

Full Articles

Structure–property modeling of metal binders using molecular fragments*

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The method of Substructural Molecular Fragments (SMF) based on splitting of a molecular graph into a limited number of topological fragments and calculation of their contributions to a given property was applied to the structure–property modeling of (i) stability constants of the complexes formed by the K⁺ cation with phosphoryl-containing podands in a mixed THF–CHCl₃ solvent, (ii) distribution coefficients for Hg and Pt extraction by podands from water into 1,2-dichloroethane, and (iii) stability constants of complexes of crown ethers with alkali metal cations in methanol. A procedure for the reduction of the number of fragment descriptors in structure–property relationship (QSPR) models based on the Student *t*-test was proposed. The use of selected variables improves the robustness of the structure–property models.

Key words: complexation, prediction of stability constants, solvent extraction of metal cations, crown ethers, phosphoryl-containing podands, structure–property modeling, substructural molecular fragments.

Binding of metal cations by specific organic molecules (ionophores) in homogeneous solutions (complexation) or in two-phase liquid–liquid systems (solvent extrac-

tion) is widely used in industry and in research laboratories. In most cases, the search for the most efficient ionophores for selective binding of a given metal is essentially empirical. Meanwhile, methods based on quantitative structure–property relationships (QSPR) could play an important role in the design of compounds with desired characteristics. Recently^{1,2} it has been shown that new compounds could be theoretically designed using an in-

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formation platform that involves three main elements: a comprehensive database, an expert system that establishes the quantitative structure—property relationships, and a generator of combinatorial libraries.

The expert system is the most important element of such “*in silico*” design, as the reliability of predictions of new compounds depends on the reliability of the structure—property models.

Generally, two main approaches are used in the QSPR studies of metal—ligand binding. The first one³ uses as descriptors some physicochemical parameters either measured experimentally or calculated by quantum-mechanical methods or by some empirical techniques. For instance, the electron-donor factors of hydrogen bonding,⁴ the group electronegativities or Taft parameters of molecular fragments,⁵ atomic charges,^{5,6} electrostatic potential distribution,^{6,7} donor—acceptor interaction energies,⁸ topological indices,⁹ and the complexation strain energy¹⁰ were used to build QSPR models for describing thermodynamic parameters of complexation and extraction of metals.

The second approach, similar to that used by Free and Wilson,¹¹ uses molecular fragments as variables in a multiple regression analysis. Molecular fragments have been long used successfully in structure—property studies^{3,12–24} and in the diversity analysis of large databases.^{25,26} The PASS^{27,28} method developed recently for estimating a wide spectrum of biological activities is also based on molecular fragments (augmented atoms).

The success of the fragment approach in QSPR studies depends on the diversity of structural fragments and on the flexibility of atom/bond classification. In the present study, we use the method of *Substructural Molecular Fragments* (SMF),^{1,2,29–31} which represents a fairly flexible structure—property tool, as it uses a large number of various types of fragments (atom/bond topological sequences and augmented atoms) as descriptors. Recently, the SMF method has been successfully applied for estimating the thermodynamic parameters of complexation (stability constants) and extraction (extraction constants, distribution coefficients) of metal cations by macrocyclic and open-chain ionophores.^{1,29} A coupling of the SMF approach with combinatorial techniques is a promising way of obtaining focused combinatorial libraries.²

An important advantage of fragment descriptors is the fact that they can be calculated without knowing the geometry and the electronic structure of molecules; in addition, they are more easily interpretable than topological indices. However, QSPR models based on fragments generally comprise much more variables than those using traditional descriptors. Reduction of the number of variables in the Free—Wilson type methods remains an important methodological problem, which still has not been sufficiently discussed in the literature.

The goal of this work is to study the structure—property relationships for complexation and extraction of ionophores of topologically different types using the SMF method. First, we report the QSPR studies performed on a structurally diverse set of acyclic phosphoryl-containing mono- and tripodands, which form complexes with the K^+ cation in a mixed THF— $CHCl_3$ solvent and extract Hg and Pt into 1,2-dichloromethane. Then we describe the specific features of the QSPR studies of macrocyclic compounds and present the models obtained for complexation of crown ethers with alkali metal cations in methanol and give a quantitative estimate of the macrocyclic effect. Unlike the previous studies of these ionophores,^{1,29,30} here we apply for the first time a procedure for the reduction of the number of SMF variables according to the *t*-test.

Calculation method

The structure—property modeling was performed using the TRAIL program, which realizes the SMF method.^{1,29} According to this method, a molecular graph is represented as a particular number of topological fragments (subgraphs) and their contributions to a given property *Y* are calculated. Two different classes of fragments are used, namely, “sequences” (**I**) and “augmented atoms” (**II**). Three subtypes, **AB**, **A**, and **B**, are defined for each class. For fragments **I**, they represent topological paths, *i.e.*, sequences of atoms and bonds (**AB**), of atoms only (**A**), or of bonds only (**B**). Only the shortest paths from one atom to another are used. For each type of sequences, the minimal (n_{min}) and the maximal (n_{max}) numbers of atoms forming the chain must be defined. For the **I(AB, $n_{min} - n_{max}$)**, **I(A, $n_{min} - n_{max}$)**, and **I(B, $n_{min} - n_{max}$)** fragments, the program generates “intermediate” sequences involving *n* atoms ($n_{min} \leq n \leq n_{max}$) (Fig. 1). The current version of TRAIL uses $n_{min} \geq 2$ and $n_{max} \leq 6$. The number of types of sequences of different lengths corresponding to $n_{min} = 2$ and $n_{max} = 6$ is equal to 15 for each of the three subtypes, **AB**, **A**, and **B**.

An “augmented atom” represents a fragment that comprises a selected atom with its environment, including either neighboring atoms and bonds (**AB**), or atoms only (**A**), or bonds only (**B**). The hybridization of atoms (**Hy**) can be taken into account for augmented atoms of type **A**.

Once a molecular graph is split into fragments, any quantitative physical or chemical property *Y* is calculated from fragment contributions using linear (1) or nonlinear (2) and (3) fitting equations.

$$Y = a_0 + \sum_i a_i N_i + \Gamma, \quad (1)$$

$$Y = a_0 + \sum_i a_i N_i + \sum_i b_i (2N_i^2 - 1) + \Gamma, \quad (2)$$

$$Y = a_0 + \sum_i a_i N_i + \sum_{i,k} b_{ik} N_i N_k + \Gamma, \quad (3)$$

where a_i and b_i (b_{ik}) are fragment contributions, N_i is the number of fragments of type *i*, and a_0 is a fragment-independent constant. The a_i and b_i (b_{ik}) contributions are calculated by

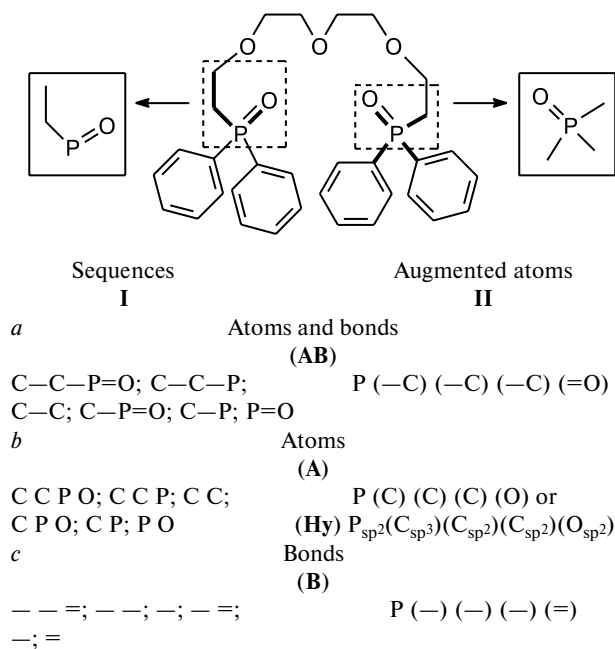


Fig. 1. Two classes of substructural molecular fragments: atom and/or bond sequences (I) and augmented atoms (II), including atoms and bonds (AB), only atoms (A), or only bonds (B). Example of sequences (I) corresponding to fragment types I(AB, 2–4) (a), I(A, 2–4) (b), and I(B, 2–4) (c). The fragments II(Hy) correspond to type II(A) with allowance for the hybridization of atoms.

regression analysis; they are the same for a given fragment in all compounds from the given set. The extra term $\Gamma = \sum c_m D_m$ can be used to describe any specific feature of the compound by means of external descriptors D_m (e.g., topological, electronic, etc.); by default, $\Gamma = 0$.

At the training stage, TRAIL builds up to 147 structure–property models including the above three (one linear and two nonlinear) fitting equations and 49 types of fragment descriptors (45 types of sequences and 4 types of augmented atoms). The molecules containing rarely encountered fragments (i.e., those found in less than 2 molecules) can be excluded from the training set. If some variables are linearly dependent, their linear combination form a new variable. For example, for a series of unsubstituted crown ethers $(\text{CH}_2\text{—O—CH}_2)_n$ the number of C—O—C fragments is twice as large as the number of C—O fragments. Therefore, for the I(AB, 2–3) partitioning, TRAIL uses an “extended fragment” (C—O—C + 2·C—O) as a new variable rather than two independent variables, C—O—C and C—O.

Using the singular value decomposition method (SVD),³² TRAIL finds the most reliable estimates for the a_i and b_i terms in Eqs. (1)–(3) and calculates the corresponding statistical characteristics (the correlation coefficient (R), the standard deviation (s), Fischer’s criterion (F), the cross-validation correlation coefficient (Q), the standard deviation of predictions (s_{PRESS}), the Kubyni’s criterion (FIT), the Hamilton R_H -factor, and the matrix of pair correlations (covariation matrix) for the terms a_i and b_i) and performs statistical tests³³ to select the best models.

If some variables in Eqs. (1)–(3) are linearly dependent, or some fragment occurs in a relatively small number of molecules,

the standard deviations Δa_i (Δb_i) for the fragment contributions a_i (b_i) can be fairly large, resulting in the corresponding t -test value ($t = a_i/\Delta a_i$) being smaller than the tabulated value of the Student criterion (t_0)³⁴ for $(n-k)$ degrees of freedom at a given significance level (n is the number of points and k is the number of variables). The following procedure is applied in order to improve the robustness of the models. First, TRAIL selects the variable with the smallest $t < t_0$; then it performs a new fitting without this variable. This procedure is repeated until $t \geq t_0$ for all variables.

A significant advantage of the SMF method is the possibility of selecting, during the training stage, several best fit models (instead of a single QSPR model) related to different fragmentation schemes in combination with three fitting equations. Using the selected QSPR models, one can calculate the average value of the property Y for the compounds of the test set; this smoothes out the inaccuracies of particular individual models, thus improving the reliability of predictions.³⁰

In TRAIL calculations, each initial data set was split into two subsets, namely, the training and test sets. The QSPR models constructed for the training set were validated by prediction calculations for the test set. When preparing the test sets, we obeyed the following recommendations:³⁵ (i) experimental methods for determination of properties in the training and test sets should be similar; (ii) property (activity) values should cover several orders of magnitude but should not exceed those for the training set by more than 10%; (iii) balance between active and inactive compounds in both sets of data should be respected.

Results and Discussion

Complexation of phosphoryl-containing podands with K^+ . Phosphoryl-containing podands are acyclic molecules with polyether spacer(s) linking two (in monopodands), three (in di- and tripodands), or four (in tripodands) terminal phosphine oxide groups.³⁶ By varying the length of the spacers, the molecular topology, and the substituents at the phosphoryl group, one can attain desirable complexation^{37–39} or extraction^{40–43} properties of the podands with respect to particular metal cations.

The initial set of 76 stability constants ($\log K$) for 1 : 1 complexes of podands **1–4** with K^+ in a THF : CHCl_3 mixed solvent (4 : 1 v/v) at 298 K^{37,38,44–49} was selected from the THECOMAC database.⁵⁰ The training and test sets included data for 71 and for 5 podands, respectively.

At the training stage, TRAIL has selected three linear models (Table 1) corresponding to reasonable correlation coefficients or cross-validation correlation coefficients ($R^2 = 0.913\text{--}0.971$, $Q^2 = 0.773\text{--}0.942$, Table 2) and to standard deviations $s = 0.32\text{--}0.44$ (in $\log K$ units) similar to typical experimental errors.^{37,38,44–49} Two of these models, I(AB, 2–3) and I(AB, 2–4) (Eq. (1)), use sequences of atoms and bonds as descriptors, while the third one, II(AB) (Eq. (1)), is based on augmented atoms. The selection of variables according to the t -test results in significant reduction of the number of fragments used. Thus for the three above models, t -test selection decreases the number of variables 2.5–3-fold (see Table 2). This

$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{R}-\text{P}-\text{X}-\text{P}-\text{R} \\ \mid \quad \mid \\ \text{R} \quad \text{R} \end{array}$					
1a–f					
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{Ph}-\text{P}-\text{X}-\text{O}-\text{C}_6\text{H}_4-\text{Y}-\text{C}_6\text{H}_4-\text{P}-\text{R} \\ \mid \quad \mid \\ \text{Ph} \quad \text{R} \end{array}$					
2a–d					
$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{R}-\text{P}-\text{X}-\text{C}_6\text{H}_4-\text{Y}-\text{C}_6\text{H}_4-\text{X}-\text{P}-\text{R} \\ \mid \quad \mid \\ \text{R} \quad \text{R} \end{array}$					
3a–e					
$\left[\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{O}=\text{P}-\text{O}-\text{C}_6\text{H}_4-\text{X}-\text{P}(\text{O})\text{Ph} \\ \mid \quad \mid \\ \text{O} \quad \text{Ph} \end{array} \right]_3$					
4					
1	R	X	n	Y	m
a	Ph	CH ₂	—	—	—
b	Ph	(CH ₂) _n O(CH ₂) _m	1	—	1–2
c	Tol	(CH ₂) _n O(CH ₂) _m	2	—	2
d	Ph	(CH ₂) _n O(CH ₂) _m	2	—	2–4
e	Ph	(CH ₂ OCH ₂) ₃	—	—	—
f	Ph	CH ₂ (CH ₂ OCH ₂) ₃ CH ₂	—	—	—
2					
a	Ph	(CH ₂) _n	0	(CH ₂) _m	0
b	Bu, Ph, Tol	(CH ₂) _n	1	(CH ₂) _m	0
c	Ph	(CH ₂) _n	3, 5	(CH ₂) _m	0
d	Ph	(CH ₂) _n	1, 3–5	(CH ₂) _m	1
3					
a	Bu, Ph, Tol	(CH ₂) _n	0	O(CH ₂) ₂ O(CH ₂) ₂ O	—
b	Bu, Ph	(CH ₂) _n	1	O(CH ₂) ₂ O(CH ₂) ₂ O	—
c	Ph	(CH ₂) _n	2	O(CH ₂) ₂ O(CH ₂) ₂ O	—
d	OEt, Ph, Tol	(CH ₂) _n	0	OCH ₂ P(O)MeCH ₂ O	—
e	Ph	(CH ₂) _n	1	OCH ₂ P(O)MeCH ₂ O	—
4		(CH ₂) _n	0, 1		

results in higher F and Q^2 and a lower s_{PRESS} parameter, but has only a slight effect on other statistical parameters of the fitting (see Table 2) or on the linear regression parameters for $\log K_{\text{calc}}$ vs. $\log K_{\text{exp}}$ (Fig. 2).

The three models developed at the training stage have been used to assess the stability constants of complexes of five podands of the test set (structures 5–9). Calculations show that the **I(AB, 2–4)** model (Eq. (1)) reproduces the experimental values less adequately than the other two models. However, averaging over the three models results in mean $\log K$ values that correlate well with experimental

data ($R^2 = 0.916$, $s = 0.58$, Table 3). When the models with a reduced number of variables are applied, the “predicted” values correlate even better with the experiment; for any model, $R^2 > 0.915$ and $s < 0.5$ and for the average data set, $R^2 = 0.962$ and $s = 0.37$ (see Table 3). Thus, the reduction of the number of variables significantly improves the quality of predictions.

The contributions of fragments may provide some useful information concerning the complexing efficiency of particular chemical groups. This can be illustrated by calculating the overall contributions to $\log K$ coming

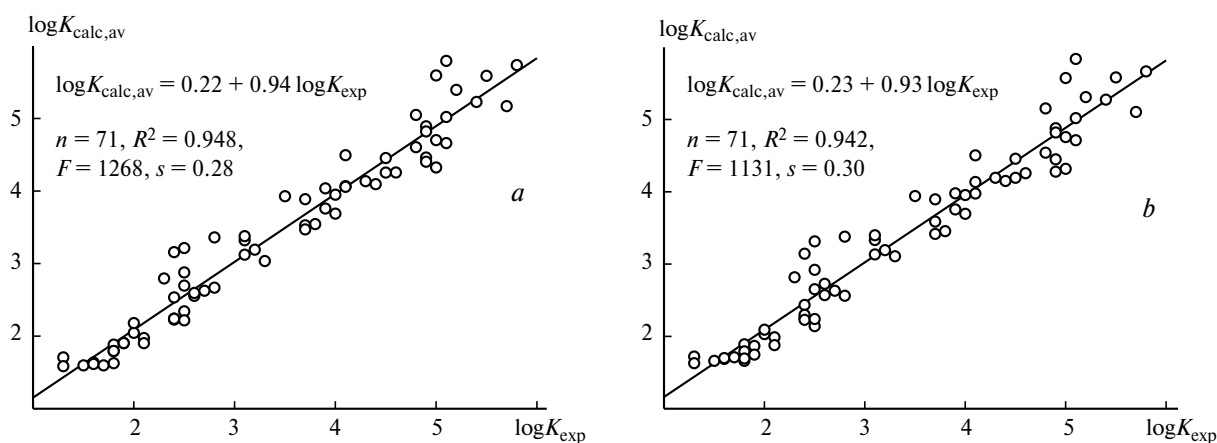


Fig. 2. SMF modeling of the stability constants ($\log K$) for the complexes of phosphoryl-containing podands with the K^+ cation in $\text{THF}-\text{CHCl}_3$ (4 : 1 v/v) at 298 K: linear correlation between the calculated (averaged over the three best fit models) and experimental $\log K$ values for the training set using all fragments (a) and fragments selected according to the t -test (b).

Table 1. Modeling of the stability constants ($\log K$) for the complexes of phosphoryl-containing podands with K^+ in THF—CHCl₃ (4 : 1 v/v) at 298 K by the SMF method: the contributions of the fragments (a_n) selected using the t -test to the stability constant $\log K$ for the best models^a

Fragment ^b	$a_n(\Delta a_n)^c$	Fragment ^b	$a_n(\Delta a_n)^c$
Model I(AB, 2–4)		Model II(AB)	
C—C	0.329 (0.063)	O(—C'—C')	0.583 (0.027)
P—C; C—P=O ^b	0.511 (0.017)	O(=P')	0.59 (0.13)
C—C—O	–0.311 (0.058)	C(\equiv C'—C'—P')	0.438 (0.055)
P—C—C—O	0.289 (0.087)	C(\equiv C'—C')	–0.084 (0.012)
C—P—C—C	–0.207 (0.034)	C(—C'—C'—P')	–0.33 (0.15)
O—C—C—O	0.837 (0.082)	a_0^e	0.69 (0.25)
C—C—C	–0.313 (0.064)	Model I(AB, 2–3)	
C—C \equiv C; C—C \equiv C \equiv C ^d	–0.139 (0.030)	P—C; C—P=O ^d	0.433 (0.064)
C—C—C \equiv C	–0.245 (0.038)	C \equiv C	–0.065 (0.013)
O—C \equiv C—O	0.380 (0.068)	P—C \equiv C	0.109 (0.046)
C—P—C—O	–0.176 (0.042)	C—C—O	0.279 (0.017)
P—O; C—P—O; O—P=O; P—O—C;		P—C—C	–0.251 (0.061)
1/2 O—P—O; C—P—O—C;		C \equiv C—O	0.165 (0.031)
C—O—P=O; C—O—P—O ^d	0.297 (0.054)	a_0^e	0.56 (0.20)
C \equiv C—P—O	0.064 (0.023)		
P—C—C—P	–0.50 (0.16)		

^a Regression equation (1) is used.^b The designation of fragments is given in Fig. 1; C—C, P=O, and C \equiv C are molecular fragments with single, double, and aromatic bonds, respectively.^c The standard deviations (Δa_n) are given in parentheses.^d Linearly dependent fragments are grouped to form a single extended fragment.^e a_0 is a fragment-independent constant (a constant contribution for a given set of compounds).**Table 2.** Modeling of the stability constants of the complexes of phosphoryl-containing podands with the K^+ cation in THF—CHCl₃ (4 : 1 v/v) at 298 K by the SMF method: statistical characteristics of the three best fit models obtained using different types of fragments^a

Fragment type	Statistical characteristics of the model ^b						
	k	R^2	F	s	Q^2	s_{PRESS}	R_H (%)
I(AB, 2–4)	38	0.971	30.2	0.32	0.942	0.50	6.02
	(14)	(0.967)	(129.4)	(0.26)	(0.951)	(0.31)	(6.44)
II(AB) ^c	19	0.921	33.1	0.42	0.860	0.58	9.98
	(6)	(0.912)	(132.7)	(0.40)	(0.891)	(0.43)	(10.55)
I(AB, 2–3)	17	0.913	35.5	0.44	0.773	0.70	10.48
	(7)	(0.906)	(103.3)	(0.41)	(0.883)	(0.46)	(10.88)

^a Hydrogen atoms were not considered. Fitting equation (1) was used. Statistical parameters obtained for the training set: the number of compounds ($n = 71$), the number of calculated parameters (k), correlation coefficient (R), Fischer's criterion (F), standard deviation (s), cross-validation correlation coefficient (Q), standard deviation (s_{PRESS}) for cross-validation, and Hamilton factor (R_H).^b For the model based on all fragments; the data based on the fragments selected by the t -test are given in parentheses.^c The calculations were carried out for 70 compounds of the training set.

from various metal-coordinated groups containing four atoms, viz., C—C—P=O, O—C—C—O, and O—C \equiv C—O. As described in the methodical section, in these calculations, one has to take into account all sequences generated by TRAIL for a given group of atoms. For example, the overall contribution from the C—C—P=O group to $\log K$ is calculated using contributions from the C—C—P=O, C—C—P, C—P=O, P=O, C—P, and C—C sequences (Fig. 3). These calculations result in values of

0.84, 0.54, and 0.38 for C—C—P=O, O—C—C—O, and O—C \equiv C—O* groups, respectively. This corresponds to the known experimental data on the relative cation binding affinities of compounds containing phosphoryl, ether, and anisole fragments.^{39,50–52}

Extraction of Hg and Pt with phosphoryl-containing monopodands. The calculations were carried out for two

* C \equiv C is the molecular fragment with an aromatic bond.

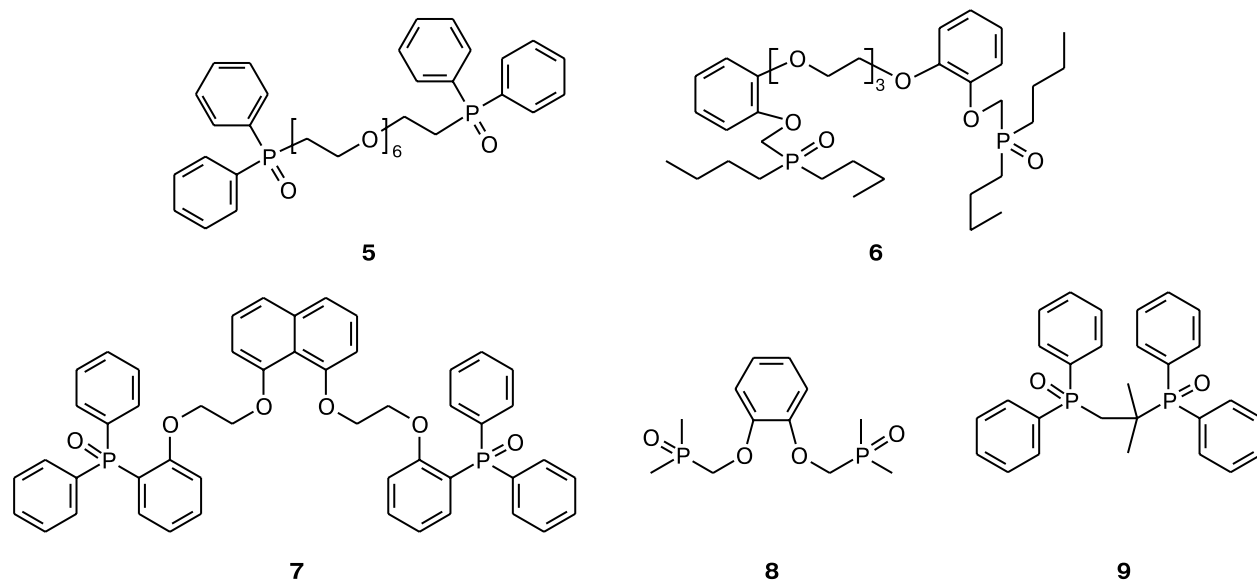


Table 3. Experimental and predicted (for the test set) stability constants ($\log K$) for the complexes of phosphoryl-containing podands with K^+ in THF— $CHCl_3$ (4 : 1 v/v) at 298 K^a

Com- po- unds	Ex- peri- ment	Calculation ^b			
		I(AB, 2—4)	II(AB)	I(AB, 2—3)	Average ^c
log <i>K</i>					
5	5.3	5.54 [5.57]	5.43 [5.45]	5.40 [5.31]	5.46 (0.07) [5.44 (0.13)]
6	4.7	4.66 [4.54]	4.69 [4.70]	4.55 [4.37]	4.63 (0.07) [4.54 (0.17)]
7	3.6	4.38 [4.15]	4.48 [3.98]	4.16 [3.82]	4.34 (0.16) [3.98 (0.17)]
8	2.54	3.03 [2.74]	3.23 [2.71]	3.22 [3.42]	3.16 (0.11) [2.96 (0.40)]
9	1.5	0.22 [0.95]	^d ^d	1.71 [1.45]	0.97 (1.05) [1.20 (0.35)]
<i>R</i> ^{2e}					
		0.892 [0.956]	0.920 [0.985]	0.957 [0.915]	0.916 [0.962]
<i>s</i> ^e					
		0.79 [0.43]	0.32 [0.18]	0.34 [0.48]	0.58 [0.37]

^a For compounds 5–9 presented in the text. Fitting equation (1) was used.

^b For the model based on all fragments; the data based on the fragments selected by the *t*-test are given in parentheses.

^c The arithmetic mean of $\log K$; the standard deviation is given in brackets.

^d For this compound, not all of the fragment contributions were estimated at the training stage.

^e Statistical characteristics (R and s) for the correlation of experimental vs. predicted (using this model) values of $\log K$.

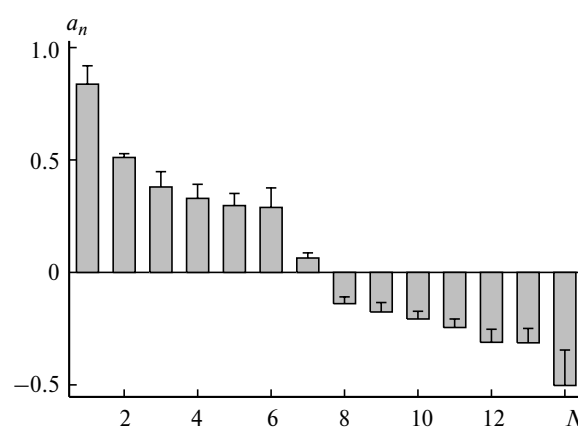


Fig. 3. SMF modeling of the stability constants ($\log K$) for the complexes of phosphoryl-containing podands with the K^+ cation in THF— $CHCl_3$ (4 : 1 v/v) at 298 K: fragment contributions (a_n) selected using the *t*-test to the stability constant $\log K$ for the model I(AB, 2–4) (Eq. (1)). The error bars show the standard deviations; C—C, P=O, and C≡C are the molecular fragments with single, double, and aromatic bonds, respectively; N are the numbers corresponding to the following fragments: O—C—C—O (1); C—P=O, P—C (2); O—C≡C—O (3); C—C (4); P—O, C—P—O, O—P—O, P—O—C, 1/2 O—P—O, C—P—O—C, C—O—P=O, C—O—P—O (5); P—C—C—O (6); C≡C—P—O (7); C—C≡C, C—C≡C≡C (8); C—P—C—O (9); C—P—C—C (10); C—C—C≡C (11); C—C—O (12); C—C—C (13); and P—C—C—P (14).

sets containing 21 distribution coefficients ($\log D$) of mercury(II) and platinum(IV) extracted by podands.⁴⁰ Eighteen compounds were used for training and three compounds were included in the test set. At the training stage, TRAIL has selected three linear models (1) based

Table 4. Modeling of the distribution coefficient ($\log D$) for mercury(II) and platinum(IV) extracted by phosphoryl-containing podands from water into 1,2-dichloroethane: the contributions of fragments (a_n) selected using the t -test to the distribution coefficient $\log D$ for the best models

Fragment	$a_n (\Delta a_n)$	Fragment	$a_n (\Delta a_n)$
Model I(A, 2–3)			
PO; 3 CPC; 3 CPO; 3 PC ^b	0.24 (0.11)	CC	–0.252 (0.044)
CO	–0.149 (0.069)	CCC	0.141 (0.030)
CC	–0.493 (0.083)	PCC	0.285 (0.047)
CCC	0.281 (0.055)	CCO	0.210 (0.027)
PCC	0.477 (0.062)		
CCO	0.537 (0.083)		
Model II(A)			
O(C'C')	0.273 (0.053)	C(O'P')	–0.156 (0.049)
C(C'C'P')	1.03 (0.12)	C(C'C'P')	0.267 (0.055)
C(C'C')	–0.223 (0.028)	C(C'C')	–0.061 (0.011)
C(C'P')	0.514 (0.077)	C(C'O')	0.090 (0.018)
C(C'C'C')	0.120 (0.053)	C(C'C'O')	0.177 (0.055)
C(C')	–0.267 (0.066)		
C(C'C'O')	0.602 (0.099)		
Model I(AB, 2–3)			
C≡C; C≡C≡C ^b	–0.134 (0.022)	C≡C; C≡C≡C ^b	–0.054 (0.013)
P–C≡C	0.400 (0.063)	P–C≡C	0.149 (0.040)
P–C–C	0.386 (0.084)	P–C–O	–0.166 (0.057)
C–C–O	0.128 (0.033)	C–C–O	0.086 (0.022)
C–C–C	–0.249 (0.051)	C–C–C	–0.063 (0.021)
C≡C–O	0.364 (0.057)	C≡C–O	0.115 (0.037)

^a Fitting equation (1) was used. The standard deviations (Δa_n) are given in parentheses. The fragment designations are given in Fig. 1: C–C and C≡C are molecular fragments with single and aromatic bonds, respectively.

^b Linearly dependent fragments are grouped to form a single extended fragment.

on I(A, 2–3), II(A), and I(AB, 2–3) fragments for both metals (Table 4). The statistical fitting parameters for Hg ($R^2 = 0.930$ – 0.932 , $Q^2 = 0.785$ – 0.825 , $s = 0.19$ – 0.24 , $F = 7.4$ – 18.8 , Table 5) are better than those obtained for Pt ($R^2 = 0.855$ – 0.858 , $Q^2 = 0.486$ – 0.676 , $s = 0.15$ – 0.19 , $F = 3.3$ – 8.4 , see Table 5). The reduction of the number of variables ac-

cording to the t -test improves the robustness of the models, especially for Pt ($R^2 = 0.807$ – 0.846 , $Q^2 = 0.589$ – 0.756 , $s = 0.13$ – 0.16 , $F = 10.0$ – 24.1 , see Table 5). The contributions of the fragments to $\log D$, selected using the t -test, are presented in Fig 4.

At the validation stage, the three best fit models were used to calculate $\log D$ values for the test set containing

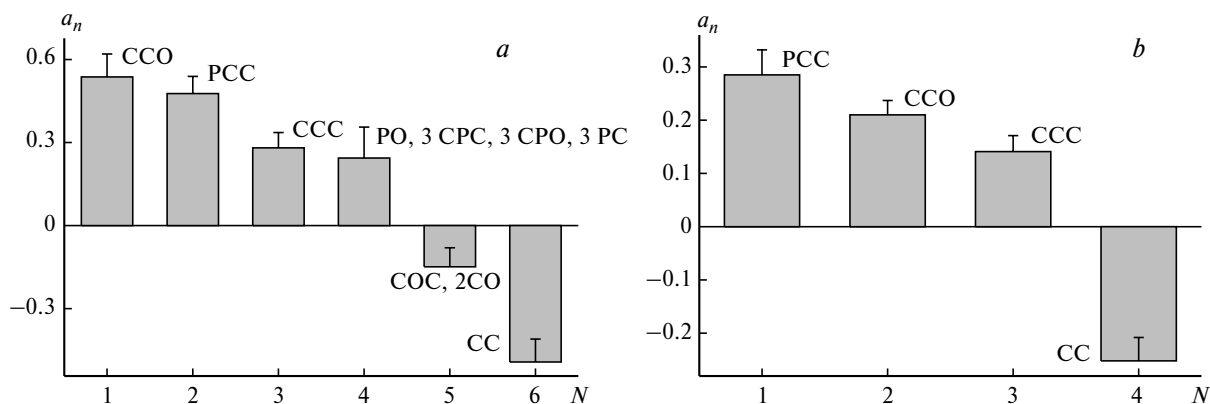


Fig. 4. Modeling of the distribution coefficients for mercury(II) (a) and platinum(IV) (b) extracted by podands from water into 1,2-dichloroethane: contributions of the fragments (a_n) selected by the t -test to the distribution coefficient $\log D$ for the best model I(A, 2–3) (Eq. (1)). The error bars show the standard deviations.

Table 5. Modeling of the distribution coefficients ($\log D$) of mercury(II) and platinum(IV) extracted with phosphoryl-containing podands from water into 1,2-dichloroethane. Statistical characteristics for the three best models using different types of fragments^a

Fragment type	Statistical characteristics of the model ^b						
	k	R^2	F	s	Q^2	s_{PRESS}	R_{H} (%)
Hg							
I(A, 2—3)	8	0.930	18.8	0.19	0.825	0.30	15.3
	(6)	(0.929)	(31.6)	(0.18)	(0.858)	(0.25)	(15.3)
II(A)	11	0.932	9.6	0.23	0.785	0.40	15.0
	(7)	(0.928)	(23.5)	(0.19)	(0.797)	(0.31)	(15.5)
I(AB, 2—3)	12	0.932	7.4	0.24	0.785	0.44	15.0
	(6)	(0.904)	(22.7)	(0.20)	(0.776)	(0.31)	(17.8)
Pt							
I(A, 2—3)	8	0.855	8.4	0.15	0.676	0.22	38.1
	(4)	(0.838)	(24.1)	(0.13)	(0.756)	(0.16)	(40.2)
II(A)	11	0.858	4.2	0.18	0.486	0.34	37.6
	(5)	(0.846)	(17.9)	(0.14)	(0.729)	(0.18)	(39.2)
I(AB, 2—3)	12	0.858	3.3	0.19	0.486	0.36	37.6
	(6)	(0.807)	(10.0)	(0.16)	(0.589)	(0.23)	(43.9)

^a Hydrogen atoms were not considered. The calculations were carried out for 18 compounds in the training set using fitting equation (1). The experimental distribution coefficients $\log D$ for metal cations extracted by 0.01 *M* solutions of phosphoryl-containing podands into 1,2-dichloroethane from a 4 *M* aqueous solution of HCl at room temperature were taken from a previous publication.⁴⁰ See the designations for statistical parameters in the note to Table 2.

^b For the model based on all fragments; the data based on the fragments selected by the *t*-test are given in parentheses.

the same three podands. It was found that the “predicted” values are well correlated with experimental data both for the models containing all fragments ($R^2 = 0.983$, $s = 0.19$ and $R^2 = 0.964$, $s = 0.14$ for Hg and Pt, respectively) and for the models with a reduced number of variables ($R^2 = 1.00$, $s = 0.01$ and $R^2 = 0.967$, $s = 0.13$ for Hg and Pt, respectively).

Complexation of crown ethers with alkali metal cations: QSPR modeling and quantitative assessment of the macrocyclic effect. The complexation properties of cyclic polyethers (crown ethers, cryptands) in solutions differ from those of their open-chain analogs (glymes, alcohols, glycols). Thus the stability constants ($\log K$) of the 1 : 1 complexes of alkali metal cations M^+ ($M^+ = \text{Na}^+$, K^+ , Cs^+) with glymes $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_{n-1}\text{CH}_3$ in methanol increase with n , whereas those of complexes of the crown ethers $(\text{CH}_2\text{CH}_2\text{O})_n$ pass through a maximum at $n = 6$ (Na^+ , K^+) and 6, 7 (Cs^+).^{50,51,53} The fact that the stabilities of crown ether complexes are regularly larger than those for the acyclic analogs is attributed to the so-called *macrocyclic effect* (*ME*),^{54,55} whose nature is still a matter of debate.^{56–59}

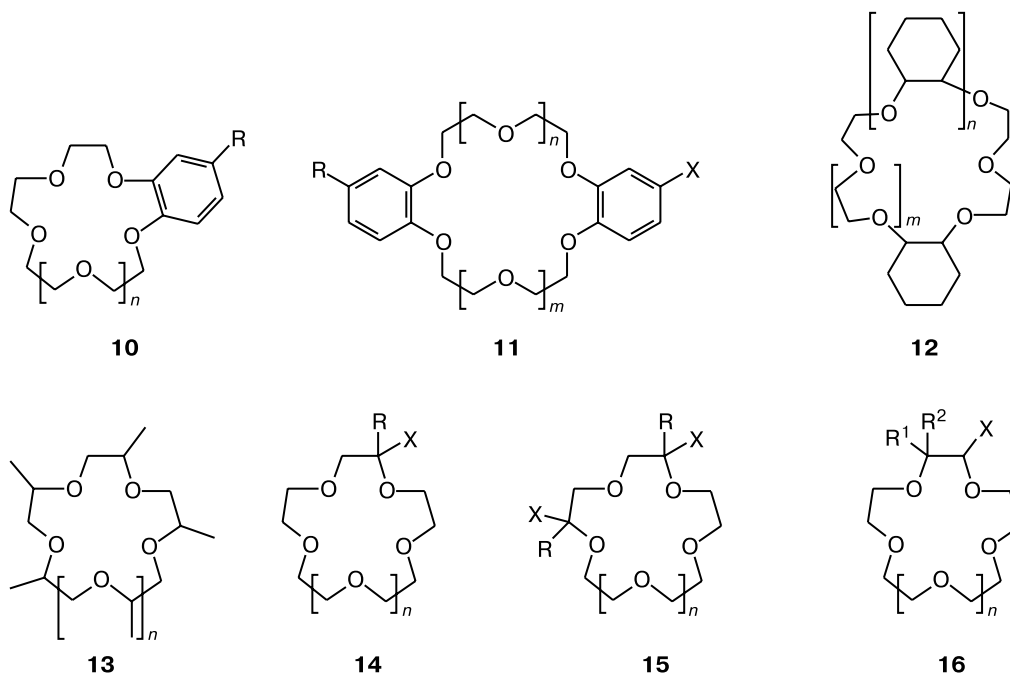
By definition, the macrocyclic effect (*ME*) is the difference between the logarithms of the stability constants of the complexes of a crown ether and its acyclic analog. In the literature,^{57,60,61} the macrocyclic effect has been discussed only for M^+ complexes with 18-crown-6 (18C6)

and benzo-18-crown-6 (B18C6). No conclusions on the *ME* of other substituted crown ethers can be drawn because of the lack of experimental data for the corresponding acyclic ligands.

The structure—property modeling for the stability of crown ether complexes with metals represents a difficult task. Indeed, the previous QSPR studies of the complexes of macrocyclic polyethers with alkali metal cations⁴ have shown a reasonable correlation between $\log K$ and the donor and acceptor descriptors of hydrogen bonding only for subsets of molecules with a definite cavity sizes but not for the whole set of macrocycles.

In this study, in addition to construction of the QSPR models for the stability constants of metal cation complexes with crown ethers, we also extract information about the macrocyclic effect hidden in the experimental data.

The calculations were performed for sets of experimental stability constants for 69 (Na^+), 123 (K^+), and 31 (Cs^+) $[M^+]\text{L}$ complexes of these metal cations with crown ethers in methanol at 298 K, critically selected from the THECOMAC database.⁵⁰ Of these, 60 (Na^+), 113 (K^+), and 28 (Cs^+) complexes were taken as the training sets. These sets include regular crown ethers with different sizes of the cavity $(\text{CH}_2\text{CH}_2\text{O})_n$ ($n = 4–12$), their benzo (**10**), dibenzo (**11**), cyclohexyl, and dicyclohexyl derivatives (**12**), neutral lariate derivatives, and sev-



10: R = H, Alk; $n = 1, 2$. **11:** R, X = H, Alk; $n = 0-3$; $m = 1-3$. **12:** $n = 0, 1$; $m = 1, 2$. **13:** $n = 0-2$.

14: R = H, Alk, Ph, $(\text{CH}_2\text{O})_k(\text{CH}_2\text{CH}_2\text{O})_m(\text{CH}_2)_p\text{H}$; X = H, Alk, R; $n = 0-5, 7, 8$

15: R = $(\text{CH}_2\text{O})_k(\text{CH}_2\text{CH}_2\text{O})_m(\text{CH}_2)_p\text{H}$; X = Me; $n = 1-3$. **16:** $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; $\text{R}^1 - \text{R}^2 = \text{O}$; X = H, Alk; $n = 1, 2$.

eral irregular crown ethers (**13–16**). The experimental $\log K$ values vary from 1.32 to 4.36 (Na^+), from 1.30 to 6.07 (K^+), and from 0.80 to 5.01 (Cs^+).

Below we report some results related to modeling of the stability of the K^+ /crown ether complexes; the stabilities of Na^+ and Cs^+ complexes were modeled in a similar way.

The first series of calculations carried out for $\Gamma = 0$ in Eqs. (1)–(3) did not result in any statistically significant models. Therefore, in order to take into account the macrocyclic effect, the ME contribution to the stability constants $\log K$ was represented in Eqs. (1)–(3) by the term $\Gamma = ME = a_{cycl}N_{cycl}$. Using this additional term, TRAIL has selected three models at the training stage, namely, **II(Hy)** (Eq. (2)), **I(AB, 2–6)** (Eq. (1)), and **I(AB, 3–5)** (Eq. (1)), with reasonable statistical criteria ($R^2 = 0.939-0.947$, $Q^2 = 0.804-0.864$, $s = 0.48-0.61$). The arithmetic mean values of $\log K$ calculated for the compounds of the training and test sets using these fitting models are well correlated with experimental data (Fig. 5, *a, c*), thus demonstrating the good robustness of the models.

The calculations show that the a_{cycl} term varies depending on the M^+ cation but not on the crown ether. For a given M^+ , the three best models result in a virtually the same a_{cycl} value ($a_{cycl} = 0.389 \pm 0.004$ (for Na^+), 0.678 ± 0.004 (for K^+), and 0.345 ± 0.010 (for Cs^+)), indicating that this parameter is model independent (at least, for the best models). This means that for a given M^+

cation, the cyclicity descriptor N_{cycl} characterizes the average macrocyclic effect (ME) for a family of crown ethers with the same macrocyclic scaffold, irrespective of whether they are substituted or not.

Among all ligands, ME reaches the maximum values for the 18C6 macrocyclic core in the case of Na^+ and K^+ and for the 18C6 and 21C7 cores in the case of Cs^+ (Fig. 6). Interestingly, the SMF calculations show that the crown ethers having the 18C5 core display a pronounced ME when complexed with Na^+ or K^+ , crown ethers with the 33C11 and 36C12 cores exhibit an ME when complexed with K^+ , whereas those with the 12C4, 14C4, and 20C6 cores show negligible macrocyclic effects. The low ME for 18C5 and the lack of ME for 20C6, whose cavity does not differ much in size from "the best" 18C6 ligand, indicate that the regularity of the CH_2OCH_2 fragments forming the ring is a very important feature for the specific cation complexation by crown ethers. Thus, the structure–property modeling allowed us to assess quantitatively the macrocyclic effect by analyzing the experimental data for diverse crown ethers, without resorting to the data for acyclic analogs.

In principle, using Eqs. (1)–(3) and the calculated fragment contributions a_i and b_i and taking that $a_{cycl} = 0$, one can estimate the stabilities of complexes formed by acyclic ligands. As can be seen from Fig. 5, *e*, the predicted stability constants are well correlated with the corresponding experimental values for K^+ complexes with glyme in methanol.

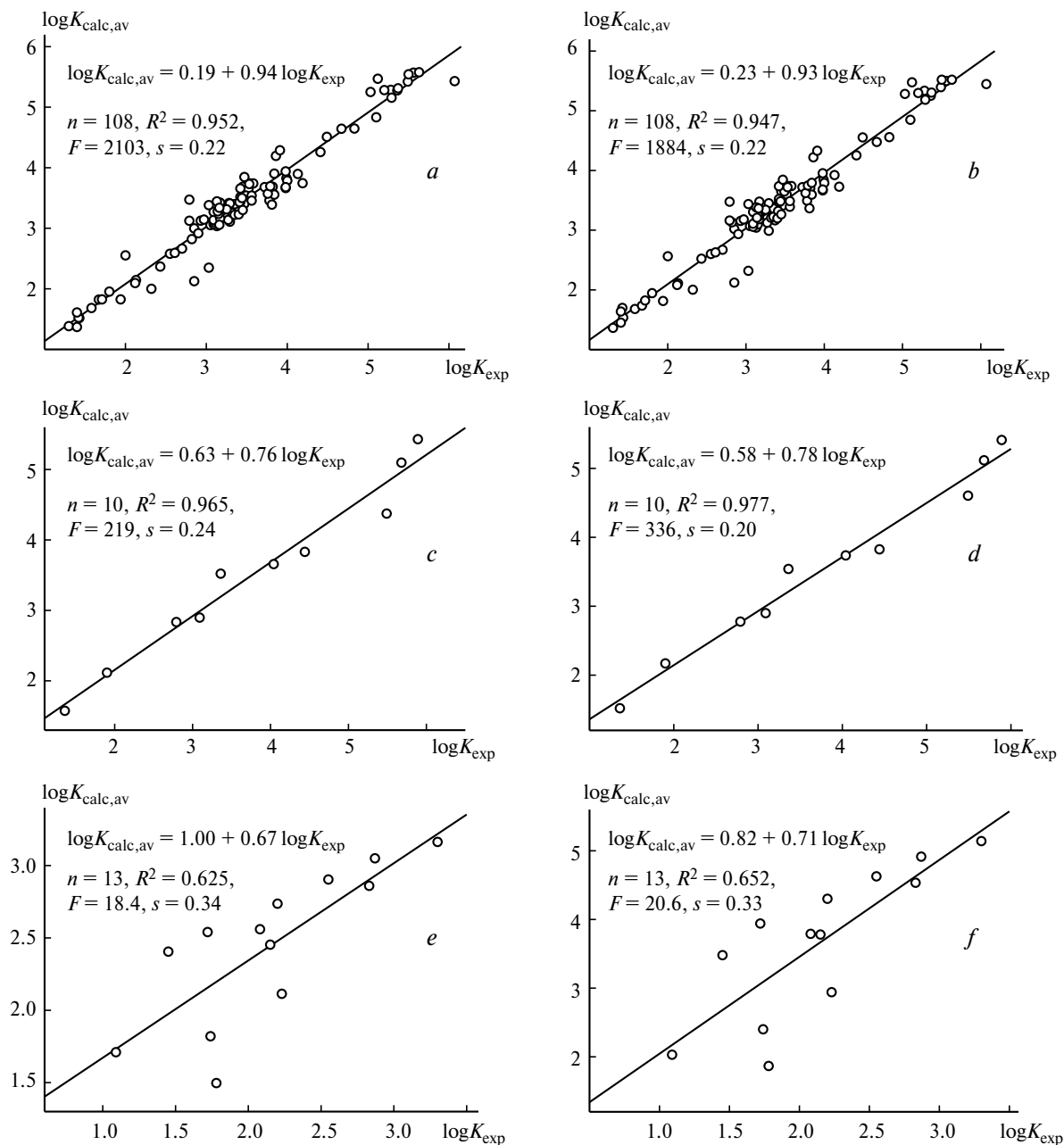


Fig. 5. SMF modeling of the stability constants ($\log K$) of complexes formed by crown ethers and their acyclic analogs with the K^+ cation in MeOH at 298 K: linear correlation between the calculated (arithmetic mean over the three best fit models) and experimental $\log K$ values for the training set (a, b), the test set of crown ethers (c, d), and the set of acyclic ligands (e, f) using all fragments (a, c, e) and the fragments selected according to the t -test (b, d, f).

As in the case of complexation and extraction by podands (see the previous sections), the selection of variables according to the t -test substantially decreases the number of fragment descriptors and improves the robustness of all three QSPR models. Fischer's criterion for the best models increases from 22.2–26.0 (all variables) to 67.8–110.7 (selected variables), and the cross-validation correlation coefficient Q^2 increases from 0.804–0.864 to

0.853–0.909, respectively. In addition, the standard deviation of predictions s_{PRESS} decreases from 0.48–0.61 to 0.32–0.43. Using the models with selected variables for the test set improves the statistical criteria for the linear regression of $\log K_{\text{calc}}$ vs $\log K_{\text{exp}}$: $R^2 = 0.977$ and $s = 0.20$ (see Fig. 5, d) instead of $R^2 = 0.965$ and $s = 0.24$ (all variables, see Fig. 5, c). Similarly, the estimation of the stability constants for acyclic compounds becomes statis-

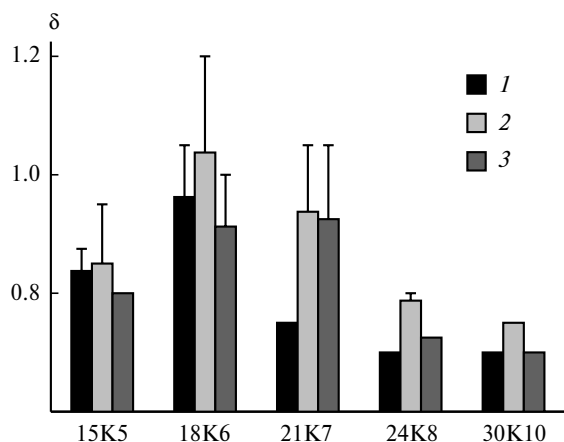


Fig. 6. Ratio (δ) of the average ME contribution to the experimental stability constant $\log K$ for complexes of crown ethers having different macrocyclic cores with Na^+ (1), K^+ (2), and Cs^+ (3). The standard deviations characterize the variation of δ within a given class of ligands.

tically more robust: $R^2 = 0.652$ and $s = 0.33$ (selected variables, Fig. 5, *f*) compared to $R^2 = 0.625$ and $s = 0.34$ (all variables, see Fig. 5, *e*).

* * *

The method of substructural molecular fragments (SMF) has been applied to estimation of the thermodynamic parameters of complexation and extraction of metal cations with cyclic and acyclic ligands. Statistically stable QSPR models were developed for (i) stability constants of K^+ complexes with phosphoryl-containing podands in a mixed THF— CHCl_3 solvent, (ii) distribution coefficients of Hg^{II} and Pt^{IV} extracted by podands from water into 1,2-dichloroethane, and (iii) stability constants of crown ether complexes with alkali metal cations in methanol.

A procedure for selection of the number of SMF variables according to the *t*-test has been proposed. It has been shown that the use of selected variables improves the robustness of QSPR models leading to a significant increase in Fischer's criterion and in the cross-validation correlation coefficient, at the training stage and to a decrease in the standard deviation of predictions. In addition, the thermodynamic parameters of complexation and extraction for compounds of the test set are better reproduced when using the set of selected variables.

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