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A NEW METHOD FOR EVALUATING THE STERIC HINDRANCE BY SUBSTITUENT

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Summary: New steric parameter, Ω_s, evaluating the steric hindrance around the reaction center was defined on the basis of molecular mechanics.

The correlation of molecular structure with chemical reactivity is a fundamental objective in organic chemistry.[1-3] Many researches have been concentrated in this field, and a variety of steric substituent parameters were proposed in order to evaluate the steric effect caused by substituents.

Molecular force field method became known as a versatile tool for the quantitative estimation of steric effects.[4] A variety of reactions have been studied by this method in the aim of predicting or justifying their steric courses and stereoselectivity. The method was applied ad hoc on particular reaction systems or, at most, a series of reactions of a similar type, and has rarely been applied for the purpose of evaluating general steric substituent parameters,[5] though the model calculations by DeTar have shown to reproduce the Taft's Es parameters.[6] On the other hand, the steric substituent parameters based on the experimental kinetic data (e.g. Taft's Es value[7]) have been suspected to include conformational effects dependent on the reactions.[8]

In order to evaluate the effect of the steric hindrance to the access of the reagent by a substituent, we have developed a new method based on the molecular force field calculation and defined a new steric substituent parameter Ω_s. In this communication, we want to describe the new method briefly. Assuming that a molecule is contoured by the van der Waals radii of constituting atoms, the steric hindrance by a substituent was estimated from the area of its shade projected to the sphere of an appropriate radius(r_s)[9] when the substrate molecule was placed in a manner that its reaction center coincides with the center of the sphere where a light source was placed (Fig. 1). The new steric parameter is defined as the area of the shade (from MM2) divided by the total surface area of the projected sphere. Since the substituent actually exists as an equilibrium mixture of several conformations, the area of shade has been calculated as the population-weighted mean of the shady area of every conformer. The new steric parameter should represent the probability of the access of a reagent to the center of a reaction in a case when the mean free path of the reagent is sufficiently long. In this respect, the new parameter is expected to be of entropic nature.

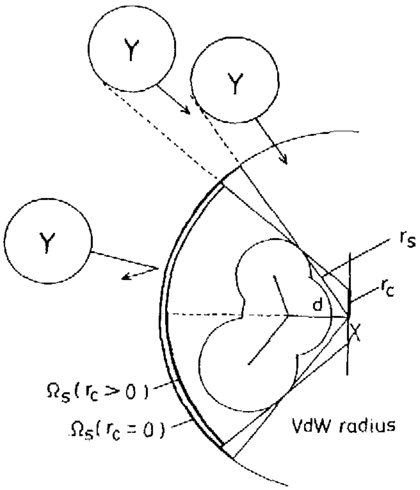


Fig.1. Definition of Ω_S.
Y; reagent

In the actual calculations, R-CH_3 was chosen as a model substrate molecule for the calculation of Ω_s for a substituent(R) in order to suppress the contribution of undesirable conformational effect to a minimum, since the three-fold symmetry of the methyl group can be expected to average out the effect. In this model, the actual reaction center was replaced hypothetically by a methyl carbon atom for the sake of facilitating the calculations.

In the next stage, we took into account the size of the reaction center(X) by assuming it as a sphere of radius(r_c). In other words, the attractive interactions of the approaching reagent with the reaction center can induce the reaction when the reagent comes within the sphere of radius(r_c) placed at the reaction center.(Fig. 1) In search for an appropriate radius (r_c) of the reaction center, the above calculations were repeated at several different r_c-values. In conclusion, the Ω_s values could be calculated as a function of three geometrical parameters, namely the radius of reaction center(r_c), the distance of bond connecting the α-carbon atom of the substituent and the reaction center(d), and the radius of the sphere on which the shade of the substituent is projected(r_s).

The values of the steric substituent parameter Ω_s at r_c=0 for some alkyl groups are given in Table 1. The Ω_s-values are affected most significantly by the branching at the α-carbon atom. For this reason, the values for each of primary-, secondary-, and tertiary-alkyl substituents constitute a group distiguishable from each other. The Ω_s-values for the straight chain alkyl groups tend to converge to a constant value with increasing the number of carbon atoms in the substituents. This tendency also holds for other steric parameters defined on the basis of the chemical reactivity. Hence, the Ω_s must represent the local steric hindrance around the reaction center which affects the chemical reactivity rather than the characteristic of the total shape of the substituent. This is reasonable from its definition and also supported by another fact that the Ω_s-values at several r_c-values correlate very poorly with the steric parameters such as van der Waals volume(Vw) (n=26, r=0.671 at r_c=0) and van der Waals (surface) area(Aw) (n=26, r=0.689 at r_c=0), expressing the characteristic of the size and shape.

Ωs should be correlated with the rates of a series of reactions among which the electronic effect of the substituent is assumed to be similar. Next, the relationship between the new steric substituent parameters and

Taft's E_s values were investigated in order to shed light on the implications of this parameter. Within the sets of primary, secondary, and tertiary alkyl substituents, an excellent correlation was found between Ω_s and E_s (Fig.2), even if the correlation becomes only fair when all classes of substituents were treated together (r=0.881). The separation of the plotted points must arise from the conformation-dependent nature of the Taft's Es, as pointed out by Dubois[8] and by Beckhaus[5] independently. The excellent agreement within the set renders a support on the usefulness of the Ω_s parameter for the evaluation of steric hindrance excluding the conformational effect.

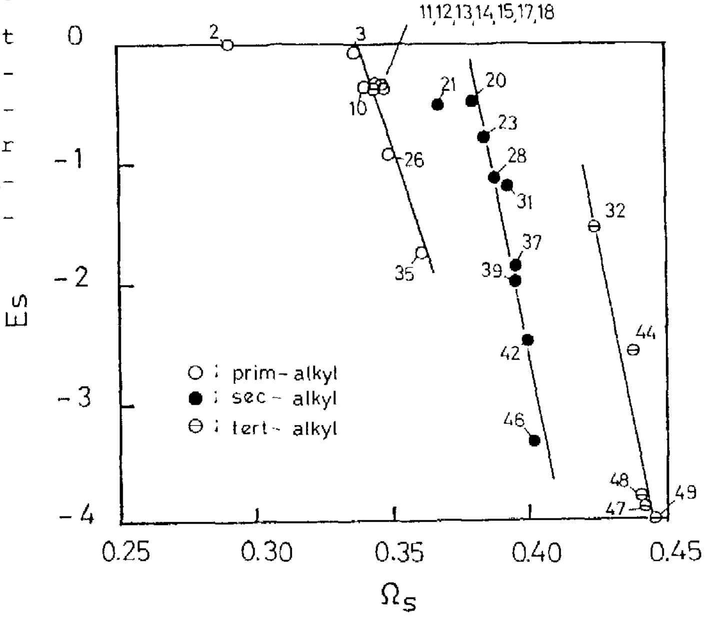


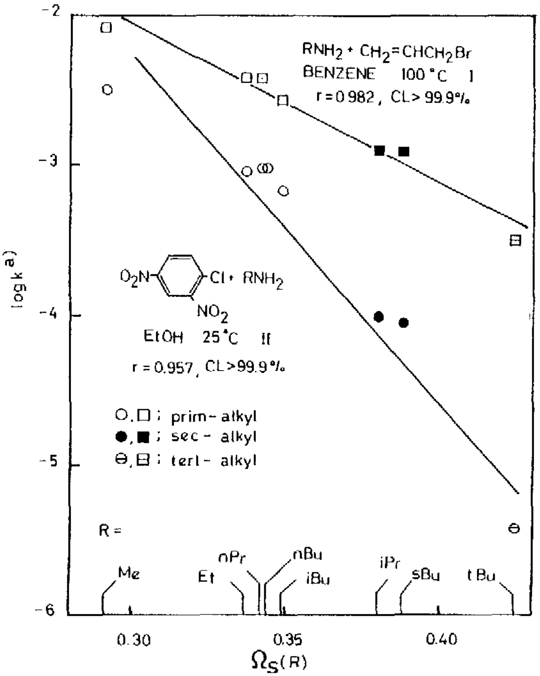
Fig. 2.
Taft's E_s vs. Ω_s plots. Correlation coefficients: n=11, r=0.949 (prim-alkyl), n=8, r=0.950 (s-alkyl), and n=5, r=0.970 (t-alkyl).

Table.1 The $\Omega_s(r_c=0)$ Parameters for Several Alkyl Groups.[a)]

Substituent(R)	Ω_s	r_s/pm	Substituent	Ω_s	r_s/pm
[primary alkyl]			$(CH_3)_2CH$-(20)	0.377	501
CH_3-(2)	0.288	369	cyclo-C_6H_{11}-(23)	0.381	695
C_2H_5-(3)	0.334	501	$CH_3(C_2H_5)CH$-(28)	0.385	590
$CH_3CH_2CH_2$-(10)	0.338	610	$C_6H_5(CH_3)CH$-(31)	0.390	765
$CH_3CH_2CH_2CH_2$-(11)	0.341	718	CH_3(neo-C_5H_{11})CH-(37)	0.392	727
$C_6H_5CH_2CH_2$-(18)	0.341	851	$(C_2H_5)_2CH$-(39)	0.392	566
$CH_3(CH_2)_4$-(12)	0.342	823	(i-$C_4H_9)_2CH$-(42)	0.398	751
$CH_3(CH_2)_7$-(14)	0.342	928	CH_3(t-C_4H_9)CH-(46)	0.399	630
t-$C_4H_9CH_2CH_2$-(15)	0.342	753	[tertiary alkyl]		
$(CH_3)_2CHCH_2CH_2$-(13)	0.344	732	$(CH_3)_3C$-(32)	0.421	500
$C_6H_5CH_2$-(17)	0.345	768	$(CH_3)_2$(neo-C_5H_{11})C-(44)	0.435	718
$(CH_3)_2CHCH_2$-(26)	0.348	619	$(C_2H_5)_3C$-(48)	0.438	613
$(CH_3)_3CCH_2$-(35)	0.361	630	$(CH_3)_2$(t-C_4H_9)C-(47)	0.439	629
[secondary alkyl]			CH_3(t-C_4H_9)(neo-C_5H_{11})C-(49)	0.445	697
cyclo-C_5H_9-(21)	0.364	616			

a) Numbers in ( ) correspond to those in Fig.2 and also to the Taft's Es.[7]

An example of its application is shown in Fig. 3, where the rates of the S_N2 reactions of primary alkylamines (RNH_2) with allyl bromide in benzene (reaction I) and with 2,4-dinitrochlorobenzene in ethanol (reaction II) are plotted against $\Omega_s(r_c=0)$. These alkylamine reactions were first analyzed by DeTar in terms of the Taft equation. He found that the rates could be correlated excellently when the E_s values for RCH_2 groups were employed.[10] However, the correlations became rather poor (r=0.868 for reactin I and r=0.852 for reaction II) when the E_s for R groups were used in place of the $E_s(RCH_2)$. In contrast, the Ω_s-values of R groups could be correlated well with the kinteic data of these reactions. This reflects the fact that the conformational effect[8] does not operate in the reaction of the amines. Furthermore, there exists a good correlation between the Ω_s for RCH_2 and the kinetic data (r=0.968 for reaction I and r=0.958 for reaction II), which is in line with the discussion by DeTar[10].



a) Reaction I: units of $M^{-1}min^{-1}$, Reaction II: units of $M^{-1}s^{-1}$

Fig.3. Example of logk vs. Ω_s.

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