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Steric Parameters Useful for the Study of Quantitative Structure-Activity Relationships: Calculation by Means of a Through-Space Interaction Model[1]

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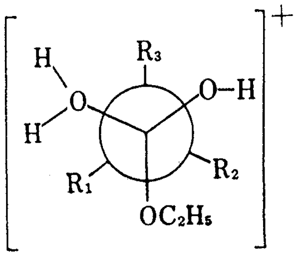
Various steric parameters used for the analysis of quantitative structure–activity relationships (QSAR) were examined in relation to CNDO/2 molecular orbital calculations. The through-space interaction energies $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ and $\varepsilon_{\mathrm{X}}^{\mathrm{T}}$ (see text for physical significance) among the atoms consisting of the outside part of $[C(R_1R_2R_3)\cdot C(OH)(OH_2)(OC_2H_5)]^+$ were calculated and employed as an index describing the steric effect. The structure was considered to be the transition state intermediate in the acid hydrolysis of $C(R_1R_2R_3)\cdot COOC_2H_5$. The correlation of $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ or $\varepsilon_{\mathrm{X}}^{\mathrm{T}}$ with steric parameters commonly used in QSAR studies was examined in detail. The characteristics of such steric parameters as $E_{\mathrm{S}}^{\mathrm{C}}$, E_{S}, molar volume, molar refractivity, parachor, $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ and $\varepsilon_{\mathrm{X}}^{\mathrm{T}}$ are discussed in relation to their usefulness for QSAR studies.

Keywords——steric parameters; quantitative structure–activity relationship; through-space interaction energy; CNDO/2; E_{S} and $E_{\mathrm{S}}^{\mathrm{C}}$ parameters; molar refractivity; molar volume; parachor; van der Waals volume

It is well known that steric effects play an important role in studies of quantitative structure–activity relationships (QSAR). Various kinds of steric parameters such as E_{S} and its modification,[2,3] which were derived from considerations of the acid hydrolysis of $R\cdot COOR'$,[4] molar volume (MV),[5,6] molar refractivity (MR),[2,6] parachor (P_{r}),[5,6] van der Waals volume (V_{w}),[6,7] *etc.* were proposed for describing steric effects in the field of QSAR studies. Since the derivations of these steric parameters are based on different kinds of physicochemical data, examination of the characteristics and interrelationships of the parameters is very important. For this purpose we have carried out quantum chemical calculations to evaluate the steric effect corresponding to the $E_{\mathrm{S}}^{\mathrm{C}}$ or E_{S} value (*vide infra*) as an ideal model. The calculated values were compared with other steric parameters as well as E_{S} and modified forms.[2]

Calculation

The acid hydrolysis of $C(R_1R_2R_3)\cdot COOC_2H_5$ is thought to occur through the transition state [I] produced by the attack of H_3O^+ on $C(R_1R_2R_3)\cdot COOC_2H_5$.[2,3a,8] The larger the steric hindrance, the greater the energy at the transition state [I], so that the acid hydrolysis rate of $R\cdot COOC_2H_5$ becomes slower compared to that of the standard compound $CH_3COOC_2H_5$. The E_{S} value,[10] defined as $E_{\mathrm{S}}=\log(k_{\mathrm{R}}/k_{\mathrm{CH_3}})_{\mathrm{A}}$, therefore takes a larger negative value with increasing steric hindrance. We have now tried to calculate the degree of the steric hindrance at the transition state [I], in order to compare the results with such steric parameters as E_{S}, $E_{\mathrm{S}}^{\mathrm{C}}$, MR MV, *etc.* (see below). When the CPK molecular models of $[C(R_1R_2R_3)\cdot C(OH)(OH_2)(OC_2H_5)]^+$ (see Form I) with various kinds of alkyl groups for R_1, R_2, and R_3 are constructed,



I

it is clear that the outside of the molecules is almost completely covered with hydrogen atoms. As an approximation of the steric factor mentioned above, we have now calculated the through-space interaction (TSI) energies among the hydrogen atoms, which were defined as $\varepsilon_{\mathrm{H}}^{\mathrm{T}}=\varepsilon_{\mathrm{H}\cdots\mathrm{H}}^{\mathrm{R}}+\varepsilon_{\mathrm{H}::::\mathrm{H}}^{\mathrm{R}\quad\mathrm{E}}$. The term of $\varepsilon_{\mathrm{H}\cdots\mathrm{H}}^{\mathrm{R}}$ means the hydrogen-hydrogen interaction (repulsion) energies among the H atoms belonging to the substituents R_1, R_2, and R_3. The term $\varepsilon_{\mathrm{H}::::\mathrm{H}}^{\mathrm{R}\quad\mathrm{E}}$ means those between the H atoms inside R_1, R_2, and R_3, and the H atoms belonging to the protonated ester group, $C(OH)(OH_2)(OC_2H_5)$. The calculation was also made for substituents with such heteroatoms as O, F, and Cl. In this case TSI energies are obtained from the equation $\varepsilon_{\mathrm{X}}^{\mathrm{T}}=\frac{1}{2}\sum_{\mathrm{XX'(X\neq X')}}\varepsilon_{\mathrm{X}\cdots\mathrm{X'}}^{\mathrm{R}}+\sum_{\mathrm{X}}\varepsilon_{\mathrm{X}::::\mathrm{H}}^{\mathrm{R}\quad\mathrm{E}}$. The term $\sum_{\mathrm{XX'(X\neq X')}}\varepsilon_{\mathrm{X}\cdots\mathrm{X'}}^{\mathrm{R}}$ stands for the sum of the TSI energies between any two atoms among hetero- and hydrogen atoms, which cover the outside of substituents R_1, R_2, and R_3. The second term on the right-hand side of the equation expresses the TSI energies between the outside hetero- and hydrogen atoms in the substituents and the hydrogen atoms belonging to the protonated ester group. The calculation was carried out with a FACOM M-140 computer using the CNDO/2 program; in this approximation, the binding energy between the two atoms A and B is given by

$$\varepsilon_{\mathrm{AB}} = \sum_{\mu}^{\mathrm{A}}\sum_{\nu}^{\mathrm{B}}[2P_{\mu\nu}\beta_{\mu\nu}^{\mathrm{AB}} - \frac{1}{2}P_{\mu\nu}^{2}\gamma_{\mathrm{AB}}] + [P_{\mathrm{AA}}\cdot P_{\mathrm{BB}}\cdot\gamma_{\mathrm{AB}}+Z_{\mathrm{A}}Z_{\mathrm{B}}R_{\mathrm{AB}}^{-1}-P_{\mathrm{AA}}V_{\mathrm{AB}}-P_{\mathrm{BB}}V_{\mathrm{BA}}]\cdot$$

Here, each notation has its usual physical meaning in this field,11) *i.e.* $P_{\mu\nu}=2\sum_{\mathrm{i}}^{\mathrm{occ}}C_{\mathrm{i}\mu}C_{\mathrm{i}\nu}$, $V_{\mathrm{AB}}=Z_{\mathrm{B}}\cdot\gamma_{\mathrm{AB}}$, $V_{\mathrm{BA}}=Z_{\mathrm{A}}\cdot\gamma_{\mathrm{AB}}$, $\beta_{\mu\nu}^{\mathrm{AB}}=\frac{1}{2}S_{\mu\nu}(\beta_{\mathrm{A}}^{\circ}+\beta_{\mathrm{B}}^{\circ})K$, and R_{AB} is the atomic distance.12),13) The

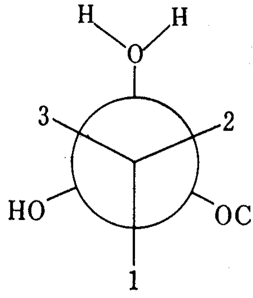
Table I. The Through-space Interaction Energy $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ and $E_{\mathrm{S}}^{\mathrm{C}}$ Values for Various Kinds of Alkyl Substituents

Groups	Component[a] α substituents 1	2	3	$E_{\mathrm{S}}^{\mathrm{C}}$	$\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ kcal/mol
Me	H	H	H	0.0	28.73
Et	Me	H	H	−0.38	30.05
Pr	Et	H	H	−0.67	31.30
Bu	Pr	H	H	−0.70	32.88
Pent	Bu	H	H	−0.71	34.63
Hex	Pent	H	H	−0.61	36.65
Hept	Hex	H	H	(−0.64)[b]	38.84
Oct	Hept	H	H	−0.64	41.10
Iso-Pr	Me	Me	H	−1.08	34.32
sec-Bu	Et	H	Me	−1.74	34.61
Iso-Bu	Iso-Pr	H	H	−1.24	39.43
Iso-Pent	Iso-Bu	H	H	−0.66	39.27
tert-Bu	Me	Me	Me	−2.46	40.76
Neo-Hex	Neo-Pent	H	H	−0.65	49.56
	Iso-Pent	H	H		41.45
	sec-Bu	H	H		40.83
Neo-Pent	*tert*-Bu	H	H	−2.05	52.06
	Pr	H	Me		36.63
	tert-Bu	H	Me	−3.90	55.31
	tert-Bu	Me	Me	−4.82	60.12
	Et	Me	Me		43.02
sec-Pent	Et	H	Et	−2.59	26.95
sec-Hept	Pr	H	Pr	−2.72	22.63
	Neo-Pent	H	Me	−2.46	106.37
	$C(Me)_2(Et)$	H	Me		57.23
	$C(Me)_2(Et)$	Me	Me		65.46

a) The substituents at 1, 2, and 3 correspond to positions 1, 2, and 3 in Form [II] in the text, respectively.

b) This is the assumed value, since the $E_{\mathrm{S}}^{\mathrm{C}}$ and E_{S} values for this substituent were not found in the literature.

geometries used for the calculation were assumed to be as follows.[14] In the protonated ester group (Form I) the bond lengths are: $r(\mathrm{C{-}O})=1.48$ Å, $r(\mathrm{O{-}H})=0.96$ Å, $r(\mathrm{H_2C{-}O})=1.43$ Å, $r(\mathrm{C{-}C})=1.54$ Å, and $r(\mathrm{C{-}H})=1.09$ Å. The bond angles are 110° and 109°28′ for $\angle(\mathrm{H_2C{-}O{-}C})=\angle(\mathrm{C{-}O{-}H})$ and the other angles,[14] respectively. For substituents R the bond lengths and bond angles are: $r(\mathrm{C{-}Cl})=1.80$ Å, $r(\mathrm{C{-}F})=1.36$ Å, $r(\mathrm{C{-}O})=1.43$ Å, $r(\mathrm{C{-}H})=1.09$ Å, $\angle(\mathrm{C{-}O{-}C})=110°$, and the other angle is 109°28′. The conformation of alkyl group carbons was assumed to be staggered, as in Form [II], and such substituents as linear alkyl groups from $\mathrm{CH_3}$ to *n*-Oct are put at position 1 of Form [II]. In the case of branched alkyl groups such as iso-Pr and *sec*-Bu, there are several possibilities with the alkyl group at the positions 1, 2, and 3 in Form [II]. Therefore the calculations of the total energy (TE) and $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ were made by using the CNDO/2 method on the various configurations of typical substituents mentioned above. Referring to these results, we have adopted the configurations given in Tables I and II for various kinds of substituents[15] which were employed for the present analysis. All of the calculation results are listed in Tables I and II.



II

TABLE II. The Through-space Interaction Energy $\varepsilon_{\mathrm{X}}^{\mathrm{T}}$ and $E_{\mathrm{S}}^{\mathrm{C}}$ Values for Various Kinds of Heteroatom-substituted Groups

Groups	Component[a] α substituents 1	2	3	$E_{\mathrm{S}}^{\mathrm{C}}$	$\varepsilon_{\mathrm{X}}^{\mathrm{T}}$ kcal/mol
$\mathrm{CCl_3}$	Cl	Cl	Cl	−2.98	−65.83
$\mathrm{CHCl_2}$	Cl	Cl	H	−2.15	−20.21
$\mathrm{CH_2Cl}$	Cl	H	H	−0.55	7.22
$\mathrm{CF_3}$	F	F	F	−2.08	−21.84
$\mathrm{CHF_2}$	F	F	H	−1.28	−7.03
$\mathrm{CH_2F}$	F	H	H	−0.55	10.23
$\mathrm{CH_2OCH_3}$	$\mathrm{OCH_3}$	H	H	−0.50	28.99
$\mathrm{CH_2SCH_3}$	$\mathrm{SCH_3}$	H	H	−0.65	−5.33

[a] The substituents at 1, 2, and 3 correspond to positions 1, 2, and 3 in Form [II] in the text, respectively.

Results and Discussion

First, we will consider alkyl substituents with aliphatic hydrocarbons. The physical significance given hitherto to $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$, which is positive (repulsive) for alkyl substituents, is that $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ values are deemed to reflect the bulkiness and shape of the substituents. On the other hand, the steric substituent constants E_{S} and $E_{\mathrm{S}}^{\mathrm{C}}$ may represent the steric hindrance which exerts an important influence upon the region near the protonated ester group. Bulky substituents located at positions far from the protonated ester group may have little effect on the E_{S} or $E_{\mathrm{S}}^{\mathrm{C}}$ values. Figure 1 shows the correlation between $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ and $E_{\mathrm{S}}^{\mathrm{C}}$ values.[16] Line 1 is the regression line for the substituents Me, Et, Pr, Bu, iso-Pr, iso-Bu, *sec*-Bu, *tert*-Bu, –CH(Me)(*tert*-Bu), and –C(Me)$_2$(*tert*-Bu) as bulky groups adjacent to a protonated ester group. The result obtained is: $E_{\mathrm{S}}^{\mathrm{C}}=-0.1435\varepsilon_{\mathrm{H}}^{\mathrm{T}}+3.8610$; $n=10$, $s=0.366$, and $r=0.976$.[19] There seems to be quite a good linear relation between $E_{\mathrm{S}}^{\mathrm{C}}$ and TSI energies. Therefore, the $\varepsilon_{\mathrm{H}}^{\mathrm{T}}$ values might also be a good measure of the steric effect in the region near the reaction center. On the other

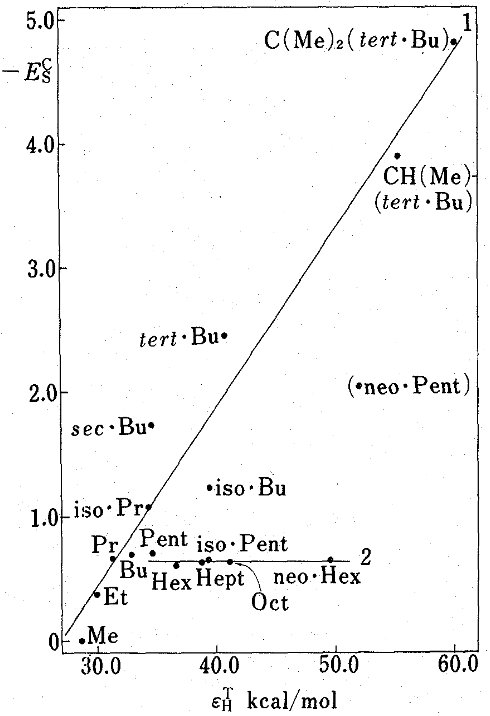


Fig. 1. Correlation between E_S^C and ε_H^T Values for Various Alkyl Groups

See the text for detailed explanation.

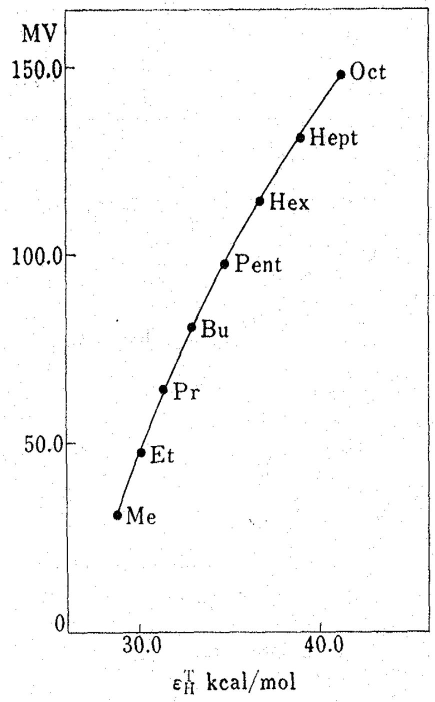


Fig. 2. Correlation between Molar Volume and ε_H^T Values for linearly Extended Alkyl Groups from CH_3 to *n*-Oct

hand, substituents such as Pent, Hex, Hept, iso-Pent, *n*-Oct, and neo-Hex fall on the straight line 2 in Fig. 1. Although a considerable change in ε_H^T values is observed with the above substituents, scarcely any change of E_S^C values is found. Keeping in mind the fact that the ε_H^T values also represent the bulkiness of the whole substituent, the above result seems reasonable. The substituents falling on line 2 may have almost the same bulkiness in the neighborhood of the protonated ester group.

On the basis of the physical significance of ε_H^T values discussed hitherto, a good correlation between ε_H^T and molar volume (MV) or molar refractivity (MR) should naturally be obtained. The latter indices are steric parameters useful for QSAR studies. Figures 2 and 3 show the relation. A slightly curved parabolic relation is obtained for substituents from CH_3 to *n*-Oct with a good correlation, as expected. The results can be written as $MV = -0.2861\ (\varepsilon_H^T)^2 + 29.21\ (\varepsilon_H^T) - 570.9$ with $n=8$, $s=1.228$, $r=0.9997$, and $MR = -0.0816\ (\varepsilon_H^T)^2 + 8.286\ (\varepsilon_H^T) - 164.8$ with $n=8$, $s=0.327$, $r=0.9997$. The values of MV and MR were taken from references 5 and 6, respectively.[20] We can now consider the meaning of the lines 2, 3, 4, 5, 6, and 7 in Fig. 3. Though the MR values are almost constant in isomeric substituents the ε_H^T values vary considerably. The E_S or E_S^C values are quite different among these isomers. These results show that the MR values may not be entirely appropriate as a parameter for describing the position adjacent to the reaction center. Careful selection is necessary to apply the various kinds of steric parameters to QSAR studies. In general, the correlation coefficient between any two of MR, MV, and parachor (P_r) is high,[5,21] so that similar attention is also necessary for the MV and P_r values. Alternatively, it may be said that the ε_H^T values describe adequately not only the steric effect on the position adjacent to a reaction center, but also the bulkiness of the whole substituent itself.

We will next consider the TSI energies ε_X^T of aliphatic substituents containing heteroatoms. Based on the data in Table II, in which all the computed data are listed, the mutual relation of E_S^C and ε_X^T is shown in Fig. 4. Note that the larger the negative shift of the E_S^C value, *i.e.* the larger the steric effect of substituents, the more negative the ε_X^T values become, just in

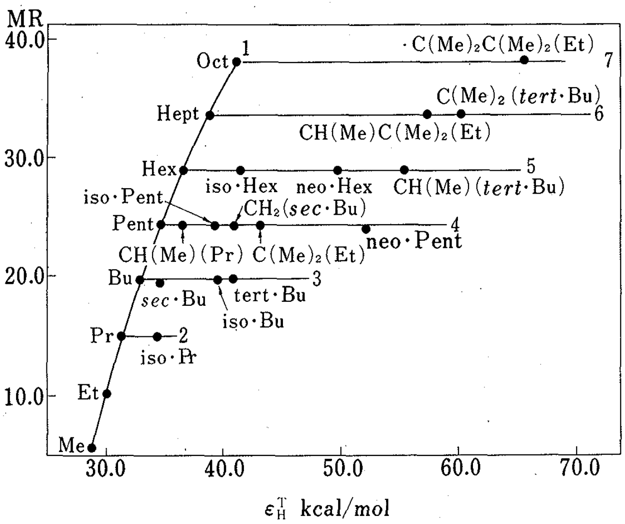


Fig. 3. Correlation between Molar Refractivity and ε^{T}_{H} Values

For a detailed explanation, see the text.

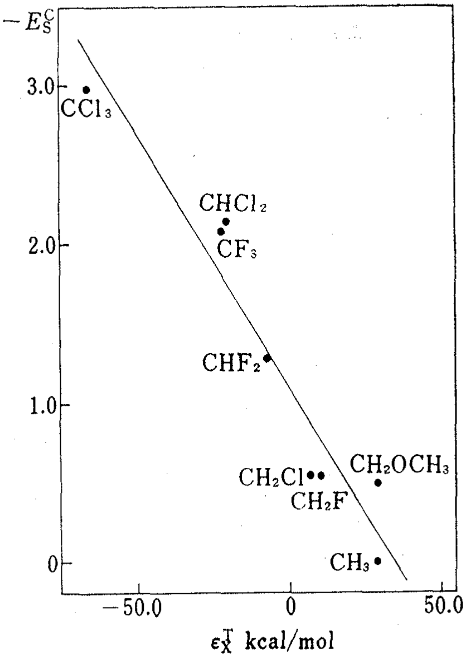


Fig. 4. The Linear Relation between E^{C}_{S} and ε^{T}_{X} Values

See the text for a detailed explanation.

the opposite direction compared to the mutual relation (see Fig. 1) between E^{C}_{S} and ε^{T}_{H} values.[22] The linearity between the E^{C}_{S} and the ε^{T}_{X} values is, however, quite good: $E^{C}_{S}=0.0319\,\varepsilon^{T}_{X}-1.103$ with $n=8$, $s=0.313$, $r=0.961$. The TSI energies ε^{T}_{X} applied to heteroatom-containing systems may also be a useful index for estimating the steric effect on the reaction center. As mentioned above, the energy contents contributing to the ε^{T}_{X} values[22] are rather complicated in comparison with those in the case of ε^{T}_{H} values. More rigorous consideration with higher-order computation seems to be necessary, especially in heteroatomic systems.[23]

References and Notes

1) This paper forms Part III of "Studies on Structure–Activity Relationships." Parts I and II are K. Ezumi and T. Kubota, *Chem. Pharm. Bull.*, **28**, 85 (1980) and T. Kubota and K. Ezumi, *ibid.*, **28**, 3673 (1980), respectively.
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8) Form [I] showing the transition state structure was proposed by Unger and Hansch,[2] and Fujita, Takayama, and Nakajima.[3a] The stable conformation of the ester was reported to be almost the eclipsed form.[9]
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12) See references 11 and 13 for a more detailed consideration.

13) N. Mataga and T. Kubota, "Molecular Interactions and Electronic Spectra," Marcel Dekker, New York, 1970.

14) These values were taken from reference 11 unless otherwise noted. A longer distance of 1.48 Å for r(C–OH), r(C–OH_2), and r(C–OEt) in the protonated ester group is postulated in the transition state. r(C–Cl) = 1.80 Å was cited from O. Kennard, D.G. Watson, F.H. Allen, N.W. Issacs, W.D.S. Mothermell, R.C. Pittersen, and W.G. Town, "Molecular Structures and Dimensions," Vol. A-1, Interatomic Distances 1960—1965, Solid State Classes 1—86, International Union of Crystallography, Printed in the United Kingdom by Union Brothers Ltd. Angles given in the text for the protonated ester group are almost the same as those used by Detar and Tenpas.[23,24]

15) The values of TE and ε_H^T among the conformers are not always consistent in order. However, these differences are small in comparison with those among the different substituents given in Table I, so that the present conclusions may not be altered by employing somewhat different configurations from those in Tables I and II.

16) The E_S^c constant is defined by the equation[17] $E_S^c = E_S - 0.306\,(3 - n_H)$. Here, n_H is the number of H-atoms located at the α-position from the protonated ester group. E_S^c was reported to express the correction due to the hyper-conjugation effect on the α-hydrogen atoms, and also to emphasize the degree of branching at the α-carbon atom.[18]

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19) The calculated ε_H^T value for neo-Pent deviates considerably from line 1. This may be due to the overestimation of H···H repulsion energies because of the adoption of inappropriate molecular geometry for this.

20) The MV and MR values are as follows (in that order): Me (31.48, 5.70), Et (48.06, 10.30), *n*-Pr (64.64, 15.0), *n*-Bu (81.22, 19.60), *n*-Pent (97.80, 24.3), *n*-Hex (114.38, 28.9), *n*-Hept (130.96, 33.6), *n*-Oct (147.54, 38.10).

21) *a*) P.N. Craig, *J. Med. Chem.*, **14**, 680 (1971); *b*) R.A. Coburn and A.J. Solo, *J. Med. Chem.*, **19**, 748 (1976).

22) The main reason for this is that the Cl···Cl TSI energy becomes negative and bonding in nature, *e.g.*, for the CCl_3 group, in spite of the positive (repulsive) energy for the F···F type, *e.g.*, in the CF_3 group, and also for the H···H type interaction discussed in the foregoing section. In addition, TSI energy of the type H···X (X=F, Cl, O) takes a negative value. Thus, the CNDO/2 method led to the result indicated in Fig. 3.

23) As far as we know, quantum chemical calculation of the steric parameter Es has not previously been reported, although its theoretical estimation by means of a model of molecular mechanics was studied for aliphatic hydrocarbon substituents.[24]

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