Steric Effect: Partitioning in Atomic and Functional Group Contributions

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The recently proposed density-based quantification of the steric effect, based on an alternative energy partition scheme where the total electronic energy is decomposed into contributions from three independent effects, steric, electrostatic, and fermionic quantum, is investigated at the atomic and functional group levels in this work. Reasonable trends and linear relationships between theoretical and experimental scales of the steric effect at both group and entire molecular levels have been observed, providing further evidence that the newly defined quantity can serve as an intrinsic measurement of the steric effect for molecular systems.

1. Introduction

The steric effect is one of the most widely used concepts in chemistry and describes "the effect on a chemical or physical property (structure, rate, or equilibrium constant) upon introduction of substituents having different steric requirements."[1] The effect is basically associated with the fact that atoms and larger parts of a molecule occupy a certain region of space. When atoms or groups are brought together, hindrance will be induced, resulting in changes in shape, energy, reactivity, etc. Steric effects arise from contributions ascribed to strain as the sum of nonbonded repulsions, bond angle strain, and bond stretches or compressions. For the purpose of correlation analysis or linear free-energy relation, various scales of steric parameters have been proposed in the literature. Taft[2] constructed a scale for the steric effect of different substituents, based on rate constants for the acid-catalyzed hydrolysis of esters in aqueous acetone. It was shown that $\log(k/k_0)$ was insensitive to polar effects, and thus, in the absence of resonance interactions, this value can be considered as being proportional to steric effects (and any others that are not field or resonance effects):

$$\log(k/k_0) = E_S^{\text{Taft}} \tag{1}$$

In this scale, hydrogen is taken to have a reference value of $E_S^{\text{Taft}} = 0$. Another scale of values was put forward by Charton.[3] These are independent of any kinetical data, as they were derived from van der Waals radii. Meyer[4] has used the volume of the portion of the substituent that is within 0.3 nm of the reaction center, derived from molecular mechanics calculations, to quantify the steric effect. Still other quantities from experimental measurements to probe the steric effect have been introduced.

In conceptual DFT or density functional reactivity theory,[5,6] chemical concepts are identified with response functions of the energy of the system with respect to either the number of electrons N or the external potential (for an isolated system, this is the potential due to the nuclei) or both. The response functions could be linked with concepts readily known by chemists but, in most cases, vaguely or empirically defined. Also, theoretical justification could be provided for a number of principles, such as Sanderson's principle of electronegativity equalization,[7,8] Pearson's hard and soft acids and bases,[9−11] maximum hardness principles,[10−13] and, more recently, minimum electrophilicity principle.[14−19] To the best of our knowledge, parameters or concepts related to the steric effect have not previously been considered in this field until very recently. Weisskopf[20] has related the steric effect to what he has called the "kinetic energy pressure" in atoms and molecules. This concept has also been related to the quantum contribution from the Pauli Exclusion Principle (Fermi hole),[21] and different implementations have been proposed within the wave function theory framework.[22−27] Recently, one of us introduced,[28] based on considerations within the framework of density functional theory, the steric energy as the Weizsäcker kinetic energy.[29] This analysis was based on an alternative energy partition scheme, where the total energy was decomposed into independent contributions from steric, electrostatic, and fermionic quantum effects with a hypothetical bosonic reference state.[30] The Weizsäcker kinetic energy can be expressed as:

$$E_S[\rho(\vec{r})] \equiv T_W[\rho(\vec{r})] = \frac{1}{8}\int \frac{|\nabla\rho(\vec{r})|^2}{\rho(\vec{r})}\,d\vec{r} \tag{2}$$

where $\rho(\vec{r})$ stands for the electron density of the system, and $\nabla\rho(\vec{r})$ denotes the density gradient. Appealing properties such as exclusiveness, repulsiveness, and extensiveness have been revealed,[28] and applications to information theory and internal rotation barriers of simple molecular systems have been carried out.[31−34]

In this Article, we will compute the steric energy for a number of different molecules and perform the integration of this quantity over different regions in space (atomic and fragmental regions), to determine their contribution to the overall steric energy. Next, we will investigate the possible correlation between computed values of the steric energies and the experimental scale of the steric effect, E_S^{Taft}, put forward by Taft. Note that the steric values of Taft that we have used in this work are from esterification and hydrolysis of aliphatic and ortho-substituted benzoated esters.[35,36]

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TABLE 1: Total Steric Energy, $E_S[\rho(\vec{r})]$, of a Series of First to Third Row Hydrides H_nX, Together with the Steric Energy Associated with the Hydrogen Atoms, $E_{S,H}[\rho(\vec{r})]$, and with the Heavy Atoms, $E_{S,X}[\rho(\vec{r})]$, in These Molecules[a]

molecule	$E_S[\rho(\vec{r})]$	$E_{S,H}[\rho(\vec{r})]$	$E_{S,X}[\rho(\vec{r})]$	$E'_S[\rho(\vec{r})]^b$	$E'_{S,H}[\rho(\vec{r})]^b$	$E'_{S,X}[\rho(\vec{r})]^b$
CH_4	32.699	0.517	30.629	32.699	0.517	30.629
SiH_4	184.114	0.484	182.178	184.335	0.633	181.803
GeH_4	1003.149	0.467	1001.280	1002.945	0.626	1000.442
NH_3	44.011	0.548	42.367	44.011	0.548	42.367
PH_3	211.794	0.470	210.382	211.931	0.671	209.917
AsH_3	1068.220	0.459	1066.842	1067.976	0.689	1065.909
H_2O	57.441	0.599	56.242	57.441	0.599	56.242
H_2S	241.594	0.461	240.673	241.709	0.708	240.293
H_2Se	1135.136	0.451	1134.234	1135.022	0.753	1133.516
HF	72.876	0.751	72.125	72.876	0.751	72.125
HCl	273.616	0.451	273.165	273.669	0.742	272.927
HBr	1203.957	0.444	1203.513	1203.932	0.817	1203.116

[a] All values are in au. [b] The geometrical parameters have been restricted to the values of the first row systems (e.g., the HCl and HBr systems are evaluated using the equilibrium geometry of the HF). For more details, see the text.

2. Computational Details

In a recent contribution by Liu,[28] the steric energy, $E_S[\rho(\vec{r})]$, was identified with the Weizsäcker kinetic energy, $T_W[\rho(\vec{r})]$. In his original paper, global values of this quantity were obtained, and integration of this property to atoms or functional groups was not considered. To obtain local values for this property for the purpose of, for example, probing the steric effect in a certain region of a molecular system, integration could be performed over a particular region of the space to obtain its contribution to the global value. Next, by taking appropriate atomic domains defined in one or another way, one can define the atomic contributions to the steric energy, $E_{S,i}[\rho(\vec{r})]$,

$$E_{S,i}[\rho(\vec{r})] = \frac{1}{8}\int_{\Omega_i} \frac{|\nabla\rho(\vec{r})|^2}{\rho(\vec{r})}\,d\vec{r} \qquad (3)$$

in such a way so that

$$E_S[\rho(\vec{r})] = \sum_{i=1}^{N} E_{S,i}[\rho(\vec{r})] \qquad (4)$$

In this work, we have used the fuzzy Voronoi polyhedra to define the atomic domains. It consists of the decomposition of the integral of eq 2 over the 3D space into a sum of integrations over single-atom components using a weight function, $\omega_i(\vec{r})$, for nucleus i in the system at every point of space $\vec{r}$ in such a way that:

$$\sum_{i=1}^{N} \omega_i(\vec{r}) = 1 \qquad (5)$$

In this scheme, the numerical integration of $E_S[\rho(\vec{r})]$ is determinated as a sum of contributions $E_{S,i}[\rho(\vec{r})]$:

$$E_S[\rho(\vec{r})] = \sum_{i=1}^{N} E_{S,i}[\rho(\vec{r})] \cong \frac{1}{8}\sum_{i=1}^{N}\int_{\Omega_i} \omega_i(\vec{r})\frac{|\nabla\rho(\vec{r})|^2}{\rho(\vec{r})}\,d\vec{r} \qquad (6)$$

where $\omega_i(\vec{r})$ has the value 1 in the vicinity of its own nucleus, but vanishes in a continuous and well-behaved manner near any other nucleus. The atomic weights $\omega_i(\vec{r})$ used in this work are derived from the fuzzy Voronoi polyhedra proposed by Becke,[37] tuned by the Bragg−Slater set of atomic radii and following Becke's suggestion to increase the radius of hydrogen to 0.35 Å.[38,39] Such atomic definition has already been successfully applied for the calculation of overlap populations, bond orders, valences,[40] or in several molecular energy decomposition schemes.[41,42] Any other disjoint (Atoms in Molecules[43]) or fuzzy (Hirshfeld[44]) decomposition of the 3D space could also be used, although we expect that the differences will be marginal and the tendencies of the steric energies will be retained, especially because in this work only covalent bonds have been considered. Note that, in previous studies, it has been shown that larger differences of atomic charges and bonds orders between different partition schemes have been found in ionic systems, but not for the covalent ones.[40,45,46] It should be remarked, however, that it was shown previously that, different from other quantifications, the present approach to probe the steric effect is able to uniquely define the contributions at the atomic, functional group, and entire molecular levels by adopting Bader's zero-flux boundary condition of atoms in molecules (AIM).[43] All geometries were optimized at the B3LYP/6-311+G(2d,2p) level; the steric energy and its atomic contributions were evaluated at the same level of theory, using the wave functions and densities obtained form the Gaussian 03 program.[47] Each atom has been integrated using Chebyshev's integration for the radial part (40 points) and Levedev's quadrature (146 points) for the angular part.[48] This level of methodology allows achieving accuracies of the order of 10^{-5} au.[49−51]

3. Results and Discussion

In the first part, we have considered the steric energy for a number of first, second, and third row hydrides H_nX. Table 1 lists the total steric energy $E_S[\rho(\vec{r})]$ (i.e., the Weizsäcker kinetic energy) of these compounds, together with the steric energy associated with the hydrogen atoms in the molecule, $E_{S,H}[\rho(\vec{r})]$, and with the heavy atoms, $E_{S,X}[\rho(\vec{r})]$. In general, as can be expected, the total steric energy of these compounds increases with the size of the central heavy atom. However, the $E_{S,H}[\rho(\vec{r})]$ decreases upon increasing size of the central atom in the hydride; for example, the values of the $E_{S,H}[\rho(\vec{r})]$ for the ammonia, phosphine, and arsine are 0.548, 0.470, and 0.459 au, respectively. This fact indicates that apparently the hydrogen atoms are contributing less to the steric energy in the heavier hydrides than in the lighter ones, which seems counterintuitive, as one would expect the hydrogens to become more sterically hindered. Insight into this can be obtained by considering the different X−H bond distances in the different compounds. It indeed appears that the decreasing hydrogen atom contribution to the

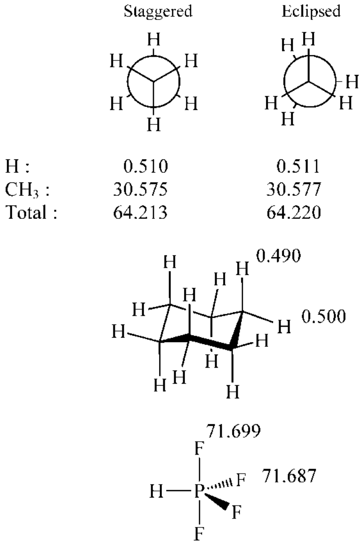

Figure 1. Atomic and functional group steric energies for a few exemplary molecules. See text for discussion. All values are in au.

steric energy is dominated by the fact the bond distance increases with increasing size of the atom X in the hydride. Consequently, we have computed the steric energies for the different hydrides fixing the geometrical parameters to the values for the corresponding first row hydride (e.g., SiH_4 and GeH_4 are evaluated using the equilibrium geometry of CH_4, whereas PH_3 and AsH_3 are evaluated using the equilibrium geometry of NH_3). As can now be seen, the steric energies of the hydrogen atoms now increase considerably, and, as could be expected, the total steric energy remained approximately the same. For instance, the values of the $E_{S,H}[\rho(\vec{r})]$ for the ammonia, phospine, and arsine now become 0.548, 0.671, and 0.689 au, respectively, reproducing the expected chemical tendency of the steric effect. This indicates that next to the intrinsic steric effect also the distance of the substituent to the relevant area on which a steric effect is measured plays an important role.

Next, we have considered the change in the steric effect on substituents in a number of typical compounds, such as the staggered and eclipsed conformations of ethane, the axial versus the equatorial positions in the chair form of cyclohexane, and the axial versus the equatorial positions in the trigonal pyramidal molecule PF_5, whose results are given in Figure 1. The calculations confirm that the steric contribution of the hydrogen atoms and methyl groups in the staggered conformation of ethane is smaller than that in the eclipsed conformation, consistent with the picture from the global results reported earlier.[32,33] It is also confirmed that the axial hydrogen atoms in the chair conformation of cyclohexane are contributing less to the steric energy than are the equatorial ones. Finally, it is also shown that the fluorine atoms in the equatorial position of PF_5 are contributing less to the steric energy than are the axial ones.

Then, one can conclude that the atomic and group steric energies can be used to discern the steric effect between atoms or groups of a same molecule. However, it is important to remark that they are only contributions to the overall steric energy. For instance, we cannot use the difference of the atomic steric energy between the axial and equatorial hydrogens of the chair form of cyclohexane (0.010 au, the result of 0.500 minus 0.490) and the difference of the atomic steric energy between the staggered and eclipsed conformations of ethane (0.001 au, the result of 0.511 minus 0.510) to affirm that the steric effect is more important for the cyclohexane than for the ethane. Thus, the atomic and group functional steric energies can be used to contrast systems with similar geometries. In contrast, the total steric energy does not present these limitations, but it cannot be applied to predict the regioselectivity of the systems at difference to the atomic and group functional steric energies.

TABLE 2: Total Steric Energy, $E_S[\rho(\vec{r})]$, of a Series of Compounds CH_3-X, Together with the Steric Energy Associated with the Methyl Groups, $E_{S,CH3}[\rho(\vec{r})]$, for These Molecules[a]

X	$E_S[\rho(\vec{r})]$	$E_{S,CH_3}[\rho(\vec{r})]$	d_{X-CH_3}	E_S^{Taft} [b]
H	32.699	32.181	1.088	0.000
F	104.568	32.597	1.394	−0.460
CN	105.739	32.053	1.457	−0.510
OH	89.045	32.333	1.424	−0.550
OMe	120.577	32.282	1.413	−0.550
NH_2	75.544	32.202	1.466	−0.610
Me	64.213	32.107	1.528	−1.240
Et	95.690	32.084	1.529	−1.310
Pr	127.164	32.080	1.529	−1.600
i-Pr	127.134	32.060	1.532	−1.710
cyclohexyl	220.376	32.054	1.529	−2.030
i-Bu	158.595	32.056	1.533	−2.170
s-Bu	158.595	32.056	1.532	−2.370
t-Bu	158.555	32.038	1.537	−2.780
neopentyl	190.001	32.032	1.538	−2.980
Et_3C	252.902	31.999	1.539	−5.040
Ph_3C	619.626	31.980	1.557	−5.920

[a] All values are in au, except for the distances, which are in angstroms. Also listed are Taft's steric effect values for the groups X, E_S^{Taft}. [b] From refs 35 and 36.

After checking that the partition of the Weizsäcker kinetic energy in atomic and functional group contributions can be used as a useful tool to evaluate the steric effect, we will analyze the possibility to establish a link between these theoretical values and the experimental ones. For that purpose, we will use the experimental constants obtained from linear free energy relationships mentioned in the Introduction, more specifically, E_S^{Taft} values.[35,36] Consequently, we have considered a number of first row and second row CH_3-X type compounds, where we have investigated the relationship between the contribution of the CH_3 functional groups to the steric energy of the molecule and the E_S^{Taft} values of the groups X. Theoretical and experimental steric effect results are tabulated in Table 2, and the correlation of the two is plotted in Figure 2. From the figure, it is seen that there exists a reasonable linear correlation between theoretical and experimental scales of the steric effect for this set of first and second row compounds:

$$E_S[\rho(\vec{r})] = -70.063E_S^{Taft} + 27.702, \text{ with } R^2 = 0.749 \quad (7)$$

If the data point for the Ph_3C group is eliminated from the correlation analysis, the R^2 becomes 0.754; eliminating both values for Ph_3C and Et_3C groups yields an R^2 of 0.647.

The slope is negative, indicating that a larger value of $E_S[\rho(\vec{r})]$ corresponds to a more negative experimental E_S^{Taft} value and thus a larger steric effect. We notice that the extensive property of the theoretical scale of eq 2 is dictated by its first-order density scaling homogeneity, but its genuine linear correlation with the experimental Taft's scaling is something theoretically unpredicted. Given that the experimental scale of the steric effect was based on rate constants for the acid-catalyzed hydrolysis of esters in aqueous acetone and the theoretical results are from gas-phase calculations at 0 K, the above correlation can be seen

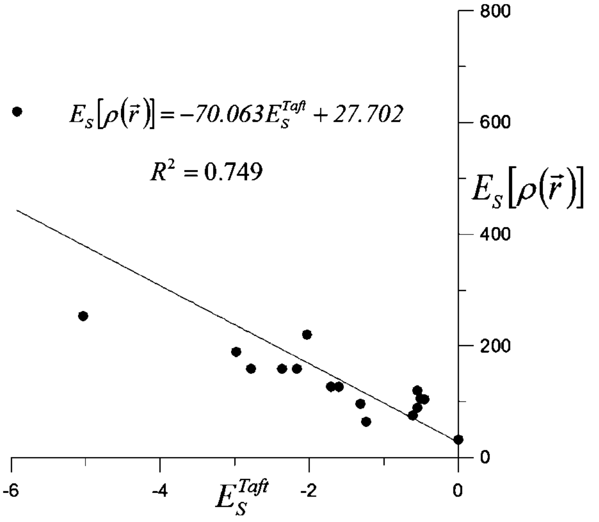

Figure 2. Linear relationship between the theoretical steric energy from eq 2 and Taft's experimental steric parameters based on eq 1 for 17 species listed in Table 2.

as the affirmative ratification that eq 2 is an intrinsic measure of the steric effect of a molecular system.

Moreover, in Table 2, we can also analyze the steric effect contribution of the CH_3 group, $E_{S,CH_3}[\rho(\vec{r})]$. For instance, the change of the hydrogen in the CH_4 for the F, OH, OMe, and NH_2 groups with more negative E_S^{Taft} values, that is, more steric effect, provokes an increase of $E_{S,CH_3}[\rho(\vec{r})]$. However, the remaining groups show smaller values of $E_{S,CH_3}[\rho(\vec{r})]$ than the CH_4, indicating that the tendencies between $E_{S,CH_3}[\rho(\vec{r})]$ and E_S^{Taft} can be opposite. Taking into account the conclusions made in the first part of this work, we know about the relevance of the geometry of the molecules in the steric energy. So, to obtain a good description of the steric effect at least, it is necessary to consider two parameters, $E_{S,CH_3}[\rho(\vec{r})]$ and d_{X-CH_3}. To prove this, a multilinear regression has been done using the $E_{S,CH_3}[\rho(\vec{r})]$, d_{X-CH_3}, and E_S^{Taft} values for 11 molecules of the Table 2. In the multilinear regression, we only consider the C−X sytems, where X is a carbon atom, to minimize the large geometry dependency of the group atomic steric energy, and we obtain the following expression:

$$E_S^{Taft} = 28.347E_{S,CH_3}[\rho(\vec{r})] - 56.740d_{H_3C-X} - 824.076 \qquad (8)$$

To validate the utility of this equation, in Figure 3 we plot the linear regression between the experimental scale from Taft's steric parameters and the fitted theoretical steric energy from eq 8, $E_S^{theor}[\rho(\vec{r}),d_{H_3C-X}]$:

$$E_S^{theor}[\rho(\vec{r}), d_{H_3C-X}] = 0.937E_S^{Taft} - 0.168 \text{ with } R^2 = 0.937 \qquad (9)$$

When eliminating the data for the X = Ph_3C system from the correlation analysis, the R^2 becomes 0.871; additionally eliminating the data for X = Et_3C systems yields $R^2 = 0.908$.

This analysis shows that the steric effect as given by $T_W[\rho(\vec{r})]$ and computed at both the global and the atomic or functional group level can be used as an estimate of the intrinsic steric effect, as, for example, quantified by the E_S^{Taft} values. It constitutes a first step to introduce the global steric effect and its atomic and functional group contributions in the applications of DFT-based reactivity indices to chemical problems.

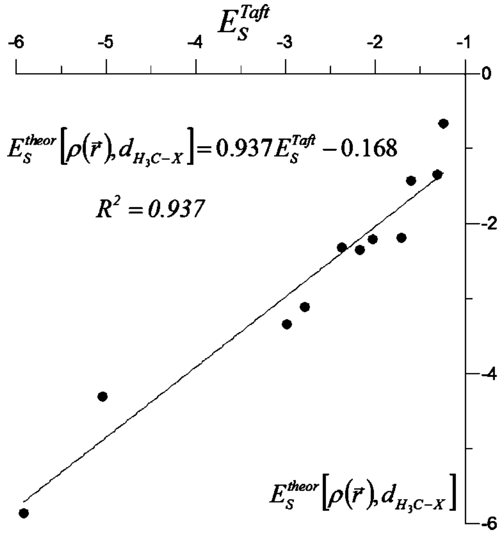

Figure 3. Comparison of the experimental scale from Taft's steric parameters and the fitted theoretical steric energy from eq 8 using CH_3 group steric energy and the C−X bond distance (where X is a carbon atom). See the text for more details.

4. Conclusions

In summary, based on a recent quantification of the steric effect in the framework of density functional theory where the total electronic energy was proposed to be decomposed into contributions from three independent effects, steric, electrostatic, and fermionic quantum, contributions of the effect at the atomic and functional groups levels are considered in this work. Reasonable linear relationships between theoretical and experimental scales at both group and entire molecular levels have been discovered, providing an additional piece of evidence affirming that the newly proposed definition serves as an intrinsic measurement of the steric effect for molecular systems. In addition, we have shown that the steric energy, $E_S[\rho(\vec{r})]$, can be a useful tool to measure the global steric effect between different molecules. However, if we want to compare the atomic and functional group contributions to the $E_S[\rho(\vec{r})]$ between different molecules, it is essential to consider the contribution from the molecular geometry (distances and angles) as well.

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