

Topological Steric Effect Index and Its Application

Chenzhong Cao* and Li Liu

School of Chemistry and Chemical Engineering, Hunan University of Science and Technology,
Xiangtan, 411201, People's Republic of China

Received November 17, 2003

This paper proposed a Topological Steric Effect Index (TSEI) of a group based on the relative specific volume of the reaction center screened by the atoms of the substituents. Investigated results show good correlations between the parameter TSEI and the dihedral angles between both phenyl rings determined by photoelectron spectroscopy for 7 alkylbiphenyl compounds and calculated by a molecular mechanics force field for 78 alkylbiphenyl compounds, whose correlation coefficients are 0.9912 and 0.9845, respectively. The TSEI value of the group is easily calculated and has a clear physical meaning. In addition, it is correlated well to dihedral angles of the 1,2-disubstituted benzene compounds, stereoselectivity of organomagnesium compounds addition to some cyclohexanones and cyclopentanones, and the relative rates of some S_N2 reactions.

1. INTRODUCTION

The steric effect is one of the important substituent effects in organic chemistry. It exists widely in organic compounds and affects the physicochemical properties of organic compounds. To evaluate the steric effect, a number of empirical or experimental methods have been developed hitherto.

The first steric effect parameter, Taft's E_s , was proposed by Taft in 1952,¹ which is based on the relative rates of the acid-catalyzed hydrolysis of esters, that is $E_s = -\log(k_{\text{rel}}) = -\log(k/k_0)$ where k is the rate constant for any esters RCOOEt and k_0 is the rate constant for ethyl acetate, under similar conditions.^{2,3} Hancock et al.⁴ thought that Taft's steric substituent constants, E_s , may contain hyperconjugation effects (α -hydrogen bonding effects) and then modified it as E_s^c , which was called the Hancock constant. Since the parameters E_s and E_s^c all originated from the hydrolysis of esters, they naturally included the effects of hydration. DeLos et al.² put forth the isoalkane–neoalkane pair model for reflecting the steric effect of esters and tetrahedral intermediate of its hydrolysis products. Furthermore they thought that steric hindrance should be proportional to differences of enthalpies of formation between hydrocarbons $\text{RCH}(\text{CH}_3)_2$ and $\text{RC}(\text{CH}_3)_3$. This model had a major advantage in that the alkane force fields were relatively well established. But it yet had some evident deficiency, such as the imperfect structural relationships between isoalkane and esters, the ineffective calculation of force fields on a highly hindered alkane, and on the systematical optimization and treating of the van der Waals strain and so on. In sequence they³ took molecules RCOOH and $\text{RC}(\text{OH})_3$ as the model to replace $\text{RCH}(\text{CH}_3)_2$ and $\text{RC}(\text{CH}_3)_3$ and gave the better modeling $\log k_{\text{rel}} = 0.340 - 0.789\Delta\text{SE}$ for the calculation of the steric effect (SE) in the acid-catalyzed hydrolysis of esters where $\Delta\text{SE} = [\text{steric energy of } \text{RC}(\text{OH})_3] - [\text{steric energy of } \text{RCOOH}]$.

The experimental steric effect parameters such as E_s and E_s^c are reliable for application and can reveal the effect of molecular structure on reactivity. However, because of the limitation by experimental conditions, it is impossible to determine the steric effects for all substituents, especially for those being designed. So the calculation methods based on the molecular structure are developed rapidly, such as Charton's^{5–7} parameter V_x and Cherkasov's^{8,9} parameter R'_s . Recently, Marco,¹⁰ Marc,¹¹ and David¹² et al., using a computing method, studied the chemical reactions $\text{Cl}^- + \text{Cl}(\text{CH}_2)_n\text{CN}$ ($n = 2-5$), the rate constant and the kinetic isotope effect of the rate-determining step in the neutral hydrolysis of *p*-methoxyphenyl dichloroacetate in aqueous solution and enantiospecific in chiral metal surfaces.

Topological parameters are intrinsically connected with molecular structures,¹³ since the molecular topology is concerned with the number and type of atoms in the molecule and the way they are connected to each other.¹⁴ Topological indices (TIs) based on the application of graph-theoretical concepts in chemistry¹⁴ are effective methods on the research of the steric effect¹⁵ and have been increasingly applied for study of quantitative structure–activity/property relationship (QSAR/QSPR). For example, the connectivity index χ^{16} was defined by Randić; Ξ ,¹⁷ reflecting the steric effect, was recently defined as a sum of three shape descriptors; SVTI^{15} was equal to the sum of the distances not greater than three bonds between the attachment site and the carbon atoms of the alkyl group. Recently, Estrada¹⁴ et al. used the local spectral moments of the bond matrix to predict 3D (geometric) structural parameters from 2D (topological) molecular descriptors and got a good result.

In this work, a novel topological parameter (called as Topological Steric Effect Index, TSEI) was proposed for quantifying the steric effects of substituents, which expressed the relative specific volume of the reaction center screened by the atoms of substituents. The correlations between the parameter TSEI and the dihedral angles of biphenyl deriva-

* Corresponding author fax: 00086-0732-8291001; e-mail: czcao@xtnu.edu.cn.

tives and 1,2-disubstituted benzenes and the stereoselectivity of organomagnesium compounds addition to cyclic ketones and the relative rates of some S_N2 reactions were investigated. Good correlations were obtained.

2. METHOD

Cherkasov⁸ et al. described the steric effect of an interested substituent as the following equation

$$R_S = -30 \log \left(1 - \sum_{i=1}^n \frac{R_{Ai}^2}{4r_i^2} \right) \quad (1)$$

where n is the number of atoms in the substituent, R_A is the atomic radius, and r is the direct distance from the i th atom of the substituent to the reaction center. Further Cherkasov⁸ et al. transformed eq 1 into a more simple expression (eq 2), since for small x values, $\log(1-x)$ is linear in x (the term $\sum (R_{Ai}^2/4r_i^2)$ is small for most substituents). Thus the steric effect parameter R'_S can be written as

$$R'_S = \sum_{i=1}^n \frac{R_i^2}{r_i^2} \quad (2)$$

R'_S reflects the specific surface of the reaction center screened by the atoms of the substituents.⁹ As we know (a) an atom can be regarded as a spherical body and (b) the rotation of a bond between atoms is free. The larger the atomic volume is, the more the specific volume of the reaction center screened by the atom will be, the larger the steric effect contributed by which will be. Thus, a better result can be expected with the relative specific volume V_{rc} than with the specific surface of the reaction center screened by the atoms of the substituents to express the steric effect. That is

$$V_{rc} = \sum_{i=1}^n \frac{\frac{4}{3} \pi R_i^3}{\frac{4}{3} \pi l_i^3} \quad (3)$$

where n is the number of atoms in the substituent, R_i is the i th atomic covalent radius,¹⁸ and l_i is the sum of the bond length from the i th atom of the substituent to the reaction center. Apparently, eq 3 can be simplified to eq 4.

$$V_{rc} = \sum_{i=1}^n \frac{R_i^3}{l_i^3} \quad (4)$$

Now, take 1,3-dimethylbutyl $R_{rc}-CH(CH_3)CH_2CH(CH_3)_2$ for example (its molecular graph as shown in Figure 1). In this molecular graph, R_{rc} is the reaction center connected with a radical atom, and the carbon atoms connected directly with R_{rc} are set as "first tier"; the next carbon atoms, "second tier"; the next next carbon atoms, third tier; and so on.

It is known that the carbon atomic covalent radius R_C is 0.772×10^{-8} cm and the bond length r_{C-C} of C-C is $(0.772+0.772) \times 10^{-8}$ cm. Based on eq 4, if the hydrogen

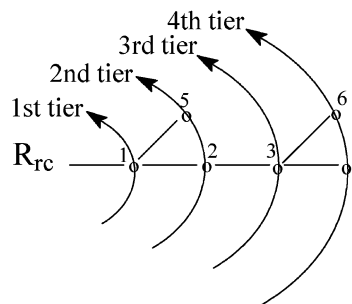


Figure 1. The tiers of carbon atoms in the substituent $R_{rc}-CH(CH_3)CH_2CH(CH_3)_2$ (the digits above the vertexes are the random numberings; R_{rc} is the reaction center).

atoms are ignored, the V_{rc} of the 1,3-dimethylbutyl substituent is

$$V_{rc[-CH(CH_3)CH_2CH(CH_3)_2]} = \frac{0.772^3}{[(0.772 + 0.772) \times 1]^3} + \frac{0.772^3}{[(0.772 + 0.772) \times 2]^3} \times 2 + \frac{0.772^3}{[(0.772 + 0.772) \times 3]^3} + \frac{0.772^3}{[(0.772 + 0.772) \times 4]^3} \times 2 \quad (5a)$$

It can be seen that each of the right items in eq 5a contains a constant k_t [$0.772^3/(0.772 + 0.772)^3$]. Thus, eq 5a can be expressed as

$$V_{rc[-CH(CH_3)CH_2CH(CH_3)_2]} = k_t \left[1 + \frac{1}{2^3} \times 2 + \frac{1}{3^3} + \frac{1}{4^3} \times 2 \right] = 1.3183k_t \quad (5b)$$

For any alkyl, it only contains carbon and hydrogen atoms. When its hydrogen atoms are ignored, eq 4 also can be simplified to eq 6

$$V_{rc} = k_t \sum_{i=1}^n \frac{1}{L_i^3} \quad (6)$$

where L_i is the topological distance number of consecutive bonds or the length from the i th atom of the substituent to the reaction center. Seen from eq 6, the relative order of the steric effect of the alkyl substituent can be quantified by the right term of $\sum_{i=1}^n (1/L_i^3)$, which is called the Topological Steric Effect Index, TSEI ($TSEI = V_{rc}/k_t$).

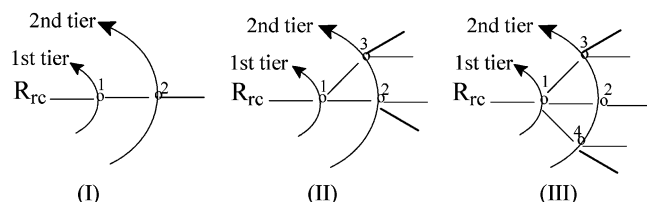
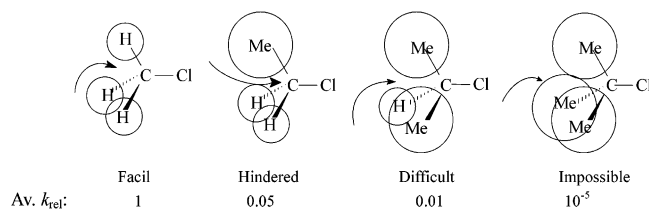
$$TSEI = \sum_{i=1}^n \frac{1}{L_i^3} \quad (7)$$

The TSEI value of an alkyl substituent is easily obtained by eq 7. Some TSEI values of normal alkyl substituents and increments of TSEI (that is, $\Delta TSEI = 1/L_i^3$) of the i th carbon atom are listed in Table 1.

For the branch alkyl substituents (I), (II), and (III) in Figure 2, their numbers of atoms in second tier are 1, 2, and 3, respectively. According to eq 7, their corresponding steric effect increments $\Delta TSEI$ caused by second tier carbon atoms should be 0.1250, 0.2500, and 0.3750, respectively. Can these values represent the real steric effect contributions of second tier carbon atoms to the reaction center? To answer this

Table 1. TSEI and Δ TSEI Values of Normal Alkyl

no.	TSEI	Δ TSEI	no.	TSEI	Δ TSEI
1	1.0000	1.0000	11	1.1983	0.0008
2	1.1250	0.1250	12	1.1989	0.0006
3	1.1620	0.0370	13	1.1993	0.0005
4	1.1777	0.0156	14	1.1997	0.0004
5	1.1857	0.0080	15	1.2000	0.0003
6	1.1903	0.0046	16	1.2002	0.0002
7	1.1932	0.0029	17	1.2004	0.0002
8	1.1952	0.0020	18	1.2006	0.0002
9	1.1965	0.0014	19	1.2007	0.0001
10	1.1975	0.0010	20	1.2009	0.0001

**Figure 2.** The tiers of atoms in the model molecular graph (the digits above the vertex are the random numberings).**Figure 3.** Steric substituent effect on S_N2 reactions (k_{rel} is the relative rate of reaction).

question, let us see as an example the S_N2 hydrolysis of chlorohydrocarbons whose center carbons are connected with a different number of methyls (see Figure 3).¹⁹ Their relative rates k_{rel} diminish from 1 of the $MeCl$ to 10^{-5} of the CMe_3Cl , which is dominated by the bulky alkyl hindering from nucleophile to approach the central atom.²⁰

Seen from Figure 3, the k_{rel} values fall drastically from the third compound (Me_2CHCl) to the fourth compound (Me_3CCl). Even for the calculation of the DFT method for the S_N2 reaction $Cl^- + RCl$, its result also showed a drastic increase in activation energies from Me_2CHCl to Me_3CCl .²⁰ It implies a drastic increment of the steric effect caused by the third carbon atom in second tier atoms of Figure 2. Clearly, the steric effect value of substituents calculated by eq 7 cannot completely interpret this phenomenon. How much is the sum of Δ TSEI for three next tier carbon atoms connecting with one carbon atom in the substituent on earth? By roughly estimating with geometric principle, the sum of the steric effect of three carbon atoms in second tier is about 6.5 times of one carbon atom in second tier (the calculation process can be seen in the Supporting Information). It is to say that when three next tier carbon atoms connected with

one carbon atom, the total Δ TSEI of these three carbon atoms is 6.5 times of that of one next tier carbon atom for alkyl. Thus TSEI of Et, *i*-Pr, and *t*-Bu are 1.1250, 1.2500, and 1.8125, respectively. When the Δ TSEI of three carbon atoms is taken as 3 times or 6.5 times of one carbon atom (that is TSEI value of *t*-Bu is 1.3750 or 1.8125), respectively, the correlation between $\log k_{rel}$ and TSEI is less for the former than the latter (see Table 2).

Here, the calculation of TSEI of heteroatoms in the substituent is introduced. Taking $R_{rc}-Cl$ for example, Cl atom is located in the first tier of substituent. Its atomic covalent radius is 0.99×10^{-8} cm and the bond length of C-Cl is $(0.772+0.99) \times 10^{-8}$ cm.

First,

$$V_{rc(Cl)} = \sum_{i=1}^n \frac{R_i^3}{l_i^3} = \frac{0.99^3}{(0.772 + 0.99)^3} = \frac{0.772^3}{(0.772 + 0.772)^3} \times \frac{(0.99/0.772)^3}{[(0.772 + 0.99)/(0.772 + 0.772)]^3} = k_t \times \frac{(0.99/0.772)^3}{[(0.772 + 0.99)/(0.772 + 0.772)]^3}$$

Second,

$$TSEI_{Cl} = \frac{V_{rc(Cl)}}{k_t} = \frac{(0.99/0.772)^3}{[(0.772 + 0.99)/(0.772 + 0.772)]^3} = 1.4190$$

From the above example, one can get the expression 8a of Δ TSEI_{i,X} caused by any heteroatom (X) with covalent radius R_X in the “*i*th tier”:

$$\Delta TSEI_{i,X} = \frac{(R_{i,X}/R_C)^3}{(l_{i,X}/l_{C-C})^3} \quad (8a)$$

where $l_{i,X}$ is the sum of the bond length from atom X in the “*i*th tier” to the reaction center, and l_{C-C} is the bond length of C-C. Let $R_{i,rel} = R_{i,X}/R_C$ and $L_{i,rel} = l_{i,X}/l_{C-C}$, we can get the TSEI_X expression of the substituent containing heteroatom X:

$$TSEI_X = \sum_{i=1}^n \Delta TSEI_{i,X} = \sum_{i=1}^n \frac{R_{i,rel}^3}{L_{i,rel}^3} \quad (8b)$$

Table 2. Relative Rates of S_N2 Hydrolysis of Chlorohydrocarbons (RCl), TSEI of Alkyls (R), and Their Correlation Equations

alkyl	Me	Et	<i>i</i> -Pr	<i>t</i> -Bu	correlation equation	<i>R</i>	<i>s</i>	<i>F</i>	<i>N</i>
TSEI ^a		1.1250	1.2500	1.3750	$\log k_{rel} = 15.7278 - 14.7959TSEI$	0.9411	0.939	7.75	3
TSEI ^b		1.1250	1.2500	1.8125	$\log k_{rel} = 4.7230 - 5.3660TSEI$	1.0000	0.020	18822.9	3
TSEI ^a	1.0000	1.1250	1.2500	1.3750	$\log k_{rel} = 12.8388 - 12.5592TSEI$	0.9566	0.756	21.56	4
TSEI ^b	1.0000	1.1250	1.2500	1.8125	$\log k_{rel} = 5.5255 - 5.8608TSEI$	0.9920	0.329	122.67	4
k_{rel}	1	0.05	0.01	10^{-5}					

^a TSEI of *t*-Bu is equal to 1.3750. ^b TSEI of *t*-Bu is 1.8125.

Table 3. Dihedral Angles (Θ) between the Phenyl Rings in Alkylbiphenyls Determined by Photoelectron Spectroscopy (PES) and the Values of Predicted Θ with the TSEI Parameter and the TSEI Values of the Substituents

compound	$\Theta_{\text{exp}}(\text{PES})^a$	Θ_{pred}^b	res ^c	TSEI ₁ ^d	TSEI ₂ ^d
biphenyl	41.6	43.5	-1.9	0.0000	0.0000
2-Me	70	66.9	3.1	0.0000	1.0000
3-Me	46	46.4	-0.4	0.0000	0.1250
4-Me	46	44.3	1.7	0.0000	0.0370
2,2'-Me	78	78.0	0.0	1.0000	1.0000
2-Et	70	69.8	0.2	0.0000	1.1250
2- <i>i</i> -Pr	70	72.7	-2.7	0.0000	1.2500

^a Taken from ref 14. ^b Based on eq 9. ^c Res = $\Theta_{\text{exp}} - \Theta_{\text{pred}}$. ^d Calculated by eq 8b. TSEI₁ and TSEI₂ are steric effects of the substituent in two rings of the alkylbiphenyl, respectively; TSEI of the hydrogen atom is ignored.

For the alkyl, $R_{i,\text{rel}}$ is 1, $L_{i,\text{rel}}$ is the topological distance number of consecutive C-C bonds, and thus eq 8b is returned to eq 7.

3. APPLICATION OF TSEI AND DISCUSSION

Neil Isaacs²¹ pointed out "There are three important sources of steric strain. (a) Prelog strain: intramolecular van der Waals repulsive forces resulting from crowding together of large atoms or groups. This can result in permanent deformations. (b) Baeyer strain: bond-angle distortion. (c) Pitzer strain." The TSEI does not express any one of the above three kinds of steric strains, and it represents the decrement of probability for an attacking atom (or group) approaching to the reaction center R_{rc} . That is, the larger the TSEI of the substituent connected with R_{rc} is, the less the probability of the attacking atom approaching R_{rc} will be.

Estimation of Dihedral Angles of Alkylbiphenyl Compounds. The dihedral angle (Θ) between the two phenyl rings depends on the size and the position of the substituents in biphenyl. In general, the larger volume of the substituent in the 2,2'-position will force a larger dihedral angle Θ . It must be a correlation between the Θ and the TSEI of the substituent. So we first selected seven dihedral angles¹⁴ (Table 3) between the two phenyl rings of biphenyl that were determined by photoelectron spectroscopy (PES) as a model. The regression analysis between the seven experimental data of dihedral angles and the parameter TSEI (calculated by taking 2 and 2' positions as reaction centers, respectively) was carried out, and the regression equation is obtained as follows:

$$\Theta_{\text{PES}}(\text{deg}) = 43.4843(\pm 1.4675) + 11.1359(\pm 2.7326)\text{TSEI}_1 + 23.3798(\pm 1.8332)\text{TSEI}_2$$

$$R = 0.9912, s = 2.43, F = 112.5, N = 7 \quad (9)$$

The intercept of eq 9 is the dihedral angle value of biphenyl. In comparison with a coefficient of 0.9636 and a standard deviation of 4.4 in ref 13, the Θ values predicted by this work are closer to the experimental one (see Table 3).

However, the experimental data set in eq 9 is too small to demonstrate the TSEI reasonability. Furthermore, there is only one bisubstituted biphenyl in this data set. Unfortunately, there are no other experimental data of 2,2'-alkylbi-

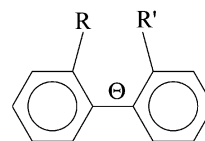


Figure 4. Dihedral angle Θ between the two phenyls in alkylbiphenyl derivatives studied here.

phenyl to be included in this model. Here we also selected a data set of 78 biphenyls having different alkyl substituents at positions 2 and 2' of the phenyl rings (see Figure 4), which were investigated by Estrada.¹⁴ Dihedral angles of these alkylbiphenyl compounds were estimated by molecular mechanics force field calculations,¹⁴ which can be widely used when the experimental data are not available. Then we correlated their dihedral angles Θ (see Table 4) with their TSEI values and got the linear regression eq 10.

$$\Theta_{\text{MM+}}(\text{deg}) = 0.8511(\pm 1.3298) + 25.1112(\pm 1.0638)\text{TSEI}_1 + 18.7279(\pm 0.4770)\text{TSEI}_2$$

$$R = 0.9845, s = 2.10, F = 1182, N = 78 \quad (10)$$

Eq 10 shows a good correlation between the Θ and the parameter TSEI. The standard deviation is 2.10, and the absolute average error between the observed and predicted Θ values is only 1.72 for the 78 alkylbiphenyl compounds in Table 4. Figure 5a shows the plot of predicted Θ versus observed Θ . Estrada et al.¹⁴ even developed a good correlation equation of a dihedral angle (Θ) with local spectral moments of the bond matrix for the same data set of 78 alkylbiphenyl compounds and got the standard error of 2.12. The present result is as good as Estrada's result.¹⁴

To further verify the steady of eq 10, the 78 samples in Table 4 were divided into three groups I, II, and III by random (the groups and the predicted dihedral angles for eqs 11a-c are listed in Table 5 of the Supporting Information). Then cross-validations (CV) were carried out, and eqs 11a-c were obtained.

Regression with groups I and II:

$$\Theta_{\text{MM+}}(\text{deg}) = 0.0074(\pm 2.1340) + 25.5242(\pm 1.6505)\text{TSEI}_1 + 19.1569(\pm 0.6017)\text{TSEI}_2$$

$$R = 0.9812, s = 2.27, F = 633.7, N = 52 \quad (11a)$$

Regression with groups I and III:

$$\Theta_{\text{MM+}}(\text{deg}) = 0.5102(\pm 1.3716) + 25.3745(\pm 1.0840)\text{TSEI}_1 + 18.5871(\pm 0.6099)\text{TSEI}_2$$

$$R = 0.9869, s = 2.05, F = 916, N = 52 \quad (11b)$$

Regression with groups II and III:

$$\Theta_{\text{MM+}}(\text{deg}) = 1.9641(\pm 1.6280) + 24.4773(\pm 1.3768)\text{TSEI}_1 + 18.4306(\pm 0.5527)\text{TSEI}_2$$

$$R = 0.9855, s = 2.00, F = 824.4, N = 52 \quad (11c)$$

Figure 5b shows the plot of predicted Θ by cross-validation versus the observed Θ . The predicted dihedral angles are also in good agreement with the dihedral angles in the literature,¹⁴ and the absolute average error is 1.79. It confirms the steady of eq 10 and the availability of TSEI parameter.

Table 4. Dihedral Angles between the Phenyl Rings Θ in Alkylbiphenyls Calculated by Molecular Mechanics Force Field (MM+) and the Values of Θ Predicted with TSEI as well as TSEI, SVTI², and R'_s Parameters of Substituents

no.	compound	Θ_{obsd}^a	Θ_{pred}^b	TSEI ^c	TSEI ^c	(SVTI ₁) ^{2d}	(SVTI ₂) ^{2d}	(R'_s) ₁ ^e	(R'_s) ₂ ^e
1	biphenyl	1.46	0.85	0.0000	0.0000			0.0000	0.0000
2	2-CH ₃	28.50	25.96	1.0000	0.0000	1		1.0000	0.0000
3	2-CH ₃ , 2'-CH ₃	46.07	44.69	1.0000	1.0000	1	1	1.0000	1.0000
4	2-CH ₃ , 2'-C ₂ H ₅	49.75	47.03	1.0000	1.1250	1	9	1.0000	1.2500
5	2-CH ₃ , 2'-n-C ₃ H ₇	49.86	47.72	1.0000	1.1620	1	36	1.0000	1.3611
6	2-CH ₃ , 2'-iso-C ₃ H ₇	53.45	49.37	1.0000	1.2500	1	25	1.0000	1.5000
7	2-CH ₃ , 2'-n-C ₄ H ₉	47.96	48.02	1.0000	1.1777	1	36	1.0000	1.4236
8	2-CH ₃ , 2'-iso-C ₄ H ₉	48.98	48.42	1.0000	1.1990	1	81	1.0000	1.4722
9	2-CH ₃ , 2'-sec-C ₄ H ₉	51.84	50.07	1.0000	1.2870	1	64	1.0000	1.6111
10	2-CH ₃ , 2'-tert-C ₄ H ₉	58.52	59.91	1.0000	1.8125	1	49	1.0000	1.7500
11	2-CH ₃ , 2'-n-C ₅ H ₁₁	48.36	48.17	1.0000	1.1857	1	36	1.0000	1.4636
12	2-CH ₃ , 2'-iso-C ₅ H ₁₁	47.55	48.31	1.0000	1.1933	1	36	1.0000	1.5347
13	2-CH ₃ , 2'-CH(C ₂ H ₅) ₂	52.47	50.76	1.0000	1.3240	1	121	1.0000	1.7222
14	2-C ₂ H ₅	30.12	29.10	1.1250	0.0000	9		1.2500	0.0000
15	2-C ₂ H ₅ , 2'-C ₂ H ₅	53.94	50.17	1.1250	1.1250	9	9	1.2500	1.2500
16	2-C ₂ H ₅ , 2'-n-C ₃ H ₇	52.97	50.86	1.1250	1.1620	9	36	1.2500	1.3611
17	2-C ₂ H ₅ , 2'-iso-C ₃ H ₇	55.69	52.51	1.1250	1.2500	9	25	1.2500	1.5000
18	2-C ₂ H ₅ , 2'-n-C ₄ H ₉	49.93	51.16	1.1250	1.1777	9	36	1.2500	1.4236
19	2-C ₂ H ₅ , 2'-iso-C ₄ H ₉	50.71	51.56	1.1250	1.1990	9	81	1.2500	1.4722
20	2-C ₂ H ₅ , 2'-sec-C ₄ H ₉	53.65	53.20	1.1250	1.2870	9	64	1.2500	1.6111
21	2-C ₂ H ₅ , 2'-tert-C ₄ H ₉	62.82	63.05	1.1250	1.8125	9	49	1.2500	1.7500
22	2-C ₂ H ₅ , 2'-n-C ₅ H ₁₁	49.88	51.31	1.1250	1.1857	9	36	1.2500	1.4636
23	2-C ₂ H ₅ , 2'-iso-C ₅ H ₁₁	49.44	51.45	1.1250	1.1933	9	36	1.2500	1.5347
24	2-C ₂ H ₅ , 2'-CH(C ₂ H ₅) ₂	53.98	53.90	1.1250	1.3240	9	121	1.2500	1.7222
25	2-n-C ₃ H ₇	30.64	30.03	1.1620	0.0000	36		1.3611	0.0000
26	2-n-C ₃ H ₇ , 2'-n-C ₃ H ₇	53.24	51.79	1.1620	1.1620	36	36	1.3611	1.3611
27	2-n-C ₃ H ₇ , 2'-iso-C ₃ H ₇	56.93	53.44	1.1620	1.2500	36	25	1.3611	1.5000
28	2-n-C ₃ H ₇ , 2'-n-C ₄ H ₉	49.83	52.09	1.1620	1.1777	36	36	1.3611	1.4236
29	2-n-C ₃ H ₇ , 2'-iso-C ₄ H ₉	51.63	52.49	1.1620	1.1990	36	81	1.3611	1.4722
30	2-n-C ₃ H ₇ , 2'-sec-C ₄ H ₉	53.19	54.13	1.1620	1.2870	36	64	1.3611	1.6111
31	2-n-C ₃ H ₇ , 2'-tert-C ₄ H ₉	63.18	63.97	1.1620	1.8125	36	49	1.3611	1.7500
32	2-n-C ₃ H ₇ , 2'-n-C ₅ H ₁₁	49.88	52.24	1.1620	1.1857	36	36	1.3611	1.4636
33	2-n-C ₃ H ₇ , 2'-iso-C ₅ H ₁₁	49.45	52.38	1.1620	1.1933	36	36	1.3611	1.5347
34	2-n-C ₃ H ₇ , 2'-CH(C ₂ H ₅) ₂	53.55	54.83	1.1620	1.3240	36	121	1.3611	1.7222
35	2-iso-C ₃ H ₇	34.01	32.24	1.2500	0.0000	25		1.5000	0.0000
36	2-iso-C ₃ H ₇ , 2'-iso-C ₃ H ₇	57.69	55.65	1.2500	1.2500	25	25	1.5000	1.5000
37	2-iso-C ₃ H ₇ , 2'-n-C ₄ H ₉	52.88	54.30	1.2500	1.1777	25	36	1.5000	1.4236
38	2-iso-C ₃ H ₇ , 2'-iso-C ₄ H ₉	53.72	54.69	1.2500	1.1990	25	81	1.5000	1.4722
39	2-iso-C ₃ H ₇ , 2'-sec-C ₄ H ₉	57.33	56.34	1.2500	1.2870	25	64	1.5000	1.6111
40	2-iso-C ₃ H ₇ , 2'-tert-C ₄ H ₉	68.47	66.18	1.2500	1.8125	25	49	1.5000	1.7500
41	2-iso-C ₃ H ₇ , 2'-n-C ₅ H ₁₁	53.43	54.45	1.2500	1.1857	25	36	1.5000	1.4636
42	2-iso-C ₃ H ₇ , 2'-iso-C ₅ H ₁₁	53.01	54.59	1.2500	1.1933	25	36	1.5000	1.5347
43	2-iso-C ₃ H ₇ , 2'-CH(C ₂ H ₅) ₂	59.60	57.04	1.2500	1.3240	25	121	1.5000	1.7222
44	2-n-C ₄ H ₉	30.81	30.42	1.1777	0.0000	36		1.4236	0.0000
45	2-n-C ₄ H ₉ , 2'-n-C ₄ H ₉	50.12	52.48	1.1777	1.1777	36	36	1.4236	1.4236
46	2-n-C ₄ H ₉ , 2'-iso-C ₄ H ₉	50.93	52.88	1.1777	1.1990	36	81	1.4236	1.4722
47	2-n-C ₄ H ₉ , 2'-sec-C ₄ H ₉	52.89	54.53	1.1777	1.2870	36	64	1.4236	1.6111
48	2-n-C ₄ H ₉ , 2'-tert-C ₄ H ₉	68.07	64.37	1.1777	1.8125	36	49	1.4236	1.7500
49	2-n-C ₄ H ₉ , 2'-n-C ₅ H ₁₁	49.75	52.63	1.1777	1.1857	36	36	1.4236	1.4636
50	2-n-C ₄ H ₉ , 2'-iso-C ₅ H ₁₁	49.42	52.77	1.1777	1.1933	36	36	1.4236	1.5347
51	2-n-C ₄ H ₉ , 2'-CH(C ₂ H ₅) ₂	54.33	55.22	1.1777	1.3240	36	121	1.4236	1.7222
52	2-iso-C ₄ H ₉	32.92	30.96	1.1990	0.0000	81		1.4722	0.0000
53	2-iso-C ₄ H ₉ , 2'-iso-C ₄ H ₉	52.18	53.41	1.1990	1.1990	81	81	1.4722	1.4722
54	2-iso-C ₄ H ₉ , 2'-sec-C ₄ H ₉	53.87	55.06	1.1990	1.2870	81	64	1.4722	1.6111
55	2-iso-C ₄ H ₉ , 2'-tert-C ₄ H ₉	66.33	64.90	1.1990	1.8125	81	49	1.4722	1.7500
56	2-iso-C ₄ H ₉ , 2'-n-C ₅ H ₁₁	50.84	53.17	1.1990	1.1857	81	36	1.4722	1.4636
57	2-iso-C ₄ H ₉ , 2'-iso-C ₅ H ₁₁	50.36	53.31	1.1990	1.1933	81	36	1.4722	1.5347
58	2-iso-C ₄ H ₉ , 2'-CH(C ₂ H ₅) ₂	54.84	55.76	1.1990	1.3240	81	121	1.4722	1.7222
59	2-sec-C ₄ H ₉	35.01	33.17	1.2870	0.0000	64		1.6111	0.0000
60	2-sec-C ₄ H ₉ , 2'-sec-C ₄ H ₉	57.42	57.27	1.2870	1.2870	64	64	1.6111	1.6111
61	2-sec-C ₄ H ₉ , 2'-tert-C ₄ H ₉	70.38	67.11	1.2870	1.8125	64	49	1.6111	1.7500
62	2-sec-C ₄ H ₉ , 2'-n-C ₅ H ₁₁	53.35	55.37	1.2870	1.1857	64	36	1.6111	1.4636
63	2-sec-C ₄ H ₉ , 2'-iso-C ₅ H ₁₁	53.23	55.52	1.2870	1.1933	64	36	1.6111	1.5347
64	2-sec-C ₄ H ₉ , 2'-CH(C ₂ H ₅) ₂	59.10	57.96	1.2870	1.3240	64	121	1.6111	1.7222
65	2-tert-C ₄ H ₉	43.00	46.37	1.8125	0.0000	49		1.7500	0.0000
66	2-tert-C ₄ H ₉ , 2'-tert-C ₄ H ₉	85.59	80.31	1.8125	1.8125	49	49	1.7500	1.7500
67	2-tert-C ₄ H ₉ , 2'-n-C ₅ H ₁₁	68.19	68.57	1.8125	1.1857	49	36	1.7500	1.4636
68	2-tert-C ₄ H ₉ , 2'-iso-C ₅ H ₁₁	69.55	68.71	1.8125	1.1933	49	36	1.7500	1.5347
69	2-tert-C ₄ H ₉ , 2'-CH(C ₂ H ₅) ₂	73.40	71.16	1.8125	1.3240	49	121	1.7500	1.7222
70	2-n-C ₅ H ₁₁	30.78	30.63	1.1857	0.0000	36		1.4636	0.0000
71	2-n-C ₅ H ₁₁ , 2'-n-C ₅ H ₁₁	50.48	52.83	1.1857	1.1857	36	36	1.4636	1.4636
72	2-n-C ₅ H ₁₁ , 2'-iso-C ₅ H ₁₁	49.42	52.97	1.1857	1.1933	36	36	1.4636	1.5347

Table 4 (Continued)

no.	compound	Θ_{obsd}^a	Θ_{pred}^b	TSEI_1^c	TSEI_2^c	$(\text{SVTI}_1)^{2d}$	$(\text{SVTI}_2)^{2d}$	$(R'_s)_1^e$	$(R'_s)_2^e$
73	2-n-C ₅ H ₁₁ , 2'-CH(C ₂ H ₅) ₂	53.09	55.42	1.1857	1.3240	36	121	1.4636	1.7222
74	2-iso-C ₅ H ₁₁	30.59	30.82	1.1933	0.0000	36		1.5347	0.0000
75	2-iso-C ₅ H ₁₁ , 2'-iso-C ₅ H ₁₁	49.98	53.16	1.1933	1.1933	36	36	1.5347	1.5347
76	2-iso-C ₅ H ₁₁ , 2'-CH(C ₂ H ₅) ₂	53.41	55.61	1.1933	1.3240	36	121	1.5347	1.7222
77	2-CH(C ₂ H ₅) ₂	34.07	34.10	1.3240	0.0000	121		1.7222	0.0000
78	2-CH(C ₂ H ₅) ₂ , 2'-CH(C ₂ H ₅) ₂	60.97	58.89	1.3240	1.3240	121	121	1.7222	1.7222

^a Taken from ref 14. ^b Predicted by eq 10. ^c TSEI₁ and TSEI₂ present the steric effect of the R and the R' substituents in Figure 4. TSEI of the hydrogen atom is ignored. ^d Taken from ref 13, this parameter will be discussed in the following part. ^e Calculated by eq 2, in which the *r* was replaced with the number of consecutive C–C bonds and the carbon atom covalent radius *R* was taken as one unit and the *R'*_s of the hydrogen atom is ignored.

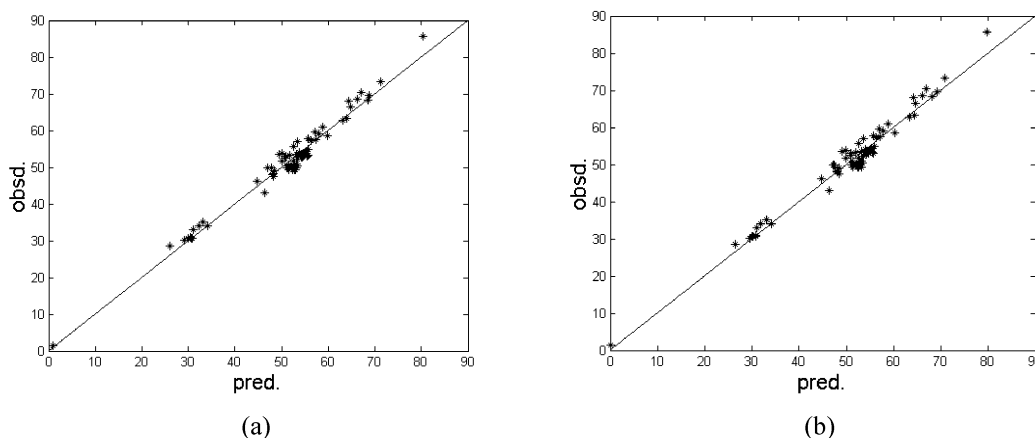


Figure 5. (a) Plot of observed Θ_{obsd} vs Θ_{pred} predicted by eq 10. (b) Plot of observed Θ_{obsd} vs Θ_{pred} by the cross-validations method.

Comparing with Parameters SVTI and R'_s . Ivanciuc¹⁵ at el. even defined a Steric Vertex Topological Index (SVTI) encoding the steric effect of an alkyl group and used its square SVTI^2 for dealing with reaction rates of esterification of alkyl substituted carboxylic acids with methanol under different conditions and got a good result. Here, the dihedral angle, Θ , was related to the parameter SVTI^2 (data see the Table 3), and the linear regression eq 12a was obtained. Comparing with the correlation eq 12b with parameter TSEI, the correlation of eq 12b is much better than that of eq 12a.

$$\Theta_{\text{MM}+}(\text{deg}) = 51.3415(\pm 1.8394) + 0.0829(\pm 0.0339)(\text{SVTI}_1)^2 + 0.0179(\pm 0.0266)(\text{SVTI}_2)^2$$

$$R = 0.3325, s = 6.95, F = 3.9, N = 66 \quad (12a)$$

$$\Theta_{\text{MM}+}(\text{deg}) = -4.7254(\pm 2.2044) + 26.0295(\pm 1.4397)\text{TSEI}_1 + 22.0981(\pm 1.2674)\text{TSEI}_2$$

$$R = 0.9603, s = 2.05, F = 373, N = 66 \quad (12b)$$

Cherkasov⁸ even used parameter R'_s to interpret successfully ionization potentials and electron affinities of C-centered radicals in terms of operational atomic contributions. If the dihedral angle Θ is also correlated with this parameter, R'_s (data see Table 3), the regression eq 12c is given.

$$\Theta_{\text{MM}+}(\text{deg}) = 6.7982(\pm 3.2534) + 17.2587(\pm 2.2318)(R'_s)_1 + 15.8733(\pm 1.0167)(R'_s)_2$$

$$R = 0.9036, s = 5.14, F = 166.8, N = 78 \quad (12c)$$

Compared with eq 10, the correlation of eq 12c is less than that of eq 10.

Estimation of Various Dihedral Angles for 1,2-Disubstituted Benzene. For the 1,2-disubstituted benzene, there is a dihedral angle, Θ , between the two groups attached to the π -bonded skeletal of benzene due to the repulsion of adjacent groups. Charton²² even correlated the dihedral angle Θ with the eq $1/\sin\Theta = a_{30}/\sum r + a_{11}$, where a_{30} and a_{11} are coefficients and r is the van der Waals radius of two adjacent groups. The Θ resulting from the repulsion of adjacent groups, we think, must be correlated with the TSEI values of the two adjacent substituents in the benzene ring. In addition, if substituents exist in another position of the benzene ring except 1- and 2-positions, the Θ also must be affected by the steric effect of those substituents. Therefore, the effect of the steric effect of all substituents in the benzene ring on the Θ was considered.

For the five kinds of compounds, 2-XC₆H₄Ac, 2-X-4-F-C₆H₃Ac, 2-X-4-F-C₆H₃CH=CH₂, 2,6-disubstituted 4-bromobiphenyls, and 2-O₂N-1,4-dialkylC₆H₃, their Θ values have been determined by NMR spectra.²² Here the Θ values were correlated with parameter TSEI of substituents, which were expressed by TSEI₁, TSEI₂, TSEI₄, and TSEI₆, for the substituents at 1-, 2-, 4-, and 6-positions of benzene ring, respectively. The correlation equation between the dihedral angles and the TSEI values (see Table 6) was given as follows:

$$\Theta = -24.9608(\pm 9.9958) + 22.3878(\pm 8.3826)\text{TSEI}_1 + 15.2626(\pm 2.4526)\text{TSEI}_2 + 17.5526(\pm 2.8318)\text{TSEI}_4 + 6.9616(\pm 2.8627)\text{TSEI}_6$$

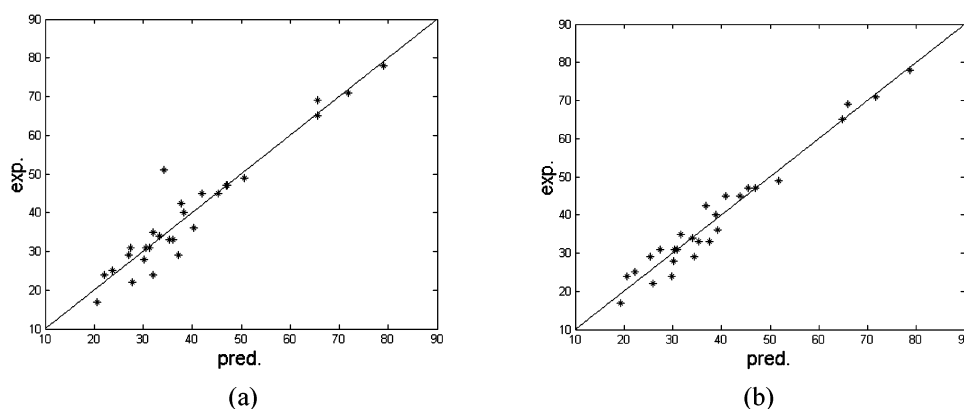
$$R = 0.9554, s = 5.01, F = 60.2, N = 28 \quad (13)$$

The correlation of eq 13 is good. Figure 6a is the plot of calculated Θ versus experimental Θ . Seen from Figure 6a,

Table 6. Dihedral Angles Θ (in Degrees) of Compounds and Parameters TSEI of Substituents

systems and determined condition	no.	X	Θ_{exp}^a	Θ_{calc}^b	TSEI ₁ ^c	TSEI ₂ ^c	TSEI ₄ ^c	TSEI ₆ ^c	σ_p^d
2-XC ₆ H ₄ Ac ¹³ C NMR	1	Me	24	20.6	1.1972	1.0362	0.1753	0.1753	0.00
	2	Et	25	22.3	1.1972	1.1581	0.1753	0.1753	0.00
	3	<i>i</i> -Pr	29	25.4	1.1972	1.3752	0.1753	0.1753	0.00
	4 ^e	<i>t</i> -Bu	51	31.8 ^f	1.1972	1.8395	0.1753	0.1753	0.00
	5	MeO	17	19.4	1.1972	0.9505	0.1753	0.1753	0.00
	6	Cl	22	26.0	1.1972	1.419	0.1753	0.1753	0.00
	7	Br	24	29.8	1.1972	1.6957	0.1753	0.1753	0.00
	8	I	29	34.5	1.1972	2.0265	0.1753	0.1753	0.00
2-X-4-F-C ₆ H ₃ Ac ¹⁹ F NMR	9	F	31	27.5	1.1972	0.7449	0.7449	0.1753	0.06
	10	Cl	42.5	36.9	1.1972	1.419	0.7449	0.1753	0.06
	11	Br	45	40.8	1.1972	1.6957	0.7449	0.1753	0.06
	12	I	47	45.4	1.1972	2.0265	0.7449	0.1753	0.06
	13	Me	35	31.6	1.1972	1.0362	0.7449	0.1753	0.06
	14	OE _t	31	31.0	1.1972	0.9939	0.7449	0.1753	0.06
	15	OMe	31	30.4	1.1972	0.9505	0.7449	0.1753	0.06
2-X-4-F-C ₆ H ₃ CH=CH ₂ ¹⁹ F NMR	16	Cl	33	35.4	1.1187	1.419	0.7449	0.1753	0.06
	17	Br	36	39.3	1.1187	1.6957	0.7449	0.1753	0.06
	18	I	45	43.9	1.1187	2.0265	0.7449	0.1753	0.06
	19	Me	28	30.1	1.1187	1.0362	0.7449	0.1753	0.06
	20	H	33	37.5	1.3081	0	1.6957	0.1753	0.23
2,6-diX 4-bromobiphenyls ¹ H NMR	21	F	49	51.8	1.3081	0.7449	1.6957	0.7449	0.23
	22	Cl	69	65.9	1.3081	1.419	1.6957	1.419	0.23
	23	Br	71	71.7	1.3081	1.6957	1.6957	1.6957	0.23
	24	I	78	78.6	1.3081	2.0265	1.6957	2.0265	0.23
2-O ₂ N-1,4-diRC ₆ H ₃ ^g ¹ H NMR	25	Me	34	34.1	1.0362	1.0354	1.0362	0.1753	-0.17
	26	Et	40	38.8	1.1581	1.0354	1.1581	0.1753	-0.15
	27	<i>i</i> -Pr	47	47.0	1.3752	1.0354	1.3752	0.1753	-0.17
	28	<i>t</i> -Bu	65	64.8	1.8395	1.0354	1.8395	0.1753	-0.20

^a Dihedral angle, taken from ref 22. ^b Predicted Θ by eq 14. ^c TSEI_{*i*} is TSEI of the substituent in the *i*-position of the benzene ring and contains the steric effect of hydrogen atoms in all substituents. ^d σ_p is the Hammett constant of the para-substituent, taken from ref 23. ^e Excluded from the correlation eq 14. ^f Calculated Θ by eq 14. ^g R presents alkyl.

**Figure 6.** (a) Plot of experimental Θ_{exp} vs Θ_{pred} predicted by eq 13. (b) Plot of experimental Θ_{exp} vs Θ_{pred} predicted by eq 14.

there is a sharp deviation point, which is 2-*t*-BuC₆H₄Ac. If it is excluded, correlation is improved greatly (see eq 14 and Figure 6b).

$$\Theta = -21.1727(\pm 6.8385) + 19.0189(\pm 5.7387)\text{TSEI}_1 + 13.9526(\pm 1.6970)\text{TSEI}_2 + 19.1977(\pm 1.9518)\text{TSEI}_4 + 6.9503(\pm 1.9476)\text{TSEI}_6$$

$$R = 0.9801, s = 3.41, F = 134.2, N = 27 \quad (14)$$

Eq 14 shows that dihedral angles of the above five kinds of compounds can be related to the same steric effect parameter TSEI. The correlation coefficient of eq 14 is better than the results obtained by Charton.²²

To investigate the effect of the electronic effect of the 4-substituent on the Θ , we take its Hammett constant σ_p to

replace the TSEI₄ of eq 14 and got the following regression equation:

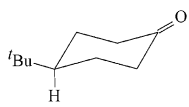
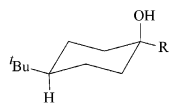
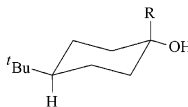
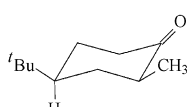
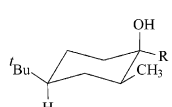
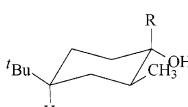
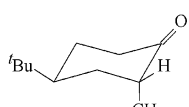
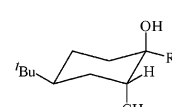
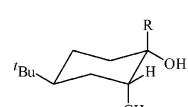
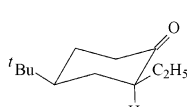
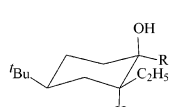
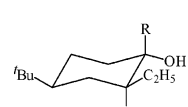
$$\Theta = -32.9965(\pm 16.8790) + 46.2214(\pm 12.4303)\text{TSEI}_1 + 6.2776(\pm 3.6216)\text{TSEI}_2 + 20.6904(\pm 4.6376)\text{TSEI}_6 - 5.0914(\pm 17.9171)\sigma_p$$

$$R = 0.8878, s = 7.90, F = 20.5, N = 27 \quad (15)$$

The correlation of eq 15 is much less than that of eq 14. It implies that the steric effect is more important than the electronic effect for the effect of the 4-substituent on the Θ .

Application in Stereochemistry of Organometallic Compound Addition to Cyclic Ketones. An important value of the steric effect is axial/equatorial equilibria in cyclohexanes. The stereochemistry of organometallic compounds

Table 7. Reactions of Organomagnesium Compounds with Cyclohexanones^a

No.	Organomagnesium compound	Ketone	Isomer percentage ^b		ln(A/E)	TSEI _R ^c	TSEI _X ^c	TSEI _A ^d
			Axial alcohol	Equatorial alcohol				
								
1	(CH ₃) ₂ Mg		62	38	0.4895	1.0362	1.0362	0.0705
2	(<i>n</i> -C ₃ H ₇) ₂ Mg		75	25	1.0986	1.1952	1.1952	0.0705
3	CH ₃ MgI		53	47	0.1201	1.0362	2.0265	0.0705
4	CH ₃ MgBr		60	40	0.4055	1.0362	1.6957	0.0705
5	CH ₃ MgCl		59	41	0.3640	1.0362	1.4190	0.0705
6	C ₂ H ₅ MgBr		71	29	0.8954	1.1581	1.6957	0.0705
7	<i>i</i> -C ₃ H ₇ MgBr		82	18	1.5163	1.3752	1.6957	0.0705
8	<i>n</i> -C ₃ H ₇ MgBr		68	32	0.7538	1.1952	1.6957	0.0705
9	<i>n</i> -C ₃ H ₇ MgI		67	33	0.7082	1.1952	2.0265	0.0705
								
10	CH ₃ MgI		83	17	1.5856	1.0362	2.0265	0.2045
								
11	CH ₃ MgI		20	80	-1.3863	1.0362	2.0265	-0.0635 ^e
								
12	<i>n</i> -C ₃ H ₇ MgBr		92	8	2.4423	1.1952	1.6957	0.2420

^a Solvents of all reaction in Table 7 are diethyl ether. ^b Taken from ref 24. ^c TSEI_R and TSEI_X represent the steric effect of the alkyl group and the haloid atom in the Grignard reagent, respectively. For the Me₂Mg and (*n*-Pr)₂Mg, TSEI_R is equal to TSEI_X. Here the steric effect of hydrogen in the substituent must be considered. ^d TSEI_A is the sum of TSEI of 2- and 4-substituted alkyl in cyclohexanone, if there is not 2-substituted alkyl, TSEI_A is equal to TSEI of 4-*t*-Bu in cyclohexanone. The TSEI_A is calculated by taking the carbonyl carbon as the reaction center. ^e Me and *t*-Bu exist on different sides of the cyclic plane, respectively, so the TSEI of Me is taken as negative.

Table 8. Reactions of Organomagnesium Compounds with Cyclopentanones

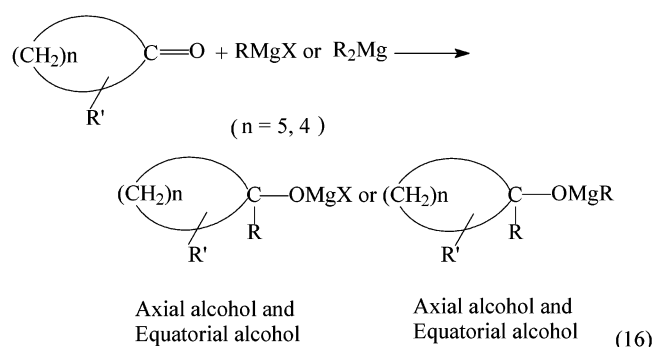
no.	organomagnesium compound	solvent	isomer percentage ^a		ln(C/T)	TSEI _R ^b	TSEI _X ^b
			cis alcohol	trans alcohol			
1	CH ₃ MgI	diethyl ether	45	55	-0.2007	1.0000	2.0265
2	CH ₃ MgBr	diethyl ether	60	40	0.4055	1.0000	1.6957
3	C ₂ H ₅ MgBr	THF	75	25	1.0986	1.1250	1.6957
4	<i>n</i> -C ₃ H ₇ MgBr	diethyl ether	80	20	1.3863	1.1620	1.6957
5	C ₆ H ₁₃ MgBr	diethyl ether	80	20	1.3863	1.1903	1.6957

^a Taken from ref 24. ^b TSEI_R and TSEI_X represent the steric effect of the alkyl group and the halide atom in the Grignard reagent, respectively.

addition to cyclic ketones has been widely investigated.²⁴ Lagersted et al.²⁵ developed a steric model for the prediction of stereoselectivity at carbonyl carbons in cyclic compounds, which emanates from the ground state geometry of the substrate, and the space available for the incoming reagent is explored for two hypothetical transition states. For the same

substrate reacting with different incoming reagents in a similar solvent, we think, its stereoselectivity at the carbonyl carbon should be predicted simply by the TSEI values of groups in the reagents and the substrate. Here, take the reactions of organomagnesium compounds with cyclohexanones (see Table 7) and cyclopentanones (see Table 8) for instance.

Ashby et al.²⁴ pointed out that (1) the observed steric course of alkylation of a cyclic ketone was primarily a function of the entering R group and of the steric requirement of the particular ketone as controlled by the steric strain and torsional in the transition state. (2) The halide of a Grignard reagent had little effect on the steric consequence of the reaction. For example, methylmagnesium chloride and bromide yielded essentially the same isomer ration in reaction with cyclopentanones and cyclohexanones, whereas methylmagnesium iodide tended to give a slightly higher percentage of attack from the more hindered side of the ketones. (3) Concerning the steric requirement of the ketone, the percentage of axial attack on methyl-substituted cyclohexanones increased as the methyl group was shifted from C-2 to C-4. (4) In reactions involving organomagnesium compounds with 2-alkylcyclopentanones, the attack occurred predominantly from the least hindered trans side (steric approach control) in the case of alkylmagnesium compounds. It is known that the Grignard reagent RMgX or dialkylmagnesium R₂Mg adds to cyclic ketone as follows:



There is selectivity (A/E) between the two sides of the carbonyl group (in which, A and E represent the isomer percentage of products, axial and equatorial alcohols, respectively) in eq 16. The experimental data (see Tables 7 and 8) show that the selectivity A/E is dominated by the steric effects of groups R and X (or R) in RMgX (or R₂Mg) and group R' in cyclic ketone, whose steric effects are expressed by symbols TSEI_R, TSEI_X, and TSEI_A, respectively. According to Lagersted's work,²⁵ this paper also proposed that selectivity A/E of eq 16 related to the TSEI:

$$A/E = k \exp(bTSEI_R + cTSEI_X + dTSEI_A) \quad (17a)$$

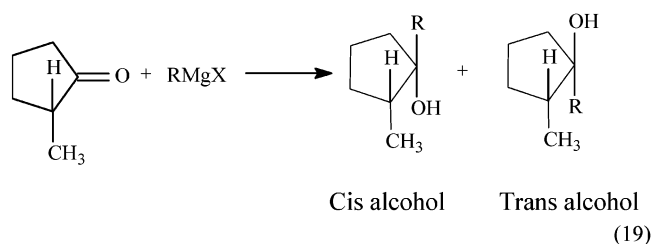
that is

$$\ln(A/E) = \ln k + bTSEI_R + cTSEI_X + dTSEI_A = a + bTSEI_R + cTSEI_X + dTSEI_A \quad (17b)$$

Therefore, the TSEI values of groups in RMgX (or R₂Mg) and cyclic ketone can be used to estimate the selectivity A/E of reaction 16. Equation 18 is the correlation equation between parameter TSEI and the selectivity A/E of cyclohexanones (see Table 7).

$$\begin{aligned} \ln(A/E) = & -3.4715(\pm 0.4347) + \\ & 3.5994(\pm 0.3417)TSEI_R - 0.4216(\pm 0.1119)TSEI_X + \\ & 10.2991(\pm 0.4921)TSEI_A \\ R = & 0.9937, s = 0.12, F = 210.8, N = 12 \quad (18) \end{aligned}$$

The reaction of 2-methylcyclopentanones with RMgX is



For eq 19, TSEI_A is a constant, and its selectivity of (cis alcohol)/(trans alcohol) (abbreviated to C/T, see Table 8) correlated only with TSEI_R and TSEI_X, that is, eq 17b can be simplified to the expression

$$\ln(C/T) = a' + bTSEI_R + cTSEI_X \quad (17c)$$

From eq 17c and Table 8, we get the correlation eq 20:

$$\begin{aligned} \ln(C/T) = & -2.2765(\pm 0.9378) + \\ & 5.6383(\pm 0.4833)TSEI_R - 1.8587(\pm 0.2863)TSEI_X \\ R = & 0.9976, s = 0.068, F = 206.7, N = 5 \quad (20) \end{aligned}$$

Eqs 18 and 20 showed that the stereoselectivity of the Grignard reagent (or other organometallic compounds) addition to cyclic ketones in a similar reaction condition can be predicted directly by the parameter TSEI.

Application in the Relative Rates of S_N2 Reactions.

Besides application in the dihedral angles of compounds and the stereochemistry of organometallic compound addition to cyclic ketones, the application of TSEI in the S_N2 reaction was also investigated. We know that the effect of the X (XCH₂Y) group on the rate of bimolecular nucleophilic substitution includes both steric and polar increments. Solvent polarity has a dramatic effect on S_N2 reaction activation energies, but, under the same solvent condition, the steric effect of an alkyl group on the rate of bimolecular substitution is a predominant facet.⁶ Equation 21a is the correlation between the relative rates (log *k*_{rel}, see Table 9) of seven S_N2 reactions (ethanolysis of alkyl bromide RBr)²⁶ and TSEI parameter. In addition, the correlations between the log *k*_{rel} and parameters *E*_s, or Cherkasov's *R'*_s or SVTI² or *V*_x, were carried out. The regression equations are given as follows together.

$$\begin{aligned} \log k_{rel} = & 16.7047(\pm 1.6350) - 14.9020(\pm 1.3771)TSEI \\ R = & 0.9793, s = 0.38, F = 117.1, N = 7 \quad (21a) \end{aligned}$$

$$\begin{aligned} \log k_{rel} = & 0.5941(\pm 0.3387) - 2.6773(\pm 0.4273)E_s \\ R = & 0.9418, s = 0.63, F = 39.3, N = 7 \quad (21b) \end{aligned}$$

$$\begin{aligned} \log k_{rel} = & 9.3921(\pm 2.4759) - 7.4786(\pm 1.7793)R'_s \\ R = & 0.8828, s = 0.88, F = 17.7, N = 7 \quad (21c) \end{aligned}$$

$$\begin{aligned} \log k_{rel} = & 0.5517(\pm 0.4302) - 0.0310(\pm 0.0065)SVTI^2 \\ R = & 0.9055, s = 0.79, F = 22.8, N = 7 \quad (21d) \end{aligned}$$

$$\begin{aligned} \log k_{rel} = & 3.5287(\pm 0.7271) - 5.6422(\pm 0.8742)V_x \\ R = & 0.9449, s = 0.61, F = 41.7, N = 7 \quad (21e) \end{aligned}$$

Seen from eqs 21a–e, the best correlation is eq 21a with the parameter TSEI.

Table 9. S_N2 Reaction Relative Rate k_{rel} of Some Alkyl Substrates as well as TSEI, Taft's E_s , R'_s , and SVTI² Parameter

R	k_{rel}^a	$\log k_{\text{rel}}$	TSEI	E_s^b	R'_s^c	SVTI ^{2d}	V_x^e
Me	30.00	1.4771	1.0000	0.00	1.0000	1	0.52
Et	1.000	0.0000	1.1250	0.07	1.2500	9	0.56
Pr	0.400	-0.3979	1.1620	0.36	1.3611	36	0.68
Bu	0.400	-0.3979	1.1777	0.39	1.4236	36	0.68
<i>i</i> -Pr	0.025	-1.6021	1.2500	0.47	1.5000	25	0.76
<i>i</i> -Bu	0.030	-1.5229	1.1990	0.93	1.5347	81	0.98
<i>t</i> -Bu-CH ₂	10 ⁻⁵	-4.0000	1.3655	1.74	1.5833	144	1.34

^a Taken from ref 26. ^b Taken from ref 1. ^c Calculated with the same method in Table 4. ^d Taken from ref 15. ^e Taken from ref 7

Table 10. Interrelation of TSEI, E_s , R'_s , SVTI², and V_x

	TSEI	E_s	R'_s	SVTI ²	V_x
TSEI	1				
E_s	0.8706	1			
R'_s	0.9222	0.7716	1		
SVTI ²	0.8275	0.9909	0.7403	1	
V_x	0.8697	0.9985	0.7749	0.9859	1

The parameter E_s is from the hydrolysis of esters, and R'_s , SVTI², and V_x are from an empirical calculation. Here, the correlations between TSEI and the sets of the conventional steric substituent scales E_s , R'_s , SVTI², and V_x (see Table 9) were investigated. The result of Table 10 shows the correlations of TSEI with E_s , R'_s , SVTI², and V_x are not good. That is to say the TSEI cannot be displaced well by the parameters E_s , R'_s , SVTI², and V_x in the application of representing the decrement of probability for an attacking atom (or group) approaching the reaction center R_{rc}.

4. CONCLUSIONS

According to the above analysis and discussions, despite the parameter TSEI is simplicity, it reveals a primary part of the steric effect that the reaction center is screened by a substituent. Its good correlations to the dihedral angle of the alkylbiphenyl compounds and the 1,2-disubstituted benzene compounds, stereoselectivity of organomagnesium compounds addition to cyclic ketones, and relative rate of the S_N2 reaction show us a valuable application in QSPR/QSAR research with the TSEI parameter. In addition, the TSEI descriptor can be calculated easily for all types of alkyl groups (even containing heteroatom) and has a clear physical meaning. It provides a new theoretical method in the field of steric effect research. It should be noted that when a substituent contains a heteroatom, an electronic effect will exist among the substituents and the reaction center. In this case, only the TSEI is not enough to quantify the dihedral angle, stereoselectivity of organomagnesium compounds addition to cyclic ketones, and the relative rate of the S_N2 reaction and so on, and the TSEI together with other electronic effect parameters of substituents must be employed.

ACKNOWLEDGMENT

The project was supported by the National Natural Science Foundation of China No. 20172043 (NSFC) and the Hunan Province Education Commission (HPEC).

Supporting Information Available: The calculation process of Δ TSEI for three carbon atoms connecting with one carbon atom in the substituent and the result of random sampling of 78 dihedral angles for alkylbiphenyl compounds (Table 5). This material is available free of charge via the Internet at <http://pubs.acs.org>.

REFERENCES AND NOTES

- (1) Taft, R. W., Jr. Polar and Steric Substituent Constants for Aliphatic and o-Benzoate Groups from Rates of Esterification and Hydrolysis of Esters. *J. Am. Chem. Soc.* **1952**, *74*, 3120–3128.
- (2) DeTar, D. F.; Tenpas, C. J. Calculations of Steric Hindrance in Ester Hydrolysis Based on Estimation of van der Waals Strain Energies of Alkanes. *J. Am. Chem. Soc.* **1976**, *98*, 4567–4571.
- (3) DeTar, D. F.; Tenpas, C. J. Theoretical Calculation of Steric Effects in Ester Hydrolysis. *J. Am. Chem. Soc.* **1976**, *98*, 7903–7908.
- (4) Hancock, C. K.; Meyers, E. A.; Yager, B. J. Quantitative Separation of Hyperconjugation Effects from Steric Substituent Constants. *J. Am. Chem. Soc.* **1961**, *83*, 4211–4213.
- (5) Charton, M. Steric Effects. Base-Catalyzed Ester Hydrolysis. *J. Am. Chem. Soc.* **1975**, *97*, 3691–3693.
- (6) Charton, M. Steric Effects. Bimolecular Nucleophilic Substitution. *J. Am. Chem. Soc.* **1975**, *97*, 3694–3697.
- (7) Charton, M. Steric Effects. 13. Composition of the Steric Parameter as a Function of Alkyl Branching. *J. Org. Chem.* **1978**, *43*, 3995–4001.
- (8) Cherkasov, A.; Jonsson, M. Substituent Effects on Thermochemical Properties of Free Radicals. New Substituent Scales for C-Centered Radicals. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 1151–1156.
- (9) Cherkasov, A.; Jonsson, M. Substituent Effects on Thermochemical Properties of C-, N-, O-, and S-Centered Radicals. Physical Interpretation of Substituent Effects. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 1057–1063.
- (10) Marco, P.; Simone, R.; Gianni, C.; Vincenzo, S. Intramolecular solvation effects in the S_N2 reaction Cl⁻ + Cl(CH₂)_nCN. *J. Chem. Phys.* **2003**, *119*(17), 9603–9072.
- (11) Marc, F. L.; Janez, M.; Herman, J. C. B. Simulation of Slow Reaction with Quantum Character: Neutral Hydrolysis of Carboxylic Ester. *J. Comput. Chem.* **1999**, *20*(8), 886–895.
- (12) David, S. S.; Aravind, A.; Timothy, D. P. Naturally Chiral Metal Surface as Enantiospecific Adsorbents. *J. Phys. Chem. B* **2001**, *21*, 4771–4782.
- (13) Gironés, X.; Amat, L.; Robert, D.; Carbó-Dorca, R. Use of electron–electron repulsion energy as a molecular descriptor in QSAR and QSPR studies. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 477–485.
- (14) Estrada, E.; Molina, E.; Perdomo, L. I. Can 3D Structural Parameters Be Predicted from 2D (Topological) Molecular Descriptors? *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1015–1021.
- (15) Ivanciuc, O.; Balaban, A. T. Design of Topological Indices. Part 6. A New Topological parameter for the Steric Effect of Alkyl Substituents. *Croat. Chem. Acta* **1996**, *69*, 75–83.
- (16) Randic, M. Characterization of Molecular Branching. *J. Am. Chem. Soc.* **1975**, *97*, 6609–6615.
- (17) Kier, L. B. A Substituent Steric Effect Index Based on the Molecular Graph. *Quant. Struct.-Act. Relat.* **1987**, *6*, 117–122.
- (18) John, A. D. *Lange's Handbook of Chemistry*, 15th ed.; McGraw–Hill, Inc.: New York, 1999; p 4.35.
- (19) Isaacs, N. S. *Physical Organic Chemistry*, 2nd ed.; 1996; p 424.
- (20) Mohamed, A. A.; Jensen, F. Steric Effect in S_N2 Reactions. The Influence of Microsolvation. *J. Phys. Chem. A* **2001**, *105*, 3259–3268.
- (21) Neil, S. I. *Physical Organic Chemistry*, 2nd ed.; 1996; pp 319–322.
- (22) Charton, M. Quantitative Description of Steric and Electrical Effects of Planar π -Bonded Groups. 1. Variation of Dihedral Angle with the Size of an Adjacent Group. *J. Org. Chem.* **1983**, *48*, 1011–1015.
- (23) Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **1991**, *91*, 165–195.
- (24) Ashby, E. C.; Laemmle, J. T. Stereochemistry of Organometallic Compound Addition to Ketone. *Chem. Rev.* **1975**, *75*, 521–546.
- (25) Lagerstedt, I. C.; Olsson, T. A Steric Model for the Prediction of Stereoselectivity at Carbonyl Carbons in Cyclic Compounds. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 896–904.
- (26) March, J. *Advanced Organic Chemistry*; McGraw-Hill: New York, 1977; p 316.

CI034266B