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Estimation of Reactivity by Correlation Analyses Using Ωs and $\Delta\chi_B$ as Substituent Parameters

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The $\Delta\chi_B$ constant, defined as the difference of Bratsch's electronegativity of a substituent group from that of CH_3, was shown to serve as a versatile polar substituent constant in the multiple regression analysis using Ω_s as the steric constant. Reactivities, which are usually expressed by the rate constants (k) and/or biological activities, could be expressed well in the form of a correlation equation using the steric (Ω_s) and electronic ($\Delta\chi_B$: Bratsch's group electronegativity) substituent parameters. As both parameters for any substituents can be obtained easily by calculations, the substituent effect on any reaction can be evaluated easily with good reliability. The correlation analyses among the Ω_s, $\Delta\chi_B$, and the well-known Taft's E_s steric parameters showed that it must be reasonable to think that the E_s parameters for the substituents containing hetero-atoms had an electronic nature to some extent as well as the steric effect.

Reactivities are usually dependent on the steric and the electronic effects of substituents. For example, 2,6-disubstituted benzoic acids are difficult to esterify, and the electron-withdrawing substituents located at para- or meta-positions accelerate the hydrolysis of ethyl esters of substituted benzoic acids.[1] With the aim of estimating reactivities with the aid of the proper parameters representing the electronic or steric nature characteristic of the substituents, a number of useful equations have been proposed to correlate the reactivity with the electronic and steric substituent parameters. The Hammett's σ's[2] and the Taft's σ^* 's[3] are the representative electronic parameters of substituents, and the Taft's E_s's[4] are well-known steric parameters. The solvent effect and acidity are other important factors influential to the reactivity. These effects are also correlated linearly by the Grunwald–Winstein relationship[5] and the Brønsted relation.[6] Such relationships are called linear free energy relationships (LFER) and have been widely applied in the field of physical organic chemistry.

In most cases, however, the substituent effect is neither purely steric nor purely electronic in nature. Since the pioneering application of multiple regression analysis by Taft (where $E_l = \sigma^*$ and $S_t = E_s$ in Eq. 1), similar dual parameter equations have been proposed to reproduce the rates and equilibrium constants in a series of similar reactions of substrates bearing common reaction centers but various different substituents. These correlations are regressed generally by Eq. 1, where S_t and E_l are appropriate parameters for steric and electronic effects, respectively.

$$R(S_t, E_l) = aS_t + bE_l + c. \tag{1}$$

This sort of linear relationships are useful because the reactivity of any molecules can be estimated easily when the substituent parameters of interest are available. However, we often encounter the problem that the necessary substituent parameters are lacking. Usually, it is rather difficult to determine the unassigned substituent parameters because the conventional substituent parameters were usually decided empirically on the basis of kinetic measurements. To evaluate reliable substituent parameters, it is necessary to synthesize a target molecule and to measure the rate constant by experiments. In addition to this difficulty, the evaluated empirical substituent parameter needs to be tested carefully, to see whether it really reflects the intrinsic steric or electronic nature of the substituent without the mixing of the other. In contrast to experiments, theory provides a means for evaluating the steric and electronic effect separately. Ab initio calculations must be useful for the very accurate evaluation on relatively simple molecules, but are not suitable for complicated organic substituents composed of many rotational isomers. Thus, we proposed a steric substituent constant Ω_s,[7] which is defined as the ratio of the shadow area of the substituent projected on the circumscribing sphere to the total surface area. If we model the atoms by the spheres having their van der Waals radii, the shadow area is calculated from the optimized geometries by molecular mechanics calculations (MM2/MM3). The calculation allows us to take into account the all possible stable conformations in the evaluations of the Ω_s value, and the Ω_s's are considered to represent the real steric effect of the substituents. Therefore, we have chosen the Ω_s as the proper steric parameter for evaluating the reactivity. The validity of Ω_s as a steric parameter for LFER was discussed in our previous paper.[8] As easily understood from its definition, Ω_s measures the pure steric effect and must be suitable for multiple regression analysis if it is used in combination with an appropriate electronic constant.

In this report, we discuss the applicability of the linear regression equation shown in Eq. 1 for evaluating the reactivity of various reactions. The accuracy and the reliability of this sort of correlation analysis were checked by using the reactivity data for many kinds of reactions. The chemical significance of the results derived by this correlation analysis was also discussed.

Theory

Bratsch's Electronegativity as an Electronic Constant. A number of parameters to characterize the electronic nature of substituents have been proposed. Empirical electronic substituent parameters such as σ^* and σ_I are generally good, if available, and have been used widely in LFER correlations. However, they have disadvantages common to the empirical parameters. The group electronegativities defined by Bratsch (χ_B)[9] and Huheey (χ_H),[10] as well as Inamoto's ι parameter[11] are also well-known as electronic substituent parameters, and parameter sets for a series for substituent groups have been assigned. Among these electronic parameters stated above, Bratsch's χ_B is the most convenient because it can be calculated easily from the Pauling's scale-electronegativities. In practice, $\chi_B(G)$ for the substituent (G) can be calculated by putting the Pauling's electronegativity (x) of atoms concerned, the number of atoms (v) of a particular element in the group (G), and the number of atoms in group formula (N_G) into Eq. 2.

$$\chi_B(G) = N_G / \sum(v/x). \qquad (2)$$

As the correlation coefficient between the χ_B and the other group electronegativity parameters are good, χ_B can be used as a reliable and good electronic parameter for the polar substituents. The advantage of the χ_B over other electronic substituent parameters is the wide applicability to any heteroatom-containing substituents.

Regression Equations to Correlate Reactivity with Substituent Parameters. In our study, the basic equation to correlate the reactivity with the steric and electronic substituent parameters (Eq. 1) can be rewritten as Eq. 3 by replacing the steric ($\boldsymbol{S}_t$) and the electronic ($\boldsymbol{E}_l$) parameters by the actual Ω_s and $\Delta\chi_B$, respectively. The reactivity is usually expressed in the form of $\log k$ (rate constant) in LFER equations.

$$\log k = a\Omega_s + b\Delta\chi_B + c. \qquad (3)$$

Here, $\Delta\chi_B$ is a relative Bratsch's group electronegativity of substituent X defined as $\chi_B(X) - \chi_B(CH_3)$; a,b, and c are constants derived by regression analyses. Equation 3 is applicable to cases in which the substituent effect from only one substituent seems to be important or dominant (CASE 1). For example, the reaction of compounds RCOX (carboxylic acids, esters, amides, ketones, aldehydes) and alcohols (ROH) can be treated by Eq. 3. However, the treatment with Eq. 3 is not proper for the reactions where the reaction center has more than one substituent (e.g. amines, phosphines, and alkenes). In general, the electronic and steric effects from the all substituents must be summed up to evaluate the total substituent effect properly. For example, the contributions from the R^1, R^2, and R^3 substituents must be taken into account in the reactions where a series of amine molecules $N(R^1R^2R^3)$ are involved (CASE 2). Thus, the reactivity ($\log k$) can be given by Eq. 4.

$$\log k = \sum a_i\Omega_{si} + b\sum \Delta\chi_{Bi} + c. \qquad (4)$$

Here, Ω_{si} and $\Delta\chi_{Bi}$ are the Ω_s and the Bratsch's group electronegativity parameters for substituents (i) bonded to the reaction center, respectively. As the spatial disposition of the substituents around the reaction center seems to affect the reactivity in view of steric effects, the steric effect from each substituent was summed up independently (each steric effect of the substituent has an individual coefficient a_i, the anisotropic steric substituent effect). As to the electronic effect, Bratsch's $\Delta\chi_{Bi}$ terms were simply added and the total value ($\sum\Delta\chi_{Bi}$) was assumed to approximate the net electronic effect for the reaction. The molecules suitable for the correlation analyses shown in Eqs. 3 and 4 are summarized in Chart 1. Equations 3 and 4 are essentially similar. However, we will discuss them separately because the steric effect by each substituent is considerably different depending on its location and needs discussion of the relative importance of the substituents.

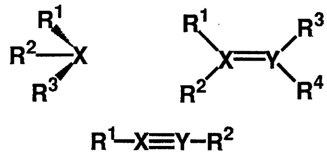
When we evaluate the relative importance of the steric

CASE 1 R–X

(carboxylic acids, esters, amides, ketones, aldehydes)

$$\log k = a\Omega_s + b\Delta\chi_B + c$$

CASE 2



$R^1{-}X{\equiv}Y{-}R^2$

(amines, phosphines, alkenes, alkynes)

$$\log k = \sum a_i\Omega_{si} + b\sum \Delta\chi_{Bi} + c$$

- R and R^i signiufy the substituent groups, and X or Y signify reaction center moiety.
- Ω_s: steric parameter for substituent R.
- $\Delta\chi_B$: Relative Bratsch's group electronegativity parameter of substituent X defined as $\chi_B(x) - \chi_B(CH_3)$. As Ω_s values range from 0 to 1, we had better use $\Delta\chi_B$ parameter instead of original χ_B in correlation equation stated above because $\Delta\chi_B$'s have comparable values to Ω_s. By comparing the coefficients number (a,b) in correlation equation, the ratio of contribution from steric and electronic effect towards reactivity can be evaluated qualitatively.

Chart 1. Correlation equations to relate the reactivities with the steric and electronic substituent parameters (Ω_s and $\Delta\chi_B$).

and the electronic effects in any reactions by dual parameter correlation analyses, we should be cautious. It is not proper to identify the relative importance of different "effects" by examining the regression coefficients (*a*,*b* in Eqs. 3 and 4) directly because each substituent parameter is measured on a different scale and has a different standard deviation. Normalization of the coefficients of steric and electronic terms is necessary to evaluate the relative importance properly. A popular method is to weight each regression coefficients by the standard deviations of the explanatory variables.[12] Thus, the percentage of the contribution of the steric effect ($\%S_t$) and of the electronic effect ($\%E_l$) in correlation Eqs. 3 and 4 could be calculated from the derived coefficients *a* and *b*, and the standard deviations of Ω_s (α) and of $\Delta\chi_B$ (β). For example, $\%S_t$ and $\%E_l$ for Eq. 3 can be given by Eqs. 5 and 6.

$$\%S_t = 100\alpha|a|/(\alpha|a|+\beta|b|), \quad (5)$$

$$\%E_l = 100\beta|b|/(\alpha|a|+\beta|b|). \quad (6)$$

We calculated $\%S_t$ and $\%E_l$ by using Eqs. 5 and 6 and examined the validity of the $\%S_t$ and $\%E_l$ values obtained for the various reactions. Good and useful information on the relative importance of the steric and electronic effects could not necessarily be found. In particular, unreasonable $\%S_t$ and $\%E_l$ values were shown in the case where the reaction data sets included only alkyl groups. If the reaction data sets have not only alkyl but also hetero-alkyl groups, $\%S_t$ and $\%E_l$ were reasonable. These results suggest that the above method using the standard deviations is not always correct when the standard deviation of one of the substituent parameters (Ω_s or $\Delta\chi_B$: in this case) used in the correlation analyses are strongly biased. Therefore, we decided to evaluate the relative importance of the steric and electronic effect in the reactions by using the regression coefficients (*a*,*b*) in a qualitative way.

Calculation of Ω_s Parameters for the Substituents Containing Hetero-Atom. We reported two types of Ω_s parameters[7] as expressed in Ω_s(R–CH$_3$) and Ω_s(R–COOH). The Ω_s(R–CH$_3$), which is called the CH$_3$-type Ω_s parameter and the reaction center X in the R–X molecule is modeled by a methyl group, is assumed to be a more isotropic steric parameter suitable for the reactions other than carbonyl compounds. Therefore, we used Ω_s(R–CH$_3$) parameters for our investigation. The Ω_s(R–CH$_3$) parameters were actually calculated by the OMEGAS90 program[13] based on the optimized geometries of the R–CH$_3$ molecule by MM2 and MM3 calculations. The stable conformations in R–CH$_3$ molecule were searched for by the MM2(91)[14] coupled with CONFLEX3 programs.[15] The optimized geometries thus obtained were used as input data for MM3(92)[16] full matrix optimization. The populations of the stable conformers were calculated from the relative steric energies obtained by MM3 full matrix optimization applying the Boltzmann theorem. The Ω_s(R–CH$_3$) parameters, for which the possible conformations of the substituent R were taken into account, could be calculated by putting the optimized geometries and the populations thus obtained into the OMEGAS90 program.

Results and Discussion

Ω_s Parameters Determined for Substituents. The Ω_s values for aralkyl, cycloalkyl, and heteroalkyl groups were newly calculated by the OMEGAS90 program and given in Table 1. For all alkyl substituents that have no hetero atoms, a good correlation (correlation coefficient r=0.953) was found between Ω_s and the well-known steric parameter E_s. However, we can find a slight deviation from the linear regression line for Ω_s versus E_s plot when the hetero-atom-containing substituents (haloalkyl, oxylalkyl groups) are also taken into account. The correlation coefficient was 0.887 when the available Ω_s and E_s parameters were used for correlation analysis. The correlation plot between E_s and Ω_s is shown in Fig. 1. A slight deviation shown in Fig. 1 suggests that Taft's

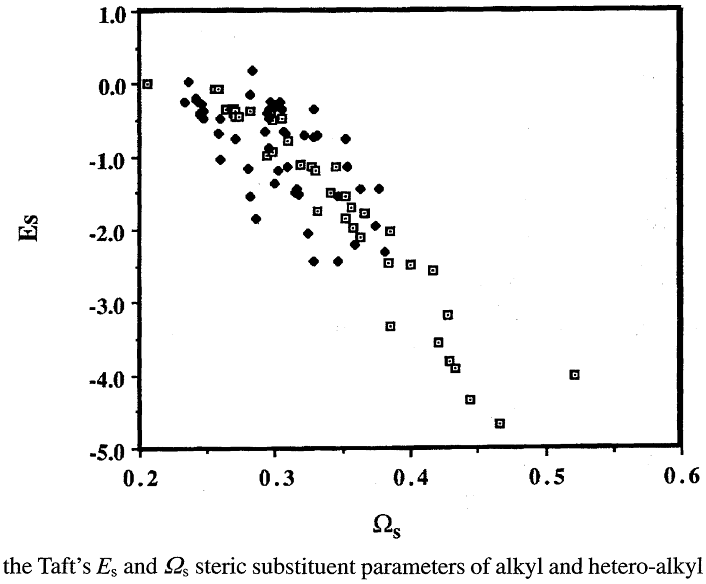


Fig. 1. Correlation between the Taft's E_s and Ω_s steric substituent parameters of alkyl and hetero-alkyl groups. □: Alkyl, ◆:Hetero-alkyl.

Table 1. The Determined Ω_s(R–CH$_3$) Steric Substituent Parameters

R	Ω_s	R	Ω_s	R	Ω_s
		Primary Alkyl			
Me	0.2052	Et	0.2550	*n*Pr	0.2680
*n*Bu	0.2684	*i*Bu	0.2976	*n*BuCH$_2$	0.2692
*i*BuCH$_2$	0.2696	*s*BuCH$_2$	0.3040	*t*BuCH$_2$	0.3315
*n*BuCH$_2$CH$_2$	0.2697	*i*BuCH$_2$CH$_2$	0.2703	*t*BuCH$_2$CH$_2$	0.2634
		Secondary Alkyl			
*i*Pr	0.3044	*s*Bu	0.3267	Et$_2$CH	0.3576
*n*PrMeCH	0.3290	*n*PtEtCH	0.3604	*i*PrEtCH	0.3893
*n*BuMeCH	0.3299	*t*BuMeCH	0.3842	*n*Pr$_2$CH	0.3629
*i*Pr$_2$CH	0.4234	*n*BuEtCH	0.3611	(*t*BuCH$_2$)MeCH	0.3523
*t*Bu*i*PrCH	0.4568	*t*Bu$_2$CH	0.4770	*i*Bu$_2$CH	0.3836
(*t*BuCH$_2$)$_2$CH	0.4274				
		Tertiary Alkyl			
*t*Bu	0.3518	EtMe$_2$C	0.3774	*i*PiMe$_2$C	0.4046
Et$_3$C	0.4292	*t*BuMe$_2$C	0.4335	*i*PrEt$_2$C	0.4610
*i*Pr$_2$MeC	0.4627	(*t*BuCH$_2$)Me$_2$C	0.4168	*i*Pr$_2$EtC	0.4849
*i*BuEt$_2$C	0.4940	*t*Bu*i*PrMeC	0.4968	*i*Pr$_3$C	0.5206
*t*Bu*i*PrEtC	0.5204	(*t*BuCH$_2$)*t*BuMeC	0.5208		
		Arylalkyl			
PhCH$_2$	0.2809	PhCH$_2$CH$_2$	0.2971	Ph(CH$_2$)$_3$	0.2734
Ph(CH$_2$)$_4$	0.2752	PhMe$_2$CCH$_2$	0.3565	PhMeCH	0.3297
PhEtCH	0.3402	Ph$_2$CH	0.3651	(PhCH$_2$)MeCH	0.3451
Ph$_2$MeC	0.4204	Ph$_2$EtC	0.4443	Ph$_3$C	0.4659
		Cycloalkyl			
c-C$_6$H$_{11}$CH$_2$	0.2943	*c*-C$_6$H$_{11}$CH$_2$CH$_2$	0.2719	*c*-C$_6$H$_{11}$(CH$_2$)$_3$	0.2709
c-C$_4$H$_7$	0.2582	*c*-C$_5$H$_9$	0.2975	*c*-C$_6$H$_{11}$	0.3091
c-C$_7$H$_{13}$	0.3189	(*c*-C$_6$H$_{11}$)Me$_2$C	0.4004	1-Me-*c*-C$_6$H$_{10}$	0.3848
c-C$_8$H$_{15}$	0.3287				
		Haloalkyl			
FCH$_2$	0.2332	F$_2$CH	0.2573	F$_3$C	0.2798
ClCH$_2$	0.2429	Cl$_2$CH	0.2816	Cl$_3$C	0.3240
BrCH$_2$	0.2460	Br$_2$CH	0.2861	Br$_3$C	0.3285
ICH$_2$	0.2475	I$_2$CH	0.2934	I$_3$C	0.3266
MeCHCl	0.2918	EtCHCl	0.3088	*n*PrCHCl	0.3101
*i*PrCHCl	0.3407	*n*BuCHCl	0.3107	*i*BuCHCl	0.3153
*s*BuCHCl	0.3439	*t*BuCHCl	0.3713	MeCCl$_2$	0.3311
Me$_2$CCl	0.3404	ClCH$_2$CH$_2$	0.2696	MeCHBr	0.2956
EtCHBr	0.3138	nPrCHBr	0.3153	*i*PrCHBr	0.3456
*n*BuCHBr	0.3173	*i*BuCHBr	0.3216	*s*BuCHBr	0.3480
*t*BuCHBr	0.3734	MeCBr$_2$	0.3372	Me$_2$CBr	0.3452
*n*C$_6$H$_{13}$CHBr	0.3164	BrCH$_2$CH$_2$	0.2716	BrCH$_2$CHBr	0.3225
MeCHI	0.2988	EtCHI	0.3178	*n*PrCHI	0.3146
*i*PrCHI	0.3532	*n*BuCHI	0.3199	*i*BuCHI	0.3258
*s*BuCHI	0.3543	*t*BuCHI	0.3812	MeCI$_2$	0.3398
Me$_2$CI	0.3488				
		Oxyalkyl			
HOCH$_2$	0.2356	MeOCH$_2$	0.2420	EtOCH$_2$	0.2420
*n*PrOCH$_2$	0.2439	*n*BuOCH$_2$	0.2435	*i*BuOCH$_2$	0.2464
*t*BuCH$_2$OCH$_2$	0.2488	PhOCH$_2$	0.2600	(EtO)$_2$CH	0.3026
MeCH(OH)	0.2826	EtCH(OH)	0.2954	*n*PrCH(OH)	0.2996
*i*PrCH(OH)	0.3264	*n*BuCH(OH)	0.2964	*i*BuCH(OH)	0.3035
*s*BuCH(OH)	0.3358	*t*BuCH(OH)	0.3585	*n*BuCH$_2$CH(OH)	0.3046
HOCH$_2$CH(OH)	0.2890	Me$_2$C(OH)	0.3311	1-OH-*c*-C$_5$H$_8$	0.3288
HOCH$_2$CH$_2$	0.2571	MeCH(OMe)	0.3066	EtCH(OMe)	0.3331
*n*PrCH(OMe)	0.3342	*i*PrCH(OMe)	0.3642	*n*BuCH(OMe)	0.3348

Table 1. (Continued)

R	Ω_s	R	Ω_s	R	Ω_s
*i*BuCH(OMe)	0.3382	*s*BuCH(OMe)	0.3736	*t*BuCH(OMe)	0.3966
$Me_2C(OMe)$	0.3625	$MeOCH_2CH_2$	0.2662	MeCH(OEt)	0.3073
MeCH(OPh)	0.3208	EtCH(OPh)	0.3530	$Me_2C(OCH_2$*t*Bu)	0.3766
$Me_2C(OO$*t*Bu)	0.3743				
		Thioalkyl			
$HSCH_2$	0.2808	$MeSCH_2$	0.2942	$EtSCH_2$	0.2951
$(EtS)_2CH$	0.3804	MeCH(SH)	0.3277	MeCH(SMe)	0.3442
MeCH(SEt)	0.3460				
		Other Heteroalkyl			
$NCCH_2$	0.2589	CH_3COCH_2	0.2706	$HOOCCH_2$	0.2506
CH_3COOCH_2	0.2223	Me_3SiCH_2	0.3229	$Me_2C(CN)$	0.3514
$CH_3COCH_2CH_2$	0.2697	$Me_3SiCH_2CH_2$	0.2734		

E_s parameters for the hetero-atom containing substituents should be contaminated by electronic effects to a lesser extent. When the E_s parameters for haloalkyl and oxyalkyl groups are expanded by the Ω_s and the electronic substituent parameters (for example, χ_B or σ_I) as $E_s=a\Omega_s+b\Delta\chi_B+c$, better correlation (correlation coefficient r=0.905, $a=-16.4$, $b=-0.31$, c=4.01) was obtained. Though the coefficient b for $\Delta\chi_B$ was smaller than a for Ω_s, it is certain that E_s's for hetero-atom-containing substituents have some electronic contribution.

The Ω_s parameter for hydrogen atom (Ω_s(H)) cannot be calculated by the OMEGAS90 program. Therefore, the Ω_s(H) value was estimated from simultaneous equations that were derived by expanding the Ω_s for some substituents ($-CR^1R^2R^3$) into each component (R^1,R^2, and R^3) as expressed in Eq. 7.

$$\Omega_s(-\mathrm{CR^1R^2R^3}) = a\Omega_s(\mathrm{R^1})+b\Omega_s(\mathrm{R^2})+c\Omega_s(\mathrm{R^3})+d. \tag{7}$$

For any substituent groups the Ω_s parameters of which have already been calculated, we can write an Eq. 7 by putting-in the calculated individual Ω_s's values for the substituents concerned. The best value for Ω_s(H) can be obtained by solving the simultaneous equations (Eq. 7) with the least-squares method. By using the available Ω_s values for alkyl substituents, the best-fit value of Ω_s(H) was found to be 0.104 (n=24, r=0.986).

Evaluation of the Reactivities by CASE 1 Correlation Equation. The results by correlation analyses with CASE 1 (Eq. 3) are shown in Table 2. Table 2 was classified according to the type of reactant molecules specified with the structure around reaction center as RCOX, ROX, RNH_2, $RPOX_2$, and other type (where X=H, alkyl, acyl, alkoxy, amino, and others). In all reactions in Table 2, only the one substituent R is expected to cause a critical substituent effect. Therefore, the correlation Eq. 3 could be reasonably applied.

For RCOX type reactions (Sets 1—41), hydrolysis of esters (Sets 1—12), amides (Sets 13—38), and thioesters (Set 39), and reduction of ketones (Sets 40,41) were compiled. Though the reactivities of the hydrolysis of esters and the reduction by $NaBH_4$ of ketones could be evaluated well with good correlation coefficients ($r>0.95$), the reactivities for the hydrolyses of amides ($RCONH_2$ type) could not be estimated well ($r<0.8$). This may be due to the neglect of the hyperconjugation effect of R adjacent to the carbonyl carbon. In contrast, the hydrolysis reactions of MeCONHR type amides (Sets 61—67 shown below) were expressed well by Eq. 3 with good correlation ($r>0.95$). The poor correlation in the hydrolysis reactions of $RCONH_2$ type amide was actually improved by introducing the (n_H-3) term (n_H: the number of hydrogen atoms bonded to the α-carbon atom) to the correlation equation. By using Eq. 8, the correlation coefficients were significantly improved to be higher than 0.97 (Sets 13—41 in Table 3).

$$\log k = a\Omega_s + b\Delta\chi_B + h(n_H-3)+c. \tag{8}$$

The parameter n_H works for taking into account the hyperconjugation effect. The hyperconjugation by a neighboring group to the amide group results in the reduction of the positive charge on the carbonyl carbon. As the C–N bond in amides has a partial double-bond character, it is reasonable to think that hyperconjugation considerably affects the reactivities of hydrolyses of amides.

The relative importance of steric and electronic effects in the Sets 1—41 was evaluated approximately in a qualitative way from the regression coefficients (a,b). In general, the steric effect was shown to be dominant for most of the reactions. The retarding effect by the bulky substituents could be found from the negative value of the coefficient a in Eq. 3. The importance of the electronic effect could be recognized well when the reaction sets have any kinetic data for hetero-atom substituents (the reaction set number are bold-typed and underlined in Tables 2, 5, and 6). For example, Set 14 (acid-catalyzed hydrolysis of amides) and Set 17 (base-catalyzed hydrolysis of amides) include 3 kinetic data for hetero-atom substituents. Looking through the rate constant (k) data of Set 17, a great increase of k by electron-withdrawing substituents could be found (k(for $ClCH_2$), k(for Cl_2CH), and k(for Cl_3C) are 10^2, 10^3, and 10^4 times faster than k(for CH_3), respectively) in Set 17. On the contrary, no significant acceleration effect by the hetero-atom substituents was rec-

Table 2. Correlation Analyses with $\log k = a\Omega_s + b\Delta\chi_B + c$ Equation

Set$^{a)}$	Reaction	*a*	*b*	*c*	*r*	*n*
[RCOX Type]						
1	RCO_2Et+OH^- in 70% MeAc at 24.8 °C 17)	−18.7	9.76	2.75	0.956	9
2	RCO_2Et+OH^- in 70% MeAc at 35 °C 17)	−18.5	12.2	2.94	0.957	9
3	RCO_2Et+OH^- in 70% MeAc at 44.7 °C 17)	−18.1	13.7	3.07	0.958	9
4	RCO_2Me+OH^- in 40% dioxane at 35 °C 19)	−11.1	7.22	3.71	0.940	8
5	RCO_2Et+OH^- in 87.8% EtOH at 30 °C 20)	−16.1	21.3	3.07	0.985	7
6	RCO_2Et+OH^- in 85% EtOH at 25 °C 21)	−21.8	35.9	2.48	0.970	10
7	RCO_2Et+OH^- in 85% EtOH at 35 °C 21)	−20.3	33.0	2.50	0.958	11
8	RCO_2Et+OH^- in 85% EtOH at 50 °C 21)	−19.3	31.3	2.75	0.959	11
9	RCO_2Et+OH^- in 85% EtOH at 25 °C 22)	−20.6	11.4	2.43	0.981	9
10	RCO_2Et+OH^- in 85% EtOH at 35 °C 22)	−23.2	5.87	3.75	0.998	7
11	RCO_2Et+OH^- in 85% EtOH at 45 °C 22)	−22.5	5.76	3.91	0.998	7
12	RCO_2Et+OH^- in 85% EtOH at 55 °C 22)	−22.1	5.53	4.13	0.930	7
13	$RCONH_2+H_3O^+$ in H_2O at 75 °C 23,24) (Hetero-atom substituent: $ClCH_2-$)	−7.40	0.06	−1.29	0.742	10
14	$RCONH_2+H_3O^+$ in H_2O at 65 °C 25) (Hetero-atom substituents: $ClCH_2-$, $BrCH_2-$, $MeOCH_2-$)	−6.17	1.16	−2.01	0.822	9
15	$RCONH_2+H_3O^+$ in H_2O at 75 °C 25) (Hetero-atom substituents: $ClCH_2-$, $MeOCH_2-$)	−10.3	0.84	−0.56	0.762	16
16	$RCONH_2+H_3O^+$ in H_2O at 85 °C 25)	−10.3	4.13	−0.28	0.725	13
17	$RCONH_2+OH^-$ in H_2O at 75 °C 23) (Hetero-atom substituents: $ClCH_2-$, Cl_2CH-, Cl_3C-)	−14.6	8.21	0.48	0.969	12
18	$RCONH_2+OH^-$ in H_2O at 75 °C 26)	−7.28	6.63	−1.35	0.768	12
19	$RCONH_2+OH^-$ in H_2O at 85 °C 26)	−7.07	5.77	−1.12	0.792	12
20	$RCONH_2+OH^-$ in H_2O at 95 °C 26)	−6.92	4.92	−0.88	0.718	13
21	N-(RCO)-imidazoles+H_2O in H_2O/imidazole at 30 °C 27)	−19.1	93.8	3.17	0.769	7
22	in H_2O/imidazolium ion at 30 °C 27)	−13.6	0.56	2.42	0.737	6
23	N-(RCO)-imidazoles+OH^- in H_2O at 30 °C 27)	−21.7	127	8.76	0.849	7
24	N-(RCO)-imidazoles + H_3O^+ in 0.1 M HCl at 30 °C 28)	−12.0	26.1	3.38	0.597	8
25	in 1.20 M HCl at 30 °C 28)	−7.55	−102	4.25	0.653	6
26	in 2.38 M HCl at 30 °C 28)	−6.27	−118	3.98	0.652	7
27	in 3.60 M HCl at 30 °C 28)	−7.24	−101	3.88	0.662	7
28	in 4.77 M HCl at 30 °C 28)	−9.64	−65.6	3.90	0.676	7
29	in 5.97 M HCl at 30 °C 28)	−11.8	−41.3	4.07	0.708	7
30	in H_2O, 1.0 M in NaCl, 0.1 M in HCl at 30 °C 28)	−5.32	−137	4.13	0.645	6
31	in H_2O, 2.0 M in NaCl, 0.1 M in HCl at 30 °C 28)	−5.45	−144	4.12	0.668	6
32	in H_2O, 3.0 M in NaCl, 0.1 M in HCl at 30 °C 28)	−5.34	−138	3.84	0.643	6
33	in H_2O, 4.0 M in NaCl, 0.1 M in HCl at 30 °C 28)	−5.80	−135	3.77	0.645	6
34	in H_2O, 5.0 M in NaCl, 0.1 M in HCl at 30 °C 28)	−5.53	−133	3.46	0.645	6
35	in 0.1 M HCl at 20.0—21.1 °C 29)	−11.8	24.8	3.11	0.579	8
36	in 0.1 M HCl at 39.3—39.7 °C 29)	−15.8	37.2	4.33	0.880	7
37	in 0.19 M HCl in 50% dioxane at 30 °C 29)	−3.93	−164	3.85	0.636	7
38	in 75% dioxane, 0.19 M in HCl at 30 °C 29)	−3.40	−154	3.20	0.620	7
39	$RCOSMe+OH^-$ in 40% dioxane at 35 °C 30)	−12.0	6.95	3.83	0.954	9
40	$RCOMe+NaBH_4$ in *i*PrOH at 50.0 °C 31)	−11.7	7.05	2.70	0.957	8
41	RCOMe+bis(1,2-dimethylpropyl)borane in THF 32)	−19.9	50.6	1.68	0.843	9
[ROX type]						
42	$PhCH_2COOR+OH^-$ in 56% MeAc at 25 °C 18)	−18.3	5.59	4.99	0.930	12
43	$PhCH_2COOR+OH^-$ in 60% dioxane at 35 °C 33)	−14.0	5.75	3.17	0.979	9
44	$AcOR+OH^-$ in 40% dioxane at 35 °C 19)	−20.1	48.5	5.46	0.965	8
45	$AcOR+OH^-$ in 70% MeAc at 20.0 °C 34)	−15.9	22.5	2.22	0.969	7
46	$AcOR+OH^-$ in 70% MeAc at 24.7 °C 34)	−18.8	16.2	3.16	0.941	9
47	$AcOR+OH^-$ in 70% MeAc at 35 °C 34)	−20.1	2.65	4.13	0.948	8
48	$AcOR+OH^-$ in 70% MeAc at 44.7 °C 34)	−19.7	5.24	4.19	0.945	8
49	$AcOR+OH^-$ in H_2O at 20.0 °C 35)	−10.3	13.7	3.06	0.974	6

Table 2. (Continued)

Set[a)]	Reaction	*a*	*b*	*c*	*r*	*n*
50	AcOR+OH^- in H_2O at 30.0 °C [35)]	−7.69	5.61	2.80	0.989	6
51	AcOR+OH^- in H_2O at 0.0 °C [36)]	−18.5	−5.86	5.17	0.918	7
52	AcOR+OH^- in H_2O at 10.0 °C [36)]	−18.1	−7.56	5.40	0.924	7
53	AcOR+OH^- in H_2O at 20.0 °C [36)]	−16.0	40.9	4.21	0.937	10
54	$(RO)PO(Et)_2$+OH^- in 83.8% DMSO at 60 °C [37)]	−17.9	13.2	6.04	0.975	7
55	$(RO)PO(Et)_2$+OH^- in 83.8% DMSO at 70 °C [37)]	−16.0	17.7	5.80	0.887	5
56	$(RO)PO(Et)_2$+OH^- in 83.8% DMSO at 80 °C [37)]	−15.5	20.0	5.91	0.878	5
57	ROH+4-NO_2-C_6H_4COCl in Et_2O at 25 °C [38)]	−15.1	−7.68	2.96	0.904	19
58	RO^-+$PhCH_2Cl$ in ROH at 50 °C [39)]	−6.06	−44.3	2.07	0.977	7
59	RO^-+$PhCH_2Cl$ in ROH at 60 °C [39)]	−6.44	−44.0	2.55	0.940	9
60	RO^-+$PhCH_2Cl$ in ROH at 70 °C [39)]	−7.07	−47.6	3.14	0.958	9
61	RO^-+$PhCH_2Cl$ in ROH at 80 °C [39)]	−8.08	−45.6	3.70	0.955	9
[RNX_2type]						
62	MeCONHR+H_3O+in H_2O at 65 °C [40)]	−8.34	3.41	−2.81	0.943	10
63	MeCONHR+H_3O+in H_2O at 75 °C [40)]	−8.12	3.14	−2.47	0.957	10
64	MeCONHR+H_3O+in H_2O at 85 °C [40)]	−7.48	2.92	−2.26	0.954	8
65	MeCONHR+H_3O+in H_2O at 95 °C [40)]	−7.43	3.95	−1.94	0.951	10
66	MeCONHR+H_3O+in H_2O at 65 °C [41)]	−12.1	13.1	0.54	0.973	5
67	MeCONHR+H_3O+in H_2O at 75 °C [41)]	−10.5	5.22	0.54	0.992	7
68	RNH_2+chloranil [42)] in cyclohexane [43)]	−14.3	−29.0	2.04	0.965	7
69	RNH_2+chloranil [42)] in $CHCl_3$ [43)]	−11.7	−26.9	1.35	0.959	7
70	RNH_2+chloranil [42)] in CH_2Cl_2 [43)]	−9.47	−18.1	0.64	0.948	7
71	RNH_2+chloranil [42)] in cyclohexane [43)]	−14.3	−27.8	2.01	0.964	7
72	RNH_2+chloranil [42)] in $CHCl_3$ [43)]	−11.7	−25.8	1.29	0.954	7
73	RNH_2+chloranil [42)] in CH_2Cl_2 [43)]	−10.1	−15.9	0.77	0.948	7
74	RNH_2+CH_2=CHCOOBu [45)]	−15.7	−26.6	1.04	0.891	10
75	RNH_2+MeOAc in dioxane 5 M in $(CH_2OH)_2$ [46)]	−21.4	0.63	3.55	0.942	10
76	RNH_2+piperonal in MeOH at 0.00 °C [47)]	−18.4	62.6	2.02	0.932	8
77	RNH_2+piperonal in MeOH at 24.97 °C [47)]	−16.7	55.9	2.14	0.940	9
78	RNH_2+piperonal in MeOH at 45.00 °C [47)]	−15.4	49.5	2.19	0.945	8
79	RNH_2+CH_2=$CHCH_2Br$ in benzene at 100 °C [48)]	−10.9	17.1	3.16	0.962	11
80	RNH_2+1-Cl-2,4-$(NO_2)_2C_6H_3$ in $C_2H_5NO_2$ at 25 °C [49)]	−28.1	83.3	7.22	0.961	8
81	RNH_2+*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in H_2O at 25 °C [50)]	−14.6	34.0	1.21	0.947	8
82	$RNMe_2$+$CHCl_3$ [51)] in cyclohexane at 35 °C [52)]	0.31	8.19	−0.66	0.380	6
83	R_2NMe+$CHCl_3$ [53)] in cyclohexane at 35 °C [52)]	−6.41	3.85	1.07	0.361	6
84	RNH_2+I_2 [53)] in heptane at 20 °C [52)]	−2.10	15.2	3.22	0.979	6
85	$RNMe_2$+I_2 [53)] in heptane at 20 °C [52)]	−2.84	7.21	4.67	0.844	6
86	RNH_2+PhOH [51)] in CCl_4 at 27 °C [52)]	0.62	−4.46	1.82	0.937	10
87	R_2NH+PhOH [51)] in CCl_4 at 27 °C [52)]	−3.52	−7.46	2.99	0.988	7
88	R_3N+PhOH [51)] in CCl_4 at 27 °C [52)]	−20.3	−2.30	7.02	0.978	6
89	RNH_2+BMe_3 [54)] in gas phase at 100 °C [52)]	−22.3	58.3	6.18	0.971	10
90	RNH_2+1,4-$(NO_2)_2C_6H_4$ [55)] in heptane at 27 °C [56)]	−6.26	−30.5	1.29	0.963	6
91	$\log k_A$ of conjugate cations of RNH_2 [52)]	−0.06	12.6	−10.7	0.865	14
92	$\log k_A$ of conjugate cations of R_2NH [52)]	2.61	−28.0	−11.2	0.448	7
[$RPOX_2$type]						
93	$RPO(OEt)_2$+OH^- in 83.3% DMSO at 70 °C [37)]	−19.1	25.6	5.94	0.932	7
94	$RPO(OEt)_2$+OH^- in 83.3% DMSO at 80 °C [37)]	−20.1	31.8	6.39	0.872	6
95	$RPO(OEt)_2$+OH^- in 83.3% DMSO at 90 °C [37)]	−17.7	28.3	6.04	0.910	7
96	2-R-2-oxo-1,3,2-dioxaphosphorinane+OH^- in 50% dioxane at 29.5 °C [57)]	−20.0	−16.8	7.24	0.943	9
97	2-R-2-oxo-1,3,2-dioxaphosphepane+OH^- in 50% dioxane at 90 °C [57)]	−24.0	−12.6	7.82	0.970	7
98	$RPO(OEt)OC_6H_4(4\text{-}NO_2)$+$OH^-$ in H_2O at 37.5 °C [58)]	−20.6	19.7	1.71	0.954	11
99	$RPO(OiPr)_2$+OH^- in H_2O, [59)] $\log k_{rel}$	−16.5	−17.1	3.45	0.994	5

Table 2. (Continued)

Set a)	Reaction	*a*	*b*	*c*	*r*	*n*
100	$RPO(O\mathit{i}Pr)_2+H_3O^+$ in H_2O, 59) $\log k_{rel}$	−0.43	−21.9	0.09	0.976	5
101	$RMe(PO)Cl+H_2O$ in 95% MeAc at 0 °C 60)	−35.0	81.7	9.56	0.912	5
102	$R(PO)Cl_2+H_2O$ in 95% MeAc at 0 °C 60)	−29.7	69.7	7.65	0.987	5
103	$RPO(OMe)Cl+H_2O$ in 95% MeAc at 0 °C 61)	−29.6	74.1	5.27	0.971	5
104	$RPO(OMe)Cl+H_2O$ in 95% MeAc at 10 °C 61)	−28.7	72.8	5.25	0.974	5
105	$RPO(OMe)Cl+H_2O$ in 95% MeAc at 20 °C 61)	−29.4	76.8	5.59	0.976	5
106	$RPO(OMe)Cl+H_2O$ in 95% MeAc at 30 °C 61)	−28.9	74.9	5.62	0.983	5
107	$RPO(OEt)Cl+H_2O$ in 95% MeAc at 20 °C 61)	−36.9	126	6.86	0.958	5
108	$RPO(OEt)Cl+H_2O$ in 95% MeAc at 30 °C 61)	−34.0	115	6.43	0.957	5
109	pk_{a1} of $RPO(OH)_2$ in H_2O at 25 °C 62)	3.22	1.29	1.67	0.944	9
110	pk_{a2} of $RPO(OH)_2$ in H_2O at 25 °C 62)	7.59	−2.07	6.17	0.985	9
111	pk_{a1} of $R(PO)HOH$ in H_2O at 25 °C 62)	9.23	−13.4	1.15	0.966	6
112	pk_a of $R_2PO(OH)$ in 75% EtOH 63)	11.4	−11.4	2.38	0.989	5
[Other types]						
113	$RCH{=}CH_2$+9-borabicyclo[3.3.1]nonane, 64) $\log k_{rel}$ (Hetero-atom substituents: $MeOCH_2$–, ICH_2–, $NCCH_2$–, $BrCH_2$–, $ClCH_2$–)	6.22	−7.00	−1.58	0.898	6
114	$RMeC{=}CMe_2+Br_2$ in MeOH/NaBr at 25 °C 65)	−29.0	58.4	12.2	0.901	8
115	$RMeC{=}CH_2$+bis(1,2-dimethylpropyl)borane in THF at 0 °C 66)	−27.0	106	4.03	0.881	8
116	$RCH{=}Ad+Br_2$ (Ad: adamantylidene) in MeOH/NaBr at 25 °C 67)	−27.8	48.6	12.3	0.972	6
117	*cis*-$PhCH{=}CHR+CH_2{=}CHCN$ at 60 °C, 68) $\log(1/r)$ 69)	−14.4	26.7	2.80	0.963	6
118	*trans*-$PhCH{=}CHR+CH_2{=}CHCN$ at 60 °C, 68) $\log(1/r)$ 69)	−14.9	37.3	3.32	0.994	6
119	$RPhCHCN+OH^-$ in isopentyl alcohol at 99.8 °C 70)	−15.7	16.9	2.85	0.846	13
120	$RPhCHCN+OH^-$ in isopentyl alcohol at 117 °C 70)	−13.4	13.9	2.67	0.807	13
121	$RCN+PhCONH_2$ in CF_3COOH at 100 °C 71) (Hetero-atom substituents: $ClCH_2$–, Cl_2CH–, Cl_3C–)	−13.0	0.85	1.57	0.921	7
122	2-R-thiazoles+MeI in $C_6H_5NO_2$ at 25 °C, 72) $\log k_{rel}$	−20.2	94.1	4.05	0.893	7
123	2-R-5-Me-thiazoles+MeI in MeCN at 25 °C, 72) $\log k_{rel}$	−19.6	89.0	3.92	0.891	7
124	$AcSR+OH^-$ in 40% dioxane at 35 °C 30)	−5.71	3.73	2.38	0.975	9
125	R_3P+EtI in Me_2CO at 34.97 °C 73)	−31.2	90.7	3.85	0.934	7
126	$RMe_2SiCl+H_2O$ in 89 mol% dioxane at 25 °C 74) (Hetero-atom substituents: $ClCH_2$–, Cl_2CH–)	−18.2	4.48	4.09	0.938	16

a) The bold-typed and underlined set number means there contain hetero-atom substituents.

ognized in Set 14 though the retardation by bulky substituents was found. The acceleration by electron-withdrawing substituents could be explained well by the reaction mechanism of base-catalyzed hydrolysis of amides (B_{AC2}) where the attack by OH^- to carbonyl carbon of amide is a rate-determining process. Electron-withdrawing substituents attached to the carbonyl carbon will increase the electrophilicity of carbonyl carbon atom and lead to the increase of the reaction constant. The bigger number of the regression coefficients (*b*) than that for Set 14 indicates the more importance of the electronic effect in Set 17. In the case where kinetic data for only the alkyl or aralkyl groups are available, the electronic effect could not be evaluated reasonably by investigating the regression coefficients because the $\Delta\chi_B$ are not very good electronic parameters to distinguish the subtle differences of the electronic properties among the alkyl and aralkyl groups.

In the reactions of Sets 42—61, the reactant molecules are ROX, which experience the hydrolysis and nucleophilic substitution reactions. The electronic and steric effect of the substituents R of alcohol derivatives could be estimated well by the CASE 1 analyses in the hydrolysis reactions of carboxylic and phosphonic acid esters.

The reactions of RNX_2 type reactants are shown in Sets 62—92. The reactants are amides and amines, which experienced many kinds of reactions, such as hydrolysis (Sets 62—67), the adduct formation via charge-transfer complexes (Sets 68—73), the addition to the double bond (Set 74), amide formation (Set 75), the formation of a Schiff base from piperonal (Sets 76—78), the nucleophilic substitution reactions (Sets 79, 80), nitrosation (Set 81), hydrogen-bond formations (Sets 82, 83, 86—88), charge-transfer complexation (Sets 84, 85), and association (Set 89). Most of the correlations on the reaction rates showed good to excellent correlations (average *r*-value, 0.952); while the reliability of the correlations on equilibrium constants varied largely. The correlation is very poor in the cases of weak hydrogen-bond formation (Sets 82, 83). It should be noticed the tendency to increase the relative importance of the steric effect in the hydrogen-bond formation reactions (Sets 86—88) where the amines varied from primary to tertiary. The regression coefficient *a* increased from 0.62 to −20.3 through the change of primary to tertiary amines. The importance of steric factors was apparent in

Table 3. Improved Correlation by Introducing (n_H-3) Term into Eq. 3 (Eq. 8)

Set	a	b	h	c	r
1	−27.0	18.9	−0.45	4.38	0.972
2	−26.3	20.8	−0.42	4.46	0.972
3	−25.2	21.6	−0.38	4.47	0.972
4	−21.0	25.0	−0.41	5.69	0.964
5	−38.9	47.6	−0.95	7.72	0.990
6	−27.7	41.6	−0.32	3.63	0.977
7	−25.7	38.4	−0.30	3.57	0.965
8	−24.6	36.5	−0.29	3.79	0.966
9	−26.8	10.8	−0.50	3.61	0.988
10	−25.9	5.84	−0.24	4.26	1.000
11	−25.3	5.73	−0.24	4.42	1.000
12	−24.8	5.50	−0.23	4.62	1.000
13	−16.9	−1.19	−0.62	0.67	0.974
14	−16.4	−0.21	−0.55	0.16	0.930
15	−21.6	−0.65	−0.79	1.71	0.959
16	−22.5	5.51	−0.81	2.15	0.983
17	−28.4	6.64	−0.91	3.28	0.990
18	−20.0	9.70	−0.64	1.33	0.955
19	−17.7	8.34	−0.54	1.13	0.944
20	−19.4	7.20	−0.58	1.83	0.948
21	−34.7	104	−1.08	6.09	0.929
22	−47.9	298	−1.54	5.43	0.966
23	−32.0	134	−0.71	10.7	0.923
24	−37.1	65.5	−1.59	8.06	0.957
25	−51.4	279	−1.97	8.10	0.980
26	−48.2	247	−1.88	7.67	0.971
27	−47.7	251	−1.81	7.43	0.967
28	−49.6	281	−1.79	7.41	0.964
29	−50.2	292	−1.72	7.44	0.960
30	−50.1	251	−2.00	8.06	0.986
31	−48.8	233	−1.94	7.93	0.983
32	−50.6	255	−2.03	7.81	0.986
33	−51.4	260	−2.04	7.77	0.983
34	−50.0	253	−1.99	7.37	0.985
35	−38.2	66.1	−1.67	8.02	0.959
36	−30.9	57.4	−1.10	7.13	0.989
37	−50.1	237	−2.07	7.90	0.979
38	−47.6	229	−1.98	7.08	0.977
39	−19.3	8.90	−0.37	5.35	0.973
40	−20.8	13.0	−0.59	4.30	0.992
41	−13.7	36.9	0.29	0.50	0.860

the hydrogen-bond formation reactions in the case of tertiary amines from these correlation analyses. The large negative a value indicated the strong retardation by bulky substituents.

In the Sets of 93—112 ($RPOX_2$ type), the reactant molecules are phosphonic acids, esters, and chlorides. The reactivities of hydrolysis reactions and pK_a values were evaluated well in terms of Ω_s and $\Delta\chi_B$ with a good correlation coefficient ($r > 0.97$). Other types of reactions were shown in the Sets of 113—126. The hydroboration of alkenes (Set 113), addition reactions (Sets 114—116) to the double bond, the monomer reactivity ratio in copolymerization (Sets 117, 118), the hydrolysis of nitriles into carboxylic acids (Sets 119, 120), exchange reactions between substituted benzamides and aliphatic nitriles (Set 121), methylation of thiazoles (Sets 122,123), hydrolysis of thioesters (Set 124), alkylation of phosphines (Set 125), and hydrolysis of alkylsilyl chlorides were compiled. Though the correlations in hydroboration of alkenes and hydrolysis reactions of nitriles are not good, the reactivities of other reactions were linearly correlated with Ω_s and $\Delta\chi_B$. The positive a value for the hydroboration of alkenes are reasonable because the boron atom becomes attached to the less sterically congested alkenyl carbon atom in the reactions. The steric effect of the substituent R is supposed to be minor or very small.

Evaluation of the Reactivities by CASE 2 Correlation Equation. In the more complete analysis using the CASE 2 equation (Eq. 4), the contributions of individual substituents to steric effects were taken into account separately; while the electronic effects of the substituents were treated as a combined effect. Actually, the rates of reactions in Table 4 are assumed to be controlled by the two substituent groups (R^1 and R^2) independently, viz. the two substituents can cause steric effect in a different manner on the reaction. This assumption leads to the following correlation equation:

$$\log k = a_1\Omega_{s1} + a_2\Omega_{s2} + b\sum\Delta\chi_{Bi} + c, \qquad (9)$$

in which the coefficients of Ω_{s1} (for R^1) and Ω_{s2} (for R^2) ($\Omega_{s1} \le \Omega_{s2}$) were varied independently. The results are shown in Tables 4 and 5.

The hydrolysis reactions of *N*,*N*-dialkyl substituted acetamides (Sets 127—131), brominations of double bond (Sets 132—138), hydrolysis of nitriles into carboxylic acids (Sets 139, 140), and hydrolysis of thioesters (Set 141) were compiled. The substituent effect on the hydrolysis of *N*,*N*-disubstituted amides could be excellently correlated by Eq. 9. The results on other reactions are good or fair. The rather poor correlations in the addition reactions to the double bond are supposed to come from the fact that the change of the π-electron density could not be evaluated well by Bratsch's group electronegativities $\Delta\chi_{Bi}$. The electronic effect is important in the electrophilic addition reactions. Another correlation analysis was done using the correlation Eq. 10 to find a simpler method to evaluate the individual electronic and steric effects from substituents.

$$\log k = a\sum\Omega_{si} + b\sum\Delta\chi_{Bi} + c. \qquad (10)$$

The correlation coefficient derived from Eq. 10 are given in the parentheses in Table 4. The derived correlation was a little worse than that from correlation Eq. 9. Therefore, it was concluded that the net steric effect on the reactivity could be evaluated more properly by summing up the each steric effect independently as in Eq. 9.

Three substituent groups were involved in the reactions shown in Table 5 (Sets 142—150). The correlation equation is

$$\log k = a_1\Omega_{s1} + a_2\Omega_{s2} + a_3\Omega_{s3} + b\sum\Delta\chi_{Bi} + c. \qquad (11)$$

$$(\Omega_{s1} \le \Omega_{s2} \le \Omega_{s3})$$

The reactant molecules were tertiary amines and phosphines. Again the rates were correlated satisfactorily and the correlations in the hydrogen-bond formation (Sets 143 and 145),

Table 4. Correlation Analyses with $\log k=a_1\Omega_{s1}+a_2\Omega_{s2}+b\sum\Delta\chi_{Bi}+c$ (9) and $\log k=a\sum\Omega_{si}+b\sum\Delta\chi_{Bi}+c$ (10)

Set	Reaction	a_1	a_2	b	c	r(Eq. 9)	r(Eq. 10)[76]	n
127	$MeCONR^1R^2+H_3O^+$ in H_2O at 75 °C[41]	−9.12	−11.8	4.22	1.44	0.975	(0.968)	11
128	$MeCONR^1R^2+OH^-$ in H_2O at 65 °C[41]	−8.42	−12.1	13.1	2.44	0.985	(0.983)	6
129	at 70 °C[41]	−24.9	−34.6	28.8	11.2	0.991	(0.984)	5
130	at 75 °C[41]	−17.4	−16.9	17.8	5.31	0.974	(0.974)	11
131	at 85 °C[41]	−25.5	−1.47	37.4	3.11	0.986	(0.976)	6
132	$R^1R^2C{=}CHMe+Br_2$ in MeOH/NaBr at 25 °C[65]	−17.9	−18.5	39.4	12.9	0.902	(0.901)	12
133	$R^1R^2C{=}CMe_2+Br_2$ in MeOH/NaBr at 25 °C[65]	−24.9	−16.3	29.4	14.9	0.893	(0.874)	12
134	$R^1R^2C{=}CH_2+Br_2$ in AcOH[75]	−12.7	−9.87	30.5	7.30	0.758	(0.757)	6
135	$R^1R^2C{=}CH_2+Br_2$ in MeOH[75]	−15.0	−12.4	35.0	9.97	0.809	(0.808)	6
136	$R^1R^2C{=}CMe_2+Br_2$ in AcOH[75]	−22.7	−12.5	38.4	12.7	0.728	(0.694)	9
137	$R^1R^2C{=}CMe_2+Br_2$ in MeOH[75]	−26.1	−16.2	40.9	15.5	0.824	(0.785)	9
138	$R^1R^2C{=}Ad+Br_2$ (Ad: adamantylidene) in MeOH/NaBr at 25 °C[67]	−21.7	−25.6	43.4	17.3	0.981	(0.977)	9
139	$PhCR^1R^2CN+OH^-$ in *i*BuCH$_2$OH at 99.8 °C[70]	−13.1	−14.3	14.4	4.99	0.850	(0.847)	20
140	at 117 °C[70]	−10.3	−11.8	10.7	4.17	0.830	(0.824)	20
141	$R^1COSR^2+OH^-$ in 40% dioxane at 35 °C[30]	−12.1	−8.01	5.81	5.50	0.982	(0.954)	24

Table 5. Correlation Analyses with $\log k=a_1\Omega_{s1}+\mathrm{a}_2\Omega_{s2}+a_3\Omega_{s3}+b\sum\Delta\chi_{Bi}+c$ (11) and $\log k=a\sum\Omega_{si}+b\sum\Delta\chi_{Bi}$ (10)

Set[a]	Reaction	a_1	a_2	a_3	b	c	r(Eq. 11)	r(Eq. 10)	n
142	$R^1R^2R^3N$+*N*-methyl-*N*-nitroso-*p*-toluene-sulfoneamide in H_2O at 25 °C[77]	−5.37	1.35	−14.0	6.63	2.93	0.962	(0.802)	16
143	$R^1R^2R^3N+CHCl_3$[51] in cyclohexane at 35 °C[52]	−5.84	−4.02	−2.39	4.82	2.14	0.719	(0.698)	29
144	$R^1R^2R^3N+I_2$[53] in heptane at 20 °C[52]	−20.6	−14.2	−8.39	28.5	12.9	0.805	(0.666)	24
145	$R^1R^2R^3N+PhOH$[51] in CCl_4 at 27 °C[52]	0.24	0.43	−0.94	−2.41	1.83	0.851	(0.838)	25
146	$R^1R^2R^3N+BMe_3$[54] in gas phase at 100 °C[52]	−47.5	−30.1	−16.9	40.8	19.2	0.877	(0.463)	14
147	$R^1R^2R^3N+EtI$ in Me_2CO at 35 °C,[52] (Hetero-atom substituent: $NCCH_2-$)	0.54	2.14	−28.0	−10.0	2.95	0.993	(0.914)	11
148	$R^1R^2R^3N+1,4\text{-}(CN)_2C_6H_4$[55] in heptane at 27 °C[56]	−36.4	−35.9	−11.3	56.3	17.6	0.905	(0.848)	13
149	$R^1R^2R^3P+EtI$ in Me_2CO at 34.97 °C[73]	−13.5	−21.3	−0.37	34.4	4.73	0.969	(0.950)	11
150	$R^1R^2R^3SiCl+H_2O$ in 89 mol% dioxane at 25 °C,[74] (Hetero-atom substituents: $ClCH_2-$, Cl_2CH-)	−10.4	−29.0	−22.5	3.89	13.5	0.959	(0.941)	22

a) The bold-typed and underlined set number means there contain hetero-atom substituents.

charge-transfer complexation (Set 144), association reaction (Set 146) were not very good. This is because that the proper estimation of the electronic effect is very difficult in the reactions where the delocalization of electrons is important. The simplified correlation analyses using an Eq. 10 were also done as was done in Table 4. The correlation coefficients derived from Eq. 10 (shown in the parentheses in Table 5) indicated that Eq. 11 is better than the Eq. 10.

Next, we investigated the reactivities in the addition reactions to the double bond (Table 6). It is a difficult problem how to evaluate each steric effect attached to the two terminal carbon atoms properly. The correlation equation we adopted was

$$\log k = a_{12}\sum\Omega_{s12} + a_{34}\sum\Omega_{s34} + b\sum\Delta\chi_{Bi} + c. \qquad (12)$$

Here, $\sum\Omega_{s12}$ and $\sum\Omega_{s34}$ mean the summation of the Ω_s value of the substituents attached to each terminal carbon atom ($\Omega_{s1}+\Omega_{s2}\leq\Omega_{s3}+\Omega_{s4}$). For comparison, the results from using Eq. 10 are shown in the parentheses in Table 6. The method where the steric effects at both side carbon atoms of the double bond were summed up independently, as Eq. 12, was proper to estimate the reactivity judging from the good correlation coefficients. In the bromination reactions of the alkenes (Sets 154—162), a better correlation than the case of Sets 132—137 (bromination of di-substituted alkenes) was obtained. This may be explained partly because the relative importance of the electronic factor decreased in the bromination of the tetra-substituted alkenes due to the increase of the steric effect in the reactant molecules. As the percentage of the contribution of the electronic effect, which is supposed not to be evaluated well for the electrophilic addition reac-

Table 6. Correlation Analyses for the Addition Reactions to the Double Bond

$$\log k = a_{12}\sum \Omega_{s12} + a_{34}\sum \Omega_{s34} + b\sum \Delta\chi_{Bi} + c \qquad (12)$$

$$\log k = a\sum \Omega_{si} + b\sum \Delta\chi_{Bi} + c \qquad (10)$$

Set[a)]	Reaction	a_{12}	a_{34}	b	c	r(Eq. 12)	r(Eq. 10)	n
151	$R^1R^2C{=}CR^3R^4$+HN=NH, [78)] $\log k_{rel}$, (Hetero-atom substituents: $MeOCH_2$–, $HOCH_2$–, $NCCH_2$–)	−6.27	−6.23	−1.76	3.20	0.962	(0.962)	11
152	$R^1R^2C{=}CR^3R^4$+9-borabicyclo[3.3.1]nonane, [64)] $\log k_{rel}$, (Hetero-atom substituents: $MeOCH_2$–, ICH_2–, $NCCH_2$–, $BrCH_2$–, $ClCH_2$–)	−12.4	6.48	−8.68	−1.51	0.982	(0.801)	12
153	$R^1R^2C{=}CR^3R^4$+$Hg(OAc)_2$, [64)] $\log k_{rel}$, (Hetero-atom substituents: $MeOCH_2$–, $ClCH_2$–)	−5.98	10.8	1.77	−2.64	0.936	(0.260)	8
154	$R^1R^2C{=}CR^3R^4$+Br^2, [64)] $\log k_{rel}$ (Hetero-atom substituents: $ClCH_2$–, $NCCH_2$–, $EtOCH_2$–)	26.9	21.9	−10.1	−16.2	0.941	(0.937)	9
155	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH/NaBr at 25 °C [65)]	−8.63	−14.9	17.3	15.7	0.910	(0.869)	44
156	$R^1R^2C{=}CR^3R^4$+Br_2 in AcOH [75)]	−5.42	−10.2	26.9	12.1	0.929	(0.913)	24
157	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH [75)]	−8.81	−12.2	29.8	15.7	0.934	(0.926)	24
158	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH/0.20 M NaBr at 25 °C, [79)] (Hetero-atom substituents: $ClCH_2$–, $HOCH_2$–, $PhOCH_2$–, *n*-BuCH(OH), $NCCH_2$–)	29.4	−75.6	−44.6	39.7	0.961	(0.639)	8
159	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH/0.10 M NaBr at 25 °C, [79)] (Hetero-atom substituents: $HOCH_2$–, $PhOCH_2$–, *n*-BuCH(OH), $NCCH_2$–)	44.9	−101	−60.9	51.6	0.989	(0.607)	6
160	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH/0.05 M NaBr at 25 °C [79)] (Hetero-atom substituents: $ClCH_2$–, $HOCH_2$–, $PhOCH_2$–, *n*-BuCH(OH), $NCCH_2$–)	32.2	−64.1	−40.2	33.5	0.969	(0.671)	7
161	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH/NaBr at 25 °C, [80)] (Hetero-atom substituent: $ClCH_2$–)	28.2	24.6	−18.2	−15.6	0.943	(0.938)	20
162	$R^1R^2C{=}CR^3R^4$+Br_2 in MeOH/NaBr at 25 °C, [81)] (Hetero-atom substituents: $ClCH_2$–, $HOCH_2$–, $NCCH_2$–)	23.9	13.2	−14.7	−4.40	0.860	(0.848)	14

a) The bold-typed and underlined set number means there contain hetero-atom substituents.

tions by Bratsch's group electronegativities $\Delta\chi_{Bi}$, became lowered, reactivities was estimated well by Eq. 12. The results of the hydroboration (Set 152) and oxymercuriation (Set 153) of alkenes should be noticed. In both reactions, boron or acetoxy mercuric ion attack the less sterically congested alkenyl carbon atom. The coefficients at the less sterically congested carbon (a_{12}) in Eq. 12 took a negative number, indicating a retardation effect by the substituents at the less hindered site. The reaction mechanism of the hydroboration and oxymercuriation of alkenes could be rationally explained by our correlation analyses.

In conclusion, the reactivities in various kinds of reactions could be evaluated with good correlation by using the steric and the electronic substituent parameters. The good and convenient substituent parameters were Ω_s for steric effects and $\Delta\chi_B$ for electronic effects judging from the good results of correlation analyses in this report and the feasibility of the calculation of parameters for any substituents. The investigation concerning the validity of $\log(1-\Omega_s)$ as another steric parameters in correlation analyses is now under way, and will be reported elsewhere. In the many reactions investigated, the use of $\log(1-\Omega_s)$ in place of Ω_s itself improved the correlations slightly. However, it is not certain which parameter is better. The use of Ω_s parameters are recommended in general discussions on the steric effects of substituents because Ω_s is a good and widely applicable steric constant to represent the intrinsic bulkiness of the substituents. When a good correlation could not be obtained by using these substituent parameters, we had better consider special effects other than the steric and the electronic effects on the reactions, or that the location of a transition state along the reaction coordinate may be far from the reactant state. As the reactivity data for the reactions involving the molecules bearing the hetero-atom-containing substituents were relatively few in the literature, the appropriateness of $\Delta\chi_B$ as an electronic parameter should be examined further.

Methods of Calculations

The Ω_s parameters were calculated with the OMEGAS90 program by using the structures and the populations of the stable conformations obtained by a molecular mechanics program. The Ω_s parameters were calculated by taking into account all the conformations with populations over 1% at ambient temperature. The possible conformations were generated by the conformation-search program (CONFLEX3). In the conformational search, the geometries were optimized with the MM2(91) program. The optimized geometries thus identified were reoptimized with the MM3(92) program by full Newton–Raphson method to obtain more accurate structures and conformational energies. The all calculations were done on the SUN SPARC station IPC.

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