additive and constitutive nature of molecules, i.e., the molecular size and shape. It has been significantly correlated to many physicochemical properties used in physicochemical–activity studies. If a biological response of a series of closely related compounds is significantly correlated to χ it is mirroring the same additive and constituitive molecular property shown in those physical properties studied thus far. Logically, it would appear that these empirical properties are intermediary measures of the very fundamental molecular structure encoded in χ and the measured biological response.

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Quantitative Structure–Activity Relationships. 1. The Modified Free–Wilson Approach

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The relationships between the linear free energy related Hansch model and the mathematical models of Free–Wilson and Boček–Kopecký are reviewed and discussed. Some examples are given to illustrate the theoretically derived relationships and to demonstrate scope and limitations of each mathematical model. The modified Free–Wilson approach is shown to be completely equivalent to a nonparabolic Hansch approach; it can be used to study additivity or nonadditivity of group contributions and to control and improve the fitting of Hansch equations. The Boček–Kopecký approach is related to the parabolic form of the Hansch approach; its practical use is limited by the great number of variables involved.

In 1964 three different approaches for studying quantitative structure–activity relationships were developed: Hansch's linear multiple regression model[1-3] (e.g., eq 1),

$$\log 1/C = k_1\pi^2 + k_2\pi + k_3\sigma + k_4E_s + k_5 \quad (1)$$

Free–Wilson's additive model[4] (eq 2), and Boček–

$$\text{biological act.} = \text{overall av} + \Sigma(\text{group contributions}) \quad (2)$$

Kopecký's interaction model[5,6] (eq 3).

$$\log 1/C = b_X + b_Y + e_Xe_Y + k \quad (3)$$

Free and Wilson's model is based on the assumption that each substituent makes an additive and constant contribution to the biological activity regardless of substituent variation in the rest of the molecule. The values of the individual group contributions are calculated by regression analysis (an excellent introduction into Hansch and Free–Wilson analysis for people not familiar with mathematics is given in ref 7).

Boček and Kopecký's interaction model may be interpreted as a Free–Wilson-like additive model with an additional term e_Xe_Y accounting for possible interactions between substituents X and Y. Although Boček–Kopecký's model is cited in almost every review article on quantitative structure–activity relationships, it has found no practical use due to the great number of parameters involved.

Singer and Purcell[8] studied the relationships among the linear free energy based Hansch approach and the two mathematical models. They could demonstrate that all models are theoretically interrelated but Free–Wilson's model is appropriate only in the case of additivity of group contributions while Boček–Kopecký's interaction model also holds in the case of parabolic dependence of biological activity on a particular physical property, e.g., Hansch's substituent constant π. In view of these relationships between the mathematical models and the Hansch approach they proposed the use of log $1/C$ values instead of linear values[4] as biological response parameters in Free–Wilson analysis. In the following years there has been some discussion whether log $1/C$ or C should be used,[9,10] but today in most instances log $1/C$ is being used. It should be noted that Bruice et al.[11] were the first ones who used log $1/C$ values and an additive model to calculate the activity of thyroxine analogues (eq 4).

$$\log \%\ \text{thyroxine-like activity} = k\Sigma f + c \quad (4)$$

Cammarata and Yau[12] and Fujita and Ban[13] used a modified Free–Wilson approach (eq 5)

$$\log 1/C = \sum_i a_i + \mu \quad (5)$$

where a_i = group contribution of substituent X_i, based on $a_H = 0.00$ (which is a definition), and μ = log $1/C$ calculated of the unsubstituted compound.[13]

The Free–Wilson model in its classical form is based on symmetry equations; therefore, the constant term is the overall average of the biological activities.

Fujita and Ban[13] described a modified Free–Wilson model without symmetry equations. In this modified model the activity contribution of each substituent is relative to H and the constant term μ, obtained by the least-squares method, is a theoretically predicted activity value of the unsubstituted compound (all R = H) itself. It must be noted that also in Hansch analysis the constant term is the theoretically predicted activity value of the unsubstituted compound provided all structural parameters ϕ_j are based on $\phi_H = 0.00$ (e.g., π or σ, but not log P or E_s). On the other hand, the constant term in the original Free–Wilson model is interpreted as the activity value of a hypothetical "naked" compound (all R absent); if the group contributions of all hydrogen substituents under consideration are added to this term, the μ value of the Fujita–Ban model results. In a similar manner the group contributions of the classical Free–Wilson model can be transformed to Fujita–Ban a_i values by subtracting the group contributions of the corresponding hydrogen substituents. Therefore the Fujita–Ban modification is a simple linear transformation of the classical Free–Wilson model (a detailed description of this modified model is given in ref 13).

Cammarata and Yau[12] used a similar, but statistically different, modified Free–Wilson model. Like the model of Fujita and Ban all activity contributions refer to H but the constant term is not obtained by the least-squares method; the observed activity value of the unsubstituted compound is arbitrarily taken as the constant term. Since all observed log $1/C$ values include an unknown experimental error ϵ_i, the constant term includes the experimental error ϵ_H of the observed log $1/C$ value of the unsubstituted compound; this is inconsistent with the definition of the least-squares method.

In accordance with these facts the Fujita–Ban modification gives better results than the Cammarata modification (only in the case of $\epsilon_H \rightarrow 0$ both models give similar results; for further discussion see below, example 1).

The Free–Wilson model and the nonparabolic form of Hansch's linear multiple regression model (e.g., eq 6) have

$$\log 1/C = k_1\pi + k_2\sigma + k_3E_s + k_4 \qquad (6)$$

been shown to be practically interrelated[12-15] and theoretically equivalent;[16] based on the assumption that the group contributions a_i of substituents X_i can be interpreted by a weighted sum of physical properties ϕ_j of the substituents, eq 7 can be derived (compare eq 3 and 4i of ref

$$a_i = \sum_j b_j\phi_j \qquad (7)$$

16), in which b_j are coefficients of different physical properties ϕ_j (e.g., substituent parameters like π, σ, or E_s).

Substitution of a_i by $\sum b_j\phi_j$ (eq 7) in the Free–Wilson type eq 5 gives eq 8.

$$\log 1/C = \sum_i \sum_j b_j\phi_j + \mu \qquad (8)$$

Equation 8 may be written in the form of eq 9 or in the

$$\log 1/C = b_1\sum_i \phi_1 + b_2\sum_i \phi_2 + \ldots + b_n\sum_i \phi_n + \mu \qquad (9)$$

more common form of eq 10, which are both Hansch type

$$\log 1/C = b_1\phi_1 + b_2\phi_2 + \ldots + b_n\phi_n + \mu \qquad (10)$$

equations.

Cammarata[16] stated that a number of statistically based structure–activity studies would support the equivalence of the additive and the linear multiple regression model, but this has never been done. On the contrary, some confusion has been added in the meantime; in comparing the Hansch and the Free–Wilson models practically, Cammarata[16] used a modified Free–Wilson approach[12] which did not give the best possible correlation between observed and calculated log $1/C$ values (see example 1). Furthermore, Cammarata's assumption that the additive model also holds in case of parabolic dependence of log $1/C$ on a particular physical property[16,17] and in case of interactions between substituents[17] is not generally true; these assumptions are valid only if a higher order term or an interaction term gives a somewhat better correlation but the absolute contribution of this term to log $1/C$ values is small.

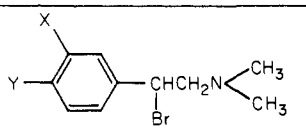
It is the purpose of this paper to give a precise practical comparison of the mathematical models and the linear multiple regression model. The following examples shall demonstrate the interrelationships of these models, the Hansch approach in its linear (e.g., eq 6) and parabolic form (e.g., eq 1), the modified Free–Wilson approach[13] (eq 5), and the Bocek–Kopecký approach (eq 3). It will be shown how the modified Free–Wilson model may be used to study additivity or nonadditivity, e.g., parabolic dependence of log $1/C$ on log P or π. In addition the modified Free–Wilson approach may be used to control and to improve the fitting of Hansch equations because in case of additivity of group contributions this approach always gives a "maximal correlation" between calculated and observed log $1/C$ values, a fact which is predictable from eq 5 ($\sum b_j\phi_j$ may be interpreted as a great number of known and unknown physical parameters in optimal weighted combination for each position of substitution).

Example 1 was chosen from the literature to demonstrate the close numerical equivalence of the additive and the linear multiple regression model in such cases where both methods give good fitting results. Example 1 also will demonstrate that in the case of additivity of group contributions the modified Free–Wilson approach (eq 5) gives an equal or even better correlation of observed and calculated log $1/C$ values than the Hansch approach; the modified Free–Wilson approach gives the "upper limit" of correlation which may be obtained with an additive, nonparabolic approach.

Hansch and Lien,[18] Cammarata,[16] and Unger and Hansch[19] analyzed the adrenergic blocking potencies of several *N,N*-dimethyl-2-bromophenethylamines[20] by Hansch and Free–Wilson analysis (the compounds and their log $1/C$ values are presented together with some structural parameters in Table I).

Cammarata[16] used a modified Free–Wilson approach to calculate log $1/C$ values for this group of compounds with de novo group contributions. However, he could not obtain the best possible correlation between observed and calculated log $1/C$ values ($r \geq 0.96$) because he used the *observed* log $1/C$ value of the unsubstituted compound (μ = 7.46) as the basis for his analysis instead of the *calculated* (theoretical) one as proposed by Fujita and Ban[13] (it was Cammarata's misfortune that the greatest deviation between observed and calculated log $1/C$ values is obtained for the unsubstituted compound, see Table II). A reexamination of the compounds of Table I with the

Table I. Antagonism of N,N-Dimethyl-2-bromophenethylamines vs. Adrenaline in the Rat



X (meta)	Y (para)	π^a	σ^{+b}	$E_s^{meta\,c}$	Log 1/C obsd[d]
H	F	0.15	−0.07	1.24	8.16
H	Cl	0.70	0.11	1.24	8.68
H	Br	1.02	0.15	1.24	8.89
H	I	1.26	0.14	1.24	9.25
H	CH_3	0.52	−0.31	1.24	9.30
F	H	0.13	0.35	0.78	7.52
Cl	H	0.76	0.40	0.27	8.16
Br	H	0.94	0.41	0.08	8.30
I	H	1.15	0.36	−0.16	8.40
CH_3	H	0.51	−0.07	0.00	8.46
Cl	F	0.91	0.33	0.27	8.19
Br	F	1.09	0.34	0.08	8.57
CH_3	F	0.66	−0.14	0.00	8.82
Cl	Cl	1.46	0.51	0.27	8.89
Br	Cl	1.64	0.52	0.08	8.92
CH_3	Cl	1.21	0.04	0.00	8.96
Cl	Br	1.78	0.55	0.27	9.00
Br	Br	1.96	0.56	0.08	9.35
CH_3	Br	1.53	0.08	0.00	9.22
CH_3	CH_3	1.03	−0.38	0.00	9.30
Br	CH_3	1.46	0.10	0.08	9.52
H	H	0.00	0.00	1.24	7.46

[a] See ref 21. [b] See ref 22. [c] See ref 23. [d] See ref 20.

correct form of the modified Free-Wilson approach (a_H = 0.00; μ = log 1/C calcd of the unsubstituted compound, see ref 13) gave a better correlation (r = 0.969; s = 0.194) than the analysis by Cammarata (r = 0.911; s = 0.214).[16] [We could not reproduce these values; from the log 1/C values given by Cammarata (ref 16, Table I) we calculated r = 0.902; s = 0.324.] The matrix used for Free-Wilson analysis and the calculated log 1/C values are given in Table II; the corresponding group contributions are listed in Table III.

From the numerous Hansch equations derived by Hansch and Lien,[18] Cammarata,[16] and Unger and Hansch,[19] five different equations (eq 11–15) were selected.

$$\log 1/C = 1.15\ (\pm 0.19)\ \pi - 1.47\ (\pm 0.38)\ \sigma^+ + 7.82 \quad (11)^{19}$$
$$n = 22;\ r = 0.944;\ s = 0.197$$

$$\log 1/C = 0.791\ (\pm 0.150)\ \pi_m + 1.479\ (\pm 0.139)\ \pi_p - 1.004\ (\pm 0.302)\ \sigma_m - 1.993\ (\pm 0.402)\ \sigma_p + 7.914 \quad (12)^{16}$$
$$n = 22;\ r = 0.946;\ s = 0.203$$

$$\log 1/C = 0.747\ (\pm 0.123)\ \pi_m - 0.911\ (\pm 0.249)\ \sigma_m + 1.666\ (\pm 0.124)\ r_{v,p} + 5.769 \quad (13)^{16}$$
$$n = 22;\ r = 0.961;\ s = 0.168$$

$$\log 1/C = 0.82\ (\pm 0.27)\ \pi - 1.02\ (\pm 0.45)\ \sigma^+ + 0.62\ (\pm 0.43)\ r_{v,p} + 7.06 \quad (14)^{19}$$
$$n = 22;\ r = 0.964;\ s = 0.164$$

$$\log 1/C = 0.83\ (\pm 0.27)\ \pi_m + 1.33\ (\pm 0.20)\ \pi_p - 0.92\ (\pm 0.50)\ \sigma_m^+ - 1.89\ (\pm 0.57)\ \sigma_p^+ + 7.80 \quad (15)^{19}$$
$$n = 22;\ r = 0.966;\ s = 0.164$$

An additional Hansch equation was derived to describe log 1/C values by π, σ^+, and E_s^{meta} (see Table I).

$$\log 1/C = 1.26\ (\pm 0.19)\ \pi - 1.46\ (\pm 0.34)\ \sigma^+ + 0.21\ (\pm 0.17)\ E_s^{meta} + 7.62 \quad (16)$$
$$n = 22;\ r = 0.959;\ s = 0.173$$

Table II. Free-Wilson Matrix Used for Calculation of de Novo Group Contributions. Calculated Log 1/C Values[a]

X (meta)					Y (para)					Log 1/C obsd	Log 1/C calcd	Δ
F	Cl	Br	I	CH_3	F	Cl	Br	I	CH_3			
					1					8.16	8.16	0.00
						1				8.68	8.59	−0.09
							1			8.89	8.84	−0.05
								1		9.25	9.25[b]	0.00
									1	9.30	9.08	−0.22
1										7.52	7.52[b]	0.00
	1									8.16	8.03	−0.13
		1								8.30	8.25	−0.05
			1							8.40	8.40[b]	0.00
				1						8.46	8.27	−0.19
	1				1					8.19	8.37	0.18
		1			1					8.57	8.59	0.02
			1		1					8.82	8.61	−0.21
	1					1				8.89	8.80	−0.09
		1				1				8.92	9.02	0.10
			1			1				8.96	9.04	0.08
	1						1			9.00	9.05	0.05
		1					1			9.35	9.27	−0.08
			1				1			9.22	9.29	0.07
			1						1	9.30	9.53	0.23
		1							1	9.52	9.51	−0.01
										7.46	7.82	0.36

[a] For values of group contributions see Table III. [b] Single point determinations.

In order to calculate group contributions a_i for each substituent, based on a_H = 0.00, the following equations were derived from eq 11–16.

From eq 11: $a_i = 1.15\ \pi - 1.47\ \sigma^+$ (17)

From eq 12: $a_{meta} = 0.791\ \pi_m - 1.004\ \sigma_m$ (18)

$a_{para} = 1.479\ \pi_p - 1.993\ \sigma_p$ (19)

From eq 13: $a_{meta} = 0.747\ \pi_m - 0.911\ \sigma_m$ (20)

$a_{para} = 1.666\ (r_{v,p} - r_{v,H})$ (21)

From eq 14: $a_{meta} = 0.82\ \pi_m - 1.02\ \sigma_m^+$ (22)

$a_{para} = 0.82\ \pi_p - 1.02\ \sigma_p^+ + 0.62\ (r_{v,p} - r_{v,H})$ (23)

From eq 15: $a_{meta} = 0.83\ \pi_m - 0.92\ \sigma_m^+$ (24)

$a_{para} = 1.33\ \pi_p - 1.89\ \sigma_p^+$ (25)

From eq 16: $a_{meta} = 1.26\ \pi_m - 1.46\ \sigma_m^+ + 0.21\ (E_s^{meta} - E_{s,H})$ (26)

$a_{para} = 1.26\ \pi_p - 1.46\ \sigma_p^+$ (27)

A comparison of Hansch-derived group contributions (eq 17–27) and de novo group contributions calculated by the modified Free-Wilson approach is given in Table III (the original structural parameters used by each author were taken for the calculations; note that Cammarata[16] and Unger and Hansch[19] used different π values).

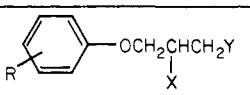
The correlation of de novo group contributions calculated by Free-Wilson analysis and the Hansch-derived group contributions is very good; eq 11–16 are "optimally adapted". The residual variance in log 1/C values not

Table III. Group Contributions (Based on $a_H = 0.00$) for Substituents X and Y of the *N,N*-Dimethyl-2-bromophenethylamines, Calculated by Free-Wilson and Hansch Analysis

Substituent	Free-Wilson parameters	Hansch-derived group contributions, calcd from eq 17	18, 19	20, 21	22, 23	24, 25	26, 27
m-H	0.00	0.00	0.00	0.00	0.00	0.00	0.00
m-F	−0.30[a]	−0.37	−0.21	−0.19	−0.25	−0.21	−0.44
m-Cl	0.21	0.29	0.18	0.19	0.22	0.26	0.17
m-Br	0.43	0.48	0.42	0.41	0.35	0.40	0.34
m-I	0.58[a]	0.79	0.65	0.62	0.58	0.62	0.63
m-CH_3	0.45	0.69	0.48	0.45	0.49	0.49	0.48
p-H	0.00	0.00	0.00	0.00	0.00	0.00	0.00
p-F	0.34	0.28	0.10	0.45	0.36	0.33	0.29
p-Cl	0.77	0.64	0.58	0.92	0.80	0.72	0.72
p-Br	1.02	0.95	1.05	1.08	1.09	1.07	1.07
p-I	1.43[a]	1.24	1.31	1.30	1.37	1.41	1.38
p-CH_3	1.26	1.05	1.11	1.28	1.22	1.28	1.11
Unsubst compd	7.82	7.82	7.91	7.77	7.80	7.80	7.88

[a] Single point determinations.

Table IV. Fungistatic Activity of Phenyl Ethers of Glycerol and Propylene Glycols[a]



Compd no.	R	X	Y	Log *P*	σ	E_s^{ortho}	Log 1/*C* obsd
1	2-Me	OH	OH	1.38	−0.14	1.24	2.26
2	2-Cl	OH	OH	1.29	0.21	1.51	2.31
3	4-Cl	OH	OH	1.40	0.23	2.48	2.31
4	2,6-Cl_2	OH	OH	1.88	0.42	0.54	2.37
5	2,4-Cl_2	OH	OH	1.99	0.44	1.51	2.61
6	2-Me, 4-Cl	OH	OH	2.08	0.09	1.24	2.33
7	3-Me, 4-Cl	OH	OH	1.91	0.16	2.48	2.90
8	2-Me, 6-Cl	OH	OH	1.97	0.07	0.27	2.33
9	2,6-Me_2, 4-Cl	OH	OH	2.76	−0.05	0.00	2.76
10	3,5-Me_2, 4-Cl	OH	OH	2.42	0.09	2.48	3.24
11	2,6-Cl_2, 4-Me	OH	OH	2.40	0.25	0.54	3.10
12	2-Me	OH	H	2.14	−0.14	1.24	2.46
13	2-Cl	OH	H	2.05	0.21	1.51	2.84
14	4-Cl	OH	H	2.16	0.23	2.48	2.81
15	2,6-Cl_2	OH	H	2.64	0.42	0.54	3.04
16	2,4-Cl_2	OH	H	2.75	0.44	1.51	3.35
17	2-Me, 4-Cl	OH	H	2.84	0.09	1.24	3.30
18	3-Me, 4-Cl	OH	H	2.67	0.16	2.48	3.30
19	2-Me, 6-Cl	OH	H	2.73	0.07	0.27	2.70
20	2,6-Me_2, 4-Cl	OH	H	3.52	−0.05	0.00	3.51
21	3,5-Me_2, 4-Cl	OH	H	3.18	0.09	2.48	3.68
22	2,6-Cl_2, 4-Me	OH	H	3.16	0.25	0.54	3.47
23	2-Me	H	OH	2.34	−0.14	1.24	2.79
24	4-Cl	H	OH	2.36	0.23	2.48	3.07
25	2-Me, 6-Cl	H	OH	2.93	0.07	0.27	2.78
26	2,6-Me_2, 4-Cl	H	OH	3.72	−0.05	0.00	3.51
27	3,5-Me_2, 4-Cl	H	OH	3.38	0.09	2.48	3.93
28	2,6-Cl_2, 4-Me	H	OH	3.36	0.25	0.54	3.67

[a] All data taken from Hansch and Lien;[24] the E_s values were taken from ref 23.

explained by Free–Wilson analysis must be due to nonadditivity and/or biological variance and/or experimental error.

Craig and Hansch[15] stated that the additive model and the linear multiple regression model give different quantitative results. This statement is valid only if the group contributions are not transformed to $a_H = 0.00$ and/or in case of nonadditivity of group contributions. Provided that the biological activity data are accurate and reliable and that both models give good correlations between observed and calculated log 1/*C* values, which are basic conditions for comparison of both models, the group contributions calculated by both models also show good correlation. In Free–Wilson analysis there may be some deviations due to single point determinations because experimental error or biological variance is completely reflected in a group contribution derived from only one log 1/*C* value.

Example 2 demonstrates how the modified Free–Wilson approach may be used to control the fitting of a Hansch equation and to improve the Hansch equation by comparison of de novo group contributions and Hansch-derived group contributions.

From the extensive work of Hansch and Lien[24] on structure–activity relationships in antifungal agents one set of compounds, substituted phenyl ethers of glycerol and propylene glycols, was reexamined by the modified Free–Wilson approach. Structures of the compounds are given in Table IV together with some structural parameters. The matrix used for Free–Wilson analysis and the calculated log 1/*C* values are given in Table V (as a simplification the assumption was made that substituents

Table V. Free-Wilson Matrix Used for Calculation of de Novo Group Contributions. Calculated Log 1/C Values[a]

R							Log 1/C	Log 1/C	
o-Me	m-Me	p-Me	o-Cl	p-Cl	X = OH	Y = OH	obsd	calcd	Δ
1					1	1	2.26	2.08	-0.18
			1		1	1	2.31	2.15	-0.16
				1	1	1	2.31	2.40	0.09
			2		1	1	2.37	2.42	0.05
			1	1	1	1	2.61	2.67	0.06
1				1	1	1	2.33	2.60	0.27
	1			1	1	1	2.90	2.81	-0.09
1			1		1	1	2.33	2.35	0.02
2				1	1	1	2.76	2.79	0.03
	2			1	1	1	3.24	3.23	-0.01
		1	2		1	1	3.10	3.02	-0.08
1					1		2.46	2.62	0.16
			1		1		2.84	2.69	-0.15
				1	1		2.81	2.94	0.13
			2		1		3.04	2.96	-0.08
			1	1	1		3.35	3.21	-0.14
1				1	1		3.30	3.14	-0.16
	1			1	1		3.30	3.35	0.05
1			1		1		2.70	2.89	0.19
2				1	1		3.51	3.33	-0.18
	2			1	1		3.68	3.77	0.09
		1	2		1		3.47	3.56	0.09
1						1	2.79	2.72	-0.07
				1		1	3.07	3.05	-0.02
1			1			1	2.78	3.00	0.22
2				1		1	3.51	3.44	-0.07
	2			1		1	3.93	3.87	-0.06
		1	2			1	3.67	3.67	0.00

[a] For group contributions, see Table VI; $\mu = 3.07$.

give equal contributions in the ortho and ortho position and likewise in the meta and meta' position; a coefficient of 2 was given to ortho,ortho'- and meta,meta'-disubstituted compounds).

Hansch and Lien[24] derived eq 28 (compounds **19** and

$$\log 1/C = 0.691\ (\pm 0.14) \log P + 0.428\ (\pm 0.51)\ \sigma + 1.213 \quad (28)$$
$$n = 26;\ r = 0.911;\ s = 0.216$$

25 were excluded) for the compounds of Table IV. For all compounds of Table IV we obtained eq 29.

$$\log 1/C = 0.665\ (\pm 0.149) \log P + 0.500\ (\pm 0.568)\ \sigma + 1.235 \quad (29)$$
$$n = 28;\ r = 0.879;\ s = 0.241$$

Free-Wilson analysis (for matrix see Table V) gave a significant better correlation of observed and calculated log 1/C values ($n = 28$; $r = 0.967$; $s = 0.145$). The high correlation coefficient demonstrates that additivity of group contributions is fulfilled for this set of compounds.

By substituting π for log P eq 30 can be derived from

$$a_i = 0.665\ \pi + 0.500\ \sigma \quad (30)$$

eq 29 to calculate group contributions.

A comparison of these Hansch-derived group contributions with de novo group contributions (Table VI) shows great deviations, especially for o-Me and o-Cl (values calculated from eq 30 are too high) and for p-Me (value calculated from eq 30 is too small). Since these deviations may be due to an unfavorable steric effect of the ortho substituents, a further Hansch analysis with log P and E_s^{ortho} (Table IV) was run (eq 31).

$$\log 1/C = 0.741\ (\pm 0.109) \log P + 0.214\ (\pm 0.078)\ E_s^{ortho} + 0.846 \quad (31)$$
$$n = 28;\ r = 0.942;\ s = 0.170$$

Table VI. Group Contributions (Based on $a_H = 0.00$) for Substituents R, X, and Y, Calculated by Free-Wilson and Hansch Analysis

			Group contributions, calcd from		
Substituent	π^a	σ^b	Eq 30	Eq 32, 33	Free-Wilson analysis
o-Me	0.68	-0.14	0.38	0.24	0.20
m-Me	0.51	-0.07	0.30	0.38	0.41
p-Me	0.52	-0.17	0.26	0.39	0.59
o-Cl	0.59	0.21	0.50	0.23	0.27
p-Cl	0.70	0.23	0.58	0.52	0.52
X = OH	-0.96		-0.64	-0.71	-0.65
Y = OH	-0.76		-0.51	-0.56	-0.54

[a] Calculated from log P values.[24] [b] From σ values of Table IV.

Equations 32 and 33 were derived from eq 31 to calculate group contributions.

$$a_{meta,para} = 0.741\ \pi \quad (32)$$

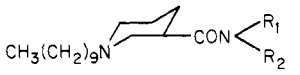
$$a_{ortho} = 0.741\ \pi + 0.214\ (E_s^{ortho} - E_{s,H}) \quad (33)$$

A comparison of group contributions calculated from eq 32 and 33 with the de novo group contributions (Table VI) shows good correlation (the deviation found for p-Me may be due to the small number of compounds bearing p-Me). This good correlation is in agreement with the fact that the σ term in eq 29 is statistically not significant ($t_\sigma = 1.811$; $p > 0.05$) while the E_s^{ortho} term in eq 31 is statistically significant ($t_{Es^{ortho}} = 5.658$; $p < 0.001$).

A combination of log P, σ, and E_s^{ortho} gives no further improvement of correlation (eq 34). Again the σ term is

$$\log 1/C = 0.751\ (\pm 0.104) \log P + 0.366\ (\pm 0.383)\ \sigma + 0.205\ (\pm 0.074)\ E_s^{ortho} + 0.782 \quad (34)$$
$$n = 28;\ r = 0.950;\ s = 0.161$$

Table VII. Hansch and Free-Wilson Analysis of Butyrylcholinesterase Inhibitory Activity of 1-Decyl-3-carbamoylpiperidines



			pI_{50} calcd by		
R_1	R_2	pI_{50} obsd	Eq 35	Eq 36	Free-Wilson analysis[b]
H	H	4.21	4.19	4.21	4.25
H	CH_3	4.46	4.47	4.46	4.46
H	C_2H_5	4.86	4.76	4.86	4.78
CH_3	CH_3	4.66	4.76	4.66	4.66
CH_3	C_2H_5[a]	5.01	5.04	5.00	4.99
C_2H_5	C_2H_5	5.28	5.33	5.29	5.32
C_3H_7	C_3H_7	5.98	5.90	5.98	5.98

[a] Compound not included in Free-Wilson analysis and calculation of eq 35 and 36. [b] See ref 25.

not significant ($t_\sigma = 1.973$; $p > 0.05$) while the E_s^{ortho} term is significant ($t_{E_s^{ortho}} = 5.677$; $p < 0.001$).

Example 3 is taken from Clayton and Purcell's comparison of Hansch and Free-Wilson analysis.[25] They studied structure-activity relationships for butyrylcholinesterase inhibitory activity of 1-decyl-3-carbamoylpiperidines by both methods and derived several Hansch equations (e.g., eq 35 and 36) and also de novo

$$pI_{50} = 0.570\,\pi + 4.187 \quad (35)$$
$$n = 6; r = 0.992; s = 0.087; F = 268$$

$$pI_{50} = -0.119\,\pi^2 + 1.205\,\pi + 0.687\,\sigma^* + 3.533 \quad (36)$$
$$n = 6; r = 0.999; s = 0.045; F = 8984$$

group contributions which fit the experimental data very well (Table VII).

Cammarata[16] concluded that this example would give evidence for the validity of Free–Wilson additivity in cases of parabolic dependence of log $1/C$ values on log P or π (eq 36). However, from Table VII one can see that pI_{50} may be described well by a nonparabolic equation (eq 35); if there is any parabolic dependence, its numerical influence is so small that additivity of group contributions is not perturbed. Despite the enormously high F value eq 36 may be a chance correlation;[26] therefore, it is not possible to demonstrate validity or nonvalidity of Free–Wilson additivity in cases of parabolic dependence of log $1/C$ values on π with this example.

Example 4 was chosen from a paper of Hansch et al.[27] on parabolic dependence of drug activity on lipophilic character to demonstrate complete breakdown of the Free–Wilson model and to demonstrate the applicability of a Boček–Kopecký-like model in cases of real nonadditivity of group contributions.

Hansch et al.[27] derived for a group of N,N'-diacylureas (for structures see Table VIII) eq 37.

$$\log 1/C = -0.177\ (\pm 0.087)\ (\log P)^2 + 0.599\ (\pm 0.222)\ \log P + 1.893 \quad (37)$$
$$n = 13; r = 0.918; s = 0.079$$

For Free–Wilson analysis N,N'-diacetylurea was taken as basis compound; therefore, all group contributions refer to $a_{COCH_3} = 0.00$ and $\mu = \log 1/C$ calcd of N,N-diacetylurea (in all cases where no "unsubstituted" compound with R = H is included, any compound may be chosen as basis compound in the modified Free–Wilson approach[28]).

For Boček–Kopecký analysis a total number of ten variables would have been needed; therefore the simplifying assumption was made that the interactions between substituents R_1 and R_2 depend only on the number of carbon atoms of these substituents (the matrix used for the Free–Wilson analysis and the Boček–Kopecký-like analysis is given in Table VIII).

Due to the parabolic character of eq 37 Free–Wilson analysis gave only a correlation which is statistically not significant ($n = 13$; $r = 0.822$; $s = 0.135$; $F = 2.93$; $p > 0.05$). A Boček–Kopecký-like analysis with the same matrix plus an interaction term $N_1 \cdot N_2$ gave a better correlation which is statistically significant ($n = 13$; $r = 0.982$; $s = 0.049$; $F = 26.55$; $p < 0.001$). The values found for de novo group contributions and the coefficient of the interaction term are given in Table IX.

That the interaction term $N_1 \cdot N_2$ is physically meaningful can be shown by the following considerations. Since log P for this group of compounds can be calculated from the total number of carbon atoms of substituents R_1 and R_2 by eq 38 (see ref 27), it is possible to correlate log $1/C$ to N^2 and N (eq 39).

$$\log P = 0.50\,N - 2.60 \quad (38)$$

$$\log 1/C = -0.044\ (\pm 0.022)\ N^2 + 0.760\ (\pm 0.334)\ N - 0.862 \quad (39)$$
$$n = 13; r = 0.918; s = 0.079$$

Table VIII. Hypnotic Activity of N,N'-Diacylureas $R_1NHCONHR_2$; Structures and Matrix Used for Free-Wilson and Boček-Kopecký Analysis[a]

	Free-Wilson matrix								
R_1, R_2	C_3	C_4	C_5	C_6	C_7	Interaction term $N_1 \cdot N_2$[a]	N_1[a]	N_2[a]	Log $1/C$ obsd[b]
Acetyl, propionyl	1					6	2	3	1.84
Propionyl, propionyl	2					9	3	3	2.06
Acetyl, butyryl		1				8	2	4	2.16
Propionyl, butyryl	1	1				12	3	4	2.23
Acetyl, valeryl			1			10	2	5	2.27
Butyryl, butyryl		2				16	4	4	2.40
Propionyl, valeryl	1		1			15	3	5	2.35
Acetyl, hexanoyl				1		12	2	6	2.46
Butyryl, valeryl		1	1			20	4	5	2.38
Propionyl, hexanoyl	1			1		18	3	6	2.25
Acetyl, heptanoyl					1	14	2	7	2.55
Valeryl, valeryl			2			25	5	5	2.32
Butyryl, hexanoyl		1		1		24	4	6	2.28

[a] N_1, N_2 = number of carbon atoms of substituents R_1, R_2. [b] See ref 29.

Table IX. Group Contributions and Interaction Terms Calculated by Free-Wilson, Boček-Kopecký, and Hansch Analysis (Based on $a_{COCH_3} = 0.00$)

Substituent	Group contributions a_i and interaction term $N_1 \cdot N_2$ calcd by: Free-Wilson analysis	Boček-Kopecký analysis	Hansch analysis (eq 42)
Acetyl	0.00	0.00	0.00
Propionyl	0.00	0.43	0.54
Butyryl	0.15	0.91	0.99
Valeryl	0.19	1.25	1.36
Hexanoyl	0.24	1.49	1.63
Heptanoyl	0.51[a]	1.81[a]	1.82
Interaction term		$-0.085\ N_1 \cdot N_2$	$-0.088\ N_1 \cdot N_2$[b]

[a] Single point determinations. [b] See eq 40.

Substitution of N by $(N_1 + N_2)$ like Singer and Purcell[8] have done in their comparison of the Hansch and Boček-Kopecký approach gives eq 40.

$$\log 1/C = -0.044\ (N_1^2 + N_2^2) - 0.760\ (N_1 + N_2) - 0.862 \quad (40)$$

Equation 40 is a Boček-Kopecky-like equation (eq 3) with additive parameters $b_X = -0.044\ N_1^2 + 0.760\ N_1$ and $b_Y = -0.044\ N_2^2 + 0.760\ N_2$ (corresponding to Free-Wilson group contributions) and an interaction term $e_{XeY} = -0.088\ N_1 \cdot N_2$.

Equation 41 can be derived from eq 40 to calculate group

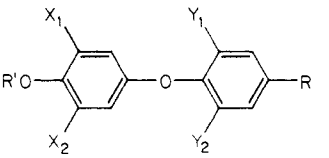
$$b_i = -0.044\ N_i^2 + 0.760\ N_i \quad (41)$$

contributions for each substituent R. Group contributions a_i based on $a_{COCH_3} = 0.00$ can be calculated from eq 42.

$$a_i = -0.044\ N_i^2 + 0.760\ N_i - 1.344 \quad (42)$$

The values of Table IX show the numerical equivalence of Boček-Kopecký analysis and parabolic Hansch analysis and the complete breakdown of Free-Wilson additivity as predicted by Singer and Purcell.[8]

Example 5 is a reinvestigation of the correlations given by Bruice et al.[11] and Hansch and Fujita[1] for the thyroxine-like activity of compounds of structure I. Bruice



I

et al.[11] derived eq 4

$$\log \%\ \text{thyroxine-like activity} = k\Sigma f + c \quad (4)$$

where

$$\Sigma f = f_{X_1} + f_{X_2} + f_{Y_1} + f_{Y_2} + f_{OR'} + f_R \quad (43)$$

(except for H it was implicated that $f_{X_1} = f_{X_2}$ and $f_{Y_1} = f_{Y_2}$).

From their f values we calculated for compounds 1–14 the values of k and c (structures and values of log A and Σf are given in Table X).

$$\log A = 2.804\ (\pm 0.853)\ \Sigma f + 13.116 \quad (44)$$
$$n = 14;\ r = 0.900;\ s = 0.523$$

Equation 45 was obtained by excluding compound 6, which is not well predicted by eq 44.

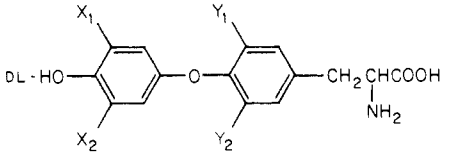
$$\log A = 3.178\ (\pm 0.314)\ \Sigma f + 14.873 \quad (45)$$
$$n = 13;\ r = 0.989;\ s = 0.183$$

Hansch and Fujita[1] derived for compounds 1–9 eq 46

$$\log A = -1.134\ \pi_x^2 + 7.435\ \pi_x - 16.323\ \sigma_x - 0.287 \quad (46)$$
$$n = 9;\ r = 0.884;\ s = 0.660$$

(π and σ values are given in Table X). The high coeffi-

Table X. Thyroxine-Like Activity on Rodents



Compd no.	X_1[a]	X_2[a]	Y_1	Y_2	π_x[b]	π[c]	σ_x[b]	E_{s,X_1}[d]	D[e]	Σf	Log A obsd[f]
1	H	I	I	I	1.15	3.45	0.28	1.24	0	−3.74	2.74
2	H	Br	I	I	0.85	3.15	0.23	1.24	0	−3.96	2.30
3	I	I	I	I	2.30	4.60	0.56	−0.16	0	−4.04	2.00
4	F	I	I	I	1.36	3.66	0.34	0.78	0	−4.28	1.45
5	Br	Br	I	I	1.70	4.00	0.46	0.08	0	−4.48	1.00
6	H	F	I	I	0.21	2.51	0.06	1.24	0	−3.98	0.38
7	F	F	I	I	0.42	2.72	0.12	0.78	0	−4.52	0.26
8	Cl	Cl	I	I	1.30	3.60	0.46	0.27	0	−4.68	−0.05
9	H	H	I	I	0.00	2.30	0.00	1.24	0	−4.80	−0.43
10	H	I	Br	Br	1.15	2.85	0.28	1.24	2	−4.02	2.11
11	H	Br	Br	Br	0.85	2.55	0.23	1.24	2	−4.24	1.64
12	I	I	Br	Br	2.30	4.00	0.56	−0.16	2	−4.32	1.10
13	Br	Br	Br	Br	1.70	3.40	0.46	0.08	2	−4.76	−0.29
14	I	I	Cl	Cl	2.30	3.60	0.56	−0.16		−4.96	−1.00

[a] For different substituents X_1 and X_2 the smaller substituent was taken as X_1 and the greater substituent was taken as X_2. [b] For better comparison original π and σ values used by Hansch and Fujita[1] were taken; other values gave similar results. [c] $\pi = \pi_x + \pi_y$. [d] See ref 23. [e] Indicator variable ($D = 0$ for Y = I; $D = 1$ for Y = Br). [f] See ref 11.

cients found for the π and σ terms are little reliable because π and σ are correlated for this group of compounds (eq 47). Therefore eq 46 may be a chance correlation.[26]

$$\pi_x = 3.713\ (\pm 0.793)\ \sigma_x - 0.003 \qquad (47)$$
$$n = 9;\ r = 0.973;\ s = 0.184$$

In order to find a better correlation of structure and activity for this group of compounds some Free–Wilson analyses were run to prove additivity of group contributions (the matrices used are not given in detail because the Free–Wilson analyses were only an aid to derive the final Hansch equation).

A first Free–Wilson analysis of compounds 1–9 (it was implicated that $a_{X_1} = a_{X_2}$) gave eq 48. The low correlation

$$\log A = \Sigma a_i + 0.67 \qquad (48)$$
$$n = 9;\ r = 0.739;\ s = 1.062$$
$$[F_X] = -0.22;\ [Cl_X] = -0.36;\ [Br_X] = 0.46;$$
$$[I_X] = 0.95 \text{ (all values based on } a_H = 0.00)$$

coefficient of eq 48 indicates that there is no additivity of group contributions; therefore, a Bočeк–Kopecký-like analysis was run with π^2 as interaction term (eq 49), which

$$\log A = -1.35\ \pi_x^2 + \Sigma a_i + 0.05 \qquad (49)$$
$$n = 9;\ r = 0.931;\ s = 0.479$$
$$[F_X] = 0.13;\ [Cl_X] = 1.09;\ [Br_X] = 2.59;\ [I_X] = 4.41 \text{ (all values based on } a_H = 0.00)$$

gave a correlation coefficient much better than that of eq 48. The interaction term in eq 49 is similar to the parabolic term of eq 46, which seems to support the biological significance of eq 46.

A second Free–Wilson analysis was run with compounds 1–14 (it was implicated that $a_{X_1} = a_{X_2}$ and $a_{Y_1} = a_{Y_2}$).

$$\log A = \Sigma a_i + 1.28 \qquad (50)$$
$$n = 14;\ r = 0.726;\ s = 1.080$$
$$[F_X] = -0.54;\ [Cl_X] = -0.66;\ [Br_X] = -0.10;\ [I_X] = 0.49 \text{ (values based on } a_H = 0.00)$$
$$[Br_Y] = -0.21;\ [Cl_Y] = -1.63 \text{ (values based on } a_I = 0.00)$$

The corresponding Bočeк–Kopecký analysis with π^2 (note that $\pi = \pi_x + \pi_y$) as interaction term gave eq 51.

$$\log A = 0.002\ \pi^2 + \Sigma a_i + 1.28 \qquad (51)$$
$$n = 14;\ r = 0.730;\ s = 1.160$$
$$[F_X] = -0.59;\ [Cl_X] = -0.67;\ [Br_X] = -0.11;\ [I_X] = 0.48 \text{ (values based on } a_H = 0.00)$$
$$[Br_Y] = -0.21;\ [Cl_Y] = -1.63 \text{ (values based on } a_I = 0.00)$$

Equation 51 demonstrates that there is no significant contribution of π^2, but there is also no additivity of group contributions as can be seen from the low correlation coefficients of eq 50 and 51.

Next a Free–Wilson analysis was run to prove the implication that substituent contributions are equal in positions X_1 and X_2 (it was implicated that $a_{X_1} \neq a_{X_2}$ and $a_{Y_1} = a_{Y_2}$; compound 8 was excluded because no differentiation is possible between Cl in position X_1 and X_2).

$$\log A = \Sigma a_i - 0.43 \qquad (52)$$
$$n = 13;\ r = 0.981;\ s = 0.387$$
$$[F_{X_1}] = -0.83;\ [Br_{X_1}] = -1.62;\ [I_{X_1}] = -0.70$$
$$[F_{X_2}] = 1.17;\ [Br_{X_2}] = 2.79;\ [I_{X_2}] = 3.07 \text{ (all values based on } a_H = 0.00)$$
$$[Br_Y] = -0.39;\ [Cl_Y] = -1.47 \text{ (values based on } a_I = 0.00)$$

Of course a Free–Wilson analysis with only 13 compounds and 8 group contributions (=9 unknowns, including μ) is strictly forbidden and it is not surprising to get a correlation coefficient of 0.981 in such an analysis. But a closer look shows that there are great differences for the group contributions in position X_1 and position X_2: all X_1 values are negative and all X_2 values are positive. Since the X_2 values are most probably π-correlated, also the X_1 values should be π-correlated but there may be a negative steric contribution for X_1.

A Hansch analysis of compounds 1–9 with π_x and E_{s,X_1} as structural parameters gave eq 53. It must be noted that

$$\log A = 2.43\ (\pm 0.88)\ \pi_x + 2.66\ (\pm 1.17)\ E_{s,X_1} - 3.42 \qquad (53)$$
$$n = 9;\ r = 0.940;\ s = 0.439;\ F = 22.81;\ p < 0.005$$

Jorgensen et al.[30] discussed a hypothetical thyroid hormone receptor with a binding receptor, a functional receptor, and a proximal steric block for substituent X_1. Corresponding to this model E_s values were used only for position X_1; in cases of different substituents X_1 and X_2 the smaller substituent was taken as X_1, since there seems to be no steric hindrance for substituents in position X_2.

Hansch analysis of compounds 1–13 gave eq 54; an indicator variable[31] D was included in order to account for all polar, electronic, and steric changes that may occur if Y = I is replaced by Y = Br. Equations 53 and 54

$$\log A = 2.54\ (\pm 0.71)\ \pi_x + 2.91\ (\pm 0.83)\ E_{s,X_1} - 0.35\ (\pm 0.30)\ D - 3.72 \qquad (54)$$
$$n = 13;\ r = 0.942;\ s = 0.408;\ F = 23.45;\ p < 0.001$$

demonstrate that doing something forbidden may come to a good end; eq 48–52 should not be discussed further; they were only presented to show how Free–Wilson analysis and Bočeк–Kopecký analysis can be used to prove additivity of group contributions and to derive better fitting Hansch equations in cases where no simple correlation of log $1/C$ with π and/or σ is given. A more detailed discussion of structure–activity relationships of thyroxine analogues will be given in the following paper.[32]

Discussion

The preceding examples show clearly the close numerical equivalence of the linear free energy related Hansch approach and the mathematical models of Free and Wilson and Bočeк and Kopecký. We hope that these examples give enough evidence to end the discussion whether Free–Wilson additivity also holds in cases of parabolic dependence of biological activity on a particular physical parameter or not; the statements made by Singer and Purcell[8] that Free–Wilson's model corresponds to the nonparabolic Hansch approach and Bočeк–Kopecký's model corresponds to the parabolic Hansch approach are established by our examples as a fact. Cammarata's opinion that the Free–Wilson approach also holds in cases

of parabolic dependence of biological activity[16,17] is valid only in these special instances where the numerical contribution of a parabolic term or an interaction term is small.

If the modified[13] Free–Wilson approach (all a_i based on $a_H = 0.00$ and $\mu = \log 1/C$ calcd of the unsubstituted compound) is used, the de novo group contributions are, within the experimental error and/or the biological variance, *identical* with Hansch-derived group contributions (provided both models give satisfactory correlations between observed and calculated log $1/C$ values). In cases of significant parabolic dependence of biological activity on a particular physical parameter an interaction term has to be included in the Free–Wilson analysis. The de novo group contributions and the coefficient of the interaction term calculated by such a Bocek–Kopecky-like approach are identical with the corresponding Hansch-derived values, if the Hansch equation is transformed in a manner as Singer and Purcell[8] have shown.

Based on this equivalence the Free–Wilson approach can be used to check additivity of group contributions for a given set of compounds, if the number of variables necessary is not too great compared to the number of compounds involved. A good correlation between observed and calculated log $1/C$ values gives evidence that there may exist a nonparabolic relationship between appropriate structural parameters and biological activity. On the other hand, an unsatisfactory correlation gives evidence for a parabolic dependence, an interaction between several substituents or the nonvalidity of a simplifying assumption (e.g., assumed equivalence of ortho and ortho' substituents; compare example 5).

If the modified Free–Wilson approach is used only to derive a significant Hansch correlation, no care has to be taken if the Free–Wilson analysis per se gives a statistical significant result (of course such a "forbidden" Free–Wilson analysis must not be used to make predictions for new compounds or to calculate Hansch equations for the de novo group contributions). A close inspection of such Free–Wilson derived group contributions may give some ideas of which structural parameters should be used in doing a Hansch analysis, as was shown in examples 2 and 5. The final Hansch equation has to be examined very carefully on its statistical significance and its physical and biochemical meaning with the criteria given by Unger and Hansch[19] in order not to abuse this method to generate some more "statistical unicorns".

The goal of every Free–Wilson or Bocek–Kopecky analysis should be the derivation of a significant Hansch equation which gives us a better understanding of how drugs act at the molecular level.

References and Notes

(1) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
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