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Weighting Functions in Order to Modify the Isotropic Character of the Steric Constant Ωs. Its Application to the Hydrolyses of Carboxamides

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In order to take into account the preferred direction of the access of reagents, weighting functions were introduced in the calculation of Ωs. A p-orbital-shaped weighting function served to improve the correlation of Ωs with the rates of the hydrolyses of alkanecarboxamides and related compounds.

Recently we proposed a steric constant termed Ωs which was defined on the basis of molecular mechanics calculations.1-5) As molecular mechanics is one of the best methods to estimate shapes and steric energies of molecules in high precision, it was applied to evaluate the steric hindrance to the access of reagents towards the reaction center. Ωs was defined as the solid angle of the substituent measured from the reaction center atom and calculated by molecular mechanics.

The regression analysis using the method developed by Dubois and coworkers6) showed that the contribution of the three α-alkyl groups to Ωs are nearly equal. In other words, Ωs is an isotropic steric constant. Thus defined Ωs has been applied to correlate the kinetic data of several reactions with the steric properties of the substituents. The performance of Ωs as a steric constant can be judged from the correlation coefficient values of $\log_{10}k$ vs. Ωs. For example, steric effects by the alkyl groups(R) on the nucleophilic substitution reactions of alkylamines (RNH_2) and alcohols (ROH) were generally correlated with Ωs of the alkyl groups better than with their Es values.4) In contrast, the reaction rates of carboxylic acid derivatives (RCOX) could be correlated far better with Es than Ωs.The correlations using Ωs were usually good, and even better than Es in several cases, but not very excellent in any case. As a German proverb "Everybody's friend is nobody's friend" teaches us, the isotropic steric constant is very widely applicable but cannot be the best steric constant for any individual reaction.

In the aim of improving this disadvantage, we introduced weighting functions in the calculations of Ωs. If we pursue further the solid angle approach, the preferential angle (θ, ω) to the access of reagent should be taken into account quantitatively in the calculation. The preferred direction can be appropriately evaluated by a weighting function, which features the shape of atomic orbital participating in the reaction. Typical examples of weighting functions are given in Fig. 1.

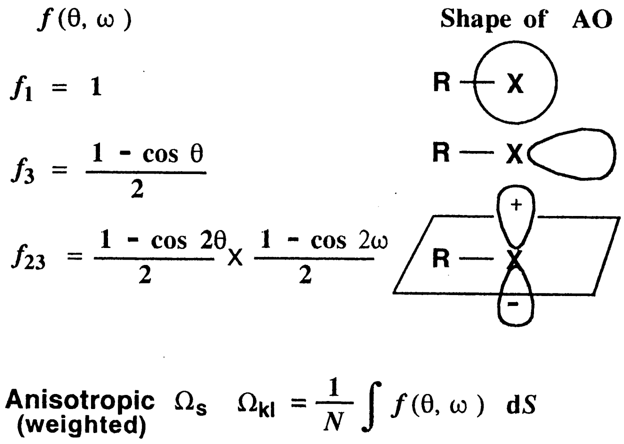


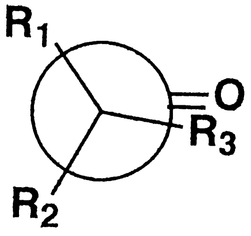
Fig. 1. Examples of weighting functions.

Table 1. Ω_3 and Ω_{23} Values for Several Alkyl Groups

Substituent	Ω_3	Ω_{23}
CH_3	0.0468	0.1194
CH_3CH_2	0.0728	0.1768
$CH_3(CH_2)_2$	0.0828	0.2020
$CH_3(CH_2)_3$	0.0841	0.2060
$Me_2CHCH_2CH_2$	0.1080	0.2634
Me_3CCH_2	0.1344	0.3006
$(CH_3)_2CH$	0.0992	0.2528
Me_2CHCH_2	0.1224	0.3185
$(CH_3)_3C$	0.1291	0.2950

The spherical function f_1 features an s-orbital and generates the isotropic Ωs conventionally used. The function f_3 features an sp^x-type hybrid orbital, taking the maximal value at the direction just opposite the C_α atom (i. e. at 180°). The function f_{23} features a p-orbital, which is stretching perpendicular to the molecular plane of a double bond such as carbonyl. In order to obtain weighted Ωs, every elementary surface (dS) was multiplied by normalized weighting function and then integrated over the shadow area (Eq. in Fig. 1). The weighted Ωs was termed Ω_{kl} so as to keep a close correspondence with the weighting function $f_{kl}(\theta, \omega)$.[7] Typical Ω_{kl} values are given in Table 1.

Dubois and coworkers[6] showed by a correlation analytical approach that Es is considerably anisotropic and that the less bulky α-alkyl substiuent R_1 which is *anti-clinal* to the carbonyl group contributes most significantly, and the *syn-periplanar* substituent R_3 the least significantly, to the Es value. This fact could be interpreted that the attack from perpendicular



to the carbonyl plane is more effective than the attack from the in-plane direction because the attack of nucleophile to the vacant p-orbital on the carbonyl carbon is assumed in the widely accepted mechanism of this sort of carbonyl reactions.

Thus, we used Ω_{23} constants which are weighted by the p-orbital shaped angular function $f_{23}(\theta,\omega)$ in order to obtain a better performance in correlating the bulkiness of the substituent R with the rates of the hydrolysis of carboxamides $RCONH_2$ and related compounds.[8)] The results are shown in Table 2.

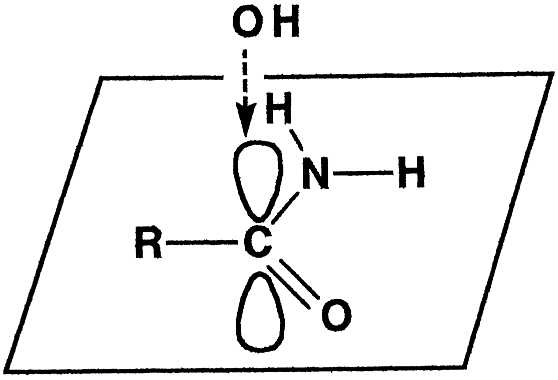


Table 2. Correlation of Ω_{23} with the Rates of the Hydrolysis of Carboxamides and Related Compounds (RCONR'R")

Reactant	n	Correlation coefficients(r)				a[f)]	c[f)]
		Es	Ωs	Ω_{23}	lg(1-Ω)[e)]		
$RCONH_2+H_3O$							
at 65 °C	6	0.855	0.767	0.857	0.862	0.59(0.22)	9.81(2.88)
at 75 °C	9	0.913	0.741	0.792	0.796	0.73(0.31)	9.29(2.93)
at 85 °C	9	0.927	0.788	0.860	0.862	0.66(0.28)	10.54(2.55)
$RCONH_2+OH^-$							
at 75 °C	8	0.899	0.836	0.906	0.910	0.57(0.16)	8.78(1.63)
at 85 °C	8	0.897	0.846	0.916	0.919	0.54(0.14)	8.37(1.45)
at 95 °C	7	0.846	0.790	0.914	0.912	0.65(0.13)	9.07(1.83)
1-AcIm[a)]+H_2O[b)]	7	0.867	0.719	0.813	0.853	1.33(0.69)	8.91(3.22)
1-AcIm+H_3O^+[c)]							
at 30 °C	7	0.831	0.724	0.826	0.848	0.94(0.67)	14.44(4.03)
at 39.5 °C	7	0.965	0.879	0.893	0.907	0.98(0.28)	12.02(1.59)
1-AcIm+OH^-[b)]	7	0.880	0.735	0.823	0.869	1.43(0.58)	12.23(3.12)
RCONHOH+H_3O^+[d)]	6	0.934	0.944	0.949	0.957	0.53(0.12)	7.82(1.28)

a) AcIm = acylimidazole. b) At 30 °C in the presence of imidazole.
c) In 0.1 M aqueous HCl. d) At 50.5 °C in the presence of TsOH.
e) Correlation with $\log_{10}(1-\Omega_{23})$.
f) Intercept a and gradient c by assuming a regression equation: $\log k = a + c\log_{10}(1-\Omega_{23})$. Standard errors are given in paretheses.

When the weighted Ω_{23} was used in place of the isotropic Ωs, the correlation was improved in all cases in Table 2. In some cases, the Ω_{23} could be correlated with the rates of hydrolyses better than Es. We do not intend to insist that our Ω_{23} is better than Es. If we speak impartially, the Ω_{23} constant barely attains the level of Es even after the improvement. However, it should be stressed that the reasonable modification in line with the reaction mechanism can improve the correlation largely.

Our computer program OMEGAS90$^{3)}$ and its revised version allows us to calculate many modification of Ωs constant, which may contribute to clarify the steric effects on organic reactions.

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7) The weighting function $f_{kl}(\theta,\omega)$ is usually expressed as the product of a latitudinal function $g_k(\theta)$ and a longitudinal function $h_l(\omega)$. In cases when $h_l(\omega)=1$, it can be denoted as $f_k(\theta)$. The angles θ and ω were measured in reference to the C_α-X bond and to the positive end of the axis of the p-orbital, respectively.
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