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Quantitative Structure–Property Relationship: XXI.[1] Steric Effect of Substituents on the Complexation Energy and Kinetics of Chemical Reactions

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Abstract — The simple approach suggested previously for estimating properties of molecules RX was applied to constructing quantitative relationships between the structure of alkyl substituent R and the properties of stable complexes and transition states considered as supermolecules RX. The enthalpies and free energies of complexation of a series of aliphatic amines with trimethylboron, the logarithms of the relative rates of esterification of aliphatic carboxylic acids, and the Taft steric constants were calculated.

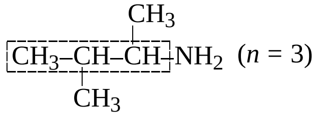
The free energies of the complexation $R–A + B \rightleftarrows R–A\cdots B$, as well as the rates of chemical reactions $R–A^* + B^* \rightleftarrows R–A^*\cdots B^* \rightleftarrows$ products, depend on the structure of substituent R affecting the interaction of this substituent with the second component of the complex or second reaction participant. The influence of the structure of R on the kinetics of some reactions was studied experimentally (see, e.g., [2–6]), and the steric constants of substituents R, reproducing the steric effect in related reactions, were obtained. In particular, to take into account the steric effect of substituents on reactions of aliphatic compounds, Taft introduced the constants E_S determined from data on the rates of acid hydrolysis of ethyl esters of carboxylic acids [3]: $E_S = \log(k/k_0)$. Here k and k_0 are the rate constants of the hydrolysis of the ester with substituent R in the acyl moiety and of the acetate, respectively. Although the constants E_S are not universal [6], they are used both for estimating the rate constants of chemical reactions and for constructing quantitative structure–activity relationships in determination of potentially active drug structures (see, e.g., [7]). In this connection, further efforts are made to find ways for quantitative estimation of the substituent effects [8, 9], so as to obtain the E_S constants applicable to a wide set of problems. However, a different goal can be formulated: to search for a common approach allowing solution of specific problems, rather than for universal parameters. This is the objective of our study.

Let us consider stable complexes $R–A\cdots B$ and transition states $R–A^*\cdots B^*$ as supermolecules RX and apply the previously developed approach [10] to estimating various properties of such systems. In accordance with [10], the expression for a property of an RX molecule is as follows:

$$P = P_{\text{lin}} + n'\alpha + n''\gamma + n'''\gamma^* + m\delta_{14} + m'\delta_{14}^* + \ldots, \qquad (1)$$

where P_{lin} is the contribution of the linear part of fragment R (the longest linear section); α, sum of the one-center and two-center contributions of the type $1\cdots 2$ for fragments not included in the linear part; γ, two-center contribution of the type $1\cdots 3$ for CCC and CXC interactions in which one of the fragments is not included in the linear part; γ^*, two-center contribution of the type $1\cdots 3$ for CCX interactions in which one of the fragments is not included in the linear part; δ_{14}, two-center contribution of the type $1\cdots 4$ for CCCC and CXCC interaction in the same fragments; δ_{14}^*, two-center contribution of the type $1\cdots 4$ for the CCCX interactions; and n', n'', n''', m, and m', numbers of the corresponding contributions. P_{lin} can be determined from the relationship $P_{\text{lin}} = k_1 + k_2/(n + 1)^4$ [1]; n is the number of C atoms in the linear part of R. Below, with propylamine and α,β-dimethylpropylamine as examples, we illustrate how the linear part is singled out (dashed lines):

$\boxed{CH_3–CH_2–CH_2–}NH_2$ (n = 3)



$$\boxed{CH_3–\underset{\displaystyle CH_3}{CH}–\overset{\displaystyle CH_3}{CH}–}NH_2 \quad (n = 3)$$

To determine the thermodynamic characteristics of $R–A\cdots B$ complexes, let us consider as specific exam-

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[1] For communication XX, see [1].

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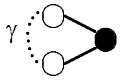
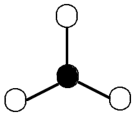
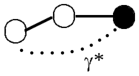
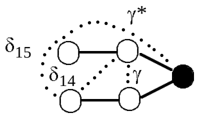
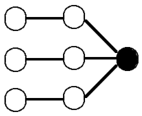
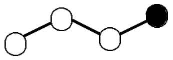
Table 1. Expressions for a property of complexes of some aliphatic amines with trimethylboron

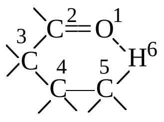
Amine	Scheme of complex[a]	n	Expression for property
NH_3		0	$k_1 + k_2$
CH_3NH_3		1	$k_1 + k_2\frac{1}{2^4}$
$(CH_3)_2NH$		1	$k_1 + k_2\frac{1}{2^4} + \alpha + \gamma$
$(CH_3)_3N$		1	$k_1 + k_2\frac{1}{2^4} + 2\alpha + 3\gamma$
$C_2H_5NH_2$		2	$k_1 + k_2\frac{1}{3^4}$
$(C_2H_5)_2NH$		2	$k_1 + k_2\frac{1}{3^4} + 2\alpha + \gamma + \gamma^* + 2\delta_{14} + \delta_{15}$
$(C_2H_5)_3N$		2	$k_1 + k_2\frac{1}{3^4} + 4\alpha + 3\gamma + 2\gamma^* + 6\delta_{14} + 3\delta_{15}$
$C_3H_7NH_2$		3	$k_1 + k_2\frac{1}{4^4}$

[a] Dark circle denotes the fragment $NH_m\cdots B(CH_3)_3$ fragment ($m = 0$–2), and light circles, the CH_i fragments ($i = 0$–3).

ple the complexation of aliphatic amines with trimethylboron in hexadecane at 25°C [11]. Expressions for a property of some amine complexes, based on relationship (1), are given in Table 1, and the calculated enthalpies and free energies of complexation of aliphatic amines with trimethylboron, in Table 2. In the calculations, we initially took into account 1···3, 1···4, and 1···5 interactions between different fragments; however, actually all the C···C interactions appeared to be insignificant, as well as the δ^*_{15} contribution. For all the complexes, the calculated values agreed well with the experimental data. Thus, approach (1) correctly reproduces the dependence of the characteristics of R–A···B complexes on the structure of R.

This approach can be applied to estimating the rates of chemical reactions. Since the transition state theory postulates a thermodynamic equilibrium between the reactants and transition complex, and the reaction rate is expressed via the constant of this equilibrium, all the reasonings for this case will be similar to those presented above. The most complete set of experimental data on the kinetics of reactions involving the R–A* component with different R is given in [2] for esterification of aliphatic carboxylic acids RCOOH with methanol. Using Eq. (1), we obtained the results given in Table 3; the logarithms of the relative rates of esterification of carboxylic acids, calculated from these data, well agree with the experimental data.

A decrease in the esterification rate with increasing length of R was attributed in [2] to formation of a six-membered ring (“rule of six”).

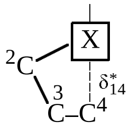


The O···H interaction stabilizes the starting reactants, complicates formation of the transition complex,

Table 2. Thermodynamic characteristics of complexation of aliphatic amines with trimethylboron

Amine	$-\Delta H_r^0$, kJ mol^{-1}		$-\Delta G_r^0$, kJ mol^{-1}	
	experiment [11]	this work[a]	experiment [11]	this work[b]
NH_3	57.68	57.61	7.77	7.97
CH_3NH_2	73.57	75.48	23.16	22.64
$C_2H_5NH_2$	75.24	76.44	21.69	23.42
$C_3H_7NH_2$	75.66	76.60	22.28	23.56
$C_4H_9NH_2$	76.91	76.64	23.16	23.59
$C_5H_{11}NH_2$	78.17	76.66	23.53	23.61
$C_6H_{13}NH_2$	77.33	76.66	23.66	23.61
i-$C_3H_7NH_2$	72.73	70.79	17.14	15.81
s-$C_4H_9NH_2$	72.31	70.95	16.97	15.94
t-$C_4H_9NH_2$	54.34	55.61	5.35	6.79
$(CH_3)_2NH$	80.67	79.41	26.21	21.23
$(C_2H_5)_2NH$	68.13	70.42	13.21	15.81
$(CH_3)_3N$	73.57	73.82	16.72	18.42
$(C_2H_5)_3N$	41.80	41.04	8.36	6.79
	r	0.9925		0.9600
	s	1.7130		2.1656

[a] k_1 76.6716 ± 0.7003, k_2 –19.0656 ± 1.8698, α 13.4618 ± 2.3908, γ –9.5286 ± 1.5813, γ^* –9.5805 ± 1.0432, δ_{15} –13.8327 ± 1.7120.
[b] k_1 23.6177 ± 0.8101, k_2 –15.6431 ± 2.3426, γ –1.4066 ± 0.7120, γ^* –6.2060 ± 1.1346.



X = C=O.

and decreases the reaction rate. In terms of our model, this corresponds to the contribution δ_{14}^*.

As seen from Table 3, this contribution is maximal: δ_{14}^* exceeds the other contributions. This means that the major contribution was, indeed, taken into account in [2], which allowed adequate (on the qualitative level) interpretation of the dependence of the relative rates of esterification of aliphatic carboxylic acids on the structure of R. Consideration of the other factors provides good quantitative estimates of the relative esterification rates for carboxylic acids with various R.

Determination of the relationship between the Taft steric constants E_S and structure of R is a problem similar to that described above. Using Eq. (1), we obtained for E_S the values given in Table 4. Within the framework of our approach, the steric constants are reproduced with a good accuracy. This relationship (with the parameters given in Table 4) can also be used for estimating E_S of other alkyl substituents, which is important for extending the potential of Taft's approach. Thus, approach (1) gives fairly accurate estimates for the steric effect of substituents. However, in different cases (Tables 3, 4), not only the numerical values of the contributions but even their number appeared to be different, which suggests that the constants E_S are not universally applicable to different reaction series.

Table 3. Relative rates of esterification $[\ln(k_{CH_3COOH}/k_{RCOOH})]$[a] of aliphatic carboxylic acids RCOOH

Substituent R	Experiment [2]	This work[b]
CH_3	0	–0.1087
C_2H_5	0.1740	0.4195
C_3H_7	0.7031	0.5084
C_4H_9	0.7031	0.5327
C_8H_{17}	0.7031	0.5480
i-C_3H_7	1.0986	1.6852
t-C_4H_9	3.2884	3.1826
$(CH_3)_2CHCH_2$	2.1483	2.3607
$(CH_3)_3CCH_2$	3.7542	4.4518
$(CH_3)_2CHCH_2CH_2$	0.7324	0.6933
$(CH_3)_3CCH_2CH_2$	0.7701	1.0926
$CH_3CH_2(CH_3)CH$	2.3125	2.0894
$(CH_3)_3C(CH_3)CH$	7.3877	6.6635
$(CH_3)_3C(CH_3)_2C$	8.9574	9.1141
$(CH_3)_3CCH_2(CH_3)CH$	4.1744	3.4475
$(CH_3)_3CCH_2(CH_3)_2C$	5.7137	6.0413
$(CH_3)_2CH(C_2H_5)CH$	7.4337	6.6444
$(C_2H_5)_3C$	8.7275	9.1715
$(C_2H_5)_2CH$	4.6052	4.4052
$(C_3H_7)_2CH$	4.6821	5.1251
$(C_4H_9)_2CH$	4.7875	4.8327
$[(CH_3)_2CHCH_2]_2CH$	5.4848	5.5177
$[(CH_3)_3CCH_2]_2CH$	7.0475	6.9441
$(CH_3)_3C(C_2H_5)CHCH_2CH_2$	2.2875	2.3069
	r	0.9906
	s	0.4802

[a] By the relative rate is usually understood the ratio of the rate constants of the reactions involving a given substance (k_{RCOOH} in this case) and a reference (k_{CH_3COOH} in this case). Here an inverse ratio is given for the sake of consistency with the presentation of the experimental data in [2].
[b] k_1 0.5496 ± 0.2090, k_2 –10.5329 ± 8.5998, α –1.2422 ± 0.5134, γ^* 2.2690 ± 0.3141, γ 0.2388 ± 0.1099, δ_{14}^* 2.6168 ± 0.3385, δ_{14} 0.3154 ± 0.1134, δ_{15}^* 0.6077 ± 0.2632, δ_{15} 0.3870 ± 0.1643.

The above-discussed examples show that both stable complexes and transition states (activated complexes) can be considered as systems RX differing

Table 4. Steric constants of the substituent ($-E_S$) in aliphatic esters $RCOOC_2H_5$

Substituent R	Experiment [3]	This work[a]
H	–1.24	–1.25
CH_3	0	0.17
C_2H_5	0.07	0.25
C_3H_7	0.36	0.26
C_4H_9	0.39	0.27
C_5H_{11}	0.40	0.27
C_8H_{17}	0.33	0.27
i-C_3H_7	0.47	0.87
i-C_4H_9	0.93	0.96
t-C_4H_9	1.54	1.50
s-C_4H_9	1.13	1.08
$(C_2H_5)_2CH$	1.98	1.98
$(CH_3)_3CCH_2$	1.74	1.66
$(CH_3)_3CCH_2CH_2$	0.34	0.66
$(CH_3)_3CCH_2(CH_3)CH$	1.85	1.48
$(C_3H_7)_2CH$	2.11	2.18
i-$(C_4H_9)_2CH$	2.47	2.57
$(CH_3)_3CCH_2(CH_3)_2C$	2.57	2.30
$[(CH_3)_3CCH_2]_2CH$	3.18	3.13
$(CH_3)_3C(CH_3)CH$	3.33	3.87
$(C_2H_5)_3C$	3.80	4.08
$(CH_3)_3C(CH_3)_2C$	3.90	4.08
		r 0.9881
		s 0.2350

[a] k_1 –0.2703±0.0774, k_2 1.5265±0.2493, γ^* –0.6221±0.0725, δ_{14} –0.1970±0.0213, δ^*_{14} –0.6968±0.0754.

Table 5. Values of $-\ln(k_{RCOOH}/k_{CH_3COOH})$ calculated by relationship (2)

Substituent R	Experiment [2]	This work[a]
CH_3	0	–0.0987
C_2H_5	0.1740	0.1880
C_3H_7	0.7031	0.9545
C_4H_9	0.7031	0.7825
C_5H_{11}	0.7031	0.7088
C_6H_{13}	0.7031	0.6842
i-C_3H_7	1.0986	1.0809
s-C_4H_9	2.3125	1.9948
t-C_4H_9	3.2884	3.3908
		r 0.9892
		s 0.1787

[a] k_1 –4.4393±0.2186, k_2 0.8191±0.0495, k_3 –0.8812±0.1342.

only in the parameters corresponding to fragment X and its interactions. For such systems, as shown in [1], one property can be expressed through another property taking into account corrections for major contributions to a property. Since for the relative rates of esterification of carboxylic acids a significant contribution is δ^*_{14}, the logarithm of the relative esterification rate can be expressed, e.g., through the free energy of complexation amines with trimethylboron (ΔG^0_r) with the correction for the number of contributions δ^*_{14} ($n_{\delta^*_{14}}$) to a property of RCOOH:

$$\ln \frac{k_{RCOOH}}{k_{CH_3COOH}} = k_1 + k_2(-\Delta G^0_r) + k_3 n_{\delta^*_{14}}. \qquad (2)$$

where ΔG^0_r is the standard free energy of formation of the complex $RNH_2 \cdots B(CH_3)_3$ in which the substituent R is the same as in the carboxylic acid. The thus estimated logarithms of the relative esterification rates are given in Table 5 and are well consistent with the experimental data. Without taking into account the contribution of $n_{\delta^*_{14}}$ to relationship (2), less accurate estimates are obtained: r 0.9081 and s 0.4735.

Thus, by considering stable complexes formed by organic compounds with various ligands and transition states (activated complexes) formed in the course of a chemical reaction as systems RX (R is an alkyl radical in one of the components of the complex or in one of reaction participants; X is the remaining fragment), it becomes possible, using the approach suggested previously for estimating molecular properties, to obtain quantitative relationships between the structure of R and properties of complexes and between the properties of stable complexes and transition states.

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