# Enthalpy–Entropy Compensation in Complexation of Cations with Crown Ethers and Related Ligands

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Thermodynamic parameters indicate that the enthalpy–entropy compensation effect holds in general for complexation of cations with glymes/podands, crown ethers, cryptands, and macrocyclic antibiotics in various solvents. Thus the $\Delta H$–$T\Delta S$ plots give fairly good linear relationships for each type of ligand, with different slopes ($\alpha$) and intercepts ($T\Delta S_0$) characteristic of the type. The nature of the cation–ligand interaction is discussed in terms of $\alpha$ and $T\Delta S_0$ values.

Largely as a result of the pioneering and extensive work by Izatt and his group,[1–11] a wide variety of thermodynamic parameters are now available to us for the complexation of cations with crown ethers,[1–18] cryptands,[13,19] glymes/podands,[5,13,15,20,21] and macrocyclic antibiotics.[22–25] The general interpretation of these parameters is one of the most fascinating, but difficult, tasks in this area. Both oversimplified and highly sophisticated/specialized rationalizations of the changes in $\Delta H$ and $\Delta S$ values resulting from cation/ligand variations have been made, and many apparently *ad hoc* explanations have been presented. Certain combinations of cations and ligands have been concluded to be enthalpy-favoured and the others entropy-favoured. Either conclusion is conceivable in terms of the specific system discussed, but unfortunately may not be applicable to other systems; furthermore this approach does not appear to promote close understanding of the complexation phenomena.

A more general treatment of this kind has been proposed by Lehn[19] and by Vögtle and Weber.[26] The thermodynamic parameters for complexations are classified in terms of the signs of $\Delta H$ and $\Delta S$, according to whether the values fall within each of the following four categories (the major contributor to $\Delta G$ comes first): (1) $\Delta H < 0$, $\Delta S > 0$, (2) $\Delta H < 0$, $\Delta S < 0$, (3) $\Delta S > 0$, $\Delta H < 0$, and (4) $\Delta S > 0$, $\Delta H > 0$. The first two cases are regarded as enthalpy-stabilized complexes with a minor positive or negative entropic contribution, and the latter two as entropy-stabilized complexes with a minor favourable or unfavourable enthalpic contribution. However this classification seems to lead nowhere in particular. Furthermore the effects of cation/ligand solvation upon $\Delta H$ and $\Delta S$ of complexation are pronounced in most cases.[27] In this context, it may not be essential or even adequate to the general description of the complexation phenomena to discuss the signs of $\Delta H$ and $\Delta S$ separately in order to rationalize the change in log $K$ or $\Delta G$ for a specific cation/ligand/solvent combination.

Izatt *et al.*[2] have shown in a study of the complexation of some metal ions with 15-crown-5 and with 18-crown-6 derivatives that '$\Delta H$ and $\Delta S$ compensate each other with $\Delta H$ being the dominant quantity in determining the magnitude of log $K$.' Michaux and Reisse[16] have recently confirmed similar $\Delta H$–$\Delta S$ compensation upon complexation of alkali cations with 3$m$-crown-$m$ ($m$ = 4—6). These are the results in homogeneous solutions. More recently,[17] we have demonstrated that the solvent extraction of aqueous metal picrates with some crown ethers exhibits an analogous tendency, giving a fairly good linear relationship between $\Delta G$ and $\Delta H$ with $\Delta H$–$\Delta S$ compensation.

However virtually no attempts have been made yet to test the universal validity of this linear $\Delta G$–$\Delta H$ or compensatory $\Delta H$–$\Delta S$ relationship over the wide range of thermodynamic data now available, and to discuss its meaning from either a quantitative or a comprehensive point of view. The purpose of this paper is to assess the scope and limitations of this unique relationship, and to deduce its origin and significance from the available thermodynamic parameters for the complexation of cations with crown ethers and their analogues.

## Results and Discussion

Thermodynamic parameters, $\Delta G$, $\Delta H$, and $T\Delta S$,† for the 1:1 complexation of cations with crown ethers, cryptands, glymes/podands, and antibiotics are compiled in Tables 1—4; those for the 1:2 complexation of cations with some crown ethers are in Table 5. All data were converted to kcal mol$^{-1}$.‡ Sets of parameters not consistent with each other (*i.e.* $\Delta G \neq \Delta H - T\Delta S$), though listed in the Tables, were not employed in the plot/calculation.

For comprehensive understanding of the complexation phenomena, we deal with these data as a whole rather than discuss the signs and magnitudes of the individual parameters. In order to test the enthalpy–entropy compensation effect, $T\Delta S$ values were plotted as a function of the corresponding $\Delta H$ values. As can be seen from Figures 1—5, fair-to-good positive correlations are found between $\Delta H$ and $T\Delta S$ for all types of ligand with 1:1, as well as 1:2, stoicheiometries with most cations. This result is exciting in view of the fact that we have used essentially all the data available to us, and therefore validates the generality of the enthalpy–entropy compensation effect upon complexation. Least-square calculations gave the slope $\alpha$ and the intercept $T\Delta S_0$ for each type of ligand, as listed in Table 6. Only a few combinations of ligand and cation show severe deviations from the regression line. They are: 1,10-dithia-4,7-diaza-15-crown-5 (**7**) with $Cu^{2+}$, 1,10-diaza-18-crown-6 (**14**) with $Hg^{2+}$, [2.2.2]cryptand (**40**) with $Hg^{2+}$, primary diamine (**47**) with $Ag^{+}$ and $Hg^{2+}$, and secondary diamine (**49**) with $Cu^{2+}$ and $Pb^{2+}$. We do not have a conclusive rationale for these exceptions at present. However, it is noteworthy that these ligands all possess two or more nitrogen donor atoms, and the cations are heavy and/or transition metals. We suggest that the combination of polyaza-ligands and some heavy/transition metal ions may form a different type of bond between the nitrogen donor and the cation, which is not the usual ion–dipole interaction but rather covalent in nature. Therefore these data were not employed in the calculation.

† All thermodynamic parameters refer to the standard state (25 °C and 1 atm): $\Delta G$, $\Delta H$, and $\Delta S$ represent $\Delta G°$, $\Delta H°$, and $\Delta S°$, respectively.
‡ 1 cal = 4.18 J.

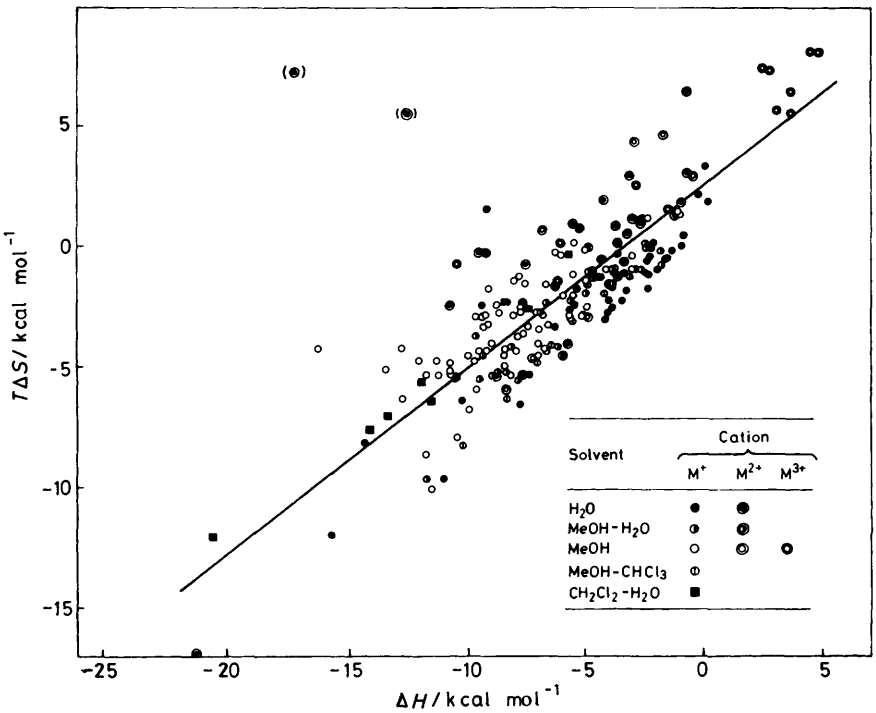



**Figure 1.** Plot of $T\Delta S$ *vs.* $\Delta H$ for 1 : 1 complexation of cations with crown ethers; the deviant plots (in parentheses) were not employed in the calculation

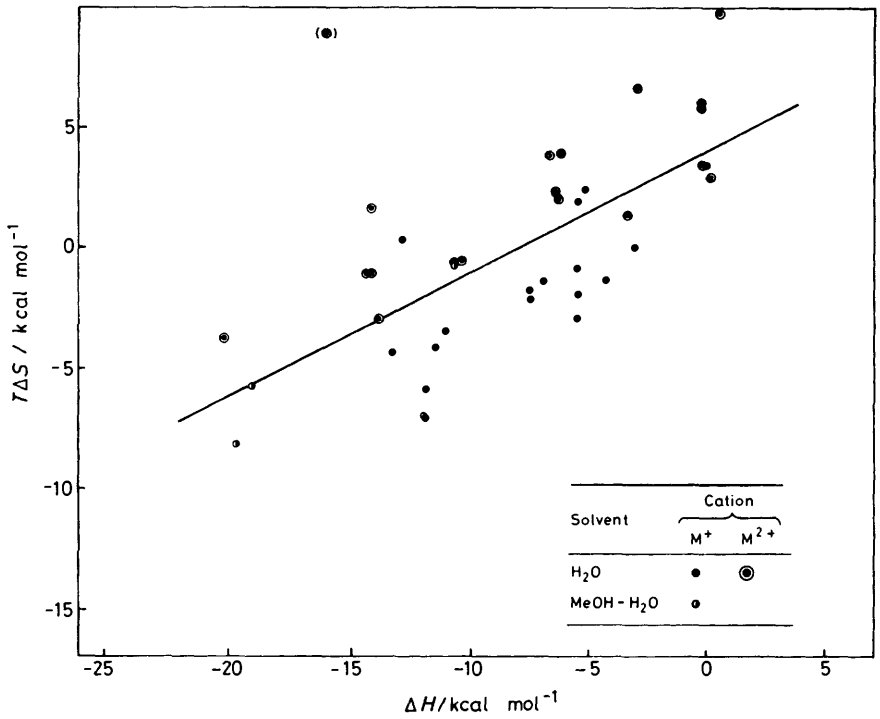



**Figure 2.** Plot of $T\Delta S$ *vs.* $\Delta H$ for 1 : 1 complexation of cations with cryptands; the deviant plots (in parentheses) were not employed in the calculation

The linear relationship between $\Delta H$ and $T\Delta S$ indicates that the change in $T\Delta S$ is proportional to the change in $\Delta H$, which leads to the expression (1). Integration of equation (1) gives (2), where $\alpha$ and $T\Delta S_0$ refer to the slope and intercept of Figures 1—5, respectively. Equation (2) shows that the entropic change consists of two components, one of which is proportional to the enthalpic change and the other independent of it. Insertion of equation (1) in the differential form of the Gibbs–Helmholtz equation (3) gives (4). We now know that the enthalpy–entropy compensation effect is synonymous with enthalpic control of complex stability.

The values obtained for the slope $\alpha$ and the intercept $T\Delta S_0$

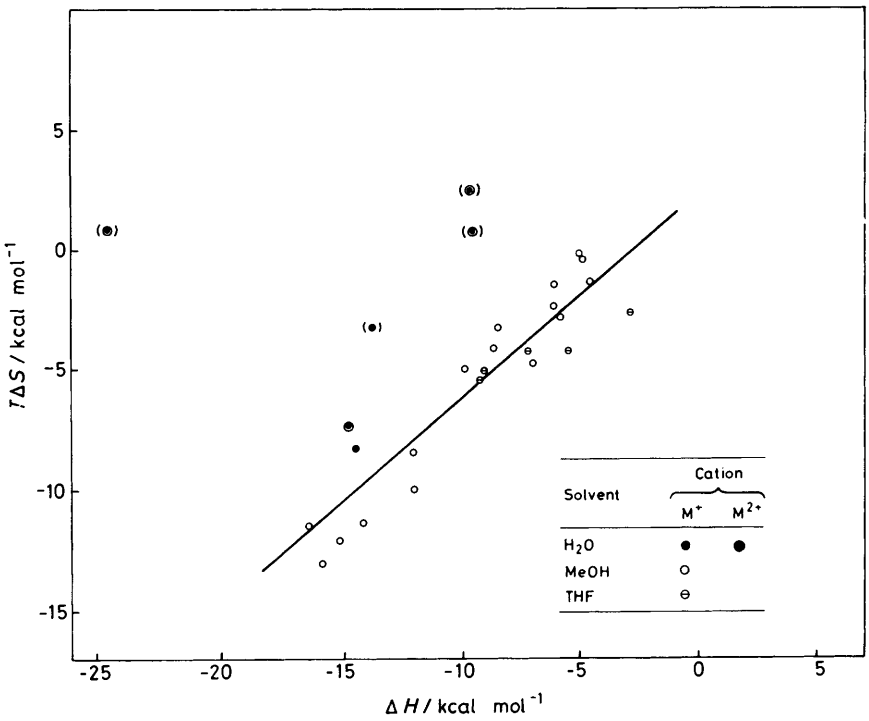



**Figure 3.** Plot of $T\Delta S$ *vs.* $\Delta H$ for 1:1 complexation of cations with glymes and podands; the deviant plots (in parentheses) were not employed in the calculation

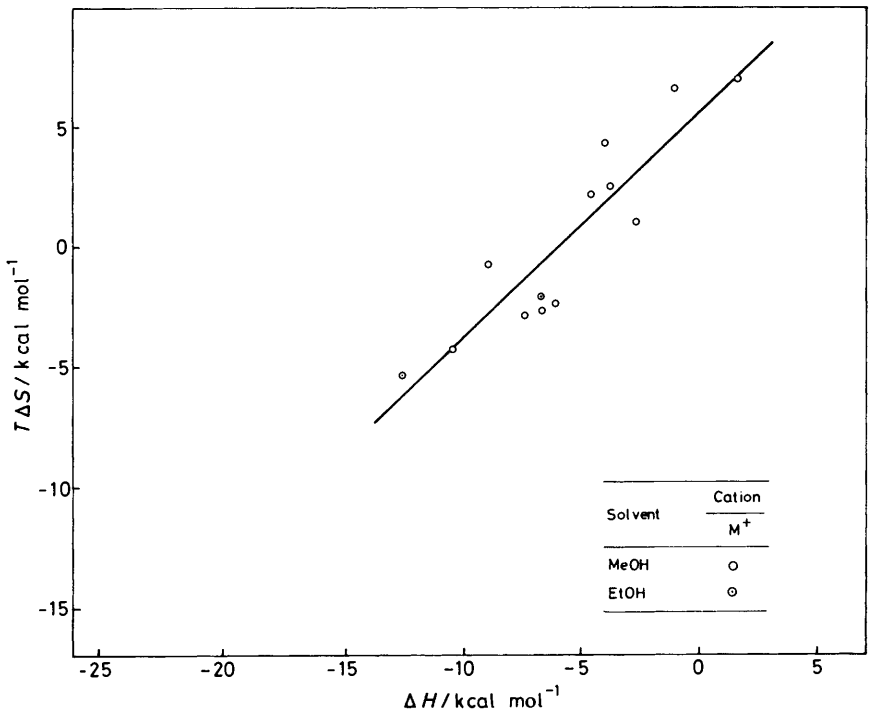



**Figure 4.** Plot of $T\Delta S$ *vs.* $\Delta H$ for 1:1 complexation of cations with antibiotics

$$T\Delta(\Delta S) = \alpha\Delta(\Delta H) \quad (1)$$

$$T\Delta S = \alpha\Delta H + T\Delta S_0 \quad (2)$$

$$\Delta(\Delta G) = \Delta(\Delta H) - T\Delta(\Delta S) \quad (3)$$

$$\Delta(\Delta G) = (1 - \alpha)\Delta(\Delta H) \quad (4)$$

were considered further, in the hope of elucidating the nature of the complexation phenomena. The following observations were made: (1) the slope $\alpha$ shows a marked variation according to the type of ligand; (2) the complex stoicheiometry does not appear to affect the $\alpha$ value; (3) the intercepts $T\Delta S_0$ are all positive, and gradually increase from 2.3 up to 5.6 kcal $mol^{-1}$ in the order: glyme/podand, crown ether, cryptand, antibiotic.

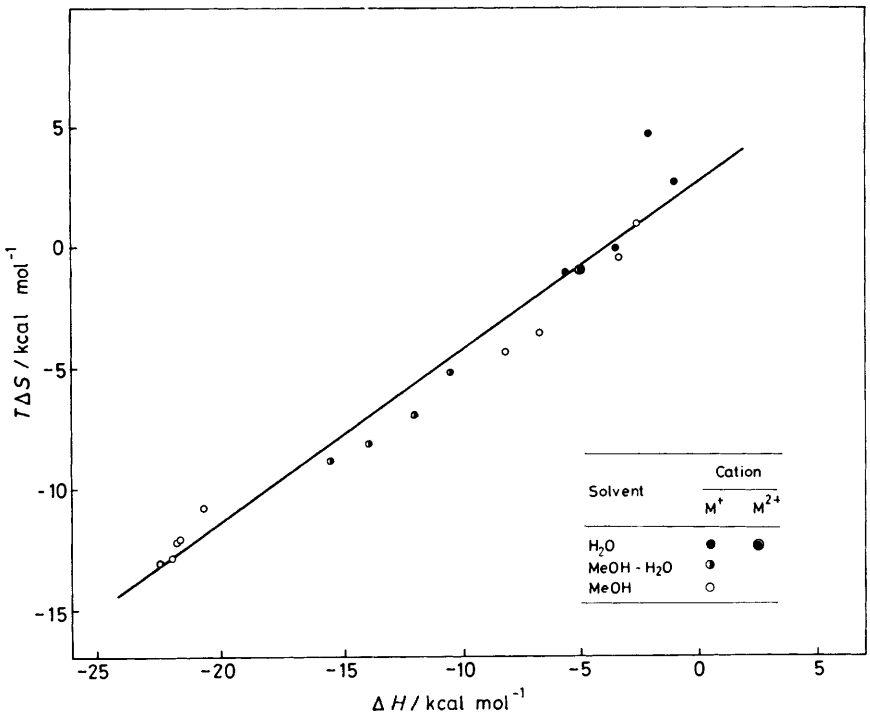
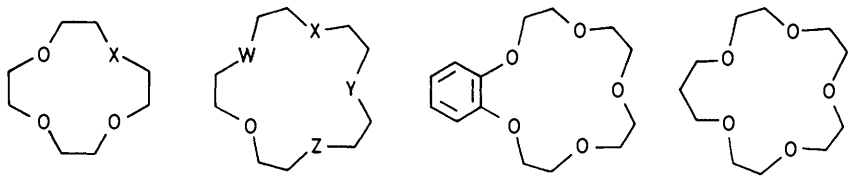



**Figure 5.** Plot of $T\Delta S$ *vs.* $\Delta H$ for 1:2 complexation of cations with crown ethers



(1) X = O
(2) X = S



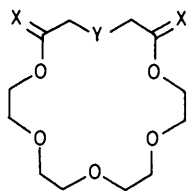
(3) W = X = Y = Z = O
(4) W = X = Y = O, Z = S
(5) W = X = O, Y = Z = S
(6) W = Y = O, X = Z = S
(7) W = Z = S, X = Y = NH



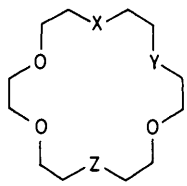
(8)



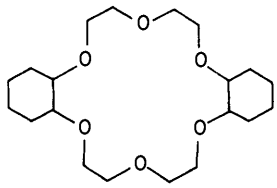
(9)



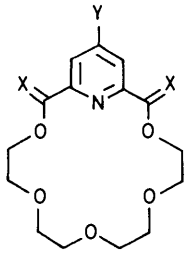
(10) X = $H_2$, Y = O
(11) X = O, Y = O
(12) X = $H_2$, Y = S
(13) X = O, Y = S



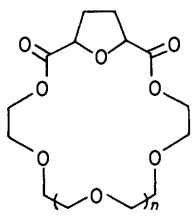
(14) X = Z = NH, Y = O
(15) X = Y = S, Z = O
(16) X = Z = S, Y = O



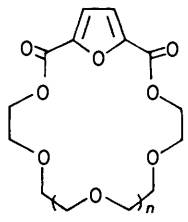
(17) *cis, syn, cis*
(18) *cis, anti, cis*



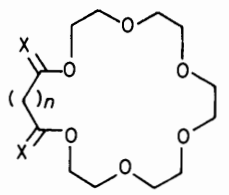
(19) X = $H_2$, Y = H
(20) X = O, Y = H
(21) X = O, Y = Cl



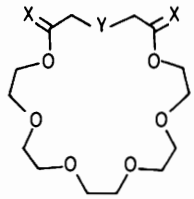
(22) *n* = 1
(31) *n* = 2



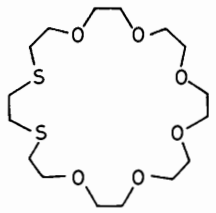
(23) *n* = 1
(32) *n* = 2
(35) *n* = 3



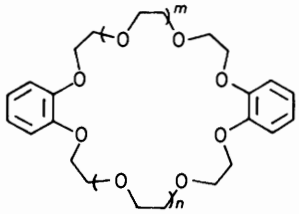
(24) $n$ = 1, X = $H_2$
(25) $n$ = 1, X = O
(26) $n$ = 2, X = O
(27) $n$ = 3, X = O



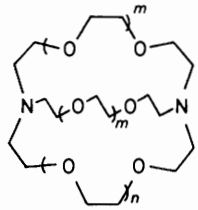
(28) X = $H_2$, Y = O
(29) X = Y = O
(30) X = O, Y = S



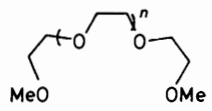
(33)



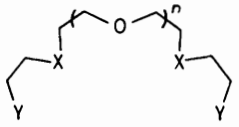
(34) $m$ = $n$ = 1
(36) $m$ = 1, $n$ = 2
(37) $m$ = $n$ = 2



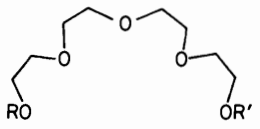
(38) $m$ = 0, $n$ = 1 (40) $m$ = $n$ = 1
(39) $m$ = 1, $n$ = 0 (41) $m$ = 1, $n$ = 2



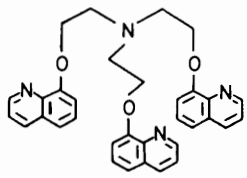
(42) $n$ = 1 (45) $n$ = 4
(43) $n$ = 2 (46) $n$ = 5
(44) $n$ = 3



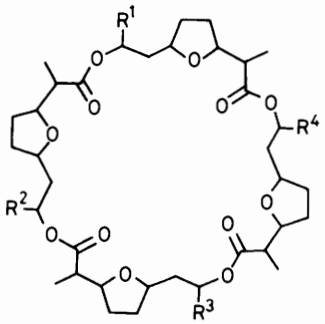
(47) $n$ = 0, X = O, Y = $NH_2$
(48) $n$ = 1, X = O, Y = SMe
(49) $n$ = 1, X = S, Y = NHMe



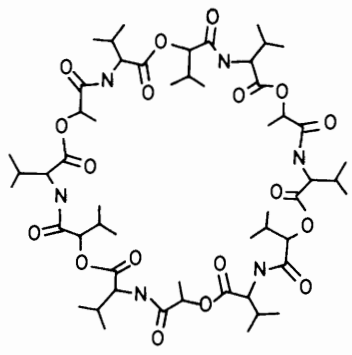
(50) R = R′=
(51) R = R′=
(52) R = R′=
(53) R = Ph, R′=



(54)



(55) $R^1$—$R^4$ = Me
(56) $R^1$—$R^3$ = Me, $R^4$ = Et
(57) $R^1$ = $R^3$ = Me, $R^2$ = $R^4$ = Et
(58) $R^1$ = Me, $R^2$—$R^4$ = Et



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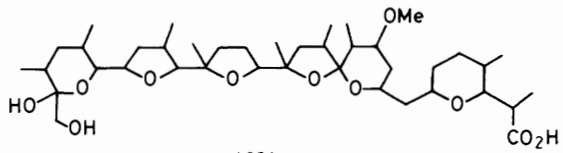

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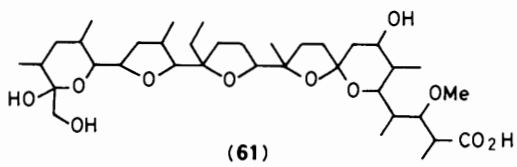

(61)

**Table 1.** Thermodynamic parameters (kcal $mol^{-1}$)[a] for 1:1 complexation of mono-, di-, and tri-valent cations with some crown ethers at 25 °C ($T$ = 298 K)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| 12-Crown-4 (**1**) | MeOH | $Na^+$ | 2.0 | 3.0 | −1.0 | *b* |
| | | $K^+$ | 2.16 | 5.10 | −2.94 | *b* |
| Thia-12-crown-4 (**2**) | $H_2O$ | $Ag^+$ | 3.70 | 10.23 | −6.53 | *c* |
| | | $Pb^{2+}$ | 1.28 | 5.86 | −4.58 | *c* |
| 15-Crown-5 (**3**) | $H_2O$ | $Na^+$ | 0.95 | 1.50 | −0.54 | *d* |
| | | $K^+$ | 1.01 | 4.1 | −3.1 | *d* |
| | | $Rb^+$ | 0.85 | 1.90 | −1.0 | *d* |
| | | $Cs^+$ | 1.1 | 1.3 | −0.2 | *d* |
| | | $Ag^+$ | 1.28 | 3.23 | −1.9 | *d* |
| | | $Tl^+$ | 1.68 | 4.01 | −2.3 | *d* |
| | | $NH_4^+$ | 2.33 | 0.24 | 2.1 | *d* |
| | | $Sr^{2+}$ | 2.66 | 0.9 | 1.8 | *d* |
| | | $Ba^{2+}$ | 2.33 | 1.14 | 1.2 | *d* |
| | | $Pb^{2+}$ | 2.52 | 3.26 | −0.75 | *d* |
| | | $Hg^{2+}$ | 2.29 | 3.6 | −1.2 | *d* |
| | MeOH | $Na^+$ | 4.27 | 5.50 | −1.23 | *b* |
| | | | 4.75 | 4.99 | −0.24 | *e* |
| | | $K^+$ | 4.90 | 7.70 | −2.80 | *b* |
| | | | 5.14 | 7.7 | −2.57 | *e* |
| | | $Cs^+$ | 2.97 | 11.7 | −8.7 | *e* |
| | | $Ag^+$ | 4.94 | 6.58 | −1.64 | *e* |
| | | $Ca^{2+}$ | 2.97 | 1.45 | 1.52 | *e* |
| | | $Sr^{2+}$ | 3.59 | 4.69 | −1.1 | *e* |
| | $CH_2Cl_2$–$H_2O$[f] | $Na^+$ | 6.2 | 13.3 | −7.1 | *g* |
| | | $K^+$ | 6.0 | 8.4 | −2.4 | *g* |
| Thia-15-crown-5 (**4**) | $H_2O$ | $Ag^+$ | 6.8 | 9.37 | −2.5 | *c* |
| | | $Tl^+$ | 1.1 | 7.7 | −6.6 | *c* |
| | | $Pb^{2+}$ | 2.25 | 5.14 | −2.89 | *c* |
| 1,4-Dithia-15-crown-5 (**5**) | $H_2O$ | $Pb^{2+}$ | 1.65 | 5.7 | −4.05 | *c* |
| 1,7-Dithia-15-crown-5 (**6**) | $H_2O$ | $Pb^{2+}$ | 2.21 | 7.6 | −5.39 | *c* |
| 1,10-Dithia-4,7-diaza-15-crown-5 (**7**) | $H_2O$ | $Cu^{2+}$ | 18.06 | 12.54 | 5.52 | *h, i* |
| | | $Pb^{2+}$ | 9.23 | 9.52 | −0.29 | *h* |
| Benzo-15-crown-5 (**8**) | MeOH–$H_2O$ (2:8) | $Na^+$ | 0.98 | 1.77 | −0.77 | *j* |
| | (4:6) | $Na^+$ | 1.60 | 2.63 | −1.04 | *j* |
| | (6:4) | $Na^+$ | 2.24 | 3.78 | −1.55 | *j* |
| | (7:3) | $Na^+$ | 2.71 | 3.82 | −1.10 | *j* |
| | (8:2) | $Na^+$ | 3.08 | 8.32 | −5.24 | *j* |
| | (0:10) | $K^+$ | 0.52 | 2.33 | −1.82 | *j* |
| | (2:8) | $K^+$ | 1.64 | 1.8 | −0.15 | *j* |
| | (4:6) | $K^+$ | 2.62 | 2.51 | 0.12 | *j* |
| | (7:3) | $Cs^+$ | 2.32 | 2.43 | −0.12 | *j* |
| 16-Crown-5 (**9**) | $CH_2Cl_2$–$H_2O$[f] | $Na^+$ | 6.2 | 11.9 | −5.7 | *g* |
| | | $K^+$ | 5.0 | 11.5 | −6.5 | *g* |
| 18-Crown-6 (**10**) | $H_2O$ | $Na^+$ | 1.1 | 2.25 | −1.1 | *d* |
| | | $K^+$ | 2.92 | 5.60 | −2.68 | *b* |
| | | | 2.77 | 6.21 | −3.40 | *d* |
| | | $Rb^+$ | 2.13 | 3.82 | −1.70 | *d* |
| | | $Cs^+$ | 1.35 | 3.79 | −2.41 | *d* |
| | | $Ag^+$ | 2.05 | 2.17 | −0.12 | *d* |
| | | $Tl^+$ | 3.10 | 4.44 | −1.34 | *d* |
| | | | 3.0 | 5.4 | −2.5 | *k* |
| | | $NH_4^+$ | 1.68 | 2.34 | −0.66 | *d* |
| | | $Sr^{2+}$ | 3.71 | 3.61 | 0.09 | *d* |
| | | $Ba^{2+}$ | 5.28 | 7.58 | −2.35 | *d* |
| | | $Pb^{2+}$ | 5.82 | 5.16 | 0.66 | *d* |
| | | | 6.0 | 3.1 | 2.9 | *k* |
| | | $Hg^{2+}$ | 3.30 | 4.69 | −1.40 | *d* |
| | MeOH | $Na^+$ | 5.95 | 7.50 | −1.55 | *b* |
| | | | 5.95 | 8.36 | −2.4 | *e, l* |
| | | $K^+$ | 8.40 | 12.70 | −4.30 | *b* |
| | | | 8.26 | 13.41 | −5.14 | *e* |
| | | $Rb^+$ | 7.25 | 12.09 | −4.83 | *e* |
| | | $Cs^+$ | 6.53 | 11.29 | −4.75 | *e* |
| | | $Ag^+$ | 6.25 | 9.15 | −2.90 | *e* |
| | | $NH_4^+$ | 5.82 | 9.27 | −3.44 | *l* |
| | | $MeNH_3^+$ | 5.80 | 10.71 | −4.91 | *m* |
| | | $EtNH_3^+$ | 5.44 | 10.65 | −5.21 | *m* |
| | | $Pr^nNH_3^+$ | 5.41 | 10.06 | −4.64 | *m* |
| | | $Pr^iNH_3^+$ | 4.85 | 9.65 | −4.79 | *m* |
| | | $Bu^tNH_3^+$ | 3.95 | 7.76 | −3.80 | *m* |

**Table 1** (*continued*)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| | | $PhNH_3^+$ | 5.18 | 9.54 | −4.36 | *m* |
| | | $2\text{-}MeC_6H_4NH_3^+$ | 3.90 | 7.59 | −3.69 | *m* |
| | | $2,6\text{-}Me_2C_6H_3NH_3^+$ | 2.73 | 5.65 | −2.92 | *m* |
| | | $Me_2NH_2^+$ | 2.40 | 6.67 | −4.27 | *m* |
| | | $PhN{\equiv}N^+$ | 3.41 | 8.41 | −5.0 | *n* |
| | | $4\text{-}NO_2C_6H_4N{\equiv}N^+$ | 4.12 | 8.39 | −4.3 | *n* |
| | | $4\text{-}MeOC_6H_4N{\equiv}N^+$ | 2.74 | 8.1 | −5.4 | *n* |
| | | $Ca^{2+}$ | 5.26 | 2.75 | 2.52 | *e* |
| | | $Ba^{2+}$ | 9.60 | 10.41 | −0.80 | *e* |
| | | $La^{3+}$ | 4.49 | −2.81 | 7.30 | *o* |
| | | $Ce^{3+}$ | 4.87 | −2.54 | 7.41 | *o* |
| | | $Pr^{3+}$ | 3.59 | −4.46 | 8.05 | *o* |
| | | $Nd^{3+}$ | 3.33 | −4.77 | 8.10 | *o* |
| | | $Sm^{3+}$ | 2.77 | −3.67 | 6.44 | *o* |
| | | $Eu^{3+}$ | 2.51 | −3.06 | 5.57 | *o* |
| | | $Gd^{3+}$ | 1.80 | −3.73 | 5.53 | *o* |
| | $MeOH\text{–}H_2O$ (9:1) | $1\text{-}Phen\text{-}NH_3^{+}$ [p] | 3.25 | 5.59 | −2.34 | *p* |
| | | $2\text{-}Phen\text{-}NH_3^+$ | 4.15 | 6.86 | −2.71 | *p* |
| | | $3\text{-}Phen\text{-}NH_3^+$ | 4.27 | 6.64 | −2.37 | *p* |
| | | $4\text{-}Phen\text{-}NH_3^+$ | 1.82 | 3.09 | −1.27 | *p* |
| | | $9\text{-}Phen\text{-}NH_3^+$ | 3.04 | 5.01 | −1.97 | *p* |
| | $MeOH\text{–}H_2O$ (7:3) | $Na^+$ | 3.76 | 4.89 | −1.13 | *j* |
| | | $K^+$ | 5.90 | 9.68 | −3.78 | *j* |
| | | $Rb^+$ | 4.72 | 9.27 | −4.56 | *j* |
| | | $Cs^+$ | 3.87 | 8.09 | −4.20 | *j* |
| | | $Ca^{2+}$ | 3.42 | 4.27 | −0.83 | *j* |
| | | $Sr^{2+}$ | 6.8 | 7.49 | −0.75 | *j* |
| | | $Ba^{2+}$ | 8.2 | 10.66 | −2.53 | *j* |
| | | $Pb^{2+}$ | 8.9 | 9.19 | −0.33 | *j* |
| | $CH_2Cl_2\text{–}H_2O$ [f] | $Na^+$ | 5.3 | 5.7 | −0.4 | *g* |
| | | $K^+$ | 8.4 | 20.5 | −12.1 | *g* |
| 2,6-Dioxo-18-crown-6 (**11**) | MeOH | $Na^+$ | 3.41 | 2.27 | 1.14 | *l* |
| | | $K^+$ | 3.80 | 5.87 | −2.06 | *l* |
| | | $Rb^+$ | 2.85 | 6.99 | −4.14 | *l* |
| | | $Ba^{2+}$ | 4.27 | 0.4 | 3.87 | *l* |
| Thia-18-crown-6 (**12**) | MeOH | $Na^+$ | 3.50 | 4.99 | −1.48 | *e* |
| | | $K^+$ | 4.92 | 9.01 | −4.08 | *e* |
| | | $Ba^{2+}$ | 4.6 | 6.1 | −1.5 | *e* |
| 3,17-Dioxothia-18-crown-6 (**13**) | MeOH | $Ag^+$ | 4.16 | 6.97 | −2.81 | *q* |
| 1,10-Diaza-18-crown-6 (**14**) | $H_2O$ | $Ag^+$ | 10.65 | 9.15 | 1.5 | *r* |
| | | $Sr^{2+}$ | 3.5 | 2.6 | 0.9 | *r* |
| | | $Ba^{2+}$ | 4.05 | 3.0 | 1.1 | *r* |
| | | $Hg^{2+}$ | 24.35 | 17.15 | 7.2 | *i*, *r* |
| | | $Cd^{2+}$ | 7.15 | 0.7 | 6.44 | *r* |
| 1,4-Dithia-18-crown-6 (**15**) | $H_2O$ | $Ag^+$ | 4.1 | 15.7 | −12 | *c* |
| | | $Tl^+$ | 1.9 | 7.3 | −5.4 | *c* |
| | | $Pb^{2+}$ | 3.59 | 8.83 | −5.24 | *c* |
| 1,10-Dithia-18-crown-6 (**16**) | $H_2O$ | $Tl^+$ | 1.27 | 11.0 | −9.73 | *c* |
| | | $Pb^{2+}$ | 4.27 | 21.2 | −16.92 | *c* |
| *cis*, *syn*, *cis*-Dicyclohexano-18-crown-6 (**17**) | $H_2O$ | $Na^+$ | 1.65 | −0.16 | 1.82 | *d* |
| | | $K^+$ | 2.75 | 3.88 | −1.13 | *s* |
| | | $Rb^+$ | 2.07 | 3.33 | −1.25 | *s* |
| | | $Cs^+$ | 1.31 | 2.41 | −1.10 | *s* |
| | | $Ag^+$ | 3.22 | −0.07 | 3.28 | *d* |
| | | $Tl^+$ | 3.33 | 3.62 | −0.30 | *d* |
| | | $NH_4^+$ | 1.81 | 2.16 | −0.36 | *s* |
| | | $MeNH_3^+$ | 1.11 | 0.77 | 0.36 | *d* |
| | | $Sr^{2+}$ | 4.42 | 3.68 | 0.75 | *s* |
| | | $Ba^{2+}$ | 4.87 | 4.92 | −0.06 | *s* |
| | | $Pb^{2+}$ | 7.21 | 5.48 | 0.89 | *d* |
| | | $Hg^{2+}$ | 3.75 | 0.71 | 3.04 | *d* |
| *cis*, *anti*, *cis*-Dicyclohexano-18-crown-6 (**18**) | $H_2O$ | $Na^+$ | 0.94 | 1.57 | −0.63 | *d* |
| | | $K^+$ | 2.22 | 5.07 | −2.86 | *s* |
| | | $Rb^+$ | 1.19 | 3.97 | −2.77 | *s* |
| | | $Ag^+$ | 2.17 | 2.09 | 0.08 | *s* |
| | | $Tl^+$ | 2.50 | 4.29 | −1.79 | *d* |
| | | $NH_4^+$ | 1.09 | 3.41 | −2.32 | *s* |
| | | $MeNH_3^+$ | 0.90 | 0.90 | 0.0 | *d* |
| | | $Sr^{2+}$ | 3.60 | 3.16 | 0.45 | *s* |
| | | $Ba^{2+}$ | 4.46 | 6.20 | −1.73 | *s* |
| | | $Pb^{2+}$ | 6.04 | 4.21 | 1.85 | *d* |
| | | $Hg^{2+}$ | 3.55 | 2.55 | 0.98 | *d* |

**Table 1** (*continued*)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| Pyridino-18-crown-6 (**19**) | MeOH | $Na^+$ | 5.58 | 5.44 | 0.14 | *e* |
| | | $K^+$ | 7.30 | 9.11 | −1.81 | *e* |
| | | $Rb^+$ | 6.22 | 8.72 | −2.50 | *e, l* |
| | | $Cu^{2+}$ | 7.17 | 2.90 | 4.3 | *e* |
| | | $Ca^{2+}$ | 6.31 | 1.68 | 4.64 | *e* |
| 3,17-Dioxopyridino-18-crown-6 (**20**) | MeOH | $Na^+$ | 5.85 | 6.19 | −0.34 | *l* |
| | | $K^+$ | 6.35 | 9.3 | −3.0 | *l* |
| | | $Rb^+$ | 5.78 | 9.07 | −3.3 | *l* |
| | | $Ag^+$ | 6.65 | 7.83 | −1.17 | *l* |
| | | $NH_4^+$ | 4.00 | 7.75 | −3.8 | *l* |
| | | $Ba^{2+}$ | 5.92 | 6.03 | −0.11 | *l* |
| 3,17-Dioxo-4-chloropyridino-18-crown-6 (**21**) | MeOH | $Na^+$ | 5.65 | 6.03 | −0.4 | *l* |
| | | $K^+$ | 6.45 | 7.97 | −1.5 | *l* |
| | | $Rb^+$ | 4.85 | 9.23 | −4.4 | *l* |
| | | $Ag^+$ | 5.13 | 8.04 | −2.9 | *l* |
| | | $NH_4^+$ | 3.90 | 6.78 | −2.9 | *l* |
| 3,17-Dioxotetrahydrofurano-18-crown-6 (**22**) | MeOH | $Na^+$ | 3.12 | 4.4 | −1.28 | *t* |
| | | $K^+$ | 3.80 | 8.4 | −4.6 | *t* |
| | | $Sr^{2+}$ | 2.39 | 4 | −1.6 | *t* |
| 3,17-Dioxofurano-18-crown-6 (**23**) | MeOH–$CHCl_3$ (1:1) | $NH_4^+$ | 2.20 | 6.4 | −4.2 | *t* |
| | | $MeNH_3^+$ | 1.53 | 7.0 | −4.9 | *t* |
| 19-Crown-6 (**24**) | $CH_2Cl_2$–$H_2O$[f] | $Na^+$ | 4.7 | 7.4 | −2.7 | *g* |
| | | $K^+$ | 6.4 | 14.1 | −7.7 | *g* |
| 17,19-Dioxo-19-crown-6 (**25**) | MeOH | $Na^+$ | 2.5 | 1.1 | 1.4 | *q* |
| | | $K^+$ | 3.48 | 7.91 | −4.43 | *q* |
| | | $Ba^{2+}$ | 1.92 | 4.88 | −3.0 | *q* |
| 17,20-Dioxo-20-crown-6 (**26**) | MeOH | $Na^+$ | 2.3 | 1.0 | 1.3 | *q* |
| | | $K^+$ | 2.65 | 5.6 | −3.0 | *q* |
| | | $Rb^+$ | 2.37 | 7.0 | −4.6 | *q* |
| 17,21-Dioxo-21-crown-6 (**27**) | MeOH | $K^+$ | 2.33 | 4.9 | −2.6 | *q* |
| | | $Rb^+$ | 2.22 | 6.6 | −4.4 | *q* |
| | | $Cs^+$ | 1.39 | 11.5 | −10.1 | *q* |
| 21-Crown-7 (**28**) | MeOH | $Na^+$ | 2.36 | 10.37 | −8.0 | *e* |
| | | $K^+$ | 5.75 | 8.59 | −2.83 | *e* |
| | | $Rb^+$ | 6.63 | 9.66 | −3.03 | *e* |
| | | $Cs^+$ | 6.83 | 11.18 | −4.34 | *e* |
| | | $Ag^+$ | 3.35 | 6.9 | −3.5 | *e* |
| | | $Sr^{2+}$ | 2.41 | 7.10 | −4.69 | *e* |
| | | $Ba^{2+}$ | 7.42 | 6.81 | 0.61 | *e* |
| 2,6-Dioxo-21-crown-7 (**29**) | MeOH | $K^+$ | 3.16 | 6.46 | −3.29 | *q* |
| | | $Rb^+$ | 3.10 | 9.86 | −6.76 | *q* |
| | | $Ba^{2+}$ | 2.36 | 8.34 | −5.98 | *q* |
| 3,20-Dioxothia-21-crown-7 (**30**) | MeOH | $K^+$ | 2.85 | 3.84 | −0.99 | *q* |
| | | $Rb^+$ | 3.44 | 5.49 | −2.05 | *q* |
| | | $Cs^+$ | 2.60 | 3.03 | −0.42 | *q* |
| 3,20-Dioxotetrahydrofurano-21-crown-7 (**31**) | MeOH | $K^+$ | 4.13 | 7.4 | −3.3 | *t* |
| | | $Cs^+$ | 3.60 | 9.6 | −6.0 | *t* |
| 3,20-Dioxofurano-21-crown-7 (**32**) | MeOH–$CHCl_3$ (1:1) | $NH_4^+$ | 3.42 | 4.9 | −1.6 | *t* |
| | | $MeNH_3^+$ | 2.40 | 5.5 | −3.1 | *t* |
| | | $PhCH_2NH_3^+$ | 1.85 | 8.3 | −6.4 | *t* |
| 1,4-Dithia-24-crown-8 (**33**) | $H_2O$ | $Ag^+$ | 6.1 | 14.3 | −8.2 | *c* |
| Dibenzo-24-crown-8 (**34**) | MeOH–$H_2O$ (7:3) | $Na^+$ | 2.10 | 7.75 | −5.63 | *j* |
| | | $K^+$ | 3.30 | 8.54 | −5.24 | *j* |
| | | $Rb^+$ | 3.48 | 8.72 | −5.24 | *j* |
| | | $Cs^+$ | 3.38 | 8.93 | −5.54 | *j* |
| 3,23-Dioxofurano-24-crown-8 (**35**) | MeOH–$CHCl_3$ (1:1) | $NH_4^+$ | 1.76 | 2.8 | −1.0 | *t* |
| | | $MeNH_3^+$ | 2.18 | 4.2 | −2.0 | *t* |
| | | $PhCH_2NH_3^+$ | 1.91 | 10.2 | −8.3 | *t* |
| Dibenzo-27-crown-9 (**36**) | MeOH–$H_2O$ (7:3) | $Na^+$ | 2.05 | 11.74 | −9.69 | *j* |
| | | $K^+$ | 3.90 | 9.50 | −5.60 | *j* |
| | | $Cs^+$ | 1.94 | 6.14 | −4.20 | *j* |
| Dibenzo-30-crown-10 (**37**) | MeOH | $Na^+$ | 2.9 | 4.1 | −1.0 | *u* |
| | | $K^+$ | 6.2 | 11.7 | −5.3 | *u* |
| | | $Rb^+$ | 6.2 | 12.7 | −6.4 | *u* |
| | | $Cs^+$ | 5.7 | 11.2 | −5.4 | *u* |

[a] 1 cal = 4.18 J. [b] Ref. 16. [c] Ref. 5. [d] Ref. 2. [e] Ref. 8. [f] Determined by solvent-extraction studies with metal picrates. [g] Ref. 17. [h] Ref. 15. [i] These values were not employed in the calculation because of the extreme deviation from the regression line; see text. [j] Ref. 3. [k] Ref. 14. [l] Ref. 7. [m] Ref. 6. [n] Ref. 10. [o] Ref. 4. [p] Calculated from the data presented in ref. 18; Phen = phenanthryl. [q] Ref. 9. [r] Ref. 13. [s] Ref. 1. [t] Ref. 11. [u] Ref. 12.

**Table 2.** Thermodynamic parameters (kcal mol$^{-1}$) for 1:1 complexation of mono- and di-valent cations with some cryptands at 25 °C ($T$ = 298 K)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| [2.1.1]Cryptand (**38**) | $H_2O$ | $Li^+$ | 7.5 | 5.1 | 2.4 | *a* |
| | | $Na^+$ | 4.5 | 5.4 | −0.9 | *a* |
| | | $Ca^{2+}$ | 3.4 | 0.1 | 3.3 | *a* |
| [2.2.1]Cryptand (**39**) | $H_2O$ | $Li^+$ | 3.4 | 0.0 | 3.4 | *a* |
| | | $Na^+$ | 7.2 | 5.35 | 1.85 | *a* |
| | | $K^+$ | 5.4 | 6.8 | −1.4 | *a* |
| | | $Rb^+$ | 3.45 | 5.4 | −1.95 | *a* |
| | | $Ca^{2+}$ | 9.5 | 2.9 | 6.6 | *a* |
| | | $Sr^{2+}$ | 10.0 | 6.1 | 3.9 | *a* |
| | | $Ba^{2+}$ | 8.6 | 6.3 | 2.3 | *a* |
| [2.2.2]Cryptand (**40**) | $H_2O$ | $Na^+$ | 5.3 | 7.4 | −2.1 | *a* |
| | | | 5.6 | 7.4 | −1.8 | *b* |
| | | $K^+$ | 7.2 | 11.4 | −4.2 | *a* |
| | | | 7.61 | 11.0 | −3.43 | *b* |
| | | $Rb^+$ | 5.9 | 11.8 | −5.9 | *a* |
| | | | 5.54 | 11.8 | −6.63 | *b* |
| | | $Ag^+$ | 13.1 | 12.8 | 0.3 | *b* |
| | | $Tl^+$ | 8.84 | 13.2 | −4.4 | *b* |
| | | $Ca^{2+}$ | 6 | 0.2 | 5.8 | *a* |
| | | | 6.23 | 0.2 | 6.02 | *b* |
| | | $Sr^{2+}$ | 10.9 | 10.3 | 0.6 | *a* |
| | | | 11.27 | 10.6 | 0.66 | *b* |
| | | $Ba^{2+}$ | 12.9 | 14.1 | −1.2 | *a* |
| | | | 13.23 | 14.3 | −1.1 | *b* |
| | | $Hg^{2+}$ | 24.85 | 15.95 | 8.9 | *b*, *c* |
| | | $Cd^{2+}$ | 9.28 | −0.5 | 9.80 | *b* |
| | | $Pb^{2+}$ | 16.86 | 13.8 | 3.01 | *b* |
| | MeOH–$H_2O$ (19:1) | $Na^+$ | 9.82 | 10.6 | −0.78 | *a* |
| | | $K^+$ | 13.27 | 19.0 | −5.73 | *a* |
| | | $Rb^+$ | 11.44 | 19.6 | −8.16 | *a* |
| | | $Cs^+$ | 4.82 | 11.9 | −7.08 | *a* |
| | | $Ca^{2+}$ | 10.35 | 6.6 | 3.75 | *a* |
| | | $Sr^{2+}$ | 15.66 | 14.1 | 1.56 | *a* |
| | | $Ba^{2+}$ | 16.3 | 20.1 | −3.8 | *a* |
| [3.2.2]Cryptand (**41**) | $H_2O$ | $K^+$ | 3.0 | 3 | 0 | *a* |
| | | $Rb^+$ | 2.8 | 4.2 | −1.4 | *a* |
| | | $Cs^+$ | 2.45 | 5.4 | −3 | *a* |
| | | $Ca^{2+}$ | 2.7 | −0.16 | 2.86 | *a* |
| | | $Sr^{2+}$ | 4.6 | 3.3 | 1.3 | *a* |
| | | $Ba^{2+}$ | 8.2 | 6.2 | 2 | *a* |

[a] Ref. 19. [b] Ref. 13. [c] These values were not employed in the calculation because of the extreme deviation from the regression line; see text.

The origin of the compensation effect is not entirely clear; it is not always attributable to a single cause, since the thermodynamic parameters are governed by several factors. However sometimes the enthalpy–entropy compensation is not unrealistic. For example, it is likely that, as the cation–ligand binding becomes stronger (as a result of changing the number or type of donor atoms), the degree of freedom of the complex is inevitably reduced, owing to increased rigidity of structure. The consequent negative change in $T\Delta S$ will then cancel at least part of the enthalpic gain from stronger binding. In the reverse situation, an enthalpic loss from looser binding is partially compensated by a simultaneous positive change in $T\Delta S$ due to the greater degree of freedom. Consequently the overall change in complex stability ($\Delta G$) tends to be smaller than might be expected from the change in either $\Delta H$ or $T\Delta S$ separately.

As can be seen from equation (1), the $\alpha$ value is a quantitative measure of the extent of this entropic cancelling effect. The finding that each type of ligand has a distinct $\alpha$ value is important. Formally the $\alpha$ value means that only a proportion (14, 24, 49, or 5%) of the increment in $\Delta H$ contributes to raise the complex stability ($\Delta G$) of glyme/podand, crown ether, cryptand, or antibiotic, respectively. It is interesting and unexpected that, in spite of the highly complicated and functionalized structure, the antibiotic ligands possess minimal additional stability ($\Delta G$), *i.e.* only 5% of the $\Delta H$ increment, which is smaller even than that for glymes/podands. With the exception of antibiotics, the unfavourable entropic contribution, as measured by the $\alpha$ values, decreases in the order acyclic, monocyclic, bicyclic ligand. This trend probably arises from the differences in preorganization and/or preorientation of the binding sites in a ligand molecule. An acyclic ligand has to reduce its degrees of freedom to a great extent when it forms the cyclic structure required for complexation, whereas a cyclic structure is already present in a monocyclic ligand (crown ether).[26–28] A monocyclic ligand in turn has a disadvantage as compared with a bicyclic ligand, which has preorganized and preorientated binding sites with a suitable spatial arrangement. The 'cyclic' and 'bicyclic' effects[26–28] upon complex stabilization may be interpreted in terms of the $\alpha$ value.

The solvation factor may also be important: upon complexation substantial change must occur in the first solvation shells of both cation and ligand.[26–28] In general the complexation of a cation with a ligand is accomplished by replacing most of the cation solvation by the donor atoms of ligand. In this context it is interesting that the intercepts ($T\Delta S_0$) of Figures 1—5 are all positive and are characteristic of the type of ligand. This positive $T\Delta S_0$ value means that, even in the absence of enthalpic gain ($\Delta H$ = 0), complex formation can take place in

**Table 3.** Thermodynamic parameters (kcal mol$^{-1}$) for 1:1 complexation of monovalent cations with some glymes and podands at 25 °C ($T$ = 298 K)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| Triglyme (**42**) | THF | $Na^+$ | 0.1 | 2.8 | −2.7 | *a* |
| Tetraglyme (**43**) | THF | $Na^+$ | 1.1 | 5.4 | −4.3 | *a* |
| Pentaglyme (**44**) | THF | $Na^+$ | 2.9 | 7.1 | −4.2 | *a* |
| Hexaglyme (**45**) | THF | $Na^+$ | 3.7 | 9.2 | −5.5 | *a* |
| Heptaglyme (**46**) | THF | $Na^+$ | 3.9 | 9.0 | −5.1 | *a* |
| (**47**) | $H_2O$ | $Ag^+$ | 10.5 | 13.75 | −3.25 | *b, c* |
| | | $Hg^{2+}$ | 25.3 | 24.5 | 0.8 | *b, c* |
| (**48**) | $H_2O$ | $Ag^+$ | 6.08 | 14.37 | −8.28 | *d* |
| | | $Hg^{2+}$ | 7.2 | 14.65 | −7.4 | *d* |
| (**49**) | $H_2O$ | $Cu^{2+}$ | 12.48 | 9.56 | 2.71 | *c, e* |
| | | $Pb^{2+}$ | 10.21 | 9.54 | 0.67 | *c, e* |
| (**50**) | MeOH | $Li^+$ | 3.20 | 15.1 | −12.1 | *f* |
| | | $Na^+$ | 4.40 | 8.6 | −4.2 | *f* |
| | | $K^+$ | 4.80 | 5.0 | −0.2 | *f* |
| | | $Rb^+$ | 4.21 | 4.8 | −0.5 | *f* |
| | | $Cs^+$ | 3.6 | 6.0 | −2.4 | *f* |
| (**51**) | MeOH | $K^+$ | 2.2 | 6.9 | −4.8 | *f* |
| (**52**) | MeOH | $Li^+$ | 4.71 | 9.80 | −4.99 | *f* |
| | | $Na^+$ | 4.71 | 16.3 | −11.4 | *f* |
| | | $K^+$ | 4.80 | 7.96 | −1.57 | *f, g* |
| | | $Rb^+$ | 4.40 | 6.00 | −1.64 | *f* |
| | | $Cs^+$ | 2.63 | 5.74 | −2.85 | *f* |
| (**53**) | MeOH | $K^+$ | 2.51 | 14.1 | −11.4 | *f* |
| (**54**) | MeOH | $Li^+$ | 3.11 | 4.54 | −1.4 | *f* |
| | | $Na^+$ | 5.00 | 8.37 | −3.3 | *f* |
| | | $K^+$ | 3.49 | 12.0 | −8.5 | *f* |
| | | $Rb^+$ | 2.80 | 15.8 | −13.1 | *f* |
| | | $Cs^+$ | 2.10 | 12.0 | −10.0 | *f* |

[a] Ref. 20. [b] Ref. 13. [c] These values were not employed in the calculation because of the extreme deviation from the regression line. [d] Ref. 5. [e] Ref. 15. [f] Ref. 21. [g] These values were not employed in the calculation/plot, since $\Delta G \neq \Delta H - T\Delta S$.

**Table 4.** Thermodynamic parameters (kcal mol$^{-1}$) for 1:1 complexation of monovalent cations with some antibiotics at 25 °C ($T$ = 298 K)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| Nonactin (**55**) | MeOH | $Na^+$ | 3.70 | 2.65 | 1.04 | *a* |
| | | $K^+$ | 6.12 | 10.4 | −4.29 | *a* |
| | EtOH | $Na^+$ | 4.47 | 6.55 | −2.09 | *a* |
| | | $K^+$ | 7.17 | 12.48 | −5.30 | *a* |
| Monactin (**56**) | MeOH | $Na^+$ | 3.54 | 6.00 | −2.4 | *a* |
| Dinactin (**57**) | MeOH | $Na^+$ | 3.94 | 6.60 | −2.6 | *a* |
| Trinactin (**58**) | MeOH | $Na^+$ | 4.37 | 7.29 | −2.9 | *a* |
| Valinomycin (**59**) | MeOH | $K^+$ | 6.68 | 4.54 | 2.15 | *b* |
| | EtOH | $K^+$ | 8.2 | 8.9 | −0.64 | *c* |
| Nigericin (**60**) | MeOH | $Na^+$ | 5.31 | −1.7 | 7.0 | *d* |
| | | $K^+$ | 7.65 | 0.98 | 6.6 | *d* |
| Monensin (**61**) | MeOH | $Na^+$ | 8.20 | 3.89 | 4.3 | *d* |
| | | $K^+$ | 6.21 | 3.73 | 2.5 | *d* |

[a] Ref. 24. [b] Ref. 25. [c] Ref. 22. [d] Ref. 23.

view of the positive entropic contribution ($T\Delta S_0 > 0$). This kind of situation may be achieved when a small enthalpic gain from weak cation–ligand binding is offset by the desolvation energy, while some positive entropic gain originating from the greater degree of freedom due to the desolvation still remains. This is indeed the case with some combinations of cations and ligands, where the complex stability originates exclusively from the positive entropic gain, and the enthalpic change is negligible or even positive; see Figures for plots in the area: $\Delta H \geqslant 0$ and $T\Delta S \geqslant 0$. The foregoing discussion suggests that the positive and characteristic $T\Delta S_0$ value is the intrinsic entropic gain upon complexation for each ligand, which is mostly attributable to the desolvation of the complexed cation. This intrinsic entropic gain indicates to what extent the cation solvation is replaced by the ligand donors. It is therefore reasonable that glymes/podands and crown ethers give similar $T\Delta S_0$ values around 2.4 kcal mol$^{-1}$, since desolvation by these ligands is not thorough and may well be similar. On the other hand, cryptands give a higher intrinsic entropic gain ($T\Delta S_0$) of 4.0 kcal mol$^{-1}$, which is probably attributable to extensive desolvation by three-dimensional complexation. In the same context, antibiotics are known to change their conformation greatly to accommodate cations in the three-dimensional hydrophilic cavity with complete desolvation; the highest $T\Delta S_0$ value of 5.6 kcal mol$^{-1}$ may well be attributable to this. In contrast with the similarity to cryptand in the $T\Delta S_0$ value, the $\alpha$ value for antibiotics is much closer to that for acyclic ligands. Since the three-dimensional cavity of the antibiotic is not inherent and sensitive to the size of cation accommodated, most enthalpic gain attained by stronger binding is lost through the accompanying conformational change upon fitting the cavity to the size of cation. It may be concluded that the high ability of antibiotics as

**Table 5.** Thermodynamic parameters (kcal mol$^{-1}$) for 1:2 complexation of mono- and di-valent cations with some crown ethers at 25 °C ($T$ = 298 K)

| Ligand | Solvent | Cation | $-\Delta G$ | $-\Delta H$ | $T\Delta S$ | Ref. |
|---|---|---|---|---|---|---|
| 12-Crown-4 (**1**) | MeOH | $Na^+$ | 3.11 | 6.7 | −3.6 | *a* |
| Thia-12-crown-4 (**2**) | MeOH–$H_2O$ (7:3) | $Ag^+$ | 5.02 | 10.54 | −5.52 | *b* |
| 15-Crown-5 (**3**) | MeOH | $K^+$ | 3.70 | 8.1 | −4.4 | *c* |
| Thia-15-crown-5 (**4**) | $H_2O$ | $Ag^+$ | 3.34 | 3.47 | −0.13 | *b* |
| 1,4-Dithia-15-crown-5 (**5**) | $H_2O$ | $Ag^+$ | 4.51 | 5.6 | −1.08 | *b* |
| 1,7-Dithia-15-crown-5 (**6**) | $H_2O$ | $Ag^+$ | 3.7 | 1.0 | 2.7 | *b* |
| | | $Hg^{2+}$ | 3.97 | 5.0 | −1.03 | *b* |
| Benzo-15-crown-5 (**8**) | MeOH–$H_2O$ (7:3) | $K^+$ | 5.66 | 13.9 | −8.22 | *d* |
| | (8:2) | $K^+$ | 6.55 | 15.5 | −8.94 | *d* |
| | MeOH–$H_2O$ (7:3) | $Rb^+$ | 5.14 | 12.0 | −7.0 | *d* |
| 18-Crown-6 (**10**) | MeOH | $Cs^+$ | 2.81 | 3.32 | −0.51 | *c* |
| | | $H_3N^+[CH_2]_2NH_3^+$ | 9.27 | 22.4 | −13.1 | *e* |
| | | $H_3N^+[CH_2]_3NH_3^+$ | 9.53 | 21.6 | −12.1 | *e* |
| | | $H_3N^+[CH_2]_4NH_3^+$ | 9.52 | 21.7 | −12.2 | *e* |
| | | $H_3N^+[CH_2]_5NH_3^+$ | 9.00 | 21.9 | −12.9 | *e* |
| | | $H_3N^+[CH_2]_6NH_3^+$ | 9.80 | 20.6 | −10.8 | *e* |
| Pyridino-18-crown-6 (**19**) | MeOH | $Ag^+$ | 3.52 | 2.58 | 0.94 | *c* |
| 1,4-Dithia-24-crown-8 (**33**) | $H_2O$ | $Ag^+$ | 6.8 | 2.1 | 4.7 | *b* |

[a] Ref. 16. [b] Ref. 5. [c] Ref. 8. [d] Ref. 3. [e] Ref. 6.

**Table 6.** The slope ($\alpha$) and the intercept ($T\Delta S_0$) of the $\Delta H$–$T\Delta S$ plots for 1:1 and 1:2 complexation with various ligands

| | 1:1 Complexation | | 1:2 Complexation | |
|---|---|---|---|---|
| Ligand | $\alpha$ | $T\Delta S_0$ | $\alpha$ | $T\Delta S_0$ |
| Glyme/podand | 0.86 ($n$ = 23, $r$ = 0.93, $p$ < 0.001)[a] | 2.3 | | |
| Crown ether | 0.76 ($n$ = 207, $r$ = 0.87, $p$ < 0.001) | 2.4 | 0.71 ($n$ = 18, $r$ = 0.98, $p$ < 0.001) | 2.7 |
| Cryptand | 0.51 ($n$ = 39, $r$ = 0.70, $p$ < 0.001) | 4.0 | | |
| Antibiotic | 0.95 ($n$ = 13, $r$ = 0.91, $p$ < 0.001) | 5.6 | | |

[a] $n$ = number of data used; $r$ = correlation coefficient; $p$ = significance level.

**Table 7.** Isoequilibrium temperatures ($\beta$) for various ligands (1:1 complexation)

| Ligand | $\beta$/K |
|---|---|
| Glyme/podand | 320 |
| Crown ether | 410 |
| Cryptand | 620 |
| Antibiotic | 410 |

both ligands and ionophores originates from the high intrinsic entropic gain ($T\Delta S_0$) upon complexation and the high conformational flexibility indicated by the high $\alpha$ value. Therefore any attempt to enhance binding ability by introducing additional binding sites or by replacing oxygen by other donor atoms will be unsuccessful.

In conclusion, the slope $\alpha$ and the intercept $T\Delta S_0$ of the $T\Delta S$–$\Delta H$ plot may provide one interpretation of both the similarities and the differences in the complexation behaviour of acyclic, monocyclic, and bicyclic ligands, including antibiotics.

The present enthalpy–entropy compensation effect is similar to the 'isoequilibrium relationship' proposed by Leffler *et al.*[29] According to Leffler's treatment, $\Delta H$ values were plotted against $\Delta S$ values for each type of ligand to give an analogous straight line with a slope of $\beta$. This relationship is expressed by a modification (5) of equation (1), where $\beta = T/\alpha$ ($T$ = 298 K). Insertion of equation (5) in equation (3) gives (6). The isoequilibrium temperature $\beta$ thus obtained for each type of ligand is listed in Table 7. At this temperature, all combinations of cations and ligands (of the same type) are considered to have nearly identical complex stabilities or $\Delta G$ values in any solvent. Beyond this point the complex-stability sequence is reversed, and opposite cation selectivities of a ligand may be observed below and above the temperature $\beta$, although complex stability itself declines greatly at high temperatures.

$$\Delta(\Delta H) = \beta\Delta(\Delta S) \quad (5)$$

$$\Delta(\Delta G) = (1\text{-}T/\beta)\Delta(\Delta H) \quad (6)$$

A major objection to the foregoing discussion relates to the relatively large deviation of the points from the regression line; *i.e.* the plots are so scattered that the claimed correlation is invalid. In fact, Leffler's examples of isoequilibrium or isokinetic plots give good to excellent straight lines of $r > 0.95$,[29] simply because he selects appropriate cases. The major difference between our analyses and Leffler's is the number of variables subject to change. Our plots include all reported data which were obtained by changing at least three factors, *i.e.* cation, ligand, and solvent, whereas Leffler's relationships were obtained mostly by changing one factor, *i.e.* substituent or solvent. The relatively large scatterings in the present case, as compared with the Leffler's, may be attributed to a combination of minimal perturbations to these variables. However, we consider

that the correlation coefficients of 0.87—0.98 obtained in this study are sufficient to give statistically meaningful results, although the result for cryptands ($r = 0.70$) seems less reliable.* The present correlations indicate that a single mechanism, *i.e.* electrostatic interaction, is operative in the complexation process of various ligands except for the heavy/transition metal ion/polyaza-ligands cases, and that the complexation phenomena may be discussed as a whole in terms of the $\alpha$ and $T\Delta S_0$ values.

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* Statistical tests of significance reveal, however, that the significance level ($p$) of the correlations for these ligands including cryptand are well below 0.001 (Table 6).

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