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Carbon-13 spin-lattice relaxation studies of complexes of ferrocene with cyclodextrins in DMSO

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Abstract

^{13}C spin-lattice relaxation times (T_1) have been measured for a number of ferrocene complexes of α, β and γ cyclodextrins (CD). Inclusion of ferrocene in β-CD appears to cause a change in conformation of the macrocycle. Evidence of strong interaction between ferrocene and its derivatives with β and γ cyclodextrin is presented both from relaxation and polarimetry studies. The α-CD complexes are much more dissociated in solution. This was confirmed by the addition of the relaxation agent chromium(III) tris-(2,4-pentanedionate) which had no effect on the deeply embedded ferrocene in the β-CD complex, but which caused significant reduction in the T_1 values of the ferrocene in the α-CD complex. A brief preliminary study of some simple aromatic inclusion complexes is also presented. These findings show that the combination of T_1 measurements and use of relaxation reagents is a powerful approach to the assessment of structures of clathrates in solution.

Introduction

Cyclodextrins were first isolated in 1891 [1] and were subsequently characterised as oligosaccharides by Schardinger [2]. These cyclic saccharides (α, β, γ six, seven and eight glucose residues respectively) have the ability to form inclusion complexes [3] with a wide variety of organic molecules and use has been made of this property in the area of catalysis [4]. They have also been used extensively as model enzyme systems and as micro-encapsulation agents [5]. Relatively little work has been done on CD complexes of organometallic compounds and these studies centre around ferrocene and its derivatives. Molecular modelling calculations [6,7] have appeared in connection with the observed dramatic accelerations in acylation of β-CD [8] by ferrocenyl acrylic esters. These studies have thrown light on the geometry of the included or guest species which suggests formation of a distorted ester in the acyl-CD which adversely affects partitioning of the tetrahedral intermediate.

In the case of ferrocene (FcH) itself, cyclodextrins form relatively stable complexes with a stoichiometry which varies with cavity size [9]. Thus β- and γ-CD form 1 : 1 complexes whereas in the smaller α-CD a 1 : 2 stoichiometry [FcH · 2(α-CD)] is found. The Mössbauer spectra of the latter complexes exhibit unusual

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behaviour in that the quadrupole splittings decrease systematically with increasing temperature which was attributed to reorientation of the guest molecule in the CD cavity [10]. From Arrhenius data it was shown that the activation energies increased with increasing guest size. Work in the solution phase has also concentrated on simple ferrocene derivatives. Circular dichroism studies [11,12] on FcH-CD systems have revealed a large positive Cotton effect for the β-CD complex but a negative spectrum for the γ-CD analogue which was interpreted as being due to a change in position of the guest ferrocene from an axial to equatorial orientation.

One of the most fruitful techniques for studying molecular dynamics is that of NMR relaxation [12]. An interesting recent study on linewidths of ^{2}H NMR signals has also provided evidence for orientational changes in the FcH–β-CD and FcH–γ-CD inclusion complexes [14]. More usually, however, ^{13}C NMR relaxation times have been used to investigate such reorientational phenomena. This paper reports a study of CD complexes with ferrocene (and other aromatics) using this technique and is a continuation of our work on molecular dynamics of iron sandwich complexes [15].

Results and discussion

A detailed analysis of the molecular dynamics of ferrocene–cyclodextrin complexes requires the knowledge of the relevant equilibrium constants and the stoichiometry of the processes. In the case of the solution phase the observed ^{13}C spin-lattice relaxation time (T_1^{obs}) is a weighted average of the "free" and complexed guest molecule.

$$\frac{1}{T_1^{obs}} = \frac{1-x}{T_1^{C}} + \frac{x}{T_1^{F}} \tag{1}$$

where x is the mole fraction of "free" molecules and T_1^{c} and T_1^{F} the relaxation times of the complexed and free molecules respectively. There has been little systematic work on the determination of dissociation constants (K_D) of complexes in non-aqueous media. However, for the 1:1 FcH–β-CD system K_D values of 20 ± 5 [16] and 21 mM (11) in solvent DMSO have been reported, although details were rather sketchy. We have used a polarimetric method to confirm these values and also to assess complex formation in other systems. The polarimetric data appear in Table 1. For both β and γ cyclodextrins systematic increases in optical rotation (α) occurred with increasing ferrocene concentration. K_D values of 14.4 and 12.1 mM respectively were obtained which indicate that the complexes are only weakly dissociated in DMSO. It is generally accepted that ferrocene is included completely within the β and γ-CD activities. Such deep penetration is thus accompanied by marked increases in α. Examination of changes in α with ferrocene structure for β-CD (Table 1) reveals some interesting features. n-Butylferrocene and dimethylaminomethylferrocene behave like ferrocene itself but the observed increases in α are much reduced. This may be due to shallower penetration of CD activity or greater dissociation of the complexes in DMSO (or both). For t-pentylferrocene a small decrease in α occurs. Such a sterically crowded molecule cannot be wholly included but the unsubstituted Cp ring may penetrate the cavity. There is little doubt that a complex forms since it proved impossible to wash out the included ferrocene with solvents such as acetone or cyclohexane (see Experimental). A

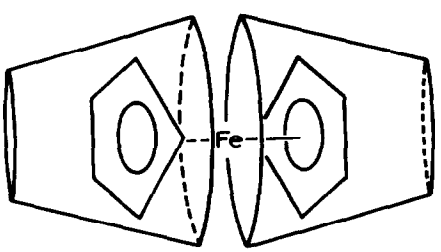
Table 1

Observed optical rotations (α) for cyclodextrin (CD) complexes of ferrocene (FcH) and related complexes in DMSO at 296 K

Cyclodextrin [a]	[CD] 10^2 M	Guest	[Guest] 10^2 M	α	$\delta\alpha$ [b]
α	2.06	–	–	5.15	–
α	2.06	FcH	2.15	5.12	−0.03
α	2.06	FcH	4.30	5.06	−0.09
α	2.06	FcH	6.45	5.05	−0.10
β	1.00	–	–	3.01	0.00
β	1.00	FcH	0.40	3.16	0.15
β	1.00	FcH	0.81	3.29	0.28
β	1.00	FcH	1.00	3.34	0.33
β	1.00	FcH	1.20	3.38	0.37
β	1.00	FcH	1.60	3.46	0.45
β	1.00	FcH	8.96	3.86	0.85
β	1.76	–	–	5.14	–
β	1.78	FcH	2.36	6.06	0.92
β	1.78	Fc-t-C_5H_{11}	2.60	5.07	−0.07
β	1.78	Fc-n-C_4H_9	2.75	5.37	0.23
β	1.78	$FcCH_2NMe_2$	2.74	5.42	0.28
β	1.78	$FcCH_2N^+Me_3I^-$	2.70	4.87	−0.27
β	1.78	$[C_6H_3(CH_3)_3Fe^+Cp$ [c]	2.27	4.94	−0.20
γ	1.00	–	–	3.41	0.00
γ	1.00	FcH	0.50	3.63	0.22
γ	1.00	FcH	1.05	3.79	0.38
γ	1.00	FcH	1.50	3.87	0.46
γ	1.00	FcH	2.00	3.95	0.54
γ	1.00	FcH	8.00	4.31	0.90

[a] α and β cyclodextrins available as hydrates. [b] Observed rotation relative to uncomplexed cyclodextrin. [c] (η^6-1,3,5-Trimethylbenzene)(η^5-cyclopentadienyl)iron(II) hexafluorophosphate.

similar but more marked behaviour is observed for $[FcCH_2NMe_3]$ [I] and [(mesitylene)FeCp][PF_6]. Both are charged species which makes it unlikely that complete incorporation occurs. In addition, for the latter species, the arene is much too bulky for inclusion. This behaviour is also apparent for ferrocene in α-CD. Analysis of this complex [11] has shown that, unlike the β and γ-CD complexes which have a 1 : 1 stoichiometry, two molecules of α-CD act as hosts. Mössbauer data [10,17] suggest differences in host–guest interactions for the α and β-CD systems and a model for the FcH · 2α-CD complex has been put forward [11].



It seems therefore that for the FcH · α-CD complex and β-CD complexes of monosubstituted ferrocenes with bulky or charged substituents only the cyclopentadienyl moiety is included and that the penetration is rather shallow [18].

^{13}C Spin-lattice relaxation studies

There has been relatively little work on ^{13}C relaxation in CD complexes. The first report of use of ^{13}C spin-lattice relaxation times (T_1) of such complexes was in 1976 [19]. T_1 values showed that for the α-CD complexes of *m*- and *p*-methylcinnamate, the methyl substituents experience hindrance due to contact with the hydrophobic cavity whereas for the sterically hindered t-butyl ester no change in T_1 occurred on complexation, suggesting that the t-butyl group is located outside the cavity core. More recent work by Inoue [20–23] has focussed on the dynamics of the CD complexes of aromatic amino acids. For molecules of medium size (MW < 2000) the tumbling motion through a solvent is rapid on the ^{13}C NMR timescale. Moreover, the mechanism of relaxation for such relatively small molecules is dominated by the dipole–dipole mode. For a carbon bearing a single proton, T_1 is related to the correlation time τ_c for molecular reorientation by equation 2

$$T_1^{-1} = \frac{\mu_0^2 \gamma_H^2 \gamma_C^2 \hbar^2 S(S+1)\tau_c}{12\pi^2 r_{CH}^6} \tag{2}$$

where μ_0 is the permeability of a vacuum, γ_H, γ_C are the gyromagnetic ratios for ^1H and ^{13}C nuclei, S is the proton spin quantum number and r_{CH} is the carbon–hydrogen bond length associated with the carbon nucleus under investigation. For isotropic tumblers

$$\tau_c = \frac{4\pi a^3 \eta f(r)}{3kT} \tag{3}$$

where a is the molecular radius of the tumbler, η the solvent viscosity and $f(r)$ a microviscosity correction factor (~ 0.16 for pure liquids). Equations 2 and 3 can be combined and yields

$$T_1^{-1} = 3.252 \times 10^{30} a^3 \eta \tag{4}$$

after putting in SI values of the relevant constants ($r_{CH} = 1.10 \times 10^{-10}$ m). This enables values of T_1 to be calculated and hence provides a means of testing for isotropic tumbling.

We first examined the effect of complexation on the T_1 values of the cyclodextrin host itself, the results for β-CD appearing in Table 2. Since the viscosity of the solutions is virtually the same, and if tumbling of the structures as a whole is isotropic, then differences in T_1 reflect differences in size of the solute. Using equation 4 and a value of a of 7.7×10^{-10} m [3] a T_1 of 0.09 s is calculated. One of the problems of such calculations is the choice of a values. More realistically the Van der Waals radii should be included which would increase a to approximately

Table 2

T_1 values (s) for β cyclodextrin and its complex with ferrocene [a]

	C2	C3	C4	C5	η [b]
β-CD	0.050	0.050	0.053	0.050	7.30
β-CD·FcH	0.037	–	0.037	–	7.36

[a] T_1 values of cyclodextrin framework carbons. 0.2 *M* in DMSO at 304 K. [b] Viscosity of solution in centipoise.

Table 3

^{13}C spin-lattice relaxation times (T_1, s) for cyclopentadienyl carbon nuclei of ferrocene and its complexes with cyclodextrins (CD) [a]

Solute	T (K)	T_1	η [b]	ηT_1
FcH	304	7.5	1.84	13.8
FcH	304	4.2 [c]	–	–
FcH + D-(+)-glucose (1.2 *M*)	304	4.3	6.13	26.3
FcH·(α-CD)$_2$	304	2.3	8.48	19.5
FcH·(α-CD)$_2$	333	5.2	–	–
FcH·(α-CD)$_2$	304	1.7 [c]	–	–
FcH·β-CD	304	0.20(0.15) [d]	7.36	1.47
FcH·β-CD	304	0.25 [c]	–	–
FcH·γ-CD	304	0.36(0.29) [d]	5.54	1.99
FcH·γ-CD	319	0.47	–	–
FcH·γ-CD	333	0.55	–	–

[a] 0.2 *M* in DMSO. [b] η in centipoise. [c] Added Cr(acac)$_3$ (3 m*M*). [d] Values in parentheses are calculated T_1 values of the complexed ferrocene estimated from measured K_D values and using eq. 1.

9.0×10^{-10} m and give a T_1 value of 0.06 s which is reasonably close to the observed average of 0.051 s. This value compares with 0.069 s obtained for solutions in aqueous NaOD [21]. These results suggest that β-CD in DMSO can be regarded as an approximately isotropic tumbler. Of more interest, however, are the significantly lower T_1 values (0.037 s) observed for the CD carbons of the FcH · β-CD complex. This suggests a change in size or shape of the cyclodextrin on complexation. The observed exaltation of optical rotation is probably another manifestation of such a conformational change. A similar phenomenon can be seen in the data of Inoue [21] for phenylalanine CD complexes. Here marked decreases in T_1 occur for the α- and β-CD complexes commensurate with deep cavity penetration. (The phenyl group will of course fit into the β-CD cavity far better than ferrocene.) For the γ-CD complex, however, relatively little change occurs which suggests that the guest is not bulky enough to exert pressure on the inside surfaces of the γ-CD torus and thus cause conformational changes.

We then examined the relaxation times of the guest species, the results of which appear in Table 3. The variations of T_1 with temperature for all complexes indicate a common dipole–dipole relaxation mode. If the included ferrocene is locked in the CD cavity and the complex simply tumbles as a whole then according to equation 4, ηT_1 should be constant. This is demonstrably not the case for the β- and γ-CD complexes. The case is less clear for α-CD complex particularly when compared with values of T_1 obtained in a glucose solution simulating the viscosity of the cyclodextrins. For both β and γ-CD complexes very marked reduction in T_1^{obs} occurs indicating that a separate and slower reorientation process is occurring within the cavity. The true T_1 values for the complexed ferrocene (as calculated by eq. 1 using experimental values of K_D) are even lower than the observed values. The true T_1 for the γ-CD complex (0.29 s) is appreciably higher than that of the β-CD analogue (0.15 s). This suggests a more rapid reorientation within the cavity which is in keeping with the larger cavity size of γ-CD. It is also possible that the rotational mode changes from axial (the only mode allowed for β-CD) to equatorial for the

Table 4

^{13}C spin-lattice relaxation times (T_1, s) for β-cyclodextrin complexes of phenyl derivatives [a]

Compounds	C2	C3	C4	Others
$PhCO_2H$	3.75	3.38	–	–
$PhCO_2H$ [b]	1.17	1.24	–	–
$PhCO_2H$·β-CD	0.99	1.09	0.54	–
$PhCO_2Me$	4.57	4.57	2.70	6.52(Me)
$PhCO_2Me$·β-CD	1.29	1.53	1.19	2.41(Me)
$PhCH_2OCOPh$ [c]	3.67	3.84	2.29	2.15(CH_2)
$PhCH_2OCOPh$·β-CD [c]	1.81	1.83	1.06	0.69(CH_2)
$PhCH_2OCOPh$·β-CD [c,d]	0.84	0.92	1.00	0.88(CH_2)
$PhCH_2OCOPh$ [e]	1.97	2.21	1.30	–
$PhCH_2OCOPh$·β-CD [e]	1.01	1.08	0.51	–
$PhCH_2OCOPh$·β-CD [d,e]	0.80	0.99	0.87	–

[a] 0.2 *M* in DMSO at 304 K. [b] T_1's measured in an equiviscous D-(+)-glucose solution in DMSO. [c] Data for the benzyl carbons. [d] Added 3 m*M* $Cr(acac)_3$. [e] Data for the benzoate carbons.

larger macrocycle. The T_1 for the α-CD complex is an order of magnitude greater than those of the β- and γ-CD complexes. It is clear that the ferrocene is only weakly bound to α-CD in DMSO. Unfortunately the changes in optical rotation and also UV absorption in the range 270–500 nm were too small to allow evaluation of K_D but the T_1 results suggest that K_D is much larger than those of the other cyclodextrins. Similar difficulties were encountered by other workers investigating α-CD complexes of aromatic aminoacids [22]. Supporting evidence for weak binding comes from the use of the relaxation reagent chromium(III)tris(2,4-pentanedionate)($Cr(acac)_3$). The addition of 3 m*M* $Cr(acac)_3$ to a 0.2 *M* solution of ferrocene in DMSO causes a 44% reduction in T_1. For the β-CD complex no reduction is observed in the Cp T_1 value which is the result expected for a structure in which the ferrocene is completely encapsulated by the cyclodextrin. For the α-CD complex, however, a 26% reduction in T_1 is found. This implies that a considerable fraction of ferrocene is unbound or at least very weakly bound.

Finally, some preliminary experiments are reported which evaluate the use of T_1 measurements generally in the structural studies of inclusion complexes. We have selected some simple phenyl derivatives for these tests (Table 4). The dissociation constants of simple aromatics are remarkably independent of the structure of the aromatic and have values of about 400 m*M* [11] in DMSO which indicates a significant concentration of "free" species. Viscosity again plays an important role as can be seen from T_1 values of benzoic acid in DMSO alone and in a glucose solution simulating the viscosity of the cyclodextrins. Complexation does, however, reduce T_1 values indicating a slowing of molecular rotation when incorporated in the CD cavity. However, a K_D value of 400 m*M* results in only 27% of the guest molecules being in the complexed form in a 0.2 *M* solution. Thus the observed reductions in T_1 for these solutions will be much smaller than those for the corresponding ferrocene/CD systems. For phenyl derivatives the value of the ratio of T_1 values of *ortho* or *meta* to *para* carbons ($T_1^{o,m}/T_1^{p}$) is often used as a probe for preferential rotation about the C1–C4 axis (for no rotation the ratio should be unity). The results listed in Table 4 show that, overall, such rotation occurs, though without a knowledge of the dissociation constants it is not possible to dissect this

data into the ratios for the free and complexed aromatic. In buffered aqueous media (pD = 11.3) using phenylalanine as a guest, K_D values of ~ 1 mM were reported [21] for the cyclodextrin complexes. Thus most of the guest molecules in such media are complexed. Evidence from ^{13}C chemical shifts [24] suggest that phenylalanine is deeply included in β-CD. However, the $T_1^{o,m}/T_1^p$ ratio does not change much compared with that in the absence of CD which shows that such preference rotation does indeed occur within the cavity. Returning to the current work, added $Cr(acac)_3$ causes the $T^{o,m}/T^p$ ratio to fall dramatically due to the domination of paramagnetic relaxation over the dipole–dipole mode. An interesting example is benzoylbenzoate which has two rings available for inclusion. The results of the T_1 studies indicate that it is the benzoyl ring which is preferentially complexed since lower T_1 values are observed. This is confirmed by the addition of $Cr(acac)_3$ which results in no overall change in the T_1 of the benzoyl carbons but a substantial reduction in the benzyl T_1 values since this group is accessible to the relaxing agent. We conclude that T_1 measurements can be of considerable value in the studies of solutions of clathrates particularly when combined with the use of relaxation agents.

Experimental

The cyclodextrin complexes were prepared using the method of Harada [11]. In addition, the FcH-β cyclodextrin was prepared as follows in DMSO, the medium used in this work.

Synthesis of cyclodextrin complex of ferrocene in DMSO

Ferrocene (0.18 g, 0.97 mmol) was dissolved in dry DMSO (5 ml) and added to a solution of β-cyclodextrin (1.25 g, 1.10 mmol) in DMSO (10 ml) at room temperature. The mixture was allowed to stand for 15 min, then added to 100 ml H_2O. The resultant pale yellow precipitate was filtered off, washed with distilled water and then acetone to remove any uncomplexed ferrocene. After air-drying, 1.06 g of a pale yellow solid was obtained which had an identical infrared spectrum to that obtained by the standard procedure [11], yield 83%.

T_1 measurements

^{13}C NMR spectra and ^{13}C relaxation times (T_1) were obtained using a Bruker WP80SY spectrometer by methods already described [15]. For the variable temperature work, the digital read-out values are reported. The true temperature may vary slightly from these figures but since the data were used in a qualitative manner only, it was not considered necessary to perform an accurate calibration.

Equilibrium constants

These were measured polarimetrically using an Optical Activity Ltd. Polarimeter AA-10 instrument at $23 \pm 1°$.

On adding ferrocene to a solution of either β or γ cyclodextrin, the optical rotation increased. Accurate readings, however, were limited to solutions of about 0.09 M strength due to absorbance by the ferrocene. To overcome this, the following iterative calculation was performed:

The observed rotation α is directly proportional to the concentration of optically active material. For pure cyclodextrin (concentration a)

$\alpha_o = fa$

where f is the proportionality constant for the cyclodextrin itself. On adding ferrocene (concentration b) an equilibrium is established and

$$\alpha_e = f(a-x) + f'x$$

where f' is the proportionality constant for the inclusion complex. Combining the above equations yields

$$x = \frac{\alpha_e - \alpha_o}{f' - f} = \frac{\Delta\alpha}{\Delta f}$$

For a 1 : 1 complex

$$\frac{1}{K_D} = K_a = \frac{x}{(a-x)(b-x)} = \frac{\Delta\alpha\,\Delta f}{(a\,\Delta f - \Delta\alpha)(b\,\Delta f - \Delta\alpha)}$$

Using pairs of data, values of Δf and hence f' can be evaluated by an iterative process. For β-CD: FcH, f' was found to be 500 ± 2 deg M^{-1} and that for the γ-CD system 444 ± 5 deg M^{-1}. Using these results dissociation constants of $14.4 \pm 0.3 \times 10^{-3}$ M and $12.1 \pm 1.2 \times 10^{-3}$ M were found, respectively.

Viscosity

Measurements were made using standard Ubbelohde viscometers.

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