JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Toward a Physical Interpretation of Substituent Effects: The Case of Fluorine and Trifluoromethyl Groups

Tomasz Siodła,*[,†] Wojciech P. Oziminski,[‡] Marcin Hoffmann,[†] Henryk Koroniak,[†] and Tadeusz M. Krygowski*[,§]

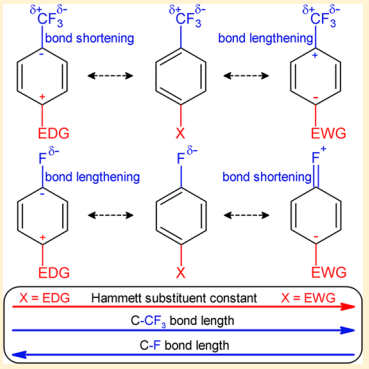
[†]Faculty of Chemistry, Adam Mickiewicz University, Umultowska 89b, 61-614 Poznań, Poland

[‡]National Medicines Institute, Chełmska 30/34, 00-725 Warsaw, Poland

[§]Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland

Supporting Information

ABSTRACT: The application of ab initio and DFT computational methods at six different levels of theory (MP2/cc-pVDZ, MP2/aug-cc-pVTZ, B3LYP/cc-pVDZ, B3LYP/aug-cc-pVTZ, M06/cc-pVDZ, and M06/aug-cc-pVTZ) to *meta*- and *para*-substituted fluoro- and trifluoromethylbenzene derivatives and to 1-fluoro- and 1-trifluoromethyl-2-substituted *trans*-ethenes allowed the study of changes in the electronic and geometric properties of F- and CF_3-substituted systems under the impact of other substituents (BeH, BF_2, BH_2, Br, CFO, CHO, Cl, CN, F, Li, NH_2, NMe_2, NO, NO_2, OH, H, CF_3, and CH_3). Various parameters of these systems have been investigated, including homodesmotic reactions in terms of the substituent effect stabilization energy (SESE), the π and σ electron donor−acceptor indexes (*p*EDA and *s*EDA, respectively), the charge on the substituent active region (cSAR, known earlier as qSAR), and bond lengths, which have been regressed against Hammett constants, resulting mostly in an accurate correspondence except in the case of *p*-fluorobenzene derivatives. Moreover, changes in the characteristics of the ability of the substituent to attract or donate electrons under the impact of the kind of moiety to which the substituent is attached have been considered as the *indirect substituent effect* and investigated by means of the cSAR model. Regressions of cSAR(X) versus cSAR(Y) for any systems X and Y allow final results to be obtained on the same scale of magnitude.



1. INTRODUCTION

Substituent effects (SEs) have been known for a long time as very efficient concepts in organic chemistry. When one group in a molecule is replaced by another one, the SE describes how this change influences the molecule's chemical, physicochemical, or biochemical properties. The importance of this concept may be documented by a statistical number of ∼10 papers published daily in which the term SE is cited in the title, abstract, or keywords (ISI Web of Science for 2010−13). The first successful attempt to quantify these effects came from fundamental papers and then a monograph by Louis P. Hammett.[1,2] A numerical characteristic of the SE, defined further as the substituent constant, σ, is given by eq 1:

$$\sigma_{p(m)} = \log K_{p(m)}(\mathrm{X}) - \log K \qquad (1)$$

where K and $K_{p(m)}(\mathrm{X})$ are dissociation constants for unsubstituted and *para* (*meta*)-X-substituted benzoic acids, respectively. Thus, already in 1940 in the fundamental monograph[2] the explanatory parameters σ_p and σ_m were successfully applied to interpret kinetic and equilibrium data for 52 reaction series. Since the original Hammett constants σ_p and σ_m have failed in some cases, particularly where the reaction site in the reaction series is strongly negatively or positively charged, many other substituent constants have been introduced, such as σ_p^- [3,4] and σ_p^+.[5] Additionally, many attempts have been made to separate particular contributions influencing the substitution effect and σ parameters, including inductive, mesomeric (resonance), field, and other specific effects.[6] All of these problems have been studied mostly on the basis of a combination of kinetic, equilibrium, or other physicochemical properties and are presented in detail in a series of review articles.[3,7−9] The above-mentioned approaches have been summarized in the review by Hansch, Leo, and Taft,[10] in which a large collection of various kinds of substituent constants are thoroughly compiled and discussed in detail.

One of the first theory-based approaches to substituent effects was reported by Dewar and Grisdale,[6,11] and then a complete theoretical approach was presented by Ehrenson,[12] who considered nonconjugative interactions by means of electrostatic interactions similarly to Kirkwood−Westheimer approach[13] and generated the $\rho\sigma$ descriptor from the linear combination of atomic orbitals to yield molecular orbitals (LCAO-MO) model.[14−16] Many of these approaches have been presented in recent reviews.[17,18]

Received: May 9, 2014
Published: July 21, 2014

   dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

In the last decades, interpretations of substituent effects based on reactivity and physicochemical properties have been replaced by quantum-chemical modeling. They have been studied via correlations of various calculated physical parameters with the original substituent constants σ. Many of these calculated parameters, such as electrostatic potentials at the ring carbon atoms or at atoms of the reaction site,[19−23] energies of the HOMO or LUMO,[24−26] the topography of the electrostatic potential near the molecular surface,[27−29] and ionization potentials,[30] have been successfully applied. Energy decomposition analysis (EDA)[31,32] has also been successfully applied to confirm that the π-electron energy of the substituent effect correlates nicely with Hammett's constants.[33] Recently, the idea of using the sum of the charges on the substituent and the *ipso* carbon atom has been introduced. This has been denoted as qSAR [the acronym coming from "charge (q) of the *s*ubstituent *a*ctive *r*egion"].[34−36] However, it is advisible to no longer employ the acronym qSAR that was introduced earlier, as there are many thousands of examples of the use of the acronym "QSAR", meaning quantitative structure−activity relationship. To avoid possible confusion, we have decided to use the acronym cSAR, originating from "*c*harge of the *s*ubstituent *a*ctive *r*egion". An important energetic characteristic based on the isodesmic reactions approach[37,38] describes the substituent effect as the substituent effect stabilization energy (SESE).[17] The last mentioned descriptor, SESE, was introduced a few decades ago for the interpretation of substituent effects.[39,40] A new simulation of the substituent effect comes from the application of the natural bond orbital (NBO) method,[41] which can be applied to estimate the occupancy of σ and π orbitals in substituted molecules, giving rise to the π and σ electron donor−acceptor indexes (pEDA and sEDA, respectively).[42−48]

In our studies on the substituent effect, we have decided to estimate the effect of many various substituents on fluorine (F) and trifluoromethyl (CF_3) groups attached to a benzene ring or a C=C bond. Thus, we can observe how the properties of F and CF_3 groups are influenced by intramolecular interactions coming from various substituents.

The unique combination of properties of fluorine makes it a remarkable substituent.[49] Its extreme electronegativity induces a strong withdrawing inductive effect, making fluorine a σ-electron acceptor, whereas the electron-donating resonance effect of its lone-pair electrons allows the fluorine atom to be considered as a π-electron donor as well. These electronic properties originating from the presence of fluorine in the molecule make the effects on, for example, acidity and basicity predictable in most cases. Fluorine is always inductively electron-withdrawing but electron-donating by resonance, while perfluoroalkyl groups (e.g., CF_3) are always electron-withdrawing. The Hammett-type substituent parameters for inductive and resonance effects are given in Table 1.[50]

These two faces of fluorine (σ acceptor/π donor) provided an opportunity in our studies to discriminate σ- and π-electron influences resulting from interactions with various substituents. On the other hand, we have also studied how the CF_3 group, as one of the most efficient electron-withdrawing groups, can reflect the strength of interactions with other substituents.

Furthermore, the substituent effect is the sole problem in many areas, especially in medicinal chemistry, where a small change in substitution can make a dramatic difference in biological activity. Replacing H with F usually causes low steric demand at receptor sites on cells or enzymes, although the fluorine atom is slightly larger than hydrogen.[51] Such substitution is a common practice in bioorganic chemistry, which results mostly in new drugs. Another practice is the replacement of a hydroxyl group with fluorine to generate a fluorinated enzyme substrate or inhibitor in a given enzymatic process.[52−56] Such a strategy is rationalized by electronic similarities between a fluorine atom and a hydroxyl group, with particular reference to polarity as well as the close isosteric relationship between fluorine and oxygen; thus, such substitution introduces a small structural disturbance.[57,58] Recently, nucleotides and nucleosides containing sugar fragments in which OH groups have been substituted with fluorine atoms are the focus of increasing interest. Some of these compounds are potential drugs, as they display anticancer activity.[59−62] Some are active against various viruses, including hepatitis B,[63−65] Epstein−Barr,[66] varicella zoster,[67] and HIV.[68−71]

Table 1. Hammett-Type Substituent Parameters for Inductive and Resonance Effects[50]

substituent	σ_I	σ_R
F	0.52	−0.34
Cl	0.47	−0.23
Br	0.44	−0.19
CH_3	0.04	−0.11
CF_3	0.42	0.10
CH_3CH_2	0.05	−0.10
CF_3CH_2	0.14	−0.05
OH	0.29	−0.43
OCH_3	0.27	−1.43
OCF_3	0.39	−0.04

Nowadays there are many drugs containing F and/or CF_3 as a substituent (in parentheses the kind of the substituent in shown), including the antipsychotics fluphenazine (CF_3),[72] flupentixol (CF_3),[73] haloperidol (F),[74] and risperidone (F);[75] the antidepressants fluoxetine (CF_3),[76] citalopram (F),[77] and fluvoxamine (CF_3);[78] and the anxiolytics[79] flunitrazepam (F)[80] and midazolam (F).[81,82]

After introducing a fluorine atom or CF_3 group in molecules having potential medical applications, one can observe a dramatic effect on the molecular properties, making it more or less selective, increasing its efficacy, or making it easier to administer. For that reason, both substituents have become of great importance in drug discovery and medicinal research.

2. METHODOLOGY

The π-electron donor−acceptor index (pEDA) is calculated by summing the π-electron orbital occupations of a ring or other planar set of selected atoms and then subtracting a certain value that can be (i) the nominal number of π electrons, which is usually equal to the number of π-electron-donating atoms in the studied π system, (ii) the number 6, corresponding to an electronic sextet, or (iii) the orbital occupation of an unsubstituted system, as in the original paper. In this work, Oziminski's approach is used.[42] The pEDA obtained in this way measures the π-electron excess or deficiency at the studied atoms. The pEDA in this work is defined according to the formula described by eq 2:

$$p\mathrm{EDA} = \sum_{i=1}^{n} \pi_i^{\mathrm{subst}} - \sum_{i=1}^{n} \pi_i^{\mathrm{unsubst}} \qquad (2)$$

where π_i is the $2p_z$ natural atomic orbital of the ith atom of the studied π-electron system and n is the number of atoms in the π system. The z axis is assumed to be perpendicular to the ring.

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

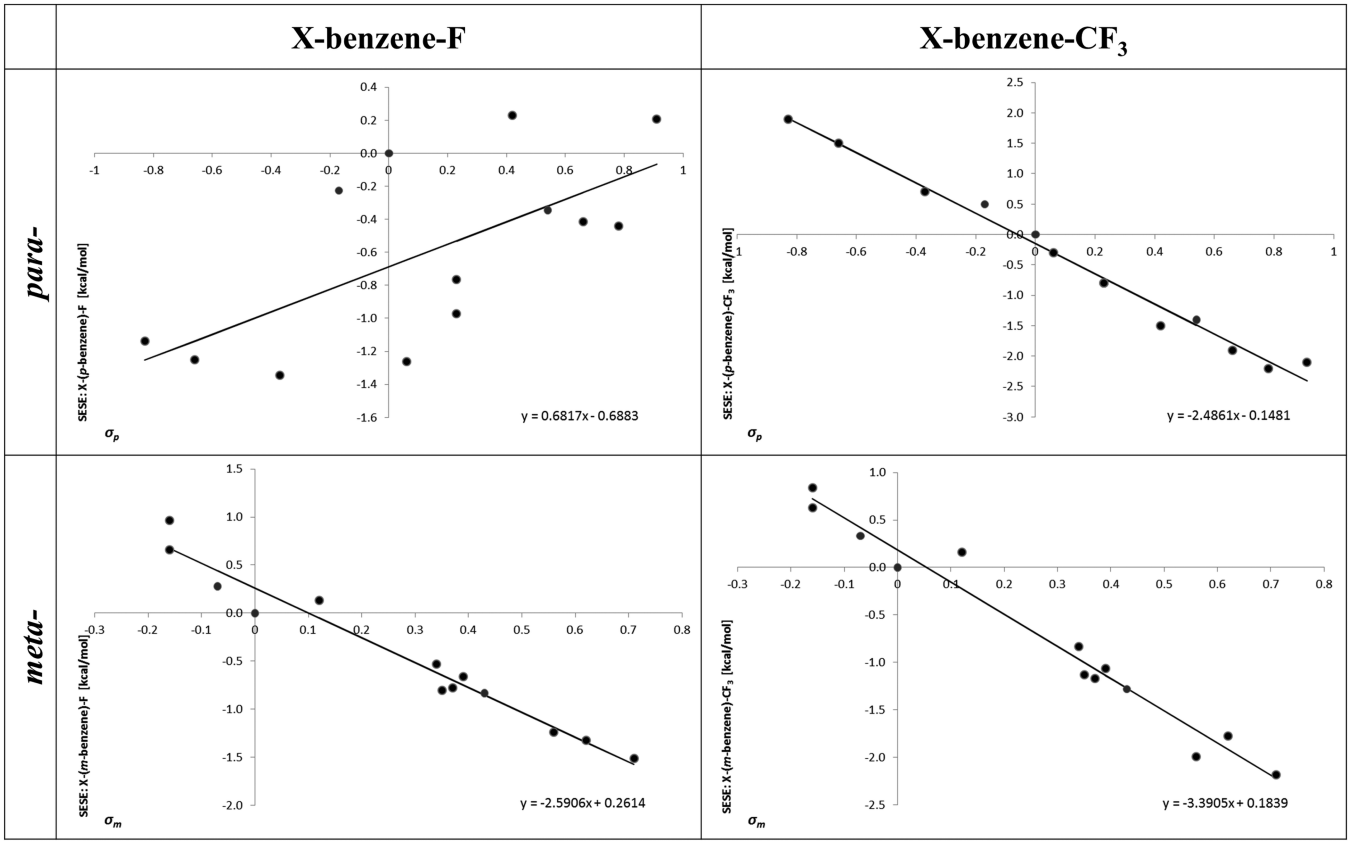


Figure 1. Dependences of SESE values for *para*- and *meta*-substituted fluoro- and trifluoromethylbenzene derivatives on the Hammett substituent constants σ_p and σ_m, respectively.

A similar procedure is undertaken in regard to σ-electron systems, and the appropriate index is called the σ electron donor−acceptor index (*s*EDA), given by eq 3:

$$sEDA = \sum_{i=1}^{n} \sigma_i^{subst} - \sum_{i=1}^{n} \sigma_i^{unsubst} \quad (3)$$

As a geometric criterion of aromaticity, the harmonic oscillator model of aromaticity (HOMA) index[83] was used. It is defined as a normalized sum of squared deviations of bond lengths from the values for a system that is assumed to be fully aromatic. For hydrocarbons, the appropriate expression in given by eq 4:

$$HOMA = 1 - \frac{\alpha}{n} \sum_{i=1}^{n} (R_{opt} - R_i)^2 \quad (4)$$

where n is the number of C−C bonds taken into consideration; α = 257.7 is an empirical normalization constant chosen to give HOMA = 0 for a completely nonaromatic system and HOMA = 1 for a system where all of the bonds are equal to R_{opt} = 1.388 Å, which is the optimal aromatic bond length; and the R_i are the experimental or computed bond lengths.

The charge of the substituent active region (cSAR) parameter[34,35] was calculated by summing the natural population analysis (NPA) charges of atoms belonging to the substituent X and the *ipso* carbon atom to which the substituent is connected (eq 5):

$$cSAR = q(X) + q(C_{ipso}) \quad (5)$$

In the case of substituted systems, the energetics of homodesmotic reactions are formulated according to known approaches.[37,38,40] Within this approach, homodesmotic reactions are considered as a measure of the substituent effects, which are sometimes expected to correlate to the Hammett substituent constants. The nonadditive energy of such reactions may be named the substituent effect stabilization energy (SESE). The greater the SESE value, the higher the stabilization energy due to the substituent effect. For a homodesmotic reaction,

$$X{-}R{-}Y + R \rightarrow R{-}X + R{-}Y \quad (6)$$

the SESE is calculated as follows:

$$SESE = E(R{-}X) + E(R{-}Y) - E(X{-}R{-}Y) - E(R) \quad (7)$$

In this model, the SESE describes the energy effect of the interaction between the substituent X and the reaction site (i.e., the probe group) Y, while R serves as a transmitting moiety. In our case, Y is F or CF_3 while R is a 1,2-disubstituted ethene or a *para*- or *meta*-disubstituted benzene.

In order to find the optimal level of theory to calculate SESE values as well as *p*EDA and *s*EDA values, the calculations for 1,2-disubstituted ethenes were carried out at six different levels of theory based on three methods (MP2,[84] B3LYP,[85,86] and M06[87]) with two basis sets each (cc-pVDZ and aug-cc-pVTZ)[88] using the Gaussian 03 program.[89] Additionally, for the calculation of *s*EDA and *p*EDA, the B3LYP/6-31G(d,p) method was applied (Tables S1−S3 and S6−S11 in the Supporting Information). The vibrational frequencies were calculated at the same level of theory, and then their positivity was applied to confirm that each of the calculated structures corresponds to a minimum on the potential energy surface. Several conformations of branched substituents were calculated with the aim of choosing the global minimum-energy structure, for which further analyses were performed. A comparison of the results from these six methods was performed using linear regression analysis with the ab initio MP2/aug-cc-pVTZ method as the reference (Tables S4 and S12). On the basis of these results, considering accuracy, sensitivity, and computational cost, two methods (MP2/cc-pVDZ and M06/cc-pVDZ) were chosen for further calculations on *para*- or *meta*-disubstituted benzenes. Finally, correlations between SESE and Hammett substituent

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

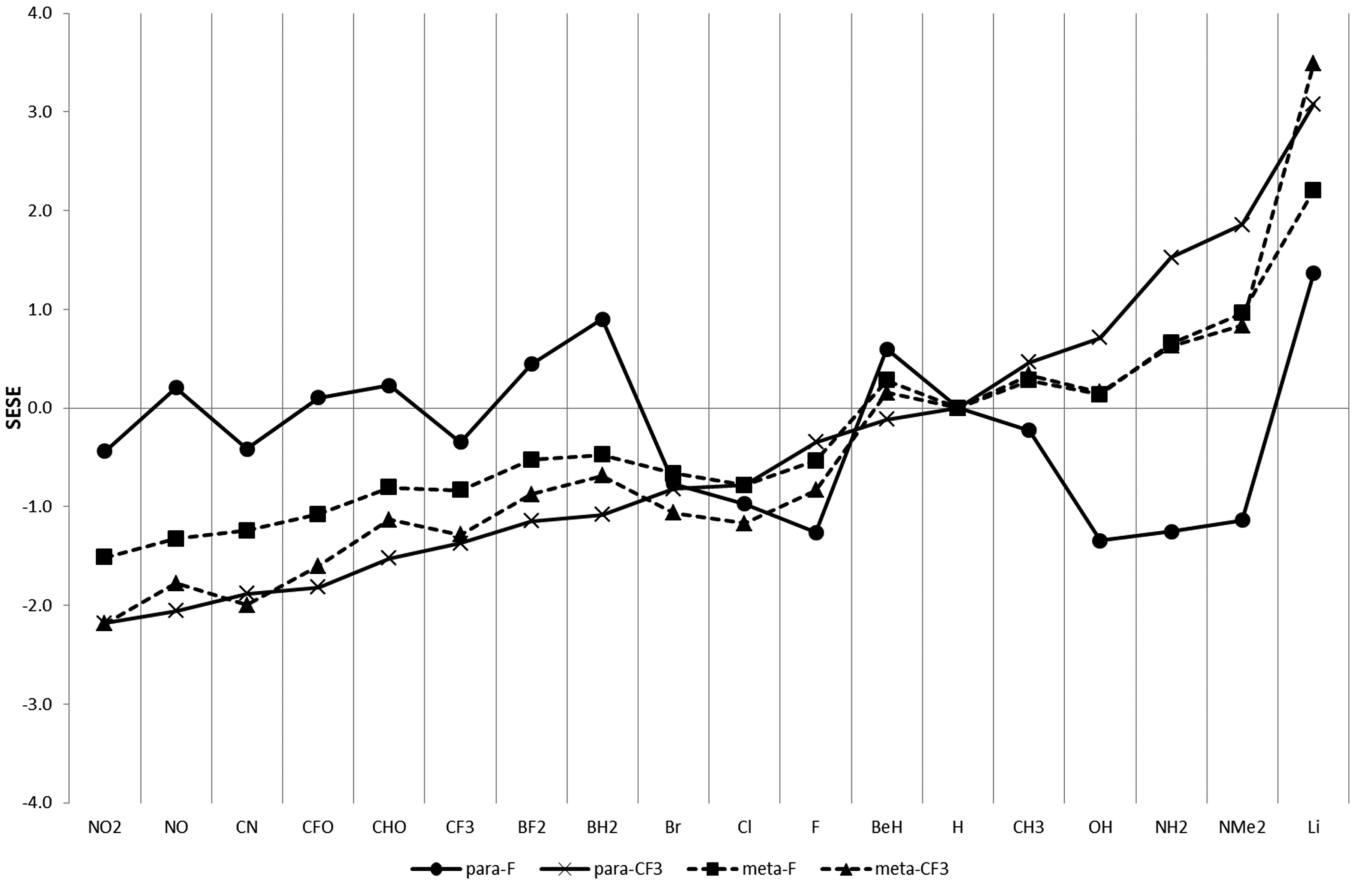


Figure 2. Comparison of SESE values for homodesmotic reactions for *para*- and *meta*-substituted derivatives of benzene.

constants were tested. All of the results presented in this paper were obtained using the M06/cc-pVDZ method.

3. RESULTS AND DISCUSSION

Hammett substituent constants have been determined for both title substituents (F and CF_3),[10,50,90] but their values are somehow inconsistent. Moreover, it is known that the substituent constants may vary substantially depending on the type of intramolecular interaction with the substituted moiety.[3,7−10,14,17,18] To clarify this situation and to look from a wider perspective, various physical approaches to SE on F and CF_3 groups have been studied. Thus, in this study they are considered as fixed groups, and the effect of many varying substituents on them is the subject of our investigation. In other words, the question is how intramolecular interactions coming from various substituents influence the properties of F and CF_3 groups. For clarity, the data resulting from different physical approaches will be presented as separate subsections.

3.1. Homodesmotic Reactions: Global Description of the Effectiveness of the Substituent Effect by Substituent Effect Stabilization Energy (SESE). The SESE approach allows the determination of a global energetic description of all kinds of interactions between two substituents present in a given molecule. The data discussed here are collected in Table S1, whereas Figure 1 presents linear dependences of SESE values for *para*- and *meta*-substituted fluoro- and trifluoromethylbenzene derivatives on the Hammett substituent constants σ_p and σ_m, respectively. A similar picture is shown in Figure S1 in the Supporting Information, where the dependences of SESE values for *trans*-substituted derivatives of fluoro- and trifluoromethylethene on σ_p and σ_m are presented.

Except for the regression of SESE versus σ_p for *p*-fluorobenzene derivatives, which is not acceptable [correlation coefficient (cc) = 0.651], all of the other ones are excellent (the worst linear correlation has cc = −0.982). This may be interpreted that in all three remaining cases, the blend of resonance/inductive/field contributions to the overall substituent effect strongly resemble phenomena that are observed in the reference reaction, namely, acid−base equilibria of *para*- and *meta*-substituted benzoic acid derivatives. Interestingly, the sensitivity parameter (the absolute value of the slope) is the highest for *m*-trifluoromethyl derivatives, whereas that for F derivatives is much smaller. Application of other substituent constants, as σ^+, σ^-, or their combinations with the original Hammett constants does not improve the correlations. Similar dependences of SESE for 2-substituted 1-fluoro- and 1-trifluoromethylethene derivatives in the *trans* configuration on σ_p and σ_m are observed (see Figure S1). The question is, why does only the regression of SESE for *para*-substituted fluorobenzenes not show a correlation with Hammett's σ_p? To some extent this may be explained by a very low range of SESE values for the analyzed *para*-substituted fluorobenzenes: ΔSESE = 1.5 kcal/mol for this series of molecules, whereas for other series these ranges are much greater, between 2.5 kcal/mol for *m*-fluorobenzene derivatives and 4.1 kcal for *p*-trifluorobenzene derivatives. Additionally, it seems that the blend of resonance/inductive/field contributions to the overall substituent effect may be different in *p*-fluorobenzene derivatives and in Hammett's reference reaction. It is known

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

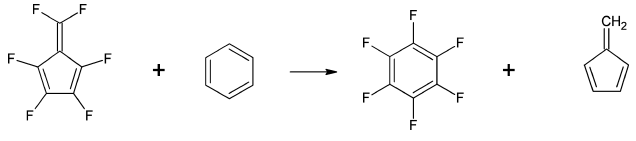
that for fluorine the substituent constants for interactions with electron-donating and electron-attracting reaction sites are very low (σ^+ = −0.07 and σ^- = −0.03, respectively).[10] These constants show that resonance interactions of fluorine with such substituents as NO_2 and NH_2 are rather weak. Thus, for SESE values, not the electron-dependent interactions (via the resonance effect) but rather the dipole−dipole interactions may be of greater importance. Qualitatively, when the dipole vectors are parallel with the same direction, then the system is more stabilized than when the vectors are in opposite directions. Thus, the balance between resonance/inductive/field effects in *para*-substituted fluorobenzenes may be different in SESE values than for dissociation constants of *para*-substituted benzoic acids.

The application of SESE for *meta*- and *para*-substituted fluoro- and trifluoromethylbenzene derivatives allows a question to arise: what are the relations between these data? The graph in Figure 2 presents the data for homodesmotic reactions for *para*- and *meta*-substituted derivatives of benzene. The data for the two *meta* systems (dashed lines) exhibit a substantial similarity, with differences always smaller than 1 kcal/mol. For the *para* series, much greater discrepancies are observed, amounting up to 3 kcal/mol. The latter appear mostly for substituents with either a strongly π-electron-donating or -accepting ability. Here the difference between the fluorine and trifluoromethyl groups plays the most important role, allowing an evaluation of the "π-electron activity" of substituents. For electron-attracting substituents, the SESE values in the fluorine series are close to zero, whereas for the CF_3 series they are between −2 and −1.

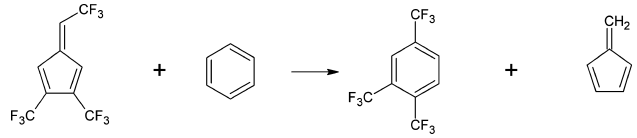
Contrary to this, for π-electron-donating substituents the SESE values for the CF_3 and *meta*-F series are positive between 0 and 2, while those for the *para*-F series are negative in the range −2 to −1. This is due to destabilization via resonance from the lone pair of the fluorine at the *para* position. In short, discounting the case of *p*-fluorinated derivatives, decreasing the electron-accepting power leads to an increase of stabilization of susbtituent interactions, as shown by the almost monotonic increase of the line for the CF_3 (and *meta*-F) series. Opposite to this, in the *para*-F series no regularity is observed, except that clear destabilization has been found for electron-donating substituents (OH, NH_2, and NMe_2). It should be noted that substantial deviations for *p*-fluoro derivatives are observed for electron-deficient groups (BF_2, BH_2, BeH, and Li), which are not typical organic substituents and were taken into account for a more general view. If these points are excluded, the dependence of SESE on the kind of substituents in Figure 2 would be almost monotonic with a negative slope. Approximately this means that the more electron-donating the substituent, the less stable is the *p*-fluorobenzene derivative.

3.2. Homodesmotic Reactions and the *p*EDA/*s*EDA Approach Applied to the Effect of Substitution of Fulvene and Benzene by F and CF_3. The application of homodesmotic reactions (Schemes 1−3) to fluoro and trifluoromethyl derivatives of fulvene and their benzene analogues allows an estimation of the thermodynamics of these kinds of reactions, whereas values of *p*EDA and *s*EDA describe the direction of π and σ electron transfer, respectively, for these reactions. In all cases, the ΔH values for the homodesmotic reactions were calculated by subtracting the enthalpies of the substrates from the enthalpies of the products. Table 2 presents the *p*EDA and *s*EDA data along with the HOMA values.[83]

Scheme 1. Homodesmotic Reaction of Hexafluorofulvene and Benzene (ΔH = 12.0 kcal/mol)



Scheme 2. Homodesmotic Reaction of 3,4,6-Tris(trifluoromethyl)fulvene and Benzene (ΔH = 2.2 kcal/mol)



Scheme 3. Homodesmotic Reaction of 3,4,6-Trifluorofulvene and Benzene (ΔH = 0.8 kcal/mol)

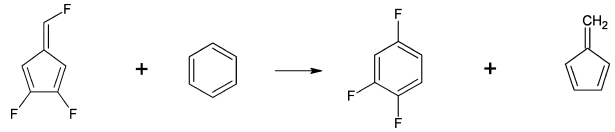


Table 2. HOMA, *s*EDA, and *p*EDA Values for Molecules Involved in the Homodesmotic Reactions in Schemes 1−3

	HOMA	*s*EDA	*p*EDA
hexafluorofulvene	0.0548	−2.5961	0.4794
3,4,6-trifluorofulvene	0.0375	−1.2879	0.2422
3,4,6-tris(trifluoromethyl)fulvene	−0.2055	−0.2597	−0.0616
fulvene	−0.1399	0.0000	0.0000
hexafluorobenzene	0.9990	−3.8840	0.4286
1,2,4-trifluorobenzene	0.9970	−1.9256	0.2181
1,2,4-tris(trifluoromethyl)benzene	0.9805	−0.3466	−0.0452
benzene	0.9936	0.0000	0.0000

In all cases, the fluorinated systems exhibit slightly higher aromaticities in comparison with their parent compounds, whereas derivatives substituted with CF_3 exhibit the change in the opposite direction. The effect of an increase in the aromaticity by π donors (and the other way around for π acceptors) is more pronounced for fulvenes,[91] which are largely affected by substitution. The aromaticity of benzene has been already confirmed to be highly robust, in contrast to, for example, imidazole and pyrazole.[92] This finding reflects well the tendency of benzene to retain its initial aromatic π-electron structure during the course of reactions leading to aromatic substitution.[93] The parameter *s*EDA, which describes the withdrawal of σ electrons from the systems in question, is higher (in its absolute value) for both F and CF_3 derivatives of benzene than for the fulvene derivatives. The opposite direction of changes is found for *p*EDA, indicating that the fulvene moiety is a stronger acceptor of π electrons for both F and CF_3 substituents. An unexpected result is found for *p*EDA: charge transfer from fluorine atoms toward the π-electron system of benzene (*p*EDA = 0.4286) is only slightly smaller than that for fulvene (*p*EDA = 0.4794), although fulvene is well-known as a strong π-electron acceptor.[44,94] On the other hand, the strong π-electron-withdrawing ability of fulvene is shown by a large

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

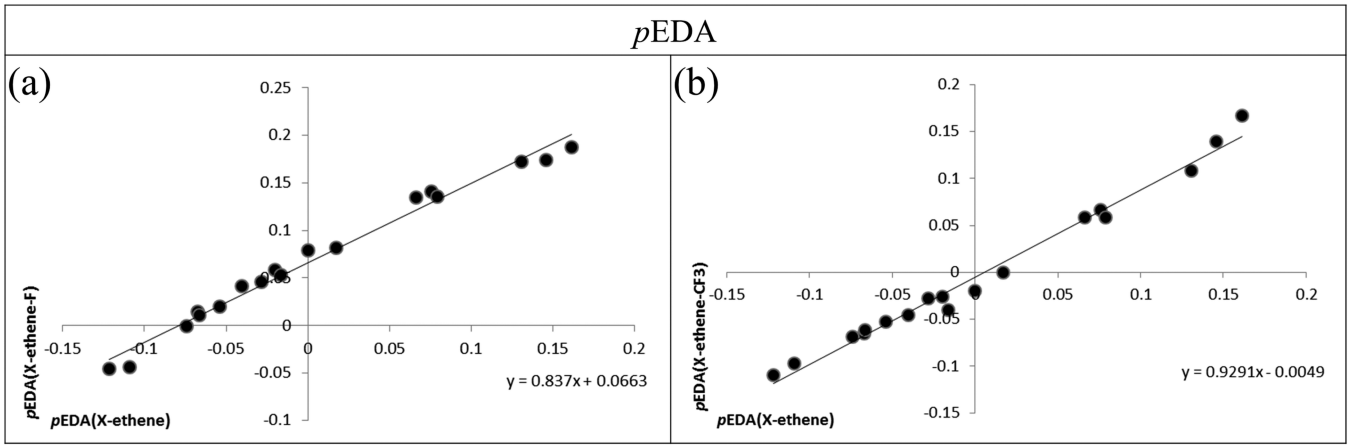


Figure 3. Dependences of *p*EDA for (a) F−R−X (cc = 0.992) and (b) CF_3−R−X (cc = 0.992) on the data for H−R−X, where R stands for the ethene moiety.

stabilization effect for perfluorinated fulvene in Scheme 1 (ΔH = 12.0 kcal/mol). Interestingly, for the other two cases (Schemes 2 and 3), the F- and CF_3-substituted fulvene derivatives are much less stabilized.

3.3. *p*EDA and *s*EDA Approach for 1,2-Substituted Ethenes and *Meta*- and *Para*-Substituted Benzenes). The *p*EDA and *s*EDA characteristics describe changes in π and σ orbital occupation in a given fragment of the molecule. Figure 3 presents the dependences of *p*EDA and *s*EDA of Y−R−X systems on the data for the H−R−X systems, where Y is either F or CF_3 and R stands for the ethene or benzene moiety. The questions are the following: Does the presence of F or CF_3 as a fixed group affect the σ and π electron structures of the substituted moieties in comparison with the systems without them? Is there any difference between the F and CF_3 reaction series?

In the cases of *s*EDA(X−ethene−F) and *s*EDA(X−ethene−CF_3) plotted against *s*EDA(X−ethene), the correlations are excellent, with cc values better than 0.999 in both cases and almost identical slopes slightly greater than 1.0 (1.022 and 1.014, respectively; see Figure S2). Contrary to this, for *p*EDA(X−ethene−F) and *p*EDA(X−ethene−CF_3) plotted against *p*EDA(X−ethene), the correlation is also very good (cc > 0.96) but the slopes are different: 0.84 for *p*EDA(X−ethene−F) and 0.93 for *p*EDA(X−ethene−CF_3). This indicates that in both cases F and CF_3 make it more difficult for the π-electron structure of ethene to transfer the substituent effect. Moreover, fluorine as a fixed group in substituted ethene derivatives makes the communication with the substituent weaker than for the CF_3 group. Figure 3 illustrates these relations.

Another way of analyzing substituent effects on the variation of *p*EDA values is a study of their dependences on substituent constants. As expected and shown in Figure 4, an increase in the electron-accepting power of the substituent (i.e., an increasing in the σ value), causes a smaller value of *p*EDA. The slopes in the regressions shown in Figure 4 and in Figures S3 and S4 are weakly differentiated, but one observation is important: the sensitivity of the π-electron structure of the ethene moiety to substituent effects is the highest in the ethene−X series (slope = −0.114) in comparison with the F−ethene−X and CF_3−ethene−X series (with slopes of −0.095 and −0.107, respectively). This means that the mobility of the π-electron structure is weakened by F and CF_3 in comparison

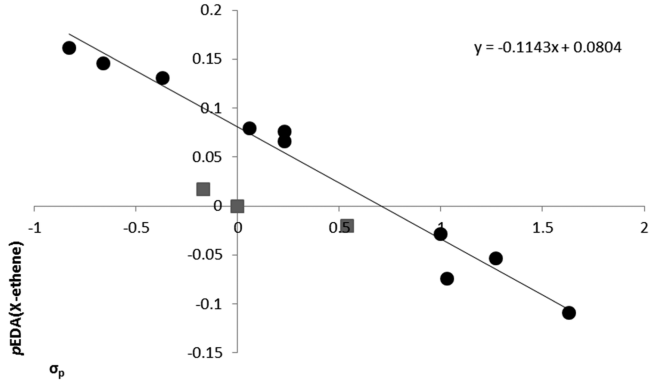


Figure 4. *p*EDA(X−ethene) vs Hammett σ_p (σ_p^- for electron-withdrawing CHO, CN, NO, and NO_2). Gray squares (H, CH_3, and CF_3) were not included in the correlation (cc = −0.985).

with monosubstituted ethene derivatives. An interesting finding was that in all three cases substituents without π electrons (H, CH_3, and CF_3) did not follow good correlations, and they were excluded from the regressions.

In all three regressions (Figure 4 and Figures S3 and S4), for π-electron-donating substituents (Br, Cl, F, NH_2, NMe_2, and OH) and the non-π ones (H, CH_3, and CF_3) the traditional Hammett σ_p constants were successfully applied, but for π-electron-attracting substituents (CHO, CN, NO, and NO_2) the σ_p^- constants were applied. In all three cases the slope has a negative value, exhibiting decreasing sensitivity to the substituent effect (absolute value of the slope) in the sequence ethene−X > CF_3−ethene−X > F−ethene−X. Again it results that the fixed group Y (F or CF_3) decreases the mobility of the π-electron structure as a result of transmission of the substituent effect from X through the ethene moiety to Y.

Similar analyses carried out for *para*, *meta*, and mono-substituted benzene derivatives lead to similar results. The only difference is that the range in values of changes in the slopes is 0.02 for ethenes, whereas for benzene derivatives it is smaller, equal to 0.008. This observation may be explained by a longer distance between fixed groups in benzene derivatives: three or two bonds for the *para* and *meta* positions, respectively, in comparison with only one bond in ethene. Interestingly, for *para* derivatives the difference is only 0.001, whereas for *meta* derivatives it is 0.004. Figure 5 presents an example of these similar regressions, whereas all of other ones are shown in the

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

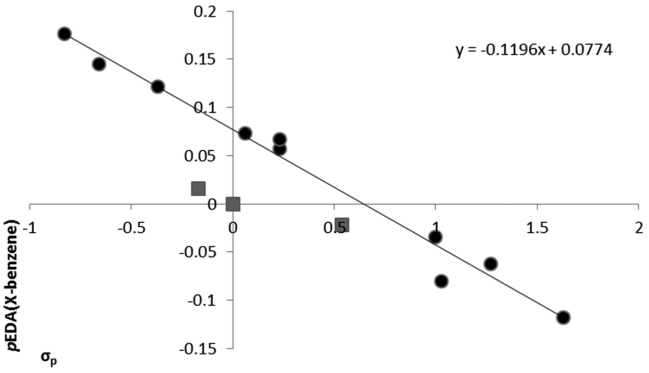


Figure 5. *p*EDA(X−benzene) vs Hammett σ_p (σ_p^- for electron-withdrawing CHO, CN, NO, and NO_2). Gray squares (H, CH_3, and CF_3) were excluded from the regression (cc = −0.990). All of the numerical data are collected in Tables S5 and S6.

Supporting Information (Figures S5−S8). An interesting finding is that for monosubstituted benzenes and *meta*- and *para*-substituted derivatives of fluoro- and trifluoromethylbenzene, the differences in slopes are very small, indicating rather weak effects of the fixed groups and the π-electron structure of the ring.

In all of the regressions (Figures 4 and 5 and Figures S3−S8), substituents that do not contain $2p_z$ electrons, and hence have no possibility for any resonance effects with the fixed groups, are clearly outliers.

3.4. Application of the cSAR Model: The Concept of Direct and Indirect Substituent Effects. It is well-known that substituent constants for the *para* position (σ_p) estimated using Hammett's reference reaction (benzoic acid dissociation)[1] differ from those estimated using, for example, substituted phenol derivatives (σ_p^-)[3] or kinetic data for solvolysis of dimethylphenylcarbinyl chlorides (σ_p^+)[5] (or other kinds of substituent constants).[10] This effect of the change of the characteristics of the substituent ability to attract or donate electrons depends on the nature of reaction site or, more generally, on the kind of moiety to which the substituent is attached. It may be considered as an *indirect* substituent effect. This differs from the *direct* substituent effect, a term which is dedicated to the influence of the substituent on the reaction site. Both the indirect and direct substituent effects may be nicely investigated by means of the cSAR model.

By definition, cSAR(X) and cSAR(Y) are numerical characteristics of the electronic states of X and Y, respectively. It is important to mention that cSAR(X) parameters are also known as good characteristics of the substituent effect correlated with the Hammett substituent constants for X.[34−36] Moreover, it was found for X−R−Y systems, where X is a varying substituent, Y is the fixed one, and R is the transmitting moiety, that there are excellent correlations of the type cSAR(Y) versus geometric parameters of Y [e.g., C_{ipso}−N bonds vs cSAR(NO) in *para*-substituted derivatives of nitrosobenzene or C_{ipso}−N bonds vs cSAR(NMe_2) in *para*-substituted derivatives of *N*,*N*-dimethylaniline].[9S] The idea presented here is to show how cSAR(X) and cSAR(Y) depend on the Hammett σ and further how they are *mutually dependent on each other*. It is important to stress that both quantities [cSAR(X) and cSAR(Y)] are on the same scale of magnitude.

As shown in Figures 6 and 7, there is good communication between the substituents (X) and the fixed group (Y = F or CF_3), expressed by linear regressions with high correlation

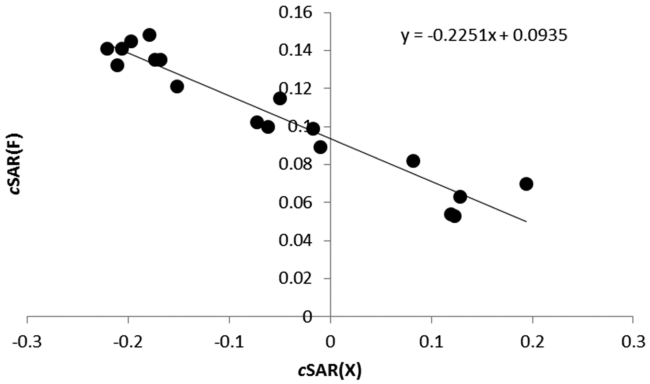


Figure 6. Dependence of cSAR(F) on cSAR(X) for X−benzene−F (cc = −0.958).

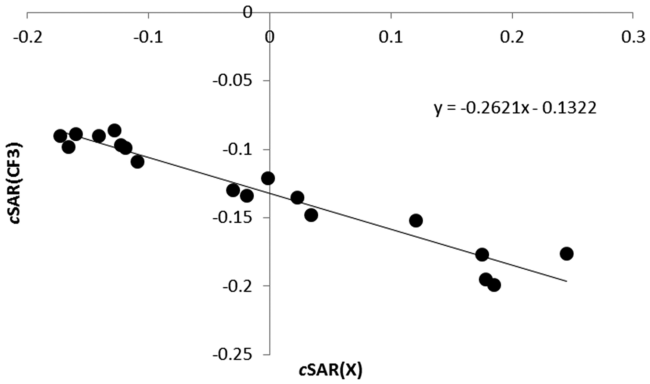


Figure 7. Dependence of cSAR(CF_3) on cSAR(X) for X−benzene−CF_3 (cc = −0.964).

coefficients (cc = −0.958 or −0.964, respectively). The slopes are slightly different, indicating slightly stronger intramolecular interactions in the CF_3 series. Direct comparison of σ_p for CF_3 and F (0.54 and 0.06, respectively) indicates that interactions with CF_3 may be significantly stronger, hence giving a steeper slope for the regression.

In order to compare the above regressions with those in which the fixed groups strongly interact with the substituents, two additional series were considered: *para*-substituted derivatives of nitrosobenzene and *para*-substituted derivatives of *N*,*N*-dimethylaniline. It can be seen from the regressions in Figures 8 and 9 that the correlations are very good (cc =

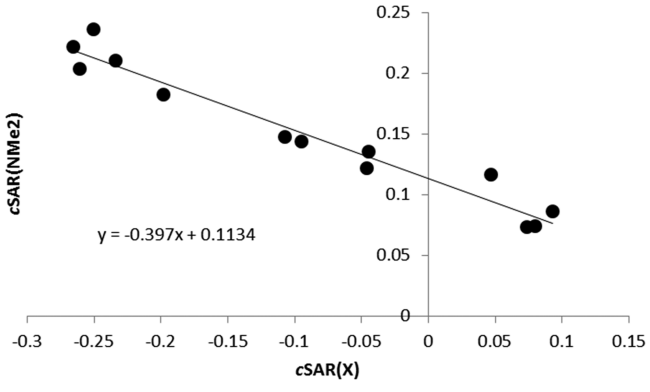


Figure 8. Dependence of cSAR(NMe_2) on cSAR(X) for X−benzene−NMe_2 (cc = −0.976).

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

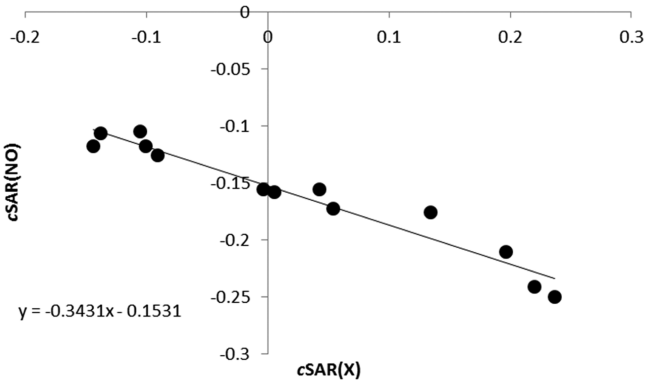


Figure 9. Dependence of cSAR(NO) on cSAR(X) for X−benzene−NO (cc = −0.971).

−0.976 and −0.971, respectively) and that the slopes (−0.397 and −0.343, respectively) are much greater than those observed for F and CF_3 derivatives. This indicates that linear regressions representing indirect substituent effects are of high precision and that this kind of procedure may be applied also in other systems, taking the *para*-substituted derivatives of benzene as a reference. In this way, studying unknown situations would allow approximate but only qualitative information about interactions between some fixed group and substituents to be found.

Table 3 and Figures 10 and S9−S11 show the dependences of cSAR(Y) and cSAR(X) on Hammett σ for fluorobenzene

Table 3. Dependences of cSAR(X) and cSAR(Y) on the Hammett Substituent Constants

X−C_6H_4−Y	cSAR correlated	slope	intercept	cc
X−C_6H_4−F	cSAR(X)	−0.1558	0.0088	−0.940
X−C_6H_4−F	cSAR(F)	−0.0419	0.0895	−0.979
X−C_6H_4−CF_3	cSAR(X)	−0.1586	0.0399	−0.935
X−C_6H_4−CF_3	cSAR(CF_3)	−0.0490	−0.1491	−0.965

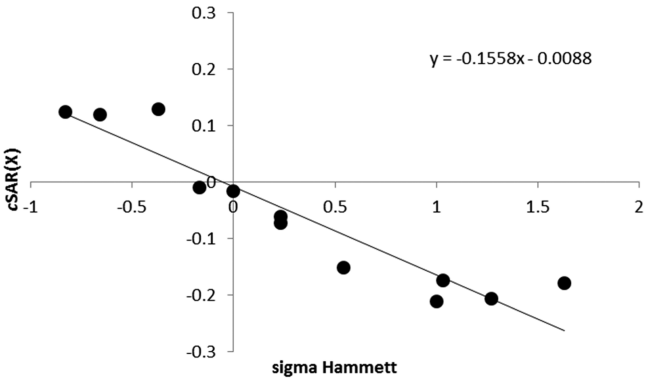


Figure 10. Dependence of cSAR(X) on Hammett σ (cc = −0.940).

derivatives and for trifluoromethylbenzene derivatives. It follows that not only cSAR(X) correlates well with the Hammett constants, as it was found by Sadlej-Sosnowska,[34,35] but also cSAR(Y) does. This in turn requires the existence of dependences shown earlier of cSAR(Y) on cSAR(X), being an illustration of indirect substituent effect. All data presented as illustration in Figures, are collected in Table S4 and S5 (Supporting Information).

3.5. Geometry-Based Analyses. Figure 11 presents the dependences of the C−F and C−CF_3 bond lengths on the Hammett substituent constants for *meta*- and *para*-substituted fluorobenzene and trifluoromethylbenzene derivatives. In this case, analysis of the slopes is very suggestive. For both the *meta*- and *para*-substituted fluorobenzene derivative series, the slopes have negative values and the correlations are good (cc = −0.986 and −0.980, respectively). This indicates that the increase in electron-attracting power of the substituent causes a shortening of the bond length. It is well-known that electron-withdrawing groups (EWGs), particularly those at the position *para* to a moiety possessing an atom Y with a lone pair (e.g., hydroxyl or fluorine), tend to decrease the C−Y bond length on the basis of standard resonance arguments.[96] For *meta*-substituted species, the strength of the interaction is weaker since resonance similar to that for *para*-substituted ones requires doubly excited resonance structures.[97] This mechanism causes the bond CF to become "more double" in character as a result of the resonance effect from F toward the C−F bond (see Figure 12).

In the case of the CF_3 series, there is another mechanism of interaction. Again, the correlation for the *para*-substituted series is also of good quality (cc = 0.984) but has a positive slope. This indicates that the stronger the electron-accepting power of the substituent, the longer is the C−CF_3 bond. For *meta*-substituted derivatives the correlation is worse (cc = 0.879), but the slope is still positive. Despite the fact that the electron-withdrawing substituents can make bonds longer by weakening them, these results can also be rationalized by a simple electrostatic model.[98,99] The three fluorine atoms in CF_3 cause the carbon atom to carry a high positive net charge. If another substituent at the *para* or *meta* position is electron-withdrawing, this makes the benzene ring partially positive. As a result, the charges at the two "neighboring" carbon atoms at C_{ipso} and C in the CF_3 group become of the same sign, and hence, the bond will lengthen as a result of their classical electrostatic interaction, as shown in Figure 12. All of the detailed data are given in Table S15.

4. CONCLUSIONS

We have introduced a few quantum-chemical models for the interpretation of the substituent effect acting on a F or CF_3 group attatched to an ethene or benzene moiety. The observed linear relationships between the results of these models confirm an assumption that various physical presentations of the substituent effects are mutually related, indicating a deeper common reason for these phenomena. Our studies allowed us to come to the following conclusions:

(1) Global estimations of the substituent effects on F and CF_3 groups in *para*- and *meta*-substituted derivatives of benzene represented by homodesmotic reactions (eq 6) and SESE values (eq 7) correlate well with Hammett's σ_p (the worst cc was −0.982). However, in case of *p*-fluorobenzene derivatives no correlation is observed (cc = 0.651). This means that the interactions between substituents and fluorine in this case differ significantly from those in *para*-substituted benzoic acids.

(2) In all cases, substitution of fulvene with F atoms increases its aromaticity; contrary to that, CF_3 causes a decrease in aromaticity. The same trend is true for benzene derivatives. Additionally, for both F and CF_3 derivatives, benzene is a stronger acceptor of σ electrons than fulvene.

dx.doi.org/10.1021/jo501013p | J. Org. Chem. 2014, 79, 7321−7331

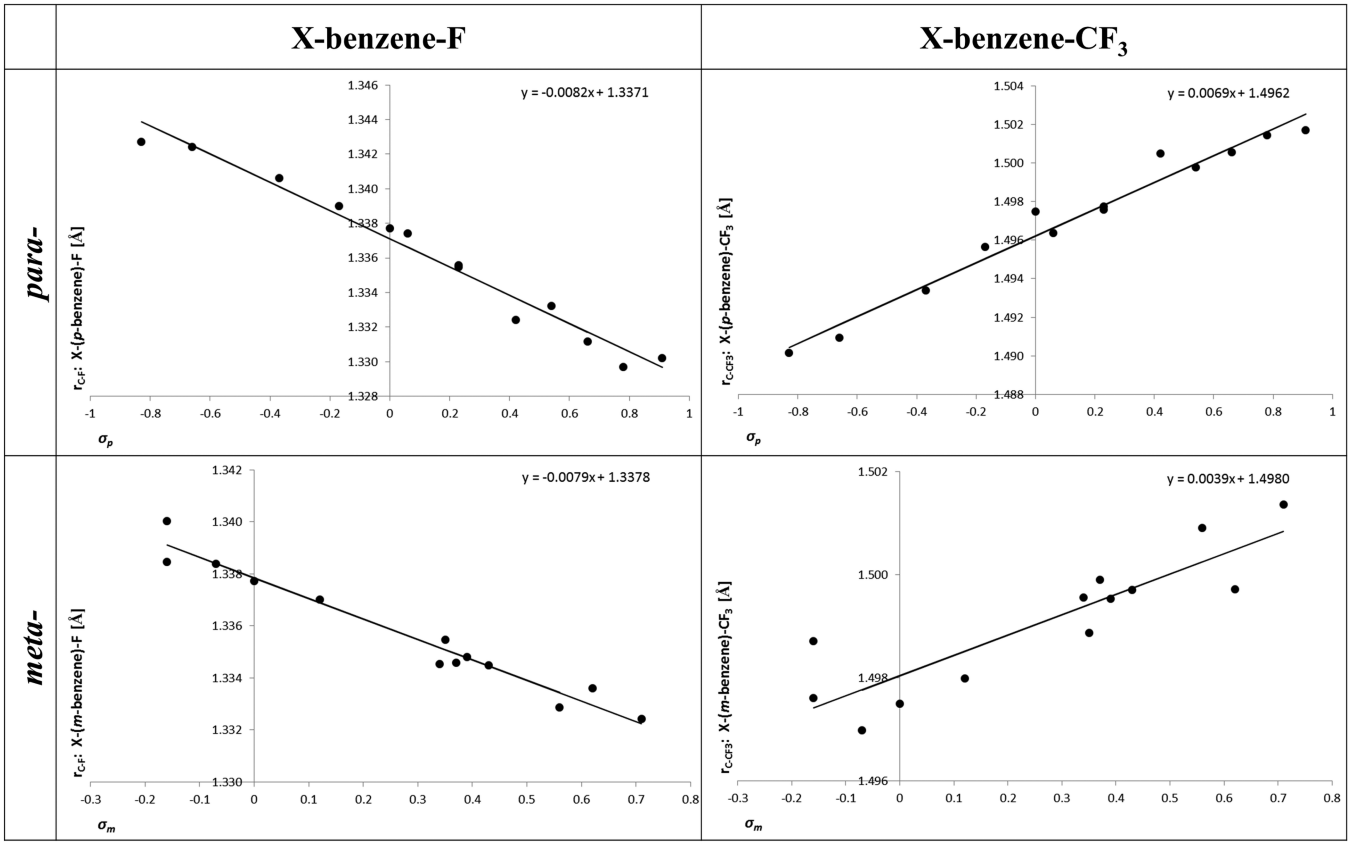


Figure 11. Dependences of C−F and C−CF_3 bond lengths on Hammett substituent constants for the *meta* and *para* positions.

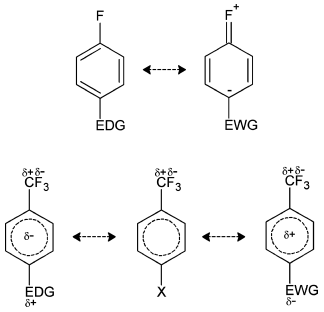


Figure 12. Scheme of the mechanism of substituent effects on −F and −CF_3 groups with an electron-donating group (EDG) or electron-withdrawing group (EWG).

(3) Application of the concept of the charge in substituent active region (cSAR) in X−R−Y-type molecules (where X is a varying substituent, Y is the so-called reaction site or a fixed group, and R is the transmitting moiety) allows the definition of two kinds of substituent effects: (i) the *direct* substituent effect, which describes the dependence of cSAR(Y) on the nature of the substituent X and is given by a linear regression of cSAR(Y) on cSAR(X), and (ii) the *indirect* substituent effect, which describes the dependence of cSAR(X) on the type of substituted moiety RY to which X is attached and is given by a linear regression of cSAR(X) on cSAR(Y) for various groups Y. This allows for a wider view of a variety of substituent constants dependent on the kind of reaction series taken into consideration. It is important to note that the parameters cSAR(X) and cSAR(Y) are quantitatively expressed on the same scale of magnitude.

(4) Plots of the C−F and C−CF_3 bond lengths against Hammett's σ constants showed that electron-attracting substituents make C−F bonds shorter via resonance effect from fluorine and C−CF_3 bonds longer as a result of the withdrawing effect and repulsive electrostatic interactions.

■ ASSOCIATED CONTENT

Supporting Information

Results obtained at the MP2/cc-pVDZ, MP2/aug-cc-pVTZ, B3LYP/cc-pVDZ, B3LYP/aug-cc-pVTZ, and M06/aug-cc-pVTZ levels of theory; results obtained for 1-fluoro- and 1-trifluoromethyl-2-substituted *trans*-ethenes; comparison of methods used for SESE and *s*EDA/*p*EDA calculations; and coordinates of discussed structures optimized using the M06/cc-pVDZ method. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tsiodla@amu.edu.pl.
*E-mail: tmkryg@chem.uw.edu.pl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Computational Grant G36-9 from the Interdisciplinary Centre for Mathematical and Computational Modelling at Warsaw University (ICM UW) is gratefully acknowledged. This

research was also supported in part by PL-Grid infrastructure. T.M.K. acknowledges the financial support from the National Science Centre of Poland (Grant UMO-2013/11/B/ST4/00531).

DEDICATION

This article is dedicated to our friend Professor Günter Häfelinger from the University of Tübingen.

REFERENCES

(1) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.
(2) Hammett, L. P. *Physical Organic Chemistry*, 1st ed.; McGraw-Hill: New York, 1940; p 194.
(3) Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.
(4) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1.
(5) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.
(6) Dewar, M. J. S.; Grisdale, P. J. *J. Am. Chem. Soc.* **1962**, *84*, 3539.
(7) Exner, O. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds; Plenum Press: London, 1972; Chapter 1, p 1.
(8) Johnson, C. D. *The Hammett Equation*; Cambridge University Press: Cambridge, U.K., 1973.
(9) Shorter, J., In *Similarity Models in Organic Chemistry, Biochemistry and Related Fields*; Zalewski, R. I., Krygowski, T. M., Shorter, J., Eds.; Elsevier: Amsterdam, 1991; Chapter 2, p 77.
(10) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(11) Dewar, M. J. S.; Grisdale, P. J. *J. Am. Chem. Soc.* **1962**, *84*, 3545.
(12) Ehrenson, S. *Prog. Phys. Org. Chem.* **1964**, *2*, 195.
(13) Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506.
(14) Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1.
(15) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(16) Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 125.
(17) Krygowski, T. M.; Stępień, B. T. *Chem. Rev.* **2005**, *105*, 3482.
(18) Exner, O.; Bohm, S. *Curr. Org. Chem.* **2006**, *10*, 763.
(19) Galabov, B.; Ilieva, S.; Schaefer, H. F., III. *J. Org. Chem.* **2006**, *71*, 6382.
(20) Galabov, B.; Ilieva, S.; Hadijeva, B.; Atanasov, Y.; Schaefer, H. F., III. *J. Phys. Chem. A* **2008**, *112*, 6700.
(21) Cheshmedzhieva, D.; Ilieva, S.; Galabov, B. *J. Mol. Struct.* **2010**, *976*, 427.
(22) Sadlej-Sosnowska, N. *J. Phys. Chem. A* **2007**, *111*, 11134.
(23) Galabov, B.; Nikolaeva, V.; Ilieva, S. *Chem.—Eur. J.* **2013**, *19*, 5149.
(24) Maurin, P.; Ibrahim-Ouali, M.; Parrain, J. L.; Santelli, M. *J. Mol. Struct.: THEOCHEM* **2003**, *637*, 91.
(25) Xu, X. P.; Au-Young, S. C. F. *J. Am. Chem. Soc.* **2000**, *122*, 6468.
(26) Williams, V. E.; Lemieux, R. P. *J. Am. Chem. Soc.* **1998**, *120*, 11311.
(27) Haeberlein, M.; Murray, J. S.; Brinck, T.; Pollitzer, P. *Can. J. Chem.* **1992**, *70*, 2209.
(28) Haeberlein, M.; Brinck, T. *J. Phys. Chem.* **1996**, *100*, 10116.
(29) Gadre, S. R.; Suresh, C. H. *J. Org. Chem.* **1997**, *62*, 2625.
(30) DiLabio, G. A.; Pratt, D. A.; Wright, J. S. *J. Org. Chem.* **2000**, *65*, 2195.
(31) Bickelhaupt, F. M.; Baerends, E. J.; Boyd, D. B. *Rev. Comput. Chem.* **2000**, *15*, 1.
(32) te Velde, G.; Bickelhaupt, F. M.; Baerends, E. J.; van Gisbergen, S. J. A.; Fonseca Guerra, C.; Snijders, J. G.; Ziegler, T. *J. Comput. Chem.* **2001**, *22*, 931.
(33) Fernandez, I.; Frenking, G. *J. Org. Chem.* **2006**, *71*, 2251.
(34) Sadlej-Sosnowska, N. *Pol. J. Chem.* **2007**, *81*, 1123.
(35) Sadlej-Sosnowska, N. *Chem. Phys. Lett.* **2007**, *447*, 192.
(36) Krygowski, T. M.; Sadlej-Sosnowska, N. *Struct. Chem.* **2011**, *22*, 17.
(37) Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4796.
(38) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1222.
(39) Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 818.
(40) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986.
(41) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
(42) Oziminski, W. P.; Dobrowolski, J. C. *J. Phys. Org. Chem.* **2009**, *22*, 769.
(43) Krygowski, T. M.; Oziminski, W. P.; Cyranski, M. K. *J. Mol. Model.* **2012**, *18*, 2453.
(44) Oziminski, W. P.; Krygowski, T. M.; Fowler, P. W.; Soncini, A. *Org. Lett.* **2010**, *12*, 4880.
(45) Mazurek, A.; Dobrowolski, J. C. *J. Org. Chem.* **2012**, *77*, 2608.
(46) Arivazhagan, M.; Subhasini, V. P.; Austine, A. *Spectrochim. Acta, Part A* **2012**, *86*, 205.
(47) Rode, M. F.; Sobolewski, A. L. *J. Phys. Chem. A* **2010**, *114*, 11879.
(48) Oziminski, W. P.; Krygowski, T. M. *Tetrahedron* **2011**, *67*, 6316.
(49) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
(50) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.
(51) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645.
(52) Walsh, C. *Tetrahedron* **1982**, *38*, 871.
(53) Prestwich, G. D. *Pestic. Sci.* **1986**, *17*, 430.
(54) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613.
(55) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381.
(56) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320.
(57) Hoffmann, M.; Rychlewski, J. *J. Am. Chem. Soc.* **2001**, *123*, 2308.
(58) Welch, J. T. *Tetrahedron* **1987**, *43*, 3132.
(59) Parker, W. B.; Shaddix, S. C.; Rose, L. M.; Shewach, D. S.; Hertel, L. W.; Secrist, J. A.; Montgomery, J. A.; Bennett, L. L. *Mol. Pharmacol.* **1999**, *55*, 515.
(60) Milas, L.; Fujii, T.; Hunter, N.; Elshaikh, M.; Plunkett, W.; Ang, K. K.; Hittelman, W. *Cancer Res.* **1999**, *59*, 107.
(61) Lesiak, K.; Watanabe, K. A.; Majumdar, A.; Seidman, M.; Vanderveen, K.; Goldstein, B. M.; Pankiewicz, K. W. *J. Med. Chem.* **1997**, *40*, 2533.
(62) Vaidyanathan, G.; Zalutsky, M. R. *Nucl. Med. Biol.* **1998**, *25*, 487.
(63) Du, J. F.; Choi, Y.; Lee, K.; Chun, B.; Hong, J. H.; Chu, C. K. *Nucleosides Nucleotides* **1999**, *18*, 187.
(64) Ma, T. W.; Lin, J. S.; Newon, M. G.; Cheng, Y. C.; Chu, C. K. *J. Med. Chem.* **1997**, *40*, 2750.
(65) Vonjantalipinski, M.; Costisella, B.; Ochs, H.; Hubscher, U.; Hafkemeyer, P.; Matthes, E. *J. Med. Chem.* **1998**, *41*, 2040.
(66) Kukhanova, M.; Lin, Z. Y.; Yasco, M.; Cheng, Y. C.; Chu, C. K. *Biochem. Pharmacol.* **1998**, *55*, 1181.
(67) Ashida, N.; Watanabe, Y.; Miura, S.; Kano, F.; Sakata, S.; Yamaguchi, T.; Suzutani, T.; Machida, H. *Antiviral Res.* **1997**, *35*, 167.
(68) Palmer, S.; Alaeus, A.; Albert, J.; Cox, S. *AIDS Res. Hum. Retroviruses* **1998**, *14*, 157.
(69) Mcintee, E. J.; Remmel, R. P.; Schinazi, R. F.; Abraham, T. W.; Wagner, C. R. *J. Med. Chem.* **1997**, *40*, 3323.
(70) Maruyama, T.; Sato, Y.; Sakamoto, T. *Nucleosides Nucleotides* **1998**, *17*, 115.
(71) Singhal, D.; Morgan, M. E.; Anderson, B. D. *Pharm. Res.* **1997**, *14*, 786.
(72) *Davis's Drug Guide for Nurses*, 8th ed.; F. A. Davis Company: Philadelphia, PA, 2005.
(73) Pöldinger, W.; Sieberns, S. *Neuropsychobiology* **1983**, *10*, 131.
(74) Giannini, A. J.; Eighan, M. S.; Loiselle, R. H.; Giannini, M. C. *J. Clin. Pharmacol.* **1984**, *24*, 202.
(75) Abou El-Magd, R. M.; Park, H. K.; Kawazoe, T.; Iwana, S.; Ono, K.; Chung, S. P.; Miyano, M.; Yorita, K.; Sakai, T.; Fukui, K. *J. Psychopharmacol.* **2010**, *24*, 1055.
(76) Amsterdam, J. D.; Shults, J. *Am. J. Psychiatry* **2010**, *167*, 792.
(77) Ou, J. J.; Xun, G. L.; Wu, R. R.; Li, L. H.; Fang, M. S.; Zhang, H. G.; Xie, S. P.; Shi, J. G.; Du, B.; Yuan, X. Q.; Zhao, J. P. *Psychopharmacology (Berlin)* **2011**, *213*, 639.

(78) Schreiber, S.; Pick, C. G. *Neuropsychopharmacology* **2006**, *16*, 464.
(79) Viukari, M.; Linnoila, M.; Aalto, U. *Acta Psychiatr. Scand.* **1978**, *57*, 27.
(80) Wolfe, T. R.; Macfarlane, T. C. *Arzneim. Forsch.* **1977**, *27*, 2383.
(81) Wolfe, T. R.; Macfarlane, T. C. *Am. J. Emerg. Med.* **2006**, *24*, 343.
(82) Lader, M. B.; Morton, S. V. *J. Psychopharmacol.* **1992**, *6*, 19.
(83) Krygowski, T. M. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 70.
(84) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503.
(85) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(86) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(87) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
(88) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007.
(89) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2004.
(90) Exner, O. In *Correlation Analysis in Chemistry—Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10, p 439.
(91) Möllerstedt, H.; Piqueras, M. C.; Crespo, R.; Ottosson, H. *J. Am. Chem. Soc.* **2004**, *126*, 13938.
(92) Curutchet, C.; Poater, J.; Solà, M.; Elguero, J. *J. Phys. Chem. A* **2011**, *115*, 8571.
(93) Krygowski, T. M.; Ejsmont, K.; Stepień, B. T.; Cyrański, M. K.; Poater, J.; Solà, M. *J. Org. Chem.* **2004**, *69*, 6634.
(94) Oziminski, W. P.; Krygowski, T. M.; Fowler, P. W.; McKenzie, A. *Phys. Chem. Chem. Phys.* **2010**, *12*, 10740.
(95) Sadlej-Sosnowska, N.; Krygowski, T. M. *Chem. Phys. Lett.* **2009**, *476*, 191.
(96) Gross, K. C.; Seybold, P. G. *Int. J. Quantum Chem.* **2001**, *85*, 569.
(97) Krygowski, T. M.; Palusiak, M.; Plonka, A.; Zachara-Horeglad, J. E. *J. Phys. Org. Chem.* **2007**, *20*, 297.
(98) Hayd, H.; Savin, H.; Stoll, A.; Preuss, H. *J. Mol. Struct.* **1988**, *165*, 87.
(99) Typke, V.; Dakkouri, M.; Oberhammer, H. *J. Mol. Struct.* **1977**, *10*, 85.