Communications to the Editor

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Utility of the Substituent Entropy Constants σ_{S° in the Studies of Quantitative Structure-Activity Relationships

Values of the substituent entropy constants σ_{s° for monosubstituted methane and benzene derivatives were determined from the standard entropy of the 3rd law of thermodynamics. This parameter is orthogonal to σ_i or σ_π, and seems preferable to π, E_S, MR, M_w, P_r and V_w. Two examples of QSAR are successfully analysed in terms of σ_{S°.

Keywords——substituent entropy constant σ_{S°; standard entropy; 3rd law of thermodynamics; quantitative structure-activity relationship; butyryl cholinesterase inhibitory potency; 1-decyl-3-carbamoylpiperidine; minimum blocking concentration; local anesthetics

Studies on quantitative structure-activity relationships (QSAR) have involved the use of several kinds of empirical parameters including electronic, steric and hydrophobic terms. The following parameters, for instance, are in current use.

1) Electronic

Several kinds of Hammett-type substituent constants, *e.g.* σ_1 and σ_π.[1]

2) Steric

Steric substituent constant E_s[2]; molar refractivity MR[3]; van der Waals volume V_w[3]; parachor P_r[4]; molar volume MV and molecular weight M_w.

TABLE I. Substituent Entropy Constants σ_{S° of Monosubstituted Methane and Benzene Derivatives

Substituent	MeR	PhR
NMe_2	0.191	0.134
NH_2	0.115	0.075
OMe	0.156	0.127
OH	0.110	0.067
iso-Pr	0.199	0.159
tert-Bu	0.210	0.173
Et	0.161	0.127
Me	0.091	0.076
H	0	0
F	0.078	0.051
Cl	0.099	0.068
Br	0.122	0.083
I	0.133	0.095
CHO	0.152	0.127
COMe	0.200	0.141
CO_2Me	0.254	*0.20*
CN	0.120	0.077
NO_2	0.170	*0.13*
CF_3	0.187	0.142
Ph	0.236	0.164
SH	0.137	0.097
SMe	0.186	*0.15*
SOMe	0.216	*0.17*
SO_2Me	0.232	*0.18*

The numbers in italics were determined by interpolation based on the linear relation between the MeR and PhR series.

TABLE II. Correlation Coefficients r of σ_{s° with Several Empirical Parameters

	r		r
π	0.562	MR	0.865
σ_i	0.146	M_w	0.492
σ_π	0.082	P_r	0.891
E_s	0.649	V_w	0.804

3) Hydrophobic substituent constant π.[2]

In an nuclear magnetic resonance (NMR) study[5] on the weak association between aliphatic or aromatic ketones and the shift reagent Eu dpm$_3$, having small K_e and ΔH, ΔS was found to be linearly related to S°_{298} of the pure ketone. This result means that ΔS can be replaced by S°_{298} in a weak association.

This communication presents a new dimensionless substituent entropy constant σ_{s° (*cf.* Table I), defined by log S°_R/S°_H, where S°_R and S°_H are referred to the S°_{298} of monosubstituted methane or benzene derivatives and their parent compounds, respectively. And, we also compared the orthogonality of this constant with several empirical parameters (*cf.* Table II). The lack of data among monosubstituted benzenes could be overcome by interpolation on the basis of a linear relation between the two series. The data summarized in Table II suggest an orthogonality of σ_{s° against σ_i or σ_π, and indicate the superiority of σ_{s° over E_s, MR, P_r and V_w.

For instance, π values of electron donating substituent groups can be expressed by a linear combination of σ_{s° and $|\sigma_\pi{+}|$ (see Eq. 1).

$$\pi = -3.87\,|\sigma_\pi^+| + 12.74\,\sigma_{s^\circ} - 0.03 \qquad (1)$$

($n=19$, $r=0.954$, $SD=0.253$[7])

The above result gives a chemical meaning to the hydrophobic term and leads an explicit role of σ_{s° in the evaluation of QSAR.

As is well known, the electronic term given by the Hammett-type substituent constant is equivalent to the contribution from the enthalpy term. In contrast to the Hammett-type substituent constant σ_i and σ_π, σ_{s° reflects the role of the entropy term in QSAR.

Two examples of QSAR using σ_{s° are given below:

1) Butyryl cholinesterase inhibitory potencies of some 1-decyl-3-carbamoylpiperidine hydrobromides[8]

The use of σ_{s° gave an excellent result (Eq. 2)

$$\mathrm{pI}_{50} = 2.67\,\sigma_{s^\circ} + 4.28 \qquad (2)$$

$$(n=7,\ r=0.982,\ SD=0.120)$$

2) Minimum blocking concentration of local anesthetics[9]

A high correlation was obtained by the use of a quadratic equation of σ_{s° (*cf.* Eq. 3)

$$\log \mathrm{MBC} = -15.8\,(\sigma_{s^\circ})^2 + 1.5\,\sigma_{s^\circ} + 3.5 \qquad (3)$$

$$(n=11,\ r=0.995,\ SD=0.108)$$

The details of this work will be reported in a subsequent paper.

References and Notes

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Facile Desulfurization of Thiocarbonyl Groups to Carbonyls by Superoxide. A Model of Metabolic Reactions

Several types of thioamides and thioureas including thiouracils were readily desulfurized to the carbonyl compounds by superoxide, generated by KO_2 and 18-crown-6 or electrolysis of oxygen in aprotic solvent at room temperature. Such desulfurization may provide a model of metabolic reactions catalyzed by oxygenases.

Keywords——desulfurization; potassium superoxide; superoxide; thiouracil; thiouridine; thiocarbonyl

Oxidative desulfurization of thio-xenobiotics is one of the important *in vivo* metabolic processes catalyzed by oxygenases.[1] Medicinal drugs,[2] thiobarbital (5,5-diethyl-2-thiobarbituric acid) and ethionamide(2-ethylthioisonicotinamide) as well as thiouracils are known to be metabolized *in vivo* to their carbonyl derivatives with no evidence to show any intervention by activated species of oxygen such as superoxide which is distributed widely in living cells.

In connection with bio-organic studies on the activation mechanism of molecular oxygen,[3] the present study was undertaken to explore the desulfurization of thio-carbonyl compounds by superoxide as a model of metabolic reactions.

The superoxide was generated by potassium superoxide (KO_2) with the catalyst crown ether or by electrolysis of oxygen.[4]

On treatment with the KO_2-crown ether reagent in aprotic solvent at room temperature, cyclic and acyclic thioureas, thio-barbital and N,N'-diphenylthiourea were readily desulfurized within 1 h to form carbonyl compounds almost exclusively (71% or 88% based on consumed