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COMPENSATION EFFECTS IN THE COMPLEXATION REACTIONS OF α- AND β-CYCLODEXTRIN

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Analysis of temperature dependent equilibrium constant data for the complexation of α-cyclodextrin with approximately 70 different substrates demonstrates the existence of a general compensation effect. Enthalpies ($kJ\ mol^{-1}$) and entropies ($J\ K^{-1} mol^{-1}$) of complexation are related by $\Delta H = -5{\cdot}70(\pm 0{\cdot}05) + [421{\cdot}1(\pm 1{\cdot}2)]\Delta S$. A few substrates deviate from the general effect, possibly owing to reorganization of internal hydrogen bonding interactions. Complexation reactions involving β-cyclodextrin are found to divide into two groups. Eleven small molecule or ion substrates undergo isoentropic complexations with $\Delta S = -5{\cdot}7 \pm 0{\cdot}2\ J\ K^{-1} mol^{-1}$. Fourteen larger substrate species exhibit a compensation effect with $\Delta H = -23{\cdot}5(\pm 0{\cdot}2) + [634(\pm 26)]\Delta S$. The compensation behavior of the two cyclodextrins is discussed in terms of bonding mechanisms and cavity size.

INTRODUCTION

In recent years, complexation reactions of α-cyclodextrin (cyclohexaamylose, here abbreviated as 6-Cy) and β-cyclodextrin (cycloheptaamylose, abbreviated as 7-Cy) have been widely studied. These compounds form inclusion complexes with numerous inorganic and organic anions, cations and molecular species. Binding in these complexes has been explained in terms of hydrophobic forces, expulsion of 'high energy water' from the cyclodextrin cavity, van der Waals forces, dispersion forces, hydrogen bonding, polar interactions or some combinations of these effects.[1–6] There is some evidence that many 1:1 complexation reactions involving 6-Cy share a common binding mechanism based on a 'compensation effect' found in these reactions.[7–9] The existence of this effect for both 6-Cy and 7-Cy complexation reactions and its role in elucidating the nature of similarities and differences among these various reactions are the subjects of this paper. The analysis shows that none of the effects previously proposed to explain the binding in these complexes is satisfactory.

THE COMPENSATION EFFECT

A van't Hoff plot of $R \ln K$ vs. $-1/T$, where K is the equilibrium constant at temperature T for a given chemical reaction, gives rise to a straight line with slope ΔH and intercept ΔS, assuming that both ΔH and ΔS are essentially independent of temperature. If van't Hoff plots are generated for a series of related chemical reactions and the resulting ΔH values are plotted against the corresponding ΔS values, this graph is often also a straight line. This linear relationship is called a compensation effect. The slope β, which has the dimensions of temperature, is termed the compensation temperature. This effect was first described by Leffler and Grunwald.[10] Since that time, compensation phenomena have been observed in a wide range of chemical processes. In a review, Linert[11] cited examples in catalysis, vaporization, thermal dissociation, electron diffusion in organic semiconductors, electrode kinetics and numerous biochemical systems.

An observed linear relationship between ΔH and ΔS for a series of chemical reactions may reflect an underlying commonality in the reactions. However, in many cases, the relationship may be no more than a statistical artifact arising from large uncertainties in the values of the equilibrium constants. We refer to this linear correlation induced by experimental errors as the 'pseudo-compensation effect' and to the effect of chemical origin simply as the compensation effect.

The nature of the pseudo-compensation effect was first described by Exner.[12] The effect arises because the slope and intercept (ΔH and ΔS) for each van't Hoff plot are statistically correlated. However, as Exner noted, the sets of values of $R \ln K$ and $-1/T$ are uncorrelated with one another since they are obtained from separate experiments. His key insight into the problem was to recognize that if a true compensation

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effect exists and if all the van't Hoff lines are plotted on a single $R \ln K$ vs $-1/T$ plane, then these lines will intersect in a single point whose abscissa is the reciprocal of the true compensation temperature.

Exner's work led to several methods for distinguishing compensation from pseudo-compensation phenomena and for estimating this true compensation temperature. Linert[13] compared the sum of the squares of the deviations of the experimental points from their van't Hoff lines obtained in two ways: first, the van't Hoff lines are constrained to pass through a single point; and second, the van't Hoff lines are not so constrained. If the ratio of these two sum-of-squares is sufficiently close to 1 as indicated by the appropriate Fisher–Pearson F-statistic, then the existence of a true compensation phenomenon can be inferred. In an alternative approach, Krug *et al.*[14] applied parametric statistical methods to the linear compensation relationship between ΔG and ΔH in order to determine the compensation temperature and its uncertainty.

Before continuing, we note one important assumption common to the previous analyses of the compensation model and the analysis conducted here. It is assumed that ΔH is essentially independent of temperature over the temperature range under investigation. According to thermodynamics, the difference between values of ΔH at two different temperatures is equal to $\int \Delta C_p \, dT$, where $\Delta C_p = C_p(\text{products}) - C_p(\text{reactants})$. The assumption that ΔH is independent of temperature is thus equivalent to assuming that ΔC_p is small.

Earlier work[15] suggested that ΔC_p may be appreciable in some cyclodextrin complexations. This does not seem to be the case in the present study. First, appreciable temperature dependences in ΔH would necessarily lead to curved van't Hoff plots. We detected no such curvature in the numerous systems studied here. The data points are almost invariably randomly scattered about the van't Hoff regression lines. Second, as will be discussed below, the compensation model based on the assumption that the values of ΔH are independent of temperature provides an acceptable fit to the experimental data.

CALCULATION OF COMPENSATION TEMPERATURES AND THEIR UNCERTAINTIES

In a recent paper, we presented a systematic method for determining the existence of the compensation effect and the value and uncertainty of the compensation temperature, when it exists.[16] Given N reactions, labeled by the index i, and n_i temperatures for reaction i, labeled by j, the thermodynamic relation $\Delta G = \Delta H - T\Delta S$ for the ith reaction carried out at temperature j can be expressed in terms of the equilibrium constant for that reaction:

$$R \ln K_{ij} = \Delta H_i(-1/T_{ij}) + \Delta S_i \qquad (1)$$

The existence of a compensation effect is indicated by a linear relationship between the entropies and enthalpies of the reactions:

$$\Delta H_i = \alpha + \beta \Delta S_i \qquad (2)$$

where β is the compensation temperature. Combining equations (1) and (2), we have

$$R \ln K_{ij} = (\alpha + \beta \Delta S_i)(-1/T_{ij}) + \Delta S_i \qquad (3)$$

Equation (3) represents a set of $\sum n_i$ equations with $n+2$ parameters: α, β and N values of ΔS_i. The values of the parameters are adjusted to best fit the model represented by equation (3).

The model equations are non-linear functions of the parameter values. Consequently, a non-linear least-squares procedure is required to determine the optimized values of the parameters. We employed the simplex method as implemented by Press *et al.*[17] to minimize

$$X^2 = \frac{\sum_{i=1}^{N} \sum_{j=1}^{n_i} (y_{ij} - Y_{ij})^2}{\sigma_{ij}^2} \qquad (4)$$

where y_{ij} are the values of $R \ln K_{ij}$ calculated from equation (3), Y_{ij} are the corresponding measured quantities and σ_{ij} are the experimental uncertainties in the Y_{ij}. The required initial estimates of ΔS_i are obtained from the van't Hoff plots; those for α and β are obtained from the intercept and slope of the plot of ΔH vs ΔS.

The determination of σ_{ij} requires some discussion. Although these quantities can be obtained from the observed scatter of $R \ln K_{ij}$ for each reaction about its van't Hoff straight line, this approach does not take account of systematic errors in K_{ij}. The equilibrium constants used in this study are derived from a variety of experimental procedures, each of which is subject to its own types of systematic errors. For example, consider the complexation constants of 6-Cy with ClO_4^-, I^-, and SCN^- at 25°C.[18] Estimates obtained from conductimetric experiments are 51 ± 8, 32 ± 12 and 41 ± 10, respectively. A pH perturbation method provided corresponding values of $45{\cdot}8 \pm 0{\cdot}9$, $19{\cdot}0 \pm 0{\cdot}3$ and $34{\cdot}6 \pm 0{\cdot}4$. In both methods, the uncertainties are standard error estimates based on assumed random fluctuations in the conductimetric or pH data. While the conductimetric and potentiometric values are consistent in these experiments, the latter methodology provides systematically lower estimates. Numerous other examples are available. Consequently, although these systematic errors may not appear as random scatter about the van't Hoff lines, they may result in incorrect slopes or intercepts. In order to incorporate these errors into the analysis, we use the following expression to estimate σ_{ij}:

$$\sigma_{ij} = \mathrm{Max}\left\{\left[\frac{\sum_{j=1}^{n_i} (y_{ij} - Y_{ij})^2}{(n_i - 2)}\right]^{1/2}, 0.15R\right\} \tag{5}$$

This procedure uses the observed scatter of $R \ln K_{ij}$ about each of the N van't Hoff lines to estimate σ_{ij} and, in addition, incorporates the effect of systematic errors that alone may amount to $0{\cdot}15R$. Using this procedure, the relative uncertainty in the equilibrium constants is approximately ±15%, a value consistent with our experience in measuring complexation constants employing a variety of experimental techniques.

Assuming that our estimate of σ_{ij} is a reasonable approximation to the correct value, substitution of the optimized values of the parameters into equation (4) provides a value of X^2 which can be interpreted as a goodness-of-fit statistic. If the data are well described by the model, X^2 will be approximately equal to the number of degrees of freedom $\sum n_i - (n+2)$; if not, X^2 is expected to be significantly larger.

In analyzing the experimental uncertainties and the goodness-of-fit of the model, it is important to compare the value of $0{\cdot}.15R$ with the range of equilibrium constant values to be analyzed, both from reaction to reaction and from temperature to temperature for a given reaction. The 6-Cy formation constants vary from about 2 to 5000, corresponding to a variation in $R \ln K_{ij}$ from about 6 to 71. An experimental uncertainty of $0{\cdot}15R$ is just 2% of this range. Variation of $R \ln K_{ij}$ values for a single reaction depends on the value of the equilibrium constant itself as well as the temperature range. The weakest complexes encountered here have essentially temperature-independent formation constants. For these complexes, the range of $R \ln K_{ij}$ is approximately zero. For example, complexation constants for ethanol are 4·6, 4·1, 4·8, 4·3 and 4·0 at 15, 25, 25, 35 and 45 °C, respectively.[19] The duplicate values at 25 °C (representing repeated measurements using the same experimental method) differ by 17%, which seems consistent with the error estimate of ±15%. In these cases, deviations from the compensation model will be difficult to detect. For the strongest complexes, the range of values of $R \ln K_{ij}$ for a given reaction as a function of temperature is as large as 18–20, about 15 times the value of $0{\cdot}15R$. In these reactions, any significant deviation from the compensation model here will result in a large contribution to X^2 and an unacceptable goodness-of-fit.

COMPENSATION EFFECTS IN 6-CY COMPLEXATION REACTIONS

The majority of the temperature-dependent thermodynamic complexation constants required for this study are given in Refs 7 and 18–26. The hydroxide ion complexation constants are derived from the acidity constant data[21] and the well known temperature-dependent values of pK_w, the autoprotolysis constant of water. Complexation constants for 6-Cy with *p*-aminobenzoic acid and *p*-methyl-aminobenzoic acid and their anionic and cationic species are given in Table 1.[27] These results were obtained previously[27] using methods described in Ref. 26.

6-Cy complexes with species of methyl orange, characterized in Ref. 22, are not included in this study for the following reason. The protonated (neutral) form of methyl orange is capable of acid–base tautomerism and both species may exist in either the *cis* or *trans* isomeric forms. Assuming that an aqueous solution of methyl orange contains the various tautomeric and isomeric forms, Cy complexation is likely to affect differentially the equilibrium concentrations of these forms. These displacements in concentration would, in turn, alter the overall formation constants and thus result in deviations from a compensation effect. Displacement of the tautomeric or isomeric equilibria in the complexation of methyl orange with 6-Cy is confirmed by spectroscopic data. Upon complexation, the intensely colored protonated neutral form ($\varepsilon = 4{\cdot}0 \times 10^4$ l mol^{-1} cm^{-1} at 530 nm) becomes essentially colorless in the entire visible region ($\varepsilon = 0{\cdot}01 \times 10^4$ l mol^{-1} cm^{-1} at 530 nm).

We also exclude from this study several other complexes of 6-Cy whose formation constants are given in the previously cited references. Complexes of 6-Cy with *p*-hydroxybenzoic acid and its monoanion are excluded because of an incorrect analysis of the data given in Ref. 7. The mixture of *p*-hydroxybenzoic acid and its conjugate base was treated as a simple monoprotic acid buffer. Unfortunately, the difference between pK_1 and pK_2 for this acid is too small to justify this approximation.

Complexes with hexanoic and decanoic acids and their anionic species are excluded because the fit of experimental to calculated pH data in these cases is poor compared with that for numerous other experimental systems. Finally, we exclude extremely weak complexes, such as the complex of 6-Cy with adamantane carboxylate, whose existence is questionable.

The remaining 74 substrate species are listed in Table 2. Of these, 68 form binary complexes [(6-Cy) · S] and six form ternary complexes [(6-Cy)$_2$ · S].

The ternary complexation reactions require further analysis. Although values of the stepwise equilibrium constants, K_1 and K_2, for the reactions

$$\text{6-Cy} + \text{S} = \text{6-Cy} \cdot \text{S} \tag{6a}$$

and

$$\text{6-Cy} \cdot \text{S} + \text{6-Cy} = (\text{6-Cy})_2 \cdot \text{S} \tag{6b}$$

respectively, show significant variation from one determination to another, the product K_1K_2 is more

Table 1. Temperature-dependent complexation constants of *p*-aminobenzoic and *p*-methylaminobenzoic acid species with 6-Cy and 7-Cy

Acid	Cyclodextrin	Temperature (°C)	$K(H_2NC_6H_4CO_2^-)$[a]	$K(H_2NC_6H_4CO_2H)$	$K(H_3NC_6H_4CO_2H^+)$
p-Aminobenzoic	6-Cy	20	3·4 ± 0·5[b]	1941 ± 50	936 ± 30
		30	5·7 ± 1·4	1054 ± 20	578 ± 15
		40	3·8 ± 0·2	570 ± 5	338 ± 6
		50	2·9 ± 0·3	325 ± 9	209 ± 8
		55	3·1 ± 0·4	245 ± 7	170 ± 6
	7-Cy	20	22 ± 2	854 ± 40	281 ± 20
		30	21 ± 2	646 ± 25	237 ± 14
		40	17 ± 1	483 ± 16	196 ± 10
		50	15 ± 1	365 ± 12	170 ± 8
		55	14 ± 1	314 ± 9	164 ± 7

Acid	Cyclodextrin	Temperature (°C)	$K(H_3NC_2C_6H_4CO_2^-)$	$K(CH_3NH_2C_6H_4CO_2H)$	$K(CH_3NH_3C_6H_4CO_2H^+)$
p-Methylaminobenzoic	6-Cy	20	10·7 ± 1·4	1925 ± 80	1061 ± 60
		30	8·5 ± 1·6	1034 ± 80	608 ± 60
		40	8·1 ± 1·4	564 ± 15	345 ± 11
		50	7·0 ± 0·7	323 ± 13	216 ± 20
	7-Cy	20	74 ± 2	1598 ± 20	586 ± 10
		30	72 ± 1	1216 ± 9	487 ± 10
		40	57 ± 2	863 ± 10	382 ± 8
		50	49 ± 2	651 ± 10	312 ± 8

[a] Equilibrium constants are thermodynamic formation constants for the complexation reactions of Cy with the substrate species listed in parentheses.

[b] Uncertainties are standard error estimates derived from propagation-of-variance calculations based on an estimated rms deviation of ±0·001 pH. Observed rms deviations of calculated vs observed pH values were less than 0·001 pH and typically about half that value.

reproducible. Consequently, we use the overall reaction

$$2(6\text{-Cy}) + S = (6\text{-Cy})_2 \cdot S \qquad (7)$$

with formation constant K_1K_2.

Having chosen this form of the reaction, it is necessary to determine the equilibrium constant appropriate for the compensation model of equation (3). ΔH and ΔS for the overall reaction are the sums of the corresponding enthalpies and entropies for the stepwise reactions. Suppose that each of the stepwise complexations conforms to equation (2). Adding the appropriate forms of equation (2) for each of the stepwise reactions and then dividing by 2, we obtain

$$\Delta H/2 = \alpha + \beta \Delta S/2 \qquad (8)$$

where ΔH and ΔS refer to the overall reaction. Thus, to include a ternary complexation reaction in the compensation model [equations (2) and (3)], the enthalpy and entropy are each set equal to half the enthalpy and entropy of the overall reaction. This enthalpy and entropy are the values for the overall reaction

$$6\text{-Cy} + \tfrac{1}{2}S = \tfrac{1}{2}(6\text{-Cy})_2 \cdot S \qquad (9)$$

The equilibrium constant for this reaction is $(K_1K_2)^{1/2}$.

In analyzing these reactions, we first assumed that all 74 could be interpreted using a single compensation temperature. For these 74 reactions, there were 313 data points $(-1/T_{ij},\ R \ln K_{ij})$ and a total of 76 adjustable parameters. The number of degrees of freedom in the model is the difference between the number of data points and the number of adjustable parameters, in this case, 237. We calculated X^2 [equation (4)] and each of the summands constituting X^2. X^2 divided by the number of degrees of freedom was about 1·3, indicating an acceptable fit of the model to the data. However, examination of the summands indicated that the following reactions were outliers: the binary complexation reactions of adamantane carboxylate, iodide, thiocyanate and a few of the dicarboxylic acid species, viz. malonic acid, monohydrogenmalonate, monohydrogensuccinate and monohydrogenglutarate.

After eliminating these reactions, 67 remained, comprising 284 data points. There were now 69 adjustable parameters and thus 215 degrees of freedom. Typically, the data for a given reaction consisted of four equilibrium constants obtained at temperatures ranging from 20 to 50 °C. Substrate species, listed in Table 2, include cations, monoanions, dianions and neutral molecules with widely differing chemical properties. For this data set, X^2/degrees-of-freedom is about 0·7.

The observed value of X^2/degrees-of-freedom is less than 1·0. This result suggests that our estimate of σ_{ij} was too conservative. Repeating the calculation using $0{\cdot}12R$ for the minimum value of σ_{ij} (corresponding to ±0·05pK units or a ±12% uncertainty in the value of

K_{ij}) led to a value of X^2/degrees-of-freedom equal to 1·1.

The two calculations, based on different estimates of the uncertainty in $R \ln K_{ij}$, gave essentially identical values of the compensation parameters, α and β (the compensation temperature): 5·70 kJ^{-1} mol^{-1} and 421 K, respectively. Optimized values of ΔS_i ranged from -107 to $+28$ J K^{-1}mol^{-1} and were also unaffected by the choice of σ_{ij}. Approximately half of the values of ΔS_i were within ±10–15 J K^{-1}mol^{-1} of the van't Hoff estimates, a range consistent with the standard error of the van't Hoff intercepts based on the uncertainties in $R \ln K_{ij}$.

Table 2. Substrates for 6-Cy complexation reactions

Binary complexes: 6-Cy + S = (6-Cy) · S
Acetic acid
Acetonitrile
1-Aminoadamantane, 1-ammoniumadamantane
1-Adamantane carboxylic acid (1-adamantane carboxylate)[a]
Adipic acid, monohydrogenadipate
p-Aminobenzoic acid, *p*-ammoniumbenzoic acid, *p*-aminobenzoate
Benzoic acid, benzoate
Butyric acid, butyrate
Cyclohexanol
m-Cyanophenol, *m*-cyanophenolate
p-Cyanophenol, *p*-cyanophenolate
Dioxane
Ethanol
Formic acid
Fumaric acid, monohydrogenfumarate
Glutaric acid (monohydrogenglutarate)
Hydroxide
m-Hydroxybenzoic acid
(Iodide)
Maleic acid, monohydrogenmaleate
(Malonic acid) (monohydrogenmalonate)
p-Methylaminobenzoic acid, *p*-methylammoniumbenzoic acid, *p*-methylaminobenzoate
2-Methyl-2-propanol
Muconic acid, monohydrogenmuconate, muconate
m-nitrobenzoic acid, *m*-nitrobenzoate
p-nitrobenzoic acid, *p*-nitrobenzoate
m-nitrophenol, *m*-nitrophenolate
p-nitrophenol, *p*-nitrophenolate
Octanoic acid, octanoate
Oxalic acid, monohydrogenoxalate
Perchlorate
Phenol
Pimelic acid, monohydrogenpimelate
Propanol
Propionic acid
Suberic acid, monohydrogensuberate, suberate
Succinic acid (monohydrogensuccinate)
(Thiocyanate)
Valeric acid, valerate
Ternary complexes: 6-Cy + 1/2S = 1/2(6-Cy)$_2$ · S
1-Aminoadamantane
1-Adamantane carboxylic acid
Octanoic acid, octanoate
Suberic acid
Trimethylacetic acid

[a] The complexation behavior of the species in parentheses deviates significantly from the compensation model.

We also examined the point-by-point deviations of the optimized values of $R \ln K_{ij}$ from the corresponding experimental ones. Using a minimum value of $\sigma_{ij} = 0{\cdot}12R$, we found that approximately 75% of the 284 optimized values were within σ_{ij} of the corresponding experimental values and approximately 4% showed differences larger than $2\sigma_{ij}$. Moreover, the deviations appear to be randomly distributed among all the reactions, irrespective of the values of $R \ln K_{ij}$. Thus, the errors in this study appear to be at least approximately normally distributed. Finally, as mentioned above, the differences between the optimized and experimental values of $R \ln K_{ij}$ showed no evidence of curvature in the regression lines. These results indicate that ΔC_p effects are small and that the compensation model equations provide a good fit to the experimental data.

The values of the pseudo-compensation parameters, the intercept and slope of the plot of van't Hoff enthalpy vs entropy, are equal to $-6{\cdot}60$ kJ mol^{-1} and 399·7 K, respectively. This pseudo-compensation temperature is sufficiently far from the harmonic mean of the measurement temperatures (approximately 310 K) to preclude a chance correlation between ΔH_i and ΔS_i.[14] This result supports our conclusion that the complexation reactions of 6-Cy with the 67 substrate species listed in Table 2 conforms to the compensation model.

Why do the seven excluded substrates fail to conform to the compensation model? In the case of adamantane carboxylate, we note that the formation constant data are obtained from conductometric measurements.[19] The derivation of these equilibrium constants from the experimental data relied on numerous assumptions and corrections that may have resulted in large systematic errors. Since binary and ternary complexes of adamantane carboxylic acid conform to the compensation model, as do the related substrates adamantanamine and adamantaneammonium ion, it is reasonable to conclude that the deviation of adamantane carboxylate from the model is due to experimental difficulties rather than to chemical phenomena.

Similar arguments apply to iodide and thiocyanate. The formation constant data are based on a pH perturbation technique[18] involving complex mixtures of a dilute benzoic acid–benzoate buffer and high concentrations of 6-Cy and iodide or thiocyanate sats. Even small amounts of impurities present in the salts could have led to significant systematic errors in formation constant values. Thus, we regard the formation constant data for adamantane carboxylate, iodide and thiocyanate ions as suspect rather than attributing their behavior to a chemical deviation from the compensation model.

The deviations of malonic acid ($HO_2CCH_2CO_2H$), its monoanion, monohydrogensuccinate [$HO_2C(CH_2)_2CO_2^-$] and monohydrogenglutarate [$HO_2C(CH_2)_3CO_2^-$] from the compensation model, on the other hand, may result from their chemistry. Each of these species is characterized by significant internal hydrogen bonding that might be affected by complexation. These changes in the internal interactions would result in contributions to the overall equilibrium constants and thus result in deviations from the compensation model. Although we are currently unable to confirm experimentally this explanation, it seems consistent with the fact that the molecular forms of both glutaric and succinic acids conform to the compensation model. In these molecular acids, internal hydrogen bonding is presumably much weaker than in their monoanions, so that disruption of these interactions upon complexation would have little or no effect on the overall complexation equilibria.

The uncertainties in the compensation parameters, α and β, were estimated using a Monte Carlo procedure.[28] To each experimental value of $R \ln K_{ij}$ is added a normally distributed random variate with mean zero and standard deviation equal to its uncertainty. The resulting set of data is analyzed using the simplex algorithm, providing new values of α and β. This procedure is repeated 200 times. Examination of the numerically ordered set of the 200 values of each parameter values provided 68% confidence intervals. Confidence intervals for α and β were found to be $\pm 0{\cdot}05\ \mathrm{kJ\,mol^{-1}}$ and $\pm 1{\cdot}2$ K, respectively.

To summarize this section, the compensation effect observed here represents a common property of the complexation behavior of 6-Cy with a large variety of substrate species. Of the 68 binary and six ternary complexations of 6-Cy investigated here, 61 of the binary reactions and all six of the ternary complexations conform to the compensation model, assuming 12–15% systematic errors in the values of the complexation constants. The compensation parameters are $\alpha = 5{\cdot}70 \pm 0{\cdot}05\ \mathrm{kJ\,mol^{-1}}$ and $\beta = 421{\cdot}2 \pm 1{\cdot}2$ K. Seven binary complexations do not conform to the model. The deviations in three of the seven complexation reactions probably arise from systematic errors in deriving the complexation constants; deviations in the remaining four may result from differences in the internal interactions in the complexed and uncomplexed substrate species.

COMPENSATION EFFECTS IN 7-Cy COMPLEXATION REACTIONS

The equilibrium constants for the complexation reactions of 7-Cy with various substrates are tabulated in Refs 20, 23, 25 and 29 and in Table 1 of this paper. Equilibrium constants for complexation with the hydroxide ion are derived from the acidity constants listed in Ref. 21 and the temperature-dependent pK_w values. As was the case with complexes of 6-Cy, we exclude complexes involving the various species of methyl orange and those few substrates that form weak complexes with poorly defined formation constants. The resulting data set consists of binary complexation reactions of 7-Cy with the 25 substrate species listed in Table 3 and contains 119 data points of the form $(-1/T,\ R \ln K)$. As discussed in the previous section, the minimum value of σ_{ij} was set at $0{\cdot}15R$.

The fit of this data set to the compensation model results in an unsatisfactory value of 3·7 for X_2/degrees-of-freedom. Examination of the data showed that the substrates could be divided into the two distinct groups shown in Table 3. The first group, consisting of 14 reactions and a total of 70 data points, results in a value of 0·36 for X_2/degrees-of-freedom. Since this value suggests that the estimate of $\sigma_{ij} = 0{\cdot}15R$ is overly conservative, we repeated the calculation using a minimum value of σ_{ij} equal to $0{\cdot}12R$ and obtained 0·6 for X^2/degrees-of-freedom.

The optimized values of the compensation parameters α and β, $-23{\cdot}5\ \mathrm{kJ\ mol^{-1}}$ and 633·7 K, respectively, and the set of values of ΔS_i were essentially identical in these two calculations. The 68% confidence intervals calculated using Monte Carlo simulations with $\sigma_{ij} = 0{\cdot}12R$ are $0{\cdot}2\ \mathrm{kJ\,mol^{-1}}$ and 25·7 K, respectively. Optimized values of ΔS ranged from -16 to $+40\ \mathrm{J\,K^{-1}\,mol^{-1}}$. Most of these values were within $10\ \mathrm{J\,K^{-1}\,mol^{-1}}$ of the corresponding van't Hoff estimates.

Table 3. Substrates for 7-Cy complexation reactions

Group 1: compensation model
1-Adamantane acetate
1-Aminoadamantane, 1-ammoniumadamantane
2-Ammoniumadamantane
1-Adamantane carboxylate
1-Adamantane methylammonium
Cyclohexane carboxylic acid, cyclohexane carboxylate
Decanoic acid, decanoate
Hexanoic acid, hexanoate
Octanoic acid, octanoate
Group 2: isoentropic model
p-Aminobenzoic acid, *p*-ammoniumbenzoic acid, *p*-aminobenzoate
Benzoic acid, benzoate
Butyric acid
Hydroxide ion
p-Methylaminobenzoic acid, *p*-methylammonium benzoic acid, *p*-methylaminebenzoate
Valeric acid

The second group, consisting of 11 complexation reactions of 7-Cy with 49 data points, could not be adequately fitted with either the general compensation model or a with model corresponding to the special case of isoenthalpic reactions. This lack of fit was indicated by the fact that calculations using the two different minimum values of σ_{ij} resulted in different compensation parameters. This type of result might be due to degeneracy, i.e., differences between values of $R \ln K_{ij}$ are small compared with σ_{ij}. However, in this case, the values of $R \ln K_{ij}$ are well distributed over a range of about $4{\cdot}8R$ and the uncertainty of $0{\cdot}15R$ is only 3% of this range. In addition, the range of $R \ln K_{ij}$ for individual reactions varied from approximately $0{\cdot}7R$ to $1{\cdot}1R$. Again, this range is large compared with the uncertainty of $0{\cdot}15R$. Thus, the range of data is adequate to determine compensation parameters if they exist. Apparently, there is no compensation effect.

The 49 data points for this group of 11 complexation reactions could be fitted to an isoentropic model. We assume that the reactions are characterized by a single value of ΔS. The enthalpies for the 11 reactions are independent and can be determined from the model

$$R \ln K_{ij} = \Delta H_i(-1/T) + \Delta S \tag{10}$$

The fitting procedure proceeds as before. There are 12 adjustable parameters, namely the 11 values of ΔH_i and the single ΔS. For this fit, again setting the minimum $\sigma_{ij} = 0{\cdot}15R$, $X^2 = 7{\cdot}9$ with 37 degrees-of-freedom. $\Delta S = -5{\cdot}7 \pm 0{\cdot}2\ \mathrm{J\,K^{-1}\,mol^{-1}}$, where the uncertainly is the 68% confidence interval derived from a Monte Carlo simulation. The values of ΔH_i ranged from $-19{\cdot}5$ to $-9{\cdot}2\ \mathrm{kJ\,mol^{-1}}$. We repeated these calculations with $\sigma_{ij} = 0{\cdot}12R$ and obtained virtually identical values of ΔS and ΔH_i. These results indicate that the group of 11 complexation reactions of 7-Cy conforms to a model of isoentropic reactions.

In interpreting these results, we note that the substrate species in these 11 reactions are smaller than the substrates in the first group of 14 reactions where a compensation effect was observed. This dichotomy is very sharp. For example, valeric acid, which is only slightly smaller than hexanoic acid, clearly fits the set of isoentropic reactions, while the latter acid fits the compensation model. Attempts to switch assignments yielded patently unsatisfactory results.

In addition, it is noteworthy that the value of ΔS obtained for the series of isoentropic reactions is strikingly similar to the value of $-R \ln 2 = -5{\cdot}76\ \mathrm{J\,K^{-1}\,mol^{-1}}$ expected for a simple association reaction. This value is derived from a theoretical treatment of a reaction $\mathrm{A + B = A \cdot B}$ that neglects solvent effects and internal degrees of freedom in the A, B and $\mathrm{A \cdot B}$.

DISCUSSION

The compensation parameters α and β for the complexation reactions of substrates with 6-Cy are significantly different from the corresponding parameters for the reactions involving 7-Cy that fit the compensation model. For reactions involving 6-Cy we find $\alpha = 5{\cdot}70 \pm 0{\cdot}05\ \mathrm{kJ\,mol^{-1}}$ and $\beta = 421{\cdot}2 \pm 1{\cdot}2$ K, while for 7-Cy, the corresponding values are $-23{\cdot}5 \pm 0{\cdot}2\ \mathrm{kJ\,mol^{-1}}$ and 634 ± 26 K. We note here that the 6-Cy and 7-Cy complexations involve many of the same substrates, for example, species of octanoic acid and 1-adamantanamine. The reactions of 7-Cy with these substrates result in a compensation effect characterized by parameters α and β. The reactions of 6-Cy with these substrates are characterized by a different set of compensation parameters. We believe that the compensation parameters reflect properties of the host–guest interaction. The present results indicate that the interactions involving 7-Cy are noticeably different from those of 6-Cy. Hence it is not the case, as has often been assumed, that the bonding interactions of all cycloamylose complexation reactions are essentially identical, with complexation constants differing only as a result of the size of the cavity of the cycloamylose host.

The compensation behavior detailed here suggests that certain chemical phenomena are common to all the complexation reactions involving a given cycloamylose with the various substrates that exhibit a compensation effect. These phenomena could involve common properties shared by the substrates, similarities in the solvation process or a pattern in the cycloamylose-substrate interactions.

It seems unlikely that the compensation phenomena can be explained on the basis of similarities among the substrates. The different substrates, which include the hydroxide and perchlorate ions, polar molecules such as formic, acetic and *p*-aminobenzoic acid and non-polar species such as 1-aminoadamantane, almost certainly engage in different types of bonding interactions with the cycloamylose and the solvent. Consider, for example, ternary complexations such as that of 6-Cy with adamantane carboxylic acid, which fit the compensation model. While the carboxylic acid group may interact with one 6-Cy molecule by means of hydrogen bonding or polar attraction, the interaction of the hydrocarbon adamantanyl group with the second 6-Cy complexon cannot employ these mechanisms.

The two distinctly different compensation effects characterizing complexes with 6-Cy and 7-Cy and also the existence of isoentropic complexation reactions with 7-Cy seem to eliminate the possibility that a hydrophobic effect, the solvent effect most often invoked to explain the relationship among these reactions, is involved. A hydrophobic effect presumably involves the expulsion of hydrocarbons and other poorly solvated species from the aqueous environment and results in the complexation of these species by the cycloamyloses. However, the same substrates are removed from the same aqueous media in very different ways by 6-Cy and 7-Cy. In addition, there seems to be little or no connection between the solvation properties of the substrate and either its complexation equilibrium constant, enthalpy or entropy.

The third possible source of the compensation phenomena lies in the interactions between the cycloamylose and substrate. The fact that ΔH and ΔS for the complexation reactions of 6-Cy are linearly related implies that a more negative ΔH, i.e. increased bonding interaction, results in a more negative bonding entropy. Thus, an increased attractive force between the substrate and a labile 6-Cy molecule results in constraints on the internal motion of 6-Cy and a resulting net decrease in system entropy. The source of the bonding interaction, whether hydrogen bonding, polar interaction or van der Waals attractions, seems immaterial.

The complexation reactions involving 7-Cy that exhibit compensation behavior follow the same pattern as those with 6-Cy. Reactions involving 7-Cy are characterized by a different compensation temperature than those with 6-Cy because of differences in the internal bonding and vibrational structure of the two cycloamylose molecules.

The existence of a set of isoentropic complexation reactions involving 7-Cy suggests that the small substrate species which exhibit this effect are able to enter and bind to the 7-Cy cavity without affecting the internal motions of the molecule. The value of ΔS for these reactions is essentially identical with the theoretical value for a simple association reaction. The possibility that this result may be simply a remarkable coincidence does not affect the interpretation offered here.

The compensation effects described in this paper suggest that certain theoretical descriptions of cycloamylose complexation reactions and the presumably related complexation reactions involving enzymes and other biochemicals may not be appropriate. Quantitative models of the reactions have invariably employed rigid cycloamylose structures with properties derived from x-ray crystallographic results. Such models make no allowance for the interplay between the binding of the substrate and the cycloamylose internal degrees of freedom. These models cannot account for the compensation effects observed here because changes in both enthalpy and entropy are important. Thus, we would expect that more sophisticated models will be needed to interpret the complexation reactions of the cycloamlyloses and, by extension, of the more complex biologically active molecules.

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