalpy) controlling these rates. This contribution focuses not on the rate but on the orientation of free radical additions, investigating the differences in activation barriers between addition on the unsubstituted and on the substituted site of monosubstituted alkenes and whether

these differences are regulated through enthalpy or polar aspects by means of reactivity indices as introduced through Conceptual DFT.<sup>23,24</sup>

## 2. Results and Discussion

In this work, we have combined the strongly nucleophilic hydroxymethyl, the moderately nucleophilic methyl, and the neutral cyanomethyl radical with some monosubstituted alkenes: the electron-rich ethenamine and ethenol, the almost “neutral” fluoroethene, and the electron-poor methyl prop-2-enoate (or methyl acrylate) and 2-propenenitrile (or cyanoethene). The activation barriers and reaction energies (at 0 K and in the gas phase) of 11 selected radical addition reactions, i.e., methyl + ethenamine/ethenol/fluoroethene/methyl prop-2-enoate/2-propenenitrile, hydroxymethyl + ethenamine/ethenol/fluoroethene/2-propenenitrile, cyanomethyl + ethenol/methyl prop-2-enoate, are listed in Tables 1 and 2. The radical addition scheme is shown in Figure 1. We have used the DFT method B3LYP/6-31G(d) for the geometry optimizations and for the calculation of the ZPVEs, which is preferable to the use of UHF and UMP2,<sup>20</sup> and we

(19) We managed to find transition states for these electrophilic radical addition reactions using the MP2 method, but comparison of reaction data for the addition of the nucleophilic methyl and hydroxymethyl and the neutral cyanomethyl radicals with literature showed that the MP2 method (largely) overestimates the experimental reaction data (see ref 20). The reason that reaction data could be obtained for the larger (in size) phenylsulfonyl, tosyl, and cyclic malonyl radicals is (probably) due to the fact that these radicals are highly stable compared to the hydroxyl and chlorine radicals (see ref 21).

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**TABLE 2.** Difference in Activation Barriers  $\Delta E_a$  (0 K), Difference in Reaction Energies  $\Delta E_r$  (0 K), Product Stabilities “stab” and Difference in Product Stabilities  $\Delta\text{stab}$  in  $\text{kJ mol}^{-1}$  for a Set of 11 Radical Addition Reactions ((a) Attack on Unsubstituted Site; (b) Attack on Substituted Site), Computed Using the B3LYP/6-311+G(d,p)/B3LYP/6-31G(d) Method

radical	alkene	a/b	$E_a$	$\Delta E_a$	$E_r$	$\Delta E_r$	stab	$\Delta\text{stab}$
methyl	ethenamine	a	27.1		-87.8		142.0	
		b	53.8	26.7	-52.5	35.3	190.5	48.4
	ethenol	a	29.0		-87.0		156.7	
		b	47.7	18.6	-62.5	24.5	193.4	36.7
	fluoroethene	a	30.4		-84.5		177.5	
		b	37.8	7.4	-88.5	-4.0	195.8	18.3
methyl prop-2-enoate	a	20.1		-104.5		149.4		
	b	35.6	15.5	-67.4	37.1	189.0	39.6	
hydroxymethyl	ethenamine	a	17.2		-119.1		126.0	
		b	37.6	20.4	-68.5	50.6	195.4	69.5
	ethenol	a	33.2		-72.2		139.4	
		b	63.2	30.0	-19.9	52.3	187.6	48.2
	fluoroethene	a	32.4		-70.9		154.7	
		b	47.8	15.4	-39.5	31.4	191.8	37.2
2-propenenitrile	a	31.6		-65.9		175.8		
	b	36.1	4.5	-60.9	5.0	192.7	16.8	
cyanomethyl	ethenol	a	25.5		-84.0		122.4	
		b	31.7	6.2	-45.0	39.0	193.0	70.6
	methyl prop-2-enoate	a	27.4		-52.1		156.8	
		b	49.7	22.3	-24.2	27.9	194.8	38.0
		a	31.2		-61.9		160.4	
		b	58.2	27.0	-10.0	51.9	198.2	37.9

performed single-point energy calculations with B3LYP/6-311+G(d,p), which in many cases provides activation barriers that are in better agreement with experiment than the corresponding MP2 and MP4 values.<sup>12,20</sup>

Although many experimental radical additions are performed in solution, the solvent effect on the reaction thermodynamics and kinetics was found to be rather limited. Radom et al.<sup>20</sup> investigated in detail the solvent effect on radical additions through the SCIPCM model and found that for a dielectric constant of 2 (a nonpolar medium, typical conditions for the addition reaction involving the methyl radical), the effect on the barrier ranges (solvent versus gas phase) from  $-1.1$  to  $+1.1$   $\text{kJ mol}^{-1}$ ; for a dielectric constant of 40 (polar medium, typical conditions for the addition of the hydroxymethyl and cyanomethyl radicals), the effects range from  $-3.0$  to  $+2.8$   $\text{kJ mol}^{-1}$ ; e.g., in the case of the addition of the most nucleophilic radical (hydroxymethyl) on the electron-poor alkene 2-propenenitrile in a polar solvent, which is the case in which the solvent effect could be anticipated to be the largest, Radom et al. conclude that the barrier decreases by  $2.8$   $\text{kJ mol}^{-1}$  and that the reaction enthalpy increases by  $5.3$   $\text{kJ mol}^{-1}$ , which is much smaller than the actual barriers ( $25.5$  and  $31.7$   $\text{kJ mol}^{-1}$  for unsubstituted and substituted site attack, respectively) and activation enthalpies ( $-84.0$  and  $-45.0$   $\text{kJ mol}^{-1}$  for unsubstituted and substituted site attack, respectively). The effect of the solvent on radical additions to double bonds was also investigated by Lalevée et al.,<sup>25</sup> the conclusions largely coinciding with the contribution of Radom et al. In addition, the effect of different solvents was investigated experimentally by Fisher et al. in 1985<sup>4</sup> for the addition of the *tert*-butyl radical to several alkenes. It was observed that at equal temperatures the rate constants for the additions of the *tert*-butyl in the different solvents were equal within statistical errors. Moreover, it can be expected that the effect of the solvent on the unsubstituted site attack reaction will be

similar to the influence on the substituted site attack reaction when the same substrate and radical are considered.

**2.1. Reaction Force Analysis.** For 6 of the 11 reactions, IRC calculations were performed, from the reactant complexes to the product radicals, and this for the attack on the unsubstituted site (**a**) as well as on the substituted site (**b**) of the double bond. A reaction force analysis, introducing three reaction regions, that is the reactant, the TS, and the product region, and each region with its own characteristics, was applied for all six reactions. The reaction force is obtained by differentiating the potential energy  $E(\xi)$  with respect to  $\xi$ , the intrinsic reaction coordinate (IRC) expressed in mass-weighted Cartesian coordinates:<sup>26</sup>

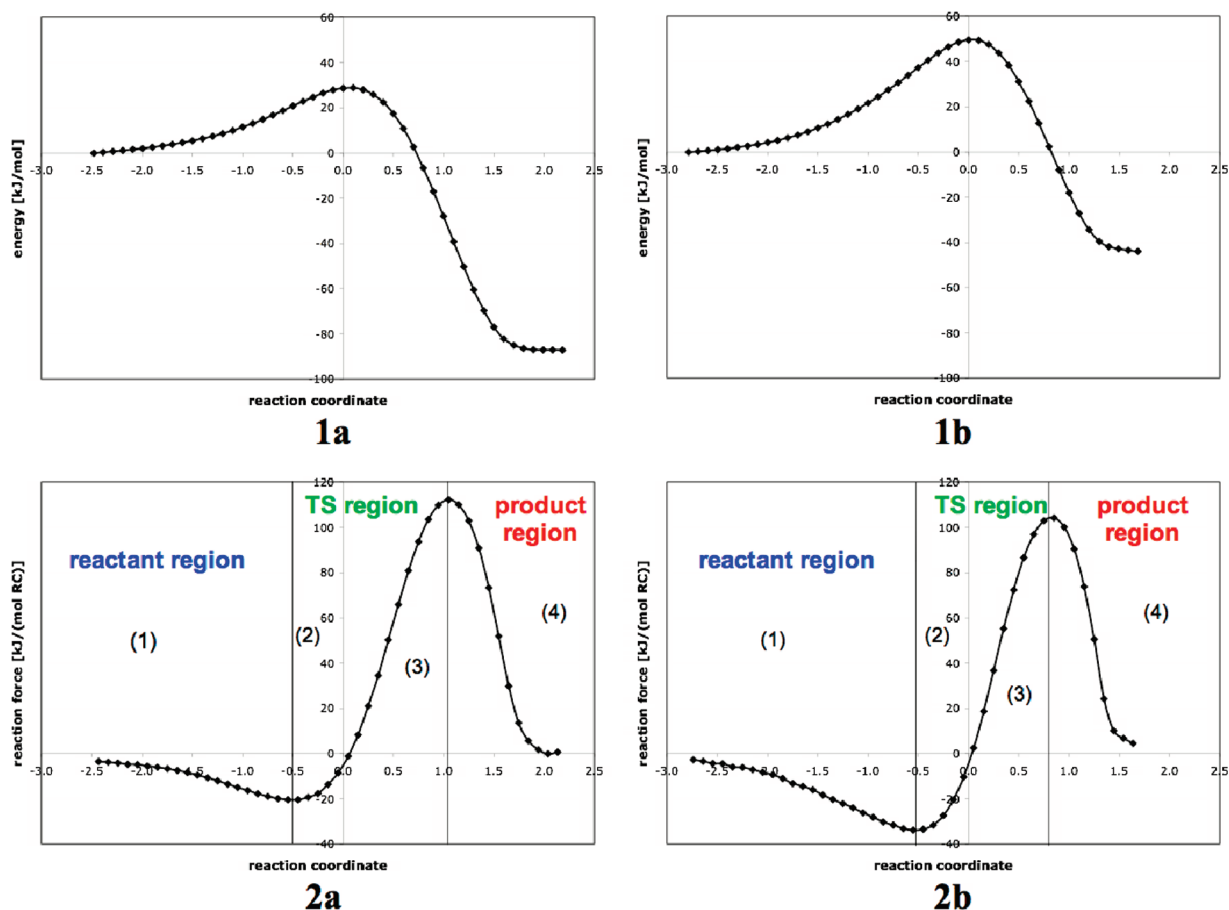
$$F(\xi) = -\frac{\partial E(\xi)}{\partial \xi} \quad (1)$$

Two extra key points are introduced: the minimum and maximum in the reaction force profile. These critical points define the three reaction regions. The first and third regions, the reactant and product regions, respectively, are mostly characterized by geometric rearrangements, i.e. preparation of the system for subsequent reaction and relaxation of the system. The actual transition to product(s), basically characterized by bond breaking and/or formation, occurs in the region between the two extrema in the reaction force profile. Figure 2 displays the potential energy and the reaction force profiles of the hydroxymethyl attack on the unsubstituted site (**a**) and on the substituted site (**b**) of ethenol.

From bond length observations, it can be seen that the double bond is being broken at the end of the transition state region, followed by the forming of the single bond in the product region between the radical center and one of the carbon atoms of the alkene. Apart from the differences in activation and reaction energy, the profiles for both attacks seem to be very alike. To examine this in more detail, we turn to a rational partitioning of the activation and reaction

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**FIGURE 2.** Potential energy and reaction force profile for the addition of the hydroxymethyl radical on ethenol ((a) attack on unsubstituted site; (b) attack on substituted site) with indication of the different regions as introduced by the five critical points in the reaction force profile.

energy into amounts of work.<sup>27</sup> The activation energy can be written as

$$\Delta E^\ddagger = W_1 + W_2 \quad (2)$$

where  $W_1$  and  $W_2$  are defined as

$$W_1 = - \int_{\xi_R}^{\xi_{\min}} F(\xi) d\xi \quad (3)$$

and

$$W_2 = - \int_{\xi_{\min}}^{\xi_0} F(\xi) d\xi \quad (4)$$

The electronic reaction energy  $E_{r,e}$  can be expressed as

$$E_{r,e} = W_1 + W_2 + W_3 + W_4 \quad (5)$$

with

$$W_3 = - \int_{\xi_0}^{\xi_{\max}} F(\xi) d\xi \quad (6)$$

and

$$W_4 = - \int_{\xi_{\max}}^{\xi_P} F(\xi) d\xi \quad (7)$$

(27) Burda, J. V.; Toro-Labbé, A.; Gutiérrez-Oliva, S.; Murray, J. S.; Politzer, P. *J. Phys. Chem. A* **2007**, *111*, 2455.

These definitions indicate the amount of work that needs to be done for geometrical reordering and preparation ( $W_1$ ), for electronic reordering and breaking/forming of bonds ( $W_2$  and  $W_3$ ), and for structural reordering and relaxation ( $W_4$ ). Previously, this partitioning was found to be adequate, e.g., in describing and suggesting whether the (ir)reversibility of side reactions in the polymerization of poly(vinyl chloride) can be attributed to structural or electronic effects or a combination of both.<sup>29</sup> Table 1 displays the values of the different works for the six reactions (listed in Table 1), two reactions per radical, as well as the percentages with respect to the sum of the works for the regions before and after the transition states.

We clearly see that there is not a wide variation in the different percentages between the **a** and **b** attack and moreover among all reactions (maybe with the exception of the cyanomethyl + methyl prop-2-enoate addition). The percentage of  $W_1$  is slightly more significant in the case of attack on the substituted site (**b**), agreeing with previous findings by Arnaud et al.<sup>30</sup> They found that the intramolecular deformation of the alkene, which represents the energy needed for the alkene to deform from equilibrium to transition state

(28) Morell, C.; Grand, A.; Gutiérrez-Oliva, S.; Toro-Labbé, A. In *Theoretical Aspects of Chemical Reactivity*; Toro-Labbé, A., Ed.; Elsevier: Amsterdam, 2004; p 101.

(29) De Vleeschouwer, F.; Toro-Labbé, A.; Gutiérrez-Oliva, S.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *J. Phys. Chem. A* **2009**, *113*, 7899.

(30) Arnaud, R.; Subra, R.; Barone, V.; Leji, F.; Olivella, S.; Sole, A.; Russo, N. *J. Chem. Soc. Perkin Trans. 2* **1986**, 1517.

geometry, provides a discrimination between the two possible attacks, favoring the less substituted site attack. Overall, the reaction force analysis suggests that all reactions proceed rather similarly, irrespective of radical, alkene or site attack. This agrees with what was found in literature, namely that the transition states for different radical additions are very similar to each other.<sup>5,12,30,31</sup>

**2.2. Effect of Product Stability.** In many previous contributions, the orientation is thought to be primarily governed by steric and enthalpy effects.<sup>2,4,5,9</sup> Nevertheless, in some of these contributions<sup>2,5</sup> it is also stated that delocalization of the unpaired electron in the adduct radical is of small importance for the orientation of radical additions. We looked at the entire variation of the spin density, localized on every atom in the system through NPA calculations,<sup>32–34</sup> along the reaction coordinate for all six reactions from above. The spin density indicates if the radical systems are able to delocalize the unpaired electron, giving an indication of the stability of the radical system (at that time). In Figure 3, the spin densities along the reaction coordinate are plotted for the attacks on the unsubstituted (**a**) and substituted (**b**) sites of the following reactions: methyl and hydroxymethyl + ethenol, cyanomethyl + methyl prop-2-enoate and hydroxymethyl + fluoroethene. In the plots, a reduced reaction coordinate  $\xi_{\text{red}}$  is used, scaling the reactions to an interval of [0,1] in reaction coordinates, making it easier to compare **a** and **b** attack:

$$\xi_{\text{red}} = \frac{\xi_{\text{R}} - \xi}{\xi_{\text{R}} - \xi_{\text{P}}} \text{ with R = reactant and P = product} \quad (8)$$

In the reactant stage of the reaction, delocalization is seen in the hydroxymethyl and the cyanomethyl radicals. Before the transition state, the double bond of the monosubstituted alkene is being polarized by the approaching radical. Note that this process starts much earlier for the attack on the unsubstituted site (**a**). Next, charge transfer occurs around the transition state, leading to the breaking of the double bond at the end of the transition state region. In the product region, where the bond between radical and substrate is being formed, there is no charge transfer occurring anymore. There is a clear difference between attack on the unsubstituted (**a**) and the substituted (**b**) site: the **a** product radical displays delocalization while the spin density on the **b** product radical center is practically 1 (so no delocalization at all). Accordingly, we expect a distinct difference in radical stabilities between **a** and **b** products.

In a recent paper,<sup>21</sup> a model was constructed that breaks down bond dissociation enthalpies (BDEs) into parts that (only) incorporate intrinsic properties of the radical fragments, like radical stability (stab), electrophilicity ( $\omega$ ), and Pauling electronegativity ( $\chi$ )

$$\text{BDE(A - B)} = \begin{cases} (\text{stab}_A + \text{stab}_B) + a\Delta\omega_A\Delta\omega_B & \text{if } \Delta\chi_A < 0 \text{ and } \Delta\chi_B < 0 \\ (\text{stab}_A + \text{stab}_B) + a\Delta\omega_A\Delta\omega_B + b\Delta\chi_A\Delta\chi_B & \text{otherwise} \end{cases} \quad (9)$$

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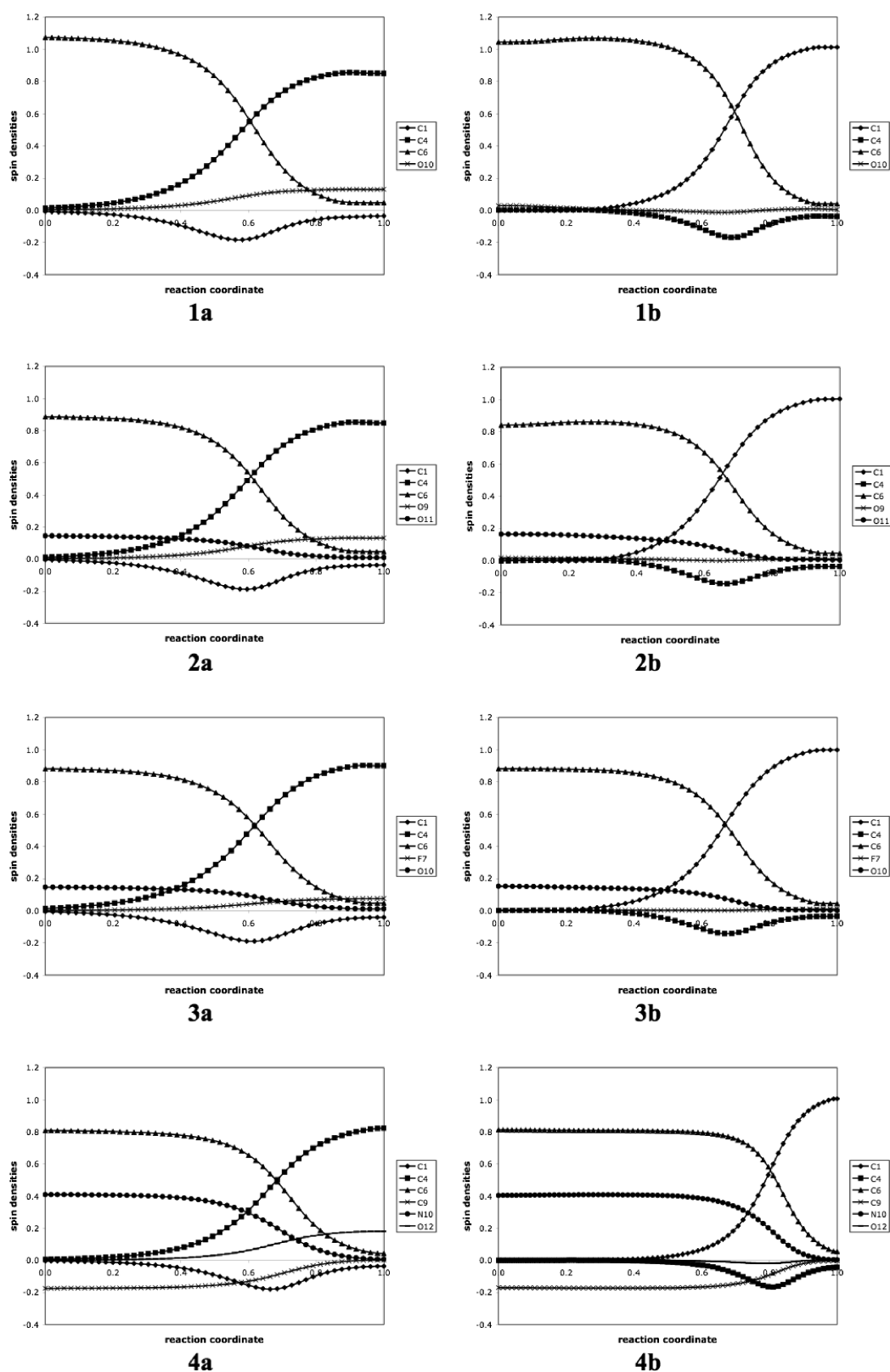
where  $\Delta\chi$ , i.e., the enhanced Pauling electronegativity of the radical centers, can be obtained simply as  $\Delta\chi = \chi - 3$ , with  $\chi = 3$  as the boundary between the strongly and the weakly electronegative radical centers, and where  $\Delta\omega$ , i.e., the enhanced electrophilicity index, is defined as the difference between the electrophilicity index  $\omega$ , as introduced by Parr et al.,<sup>35</sup> and the borderline between electrophilicity and nucleophilicity for radicals. The borderline is situated around 2 eV ( $\Delta\omega = \omega - 2$ ), which resulted from a comparison of our previously introduced radical electrophilicity scale with other classifications from literature concerning the electrophilic or nucleophilic behavior of radicals.<sup>14</sup> More information on how the different terms in the model contribute to the BDEs can be found in detail in ref 21. This model allows us to compute stabilities in a fairly easy way, not only for radicals but also for other reactive intermediates that display some sort of radical character like the divalent silylenes and the biradical *p*-benzynes.<sup>36</sup> We have computed the stabilities of the **a** and **b** product radicals for all 11 reactions as listed above, using calculated BDEs of their combination with the hydrogen atom (A = H and B = adduct radical). The values are given in Table 2. Note that a low value for the property “stab” means we are dealing with a stable radical.

Looking at the values for the property stab, going from 122.4 to 177.5 kJ mol<sup>-1</sup> for the **a** attacks and from 187.5 to 198.2 kJ mol<sup>-1</sup> for the **b** attacks, we can conclude that all radicals are moderately stable when comparing the values with the radical stability scale in ref 21. The difference between the two product radicals,  $\Delta\text{stab}$ , is always prominently positive, indicating that the products obtained through attack on the unsubstituted site of the substrate of the reactions under consideration are intrinsically more stable than the ones obtained through attack on the substituted site. Examining the values for  $\Delta\text{stab}$  more carefully, large variations are encountered when the substrate is changed for a particular radical, e.g., 18.3 kJ mol<sup>-1</sup> for methyl + fluoroethene versus 69.5 kJ mol<sup>-1</sup> for methyl + 2-propenenitrile, but not when the radical is changed for a particular substrate, e.g., 36.7 kJ mol<sup>-1</sup> for methyl + ethenol versus 37.2 kJ mol<sup>-1</sup> for hydroxymethyl + ethenol versus 38.0 kJ mol<sup>-1</sup> for cyanomethyl + ethenol.

As we are interested in the orientation of radical additions, the difference in activation barriers  $\Delta E_a$ , reaction energies  $\Delta E_r$  and radical stabilities  $\Delta\text{stab}$  is sufficient to examine the effects that govern the regioselectivity. This also allows us to work with quite reliable theoretical data, as possible computational errors will probably cancel each other out when subtracting the values for **a** and **b** attack. As a matter of fact, it seems that the order of the barriers is different for every theoretical method used, as we have learned from our own experience and from the literature.<sup>12,9,20</sup> Table 2 lists all values for  $\Delta E_a$ ,  $\Delta E_r$ , and  $\Delta\text{stab}$ . Changing the radical for a particular electron-rich or neutral alkene (ethenamine, ethenol, fluoroethene) does not alter  $\Delta E_a$  very much, in line with the observations in the product stability differences. However, the same observations cannot be made for  $\Delta E_a$  of the electron-poor alkenes (2-propenenitrile, methyl prop-2-enoate). Therefore, we investigated the relation between the difference in activation barriers and product radical stabilities.

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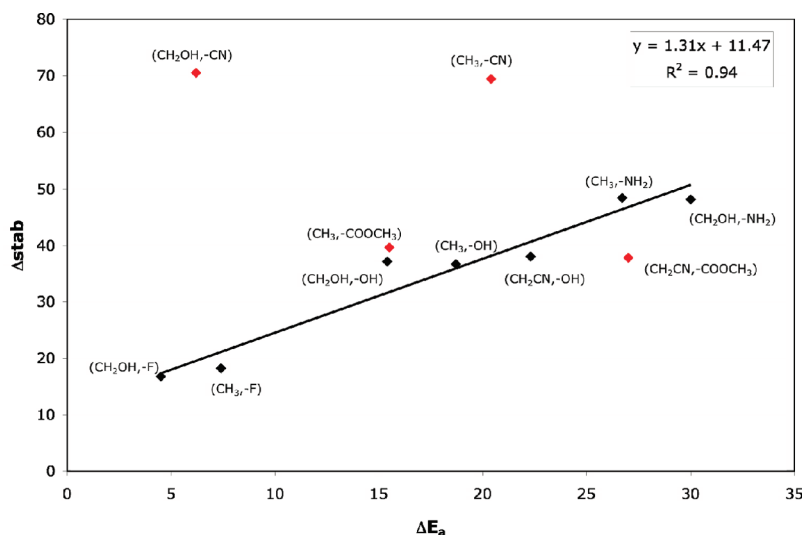
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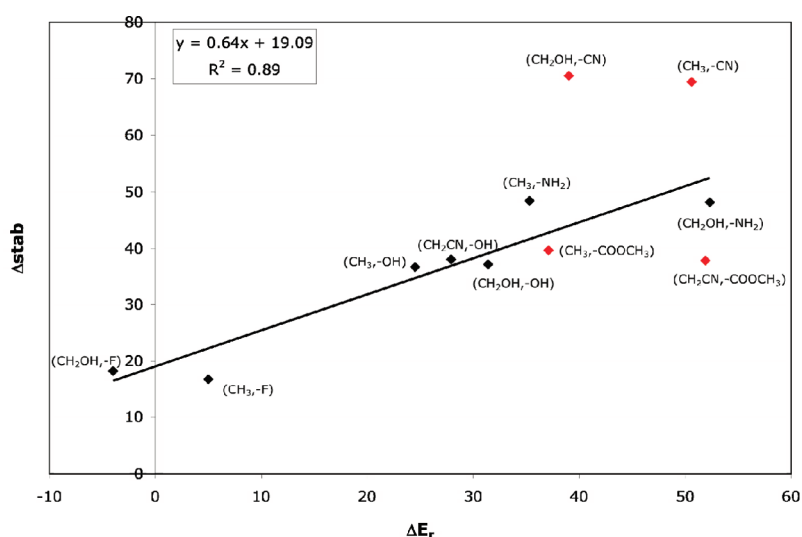
**FIGURE 3.** Spin densities along the reaction coordinate for attack (radical center: C<sub>6</sub>) on the unsubstituted (a) site C<sub>1</sub> and the substituted (b) site C<sub>4</sub> for **1** methyl + ethenol, **2** hydroxymethyl + ethenol, **3** hydroxymethyl + fluoroethene, and **4** cyanomethyl + methyl prop-2-enoate.

The correlation is plotted in Figure 4 for all reactions. The dots in black concern the reactions with the electron-rich and -neutral substrates; the ones in red refer to the reactions

with the electron-poor alkenes. An excellent correlation ( $R^2 = 0.94$ ) is found for the electron-rich and -neutral substrate reactions. The reactions with methyl prop-2-enoate and



**FIGURE 4.** Correlation between the difference in activation barriers and the difference in product stabilities (unsubstituted versus substituted site attack) in  $\text{kJ mol}^{-1}$ .



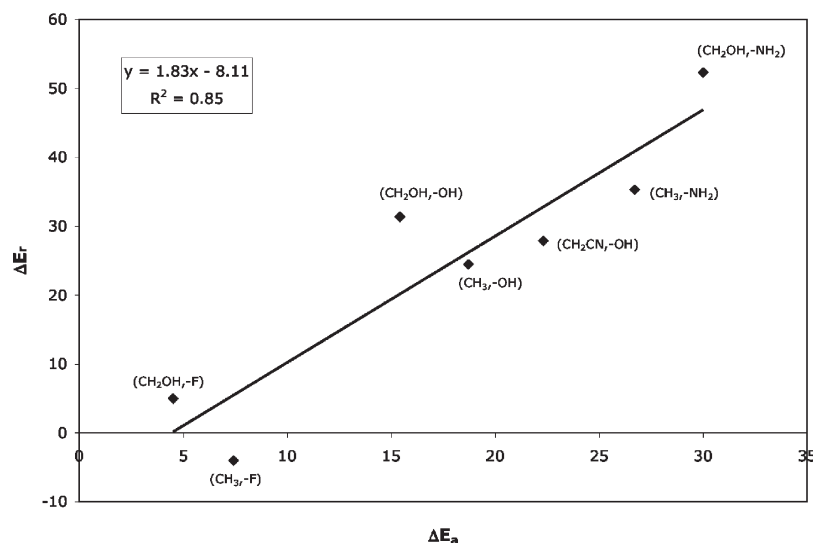
**FIGURE 5.** Correlation between the difference in reaction energies and the difference in product stabilities (unsubstituted versus substituted site attack) in  $\text{kJ mol}^{-1}$ .

2-propenenitrile (strongly) deviate from the trend line. According to the stability values of the products, the following activation barrier differences were expected: 45.1 instead of  $6.2 \text{ kJ mol}^{-1}$  for  $\text{CH}_2\text{OH} + 2\text{-propenenitrile}$ , 44.3 instead of  $20.4 \text{ kJ mol}^{-1}$  for  $\text{CH}_3 + 2\text{-propenenitrile}$ , 21.5 instead of  $15.5 \text{ kJ mol}^{-1}$  for  $\text{CH}_3 + \text{methyl prop-2-enoate}$ , and 20.1 instead of  $27.0 \text{ kJ mol}^{-1}$  for  $\text{CH}_2\text{CN} + \text{methyl prop-2-enoate}$ . Except for the latter reaction, the expected values are all clearly above the actual ones. This indicates that other effects are promoting the attack on the substituted site. Also remark that the higher the nucleophilic character of the radical, the smaller the difference in activation barrier between attack on the unsubstituted and the substituted site. Figure 5 plots the link between the stability differences and the reaction energy differences for all 11 reactions. A correlation coefficient  $R^2$  of 89% is found. It could be remarked that it seems somewhat odd that the correlation is worse than the one with the activation barriers. However, the reaction energy is calculated from the reactant complexes and *not*

from the individual reactants. When the latter definition is used, the correlation improves to 98% for the reactions concerning electron-rich and neutral substrates, and to 95% when the reactions with 2-propenenitrile are included. Nevertheless, this means that there should be a good correlation between the differences in activation barriers and in reaction energies, as is shown in Figure 6.

**2.3. Polar Effects.** These results for electron-rich and neutral substrates agree to a great extent with the conclusions drawn in some previous contributions,<sup>2,4,5,9</sup> namely that the orientation is principally thermodynamically controlled. In addition, we conclude that this is mainly due to the difference in stability of the adduct radicals. However, for the electron-poor substrates, polar effects at the initial stage of the reaction may play an important role, lowering the extent of regioselectivity toward the unsubstituted sites, as predicted from the stability differences. Within conceptual density functional theory, many descriptors exist that can describe electronic effects within a spin-polarized framework





**FIGURE 6.** Correlation between the difference in activation barriers and the difference in reaction energies (unsubstituted versus substituted site attack) in  $\text{kJ mol}^{-1}$ .

(e.g., radical systems, excited state chemistry, ...).<sup>23,24,37</sup> A particularly interesting reactivity descriptor for this problem is the spin-polarized and *local* dual descriptor  $\Delta f_{\text{NN}}$ , as initially proposed by Morell et al.<sup>38</sup> and later refined by Chamorro et al.<sup>39</sup>

$$\Delta f_{\text{NN}}(\mathbf{r}) = f_{\text{NN}}^+(\mathbf{r}) - f_{\text{NN}}^-(\mathbf{r}) \quad (10)$$

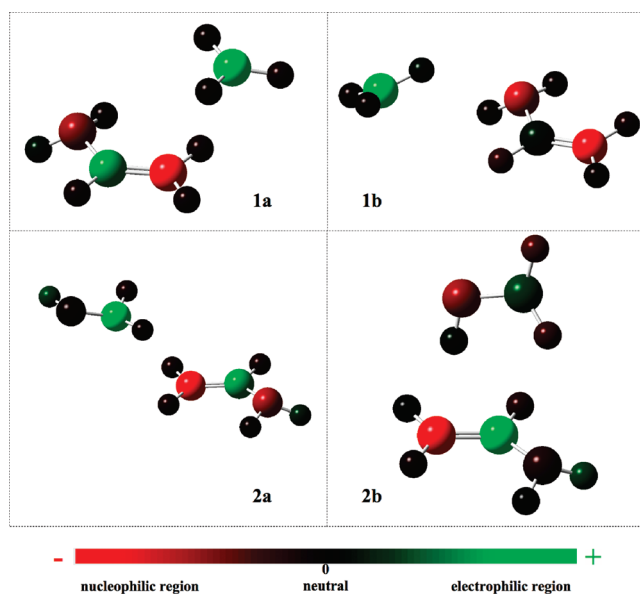
with  $f_{\text{NN}}^+(\mathbf{r})$  as the spin-polarized Fukui function for a nucleophilic attack and  $f_{\text{NN}}^-(\mathbf{r})$  as the spin-polarized Fukui function for an electrophilic attack, both at constant spin number  $N_S$  (i.e., the difference between the number of  $\alpha$  and  $\beta$  electrons):<sup>40</sup>

$$f_{\text{NN}}^+(\mathbf{r}) = \left( \frac{\partial \rho(\mathbf{r})}{\partial N} \right)_{N_S, v(\mathbf{r})}^+ \quad \text{and} \quad (11)$$

$$f_{\text{NN}}^-(\mathbf{r}) = \left( \frac{\partial \rho(\mathbf{r})}{\partial N} \right)_{N_S, v(\mathbf{r})}^-$$

For a particular region in the molecule,  $\Delta f_{\text{NN}}(\mathbf{r}) > 0$  indicates that an electrophilic region has been determined and a nucleophilic attack is favored. On the other hand, if  $\Delta f_{\text{NN}}(\mathbf{r}) < 0$ , the region is nucleophilic and it may be prone for an electrophilic attack. It is favorable to align electrophilic with nucleophilic regions. This dual descriptor already has proven to be a highly performant reactivity indicator.<sup>28,29,41,42</sup>

Figures 7–11 depict the dual descriptor, condensed to all atoms of the reactant complexes using NPA, for all 11 reactions, and this for attack on the unsubstituted as well as on the substituted site. The legend of the color scale is shown in all of the figures: red indicates a nucleophilic site



**FIGURE 7.** Dual descriptor (applied on the reactant complexes) for the attack on the unsubstituted (a) and the substituted (b) site on ethenamine: **1** ethenamine + methyl, **2** ethenamine + hydroxymethyl.

while green indicates an electrophilic site, and the brighter the color, the higher the nucleophilic or electrophilic character. We will now go through each reaction in detail. For the substrates ethenamine and ethenol (Figures 7 and 8), both the **a** and **b** reactant complexes favor addition on the unsubstituted site (match of the electrophilic radical center with the nucleophilic unsubstituted site of the double bond and *not* with the electrophilic or less nucleophilic substituted site of the double bond). Note that the intrinsic nucleophilic character of the adding radical (center) has shifted to electrophilic, due to the nucleophilic character of the electron-rich substrates. For the electron-rich alkenes, the dual descriptor clearly promotes attack on the unsubstituted site. When we look at the reactions with the almost neutral fluoroethene, i.e., methyl + fluoroethene and hydroxymethyl

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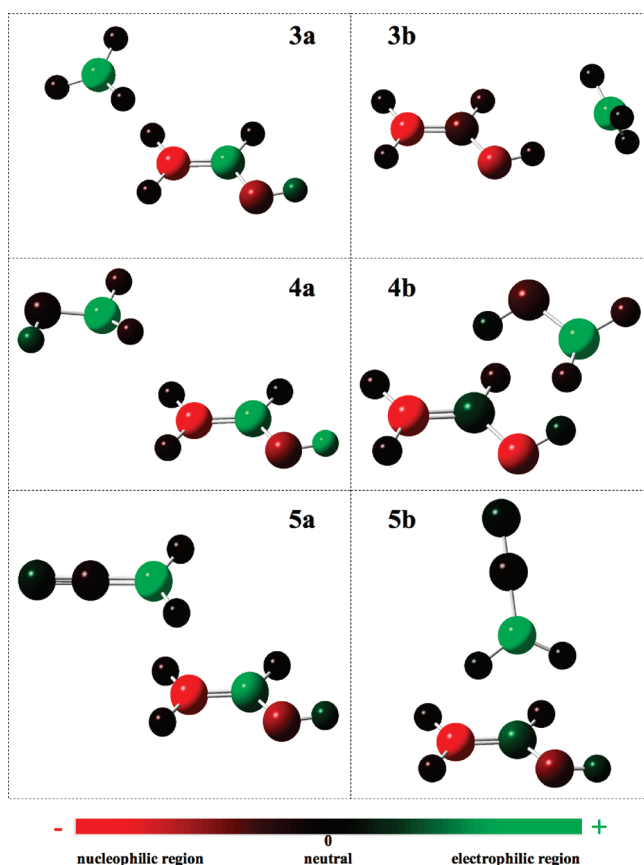
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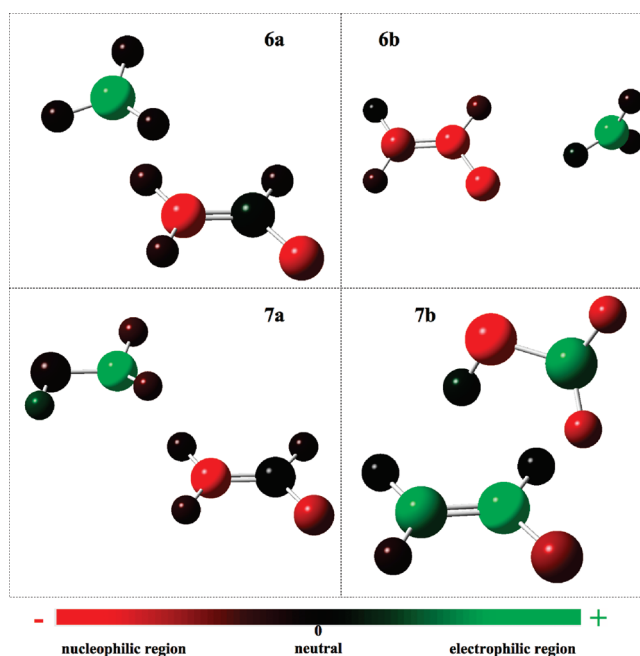
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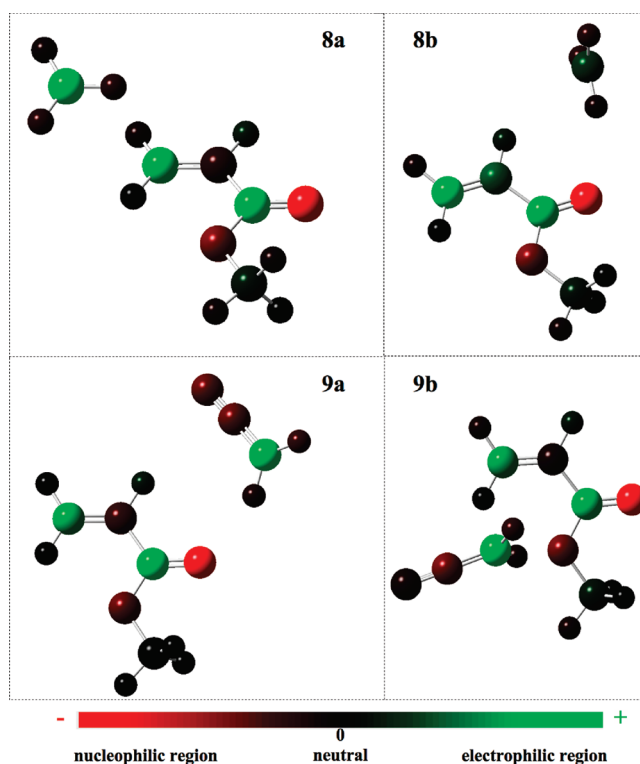


**FIGURE 8.** Dual descriptor (applied on the reactant complexes) for the attack on the unsubstituted (**a**) and the substituted (**b**) site on ethenol: **3** ethenol + methyl, **4** ethenol + hydroxymethyl, **5** ethenol + cyanomethyl.

+ fluoroethene in Figure 9, differences are noticed between **a** and **b** attack. The reactant complex in Figure 9 (**6a**) indicates attack on the unsubstituted site, while the reactant complex in Figure 9 (**6b**) favors attack on the substituted site, but not by much. The **a** reactant complex in Figure 9 (**7a**) again indicates addition on the unsubstituted carbon atom. The **b** reactant complex in Figure 9 (**7b**) clearly does not favor attack on any of the two sites, though attack on the unsubstituted site is disfavored slightly less. In general, attack of a nucleophilic radical on the unsubstituted site of the fluoroethene is still preferred on the basis of polar effects. Finally, we consider the electron-poor substrates methyl prop-2-enoate and 2-propenenitrile. The **8a**, **9a**, and **9b** reactants show the preference for addition on the substituted site of the methyl prop-2-enoate (Figure 10), while attack on the unsubstituted site of methyl prop-2-enoate is disfavored for **8b**. The conclusions for attack on the 2-propenenitrile are less transparent. For the addition of methyl in Figure 11, addition on the unsubstituted site of the double bond carbon atoms is not favored, based on polar effects. The addition of the hydroxymethyl shows different results concerning the dual descriptor. The **a** reactant complex prefers addition on the unsubstituted site slightly more than on the substituted site, while the **b** reactant complex undoubtedly points to addition on the substituted carbon atom. Note also the change of radical character in the case of hydroxymethyl in Figure 11a. In the neighborhood of the electron-poor 2-propenenitrile, the

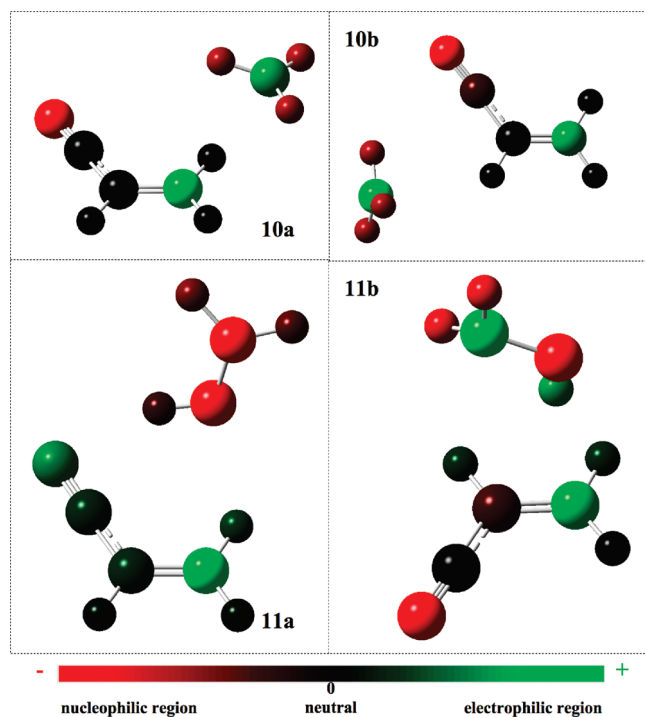


**FIGURE 9.** Dual descriptor (applied on the reactant complexes) for the attack on the unsubstituted (**a**) and the substituted (**b**) site on fluoroethene: **7** fluoroethene + hydroxymethyl, **6** fluoroethene + methyl.



**FIGURE 10.** Dual descriptor (applied on the reactant complexes) for the attack on the unsubstituted (**a**) and the substituted (**b**) site on methyl prop-2-enoate: **8** methyl prop-2-enoate + methyl, **9** methyl prop-2-enoate + cyanomethyl.

hydroxymethyl radical, intrinsically highly nucleophilic of character, is still acting as a nucleophile.



**FIGURE 11.** Dual descriptor (applied on the reactant complexes) for the attack on the unsubstituted (**a**) and the substituted (**b**) site on 2-propenenitrile: **10** 2-propenenitrile + methyl, **11** 2-propenenitrile + hydroxymethyl.

### 3. Computational Details

All calculations were performed within the Kohn–Sham framework, using the Gaussian 03 software package.<sup>43</sup> The DFT hybrid functional B3LYP<sup>44,45</sup> with basis set 6-31G(d) was used to optimize all geometries (reactant complexes, transition states, products, and all points along the IRC path) and to compute the ZPVEs through frequency calculations. This method was found to give geometries similar to those obtained with the QCISD/6-31G(d) method.<sup>20</sup> In addition, B3LYP has been found to be very suitable for ZPVE calculations.<sup>9,46,47</sup> Next, single-point energies on the optimized structures of the radical systems were performed at the B3LYP/6-311+G(d,p) level of theory. Our choice of the B3LYP functional for the computation of reaction barriers and reaction enthalpies was based on the intensive and detailed analysis of Radom et al. of these quantities for radical addition reactions.<sup>20</sup> From the analysis of an elaborate set of radical addition barriers, these authors concluded that the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) procedure performs very well for this quantity, with a mean absolute deviation from experiment of about 5.6 kJ mol<sup>-1</sup> for additions of the hydroxymethyl radical, the methyl radical, and the cyanomethyl radical on different substituted alkenes. In addition, the barriers with the 6-311+G(d,p) basis set were found to lie within 1 kJ mol<sup>-1</sup> of the 6-311+G(3df,2p) values, while for reaction enthalpies, the difference between 6-311+G(d,p) and 6-311+G(3df,2p) values is only slightly greater at 2–3 kJ mol<sup>-1</sup>. Also, the performance of B3LYP/6-311+G(3df,2p) in predicting the

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barriers of these radical addition reactions was found to be not as good as that of CBS-RAD but slightly better than that of G2(MP2,SVP). The Cartesian coordinates and energies of the optimized structures can be found in the Supporting Information. For details on the computation of radical stabilities through the BDEs model, as shown in eq 9; see ref 21. For the computation of the spin densities and the condensing of the Fukui functions, atomic populations were obtained with the “Natural Population Analysis” method,<sup>32–34</sup> again using Becke’s hybrid three-parameter functional B3LYP with basis set 6-311+G(d,p).

### 4. Conclusions

In this paper, we have investigated the influence of the nucleophilic character of the radical, ranging from strongly over moderately nucleophilic to neutral, on the orientation of radical addition reactions on monosubstituted electron-poor, electron-rich and (almost) neutral alkenes. A reaction force analysis of fully computed reaction paths suggests that all reactions proceed rather similarly based on the work percentage values (i.e., amount of work needed for preparation, electronic reordering (through bond breaking and bond forming) and relaxation of the system), irrespective of radical, alkene, and site of attack. However, in the first phase of the reaction slightly more energy is needed for the initial geometrical rearrangement in the case of additions on the substituted site of the double bond. Looking at the spin densities along the reaction coordinate, condensed on all atoms of the system, we detected that polarization starts earlier for the attack on the unsubstituted site. In addition, there is a clear difference between attack on the unsubstituted (**a**) and the substituted (**b**) site concerning the adduct radicals: unlike the **b** product radical, the **a** product radical displays delocalization. Computed product stabilities (using a BDEs model) agree with the previous observations on spin densities. An excellent correlation between the differences in activation barriers (unsubstituted versus substituted site attack) and the differences in intrinsic product stabilities is found for addition reactions on electron-rich and neutral substrates. Also, and again only for the electron-rich and -neutral substrates, a good correlation is found between the differences in activation energies and the differences in reaction energies. We conclude that for these substrates the orientation is principally thermodynamically controlled. However, for additions on electron-poor alkenes polar effects play a significant role in the orientation of these reactions. This was confirmed through the calculation of an on atoms condensed reactivity descriptor, namely the spin-polarized dual descriptor. On the basis of the values of  $\Delta f_{\text{NN}}$ , attack of a nucleophilic radical is favored on the *unsubstituted* site of electron-rich or -neutral alkenes and on the *substituted* site of electron-poor alkenes.

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**Supporting Information Available:** Computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.