Communication

Steric vs Electronic Effects: A New Look Into Stability of Diastereomers, Conformers and Constitutional Isomers

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Abstract: A quantum chemical investigation of the stability of compounds with identical formulas was carried out on 23 classes of halogenated compounds made of H, F, Cl, Br, I, C, N, P, O and S atoms. All possible structures were generated by combinatorial approach and studied by statistical methods. The prevalence of formula in which its *Z* configuration, *gauche* conformation and meta isomer are the most stable forms is calculated and discussed. Quantitative and qualitative models to explain the stability of the 23 classes of halogenated compounds were also proposed.

Keywords: Steric effect; electronic effect; cis effect; gauche effect

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1. Introduction

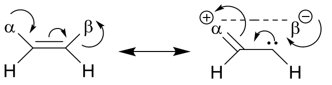
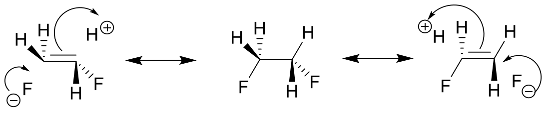
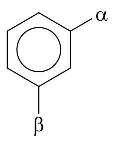
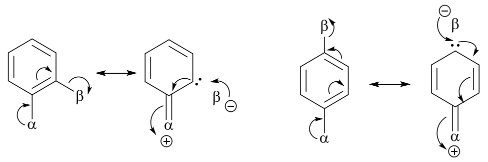
Steric effects, non-bonded interactions leading to avoidance of spatial congestion of atoms or groups, are often the central theme in the discussion of stability of diastereomers, conformers and constitutional isomers. Reasonings based on steric effects are relatively intuitive and give rise to a generally accepted rule of thumb that *E* configuration, *anti* conformer and para isomer in diastereomers, conformational and constitutional isomers, respectively, should be the most stable forms.

Many findings in contrary to steric predictions exist in the literature. Table 1 shows a comprehensive review of experimental and theoretical evidence of the *Z* configuration, *gauche* conformer and meta isomer being the most stable forms. The experiments include heat of combustion/hydrogenation and spectroscopic measurement while the theoretical studies are mainly quantum mechanical methods.

Even when steric effect reasoning correctly predicts the result, controversy ensues. For example, a number of organic chemistry textbooks attributed the relative stability of the staggered conformation of ethane to steric factor alone. This has led to controversy discussed at length across the scientific community over eight years.[1-8]

Electronic effects, on the other hand, are relatively more complicated. The reasoning for energy prediction often involves resonance structures[9-15] (formerly called mesomeric effect) or hyperconjugation[16-19] (delocalization) of orbitals. Specific electronic reasonings for each case of exceptions to steric prediction are shown in Table 1. The preference of *Z* configuration and *gauche* conformer are primarily due to hyperconjugation in a similar vein to the ethane case[17, 18] but the reasoning for preference of meta isomer is still lacking.

Table 1. Summary of exceptions to steric prediction for carbon-backbone compounds*.

Case	Exceptions to steric prediction and reasoning
Z configuration[18, 20-33]	CHF=CHF CHF=CHCl CHF=CHBr CHF=CHI CHCl=CHCl CHBr=CHBr Halogens can be both donors and acceptors of electronic charges. When the donor and acceptor are on the same side, the structure is more stable due to the interaction of α and β substituents in the scheme below.[34] This is consistent with *n* to $\pi_{C=C}^*$ delocalization. Demiel has also suggested earlier that the more electronegative atoms should be on the same side.[11, 13] 
***Gauche* conformation[16, 17, 35-44]**	For CH_2F-CH_2F, the *gauche* form is preferred[34] due to the hyperconjugative interaction (primarily in the antiperiplanar $\sigma_{C\text{-}H}$ to $\sigma_{C\text{-}F}^*$ delocalization[17]) described in the scheme below. The twofold (V_2) potential actually has an energy minimum when the F-C-C-F torsional angle is ± 90°.[40] Alternatively, "bent bond" may offer an explanation for the destabilization of the *anti* conformer.[17, 41, 42] 
Meta isomer[45, 46]	 In most cases, meta isomers are the most stable forms for dihalobenzenes. This observation was attributed to the absence of electronic interactions (shown below) between the two halogen substituents when they are at 1,3- positions.[46] 

* The information is shown for gas-phase only. In the case of conformers, the rotational barrier is small such that the shift in equilibrium can be easily observed when polar solvents promote the interconversion of *anti* to *gauche* conformers.

In addition to carbon-backbone compounds in Table 1, there are many experimental and theoretical studies for other backbones such as N=N[33, 47-52], C=N[53, 54], N=P[55], C=P[56], P=P[57, 58] and N-N.[59]

Inspired by Bent's rule,[60, 61] which states how orbital hybridizations can explain trends of bond lengths and bond angles in a series of compounds correctly while the steric argument fails, in this communication, we want to advance the understanding of energy prediction of chemical structures that are derived from the same molecular formula.

Non-superimposable structures of the same molecular formula can be enantiomers, diastereomers, conformers and constitutional isomers (structural isomers). As energies of enantiomers are identical, they are excluded from our investigation. For the other three types of isomerism, *E* and *Z* configurations in A=A′ compounds and halocyclopropanes represent diastereomerism, *gauche* and *anti* conformers in A-A′ compounds represent conformational isomerism and *ortho*, *meta* and *para* structure in halobenzenes represent constitutional isomerism.

2. Materials and Methods

2.1 Quantum chemical calculations and datasets

All possible structures made of two atoms (A,A′ ∊ {C,N,P,O,S}) or cyclopropane or benzene as the core structure and combinations of halogen (H,F,Cl,Br,I) as substituents were previously generated by our group.[62-64] Up to four levels of theory (HF, B3LYP, MP2 and CCSD) were used in these studies and frequency calculations were completed for all structures at least from HF to B3LYP level. For the purpose of this communication, we improved upon existing results by performing single-point electronic energy calculation at CCSD(T)/6-311++G(d,p) on majority of the structures. Due to prohibitive computational cost, this applies to most compounds except for some classes of compounds that original MP2/6-311++G(d,p) energies were used as shown in Table 2.

Sample frequency calculations at MP2/6-311++G(d,p) were performed on all classes and only the benzene class was found to have imaginary frequencies. The issue is well known[65] and the geometry optimization for this class of compounds was performed again at MP2/6-311G(d,p). The choice of basis sets of 6-311G(d,p) and 6-311++G(d,p) for the current calculation and previous studies was due to the availability of iodine atom and reasonable computational cost.

Optimized geometries of selected A=A′, A-A′ and halobenzene compounds were compared to gas-phase experimental data in previous studies.[18, 66, 67] The current level of theory and/or basis set yields acceptable results. Additional confirmation with solid-phase X-ray structures from the Cambridge Structural Database (CSD)[68] shows good agreement between calculated geometries from the current work and experimental results from the database for dichlorobenzenes.

Revised dataset of all classes of compounds in the previous studies together with addition from this work are available online in Open Science Framework. This new data repository is intended to supersede the three separate datasets.[62-64] Raw Q-Chem[69] output, list of structures with PubChem CID, detailed methodology and source codes are included.

2.2 Definitions of convention and labels

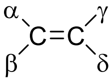
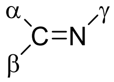
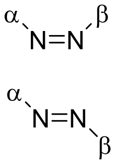
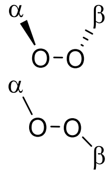
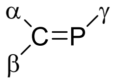
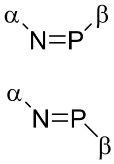
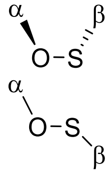
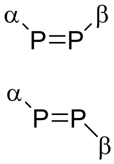
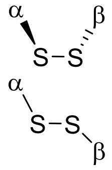
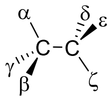
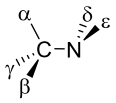
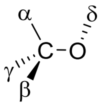
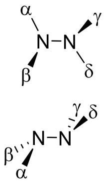
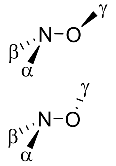
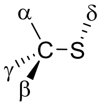
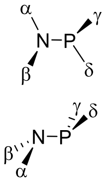
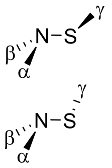
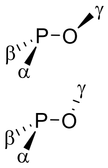
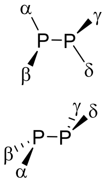
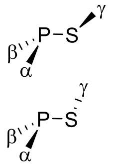
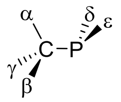
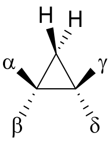
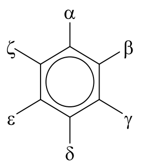
We followed the standard definition as per the Cahn–Ingold–Prelog (CIP) sequence rules and the International Union of Pure and Applied Chemistry (IUPAC)’s definitions. The relative bulkiness of all substituents (by covalent or van der Waals radii) in this study also follows the priority rule.

For *E* and *Z* configuration of diastereomers, if all four substituents are different, there are six possible isomers on a halo-substituted C=C. To differentiate them, labels of *E*a, *E*b, *E*1, *E*2, *E*3, *Z*a, *Z*b, *Z*1, *Z*2, *Z*3, *G*0, *G*1, *G*3 (*G* stands for geminal.) were used for C=C and six other classes of compounds in accordance with the previous study.[62] Therefore, energy comparison can be made within a diastereomeric pair (same label such as *E*1 vs *Z*1) and geminal compounds were excluded from the current study.

In a similar manner, for *gauche* and *anti* conformers, the torsional angle of the highest-priority substituents per CIP rules from the two ends of the molecule are considered. The angles of (-120°, 120°) are treated as *gauche* and the angles of [-180°, -120°) or (120°, 180°] are counted as *anti*. Unlike the previous definition of *gauche* effect,[70] for simplicity, ambiguous cases (compounds with at least one conformer having ambiguity in labeling) are not considered. For example, all conformers of CBr_2Cl-CF_2Cl are not considered since the presence of the two Br atoms as the highest priority atoms on the left leads to an ambiguity in labelling the conformations as *gauche* or *anti*. However, compounds with more than one *gauche* conformer are considered normally in this communication.

For constitutional isomers of halobenzene, we extended the standard nomenclature ortho, meta, para in disubstituted benzenes to highly substituted benzenes if it can be done by using the two highest priority substituents without ambiguity for all isomers in an empirical formula. For example, $C_6F_4Cl_2$ isomers can be considered but $C_6Cl_4F_2$ isomers are not included in our analysis.

Table 2. Class of compounds and the highest level of calculation method employed.

Calculation method	**Class of compound and total number of structures***					
CCSD(T)/6-311++G(d,p)// CCSD/6-311++G(d,p)	 110	 100	 30	 30		
		 100	 50	 50		
			 30	 30		
CCSD(T)/6-311++G(d,p)// B3LYP/6-311++G(d,p)	 730	 900	 250	 320	 150	
		C-P pending	 250	 600	 150	 150
				 320	 150	
MP2/6-311++G(d,p)// MP2/6-311++G(d,p)	 900	 110	 830			

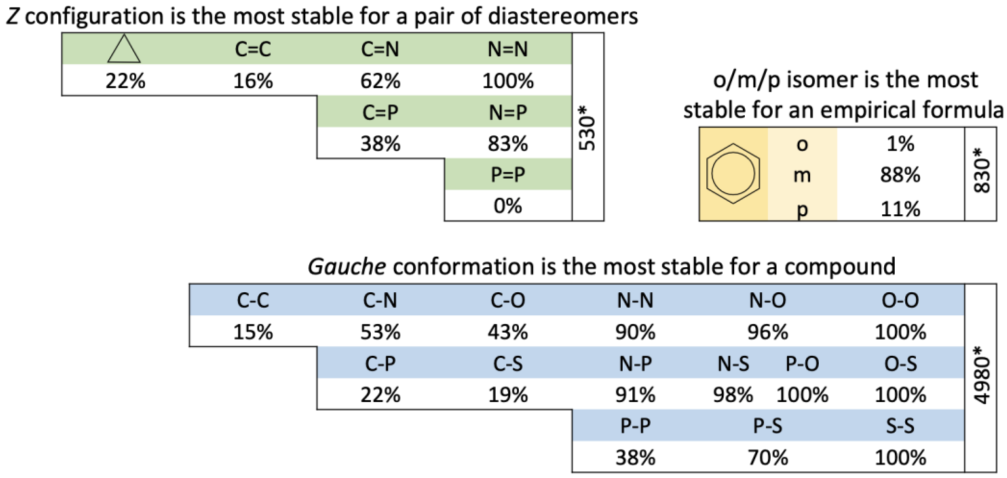
* In geometry optimization at CCSD/6-311++G(d,p) level of theory, NBr=NI and NI=NI disintegrated into N_2 and halogen moieties. Similarly, for conformers, some structures interconverted during the optimization process. Therefore, the number of actual structures in consideration can be less the number in the table.

As per the definition above, steric effects therefore predict that the E configuration, the *anti* conformer and the para isomer for compounds in this study are the most stable structure. Herein, deviations from these expectations are called Z configuration effect, *gauche* conformation effect and meta isomer effect respectively. Preliminary exclusion of irrelevant structures mentioned above reduced the total number of structures for the three groups from 710, 8365 and 1505 in previous studies to 530, 4980 and 830 in the current study, respectively.

3. Results and Discussion

3.1 Prevalence rate, quality of energetic results and comparison to other studies

The main results are shown as the percentage of total cases for the three groups, the first made of 7 classes of E/Z disastereomers, the second made of 14 classes of *anti*/*gauche* conformers and the third made of one class of ortho/meta/para isomers. These prevalence rates can be simply interpreted as how often the steric reasoning fails to identify the most stable structure in these classes of compounds. For two large classes of carbon compounds (C=C and C-C), the rates between 15% to 20% are not negligible. There are relatively small classes where the rates are as extreme as 0% (P=P only) and 100% (N=N, O-O, P-O, O-S and S-S). The increasing trend toward the upper right side of periodic table can be seen from the figure. For the purpose of this communication, prevalence rates can be regarded as cases in which electronic effects are in the counteracting direction and are relatively stronger than steric effects.



Z configuration is the most stable for a pair of diastereomers

△	C=C	C=N	N=N	
22%	16%	62%	100%	530*
		C=P	N=P	
		38%	83%	
			P=P	
			0%	

o/m/p isomer is the most stable for an empirical formula

⬡			
	o	1%	830*
	m	88%	
	p	11%	

Gauche conformation is the most stable for a compound

C-C	C-N	C-O	N-N	N-O	O-O	
15%	53%	43%	90%	96%	100%	4980*
	C-P	C-S	N-P	N-S P-O	O-S	
	22%	19%	91%	98% 100%	100%	
			P-P	P-S	S-S	
			38%	70%	100%	

Figure 1. Percentages of cases in which steric reasoning failed to predict the most stable structure. (* stands for the total number of structures for the compound group)

For uncertainty in computational results, the change in level of theory from MP2 in previous studies to CCSD(T) in the present study leads to a change in prevalence rate in Figure 1 of at most 7% (C-N). The prevalence rates at various other levels of theory and the code that generate them are available at the data repository. The basis set change from 6-311++G(d,p) to 6-311G(d,p) in MP2 optimization jobs of halobenzene compounds has no effect on the distribution of three isomers in the figure. There are borderline cases in both experimental and computational results as the difference in energy can be extremely small. For the example of CHBr=CHBr in Table 1, the gas-phase experimental value for a configuration conversion from E to Z is -100±160 cal/mol in one source[20] and revised to 90±240 cal/mol in another.[26] The present CCSD(T) electronic energy agrees with the later source that the E configuration is more stable. However, similar to the conformer case mentioned in the footnote of Table 1, the Z structure is preferred in liquid.[26]

The main results here agree with experimental and computational studies previously mentioned in the introduction. The well-known cases in carbon compounds in Table 1 summarized by the infamous book by Eliel, Wilen and Mander[34] were reproduced in the current work. Moreover, the extreme cases of 0% (P=P) and 100% (N=N) are also in line with previous work by others.[50, 52, 57, 58] For halobenzenes, in contrast to steric prediction, meta isomers are the most stable forms. This is confirmed by results in dihalobezenes.[46] Similar observations in polychlorinated compounds confirm this meta preference e.g. for the first few chlorine substitutions to biphenyls (PCB), dibenzo-*p*-dioxins (PCDD) and dibenzofurans (PCDF), the most stable chlorination occurs at meta positions with respect to the other ring.[71]

3.2 Quantitative and qualitative models to predict relative stability

To gain an insight into stability of *Z* configuration, *gauche* conformation and meta isomer, previous studies have focused on a small number of representative compounds. The total energy of these chemical structures can be partitioned by quantum mechanical methods into parts, for example, exchange repulsion (for steric effect), four different types of electron delocalization (for electronic effect).[18] Our approach in this communication is different in two ways. First, all possible permutations in a class of compounds were used in the study. Second, the energies were partitioned by statistical methods. The roles of steric and electronic factors in determining the stability of structures were explored using quantitative and qualitative models as shown in Figure 2.

Simple predictors in which their periodic trends are obvious were selected for our preliminary analysis here. To represent steric interaction, one from three measures of atomic size, covalent radius (R_C), van der Waals radius (R_V) and atomic radius (R_A) was used; the first two exhibit the typical trend of $R(\mathrm{H}) < R(\mathrm{F}) < R(\mathrm{Cl}) < R(\mathrm{Br}) < R(\mathrm{I})$ whereas the last leads to the trend of $R(\mathrm{F}) < R(\mathrm{H}) < R(\mathrm{Cl}) < R(\mathrm{Br}) < R(\mathrm{I})$. To represent electronic interactions, one from two measures, electronegativity (Pauling's EN scale, $EN(\mathrm{F}) > EN(\mathrm{Cl}) > EN(\mathrm{Br}) > EN(\mathrm{I}) > EN(\mathrm{H})$) and $\mathrm{p}K_b$ of the conjugate base X^- ($\mathrm{p}K_b(\mathrm{H}^-) < \mathrm{p}K_b(\mathrm{F}^-) < \mathrm{p}K_b(\mathrm{Cl}^-) < \mathrm{p}K_b(\mathrm{Br}^-) < \mathrm{p}K_b(\mathrm{I}^-)$) was used.

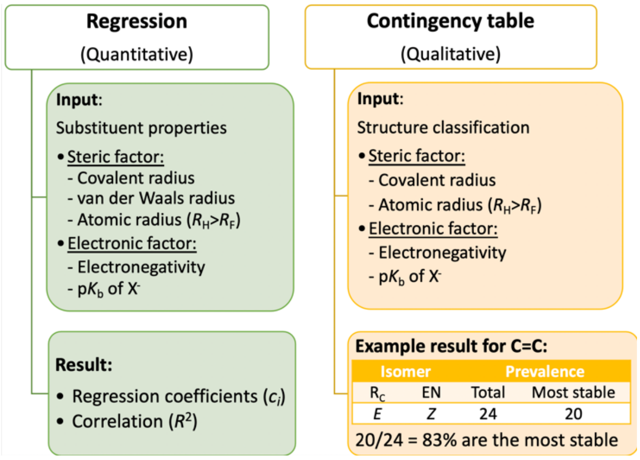


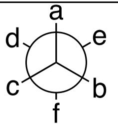
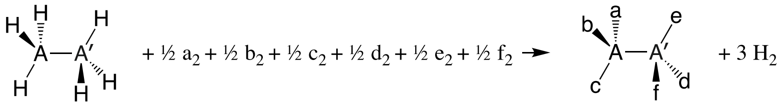
Figure 2. Two approaches to predict the preference for *Z*, *gauche* and meta structures.

3.2.1 Quantitative model

The quantitative models were constructed using a multiple linear regression analysis to predict formation energy based on steric and electronic factors. Given that the electronic energy of a structure is determined primarily from the steric and electronic interactions among its substituents, the aim of this analysis is to depict the counteracting effects of steric and electronic interactions. Linear regression models are composed of up to three-body terms of one representation of steric interaction and one representation of electronic interaction, to predict the energy of formation (E_f) (see scheme in Table 3). E_f is predicted from the sum of steric interactions (E_r) and the sum of electronic interactions (E_e). Table 3 shows the composition of E_r and E_e terms by the example of *R*c vs *EN* model, together with examples of prediction results from the model.

Table 3. Example of *R*c vs *EN* model and its prediction of E_f based on electronic energies at MP2/6-311++G(d,p).

Class of compound: C-C

Structure	Energy of formation (E_f)
	

Model:

Type of interaction			Predictor*	Coefficient
			1 (constant term)	50.244
E_{R_C}	1-body	geminal	$r_a + r_b + r_b$	6.008
			$r_d + r_e + r_f$	6.008
	2-body	geminal	$r_a r_b + r_a r_c + r_b r_c$	0.364
			$r_d r_e + r_d r_f + r_e r_f$	0.364
		gauche	$r_a r_d + r_c r_d + r_a r_e + r_b r_e + r_b r_f + r_c r_f$	0.254
		anti	$r_b r_d + r_c r_e + r_a r_f$	0.164
E_{EN}	1-body	geminal	$e_a + e_b + e_c$	-3.711
			$e_d + e_e + e_f$	-3.711
	2-body	geminal	$e_a e_b + e_a e_c + e_b e_c$	-0.667
			$e_d e_e + e_d e_f + e_e e_f$	-0.667
		gauche	$e_a e_d + e_c e_d + e_a e_e + e_b e_e + e_b e_f + e_c e_f$	0.094
		anti	$e_b e_d + e_c e_e + e_a e_f$	0.047

Prediction results:

CClFH-CFHI (SS)	Actual E_f	Predicted E_f	E_{R_V}	E_{EN}
gauche (structure 1)	-19.921	-19.515	26.917	-96.675
gauche (structure 2)	-19.707	-19.509	26.953	-96.705
anti	-19.884	-19.445	26.890	-96.578
CFHH-CHHI	**Actual E_f**	**Predicted E_f**	**E_{R_V}**	**E_{EN}**
gauche	-8.458	-8.057	20.282	-78.582
anti	-8.769	-8.120	20.256	-78.620

*r_i and e_i are values of the steric factor *r* (*R*v) and the electronic factor *e* (*EN*), respectively, of the substituent *i*, $i \in \{a,b,c,d,e,f\}$.

Our expectation was that the energy from the electronic terms for *Z*, *gauche* or meta structures should be lower than those for their counterparts, and vice versa for the steric terms. However, the example of prediction in Table 3 shows that the electronic term predicts a *gauche* conformation to be the most stable form in some cases (CClFH-CFHI (SS)) while favouring the *anti* conformation in others (CFHH-CHHI). Addition of more predictors did not help meet the expectation as periodic properties of the elements are highly correlated. With different combinations of steric and electronic effect representations and different possible mathematical models up to three-body terms, there is no unified model that performs as expected for all 23 classes of compounds. Nevertheless, having electronic terms predict a mixture of structures (shown in the example for C-C conformers) supports previous orbital-based energy partition schemes, in that electronic effects can stabilize *anti* conformers and *E* isomers as well. [18, 39]

3.2.2 Qualitative model

In our qualitative model, contingency tables made of different structure classification were constructed. Structures were classified by one steric factor (R_c and R_A since only the ranking is important here, R_v is not needed.) and one electronic factor (EN and pK_b). As a result, there are four possible combinations arising from these choices of electronic and steric predictors.

Classification of isomers was done using a combination of a steric and an electronic factor in a similar manner to how atomic numbers are used in the CIP rule. Contingency tables were made by finding the total number of each kind of structure and the number of cases in which it is the most stable form. These two factors may be in the same direction or counteracting. In the former case, we would expect prevalence rate of 0% or 100% if the two predictors are correct.

As an example for diastereomers, in Figure 2, there are a total of 24 C=C structures classified as *E* using covalent radius (E_{RC}) and *Z* using electronegativity values (Z_{EN}) of which 20 are the most stable when compared to its counterpart (Z_{RC} and E_{EN}), leading to 20/24=83% of E_{RC} and Z_{EN} structures being the most stable of their isomers. If Demiel's hypothesis[11, 13] of high electronegativity atom model (explained in Table 1) were true, the number should have been 100%. The other three combinations of steric and electronic predictors were also explored and consistent 100% in E_{steric} and $Z_{electronic}$ for all classes of compounds could not be attained. Figure 1 can be considered as the results from the simplest combination of the four in which steric factor (R_C) and electronic factor (pK_b) have exactly opposing trends and the prevalence rates are for the Z_{RC} and Z_{pKb} case. In this model only, we do not have an expectation of 100% in diastereomer contingency tables as the configuration E_{RC} and Z_{pKb} is not possible.

3.3 Improvement on the two models

Deviations from expected results in both quantitative and qualitative models above could be explained or addressed in three ways.

- There could be a third factor affecting the results. For example, the deviation from idealized geometry was considered by performing both quantitative and qualitative analyses on the unoptimized structures by using standard bond lengths and bond/torsional angles. Improved trends were observed as shown in the data repository.
- Steric and electronic predictors are highly correlated as per the periodic trend. A more appropriate electronic predictor may help improve the model. Steric factors may, in fact, be negligible when compared to electronic factors for studied classes of compounds after appropriate treatment of electronic terms are employed.
- In cases of qualitative models for conformers and constitutional isomers, only considering the pair of highest priority substituents has an inherent flaw and may not reflect the summative effect of all substituents.

4. Conclusions, implications and future work

Most previous studies focused on a few model compounds and orbital-based energy partition schemes. To the best of our knowledge, our work is the first attempt to use a combinatorial approach on all possible compounds and to employ statistical methods for energy partition schemes. The prevalence rates (varying significantly from 0% to 100%) strongly support that the phenomenon[8] of *Z* configuration effect, *gauche* conformation effect and meta isomer effect are real and not negligible.

The implications for teaching are manifold. Many chemistry textbooks[72-74] mention the relative stability of cis-trans (or *E*/*Z*) isomers but neglect to mention these phenomena probably for simplicity or because the phenomena were thought to be rare. There are two possible changes. First, one must be apprehensive when the steric reasoning is used to make stability predictions of compounds based on the size of halogen substituents. Second, for reasoning of these phenomenon, there should be a more balanced view or a shift from teaching of VSEPR (steric-driven reasoning) to Bent's rule[75] and hyperconjugation (electron delocalization-driven reasoning). The call to move away from VSEPR[76, 77] has been discussed elsewhere and this communication only provides an additional piece of supporting evidence. It is important to note that even in the case that the steric prediction is right, the hyperconjugation energy can still be dominant as in the controversial case of ethane rotational barrier.

The data presented should lead to a renewed interest in finding a new approach to describe stability of chemical compounds. The dataset is open for further analysis and use in many ways. For example, the models can be applied in molecular mechanics force field construction. Also, we are aware that constitutional isomers exist within the first group (only C=C, C=N, and C=P) data set. There is currently no specific naming convention for the relationship. Preliminary analysis shows that the failure rate of steric prediction is 24/55, 32/50 and 25/50, respectively for the three classes. Similarly, constitutional isomers do exist within the second group too but an exchange of two substituents will have the constitutional isomer effect intertwined with conformational isomer effect. Application of machine learning techniques may help make a better sense of the dataset.

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