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Solvent Effects on the Thermodynamics of Aquocobalamin Chloride and Model Compounds in Dioxane–Water Mixtures

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The solubilities of aquocobalamin chloride and eight other cobalt(III) complexes have been measured in dioxane–water mixtures. For aquocobalamin chloride, aquanitrocobaloxime and aquamethylcobaloxime solubilities have also been measured as a function of temperature. The transfer thermodynamic functions $\delta_m G^\circ$, $\delta_m H^\circ$ and $\delta_m S^\circ$ have been calculated. The results may be accounted for in terms of the cavity energy and specific interactions. A difference has been found between the transfer functions of the aquocobalamin cation in dioxane–water mixtures and those in acetonitrile–water mixtures.

In a series of investigations$^1$ into the reactivity of aquocobalamin and model compounds we have attempted to obtain insight into the factors that determine the solvent dependence of the kinetic parameters by separating the solvent effects in initial-state and transition-state contributions. The transfer Gibbs energies of the reacting compounds in mixed solvents, necessary for this approach and calculated from measured solubilities, in themselves provide interesting information on the solute–solvent interactions and the factors that control the kinetics. In this study we present the solubilities in dioxane–water mixtures of the following complexes: aquocobalamin chloride ([B$_{12}$H$_6$O]Cl), trans-bis(diaminoethane)diazidocobalt(III) perchlorate ([Co(N$_2$)$_2$(en)$_2$]ClO$_4$), aquachlorocobaloxime [ClCo(DH)$_2$H$_2$O], aquamethylcobaloxime [CH$_3$Co(DH)$_2$H$_2$O], aquanitrocobaloxime [NO$_2$Co(DH)$_2$H$_2$O], aquapyridinecobaloxime perchlorate ([pyCo(DH)$_2$H$_2$O]ClO$_4$), benzimidazolechlorocobaloxime [bimCo(DH)$_2$Cl], aqua-N-methylbenzimidazolecobaloxime perchlorate ([mbimCo(DH)$_2$H$_2$O]ClO$_4$), aqua-N-methylbenzimidazole-2-butanolone-3,3'[(1,3-propanediyl)bis(dinitrilo)]bisdioximato (III) perchlorate ([mbimCo(DO)(DOH)$_2$H$_2$O]ClO$_4$)$_2$. These are compared with published data for aquocobalamin chloride and hexa-amminecobalt(III) chloride in acetonitrile–water mixtures.$^{10,2}$ For aquocobalamin chloride, CH$_3$Co(DH)$_2$H$_2$O and NO$_2$Co(DH)$_2$H$_2$O the temperature dependence of the solubility in the mixtures is also presented. These values are discussed in terms of cavity formation energy and specific interactions.

**Experimental**

**Materials**

The following cobalt complexes were prepared by established procedures.

[Co(N$_2$)$_2$(en)$_2$]ClO$_4$ was prepared according to Staples.$^5$ Elemental analysis was 16.1% Co (calc. 16.25%), analysis for the ClO$_4^-$ ion gave 27.3% (calc. 27.42%).

$^\dagger$ Abbreviations: en = diaminoethane, bim = benzimidazole, mbim = N-methylbenzimidazole, py = pyridine, DH = dimethylglyoximato group, (DO)(DOH)$_2$ = 2-butanolone-3,3'[(1,3-propanediyl)bis(dinitrilo)]-bisdioximato group, [B$_{12}$H$_6$O]Cl = aquocobalamin chloride.

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ClCo(DH)$_2$(DH)$_2$H$_2$O was prepared according to Babko. Elementary analysis was 17.0% Co (calc. 17.3%).

CH$_3$Co(DH)$_2$H$_2$O was prepared according to Schrauzer. Elementary analysis was 18.0% Co (calc. 18.29%), 33.64% C (calc. 33.55%), 6.00% H (calc. 5.94%), 17.47% N (calc. 17.39%), 24.68% O (calc. 24.83%).

NO$_3$Co(DH)$_2$H$_2$O was prepared according to Tschugaeff. Elementary analysis was 16.5% Co (calc. 16.69), 27.05% C (calc. 27.20%), 4.49% H (calc. 4.57%), 19.78% N (calc. 19.83%), 31.95% O (calc. 31.71%).

$[\text{pyCo(DH)}_2\text{H}_2\text{O}]\text{ClO}_4$ was prepared from $\text{pyCo(DH)}_2\text{Cl}_2$ by reaction with an equimolar amount of AgClO$_4$ in 50% ethanol–water v/v (20 cm$^3$ of the mixture per gram cobaloxime) at 70 °C for 1 h. The solution was filtered and cooled. The resulting brown needles were collected and recrystallised from 50% ethanol–water v/v (yield 70%). Elementary analysis was 12.26% Co (calc. 12.13%).

bimCo(DH)$_2$Cl was prepared from H[Co(DH)$_2$Cl]$_2$ by reacting with equimolar amounts of KOH and bim. To a solution of 5 g (0.0126 mol) H[Co(DH)$_2$Cl]$_2$·2H$_2$O and 0.71 g KOH (0.0126 mol) in 250 cm$^3$ ethanol, a solution of 0.84 g (0.0123 mol) bim in 100 cm$^3$ ethanol was slowly added (1.5 h). After 1 h the solution was filtered and the brown crystals were washed with water, ethanol and ether (yield 76%). Elementary analysis was 13.3% Co (calc. 13.31%).

$[\text{mbimCo(DH)}_2\text{H}_2\text{O}]\text{ClO}_4$·2H$_2$O was prepared from mbimCo(DH)$_2$Br [prepared in a similar way as bimCo(DH)$_2$Cl] by addition of AgClO$_4$ as described for the synthesis of $[\text{pyCo(DH)}_2\text{H}_2\text{O}]\text{ClO}_4$ (yield 74%). Elementary analysis was 10.1% Co (calc. 10.25%), analysis for H$_2$O gave 5% (calc. 6.26%).

$[\text{mbimCo(DO)(DOH)}_2\text{H}_2\text{O}]\text{ClO}_4$ was prepared from Co(DH)(DOH)$_2$Br$_2$·8$^{250}$ mg was dissolved in 25 cm$^3$ 50% acetone–water v/v at 40 °C. To this solution a solution of 72 mg mbim in 2 cm$^3$ acetone was added. After 5 min a solution of 2 equivalents AgClO$_4$ in 2 cm$^3$ water was added. After 10 min the solution was filtered. The filtrate was left standing for 24 h. The resulting brown crystals were filtered and washed with water. The compound was purified by extracting impurities from the solid with chloroform (yield 50%). Elementary analysis was 9.10% Co (calc. 9.10%), 35.64% C (calc. 35.25%), 4.76% H (calc. 4.52%), 13.07% N (calc. 12.99%), 27.09% O (calc. 27.19%), analysis for the ClO$_4^-$ anion gave 30.0% (calc. 30.7%). Chemicals of analytical-reagent grade were used throughout this study. Acetonitrile (Baker) was used without purification and dioxane (Baker) was purified as described before.$^{1a}$

**Apparatus and Procedures**

The solubilities of all compounds were measured as previously described$^{1c}$ in a specially designed solubility tube; equilibration for 2 h [bimCo(DH)$_2$Cl within 10 min]. The temperature accuracy was always better than 0.1 °C. The temperature region for the measured solubilities was 20–35 °C for aquocobalamin chloride, 15–45 °C for NO$_3$Co(DH)$_2$H$_2$O and 15–35 °C for CH$_3$Co(DH)$_2$H$_2$O.

The $^1$H n.m.r. and $^{59}$Co n.m.r. spectra were recorded on a Bruker WM-250 spectrometer. The $^{58}$Co n.m.r. spectra were measured at a frequency of 59.73 MHz. U.v.–visible spectra were recorded on a Beckman Acta MIV spectrophotometer. Hydrolysis reactions of the cobalt complexes were followed on a Zeiss M400III photometer. Infrared spectra were measured with a Perkin-Elmer 580 B spectrophotometer; the compounds were suspended in paraffin oil and measured between NaCl discs.

**Results**

All compounds show the expected $^1$H n.m.r. spectra. For the compound $[\text{mbimCo(DO)(DOH)}_2\text{H}_2\text{O}]\text{ClO}_4$ two types of crystals were isolated. The cobalt
Table 1. Extinction coefficients of the compounds used in the solubility measurements and diameters used in the calculations

<table>
<thead>
<tr>
<th>compound</th>
<th>λ/nm</th>
<th>$\varepsilon$/mol$^{-1}$ dm$^3$ cm$^{-1}$</th>
<th>$D$/Å</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Co(N$_3$)$_2$(en)$_3$]ClO$_4$</td>
<td>562</td>
<td>$3.37 \times 10^2$</td>
<td>7.5</td>
</tr>
<tr>
<td>[pyCo(DH)$_2$H$_2$O]ClO$_4$</td>
<td>300</td>
<td>$4.80 \times 10^2$</td>
<td>9.43</td>
</tr>
<tr>
<td>ClCo(DH)$_2$H$_2$O</td>
<td>300</td>
<td>$4.78 \times 10^3$</td>
<td>8.59</td>
</tr>
<tr>
<td>[mbimCo(DH)$_2$H$_2$O]ClO$_4$⋅2H$_2$O</td>
<td>340</td>
<td>$2.08 \times 10^3$</td>
<td>9.90</td>
</tr>
<tr>
<td>bimCo(DH)$_2$Cl</td>
<td>300</td>
<td>$3.89 \times 10^3$</td>
<td>9.83</td>
</tr>
<tr>
<td>NO$_3$Co(DH)$_2$H$_2$O</td>
<td>375</td>
<td>$1.53 \times 10^3$</td>
<td>8.72</td>
</tr>
<tr>
<td>CH$_3$Co(DH)$_2$H$_2$O</td>
<td>441</td>
<td>$1.47 \times 10^3$</td>
<td>8.63</td>
</tr>
<tr>
<td>aquocobalamin chloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="ClO$_4$">mbimCo(DO)(DOH)$_2$H$_2$O</a>$_2$</td>
<td>350</td>
<td>$2.62 \times 10^3$</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>$4.07 \times 10^3$</td>
<td>9.63</td>
</tr>
</tbody>
</table>


analysis and u.v.–visible spectra are identical but the infrared spectra in the solid state show differences. The first fraction is brown and consists of [mbimCo(DO)(DOH)$_2$H$_2$O](ClO$_4$)$_2$. The second fraction of crystals is more red–brown, and in the infrared spectrum shows indications of perchlorate coordination. It probably consists of [mbimCo(DO)(DOH)$_2$ClO$_4$]. In aqueous solution evidence of perchlorate coordination was also found in the $^1$H n.m.r. spectra. Two sets of peaks were found, of which the ratio of the integrals shows concentration dependence. The ratio also changes on addition of sodium perchlorate. From the ratio [mbimCo(DO)(DOH)$_2$ClO$_4$]: [mbimCo(DO)(DOH)$_2$ClO$_4$] as a function of sodium perchlorate concentration, an equilibrium constant of 3 dm$^3$ mol$^{-1}$ was estimated. $^1$H n.m.r. in D$_2$O (relative to (CH$_3$)$_3$SiC$_3$H$_5$SO$_4$Na): [mbimCo(DO)-(DOH)$_2$H$_2$O](ClO$_4$)$_2$: 2.33 (m, 2H), 2.62 (s, 6H), 2.73 (s, 6H), 4.06 (s, 3H), 4.13 (t, 4H), 7.4–7.8 (m, 4H), 8.96 (s, 1H); [mbimCo(DO)(DOH)$_2$ClO$_4$]: 2.24 (m, 2H), 2.57 (s, 6H), 2.73 (s, 6H), 3.76 (s, 3H), 4.33 (t, 4H), 7.42 (m, 4H).

For CH$_3$Co(DH)$_2$H$_2$O and NO$_3$Co(DH)$_2$H$_2$O, $^1$H n.m.r. and u.v.–visible spectra exclude coordination of dioxane in the solvent mixtures used. In 98% dioxane–water v/v the methyl peak of CH$_3$Co(DH)$_2$H$_2$O shows a shoulder, probably caused by coordination of dioxane or dimerisation. During the course of the solubility measurements no appreciable hydrolysis of the compounds occurs. Usually the solubility determinations were reproducible to within 5%. The concentrations of the saturated solutions were measured photometrically after dilution with water or 50% ethanol–water v/v (table 1). The wavelengths and extinction coefficients used are given in table 1. The solubilities are given in table 2.

The solubilities of aquocobalamin chloride in dioxane–water mixtures at 298.15 K were measured previously by us with a different method. The solubilities were found to be equal within experimental error for the two methods.

For the calculation of the transfer Gibbs energies in dioxane–water mixtures the contributions of the perchlorate or chloride ion (after conversion to the molarity scale) were subtracted. The transfer Gibbs energies ($\tilde{c}_mG^\circ_{\text{exp}}$) were calculated with the following formula

$$\tilde{c}_mG^\circ_{\text{exp}} = -RT \ln K_m^s/K_w^s$$

(1)

where $K_m^s$ is the solubility or the solubility product in water and $K_m^s$ that in the mixture (molarity scale). In fig. 1 the transfer parameters are shown for the dioxane–water
### Table 2. Solubilities (units mol dm$^{-3}$) as a function of solvent composition and temperature

<table>
<thead>
<tr>
<th></th>
<th>[B$_{12}$H$_2$O]Cl ($\times 10^{-2}$)</th>
<th>NO$_2$Co(DH)$_2$H$_2$O ($\times 10^{-2}$)</th>
<th>CH$_3$Co(DH)$_2$H$_2$O ($\times 10^{-2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>dioxane (vol%)</td>
<td>20°C</td>
<td>25°C</td>
<td>30°C</td>
</tr>
<tr>
<td>0</td>
<td>7.73</td>
<td>8.04</td>
<td>8.56</td>
</tr>
<tr>
<td>10</td>
<td>10.3</td>
<td>10.7</td>
<td>11.2</td>
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<td>20</td>
<td>10.7</td>
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<td>12.6</td>
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<td>30</td>
<td>9.5</td>
<td>10.1</td>
<td>11.6</td>
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<td>40</td>
<td>8.1</td>
<td>8.6</td>
<td>10.0</td>
</tr>
<tr>
<td>50</td>
<td>3.0</td>
<td>3.5</td>
<td>4.3</td>
</tr>
<tr>
<td>60</td>
<td>2.2</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>70</td>
<td>3.0</td>
<td>3.5</td>
<td>4.3</td>
</tr>
<tr>
<td>80</td>
<td>2.2</td>
<td>2.2</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>[Co(N$_2$)$_2$(en)$_2$]ClO$_4$</th>
<th>[pyCo(DH)$_2$H$_2$O]Cl</th>
<th>CIoCo(DH)$_2$H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.5 × 10$^{-2}$</td>
<td>4.2 × 10$^{-2}$</td>
<td>1.2 × 10$^{-2}$</td>
</tr>
<tr>
<td>20</td>
<td>2.0 × 10$^{-2}$</td>
<td>5.2 × 10$^{-2}$</td>
<td>2.6 × 10$^{-2}$</td>
</tr>
<tr>
<td>45</td>
<td>2.9 × 10$^{-2}$</td>
<td>1.0 × 10$^{-1}$</td>
<td>5.3 × 10$^{-2}$</td>
</tr>
<tr>
<td>70</td>
<td>2.0 × 10$^{-2}$</td>
<td>1.4 × 10$^{-1}$</td>
<td>7.3 × 10$^{-2}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>[mbimCo(DH)$_2$]ClO$_4$</th>
<th>bimCo(DH)$_2$Cl</th>
<th><a href="ClO$_4$">mbimCo(DO)(DOH)$_2$H$_2$O</a>$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>dioxane (vol%)</td>
<td>25°C</td>
<td>25°C</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9.5 × 10$^{-3}$</td>
<td>0.77 × 10$^{-4}$</td>
<td>1.2 × 10$^{-2}$</td>
</tr>
<tr>
<td>20</td>
<td>2.8 × 10$^{-2}$</td>
<td>4.8 × 10$^{-4}$</td>
<td>2.9 × 10$^{-2}$</td>
</tr>
<tr>
<td>45</td>
<td>1.1 × 10$^{-3}$</td>
<td>4.0 × 10$^{-3}$</td>
<td>8.7 × 10$^{-2}$</td>
</tr>
<tr>
<td>70</td>
<td>3.0 × 10$^{-3}$</td>
<td>2.1 × 10$^{-2}$</td>
<td>2.1 × 10$^{-1}$</td>
</tr>
</tbody>
</table>
mixtures and in fig. 2 for the acetonitrile–water mixtures. The values for the Co(NH$_3$)$_6^{3+}$ ion were calculated from the solubilities of the chloride salt given by Brisset, together with the transfer Gibbs energies for the chloride ion in acetonitrile–water mixtures given by Kundu et al.

From the temperature dependence of the solubilities of NO$_2$Co(DH)$_2$H$_2$O, CH$_3$Co(DH)$_2$H$_2$O and aquocobalamin chloride in the mixtures, the transfer enthalpy and transfer entropy values were calculated according to

$$
\delta_m G^o = \delta_m H^o - T \delta_m S^o.
$$

(2)
The transfer enthalpy values for the chloride ion in dioxane–water mixtures, necessary to calculate the transfer enthalpy values for the aquocobalamin cation, were calculated from values of Bhatnagar;\(^{18}\) the transfer entropy values were calculated with these and the transfer Gibbs energies. The results are shown in fig. 3, where for comparison the previously published\(^{10}\) transfer values for the aquocobalamin cation in acetonitrile–water mixtures are included.

Calculations and Discussion

The transfer Gibbs energy curves (fig. 1) all decrease at first on addition of dioxane to water. The more hydrophobic complexes are more strongly stabilized on addition of dioxane. The complexes ClCo(DH)\(_2\)H\(_2\)O, CH\(_3\)Co(DH)\(_2\)H\(_2\)O, [Co(N\(_3\))\(_2\)(en)\(_2\)]\(^+\) and the aquocobalamin cation show a minimum in transfer Gibbs energy, which is more pronounced for the latter two compounds.

The transfer Gibbs energy can be considered as the sum of three terms:\(^{13,14}\) (a) the cavity term, the energy needed to create a cavity in the solvent of suitable size to accommodate the solute molecule; (b) the coulomb interaction, the Born-type interaction between the charge of the solute and the solvent; (c) the specific interaction, including dispersion interactions and hydrogen bonding:

\[
\varphi_m G^0 \text{exp} = \varphi_m G^0 \text{cav} + \varphi_m G^0 \text{coul} + \varphi_m G^0 \text{spec}. \tag{3}
\]

For the metal complexes used here the coulomb term is small [Co(NH\(_3\))\(_8\)]\(^+\) excepted.
The cavity term can be calculated with the scaled particle theory (SPT).\textsuperscript{13, 15}

\[
G_{\text{cav}} = G_{\text{c}} + RT \ln \left( \frac{RT}{V} \right)
\]

\[
G_{\text{c}} = -RT \ln \left( 1 - Y_0 \right) + RT \left[ 3Y_2/(1 - Y_0) \right] D
\]

\[
+ RT \left[ 3Y_1(1 - Y_0) + 4.5Y_2(1 - Y_0)^2 \right] D^2 - 1/6\pi NP D^3
\]

where

\[
Y_n = (\pi N/6V) \left( x_1a^n + x_2b^n \right) (n = 1-3)
\]

\[
V = (x_1M_1 + x_2M_2)/d_0.
\]

\(x_1\) and \(x_2\) are the mole fractions and \(M_1\) and \(M_2\) the molecular weights of the two solvents, \(d_0\) is the density of the solvent mixture, \(N\) is Avogadro’s number, \(a\) and \(b\) are the diameters of the two solvent molecules, \(D\) is the diameter of the solute molecule and \(P\) is the pressure.

The SPT has been successful in predicting transfer Gibbs energies, enthalpies and entropies of large organic solutes and apolar gases.\textsuperscript{14, 16, 17} Recently this theory was also applied to metal complexes; the partition coefficients of some acetylacetonatometal complexes for the partition between water and an organic phase were successfully calculated.\textsuperscript{18} Also, solubilities of tris(acetylactonato)chromium(III) in aqueous alcohol mixtures were calculated with the SPT.\textsuperscript{19} It has been argued that the SPT cannot be applied to solutes that have strong and directional interactions with the solvent molecules. In that case the additivity of the cavity term and the specific interaction term is questioned.\textsuperscript{20} In our case the metal complexes do have these specific interactions. We fully recognise the limited applicability of the SPT in this case, but we only want to establish the order of magnitude of the cavity term and not a quantitative agreement between experiment and theory.

The following constants were used in the calculation of the cavity term; for the densities of the dioxane–water mixtures those of Griffiths\textsuperscript{21} and for the acetonitrile–water mixtures those of Maslan \textit{et al.}\textsuperscript{22} The diameters of the cavities that water, dioxane and acetonitrile occupy were taken as 2.76,\textsuperscript{17} 5.24\textsuperscript{23} and 4.12\textsuperscript{17} respectively. The diameters of the cobaloximes could be estimated from the partial molar volume of NO\textsubscript{3}Co(DH)\textsubscript{2}H\textsubscript{2}O\textsuperscript{24} and the principle of group additivity.\textsuperscript{25, 26} The same principle was used for [Co(N\textsubscript{3})\textsubscript{2}(en)\textsubscript{2}]\textsuperscript{2+}, where the crystal structure parameters of [Co(NO\textsubscript{3})\textsubscript{2}(en)\textsubscript{2}]\textsuperscript{27} were taken to estimate the diameter of the complex. The electrostriction was estimated from the relation found by van Eldik\textsuperscript{28} for cobaltammine complexes. The diameters are given in table 1. These values may not be very accurate, and are only used here for comparison. The cavity energy is not very sensitive to variations in the diameter of the solute, but is very sensitive to variations in the diameter of the solvent.

The partial molar volumes of NO\textsubscript{3}Co(DH)\textsubscript{2}H\textsubscript{2}O and aquocobalamin chloride were measured in dioxane–water mixtures and were found to vary by no more than 5 and 2\%, respectively.\textsuperscript{24} The partial molar volumes of aquocobalamin chloride were also measured in acetonitrile–water mixtures; in these mixtures a dramatic increase in partial molar volume of 20\% was found.\textsuperscript{24} The cavity term was calculated for this system, using both a constant diameter for aquocobalamin chloride (14.4 Å) and a variable diameter, calculated from the partial molar volume in the mixtures.

The transfer Gibbs energies of cavity formation were calculated. As expected, there is not much difference for the cobaloximes in the magnitude of the cavity term, the difference between water and 80\% dioxane–water v/v being ca. 10 kJ mol\textsuperscript{-1}. Aquocobalamin chloride shows the largest stabilisation caused by the decrease of the cavity term, the difference between water and 80\% dioxane–water v/v being 30 kJ mol\textsuperscript{-1}.

From the difference between \(\delta_mG_{\text{exp}}^o\) and \(\delta G_{\text{cav}}^o\) we find the specific interaction transfer Gibbs energy (\(\delta_mG_{\text{spec}}^o\)), which is shown in fig. 4. The \(\delta_mG_{\text{spec}}^o\) curve for the small cobaloximes remains almost constant up to 50\% dioxane–water v/v, after which
a destabilisation sets in, probably caused by the loss of hydrogen bonds as a consequence of the replacement of water by dioxane in the second coordination sphere. From the shape of the $\Delta_m G^\circ_{\text{spec}}$ curve it can be concluded that the small cobaloximes NO$_3$Co(DH)$_2$H$_2$O, CH$_3$Co(DH)$_2$H$_2$O and ClCo(DH)$_2$H$_2$O are preferentially solvated by water. Aquocobalamin chloride also shows preferential solvation up to 40% dioxane–water v/v, as concluded before.$^b$

An independent indication of the preferential solvation of these complexes can be obtained from $^{59}$Co n.m.r. spectra in the solvent mixtures. The $^{59}$Co n.m.r. chemical shifts are known to be very sensitive to changes in the chemical environment.$^{29, 30}$ A decrease in the donor properties of the solvent results in a decrease in electron density at the cobalt ion causing an upfield shift.$^{29}$ We were able to measure the $^{59}$Co n.m.r. spectra in the mixtures for CH$_3$Co(DH)$_2$H$_2$O, for which compound the solubilities are large enough over the whole composition range. The spectra were measured of almost saturated solutions. The linewidth was ca. 6000 Hz. In fig. 5 the chemical shift relative to an external reference of a solution of [Co(NH$_3$)$_6$]Cl$_3$ in water is shown as a function of solvent composition. In pure dioxane the linewidth of the $^{59}$Co n.m.r. peak almost doubled, indicating a chemical change in the complex, which could be substantiated from the $^1$H n.m.r. spectra. We were not able to find $^{59}$Co n.m.r. signals for aquocobalamin chloride, NO$_3$Co(DH)$_2$H$_2$O and [pyCo(DH)$_2$H$_2$O]ClO$_4$. If the $\Delta_m G^\circ_{\text{spec}}$ term is plotted against the $^{59}$Co n.m.r. shift for the different mixtures, a straight line is obtained with a correlation coefficient of 0.97 ($R$). It is clear that both parameters, $\Delta_m G^\circ_{\text{spec}}$ and the $^{59}$Co n.m.r. shift, reflect the same changes in the composition of the second coordination sphere.

The shape of the $\Delta_m G^\circ_{\text{spec}}$ curves is determined by a balance between hydrophobic and hydrophilic interactions. Aquocobalamin and [Co(N$_3$)$_2$(en)$_2$]$^+$ show the largest

Fig. 4. Transfer Gibbs energies of specific interactions (spec) [calculated with eqn (3) and (4)]. Symbols as used in fig. 1.
Fig. 5. $^{59}$Co n.m.r. chemical shifts (ppm) of CH$_3$Co(DH)$_2$H$_2$O in dioxane–water mixtures at 294.75 K (external reference [Co(NH$_3$)$_6$]Cl$_3$ in water).

Fig. 6. Transfer Gibbs energies of cavity formation for aquocobalamin$^+$ in acetonitrile–water mixtures calculated with eqn (4); $\Delta$, variable diameter for the solute; $\bigcirc$, constant diameter for the solute.

Destabilisation in the dioxane-rich mixtures, whereas the cobaloximes with large hydrophobic ligands [mbim Co(DH)$_2$H$_2$O]$^+$, [mbim Co(DO)(DOH)$_n$H$_2$O]$^{2+}$, bimCo(DH)$_2$Cl and [pyCo(DH)$_2$H$_2$O]$^+$, show a stabilisation upon addition of dioxane, up to ca. 50% dioxane–water v/v. Apparently at that composition the gain of hydrophobic interaction energy with dioxane is compensated by the loss of hydrogen-bond energy. The position of the minimum reflects the balance between hydrophobic and hydrophilic groups in the molecule. From this, vitamin B$_{12}$ can be characterized as a mainly
hydrophilic molecule, as reflected also by its general solubility behaviour in several solvents. The order of increasing ratio hydrophilic/hydrophobic character as concluded from the $\delta_m G_{\text{spec}}$ curves is $[\text{mbimCo(DO)(DOH)}_n\text{H}_2\text{O}]^{2+} > [\text{mbimCo(DH)}_n\text{H}_2\text{O}]^{2+} > \text{bimCo(DH)}_3\text{Cl} > [\text{Co(NH}_3)_2\text{(en)}]^{2+} \approx \text{aquocobalamin}^{2+} \approx [\text{pyCo(DH)}_n\text{H}_2\text{O}]^{2+} > \text{NO}_2\text{Co(DH)}_2\text{H}_2\text{O} \approx \text{ClCo(DH)}_2\text{H}_2\text{O} \approx \text{CH}_3\text{Co(DH)}_2\text{H}_2\text{O}$.

The transfer Gibbs energy of the aquocobalamin cation in acetonitrile–water mixtures shows a maximum in the water-rich mixtures (fig. 2). This maximum has previously been ascribed to an increase in solvent structure at low acetonitrile contents. A roughly similar shape of the transfer Gibbs energy curve in these mixtures is found for $[\text{Co(NH}_3)_2\text{H}_2\text{O}]^{2+}$ (fig. 2). The transfer Gibbs energies of cavity formation for aquocobalamin chloride calculated with either a constant or a variable diameter (calculated from the partial molar volumes) are shown in fig. 6. In the latter case a maximum is observed at a higher percentage of acetonitrile than observed for $\delta_m G_{\text{exp}}$. It is not clear whether the partial molar volume changes in the acetonitrile–water mixtures for aquocobalamin chloride are completely caused by the changes in the size of the solute molecule or that other factors are involved. A full discussion of the partial molar volumes of aquocobalamin chloride and $\text{NO}_2\text{Co(DH)}_2\text{H}_2\text{O}$ will be published separately.

We verified that the conclusions are not affected by the choice of the scale for the transfer parameters (i.e. molarity or mole fraction scale).

It is not possible to calculate cavity formation contributions to the transfer enthalpy and entropy values in the two mixtures, because the available thermal expansibilities do not cover the entire composition range necessary for these calculations. The $\delta_m H^0$ and $\delta_m S^0$ curves show the familiar compensation effect (fig. 3). Although the $\delta_m G_{\text{exp}}$ values for $\text{CH}_3\text{Co(DH)}_2\text{H}_2\text{O}$ and $\text{NO}_2\text{Co(DH)}_2\text{H}_2\text{O}$ are very similar (fig. 1), the $\delta_m H^0$ and $\delta_m S^0$ values differ considerably in the dioxane-rich mixtures. Values for $\text{CH}_3\text{Co(DH)}_2\text{H}_2\text{O}$ increase in the dioxane-rich mixtures, whereas the values for $\text{NO}_2\text{Co(DH)}_2\text{H}_2\text{O}$ decrease. The $\delta_m H^0$ and $\delta_m S^0$ curves for aquocobalamin show a maximum at 60% dioxane–water v/v. The aquocobalamin cation behaves similarly in the two solvent systems. In the acetonitrile–water mixtures a maximum is present at 10 vol%, just as in the $\delta_m G_{\text{exp}}$ values (fig. 2). After 70 vol% organic cosolvent differences occur: values for $\delta_m H^0$ and $\delta_m S^0$ for the aquocobalamin cation decrease more in the dioxane–water mixtures. The solvent dependence of the partial molar volumes of aquocobalamin chloride is totally different in the two solvent systems. Therefore it might be interesting to compare the temperature and pressure dependence of the kinetics of axial ligand substitution reactions in the two solvent systems.

Maxima and minima in $\delta_m H^0$ profiles are generally attributed to changes in solvent structure and solvation/desolvation of the solutes. The nature of the dioxane–water interactions in the water-rich region is still controversial as to whether dioxane enhances or breaks the water structure.

When we compare the results for aquocobalamin in dioxane–water and acetonitrile–water mixtures and attribute the maximum at 10 vol% in the $\delta_m G^0$ values to structure enhancement in acetonitrile–water, then dioxane is effectively a structure breaker when added to water. Both for dioxane and acetonitrile mixtures eventually the structure of water is broken down. The differences in the $\delta_m H^0$ and $\delta_m S^0$ profiles for the studied compounds between the two solvent systems might be partially attributed to a difference in solvation after 70 vol% cosolvent.

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References


