

## The Markovnikov Regioselectivity Rule in the Light of Site Activation Models

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The electrophilic addition of HCl to a series of asymmetric alkenes—propene, 2-methyl-2-butene, styrene, 2-phenylpropene, and 1-cyanopropene—is used as a model system to study the regioselectivity Markovnikov rule using density functional theory reactivity descriptors. The results show that this rule may be interpreted on the basis of a site activation model that goes beyond the Li–Evans model of selectivity if both the fluctuations in global softness and Fukui functions at the active site are taken into account. A local static analysis based on the condensed Fukui function at the ground state of alkenes was also performed. For all the systems considered, the Markovnikov carbon (M) atom (i.e., the less substituted one) displays electrophilic Fukui function values that are larger than those associated with the more substituted anti-Markovnikov (AM) carbon atom at the double bond. In most cases, they are also larger than the corresponding nucleophilic Fukui function values at both carbon centers of the ethylenic functionality. Site activation at the nucleophilic and electrophilic centers of the alkenes considered was probed by changes in regional softness with reference to the transition state structures. The results are consistent with the empirical Markovnikov rule. A global analysis of involved structures in the electrophilic addition of HCl shows that while the ground state and transition state structures display relative values of the energy and molecular hardness ordered in a way that is consistent with the maximum hardness principle (MHP), the comparison between the Markovnikov and anti-Markovnikov transition state structures do not: the Markovnikov channel presents a transition state which is lower in energy and softer than the one corresponding to the anti-Markovnikov addition.

### 1. Introduction

The chemistry of alkenes depends mainly on the characteristic double bond between two carbon atoms. This is a good example that illustrates the usefulness of the concept of functional groups in molecules: since the  $\sigma$ -bonding molecular orbitals involved in simple bonds are in general more stable than those having  $\pi$  symmetry involved in multiple bonds, it is naturally expected that reactions at the double bond will lead to the formation of saturated compounds.<sup>1,2</sup> This is the usual reactivity pattern displayed by alkenes in addition reactions.<sup>1,3</sup> In these chemical processes, two groups are selectively added to each carbon atom participating in the double bond of alkenes.<sup>4–6</sup> A wide variety of reactions that include hydrogen halogenides, water, halogens, oxidants, and other alkenes as reagents have been observed.<sup>1</sup> In electrophilic addition reactions, the reagent presents the general form of an electrophile–nucleophile pair ( $E^+ : Nu^-$ ), where  $E^+$  and  $Nu^-$  represent the electrophilic and nucleophilic moieties of the substrate, respectively. The preference of the electrophile  $E^+$  to react with the carbon C1 or C2 of the double bond, or the nucleophile  $Nu^-$  to attack the C1 or C2 centers, defines what is known as the *regioselectivity* or orientation of the addition reaction.<sup>1–3</sup> The *regioselectivity* of the addition

reaction depends on the substituents that the centers C1 and C2 may bear. This selectivity toward electrophilic addition has been proposed to follow the well-known empirical Markovnikov rule.<sup>3</sup> The original statement of this rule is *the addition of an acidic proton to a double bond of an alkene yields a product where the proton is bound to the carbon atom bearing the largest number of hydrogen atoms*.

The generalized version of this rule may be stated as follows: *in an electrophilic addition reaction to alkenes, the electrophile adds in a form that leads to the formation of the most stable carbocation*.<sup>1,3</sup> Stated in either of the two forms, this empirical rule is essentially a selectivity rule. Selectivity toward electrophilic and nucleophilic reactions may be conveniently described in terms of regional reactivity indices.<sup>7–9</sup> Selectivity has been recently explained within a generalized hard and soft acid and bases (HSAB) principle, by Li and Evans,<sup>10,11</sup> that only takes into account the variations in the regional Fukui functions. This generalized HSAB rule has also been used to justify the empirical energy-density relationships condensed in the Hammett equation for some gas-phase acid–base equilibria.<sup>12</sup>

In this work, we intend to show that the Markovnikov rule may be also interpreted within a site activation model, having the regional Fukui function and regional softness<sup>8,9,13</sup> as the natural descriptors of selectivity. This new approach may be understood as an extension of the Li–Evans rules, in the sense that, apart from the variation in the Fukui function, the variations in global softness with reference to the transition state (activation

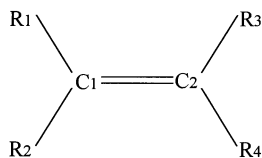
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Molecule	Substituents
Ethylene (1)	R <sub>1</sub> = R <sub>2</sub> = R <sub>3</sub> = R <sub>4</sub> = H
Propene (2)	R <sub>1</sub> = CH <sub>3</sub> R <sub>2</sub> = R <sub>3</sub> = R <sub>4</sub> = H
2-Methyl-2-butene (3)	R <sub>1</sub> = R <sub>2</sub> = R <sub>3</sub> = CH <sub>3</sub> R <sub>4</sub> = H
Styrene (4)	R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> R <sub>2</sub> = R <sub>3</sub> = R <sub>4</sub> = H
2-phenylpropene (5)	R <sub>1</sub> = C <sub>6</sub> H <sub>5</sub> R <sub>2</sub> = CH <sub>3</sub> R <sub>3</sub> = R <sub>4</sub> = H
<i>Cis</i> -1-cyanopropene (6)	R <sub>1</sub> = CN R <sub>3</sub> = CH <sub>3</sub> R <sub>2</sub> = R <sub>4</sub> = H
<i>Trans</i> -1-cyanopropene (7)	R <sub>1</sub> = CN R <sub>4</sub> = CH <sub>3</sub> R <sub>2</sub> = R <sub>3</sub> = H

Figure 1. Structure of the substituted ethylenes.

softness) are incorporated. To test this hypothesis, density functional theory (DFT) calculations have been performed on the addition of HCl to ethylene, propene, 2-methyl-2-butene, styrene, 2-phenylpropene, and 1-cyanopropene (see Figure 1). Ethylene is included as a reference system to assess the substituent effects of the methyl groups in the carbocation intermediate stability. The remaining alkenes are capable of forming different types of carbocations, depending on either the number or the nature of the substituents. Regional quantities at the transition state (TS) structure are incorporated to assess site activation within a simple model based on the variations of regional softness that include both the changes in global softness and the changes in the regional electrophilic and nucleophilic Fukui functions at the active sites of the alkenes.

The article is organized as follows: in section 2 we present a brief summary containing the definition of the basic quantities needed to perform the global and local analysis of reactivity. Section 3 summarizes the computational details. Section 4 contains the main results of the present study and a general discussion gathering the results obtained in the different test cases around a common model of site activation. Section 5 summarizes the main conclusions of the present study.

## 2. Reactivity Indices and Principles

Density functional theory (DFT) has provided modern chemistry with a complete hierarchy of global, local, and nonlocal quantities.<sup>7</sup> Global quantities such as the electronic chemical potential ( $\mu$ ),<sup>14</sup> chemical hardness ( $\eta$ ),<sup>15</sup> and global softness ( $S$ )<sup>16</sup> have proven to be useful tools to analyze chemical reactivity and stability patterns of molecules. For instance, the electronic chemical potential (the negative of electronegativity) has been successfully used to discuss charge-transfer processes during a chemical reaction.<sup>17,18</sup> It has been given the following operative definition in terms of the vertical ionization potential  $I$  and electron affinity  $A$ ,  $\mu \approx -(I + A)/2$ , or, in terms of the one electron energy levels of the frontier molecular orbitals HOMO and LUMO,  $\mu \approx (\epsilon_{\text{homo}} + \epsilon_{\text{lumo}})/2$ .

Chemical hardness and softness permit the establishment of semiquantitative criteria on the stability of molecular systems on one hand, through the maximum hardness principle (MHP),<sup>19,20</sup> and also on the thermodynamic affinity of two interacting molecules, through the hard and soft acids and bases (HSAB) principle.<sup>19,21</sup> Chemical hardness has also been approached within a finite difference formula as  $\eta \approx (I - A)/2 \approx (\epsilon_{\text{lumo}} - \epsilon_{\text{homo}})/2$ . Chemical softness is simply the inverse of chemical hardness, namely  $S = 1/\eta$ . Furthermore, chemical softness has been recently related to the molecular dipole polarizability,<sup>22–25</sup> so that a new empirical rule, namely the minimum polarizability principle (MMP), has been proposed to complement the MHP to discuss relative stability of molecular species.<sup>26,27</sup>

Local quantities on the other hand have been related to selectivity.<sup>7</sup> They are expressed in general as derivatives of the electron density with respect to the number of electrons  $N$  (Fukui function), or derivatives of electron density with respect to the chemical potential (local softness), at constant external potential. The electronic Fukui function  $f(\mathbf{r})$  is defined as<sup>13</sup>

$$f(\mathbf{r}) = \left[ \frac{\partial \rho(\mathbf{r})}{\partial N} \right]_{v(\mathbf{r})} \quad (1)$$

This local reactivity index has proven to be a powerful tool to describe selectivity in polyfunctional systems.

The semilocal (regional) formulation of this reactivity index permits the analysis of chemical reactivity associated with atoms or groups in a molecule. The regional or condensed to atoms Fukui functions have been evaluated by means of a finite difference approach involving atomic charges<sup>13,28</sup> or, more simply, by approximating the Fukui function as the electron density of the frontier molecular orbital involved in the reaction.<sup>13,29,30</sup> Condensed to atom or group Fukui functions for nucleophilic ( $f_k^+$ ), electrophilic ( $f_k^-$ ), and radical ( $f_k^0$ ) attacks may be obtained in terms of the frontier molecular orbital coefficients and the overlap matrix, by a simple method described elsewhere.<sup>8,9</sup> Regional softness  $s_k^+$ ,  $s_k^-$ , and  $s_k^0$ , for nucleophilic, electrophilic, and radical attacks respectively, may be readily obtained from the exact relationship<sup>31,32</sup>

$$s(\mathbf{r}) = \left[ \frac{\partial \rho(\mathbf{r})}{\partial \mu} \right]_{v(\mathbf{r})} = f(\mathbf{r})S \quad (2)$$

in terms of the Fukui function and the global softness.

From the definition given by eq 2, site activation (deactivation) may be conveniently described in terms of variations in local softness as

$$ds(\mathbf{r}) = f(\mathbf{r}) dS + S df(\mathbf{r}) \quad (3)$$

It is interesting to note that eq 3 may be regarded as a generalization of the Li–Evans reactivity and selectivity rules.<sup>10,11</sup> These authors proposed that similarity in chemical reactivity in a series of related molecules can be described by global reactivity indices, but when those global indices fall in a very narrow range of variations, for example,  $\Delta S \approx 0$ , the natural descriptor of selectivity becomes the Fukui function scaled by an almost constant value of  $S$ . Therefore, site activation may be described by the variations of the Fukui function at the active sites of the molecule. This result seems to be true for a family of related molecules in their ground state. However, applied to a chemical reaction, if activation is correctly referred to the transition state of the reaction, from the maximum hardness principle, one should expect the global softness value of the reactant ground state to be very different from the one displayed by the system at the transition state structure. In such

a case, the Li–Evans selectivity rule is expected to markedly fail, since the reactivity prerequisite (i.e., similarity in the global reactivity indices) is no longer valid and eq 3 must be used instead.

Finite changes in the regional or condensed to atom with reference to the transition state structure may be approached as  $\Delta s_k = s_k^\ddagger - s_k^0$ , with  $s_k^\ddagger$  and  $s_k^0$  the local softness at site  $k$  at the transition and ground state structures, respectively. Site activation ( $\Delta s_k > 0$ ) or deactivation ( $\Delta s_k < 0$ ) may be further cast into a partitioned form by adding and subtracting the quantity  $S^0 f_k^\ddagger$  to the expression  $\Delta s_k = s_k^\ddagger - s_k^0$  to get

$$\Delta s_k = S^0 \Delta f_k + f_k^\ddagger \Delta S \quad (4)$$

with

$$\Delta f_k = f_k^\ddagger - f_k^0, \quad \Delta S = S^\ddagger - S^0 \quad (5)$$

Therefore, while the first term of eq 4 assesses the *local activation* at the site, described by the term  $\Delta f_k$ , the second contribution takes into account the *global activation* of the whole system from the reactant ground state to the transition state structure. We will show below that our working equation, eq 4, becomes a central relationship to discuss the regioselectivity Markovnikov rule within a generalized site activation model.

### 3. Computational Details

All calculations were done at the B3LYP/6-311G\*\* level of theory, as implemented in the Gaussian 98 package of programs.<sup>33</sup> Electronic chemical potential and chemical hardness and softness were calculated from the frontier molecular orbital (FMO) eigenvalues. Electrophilic and nucleophilic Fukui functions were evaluated by a procedure that performs a single point calculation on the optimized structure of the alkenes shown in Figure 1. The regional Fukui functions were evaluated in terms of the coefficients of the FMOs and the overlap matrix.<sup>8,9</sup> With the values of regional Fukui functions at hand, the corresponding regional softness was readily obtained via eq 3. Site activation as described by the variations in local softness at the site was evaluated using eq 4. The transition state structures associated with the Markovnikov and anti-Markovnikov channels for the electrophilic additions of HCl to compounds **2–7** were also located at the B3LYP/6-311G\*\* level. Their imaginary frequencies and other properties can be found in Table 13; the corresponding geometries are available from the authors upon request.

### 4. Results and Discussion

Within the generalized HSAB rule proposed by Li and Evans,<sup>10,11</sup> the electrophilic and nucleophilic Fukui functions become the natural descriptors of selectivity. Tables 1, 3, 5, 7, 9, and 11 summarize the static local reactivity picture developed around the ground states of the asymmetric alkenes (GS1) considered in the present study. It may be observed that within the whole series, the Markovnikov carbon atom (M) systematically shows the highest value in regional Fukui function for an electrophilic attack by a proton. Note that in compounds **2–5**  $f_k^-$  at M is predicted to be higher than the corresponding anti-Markovnikov carbon center (AM), and greater than the corresponding  $f_k^+$  for nucleophilic attack at both the M and AM centers. These results may suggest that the addition of HCl takes place via an electrophilic attack at the Markovnikov center by a proton, prior to the nucleophilic attack of  $\text{Cl}^-$  on the most stable carbocation. In compounds **6** and **7**, the opposite effects

**TABLE 1: Local Reactivity Description for Electrophilic and Nucleophilic Addition to the Markovnikov (C1) and anti-Markovnikov (C2) Sites in the Reaction between HCl and Propene (2)<sup>a</sup>**

structure	S	site ( $k$ )	$f_k^-$	$f_k^+$
GS1	7.291	C1	<i>0.499</i>	0.471
		C2	<i>0.399</i>	0.460
TS (M)	16.978	C1	0.109	<i>0.064</i>
		C2	0.021	<i>0.641</i>
TS (AM)	15.102	C1	0.026	<i>0.638</i>
		C2	0.137	<i>0.085</i>

<sup>a</sup> In Tables 1, 3, 5, 7, 9, and 11, italic numbers highlight the active sites.

**TABLE 2: Global and Local Contributions to Nucleophilic Activation (Deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) Sites of the Carbocations Formed in the Protonation of Propene (2)<sup>a</sup>**

structure	site ( $k$ )	$\Delta s_k$	$f_k^\ddagger \Delta S$	$S^0 \Delta f_k$
TS (M)	C1	-2.347	0.620	-2.967
	C2	7.529	<i>6.209</i>	1.320
TS (AM)	C1	6.201	<i>4.983</i>	1.218
	C2	-2.070	0.664	-2.734

<sup>a</sup> In Tables 2, 4, 6, 8, 10, and 12, italic numbers highlight electrophilic/nucleophilic site activation.

**TABLE 3: Local Reactivity Description for Electrophilic and Nucleophilic Addition to the Markovnikov (C1) and anti-Markovnikov (C2) Sites in the Reaction between HCl and 2-Methyl-2-butene (3)**

structure	S	site ( $k$ )	$f_k^-$	$f_k^+$
GS1	7.690	C1	<i>0.430</i>	0.410
		C2	<i>0.363</i>	0.363
TS (M)	18.843	C1	0.074	<i>0.047</i>
		C2	0.021	<i>0.620</i>
TS (AM)	16.566	C1	0.026	<i>0.622</i>
		C2	0.099	<i>0.063</i>

**TABLE 4: Global and Local Contributions to Nucleophilic Activation (Deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) Sites of the Carbocations Formed in the Protonation of 2-Methyl-2-butene (3)**

structure	site ( $k$ )	$\Delta s_k$	$f_k^\ddagger \Delta S$	$S^0 \Delta f_k$
TS (M)	C1	-2.267	0.524	-2.791
	C2	8.891	<i>6.915</i>	1.976
TS (AM)	C1	7.151	<i>5.521</i>	1.630
	C2	-1.748	0.559	-2.307

**TABLE 5: Local Reactivity Description for Electrophilic and Nucleophilic Addition to the Markovnikov (C1) and anti-Markovnikov (C2) Sites in the Reaction between HCl and Styrene (4)**

structure	S	site ( $k$ )	$f_k^-$	$f_k^+$
GS1	10.576	C1	<i>0.283</i>	0.271
		C2	<i>0.114</i>	0.136
TS (M)	26.140	C1	0.066	<i>0.038</i>
		C2	0.017	<i>0.396</i>
TS (AM)	15.464	C1	0.032	<i>0.616</i>
		C2	0.105	<i>0.079</i>

of the electron-withdrawing nitrile substituent and the electron-releasing character of methyl group lead to the loss of regioselectivity, and a local reactivity pattern similar to that found in ethylene is observed. It is interesting to note that the local reactivity picture developed around the Fukui functions at the GS of molecules produces results that are consistent with those obtained by Suresh et al.<sup>5</sup> and Saethre et al.<sup>6</sup> based on the variation of the molecular electrostatic potentials at their characteristic (minimum) values.

**TABLE 6: Global and Local Contributions to Nucleophilic Activation (Deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) Sites of the Carbocations Formed in the Protonation of Styrene (4)**

structure	site ( <i>k</i> )	$\Delta s_k$	$f_k^{\ddagger} \Delta S$	$S^0 \Delta f_k$
TS (M)	C1	-1.873	0.591	-2.464
	C2	8.913	6.163	2.750
TS (AM)	C1	6.660	3.011	3.649
	C2	-0.217	0.386	-0.603

**TABLE 7: Local Reactivity Description for Electrophilic and Nucleophilic Addition to the Markovnikov (C1) and anti-Markovnikov (C2) Sites in the Reaction between HCl and 2-Phenylpropene (5)**

structure	S	site ( <i>k</i> )	$f_k^-$	$f_k^+$
GS1	10.032	C1	0.299	0.235
		C2	0.128	0.122
TS (M)	26.922	C1	0.046	0.030
		C2	0.013	0.420
TS (AM)	14.660	C1	0.030	0.589
		C2	0.106	0.087

**TABLE 8: Global and Local Contributions to Nucleophilic Activation (Deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) Sites of the Carbocations Formed in the Protonation of 2-Phenylpropene (5)**

structure	site ( <i>k</i> )	$\Delta s_k$	$f_k^{\ddagger} \Delta S$	$S^0 \Delta f_k$
TS (M)	C1	-1.550	0.507	-2.057
	C2	10.083	7.094	2.990
TS (AM)	C1	6.277	2.726	3.551
	C2	0.052	0.403	-0.351

**TABLE 9: Local Reactivity Description for Electrophilic and Nucleophilic Addition to the Markovnikov (C1) and anti-Markovnikov (C2) Sites in the Reaction between HCl and *cis*-1-Cyanopropene (6)**

structure	S	site ( <i>k</i> )	$f_k^-$	$f_k^+$
GS1	8.768	C1	0.319	0.244
		C2	0.307	0.444
TS (M)	15.849	C1	0.154	0.054
		C2	0.024	0.631
TS (AM)	22.316	C1	0.030	0.452
		C2	0.112	0.062

**TABLE 10: Global and Local Contributions to Nucleophilic Activation (Deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) Sites of the Carbocations Formed in the Protonation of *cis*-1-Cyanopropene (6)**

structure	site ( <i>k</i> )	$\Delta s_k$	$f_k^{\ddagger} \Delta S$	$S^0 \Delta f_k$
TS (M)	C1	-1.284	0.382	-1.666
	C2	6.108	4.468	1.640
TS (AM)	C1	7.947	6.124	1.824
	C2	-2.509	0.840	-3.349

To make more reliable comparisons between the relative static reactivity along the alkene series, it is necessary to renormalize the Fukui function values at the M and nucleophilic centers, since the Fukui function distribution is normalized to 1 in systems with different numbers of centers. A simple way to achieve this is writing  $f_k^{\text{rel}} = f_k / (f_M + f_{\text{AM}})$ . On the basis of the relative reactivity scale between the M and AM centers, the predicted selectivity order for the electrophilic addition of a proton to the M center of the alkenes **2–7** becomes *cis*- and *trans*-1-cyanopropene (51%) < propene  $\approx$  2-methyl-2-butene (55%) < 2-phenylpropene  $\approx$  styrene (71%).

The nucleophilic attack by  $\text{Cl}^-$  at the nucleophilic center is assumed to take place on the unprotonated carbon atom. From a static reactivity picture, the Fukui function,  $f_k^+$ , at the GS1s of the alkenes shows comparable values at the M and nucleo-

**TABLE 11: Local Reactivity Description for Electrophilic and Nucleophilic Addition to the Markovnikov (C1) and anti-Markovnikov (C2) Sites in the Reaction between HCl and *trans*-1-Cyanopropene (7)**

structure	S	site ( <i>k</i> )	$f_k^-$	$f_k^+$
GS1	8.770	C1	0.308	0.253
		C2	0.302	0.446
TS (M)	15.705	C1	0.164	0.057
		C2	0.023	0.633
TS (AM)	22.026	C1	0.030	0.456
		C2	0.116	0.065

**TABLE 12: Global and Local Contributions to Nucleophilic Activation (Deactivation) at the Markovnikov (C1) and anti-Markovnikov (C2) Sites of the Carbocations Formed in the Protonation of *trans*-1-Cyanopropene (7)**

structure	site ( <i>k</i> )	$\Delta s_k$	$f_k^{\ddagger} \Delta S$	$S^0 \Delta f_k$
TS (M)	C1	-1.324	0.395	-1.719
	C2	6.030	4.390	1.640
TS (AM)	C1	7.825	6.045	1.780
	C2	-2.480	0.862	-3.341

philic centers in propene. Note, however, that in 2-methyl-2-butene, styrene, and 2-phenylpropene, the static analysis performed on the basis of the nucleophilic Fukui function shows a higher value at the Markovnikov center. This comparison seems to indicate that there is a contradiction with the empirical Markovnikov selectivity rule. However, this apparent contradiction vanishes when the local reactivity analysis for the nucleophilic attack of  $\text{Cl}^-$  is performed at the TS structure, where the Markovnikov site is partially bound to the proton. In other words, the interaction of the proton and the Markovnikov site is expected to *activate* the AM site toward the nucleophilic attack by the  $\text{Cl}^-$  species. Site nucleophilic activation may be evaluated at the Markovnikov TS channel using the model condensed in eq 4. The results are summarized in Tables 2, 4, 6, 8, 10, and 12.

It can be observed that the interaction of the  $\text{H}^+$  electrophile at the Markovnikov center significantly enhances the nucleophilic activity at the unprotonated carbon, as described by the variation in local softness at that site. Note that site activation encompasses both global and local effects given by the variation in global softness and the regional Fukui function for nucleophilic attacks, respectively. For the Markovnikov carbocations, activation at the unprotonated center is dominated by the variation in global softness, while the change in the Fukui function represents the main contribution to the deactivation of the protonated site. The same behavior is observed in most of the anti-Markovnikov carbocations, with the exception of styrene and 2-phenylpropene, where both the local and global contributions drive the nucleophilic activation at the unprotonated carbon atom toward the nucleophilic attack of  $\text{Cl}^-$ . Within the whole series, the nucleophilic site activation at the unprotonated carbon is consistently predicted to be more significant than that associated with the protonated M site, which is deactivated in most of the cases, and these predictions are in agreement with the observed reactivity pattern. It is also interesting to notice that, upon the interaction with a proton at the transition state, the electrophilic site becomes systematically deactivated for both the Markovnikov and anti Markovnikov channels. The predicted activation pattern propene < 2-methyl-2-butene < styrene < 2-phenylpropene may be traced to the presence of phenyl group in compounds **4** and **5**, which makes the transition states become softer than the corresponding alkyl-substituted structures. Therefore, the nucleophilic site activation at the transition state associated with the Markovnikov channel is described as an

**TABLE 13: Energy ( $E$ ), Number of Imaginary Frequencies ( $n_i$ ), and Frequency Values ( $\nu$ ) from Harmonic Vibrational Analysis, Chemical Hardness ( $\eta$ ), and Mean Dipole Polarizability ( $\langle\alpha\rangle$ ) for Species Involved in the Addition of HCl to Substituted Ethylenes**

alkene	structure	$-E$	$n_i$	$\nu$	$\eta$	$\langle\alpha\rangle$
ethylene (1)	reactants	539.447 445	0		0.1407	22.305
	TS	539.389 946	1	1437.0i	0.0650	43.475
	products	539.479 321	0		0.1559	34.105
propene (2)	reactants	578.777 510	0		0.1372	34.731
	TS (M)	578.729 494	1	1127.3i	0.0589	57.457
	TS (AM)	578.717 268	1	1315.8i	0.0662	55.802
	products (M)	578.807 497	0		0.1544	46.676
	products (AM)	578.803 587	0		0.1559	45.746
2-methyl-2-butene (3)	reactants	657.432 971	0		0.1300	59.568
	TS (M)	657.391 250	1	779.6i	0.0531	82.022
	TS (AM)	657.380 574	1	989.2i	0.0604	80.912
	products (M)	657.456 712	0		0.1498	70.160
	products (AM)	657.454 281	0		0.1541	69.338
styrene (4)	reactants	770.560 678	0		0.0946	87.441
	TS (M)	770.519 651	1	712.9i	0.0383	127.376
	TS (AM)	770.497 959	1	1320.1i	0.0647	110.573
	products (M)	770.583 644	0		0.1122	96.052
	products (AM)	770.581 404	0		0.1187	93.228
2-phenylpropene (5)	reactants	809.886 537	0		0.0997	97.555
	TS (M)	809.849 619	1	557.3i	0.0371	136.379
	TS (AM)	809.823 382	1	1150.4i	0.0682	121.590
	products (M)	809.906 562	0		0.1115	107.958
	products (AM)	809.903 980	0		0.1198	105.246
<i>cis</i> -1-cyanopropene (6)	reactants	671.045 562	0		0.1141	47.691
	TS (M)	670.984 261	1	1429.6i	0.0631	70.586
	TS (AM)	670.971 855	1	1305.6i	0.0448	74.873
	products (M)	671.063 088	0		0.1537	57.030
	products (AM)	671.055 562	0		0.1400	57.599
<i>trans</i> -1-cyanopropene (7)	reactants	671.045 379	0		0.1140	49.493
	TS (M)	670.982 647	1	1471.1i	0.0637	70.897
	TS (AM)	670.971 573	1	1315.7i	0.0454	75.465
	products (M)	671.062 827	0		0.1539	57.509
	products (AM)	671.055 495	0		0.1405	58.153

enhancement in local softness at the unprotonated site that favors the softer interaction with the  $\text{Cl}^-$  nucleophile, and the Markovnikov regioselectivity predicted for the second step in the addition reactions may be again explained within the generalized site activation model. Both steps in the electrophilic addition of HCl, namely, the electrophilic attack of a proton at the Markovnikov carbon atom and the nucleophilic attack of  $\text{Cl}^-$  at the unprotonated center may be therefore explained within a common electronic framework.

Finally, to test the energy–hardness inverse relationship dictated by the maximum hardness principle (MHP), we compare energies and hardnesses in Table 13 for all the stationary points found in the potential energy surface for electrophilic addition in compounds 2–7, including the Markovnikov and anti-Markovnikov transition state structures. The MHP is fulfilled for the transition state structures with reference to the corresponding ground states of reactants (GS1) and products (GS2) of each channel, and between reactants and products, but the energy–hardness relationship between both the Markovnikov and anti-Markovnikov transition state structures markedly fails. For all the studied cases, the chemical hardness values at the GSs are larger than those of the transition states at both M and AM channels. All the reactions are exothermic—consistently the chemical hardnesses at the products (GS2) are larger than those displayed by the reactants (GS1). The M transition state structures always display lower energies than the corresponding AM transition structures; nevertheless, with the only exception of 1-cyanopropene, the hardness values of the M transition states are systematically smaller than the values shown by the AM transition state structures, in contradiction with the MHP rule. On this line, it is interesting to notice that this result matches the HSAB rule: since the chloride anion

is a soft species, the Markovnikov channel for the electrophilic addition in asymmetric alkenes is softer (i.e., more polarizable) than the transition state structure associated with the anti-Markovnikov channel. This result apparently contradicts the minimum polarizability principle.<sup>26,27</sup>

## 5. Concluding Remarks

The electrophilic addition of HCl to propene, 2-methyl-2-butene, styrene, 2-phenylpropene, and the push–pull 1-cyanopropene has been analyzed at the B3LYP/6-311G\*\* level of theory. A static local analysis based on the electrophilic and nucleophilic regional Fukui functions have been performed on the asymmetric alkenes considered. The regional Fukui function analysis shows that the electrophilic addition of the proton to the Markovnikov center is preferred. The interaction between the proton and the Markovnikov carbon atom strongly activates the nucleophilic (unprotonated) center of the double bond toward the subsequent attack by  $\text{Cl}^-$ . The activation of the nucleophilic center in the carbocation is described in terms of the enhancement in local softness for nucleophilic attacks and encompasses both the variation in global softness and the fluctuation in the nucleophilic Fukui function at this center. These results may be interpreted within a generalized site activation model that goes beyond the Li–Evans selectivity rule which is limited to a series of compounds with similar softness values. This model of activation takes into account the effect of both global and local indices and allows the comparison between systems with different sizes or structures. Transition state structures for the Markovnikov and anti-Markovnikov channels have been located, and the effects of the substituent on the activation energy have been analyzed. Energy and chemical hardness of the ground

states with reference to the transition state structures seem to follow an MHP rule, yet the comparison of the transition state energy and hardness values of the different Markovnikov and anti-Markovnikov channels do not.

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