

# The Incremental Description of Host–Guest Complexes: Free Energy Increments Derived from Hydrogen Bonds Applied to Crown Ethers and Cryptands<sup>1</sup>

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The analysis of literature data for crown ether and cryptand–cation complexes with the principle of additive pairwise interactions yield excellent linear correlations between observed and calculated complex stabilities as long as geometric fit between ligand site and cation is present and no substantial strain is built up during complexation. These conditions are controlled partially by molecular mechanics simulations and partially by comparison to X-ray data. The cornerstone values used for each single ligand–cation interaction are taken from the electron donor parameters ED/Ci which have been derived earlier from over 900 hydrogen bond associations in carbon tetrachloride. The observed electron acceptor abilities EA of the different cations (alkali metal and ammonium ions) are a linear function of, e.g., hydration energies of these ions. Thus, a simple procedure is provided to calculate the stability of over 120 complexes on the basis of one EA parameter for each cation and only 11 ligand ED parameters (same for crowns and cryptands) which moreover are derived from independent sources and do not need to be adjusted.

Intermolecular associations are based on a bewildering number of noncovalent binding mechanisms which complicates quantitative structure–activity correlations. Although macrocyclic ionophores represent the oldest and most developed class of host–guest complexes, also in terms of practical applications,<sup>2</sup> a quantitative understanding of such complexes, or the ability to predict complexation energies for given structures as a prerequisite for the rational design of ligands, is still in the state of infancy. Although force field, molecular dynamics, as well as free energy perturbation calculations for crown ethers and related hosts were greatly advanced recently,<sup>3</sup> reliable computations of corresponding complexation energies are essentially limited to associations with electroneutral guests.<sup>4</sup> Thus,

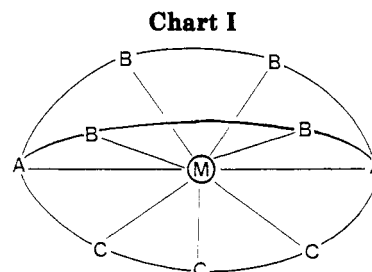


Table I. ED<sup>a</sup> and I<sub>K<sup>+</sup></sub><sup>b</sup> Increments

no.	fragment	ED <sup>a</sup>	I <sub>K<sup>+</sup></sub> <sup>b</sup>	
			CH <sub>3</sub> OH	H <sub>2</sub> O
1		2.1	-6.83	-5.10
2	CH <sub>2</sub> OCH <sub>2</sub>	1.7	-5.53	-4.13
3	H-CH <sub>2</sub> OCHR- <sup>c</sup>	1.0	-3.25	-2.43
4	=CHOCH <sub>2</sub> -	1.1	-3.58	-2.67
5	(O=C)CH <sub>2</sub> O*CH <sub>2</sub> -	0.9	-2.93	-2.19
6		0.4	-1.30	-0.97
7	(O=C)O*CH <sub>2</sub>	0.0	0.00	0.00
8	R <sub>3</sub> N	3.5	-11.38	-8.51
9		2.6	-8.45	-6.32
10	(O=C)N*R <sub>2</sub>	0.0	0.00	0.00
11		3.0	-9.75	-7.29

<sup>a</sup> Electron Donor parameters, derived from hydrogen bond associations in CCl<sub>4</sub>; see text; the asterisk denotes the binding element.  
<sup>b</sup> Increments for potassium complexation (kJ/mol) (for other cations, see Table III). <sup>c</sup> R = alkyl.

Kollman, Wipff, and others have, e.g., demonstrated early the dependence of calculated complex stabilities on the

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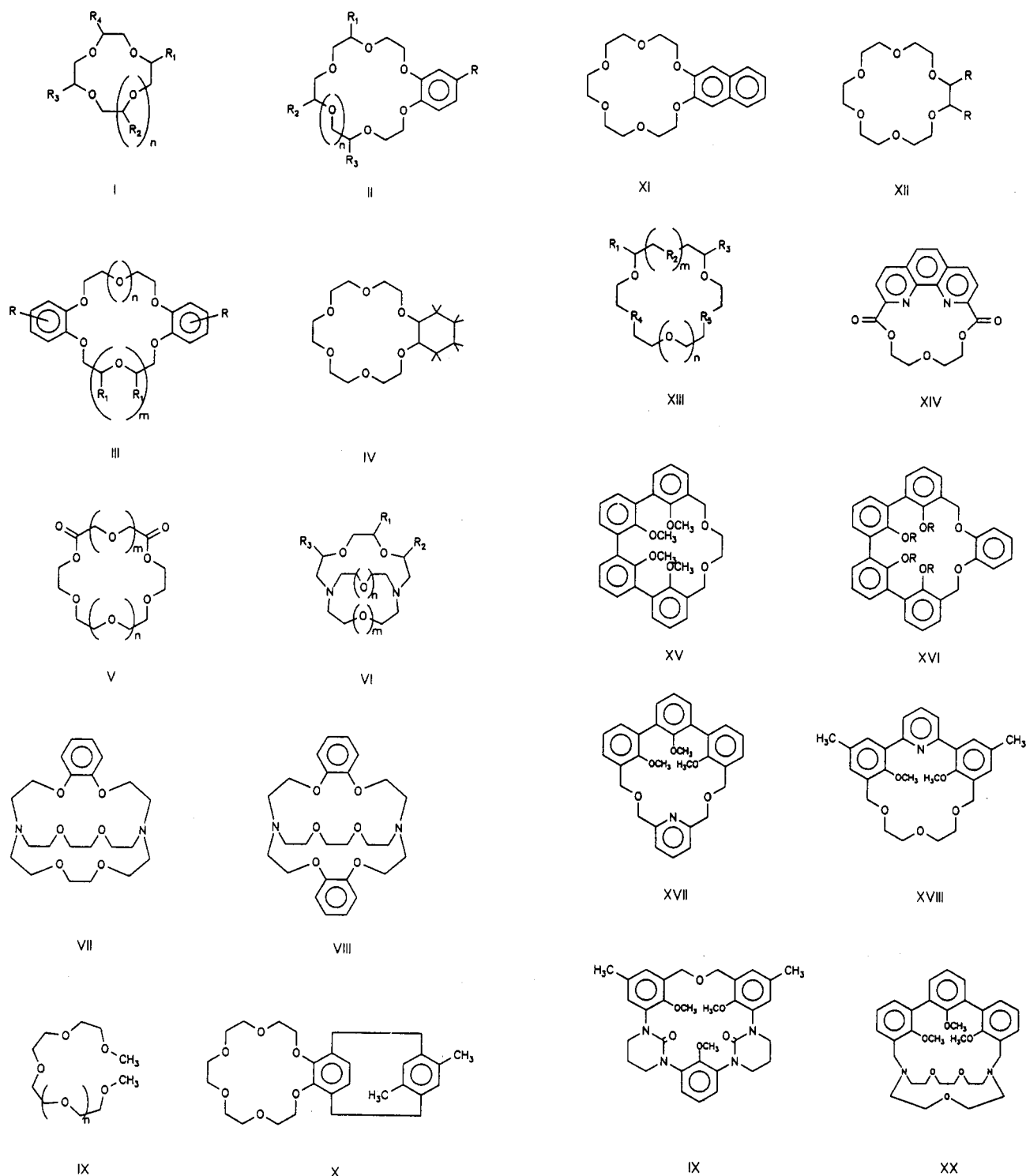
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Scheme I



chosen permanent and induced charges.<sup>3a</sup> We calculate, e.g., up to 10% changes of the potassium-oxygen distances by rather arbitrary choices of the used dielectric constant between 1 and 3 D (see below).

It would be of considerable advantage if the noncovalent forces in ionophore complexes could be predicted by simple additive schemes reminiscent of the long-standing LFER-type description for covalent bond making and breaking. Such attempts were made many years ago by Cram et al.,<sup>5</sup> but with eight parameters for the description of nine

complexes the results of this early attempt were not very encouraging. The Saarbrücken group has recently shown that the free complexation energy  $\Delta G_t$  in many supramolecular complexes can be partitioned in single contributions by linear correlations between  $\Delta G_t$  and the sum of single interactions.<sup>6</sup> In a typical ionophore complex we may encounter, e.g., three different interactions of a metal cation  $M^+$  and binding sites A, B, and C (representing, e.g., alkyl-O, aryl-O, and N). For such a complex (Chart

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I) the total  $\Delta G_t$  would be the sum of the individual increments:

$$\Delta G_t = n_A \Delta G_A + n_B \Delta G_B + n_C \Delta G_C + \dots \quad (1)$$

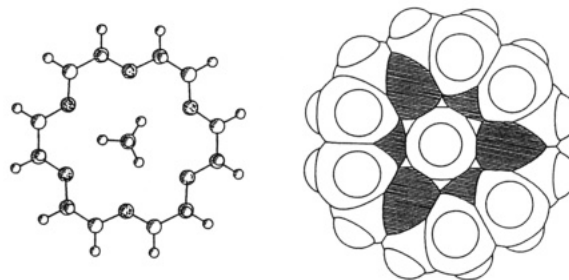
In our earlier analyses we have obtained the individual increments  $\Delta G_A$  etc. directly from the correlations, leading, e.g., to a surprisingly constant value of  $\Delta G = 5 \pm 1$  kJ/mol per single salt bridge in now more than 50 different ion pair complexes,<sup>6</sup> which range from zinc sulfate<sup>6d</sup> to DNA/polyammonium interactions.<sup>6c</sup> In the present analysis of ionophores we choose another approach and set out to use increments for the different binding sites from independent sources.

These increments which should quantify the interaction of a single ligand site and a cation obviously must reflect primarily the ligand electron donor capacity. Such numbers—referring, however, to Lewis base complexes with  $\Delta H$  instead of  $\Delta G$  values—are available from the extensive studies by Gutmann et al.,<sup>7</sup> as well as by Drago et al.,<sup>8</sup> the latter approach being based on three terms accounting for electrostatic, covalent, and CT interactions. In related attempts Abraham, Kamlet, Taft et al. have correlated hydrogen bond complex free energies with acidities and basicities of the components.<sup>9</sup> The Chernogolovka/Moscow group of the present authors, starting from earlier proposals by Iogansen et al.,<sup>10</sup> has derived  $\Delta H$  and  $\Delta G$  increments from a large body of thermodynamic data for single hydrogen bond complexes based on eq 2 which allows to extract electron-withdrawing and -donating energy factors  $C_a$  and  $C_b$  from many 1:1 equilibria in carbon tetrachloride.<sup>11,12</sup>

$$\Delta G_t = 2.43C_a C_b + 5.70 \quad (2)$$

The electron-donating increments to be used for the ionophores, later called ED factors, are listed in Table I; they have been found to represent on a uniform scale the minimum set of parameters for good correlations (coefficients  $r \geq 0.980$  usually) for more than 900 hydrogen bond complexes.<sup>11,12</sup> One incentive of this study was to see whether parameters derived, e.g., from such hydrogen bond complexes in carbontetrachloride,<sup>11,12</sup> are of sufficient fundamental significance for the prediction of ionophore-complex stabilities in protic solvents.

Complexation energies for a large and representative series of ionophores (Scheme I) with alkali metal cations and tentatively also with ammonium ions were assembled



**Figure 1.** Plots for the 18-crown-6/ $+NH_4$  complex from energy-minimized structures, showing the  $D_{3d}$  symmetry. Shaded circles indicate oxygen atoms.

from the literature<sup>2</sup> (Table I\*, supplementary material). Taking into consideration the dependence of the complexation free energy  $\Delta G_t$  also on cation, anion, and ligand desolvation/solvation as well as on the solvent,<sup>2,13</sup> only complexes with the same anion (mostly chloride) and the same solvent (mostly methanol) were used for the correlations. The application of pairwise interaction increments rested until now on the presence of sufficient contacts between the individual binding sites in host and guest.<sup>6</sup> Therefore, the complex structures used in the correlations were checked to meet this condition (e.g., mismatch of distances between metal and ligand atoms  $<20\%$ ), partially on the basis of corresponding X-ray analyses<sup>13</sup> and also partially by molecular modeling with the aid of the CHARMM<sup>14</sup> force field (see below).

Furthermore, it must be shown that the required fit between host and guest is accompanied by strain energy changes of the ionophore which are small compared to the overall complexation energy. Ligand reorganization by induced fit is expected to be particularly important for ionophores which require simultaneous interactions between convergent host functionalities in a crowded environment and an usually small ion. Whereas accommodation of organic molecules in larger host cavities is often characterized by small strain energy variations<sup>15</sup> larger conformational changes in the ligand are more typical for metal complexes<sup>2e</sup> and can be approximated by molecular mechanics calculations.<sup>16</sup> In order to circumvent some of the arbitrariness of the complex energy calculations we apply the following procedure: ligand structures are simulated without ion, as well as after ion complexation; by taking out the ion after obtaining the energy-minimized ligand structure we obtain the ligand strain changes  $\Delta H_L$  accompanying the complexation. The results (Table V\*, supplementary material) indicate that, e.g., 18-crown-6 ( $I, n = 3$ ) builds up strain energies below 1.5 kJ/mol upon complexation of  $Na^+$ ,  $K^+$ , or  $RNH_3^+$ , although a highly symmetrical ( $D_{3d}$ ) structure with very constant  $O \cdots M^+$  distances is observed (Figure 1). With 15-crown-5 ( $I, n = 2$ ) slightly higher strain changes were obtained (Table V\*, supplementary material). Obviously strain changes of, e.g., 2 kJ/mol must lead to  $\Delta G_t$  deviations of corresponding size; they would be as small as approximately  $\pm 10\%$ , e.g., for  $K^+$  + crown ethers, and  $\pm 5\%$  for  $K^+$  + cryptands.

With more than 120 ionophore complexes which meet the above-mentioned criteria and represent the most often used crown ethers and cryptands we now observe gratifying

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Table II. Correlations of Complexation Energies<sup>a</sup>

case	cation	solvent	ligand type	<i>a</i>	<i>b</i>	<i>n</i>	<i>R</i>	SD	<i>F</i>
1	Na <sup>+</sup>	MeOH	all types	-2.40	2.42	35	0.726	8.35	36.8
2			all except large	-6.93	3.24	29	0.947	4.09	234.1
3			R-[15C]+R-[2.2.1]	-17.43	4.64	9	0.993	1.61	493.6
4			R-[12C4]+R-[18C6]+ R-[2.2.2]	-5.43	3.01	20	0.954	3.90	183.7
5			large macrocycles	11.90	0.09	6	0.104	1.70	0.1
6	K <sup>+</sup>	MeOH	all types	13.82	1.24	38	0.473	11.40	10.4
7			R-[18C6]+R-[2.2.2]	1.30	3.25	20	0.993	1.37	1192.0
8			R-[18C6]+R-[2.2.2]	-3.89	0.83	12	0.978	3.34	221.6
9		H <sub>2</sub> O	R-[18C6]+R-[2.2.2]	-11.02	2.43	6	0.994	1.04	318.8
10			R-[15C5]+R-[2.2.1]	-7.44	3.49	7	0.967	3.40	72.6
11		MeOH	R-[12C4]+[2.1.1]	3.86	0.70	5	0.994	0.32	228.0
12			large macrocycles	22.94	-0.01	6	0.050	2.81	0.1
13	Rb <sup>+</sup>	MeOH	all types	2.47	2.13	29	0.748	6.75	34.3
14			all except large mc	-0.24	2.51	22	0.767	7.08	28.6
15			R-[18C6]+R-[2.2.2]	0.70	2.83	13	0.965	2.83	148.2
16			R-[18C6]+R-[2.2.2] R-[15C5]+R-[2.2.1]+ R-[21C7]	-1.66	2.88	19	0.926	4.04	102.4
17			large macrocycles	20.53	0.42	7	0.518	1.56	1.8
18	Cs <sup>+</sup>	MeOH	al types	13.37	0.61	31	0.445	4.46	7.2
19			R-[18C6]	-1.47	2.75	10	0.982	0.52	211.1
20			R-[21C7]+R-[15C5]	-10.36	3.32	6	0.964	2.06	52.5
21			R-[2.2.2]	-44.14	3.90	4	0.881	2.56	7.0
22			large macrocycles	24.49	0.02	8	0.020	2.14	16.1
23	+NH <sub>4</sub> <sup>b</sup>	CDCl <sub>3</sub>	all types	-17.83	6.87	7	0.910	4.35	24.0
24	+NH <sub>4</sub> <sup>b</sup>	D <sub>2</sub> O/satd CDCl <sub>3</sub>	all types	3.80	4.33	8	0.910	8.00	27.8
25	t-Bu <sup>+</sup> NH <sub>3</sub> <sup>c</sup>	CHCl <sub>3</sub>	all types	-3.92	3.78	8	0.943	2.54	48.4

<sup>a</sup> From plots of  $G_t$  (in kJ/mol, see supplementary material, Table I\*) vs  $\sum ED$ , unless noted otherwise. Anion chloride unless noted otherwise: *a*, abscissa; *b*, slope; *n*, number of complexes included in correlation; *R*, linear correlation coefficient; SD, standard deviation in  $G_t$ ; *F*, Fisher<sup>19</sup> parameter. <sup>b</sup> Picrate anion. <sup>c</sup> Isocyanate anions.

linear correlations between the free complexation energy  $\Delta G_t$  and the sum  $\sum ED$  of the contributing binding site increments (Table II, Figure 2, and supplementary material) even if ligands are included which violate the hole-size concept, such as 18C6 or the 222 cryptand (I, VI, respectively, with all R = H) for Na<sup>+</sup> (Table II). We illustrate the calculation with structure VII (compound 55): 4 CH<sub>2</sub>OCH<sub>2</sub> fragments ( $\sum ED = 4(1.7) + 2 R_3N$  fragments (2(3.5) + 2 =CHOCH<sub>2</sub> fragments (2(1.1), total  $\sum ED = 16.0$ ). Closer inspection of correlations observed with single classes reveals the increasing quality of the postulated dependence on  $\sum ED$  with the goodness of the geometric fit between host and guests (Figure 2, containing representative potassium complexes; for others see supplementary material). If all macrocycles including those with unsatisfactory geometric fit are included a poor correlation is found (Figure 2a), particularly with ligands too large for a simultaneous contact of all binding sites to the ion (Figure 2g). Open-chain ligands also deviate substantially (supplementary material) which is rationalized by the considerable strain which must be built up by the bending of the open-chain all-transoid conformation to the cyclic one needed for complexation: the CHARMM calculated strain increase amounts to, e.g., 15 kJ/mol in the case of the pentaglyme-sodium complex (Table V\*, supplementary material).

The cavities of 15C5 and 221 (I, VI, *n* = 2 and *m* = 1, respectively, all R = H) are known to provide almost ideal cavity sizes for Na<sup>+</sup>, as does 18C6 and cryptand 222 (I, VI, *n* = 3 or *n* = *m* = 2, respectively, all R = H) for K<sup>+</sup>, and, to a lesser degree, for Rb<sup>+</sup> and Cs<sup>+</sup>. This is visible in the superior correlations obtained for these classes (Figure 2b,d, Table II, cases 2-4), whereas the 222 cryptand is already too small for Cs<sup>+</sup> (case 19). It is remarkable that ammonium ions also obey the correlations, indicating

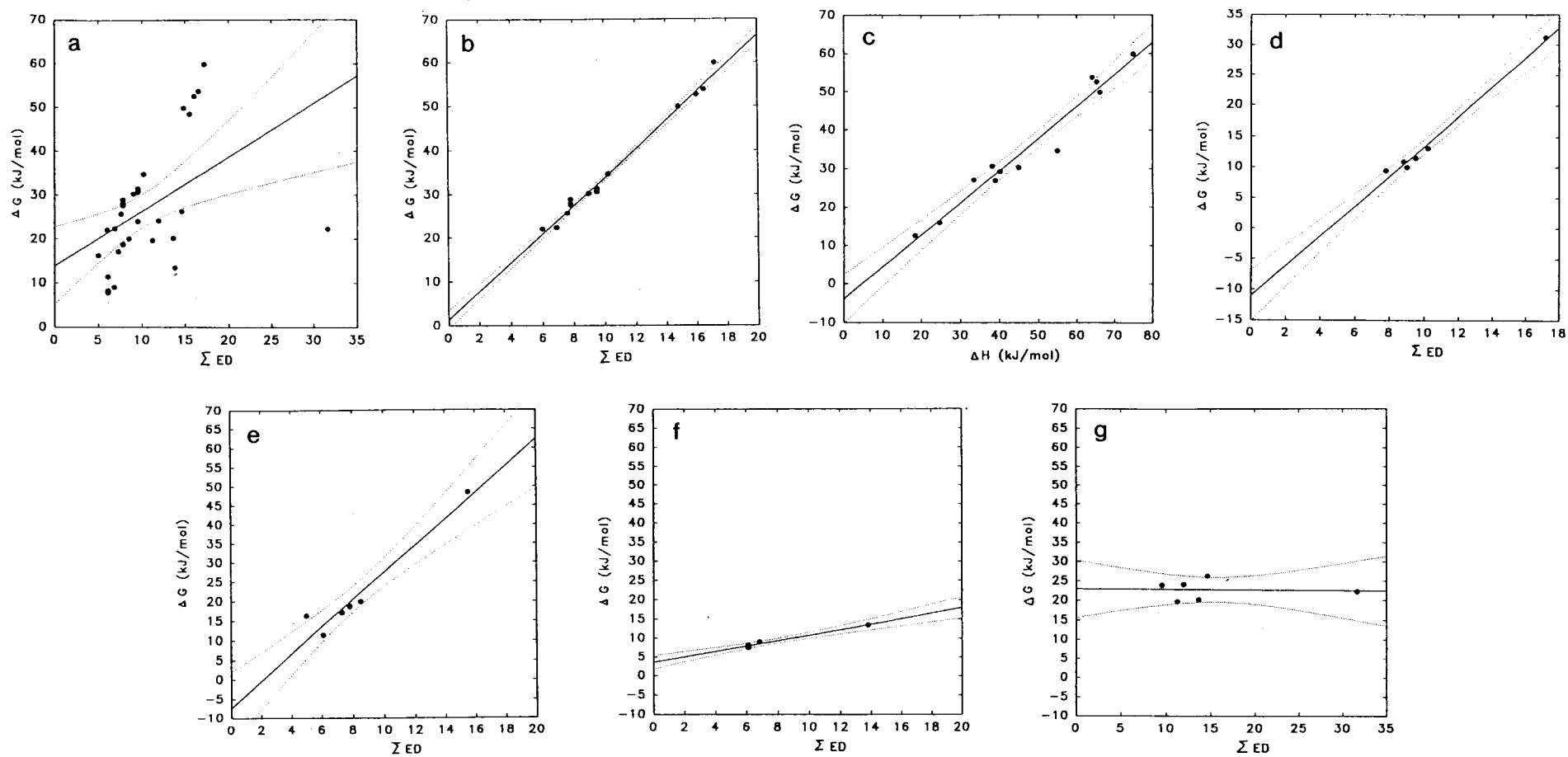
similar binding mechanisms as for the metal ions without large contributions of special hydrogen bond interactions which were assumed until now to play an important role here.<sup>2,5</sup>

In water instead of methanol as solvent we find in the one series for which sufficient data were available again a linear dependence of  $\Delta G_t$  on  $\sum ED$  (case 9 in Table II). The slope *b*, however, is significantly smaller than with methanol. In view of the often large entropy contributions to metal complexations<sup>17</sup> it is of particular interest that in the case of sufficient fit between ligand and cation the available data (Table III) show that the complexation enthalpies  $\Delta H_t$  also depend linearly on  $\sum ED$ , which is of course a consequence of the observed linear  $\Delta H/\Delta G$  correlation observed, however, only in these cases (Figure 2c).

Finally, we address the question of the cation influence on the complexation free energies. From the  $\Delta G_t$  correlations with  $\sum ED$  in the various systems one can derive EA values characterizing now the electron acceptor power of the different cations. It is gratifying, that these EA parameters on the other hand show a linear correlation with known hydration energies of the cations (Figure 3). This now allows us, on the basis of eq 3, to calculate complexation energies for different cations with the whole series of the crown ethers and cryptands as soon as hydration energies, or of course EA values, are known for the ion.

$$\Delta G_t = k_o + 2.43 \sum EA(\sum ED) \quad (3)$$

**Conclusions.** The incremental approach based on the analysis of pairwise interactions allows to our knowledge for the first time a comprehensive and simple evaluation



**Figure 2.** Complexation energy correlations for potassium in methanol (cases 6–12 in Table II): (a) with all ligand types; (b) with 18C6 crown and 221-cryptand derivatives; (c)  $\Delta G$  vs  $\Delta H$  for  $K^+$  with ligands as in b; (d) with ligands as in b, but in water; (e) with 18C5-crown

and 221-cryptand derivatives; (f) with 12C4-crown and 221-cryptand derivatives; (g) with too large macrocycles.

Table III. Electron Acceptor Increments EA<sup>a</sup> for Cations

cation	anion	solvent	EA	k <sub>o</sub>
Na <sup>+</sup>	Cl	CH <sub>3</sub> OH	-1.91	17.43
K <sup>+</sup>	Cl	CH <sub>3</sub> OH	-1.34	-1.30
		H <sub>2</sub> O	-1.00	11.02
		CH <sub>3</sub> OH	-1.16	-0.70
Rb <sup>+</sup>	Cl	CH <sub>3</sub> OH	-1.13	1.47
Cs <sup>+</sup>	Cl	CH <sub>3</sub> OH	-1.13	1.47
NH <sub>4</sub> <sup>+</sup>	picrate	CDCl <sub>3</sub>	-2.83	17.83
		D <sub>2</sub> O	-1.78	-3.80
H <sub>3</sub> N <sup>+</sup> - <i>t</i> -Bu	NCS	CHCl <sub>3</sub>	-1.56	3.92

<sup>a</sup> Obtained from the equation  $\Delta G_t = k_o + 2.43EA(\Sigma ED)$  ( $\Delta G_t$  in (kJ/mol)).

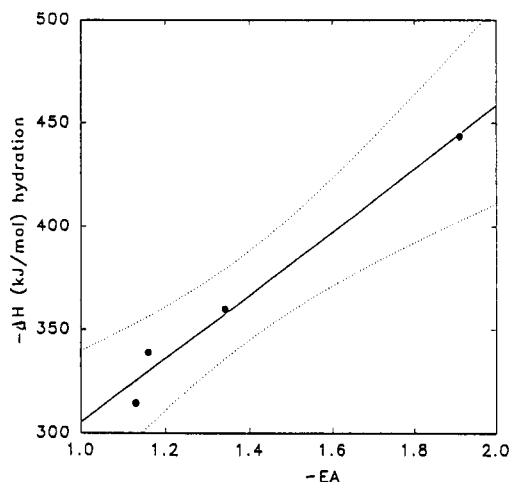


Figure 3. Correlation between free enthalpy of hydration and EA parameters.

of ionophore complexation energies as a function of structure for systems which due to their large charges are particularly difficult to assess by theoretical calculations. Complexation constants with crown ethers and cryptands independent of their size and flexibility become predictable as long as the geometric conditions with respect to negligible mismatch and strain changes are given. The successful use of the ED increments derived from hydrogen bonds in carbontetrachloride demonstrates the vast potential of these empirical factors for the prediction of all kinds of polar noncovalent interactions. It should be stressed that we did not need to treat the increments used as *adjustable* parameters. The results show that substituent effects on the electron donor or acceptor ability of coordination sites are quantitatively described both for hydrogen bonds and cation-ligand interactions in quite different solvents including water on the basis of the same incremental approach. In line with long standing observations<sup>2e,11,12</sup> the variation of electron donor and acceptor can be described by *multiplicative* combination of the independent factors ED and EA, the latter being a direct function of hydration energy. The availability of these increments will in the future allow the design of new ionophores with optimal binding capacities.

As with other LFER these analyses also help to further the understanding of noncovalent binding mechanisms: the observation of a common dependence of binding strength on general parameters ED and EA indicates a common dominating mechanism of mostly electrostatic nature for metal ion, ammonium ion, and hydrogen bond associations. Earlier analyses, based partially on X-ray-derived solid-state structures, have led to the conclusion of significantly different distances and binding contributions, e.g., between the different oxygen host atoms and

the <sup>+</sup>NH guest groups in 18C6,<sup>5,18</sup> with hydrogen bonding contributions assumed to be three times larger than the three electrostatic interactions.<sup>5</sup> Recent MD and MC calculations have even for cryptands emphasized the asymmetry, as well as the special role of solvent induced ligand preorganization in the energy minimized single complex structures.<sup>3c</sup> Our results indicate that these asymmetries which also occur with respect to lone pair orientations and special solvation factors—which are expected to differ, e.g., between crowns and cryptands—are essentially wiped out by time averaging. Also, as consequence of the “soft” geometry dependencies of the dominating electrostatic potentials the asymmetries are of little importance when it comes to the actual performance of these ligands in solution: namely to ion-specific complexation free energies, and—with regard to their selectivity—to the corresponding energy differences. Further efforts toward the extraction of generalizable factors from experimental data will be directed toward the role of anions and solvents, toward the factorization of other binding mechanisms, and toward the quantification of cases with less satisfactory geometric fit. It is hoped that the effectiveness and inherent simplicity of the applied energy partitioning strategy will help to open up the use of free-energy-type correlations for noncovalent bonds in supramolecular structures, including biopolymers.

### Computational Details

Regression analyses were performed with standard programs yielding the statistical criteria such as correlation coefficients R, student factors F, and standard deviations SD besides slopes and abscissas, the latter being close to zero within statistical error in most cases. Experimental data and their sources together with the identification of points used in the correlations are given in the supplementary material.

CHARMm simulations were performed for selected crown ethers using QUANTA, version 3.2 (Polygen /MSI) on Silicon Graphics workstations. In order to obtain realistic strain energy changes for the basic ethylene glycol unit the dielectric constant was set to 3.0 D (constant) with point charges of +1.0 at the cation and -0.36 eu at O,<sup>3a</sup> which furnished for dimethoxyethane a gauche-trans energy difference of  $\Delta H_{\text{strain}} = 1.76$  kJ/mol in acceptable agreement with the literature.<sup>3a</sup> DC values of, e.g., 1.0 D yielded unrealistic  $\Delta H_{\text{strain}}$  differences of 4.8 kJ/mol. The dependence of complex energies and structures on the chosen local densities is illustrated by selected simulations (supplementary material). The overall geometries and symmetries which were partially checked by conformational searches using restricted rotation were in general agreement with the more extensive literature investigations<sup>9</sup> (supplementary material).

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**Supplementary Material Available:** Tables I\*–VI\* (literature data for complexation energies, identification of compounds used in the correlations, selected enthalpy values, and internal coordinates with schematic representations from CHARMm simulations) and Figures 1\*–4\* (complexation energy correlations for Na<sup>+</sup>, Rb<sup>+</sup>, Cs<sup>+</sup>, and NH<sub>4</sub><sup>+</sup> cations) (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) Goldberg, I. In ref 2b, pp 358, 385, 399.

(19) For the Fisher parameter see: Affi, A. A.; Azen, S. P. *Statistical Analysis*; Academic Press: New York, 1979.