Hydrogen bonding effects on the cyclodextrin encapsulation of transition metal complexes: 'molecular snaps'

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Hydrogen-bonding with buffers dramatically influences the magnitude of cyclodextrin inclusion of transition metal complexes by acting as 'molecular snaps'.

In contrast to the vast number of organic inclusates reported, the use of metal complexes as guest molecules in cyclodextrin (CD) inclusion studies is very limited. However, during the past few years, interest in the encapsulation of transition metal complexes has increased significantly. This is in part due to the possible use of cyclodextrins as drug delivery agents and their potential exploitation in molecular recognition processes.

The majority of studies have involved complexation of ferrocene or its substituted derivatives[1,2] although crystallographic studies of metal–cyclodextrin inclusates have been reported. These include $[Rh(cod)(NH_3)_2 \cdot \alpha\text{-}CD][PF_6]$[3] and $[Cl(en)_2Co\{NH_2CH_2CH_2NH_2 \cdot \alpha CD\}\text{-}Co(en)_2Cl]Cl_4$.[4] Recently, functionalized cyclodextrins have been used in the synthesis of model hydrolytic metalloenzymes by attaching a pendant cyclodextrin to the first coordination sphere of a metal.[5,6] The hydrophobic CD cavities furnish well-suited receptacles for inclusion of apolar substrates, phenyl groups in particular. Encapsulation by cyclodextrins of portions of guest molecules adjacent to a metal centre has provided catalytic regiospecificity and stereoselectivity in product formation.[6,7]

In our initial publication on the effects of cyclodextrin encapsulation on the rate of electron transfer between metal complexes, we were unable to explain the observed rate decreases adequately.[8] Later we reported that these electron transfer effects may be a result of hydrogen bonding between the metal complexes and the host cyclodextrin.[9] Following these studies, other researchers have become interested in metal complex–cyclodextrin effects on reaction kinetics.[10] For example, Macartney has examined the effects of cyclodextrins on the substitution reactions of pentacyanoferrate(II) complexes with nitrogen heterocycles. He has also studied the effect of encapsulation of catechol on its rate of oxidation by metal complexes. To provide much needed information on encapsulation constants of free ligands, we have reported on the binding of nitrogen heterocycles with cyclodextrins using fluorescent techniques.[11]

While pursuing binding studies of metal–CD interactions, it was observed that the size of the equilibrium constants, K_{CD}, for inclusion of the pentamineruthenium(II) complexes was quite sensitive to the concentration and nature of the buffer used. For example, when a bicarbonate–carbonate buffer system was used, the size of the inclusion constant increased as the total buffer concentration increased (Fig. 1). While maintaining constant pH and ionic strength (0.1 mol dm^{-3} using $NaClO_4$) extrapolation to zero bicarbonate gives the same value for the binding constant as measured in the absence of bicarbonate (in 0.1 mol dm^{-3} sodium perchlorate). When phosphate is used instead of bicarbonate, the effect is even more pronounced. Acetate shows a similar although less dramatic enhancement of the observed binding constant. In contrast, replacement of perchlorate with chloride shows no significant enhancement of the binding constant, K_{CD}. This indicates that the differences in reactivity must be due to the ability of the substituting electrolytes to hydrogen bond. These buffer effects can be explained by postulating the formation of a ternary complex composed of metal complex, cyclodextrin, and buffer held together *via* hydrogen bonding.

Further evidence for involvement of hydrogen bonding may be found in the bicarbonate buffer system. The binding constant is sensitive to the pH, *i.e.* the binding constant increases with increases in pH. Since neither the metal complex nor the cyclodextrin have ionizable protons in the pH range studied, the effect must be due to deprotonation of the bicarbonate ion. This suggests that the carbonate ion is better able to enhance the binding of cyclodextrins to the metal centre.

The structure of this ternary complex is best understood if the buffer ion is envisioned to act as a hydrogen-bonded bridge between the hydroxy groups on the CD rim and the ammines of the ruthenium centre. We describe these buffers as acting like 'molecular snaps' which anchor the CD to the metal *via* H-bonding. The bicarbonate–carbonate system, Fig. 2, serves to illustrate how a buffer could enhance encapsulation.† Hydrogen bonding within the first coordination sphere of ion-pairs of

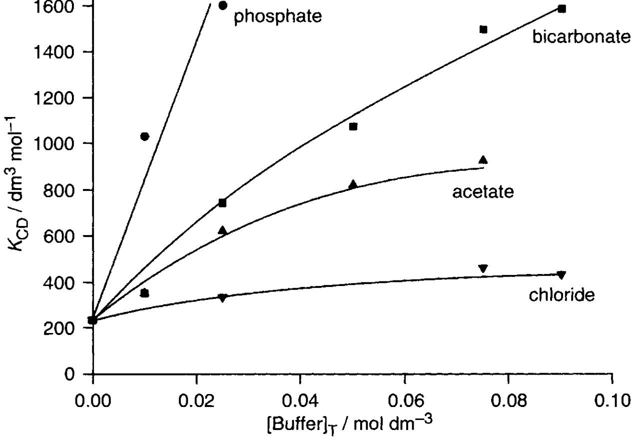

Fig. 1 Effect of electrolytes on the magnitude of K_{CD}. [I] = 0.1 mol dm^{-3} ($NaClO_4$), pH = 8.5, T = 16 °C.

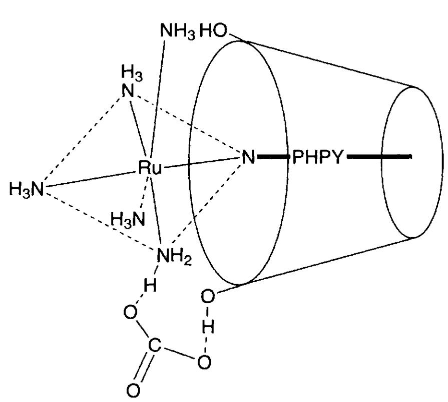

Fig. 2 Diagram of ternary complex

transition metal complexes has been demonstrated by Lappin and others.[12] To our knowledge, this is the first example of how the second coordination sphere of the metal complex participates in ion-pairing. This diagram should not be construed as a detailed picture of this clasp, but rather a working model. To determine the binding site and stucture conclusively, the preparation of crystals of encapsulated metal complexes suitable for X-ray crystallographic studies is underway.

As a test of this hypothesis, we examined the binding of methylated cyclodextrins to $[Ru(NH_3)_5 4\text{-phpy}]^{2+}$ (4-phpy = 4-phenylpyridine). If the hydroxy groups along the cyclodextrin rim are involved in hydrogen bonding with buffers, then methylation should inhibit it. Fig. 3 illustrates the results of these studies. 2,6-Dimethyl-β-cyclodextrin binds equally well with the ruthenium complex as does β-cyclodextrin at the various bicarbonate concentrations. In contrast however, the encapsulation constant for 2,3,6-trimethyl-β-cyclodextrin was unaffected by the presence of buffers.

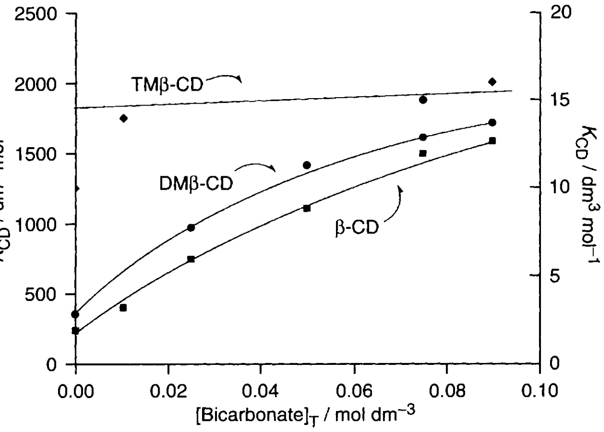

Fig. 3 The values of K_{CD} with methylated cyclodextrins at various bicarbonate concentrations. [I] = 0.1 mol dm^{-1} ($NaClO_4$), pH = 8.5, T = 16 °C. Right axis for β and DMβ, left axis TMβ.

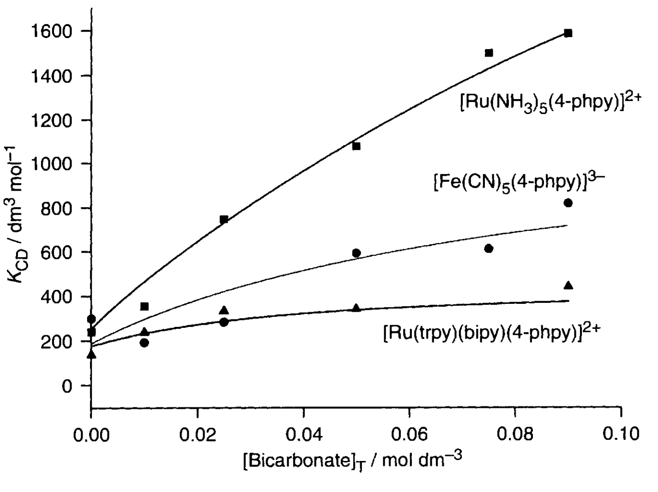

Fig. 4 The values of K_{CD} for the β-CD/bicarbonate encapsulation of various metal complexes. [I] = 0.1 mol dm^{-3} ($NaClO_4$), pH = 8.5, T = 16 °C.

The binding of cyclodextrin metal complexes, that do not possess hydrogen bonding capabilities and have different charges, was studied so that electrostatic effects could be examined along with a further test for hydrogen bonding. As may be seen in Fig. 4, when ammonia molecules are present in the primary coordination sphere, the introduction of bicarbonate increases the size of K_{CD}. When cyanides or polypyridyls are present as ancillary ligands, little or no effect on the size of K_{CD} is observed upon introduction of bicarbonate. The pentacyanoferrate complex may exhibit some effect since the cyanide nitrogen could be involved in a very weak hydrogen bond, the polypyridyl system is completely insensitive to the presence of bicarbonate. This would be anticipated if hydrogen bonding is indeed a significant factor in the formation of a clasped ternary ion pair. In addition, the nature of the charge on the metal complex appears to be unimportant.

Footnote

† Whether the 2 or 3 position hydroxy group is best able to participate in hydrogen bonding remains unclear from these studies.

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