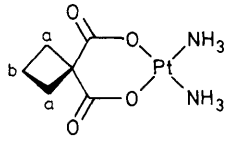
The Binding of Cyclobutane-1,1-dicarboxylatodiammineplatinum(II) by α-Cyclodextrin in Aqueous Solution

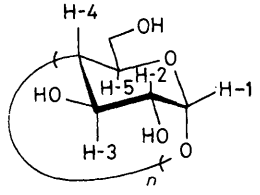
David R. Alston, Terence H. Lilley, and J. Fraser Stoddart
Department of Chemistry, The University, Sheffield S3 7HF, U.K.

Microcalorimetry and ^{1}H n.m.r. spectroscopy have established that $Pt(NH_3)_2(CBDCA)$ (CBDCA = cyclobutane-1,1-dicarboxylato) and α-cyclodextrin (α-CD) form a 1 : 1 adduct in water with a standard free energy change ($-\Delta G^\circ$) in the region of 10.4—13.0 kJ mol^{-1} at 22—25 °C.

A series of structure–activity studies,[1] which followed the discovery[2] of the anti-tumour activity of cisplatin [*cis*-$Pt(NH_3)_2Cl_2$], has led to the development of a range of potential second generation drugs. Foremost amongst these[3] is cyclobutane-1,1-dicarboxylatodiammineplatinum(II) [$Pt(NH_3)_2(CBDCA)$]; its anti-tumour activity is comparable with that of cisplatin, its aqueous solubility is much higher, and its toxicity is much lower.



$Pt(NH_3)_2(CBDCA)$



α-CD $n = 6$
β-CD $n = 7$
γ-CD $n = 8$

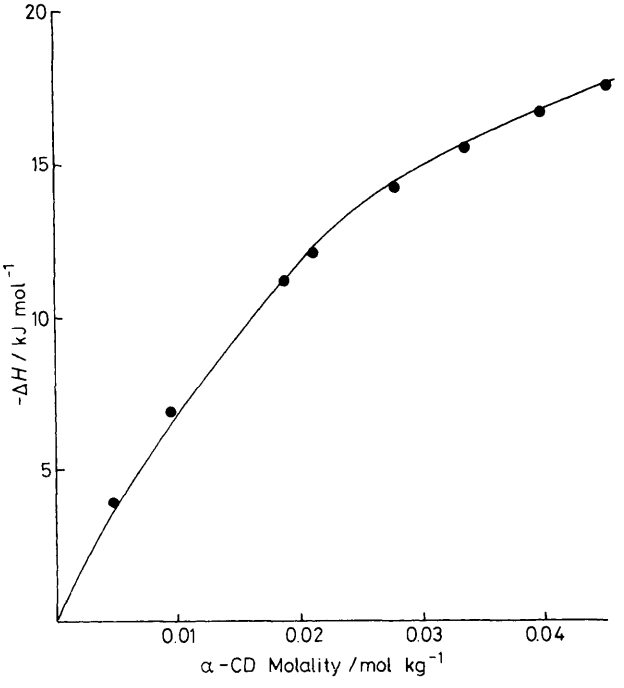


Figure 1. The molar enthalpy of $Pt(NH_3)_2(CBDCA)$ with α-CD as a function of the α-CD molality. The filled circles denote experimental points and the line the analysis obtained using equation (2).

Recently, cyclodextrins, which act[4,5] as molecular hosts towards a wide range of guests, have found a number of pharmaceutical applications[5] on account of their ability to increase (i) the aqueous solubility of drugs sparingly soluble in water,[6—9] (ii) the stability of sensitive drugs towards heat,[6,7] light,[6] oxidising reagents,[6] and acidic conditions,[8] and (iii) oral absorption[6,8—10] of drugs, whilst reducing their damage to the stomach wall.[11] Since inspection of space-filling molecular models revealed that the CBDCA ligand of $Pt(NH_3)_2(CBDCA)$ fits snugly into the cavity of α-cyclodextrin (α-CD), we were encouraged to investigate the binding of the platinum complex by α-CD in aqueous solution.

Qualitative evidence for host–guest binding comes from a study of the aqueous solubility of $Pt(NH_3)_2(CBDCA)$ in the presence of α-CD.† At least 87 mM concentrations can be attained at room temperature when an aqueous solution of α-CD (0.6 mol. equiv.) is employed to dissolve the platinum complex compared with only 50 mM concentrations in the absence of α-CD. The interaction between α-CD and $Pt(NH_3)_2(CBDCA)$ was investigated quantitatively by a microcalorimetric procedure and by ^{1}H n.m.r. spectroscopy. For the microcalorimetry experiments, a solution of the platinum complex (0.02366 mol kg^{-1}) in water was mixed with a range of aqueous solutions of α-CD (*ca.* 0.01—0.1 mol kg^{-1}) in a batch calorimeter[12] operating at 25 °C. A series of preliminary experiments were performed so that corrections for the contributions arising from the enthalpy of dilution of the two solutes could be made. The expression linking the enthalpy change per mol (ΔH) of $Pt(NH_3)_2(CBDCA)$ to the final molalities of it and α-CD and to the equilibrium constant (K_a) and the standard enthalpy change (ΔH°) for the equilibrium (1) is given in equation (2). From values of ΔH and [α-CD] obtained from experiment, equation (2) was solved using a non-linear least-squares routine to give $K_a = 60$ mol^{-1} kg and $\Delta H^\circ = -25.3$ kJ mol^{-1}. The quality of the results obtained is clear from inspection of Figure 1. The K_a value corresponds to a standard free energy change ($-\Delta G^\circ$) of 10.4 kJ mol^{-1}. This ΔG° value, together with the ΔH° value and the standard entropy change ($\Delta S^\circ = -42$ J K^{-1} mol^{-1}), indicate that $Pt(NH_3)_2(CBDCA)$ has a very marked tendency to associate with α-CD in water. This conclusion is supported by ^{1}H n.m.r. spectroscopic investigations performed on $Pt(NH_3)_2(CBDCA)$·α-CD in D_2O at *ca.* 22 °C. The magnitudes of the chemical shift changes (Figure 2) for H-3 and H-5, relative to those for the other glucopyranosidic

† The binding of $Pt(NH_3)_2(CBDCA)$ by cyclodextrins is highly host-specific. Both β- and γ-cyclodextrins (β- and γ-CD) fail to bind $Pt(NH_3)_2(CBDCA)$ as shown by solubility studies and ^{1}H n.m.r. spectroscopic investigations. Both guest and host proton probes experience no changes in their chemical shifts on addition of $Pt(NH_3)_2(CBDCA)$ to D_2O solutions of β- and γ-CD.

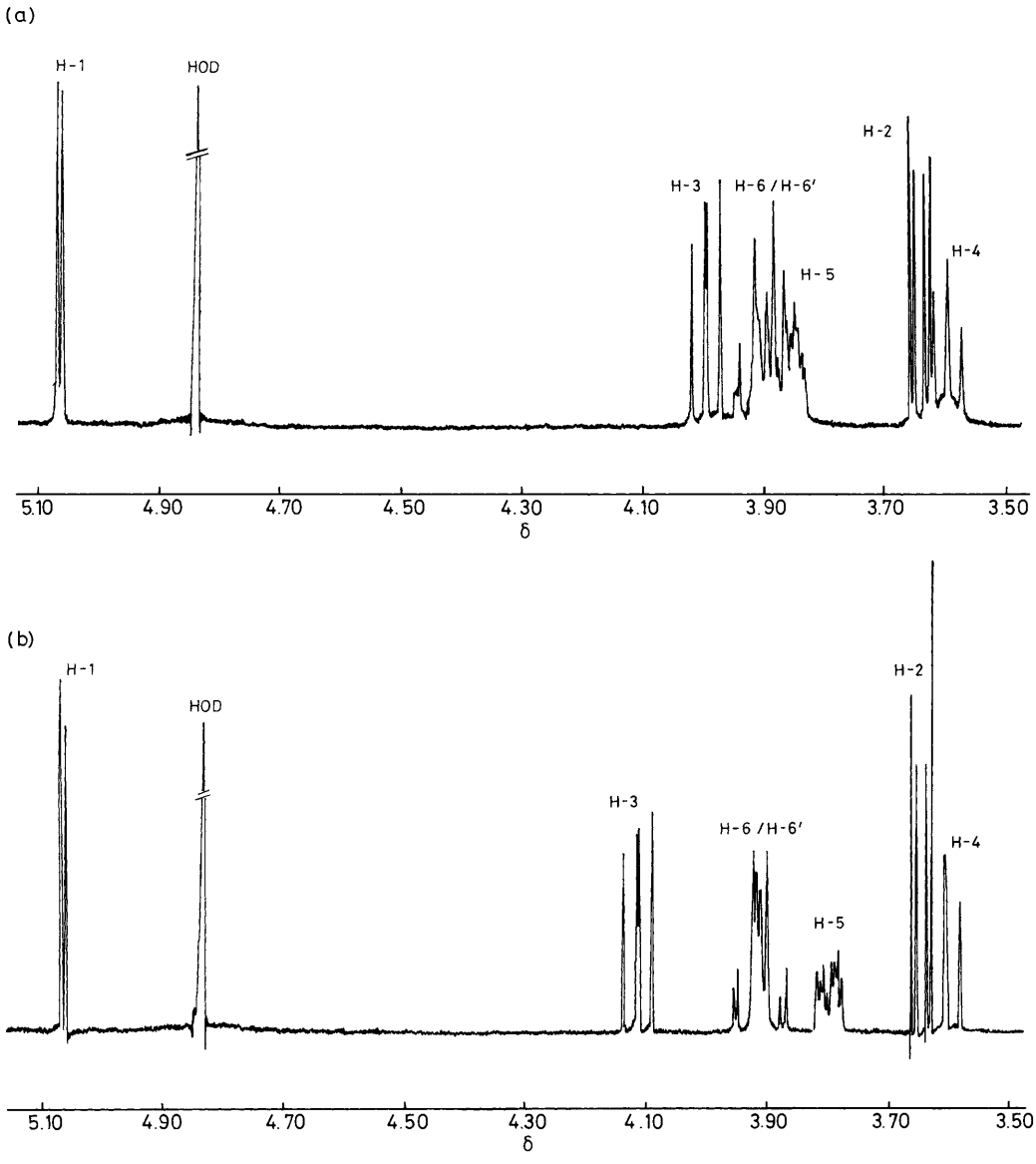


Figure 2. The 400 MHz ^{1}H n.m.r. spectra of (a) α-CD and (b) $Pt(NH_3)_2$(CBDCA)·α-CD in D_2O at concentrations of approximately 0.013 mol kg^{-1}.

protons in α-CD, and the larger shifts to higher frequencies of the signals for H-a and H-b on the CBDCA ligand of $Pt(NH_3)_2$(CBDCA) indicate that those pairs of host and guest protons are in propinquity, *i.e.* it is the CBDCA ligand of the platinum complex which penetrates the α-CD cavity. The chemical shift differences for H-3 in α-CD and for H-a in $Pt(NH_3)_2$(CBDCA), observed on changing progressively the concentration x (in mol kg^{-1}) of the 1 : 1 adduct, were analysed using equation (3), where the Δ's are the differences between the observed chemical shifts of the probe protons in

$$\alpha\text{-CD} + Pt(NH_3)_2(CBDCA) \rightleftharpoons Pt(NH_3)_2(CBDCA)\cdot\alpha\text{-CD} \quad (1)$$

$$K_a = \Delta H\cdot\Delta H^\circ/\{(\Delta H^\circ[\alpha\text{-CD}] - \Delta H[Pt(NH_3)_2\text{-}(CBDCA)])\,(\Delta H^\circ - \Delta H)\} \quad (2)$$

$$\Delta = \Delta_0 - (\Delta/x)^{1/2}\cdot(\Delta_0/K_a)^{1/2} \quad (3)$$

D_2O solutions of the 1 : 1 adduct at equilibrium (equation 1) and those for the same protons in the free components, and the Δ_0's are the differences between the limiting chemical shifts of the probe protons in the 1 : 1 adduct (assumed fully formed) and those for the same protons in the free components. Corrections were made in the processing of the chemical shift data for the concentration dependences of H-3 (on [α-CD])‡ and H-a {on [$Pt(NH_3)_2$(CBDCA)]}. For both H-3 and H-a, plots of Δ against $(\Delta/x)^{1/2}$ gave (Figure 3) good straight lines, as required by equation (3) from which K_a values of 130 and 200 mol^{-1} kg, respectively, were calculated. The derived $(-\Delta G^\circ)$ values of 11.9 and 13.0 kJ mol^{-1}, respectively, are in acceptable agreement with each other and

‡ It is known (K. Miyajima, M. Sawada, and M. Nakagaki, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3556) that α-CD has a marked tendency to associate in D_2O.

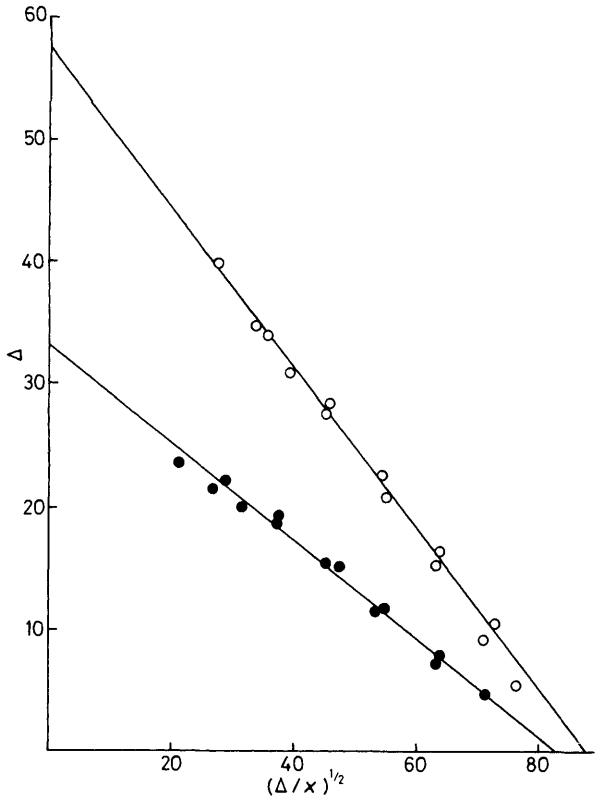


Figure 3. Plots of Δ against $(\Delta/x)^{\frac{1}{2}}$ for (●) H-a in $Pt(NH_3)_2(CBDCA)$ and (○) H-3 in α-CD in the quantitative ^1H n.m.r. experiment.

also with that ($-\Delta G^{\circ} = 10.4$ kJ mol^{-1}) obtained by microcalorimetry.

Although the strength of 1:1 adduct formation in D_2O solution between the neutral $Pt(NH_3)_2(CBDCA)$ and α-CD is less than that observed[13] for $[Rh(COD)(NH_3)_2\cdot\alpha\text{-CD}][PF_6]$ (COD = cyclo-octa-1,5-diene), the isolation of single crystals of $[Pt(NH_3)_2(CBDCA)\cdot\alpha\text{-CD}]$, suitable for *X*-ray crystallography, has been achieved.[14]

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