

Assessment of the Macrocyclic Effect for the Complexation of Crown-Ethers with Alkali Cations Using the Substructural Molecular Fragments Method

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The Substructural Molecular Fragments method (Solov'ev, V. P.; Varnek, A. A.; Wipff, G. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 847–858) was applied to assess stability constants ($\log K$) of the complexes of crown-ethers, polyethers, and glymes with Na^+ , K^+ , and Cs^+ in methanol. One hundred forty-seven computational models including different fragment sets coupled with linear or nonlinear fitting equations were applied for the data sets containing 69 (Na^+), 123 (K^+), and 31 (Cs^+) compounds. To account for the “macrocyclic effect” for crown-ethers, an additional “cyclicality” descriptor was used. “Predicted” stability constants both for macrocyclic compounds and for their open-chain analogues are in good agreement with the experimental data reported earlier and with those studied experimentally in this work. The macrocyclic effect as a function of cation and ligand is quantitatively estimated for all studied crown-ethers.

INTRODUCTION

Complexation properties of cyclic polyethers (crown-ethers, cryptands) in solution differ from those of their open-chain analogues (glymes, alcohols, glycols). Thus, stability constants ($\log K$) of the 1:1 complexes of alkali cations M^+ ($\text{M}^+ = \text{Na}^+, \text{K}^+, \text{Cs}^+$) with glymes $\text{CH}_3\text{—O—}(\text{CH}_2\text{—CH}_2\text{—O})_m\text{—CH}_3$ in methanol increase with m , whereas those of the complexes of crown-ethers $(\text{—CH}_2\text{—CH}_2\text{—O—})_n$ pass through the maximum at $n = 6$ (Na^+, K^+) and 6, 7 (Cs^+).^{1–5} The fact that the complexes of crown-ethers are systematically more stable than those of acyclic analogues is attributed to so-called “macrocyclic effect” (ME)^{6–8} whose nature is still a matter of debate.^{9–17}

Quantitatively, ME is defined as a difference between the stability constants ($\log K$) of the complexes of a given crown-ether and corresponding open-chain analogue. For the complexes with alkali cations, this procedure led to an estimation of the ME for the $18c6\cdot\text{Na}^+$,^{10,13} $18c6\cdot\text{K}^+$,^{10,13} and benzo- $18c6\cdot\text{M}^+$ ⁹ complexes. Similar comparisons based on experimental data retrieved from the THECOMAC² and IUPAC SC¹ databases show that 15c5, 21c7, and 24c8 also display a ME for M^+ .

In this paper, unlike earlier experimental^{9–12,18–22} and theoretical¹⁷ works, we use the data mining methods to estimate ME for parent data sets containing experimental stability constants for 69 (Na^+), 123 (K^+), and 31 (Cs^+) complexes of crown-ethers without explicit comparison with their acyclic analogues. As a structure–property tool we used the Substructural Molecular Fragments (SMF) method^{23,24} based on the decomposition of a molecular graph into fragments and calculation of these fragments contributions

to a given property using linear or nonlinear fitting equations. Recently, the SMF method was successfully applied to assess $\log K$ for the K^+ complexes of phosphoryl-containing podands in the mixed $\text{THF}:\text{CHCl}_3$ solvent, for Na^+ –crown-ether complexes in methanol and for the complexes of β -cyclodextrin with substituted benzenes in water,²³ extraction constants for the complexes of uranyl cation with phosphoryl-containing ligands,^{23,24} and distribution coefficients of some heavy metals extracted by podands or amides.^{23,24}

Here, to assess the stability constants of crown-ethers with M^+ ($\text{M}^+ = \text{Na}^+, \text{K}^+, \text{Cs}^+$) in MeOH , we use the “standard” SMF method previously tested on the modeling of complexation properties of open-chain molecules. As shown previously,²³ explicit account of cyclicality is necessary to assess stability constants of the metal complexes of cyclic ligands. We therefore included a “cyclicality” term in the fitting equations, in relation with the ME . This new model led to reasonable quantitative description of stability constants for the compounds from the learning set and allowed us to “predict” $\log K$ values for the compounds from the validation set, involving molecules experimentally studied in this work. The robustness of the SMF approach was controlled by testing calculations on four different learning/validation sets for the K^+ –crown-ether complexes.

In agreement with the experiment, the structure–property modeling reported in this paper shows that for M^+ the macrocyclic effect is displayed by unsubstituted 15c5, 18c6, 21c7, and 24c8. We demonstrate below that all derivatives of these ionophores also exhibit ME . Furthermore, our calculations have found ME for some other crown-ethers and their derivatives: 18c5 (for Na^+ and K^+), 27c9 and 30c10 (for Na^+, K^+ and Cs^+), and 33c11 and 36c12 (for K^+). For the purpose of comparison, the SMF calculations were also

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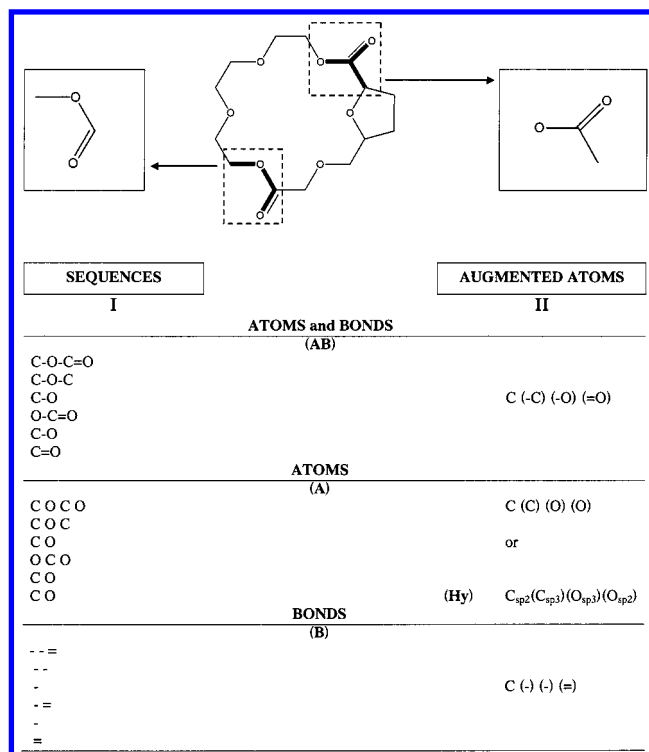


Figure 1. Substructural molecular fragments: atom/bond sequences and augmented atoms. Shortest paths sequences (I) and augmented atoms (II) including atoms and bonds (AB) only atoms (A) or only bonds (B). From top to bottom: the sequences (I) correspond to the I(AB, 2–4), I(A, 2–4), and I(B, 2–4) types involving paths between each pair of atoms. The II(Hy) augmented atoms correspond to the II(A) type, where hybridization of atom is taken into account.

performed on the set containing acyclic glymes and ethylene glycols which also form 1:1 complexes with K⁺ in methanol.

It should be noted that structure–property modeling of crown-ether complexes with metals represents a difficult task. Thus, previous quantitative structure–properties relationship (QSPR) studies on the complexes of macrocyclic polyethers with alkali cations of Schneider et al.²⁵ show reasonable correlation between ΔG of complexation and hydrogen bonding donor and acceptor descriptors only for subsets of molecules of given cavity size but not for the whole set of macrocycles. Neural network modeling of Gakh et al.²⁶ were reported on the limited set of regular crown-ethers (–CH₂–CH₂–O–)_n (*n* = 4–11) and their benzo- and dibenzo-derivatives. Multiple linear regression studies by Shi et al.²⁷ on 314 cation-macrocyclic-solvent systems resulted in reasonable statistical criteria but were based on energy descriptors preliminary calculated using AMBER and MMP2 force fields.

In this paper, we report a QSPR studies of stabilities of crown-ether complexes with alkali cations (M⁺ = Na⁺, K⁺, and Cs⁺) using recently developed SMF method which applies 147 computational models based on 49 sets of descriptors (molecular fragments). Our calculations show that the SMF method is a reliable structure–property tool to assess log*K* values for the alkali metal complexes of a large variety of crown-ethers with different cavity sizes and substituents. Moreover, using the fragment contributions obtained from macrocyclic ligands, we were able to “predict” log*K* values for the metal complexes of acyclic molecules, which were not present in the learning set. It should be noted

that neither preliminary calculated nor measured experimentally parameters were used in these calculations as descriptors. To our knowledge, this is the first application of data mining methods for systematic estimation of the macrocyclic effect for the complexation of crown-ethers.

2. COMPUTATIONAL PROCEDURE

2.1. Substructural Molecular Fragments Method and Related Computer Tools. To establish relationships between the structure of crown-ethers and their complexation properties, we used the recently developed Substructural Molecular Fragments (SMF) method,^{23,24} which is based on the representation of the molecular graph by fragments and on the calculation of their contributions to a given property.

Two different types of fragments are considered: “sequences” (I) and “augmented atoms” (II) (Figure 1). “Sequences” represent sequences of atoms and bonds (AB), of atoms only (A), or of bonds only (B). The length of sequences varies from 2 to 6 atoms. For any sequence containing from *N*_{min} to *N*_{max} atoms, all fragments of *N*_{max}, *N*_{max} – 1, *N*_{max} – 2, . . . , *N*_{min} length are considered. For example, the I(AB, 2–6) decomposition scheme corresponds to five sequences containing 6, 5, 4, 3, and 2 atoms and linking bonds, the I(A, 2–6) scheme corresponds to similar sequences containing atoms only, and the I(B, 2–6) scheme corresponds to the sequences of bonds, which link the above sequences of atoms.

An “augmented atom” represents a selected atom with its environment including either neighboring atoms and bonds (AB), or atoms only (A, without taking hybridization of neighbors into account, or Hy, where hybridization of neighbors is accounted for), or bonds only (B).

When a compound is split into constitutive fragments, the fragments contributions to the stability constant (log*K*) or to any other physical or chemical property are calculated using linear (1) or nonlinear (2) and (3) fitting equations:

$$\text{Log}K = a_o + \sum_i a_i N_i + \Gamma \quad (1)$$

$$\text{Log}K = a_o + \sum_i a_i N_i + \sum_i b_i (2N_i^2 - 1) + \Gamma \quad (2)$$

$$\text{Log}K = a_o + \sum_i a_i N_i + \sum_{i,k} b_{ik} N_i N_k + \Gamma \quad (3)$$

Here, *a_i* and *b_i* (*b_{ik}*) are contributions of fragments, and *N_i* is the number of fragments of *i* type. The *a_o* term is fragment independent. The *a_i* and *b_i* (*b_{ik}*) are the same for corresponding fragment for all compounds from the given set. An extra term Γ can be used to describe any specific feature of the compound (here, the cyclicity term); by default $\Gamma = 0$.

The fragments contributions as fitted coefficients in the eqs 1–3 at the learning stage are used to “predict” log*K* for the compounds from the validation set.

The TRAIL program has been developed to establish structure–property relationships based on the SMF partitioning.^{23,24} The program inputs data in the SDF format²⁸ containing structural and properties information. The graphical interface of TRAIL allows to attribute data to the learning or to the validation sets and to set up the parameters of calculations (type of fragments, minimal and maximal number of atoms/bonds in the sequences, type of environ-

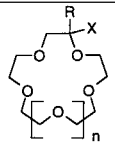
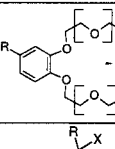
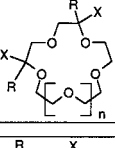
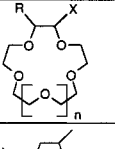
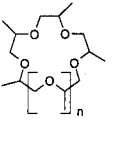
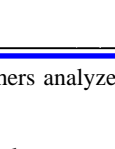
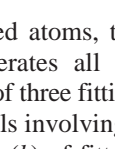
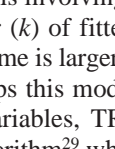
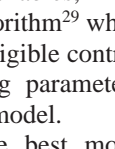
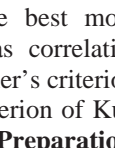
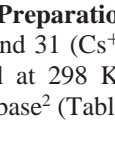
Crown ethers	n	R	X	k	m	p
	a: 0-5,7,8	H	H	-	-	-
	b: 0,1	CH ₂ OCH ₂ Ph	H	-	-	-
	c: 0	(CH ₂ O) _k (CH ₂ CH ₂ O) _m (CH ₂) _p H	H	1	0	0,8
	1			0	0	1,2,6,8,10
	2			0	0	1
	2			0,1	0	8,12
	2			1	1,2	8
	1			1	0	0,1,8,12
	1			1	1	1,4,8
	1			1	2	1,8
	1			1	3	0,1
	d: 1,2	Ph	H	-	-	-
	e: 1	CH ₂ O(2- or 4-C ₆ H ₄ OMe)	H, Me	-	-	-
	f: 1	Me; CH ₂ Br	Me	-	-	-
	g: 1	(CH ₂ O) _k (CH ₂ CH ₂ O) _m (CH ₂) _p H	Me	1	1,2,3	0
	1			1	0	6,8,12
	1			1	1	1,8,12,14
	1			1	2	1,8
	1			1	3	1
	1		CH ₂ Br	0	0	6,8
	1		(CH ₂) ₆ H	1	1,2,3	1
	1			1	0	6,8
	1			1	1,2	8
	1		(CH ₂) ₆ H	1	1,2,3	1
	1		X=R	1	1,2	1
	h: 1	CH ₂ N(CH ₂) ₆ H	Me	-	-	-
	a: 0	H	H	-	1	-
	b: 1	H; C(O)(CH ₂) ₄ H	H	-	1	-
	c: 1,2	H	H	-	2,3	-
	d: 3	Me; Et; t-Bu	Me; Et; t-Bu	-	3	-
	a: 1	CH ₂ Br	Me	-	-	-
	b: 1	(CH ₂ O) _k (CH ₂ CH ₂ O) _m (CH ₂) _p H	Me	1	1	1
	c: 2,3	=O	-	-	-	-
	n	R	X			
	a: 1	=O	H			
	b: 1	=O	(CH ₂) ₆ H			
	c: 2	Me	Me			
	n	R	X			
	a: 1	H; CH(OH)CH ₂ NMe				
	b: 2	H; Et; t-Bu; C(O)H				
	n	m				
	a: 0	1				
	b: 0	2				
	n	m				
	a: 0	1				
	b: 0	2				
	n	m				
	a: 0	1				
	b: 0	2				
	n	m				
	a: 0	1				
	b: 0	2				
	n	m				
	a: 0	1				
	b: 0	2				
	n	m				
	a: 0	1				
	b: 0	2				

Figure 2. Crown-ethers analyzed by the SMF method.

ment for augmented atoms, type of equation (1, 2, or 3), etc.). TRAIL generates all possible types of fragments coupled with each of three fitting eqs 1–3, which correspond to 147 fitting models involving 49 typical sets of fragments. If the total number (k) of fitted terms a_i and b_i for a given computational scheme is larger than the number of molecules n , the program skips this model and moves to another one. To fit a_i and b_i variables, TRAIL uses the singular value decomposition algorithm²⁹ which allows the user to exclude variables with negligible contributions, to check correlation between the fitting parameters, and thus to control the robustness of the model.

Selection of the best models is based on statistical parameters such as correlation coefficient (R), standard deviation (s), Fischer's criterion (F), R_H -factor of Hamilton, and the fitness criterion of Kubinyi (FIT).^{30,31}

2.2. Data Sets Preparation. Stability constants for 69 (Na⁺), 123 (K⁺), and 31 (Cs⁺) metal complexes of crown-ethers in methanol at 298 K critically selected from the THECOMAC database² (Tables 1 and SM1, SM4, and SM7

in Supporting Information). These sets include unsubstituted crown-ethers with different cavity sizes ($-\text{CH}_2-\text{CH}_2-\text{O}-$) _{m} ($m = 4-12$), their benzo, dibenzo, cyclohexyl, dicyclohexyl, and neutral lariat derivatives, and several "nonregular" crown-ethers (Figure 2, Tables 1 and SM1, SM4, and SM7 in Supporting Information). 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⁺) for the learning sets.

Prediction calculations were performed on the validation sets of crown-ethers of different cavity sizes randomly selected from the original parent sets (about 10% of the compounds); the remaining data constituted the learning sets. These validation sets involved nine (Na⁺) and three (Cs⁺) crown-ethers with different cavity sizes and substituents, stability constants for which varied by 2.5–4 order of magnitude ($\log K = 1.35-4.17$ (Na⁺) and 1.73–4.25 (Cs⁺)).

To check the robustness of the SMF method, four different learning/validation sets were selected from the parent set for the K⁺ complexes. The compounds for the validation set for the K⁺ complexes were randomly selected from the subsets

Table 1. Stability Constants ($\text{Log}K_{\text{exp}}$) for the 1:1 (M:L) Complexation of Crown-Ethers with K^+ in MeOH at 298 K^a Used in Four Learning and Four Validation Sets^b


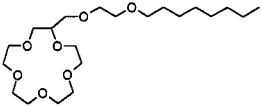
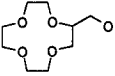
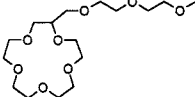
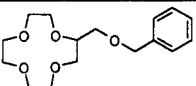
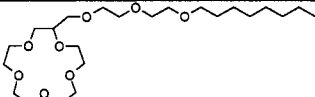
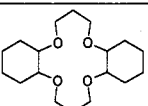
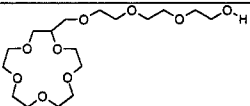

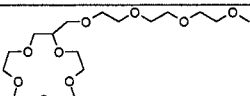
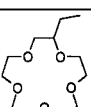
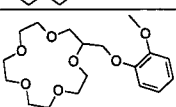
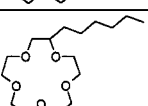
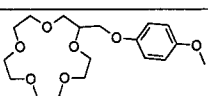
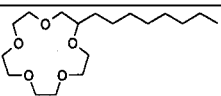
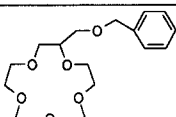
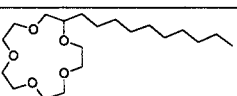
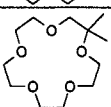
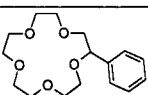
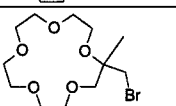
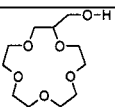
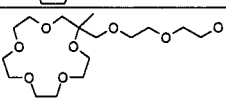
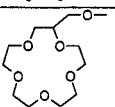
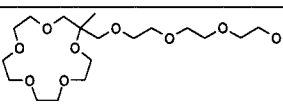
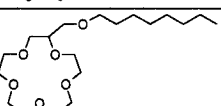
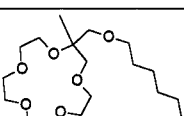
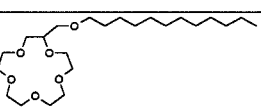
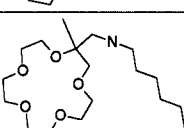
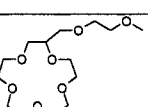
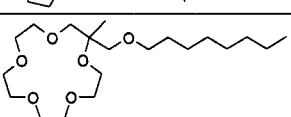
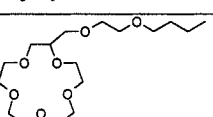
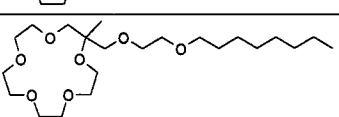
no.	crown-ether	$\text{Log}K_{\text{exp}}$	no.	crown-ether	$\text{Log}K_{\text{exp}}$
1		1.58	17		3.14
2		1.43	18		3.50
3		1.42	19		3.28
4		1.30	20		3.45
5		3.35	21		3.52
6		3.29	22		3.32
7		3.13	23		3.17
8		3.05	24		3.16
9		3.15	25		2.85
10		3.38	26		2.70
11		3.09	27		3.82
12		3.27	28		3.99
13		3.09	29		3.35
14		3.09	30		2.94
15		3.20	31		3.15
16		3.37	32		3.47

Table 1. Continued

no.	crown-ether	LogK _{exp}	no.	crown-ether	LogK _{exp}
33		3.79	47		3.84
34		3.09	48		3.72
35		3.42	49		2.93
36		3.78	50		2.97
37		3.42	51		3.25
38		3.98	52		3.56
39		4.00	53		2.61
40		3.14	54		3.17
41		3.49	55		3.76
42		3.35	56		3.79
43		3.56	57		3.44
44		3.41	58		3.98
45		2.55	59		3.13
46		3.29	60		3.54

Table 1. Continued

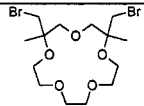
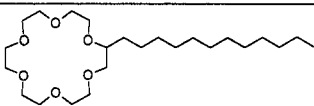
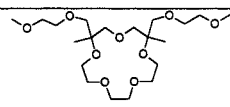
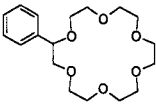
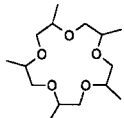
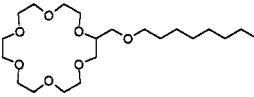
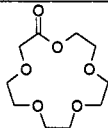
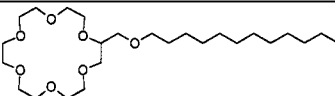
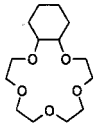
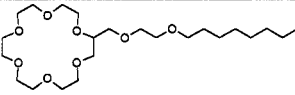
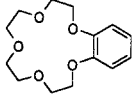
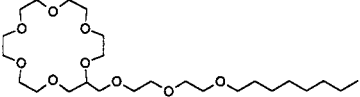
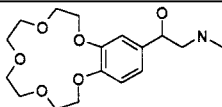
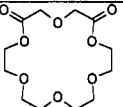
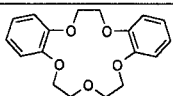
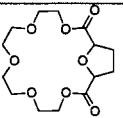
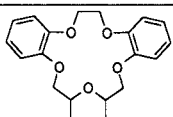
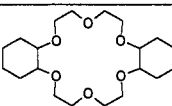
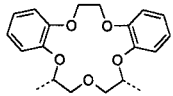
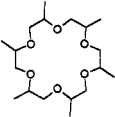
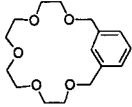
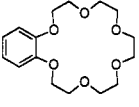
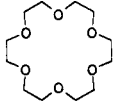
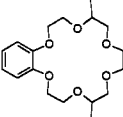
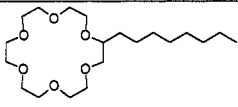
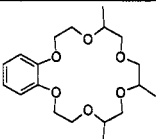
no.	crown-ether	Log K_{exp}	no.	crown-ether	Log K_{exp}
61		2.13	74		5.28
62		3.58	75		5.56
63		2.85	76		5.36
64		2.12	77		5.37
65		3.40	78		5.49
66		2.90	79		5.50
67		2.63	80		2.79
68		2.00	81		2.79
69		1.40	82		5.63
70		1.40	83		3.86
71		2.82	84		5.29
72		6.07	85		4.49
73		5.03	86		3.91

Table 1. Continued

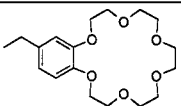
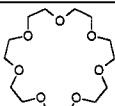
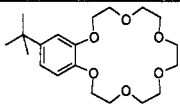
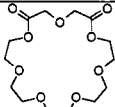
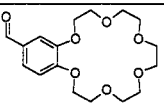
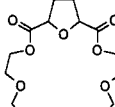
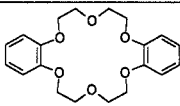
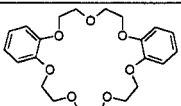
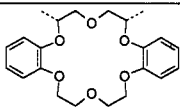
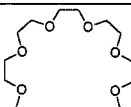
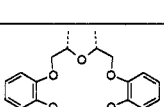
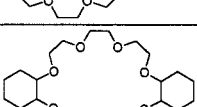
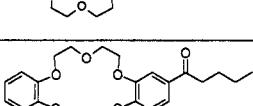
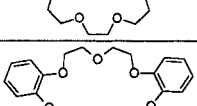
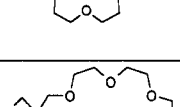
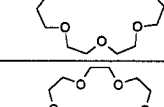
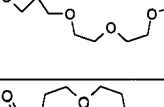
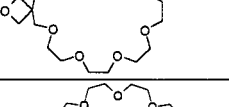
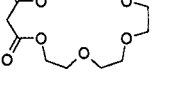
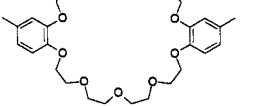
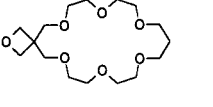
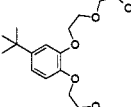
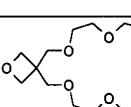
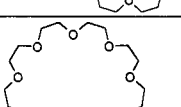
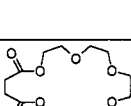
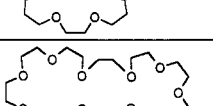
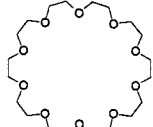
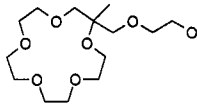
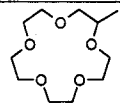
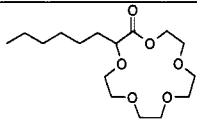
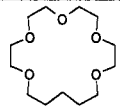
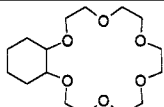
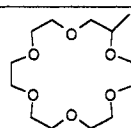
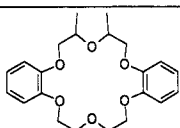
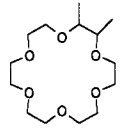

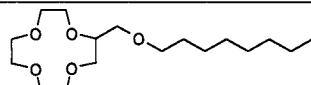
no.	crown-ether	Log K_{exp}	no.	crown-ether	Log K_{exp}
87		5.20	100		4.41
88		5.12	101		2.32
89		4.93	102		3.03
90		5.10	103		4.19
91		4.13	104		3.53
92		3.42	105		3.84
93		4.56	106		3.45
94		3.81	107		2.43
95		2.55	108		4.67
96		1.67	109		4.83
97		1.80	110		3.47
98		1.94	111		3.16
99		1.71	112		3.03

Table 1. Continued

no.	crown-ether	Log K_{exp}	no.	crown-ether	Log K_{exp}
113		3.98	119		3.36
114		3.09 ^c	120		1.90
115		2.79	121		5.89
116		5.68 ^c	122		4.04
117		5.49 ^c	123		4.44
118		1.36			

^a Experimental stability constants were critically selected from the THECOMAC database.² ^b The following compounds were selected for four validation sets: 114–123 (set 1); 2, 6, 19, 40, 57, 62, 77, 88, 103, 128 (set 2); 3, 8, 16, 25, 39, 74, 78, 87, 105, 109 (set 3); 1, 7, 21, 27, 35, 46, 65, 73, 76, 106 (set 4). Other compounds from the parent set were included in corresponding learning sets 1–4. ^c Experimental stability constant has been estimated in this work by ISE method.

such as for the Na⁺ and Cs⁺ complexes. Each validation set contained 10 compounds which differ completely from one set to the others (Table 1).

An additional test of predictability of the SMF method was performed on the validation set of 13 1:1 complexes of K⁺ with acyclic glymes and ethylene glycols, whose stability constants in methanol were taken from the IUPAC Stability Constants Database.¹ In Section 3.3, we show that the models fitted on the learning set of macrocyclic compounds reproduce well enough experimental data for acyclic ligands from the additional validation set.

The stability constants of three crown-ethers (Me-15c5, Me-18c6, and 2,3-Me₂-18c6) with Na⁺ and K⁺ were experimentally determined in this work (see Tables 11 and 12). In fact, stabilities of these complexes are substantially smaller than for those of unsubstituted 15c5 and 18c6, respectively. Thus, inclusion of new experimental data in the validation sets allows us to test if the SMF method can reproduce large variations of log K which correspond to minor structure modifications of crown-ethers.

3. RESULTS

3.1. Fitting the “Macrocyclic Effect” Terms. The first series of learning stage calculations were performed without a “cyclicality” term ($\Gamma = 0$), as used for open-chain ligands.²³ This led to statistically poor models with regression coefficients $R < 0.69$ (Na⁺), $R < 0.73$ (K⁺), and $R < 0.87$ (Cs⁺).

This poor fitting is not surprising since complexation properties of crown-ethers differ from those of open-chain ligands, and therefore corresponding mathematical models describing both classes of ionophores should be different. To account for the macrocyclic effect in eqs 1–3, we introduced the term $\Gamma = a_{\text{cycl}}N_{\text{cycl}}$, where cyclicality descriptor N_{cycl} is an integer number (by analogy with N_i). The a_{cycl} and N_{cycl} variables were fitted in two steps.

First, calculations were performed on the subsets containing nine unsubstituted crown-ethers $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $m = 4-12$.^{2,32} Since these molecules contain the same repetitive unit $(-\text{CH}_2-\text{CH}_2-\text{O}-)$, any fragment decomposition scheme (I or II) involves linearly dependent fragments, which, therefore, form one extended fragment. Thus, for the given set of unsubstituted crown-ethers, the modified eq 1 has only three fitted parameters a_0 , a_1 , and a_{cycl} coupled with integers N_{cycl} fitted independently by a Monte Carlo method. These calculations resulted in reasonable statistical characteristics: $n = 9$, $R = 0.993$, $s = 0.12$, $F = 222$, $\text{FIT} = 34.1$ (Na⁺); $n = 9$, $R = 0.994$, $s = 0.14$, $F = 270$, $\text{FIT} = 41.5$ (K⁺) and $n = 8$, $R = 0.999$, $s = 0.06$, $F = 1081$, $\text{FIT} = 180.2$ (Cs⁺). N_{cycl} values for “regular” $(-\text{CH}_2-\text{CH}_2-\text{O}-)_m$, $m = 4-12$ crown-ethers were then used to fit this parameter for “nonregular” 14-crown-4, 18-crown-5, 19-crown-6, 20-crown-6, 21-crown-6, 25-crown-8, and their derivatives on the whole learning sets together with the a_{cycl} term.

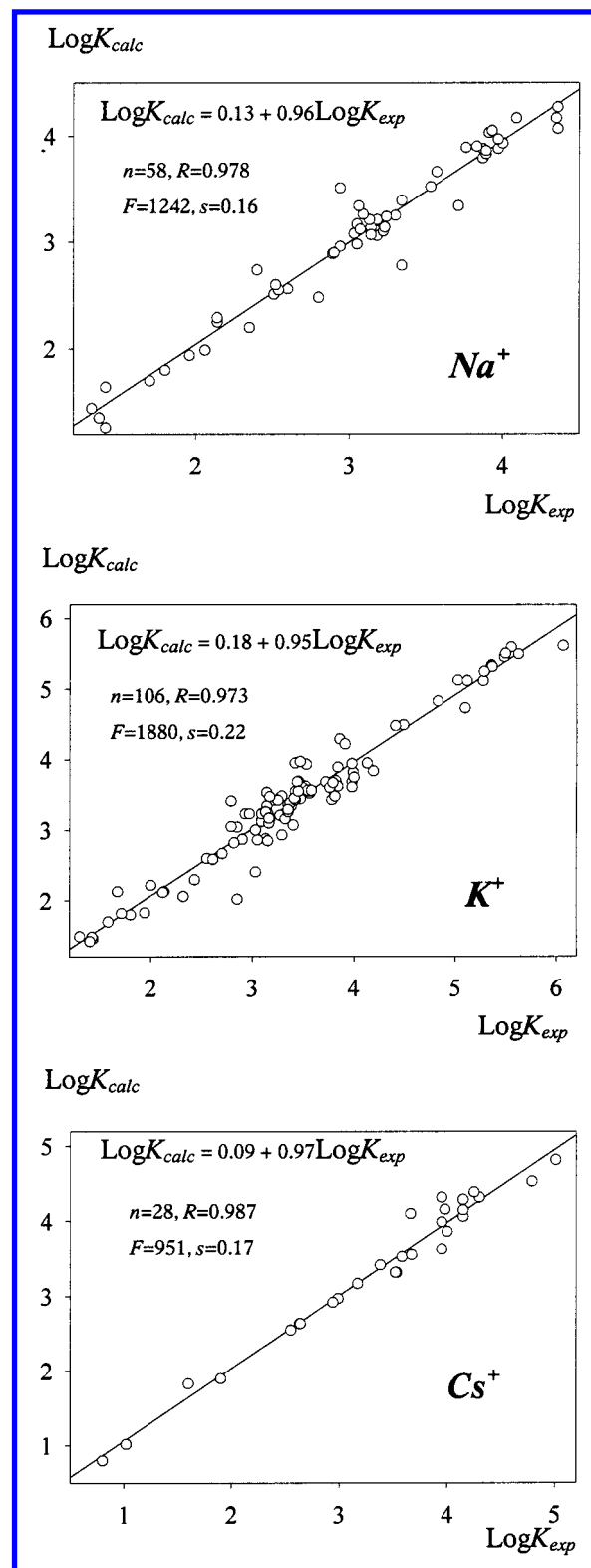
Table 2. Modeling of Stability Constants ($\log K$) for the 1:1 (M:L) Complexation of Crown-Ethers with K^+ in MeOH at 298 K^a

no.	fragment set	fitting eq	<i>n</i>	<i>k</i>	<i>R</i>	<i>F</i>	FIT	<i>s</i>
Learning Set 1 ^b								
1	II(Hy)	2	106	44	0.973	26.0	0.57	0.30
2	I(AB, 2-6)	1	104	44	0.970	22.2	0.49	0.32
3	I(AB, 3-5)	1	107	32	0.969	37.0	1.07	0.30
4	I(AB, 2-5)	1	107	35	0.969	32.7	0.88	0.30
5	II(Hy)	1	106	23	0.957	40.8	1.52	0.33
6	I(AB, 2-4)	1	113	30	0.946	24.2	0.74	0.38
Learning Set 2 ^b								
1	II(Hy)	2	107	44	0.976	29.4	0.65	0.30
2	I(AB, 2-6)	1	105	46	0.972	22.7	0.48	0.33
3	I(AB, 3-5)	1	107	32	0.972	40.7	1.18	0.30
4	I(AB, 2-5)	1	107	35	0.972	36.1	0.97	0.31
5	II(Hy)	1	107	23	0.965	52.1	1.94	0.31
6	I(AB, 2-4)	1	113	30	0.954	28.8	0.87	0.37
Learning Set 3 ^b								
1	II(Hy)	2	105	42	0.972	26.7	0.61	0.31
2	I(AB, 2-6)	1	105	46	0.972	22.1	0.47	0.33
3	I(AB, 3-5)	1	107	32	0.970	38.7	1.12	0.30
4	I(AB, 2-5)	1	107	35	0.971	34.6	0.93	0.30
5	II(Hy)	1	105	22	0.961	47.3	1.82	0.32
6	I(AB, 2-4)	1	113	30	0.949	25.7	0.78	0.38
Learning Set 4 ^b								
1	II(Hy)	2	107	46	0.975	26.4	0.56	0.31
2	I(AB, 2-6)	1	105	46	0.970	20.8	0.44	0.35
3	I(AB, 3-5)	1	107	32	0.970	38.1	1.11	0.31
4	I(AB, 2-5)	1	107	35	0.970	33.5	0.90	0.32
5	II(Hy)	1	107	24	0.962	44.4	1.61	0.33
6	I(AB, 2-4)	1	113	30	0.952	27.5	0.83	0.38

^a Statistical criteria of six best models for four learning sets, including a term $\Gamma = a_{cycl}N_{cycl}$ at the learning stage using different types of fragments. Molecules are represented without hydrogen atoms. See text for the fragments definition. Statistical parameters calculated for the learning set: number of compounds in the learning set (*n*), the number of fitted coefficients (*k*), correlation coefficient (*R*), Fisher's criterion (*F*), fitness function (FIT), and standard deviation (*s*). From the initially selected 113 compounds those containing "rare" fragments were removed. ^b The compounds in the learning and validation sets are specified in footnote of Table 1.

3.2. Structure–Complexation Properties Modeling of the M^+ –Crown-Ether Complexes. Here we report results of the SMF calculations on the M^+ –crown-ether complexes ($M^+ = Na^+, K^+, Cs^+$) for learning and validation sets. To check whether calculated results depend on the partitioning of compounds from a given parent set between learning and validation sets, we divided the parent set for K^+ (the largest experimental data set used) in four different ways, thus preparing four learning and four validation sets, respectively. No molecule in a given validation set was present in the other sets. Results given in Section 3.2.1 show that the different ways of partitioning the parent set for K^+ into learning/validation sets did not significantly effect neither type nor statistical criteria of the best models selected by TRAIL. Therefore only one learning set and one validation set were further used to the model the stabilities of Na^+ and Cs^+ complexes.

At the learning stage, TRAIL has selected six "best" models corresponding to $R \geq 0.95$ (Na^+), 0.95 (K^+), and 0.98 (Cs^+) (Tables 2, 4, and 6, respectively). Standard deviations (0.21–0.30 for Na^+ , 0.30–0.38 for K^+ , and 0.23–0.28 for Cs^+) (Figure 3) were of the same order of magnitude as typical errors for different experimental techniques used for determination of stability constants.^{2,3} Each of the six models was then used for "prediction" calculations on a

**Figure 3.** Stability constants ($\log K$) for the (M^+)L complexes of crown-ethers (L) with Na^+ , K^+ (data set 1) and Cs^+ in MeOH at 298 K: calculated vs experimental $\log K$ values for the learning set.

validation set. To improve the predictability of the SMF calculations and to estimate standard deviations for "predicted" stability constants, we computed average data sets, in which $\log K$ for a given compound was averaged from the best models.

The molecular structures of the compounds from learning and validation sets calculated with the best models and

Table 3. Modeling of the 1:1 (M:L) Complexation of Crown-Ethers with K^+ in MeOH at 298 K: Experimental and “Predicted” Stability Constants ($\log K$) for the Compounds from the Validation Sets 1–4^a

		LogK						
compd no.	exp.	II(Hy) ^b	I(AB, 2–6)	I(AB, 3–5)	I(AB, 2–5)	II(Hy)	I(AB, 2–4)	mean ^c
Validation Set 1								
114	3.09	2.94	2.80	2.95	2.95	3.00	3.03	2.94 (0.08)
115	2.79	2.65	3.03	2.82	2.88	2.55	2.31	2.71 (0.27)
116	5.68	5.21	4.97	5.11	5.10	5.23	5.16	5.13 (0.10)
117	5.49	4.88	3.58	4.65	4.58	4.96	5.00	4.61 (0.56)
118	1.36	1.54	1.60	1.58	1.61	1.57	1.70	1.60 (0.06)
119	3.36	3.51	3.57	3.48	3.51	3.46	3.26	3.46 (0.11)
120	1.90	2.10	<i>e</i>	2.12	2.19	1.99	2.05	2.09 (0.09)
121	5.89	5.34	5.48	5.47	5.45	5.46	5.13	5.39 (0.14)
122	4.04	3.95	3.48	3.54	3.52	4.14	4.19	3.80 (0.34)
123	4.44	<i>e</i>	3.65	4.01	4.19	<i>e</i>	4.10	3.99 (0.38)
<i>R</i> ^d		0.996	0.907	0.991	0.988	0.994	0.987	0.993
<i>s</i> ^d		0.14	0.51	0.18	0.20	0.17	0.23	0.16
Validation Set 2								
2	1.43	1.40	1.42	1.64	1.51	1.62	1.69	1.55 (0.12)
6	3.29	2.99	2.63	3.24	3.34	3.05	3.06	3.05 (0.25)
19	3.28	3.44	3.36	3.34	3.35	3.38	3.43	3.38 (0.04)
40	3.14	3.60	2.98	3.23	3.22	3.52	3.33	3.31 (0.22)
57	3.44	3.81	3.43	3.49	3.46	3.85	3.91	3.66 (0.22)
62	3.58	3.54	3.85	3.86	3.86	3.74	3.82	3.78 (0.13)
77	5.37	5.37	5.34	5.38	5.36	5.36	5.46	5.38 (0.04)
88	5.12	<i>e</i>	5.92	5.93	5.93	<i>e</i>	6.02	5.95 (0.05)
103	4.19	3.73	3.54	3.51	3.50	3.30	3.10	3.45 (0.22)
108	4.67	<i>e</i>	4.32	4.05	3.55	<i>e</i>	4.26	4.05 (0.35)
<i>R</i> ^d	0.988	0.945	0.934	0.903	0.924	0.901	0.929	
<i>s</i> ^d	0.16	0.45	0.45	0.55	0.42	0.57	0.48	
Validation Set 3								
3	1.42	1.51	1.61	1.61	1.60	1.57	2.03	1.66 (0.19)
8	3.05	2.86	3.19	3.20	3.20	2.97	3.20	3.10 (0.15)
16	3.37	3.43	2.44	3.03	3.07	3.31	3.20	3.08 (0.35)
25	2.85	3.17	2.48	2.76	2.63	3.29	3.16	2.92 (0.33)
39	4.00	3.76	3.79	3.79	3.79	3.77	3.70	3.77 (0.04)
74	5.28	5.14	5.54	5.60	5.58	5.22	5.51	5.43 (0.20)
78	5.49	5.51	5.47	5.43	5.45	5.56	5.52	5.49 (0.05)
87	5.20	<i>e</i>	5.77	5.72	5.79	<i>e</i>	5.63	5.73 (0.07)
105	3.84	3.86	3.89	3.95	3.95	3.53	3.15	3.72 (0.32)
109	4.83	<i>e</i>	3.15	3.27	3.08	<i>e</i>	3.79	3.32 (0.32)
<i>R</i> ^d		0.991	0.890	0.908	0.892	0.985	0.919	0.914
<i>s</i> ^d		0.18	0.70	0.60	0.67	0.24	0.52	0.57
Validation Set 4								
1	1.58	1.70	1.74	1.69	1.70	1.74	1.70	1.71 (0.02)
7	3.13	2.89	3.17	3.13	3.14	2.99	3.12	3.07 (0.11)
21	3.52	3.70	3.70	3.70	3.70	3.64	3.78	3.70 (0.04)
27	3.82	3.64	3.60	3.54	3.57	3.54	3.35	3.54 (0.10)
35	3.42	3.40	3.39	3.41	3.41	3.35	3.34	3.38 (0.03)
46	3.29	3.48	3.41	3.40	3.40	3.42	3.53	3.44 (0.05)
65	3.40	3.13	3.41	3.38	3.38	3.28	3.04	3.27 (0.15)
73	5.03	5.22	5.40	5.41	5.41	5.26	5.40	5.35 (0.09)
76	5.36	5.42	5.30	5.30	5.29	5.41	5.38	5.35 (0.06)
106	3.45	3.48	3.03	3.02	3.01	2.76	2.58	2.98 (0.30)
<i>R</i> ^d		0.986	0.978	0.978	0.978	0.968	0.942	0.977
<i>s</i> ^d		0.19	0.23	0.24	0.24	0.29	0.41	0.25

^a Compound numbers are given according Table 1. Unless specified, fitting eq 1 was used. ^b Fitting eq 2 was used. ^c Average predicted $\log K$ value for which standard deviation is given in parentheses. ^d Statistical characteristics (R and s) for the correlation between experimental and predicted (by given model) $\log K$ values. ^e Fragment contributions for this compound was not available on the learning stage.

experimental stability constants for these compounds as well as fragment contributions (a_i) corresponding to the best models are available in the Supporting Information.

3.2.1. K^+ Complexes. At the learning stage, TRAIL performs fitting fragment contributions and orders computational models according to statistical criteria R , s , F , and FIT. This allowed us to select six “best fit” models (Table 2). The II(Hy) fragments coupled with eq 2 is on the top of the list of the “best” models for any learning set ($R > 0.97$, $s = 0.31$, $F = 26$, FIT > 0.55). Other models correspond to

I(AB, 2–6), I(AB, 3–5), I(AB, 2–5), II(Hy), and I(AB, 2–4) fragments coupled with eq 1 ($R = 0.95$ – 0.97 , $s = 0.30$ – 0.38 , $F = 22$ – 52 , FIT $= 0.5$ – 1.9); their order as a function of R slightly changes from one set to the others (Table 2).

Models obtained at the learning stage were tested on four validation sets (Table 3) containing 10 crown-ethers of different cavity sizes (12- to 30-membered) with alkyl, phenyl, carbonyl, and polyether substitutes, for which $\log K$ varies from 1.36 to 5.89. Three molecules (nos. 114, 116,

Table 4. Modeling of Stability Constants ($\log K$) for the 1:1 (M:L) Complexation of Crown-Ethers with Na^+ in MeOH at 298 K^a

no.	fragment set	fitting eq	<i>n</i>	<i>k</i>	<i>R</i>	<i>F</i>	FIT	<i>s</i>
1	I(A, 3–6)	1	58	24	0.978	32.8	1.28	0.21
2	II(B)	2	60	24	0.970	24.9	0.97	0.24
3	II(AB)	1	57	14	0.965	45.4	2.61	0.24
4	I(AB, 2–4)	1	60	22	0.969	27.6	1.16	0.24
5	I(AB, 3–4)	1	60	20	0.960	25.0	1.13	0.26
6	I(AB, 2–3)	2	60	24	0.955	16.3	0.64	0.30
7	I(A, 3–5)	1	58	16	0.948	24.9	1.32	0.30
8	I(AB, 4–4)	1	60	17	0.948	23.8	1.21	0.29
9	I(A, 2–5)	1	58	18	0.948	21.0	1.03	0.30
10	I(B, 3–6)	1	58	18	0.947	20.3	0.99	0.29
11	I(B, 4–6)	1	58	17	0.946	22.0	1.12	0.29
12	I(B, 5–6)	1	58	14	0.945	28.3	1.62	0.28
13	I(A, 2–4)	1	60	15	0.930	20.5	1.12	0.33
14	I(B, 2–4)	1	60	10	0.917	29.4	1.87	0.34
15	I(A, 3–4)	1	60	13	0.917	20.7	1.22	0.35
16	I(B, 2–5)	1	58	13	0.917	19.8	1.17	0.34
17	II(B)	1	60	13	0.916	20.5	1.22	0.35
18	I(B, 3–4)	1	60	9	0.914	32.5	2.10	0.34
19	I(B, 4–5)	1	58	11	0.914	23.8	1.51	0.34
20	I(A, 6–6)	1	58	11	0.914	23.8	1.50	0.36
21	I(B, 3–5)	1	58	12	0.914	21.3	1.31	0.34
22	I(A, 4–5)	1	58	13	0.914	19.1	1.14	0.36
23	I(AB, 2–3)	1	60	13	0.913	19.7	1.16	0.36

^a Statistical criteria of models, including a term $\Gamma = a_{\text{cyc}}N_{\text{cyc}}$ at the learning stage using different types of fragments. Molecules are represented without hydrogen atoms. See text for the fragments definition. See footnotes for Table 2 for definition of statistical parameters.

and 117 in Tables 1 and 3) from the validation set 1 were studied experimentally in this work.

For any validation set, all six models selected at the learning stage yield a good correlation between experimental and calculated $\log K$ ($R = 0.890$ – 0.996 and $s = 0.14$ – 0.70 for the linear regression $\log K_{\text{calc}} = a + b \cdot \log K_{\text{exp}}$) (Table 3).

Another way to smooth inaccuracies in particular models and to estimate standard deviations for predicted $\log K$ consists of averaging the data calculated with the SMF models for a given compound from a validation set. These “average” data sets calculated for all four validation sets correlate well with the experimental data ($R = 0.914$ – 0.993 and $s = 0.16$ – 0.57) and have low random errors (Table 3).

3.2.2. Na^+ Complexes. The “best” six models ($R > 0.95$, $s = 0.30$, $F > 16$, $\text{FIT} > 0.6$) correspond to I(A, 3–6), II(AB), I(AB, 2–4), or I(AB, 3–4) fragments coupled with eq 1 and to the II(B) or I(AB, 2–3) fragments coupled with eq 2 (Table 4).

“Prediction” calculations with these models were performed on nine crown-ethers with alkyl, benzyl, and polyether substituents and different macrocyclic ring sizes (from 12- to 27-membered), whose stability constants range from 1.35 to 4.17. Comparison between validated and experimental values (Table 5) shows that models with II(B), II(AB), I(AB, 2–4), I(AB, 3–4), or I(AB, 2–3) fragments reproduce well the experimental data ($R = 0.920$ – 0.990 and $s = 0.13$ – 0.35 for the correlations between experimental and calculated $\log K$ in the validation set), whereas the model based on I(A, 3–6) fragments leads to poor statistical criteria ($R = 0.670$ and 0.80). However, averaging over the six best models leads to a good correlation with the experimental data ($R = 0.978$ and $s = 0.18$), and the random errors for average predicted $\log K$ values (Table 5) are generally lower than the

best models standard deviations s (Table 4), with the exception of 18-crown-5.

3.2.3. Cs^+ Complexes. The best six models ($R \geq 0.98$, $s = 0.28$, $F > 23$, $\text{FIT} > 1.2$) correspond to I(A, 4–5), I(A, 2–4), I(A, 3–5), I(AB, 2–4), and II(B) fragments coupled with eq 1 and to II(A) fragments coupled with eq 2 (Table 6).

Three crown-ethers (dimethyl derivative of 16-crown-5, dicyclohexyl-18-crown-6, and dibenzo-24-crown-8), for which $\log K$ varies from 1.73 to 4.25, were tested at the validation stage. Comparison between validated and experimental values (Table 7) shows that these selected models reproduce well the experimental data ($R = 0.987$ – 0.999 and $s = 0.02$ – 0.29). Averaging values obtained from the six best models leads to a good correlation with experiment ($R = 0.999$ and $s = 0.09$, Table 7).

3.3. Complexation of Glymes and Ethylene Glycols with K^+ . The question arises whether the fragment contributions obtained from macrocyclic ionophores could be used to assess the thermodynamics parameters of complexes formed by their open-chain analogues. Formally, $\log K$ for these compounds can be calculated according to eqs 1–3 taking $\Gamma = 0$. To test this assumption, the calculations with a_o , a_i , and b_i (b_{ik}) parameters fitted for the six models from Table 2 (learning set 1) were performed on the sets of 13 acyclic glymes and ethylene glycols which form 1:1 complexes with K^+ in methanol.










These calculations resulted in reasonably good standard deviations s ($s = 0.28$ – 0.61) but poor correlation coefficients ($R = 0.671$ – 0.796) (Table 8). This could be explained by the narrow range of experimental $\log K$ values (from 1.09 to 3.30) where even small variations in calculated data may effect the statistical correlation criteria.

The average (of the six) data set, nevertheless, reasonably well “predicts” experimental stability constants: the standard deviation is rather small ($s = 0.31$) and similar to that obtained for the best models (see Tables 8 and 2).

4. DISCUSSION

4.1. Substructural Molecular Fragment Method as a Flexible and Reliable Structure–Property Tool. Additive schemes in which a given molecular property is calculated from the contributions of molecular fragments are widely used in chemistry. Thus, formation enthalpies and heat capacities,³³ octanol–water partition coefficients,³⁴ oil-gas partition coefficients,³⁵ and aqueous solubilities³⁶ can be calculated using contributions of a priori defined fragments (atoms, bonds, or functional groups increments). Unlike any traditional approach, which uses only one type of fragments, the SMF method allows for generating a large number of models involving 49 types of fragments used in combination with three fitting equations. Thus, the SMF method is not restricted to any particular decomposition scheme but considers several decomposition schemes and fitting models. Simultaneous utilization of several models (instead of a single one) on the validation stage may improve the predictability of structure–property calculations. Indeed, any particular model involving relatively large number of variables may lead to excellent statistical parameters for the learning set but very poor correlation with experimental data at the validation stage. When several “best” SMF models are used

Table 5. Modeling of the 1:1 (M:L) Complexation of Crown-Ethers with Na⁺ in MeOH at 298 K: Experimental and "Predicted" Stability Constants (logK) for the Ligands from the Validation Set^a

no.	Compound	LogK						
		exp.	predicted					
			I(A, 3-6)	II(B) ^b	II(AB)	I(AB, 2-4)	I(AB, 3-4)	I(AB, 2-3) ^b
1		3.05 ^c	3.10	3.19	3.16	3.17	3.18	3.20
2		2.46 ^d	4.62	2.44	2.46	3.28	2.22	2.47
3		3.90 ^c	3.93	3.97	3.97	3.98	3.99	3.98
4		3.77 ^c	3.58	3.87	3.86	3.28	3.27	3.90
5		1.35	1.51	1.58	1.63	1.48	1.53	1.54
6		3.04	2.37	2.94	3.14	3.04	3.04	3.49
7		4.17	4.22	4.01	4.00	4.16	4.10	4.02
8		3.53	3.79	3.68	3.80	3.90	3.91	3.67
9		2.41	2.44	2.38	2.33	2.39	2.38	2.42
<i>R</i> ^f			0.670	0.990	0.987	0.920	0.959	0.983
<i>s</i> ^f			0.80	0.13	0.15	0.35	0.27	0.17

^a Unless specified, fitting eq 1 was used. ^b Fitting eq 2 was used. ^c Experimental stability constant has been estimated in this work by ISE method. ^d Experimental data from ref 43. ^e Average predicted logK and standard deviation (in parentheses). ^f Statistical characteristics (*R* and *s*) for the correlation between experimental and predicted (for given model) logK values.

for validation, one may calculate an average data set, where inaccuracies of individual data sets are smoothed. In this work, such averaging always led to good correlation between experimental and calculated stability constants, although some particular models were not predictive enough (Tables 3, 5, and 7). Due to its ability to adapt to any particular set of compounds and properties, the SMF method is able to assess logK for a large variety of cyclic and acyclic compounds. The results reported here show that the method is sensible enough to account for the effect of minor structure modifications on the complexes stability. Thus, for the Na⁺ and K⁺ complexes, our calculations reproduced the experimentally determined decrease of logK which resulted from the substitution of one H atom by the Me group in 15c5 and 18c6 (Tables 3 and 5).

4.2. Assessment of the Macrocyclic Effect in the Cation Complexation by Crown-Ethers. By definition, the mac-

rocyclic effect is the difference ($\delta\log K$) between stability constants of the complexes of a crown-ether ($\log K_{CE}$) and its acyclic analogue ($\log K_{acycl}$). In the literature, macrocyclic effect for M⁺ complexes was discussed only for 18c6 and benzo-18c6.^{9,10,13} No conclusions concerning *ME* of other substituted crown-ethers could be drawn because of lack of experimental data on the corresponding acyclic ligands.

To extract more information on *ME* from the experimental data, stability constants of unsubstituted crown-ethers ($-(CH_2-CH_2-O-)_n$, $n = 4-10$, in methanol at 298 K, were selected from the THECOMAC database² and for glymes $CH_3-O-(CH_2-CH_2-O-)_m-CH_3$, $m = 4-7$, from IUPAC SC database.¹ Missing values for glymes with $m = 3, 8$, and 9 were extrapolated assuming a linear dependence between $\log K_{acycl}$ and m . Table 9 shows that only 12c4 (for all M⁺) and 27c9 and 30c10 (for Na⁺ and K⁺) display negligible macrocyclic effect. For other crowns $\delta\log K$ is much larger

Table 6. Modeling of Stability Constants (log*K*) for the 1:1 (M:L) Complexation of Crown-Ethers with Cs⁺ in MeOH at 298 K^a

no.	fragment set	fitting eq	<i>n</i>	<i>k</i>	<i>R</i>	<i>F</i>	FIT	<i>s</i>
1	I(A, 4-5)	1	28	13	0.986	45.6	3.18	0.23
2	I(A, 2-4)	1	28	12	0.982	40.4	2.98	0.25
3	I(A, 3-5)	1	28	16	0.986	29.2	1.73	0.26
4	I(AB, 2-4)	1	26	15	0.986	27.1	1.71	0.27
5	II(A)	2	27	18	0.989	23.5	1.26	0.26
6	II(B)	1	27	11	0.976	32.8	2.58	0.28
7	II(AB)	1	27	12	0.976	28.0	2.08	0.29
8	I(A, 2-3)	2	28	14	0.977	22.6	1.49	0.31
9	II(A)	1	27	10	0.973	33.4	2.79	0.29
10	I(AB, 2-3)	1	28	10	0.937	14.5	1.20	0.45
11	I(A, 2-3)	1	28	8	0.934	19.4	1.77	0.44
12	I(A, 3-3)	1	28	6	0.912	21.8	2.06	0.48
13	I(AB, 3-3)	1	28	8	0.914	14.6	1.33	0.49

^a Statistical criteria of models, including a term $\Gamma = a_{cycl}N_{cycl}$ at the learning stage using different types of fragments. Molecules are represented without hydrogen atoms. See text for the fragments definition. See footnotes for Table 2 for definition of statistical parameters.

than typical differences (0.20–0.50 log*K* units) obtained from one experiment to the other.^{1–5}

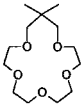
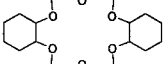
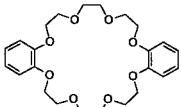
In the SMF method, the *ME* contribution $\delta\log K$ to the stability constant log*K* is accounted for by the term $\Gamma = a_{cycl}N_{cycl}$ in eqs 1–3. Fitting the a_{cycl} term shows that it varies as a function of M⁺ but not of the crown-ether. For a given M⁺, six best models led practically to the same a_{cycl} value ($a_{cycl} = 0.399 \pm 0.017$ (for Na⁺), 0.671 ± 0.012 (for K⁺), and 0.350 ± 0.010 (for Cs⁺)), which indicates that this parameter is model independent (at least, for the studied best models). This means that for a given M⁺, the cyclicity descriptor N_{cycl} characterizes the *average* macrocyclic effect ($\delta\log K = a_{cycl}N_{cycl}$) for a family of crown-ethers which possess the same ring scaffold, be they substituted or not. One may see that the average $a_{cycl}N_{cycl}$ values for a given crown-ether family (Table 10) are of the same order of magnitude as $\delta\log K$ estimated from experimental data for unsubstituted crowns, based on the comparison with their acyclic analogues (Table 9). Among all ligands, *ME* reaches

its maximal values with the 18c6 scaffold for Na⁺ and K⁺ and with the 18c6 and 21c7 scaffolds for Cs⁺. Interestingly, the SMF calculations show that crown-ethers having the 18c5 scaffold display the *ME* for Na⁺ and K⁺, crown-ethers with 33c11 and 36c12 scaffolds exhibit *ME* for K⁺, whereas those with 12c4, 14c4, and 20c6 scaffolds have negligible macrocyclic effect (Table 10). The small *ME* for 18c5 and the absence of *ME* for 20c6 which are not very different in size to “the best” complexant 18c6 indicate that the “regularity” of –CH₂–O–CH₂– constitutive fragments is a very important feature for specific cation complexation by crown-ethers. For a given metal, depending on the ring skeleton, the *ME* contribution ($\delta\Delta G = -2.3RTa_{cycl}N_{cycl}$ in kJ/mol at 298 K) to the total free energy of complexation ΔG ranges from –2.3 to –13.6 (Na⁺), from –3.8 to –19.2 (K⁺), and from –4.0 to –12.0 (Cs⁺) (Table 10). The ratio of the average *ME* contribution ($\delta\log K = a_{cycl}N_{cycl}$) and experimental log*K* values reveals the importance of macrocyclic effect on the binding affinities of crown-ethers. Depending on the substituents, this ratio is equal to 0.40–0.55 (Na⁺), 0.30–0.70 (K⁺), and 0.40 (Cs⁺) for the 15c5 scaffold; 0.55–0.90 (Na⁺), 0.55–1.20 (K⁺), and 0.45–0.80 (Cs⁺) for the 18c6 scaffold; 0.30 (Na⁺), 0.45–0.90 (K⁺), and 0.40–0.90 (Cs⁺) for the 21c7 scaffold; 0.20 (Na⁺), 0.35–0.40 (K⁺), and 0.25 (Cs⁺) for the 24c8 scaffold; 0.20 (Na⁺), 0.30 (K⁺), and 0.20 (Cs⁺) for the 30c10 scaffold (see Tables 10, SM1, SM4, and SM7).

The assessment of *ME* of crown-ethers allows one to also estimate the stabilities of the complexes of related acyclic ionophores using eqs 1–3 and fragment contributions a_i and b_i calculated for crown-ethers, and setting $a_{cycl} = 0$, as we have done for the K⁺ complexes of glymes and glycols (Tables 8 and 9). Conversely, the a_{cycl} and N_{cycl} parameters tabulated for macrocyclic scaffolds can be used to estimate log*K* values of crown-ethers using the stability constants of the corresponding acyclic analogues.

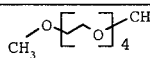
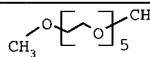
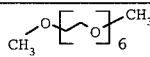
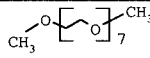
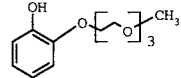
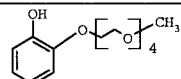
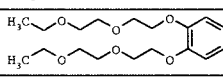
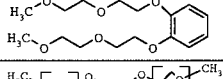
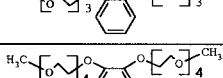
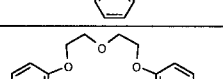
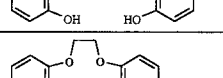
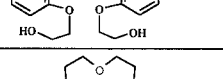
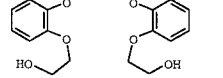
Thus, data mining methods allowed us to quantitatively assess the contribution of the macrocyclic effect to stability

Table 7. Modeling of the 1:1 (M:L) Complexation of Crown-Ethers with Cs⁺ in MeOH at 298 K: Experimental and “Predicted” Stability Constants (log*K*) for the Ligands from the Validation Set^a

		LogK							
no.	compound	exp.	predicted						
			I(A, 4-5)	I(A, 2-4)	I(A, 3-5)	I(AB, 2-4)	II(A) ^b	II(B)	mean ^e
1		1.73 ^c	^d	2.51	1.21	1.07	1.50	0.64	1.39 (0.87)
2		4.25	4.10	4.05	4.10	4.38	3.82	4.36	4.14 (0.22)
3		3.85	3.62	3.57	3.62	3.47	3.67	3.56	3.58 (0.07)
	<i>R</i> ^f	-	0.987	0.999	0.993	0.996	0.998	0.999	
	<i>s</i> ^f	-	0.18	0.02	0.29	0.17	0.16	0.09	

^a Unless specified, fitting eq 1 was used. ^b Fitting eq 2 was used. ^c Log*K* value from IUPAC SC Database. ^d Learning set does not have some fragment contributions for this compound. ^e Average predicted log*K* values and standard deviations (in parentheses). ^f Statistical characteristics (*R* and *s*) for the correlation between experimental and predicted (by given model) log*K* values.

Table 8. 1:1 (M:L) Complexation of Noncyclic Polyethers and Glymes with K⁺ in MeOH at 298 K: Experimental and "Predicted" Stability Constants (logK) for the Ligands from the Validation Set^a

		LogK							
no.	compound	exp.	Predicted						
			II(Hy) ^b	I(AB, 2-6)	I(AB, 3-5)	I(AB, 2-5)	II(Hy)	I(AB, 2-4)	mean ^d
1		1.72	1.43	3.35	2.84	2.86	1.35	2.07	2.32 (0.87)
2		2.20	1.71	3.50	3.00	3.02	1.50	2.21	2.49 (0.84)
3		2.55	1.92	3.64	3.15	3.17	1.66	2.36	2.65 (0.83)
4		2.87	2.05	3.79	3.31	3.33	1.81	2.51	2.80 (0.83)
5		1.45	^c	2.29	2.52	2.59	^c	1.31	2.18 (0.94)
6		2.08	^c	2.44	2.68	2.75	^c	1.45	2.33 (0.96)
7		1.78	1.40	1.52	1.57	1.58	1.09	1.30	1.41 (0.20)
8		2.15	1.32	3.30	2.74	2.77	1.09	1.80	2.17 (0.94)
9		2.83	1.92	3.60	3.06	3.09	1.40	2.09	2.53 (0.89)
10		3.30	2.22	3.89	3.38	3.40	1.70	2.38	2.83 (0.89)
11		1.09	^c	1.22	2.20	2.32	^c	0.55	1.57 (1.34)
12		1.74	-0.22	3.25	2.43	2.53	0.70	1.00	1.62 (1.39)
13		2.23	0.35	3.40	2.59	2.69	0.86	1.14	1.84 (1.28)
<i>R^e</i>			0.671	0.782	0.760	0.736	0.714	0.796	0.771
<i>s^e</i>			0.61	0.57	0.33	0.34	0.28	0.39	0.31

^a Unless specified, fitting eq 1 was used. ^b Fitting eq 2 was used. ^c Learning set does not have some fragment contributions for this compound.^d Average predicted logK values and standard deviations (in parentheses). ^e Statistical characteristics (*R* and *s*) for the correlation between experimental and predicted by given model logK values.

constants, analyzing experimental data for crown-ethers only, without any knowledge of experimental logK values for corresponding acyclic analogues.

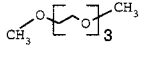

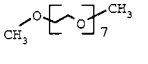

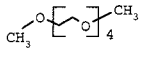

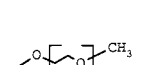

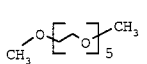

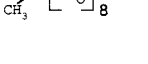

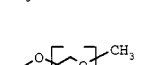

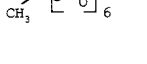



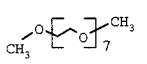

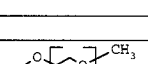



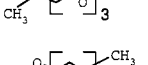

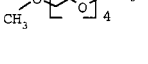

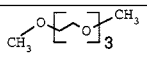

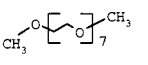

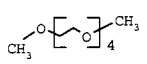

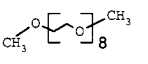

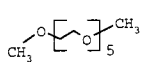

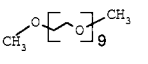

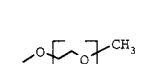

4.3. Modeling of Thermodynamic Parameters of Complexation: SMF Method vs Traditional QSPR Approaches. To our knowledge, in the literature there are very few publications devoted to structure-property modeling of stabilities of metal complexes in solution. Thus, the articles by Shi et al.²⁷ and by Schneider et al.²⁵ concern application of the linear regression models using various physicochemical descriptors. In ref 25, H-bonding electron-donor factors^{37,38} (HB factors) of binding sites of ligands were used as descriptors in order to assess the stability of complexes of some crown-ethers and cryptands with alkali cations. A reasonable correlation (*R* = 0.77–0.99) between Δ*G* of complexation and HB factors was reached only for subsets of molecules of given cavity size but not for the whole sets

of studied macrocycles. One may notice the large standard deviations (up to 1.2 logK units) obtained in these correlations.

In a multiple linear regression analysis reported in ref 27, Shi et al. used various experimental and calculated parameters (radius and electronegativity for metal cations, dielectric constant for solvents, total energy and its components for ligand, and some others) as descriptors to assess the stability constants of 300 complexes of Na⁺, Ca²⁺, and Zn²⁺ with crown-ethers and cryptands in different solvents. Some of these descriptors were preliminary calculated using AMBER and MMP2 force fields. The calculations for the validation set resulted in reasonable *s* values, similar to those obtained here for the Na⁺–crown-ether complexes.

Neural networks modeling has been used by Gakh et al.²⁶ to assess complexation stability constants of Na⁺, K⁺, and Cs⁺ with regular crown-ethers and their benzo- and dibenzo-

Table 9. Estimation of Macrocylic Effect ($\delta\log K = \log K_{CE} - \log K_{acycl}$) for the Complexation of Regular Crown-Ethers with Na⁺, K⁺, and Cs⁺ in MeOH at 298 K Using Experimental^a and Extrapolated^b Stability Constants for Their Acyclic Analogues

no	acyclic ligand	$\log K_{acycl}$	crown-ether (CE)	$\log K_{CE}^c$	$\delta\log K$	no	acyclic ligand	$\log K_{acycl}$	crown-ether (CE)	$\log K_{CE}^c$	$\delta\log K$
Na⁺						K⁺					
1		1.18 ^a		1.41	0.23	12		2.87 ^b		3.53	0.66
2		1.28 ^b		3.30	2.02	13		3.28 ^a		3.47	0.19
3		1.47 ^b		4.36	2.89 2.92 ^d 2.03 ^e	14		3.66 ^a		3.98	0.32
4		1.60 ^b		2.54	0.94	Cs⁺					
5		1.67 ^b		2.35	0.68	15		1.17 ^a		1.6	0.43
6		1.83 ^a		2.14	0.18	16		1.45 ^b		3.58	2.13
7		1.96 ^a		2.14	0.18	17		1.85 ^b		4.79	2.94
K⁺						18		2.17 ^b		5.01	2.84
8		1.38 ^a		1.58	0.20	19		2.41 ^b		4.15	1.74
9		1.72 ^b		3.35	1.63	20		2.77 ^a		3.95	1.18
10		2.20 ^b		6.07	3.87 3.96 ^d 2.93 ^e	21		3.09 ^a		4.15	1.06
11		2.55 ^b		4.41	1.86						

^a Calculated values (see Section 4.2). ^b Experimental $\log K$ values from IUPAC Stability Constants Database.¹ ^c Values selected from THECOMAC database. ^d "Macrocylic effect" experimentally estimated as a difference between stability constants ($\log K$) of the complexes of 18-crown-6 and pentaglyme.^{10,13} ^e "Macrocylic effect" experimentally estimated as a difference between stability constants ($\log K$) of the complexes of benzo-18-crown-6 and 2-hydroxyphenyl-3,6,9,12-tetraoxatridecyl ether.⁹

derivatives in methanol. Only the number of aromatic moieties, the ring size, and the number of ether oxygens were used as input, which limited the number of studied macrocycles to 14–16. The average error for the validation sets (about 0.3 $\log K$ units) is similar to that obtained in our calculations.

Results of QSPR calculations reported by Shi et al.²⁷ and by Schneider et al.²⁵ show that structure–complexation property relationships are very sensitive to the choice of descriptors. Although, reasonable correlations were obtained using selected descriptors for particular sets of cation–ligand complexes,²⁷ it is not clear whether the same descriptors can be used to predict thermodynamic properties of complexation of other classes of ionophores.

The SMF method generates up to 49 consistent sets of descriptors derived from 2D molecular structures which, being coupled with one of three different fitting equations, lead to 147 computational models without any need of the

experimentally or theoretically derived parameters. Such a large number of simultaneously applied models allows the user to select several "best fit" models and to use them for prediction calculations. Our experience shows that the SMF approach is a reliable tool to assess thermodynamic parameters of cation–ligand complexation in solution and in biphasic liquid–liquid systems.^{23,24} Compared to the neural networks studies by Gakh et al., the SMF method has no restriction concerning the type of ionophores in the parent set and, generally, is less CPU time-consuming than neural networks calculations.

CONCLUSIONS

The Substructural Molecular Fragments method²³ was applied to assess the stability constants ($\log K$) of the complexes of crown-ethers, polyethers, and glymes with Na⁺, K⁺, and Cs⁺ in methanol. One hundred forty-seven models including different fragment sets coupled with linear or

Table 10. 1:1 (M:L) Complexation of Crown-Ethers with Na⁺, K⁺, and Cs⁺ in MeOH at 298 K: Cyclic Descriptor (N_{cycl}), Estimated “Macroscopic Effect” Contribution to the Stability Constant ($\delta\log K = a_{cycl}N_{cycl}$) and to the Free Energy ($\delta\Delta G$) of Complexation of 69 (Na⁺), 123 (K⁺), and 31 (Cs⁺) Crown-Ethers and Their Derivatives^a

no.	macrocyclic skeleton ^b	Na ⁺			K ⁺			Cs ⁺		
		N_{cycl}	$\delta\log K$	$-\delta\Delta G$, kJ/mol	N_{cycl}	$\delta\log K$	$-\delta\Delta G$, kJ/mol	N_{cycl}	$\delta\log K$	$-\delta\Delta G$, kJ/mol
1	12C4	0	$\leq 0.30^c$	≤ 1.7	0	$\leq 0.40^c$	≤ 2.3	0	$\leq 0.30^c$	≤ 1.7
2	14C4				0	$\leq 0.40^c$	≤ 2.3			
3	15C5	4	1.60 (0.07) ^a	9.1 (0.4)	2	1.34 (0.02)	7.6 (0.1)	4	1.40 (0.04)	8.0 (0.2)
4	18C5	2	0.80 (0.04)	4.6 (0.2)	1	0.67 (0.01)	3.8 (0.1)			
5	18C6	6	2.39 (0.10)	13.6 (0.6)	5	3.36 (0.06)	19.2 (0.3)	6	2.10 (0.06)	12.0 (0.3)
6	20C6	0	$\leq 0.30^c$	≤ 1.7	0	$\leq 0.40^c$	≤ 2.3	0	$\leq 0.30^c$	≤ 1.7
7	21C7	2	0.80 (0.04)	4.6 (0.2)	3	2.01 (0.04)	11.5 (0.2)	6	2.10 (0.06)	12.0 (0.3)
8	24C8	1	0.40 (0.02)	2.3 (0.1)	2	1.34 (0.02)	7.6 (0.1)	3	1.05 (0.03)	6.0 (0.2)
9	27C9	1	0.40 (0.02)	2.3 (0.1)	2	1.34 (0.02)	7.6 (0.1)	2	0.70 (0.02)	4.0 (0.1)
10	30C10	1	0.40 (0.02)	2.3 (0.1)	2	1.34 (0.02)	7.6 (0.1)	2	0.70 (0.02)	4.0 (0.1)
11	33C11	0	$\leq 0.30^c$	≤ 1.7	1	0.67 (0.01)	3.8 (0.1)			
12	36C12	0	$\leq 0.30^c$	≤ 1.7	1	0.67 (0.01)	3.8 (0.1)	0	$\leq 0.30^c$	≤ 1.7

^a $\delta\Delta G = -2.3RTa_{cycl}N_{cycl}$, $T = 298$ K. Averaged of $a_{cycl}N_{cycl}$ values obtained from six “best fit” models (see Tables 2, 4, and 6). The random error for 95% confidence interval is given in parentheses. ^b Including all studied derivatives. ^c Estimated macrocyclic effect $\delta\log K$ is smaller than standard deviation for the best models ($s = 0.30$ (Na⁺), 0.40 (K⁺), and 0.30 (Cs⁺)).

Table 11. Complexation of Crown-Ethers with K⁺ and Na⁺ in MeOH at 298 K: Total Concentrations of Reagents Used in Potentiometric Measurements^a

no.	ligand	salt	C _L mmol/L	C _S mmol/L
1	Me18C6	NaI	6.92–7.94	1.27–16.6
2		KI	7.63–8.97	1.16–15.8
3	2,3-Me ₂ 18C6	NaI	6.89–7.76	1.27–14.7
4		KI	8.09–9.51	1.45–16.1
5	Me15C5	NaI	7.29–8.29	1.27–15.7
6		KI	8.17–9.59	2.60–24.4

^a C_L is total concentration of ligand, and C_S is total concentration of a salt.

Table 12. Stability Constants and Free Energies for the Complexation of Crown-Ethers with K⁺ and Na⁺ in MeOH at 298 K Obtained by ISE Method^a

no.	ligand	salt	solvent	$\log K$	$-\Delta G$, kJ/mol
1	Me18C6	NaI	MeOH	3.90(0.05)	22.2(0.3)
2	Me18C6	KI	MeOH	5.68(0.07)	32.4(0.4)
3	2,3-Me ₂ 18C6	NaI	MeOH	3.77(0.03)	21.5(0.2)
4	2,3-Me ₂ 18C6	KI	MeOH	5.49(0.05)	31.3(0.3)
5	Me15C5	NaI	MeOH	3.05(0.02)	17.4(0.1)
				5.08(0.05) ^b	29.0(0.3)
6	Me15C5	KI	MeOH	3.09(0.05)	17.6(0.3)
				5.48(0.07) ^b	31.3(0.4)
7	18C6 ^c	Na ⁺	MeOH	4.36	24.9
8	18C6 ^c	K ⁺	MeOH	6.07	34.6
9	15C5 ^c	Na ⁺	MeOH	3.30	18.8
10	15C5 ^c	K ⁺	MeOH	3.35	19.1

^a The logarithm of stability constant and standard deviation (in parentheses) are given for the reaction $M^+ + L = ML^+$. The background electrolyte is Et₄NI at 0.05 M concentration. ^b The logarithm of stability constant $\log\beta$ and standard deviation (in parentheses) are given for the reaction $M^+ + 2L = ML_2^+$. ^c Lit. data³ for a comparison.

nonlinear fitting equations were trained on the learning sets containing 60 (Na⁺), 113 (K⁺), and 28 (Cs⁺) compounds. To account for the *ME* which varies as a function of the crown-ether's topology and cation's size, the fitting equations included a “cyclic” descriptor. “Predicted” stability constants are in good agreement with the experimental data in MeOH reported earlier or with those obtained in this work for the Na⁺ and K⁺ complexes of methyl-15-crown-5, methyl-18-crown-6, and 2,3-dimethyl-18-crown-6.

The contribution of macrocyclic effect to the stability constants as a function of cation (Na⁺, K⁺, and Cs⁺) and ligand is quantitatively estimated for all studied crown-ethers. In agreement with experiment, the structure–property modeling reveals that unsubstituted 15c5, 18c6, 21c7, and 24c8, as well as their derivatives exhibit some macrocyclic effect. This effect is also found for other crown-ethers and their derivatives: 18c5 (for Na⁺ and K⁺), 27c9 and 30c10 (for Na⁺, K⁺, and Cs⁺), and 33c11 and 36c12 (for K⁺). For 12c4 (Na⁺, K⁺, and Cs⁺), 14c4 (K⁺), 20c6 (Na⁺, K⁺, and Cs⁺), 33c11 (Na⁺), and 36c12 (Na⁺) scaffolds there is no evidence for *ME*. The parameters fitted on cyclic compounds allow to predict the binding properties of acyclic ethers as well as of cyclic ones.

EXPERIMENTAL SECTION

Materials. The commercial compounds methyl-15-crown-5, methyl-18-crown-6, and 2,3-dimethyl-18-crown-6 were identified by IR spectra. KI (99.9%) and NaI (99.7%) from Merck were used without additional purification. Tetraethylammonium iodide (TEAI) (99.7%) was recrystallized twice from methanol, washed with ether, and dried under vacuum (1 Pa) at 333 K. MeOH was rectified over magnesium methanolate under nitrogen.

Potentiometric measurements were carried out using ion selective and reference electrodes, one in the reaction vessel, the other in the reference cell. The two half cells were connected by a salt bridge filled with a 0.05 M tetraethylammonium iodide solution in MeOH. The reference Ag/Ag⁺ electrode used in all titrations was immersed in the solution identical to that in the salt bridge. The ionic strength of the solutions was constant in all three compartments.

Stability constants of complexation of crown-ethers with Na⁺ or K⁺ were determined by potentiometric titration of a ligand solution with a NaI or KI solution at 298 K. The concentrations of uncomplexed Na⁺ or K⁺ was measured, respectively, by solid-state sodium selective electrode or potassium selective electrode from Moscow Institute of General and Inorganic Chemistry. The electrode responses in pure MeOH were 54.7 for K⁺ and 53.9 mV for Na⁺. Potentials were measured using a diode-modulating impedance transformer (Knick, Type 646).

Stability Constants Calculations. The evaluations of stability constants with the program *ChemEqui* were performed according to the procedure described in the refs 3 and 39. Reagents concentrations for the titrations are given in Table 11. The reliability of used ISE potentiometric procedure was tested on the model $18c6 + K^+ = 18c6 \cdot K^+$ complexation reaction in methanol and in water for which complexation stability constants are available in the literature. Measured stability constants $\log K$ (2.04 ± 0.02 in water and 6.22 ± 0.04 in methanol) are similar to earlier reported values ($2.03^{40,41}$ and 6.08^{42} respectively).

Stability constants and free energies of the complexation of three crown-ethers with M^+ in MeOH at 298 K estimated by the ISE method are presented in Table 12. Our experiments show that methyl-15-crown-5 forms ML^+ and ML_2^+ complexes, whereas methyl-18-crown-6 and 2,3-dimethyl-18-crown-6 form ML^+ complexes only. Table 12 shows that the complexes of substituted crown-ethers are less stable than those of nonsubstituted 15c5 or 18c6 ligands.

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Supporting Information Available: Tables of experimental, calculated for the "best" models from the learning sets, and predicted stability constants $\log K$ from the validation sets for the complexation of crown-ethers with Na^+ , K^+ , and Cs^+ in MeOH solvent at 298 K, 2D structures of the crown-ethers, and fragment contributions to stability constants. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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