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ORIGINAL ARTICLE

How does β-cyclodextrin affect the aggregation of sodium perfluoroheptanoate in aqueous solution: a ^{19}F NMR study

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Abstract ^{1}H and ^{19}F NMR spectra were recorded for D_2O solutions of sodium perfluoroheptanoate with defined concentrations up to 200 mM, in the absence and presence of β-cyclodextrin (15 mM). Analysis of ^{1}H chemical shift data obtained by the method of continuous variations (Job's method) confirms the formation of 1:1 inclusion complexes for the perfluoroheptanote anion in β-cyclodextrin and leads to an estimate for the apparent inclusion constant ($\geq 10^4$ M^{-1}). In addition, analysis of ^{19}F chemical shift data based on two simplifying assumptions (monodisperse perfluoroheptanoate solutions below the critical micellar concentration (CMC), and a single self-associated state after the CMC) enables to interpret all the experimental chemical shift data and allows to determine CMC values for the absence and presence of β-cyclodextrin (104 and 116 mM). It is shown that the self-association of perfluoroheptanoate and its inclusion in β-cyclodextrin lead to shielding and deshielding of the fluorine atoms, respectively.

Keywords Aqueous solution · β-Cyclodextrin · Critical micellar concentration · Inclusion · NMR chemical shifts · Self-association · Sodium perfluoroheptanoate

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Introduction

Perfluorocarbons (PFCs) are well known for their hydrophobicity and rigid molecular skeleton [1–6]. They are powerful wetting agents and indispensable as emulsifiers in many industrial applications, including emulsion polymerization of chlorocarbons and fluorocarbons, and in a variety of biomedical applications, including the development of oxygen-carrying fluorocarbon emulsions, pulmonary drug and gene delivery [7, 8]. However, these compounds are strongly hydrophobic, and for this reason their study in aqueous solutions is only possible if they are previously transformed to increase their solubility in water. A high surface tension can be added to the properties of PFCs when a hydrophilic group is bonded to a PFC chain originating an amphiphilic molecule [9]. Other attempts to solubilize highly fluorinated compounds in aqueous media may consist of their inclusion into native cyclodextrins—cyclic oligosaccharides composed of six (α-cyclodextrin, αCD), seven (β-cyclodextrin, βCD) or eight (γ-cyclodextrin, γCD) α(1-4)-linked glucopyranose residues [10–12]. Previous studies have concluded that the inclusion strongly depends on the cavity diameter, suggesting that the fluorocarbon chain cannot fit into the cavity of αCD, fits snugly inside the cavity of βCD, and loosely inside the cavity of γCD [13–19]. A recent study about oxygen solubility in aqueous solution of PFCs shows that oxygen preferentially interacts with the PFC surfactant molecules in the formed micellar aggregates [20]. If βCD is added to the aqueous solution containing the PFC surfactant, the PFC chain includes in the βCD cavity with the subsequent increase of the PFC surfactant critical micellar concentration (CMC) [20]. In addition, experimental evidence has been recently provided suggesting that the βCD·PFC inclusion complexes might disturb the formation of surfactant micellar aggregates [20, 21]. As these two latter effects retard and disrupt the formation of surfactant aggregates, oxygen solubility passes through a minimum as the PFC surfactant molecule initial concentration increases for a defined βCD concentration [20].

The topology of the βCD macrocycle and the mode and extent of host–guest interactions can be effectively probed by ^{1}H-NMR, in particular, by the chemical shifts variations of the H3 and H5 protons inside the βCD cavity [22, 23]. Since the host–guest systems are in the NMR fast exchange chemical shift limit, the observed chemical shifts of the host and guest resonances are averages of the chemical shifts for the free and complexed states, weighted by the mole fractions of each state [24]. When sodium perfluoroheptanoate (PFH) aggregates are formed in the presence of βCD, a competition is set up between PFH inclusion in βCD and its self-association in the dispersion medium [20]. Since guest inclusion and self-association processes are interdependent processes, one may expect variations in the chemical shifts of the observed PFH fluorine atoms that might lead to a better understanding of the βCD influence on the PFH self-association process [25].

In this work, the aggregation process of sodium perfluoroheptanoate in the presence of βCD is monitored by analysis of the recorded NMR chemical shift variations for the various PFH fluorine atoms. The effect caused by the cyclodextrin presence in the formation of PFH aggregates, as the initial concentration of PFH, $[\mathrm{PFH}]_o$, increases for a defined value of $[\beta\mathrm{CD}]_o$, is considered and discussed.

Materials and methods

Perfluoroheptanoic acid (Aldrich, >98%), βCD (kindly donated by Wacher), NaOH (Merck, >99%) and 1-butanol (Lab-Scan, 99%) were used as received without further purification. Sodium perfluoroheptanoate was prepared by neutralizing 25.0 g of the corresponding acid with 2.8 g of NaOH in ca. 100 mL of 1-butanol. After recrystallizing the salt from 1-butanol, 14.4 g of PFH were obtained and dried in high vacuum for several hours at ca. 200 °C. The purity of PFH was confirmed by ^{1}H-NMR in DMSO and by IR.

^{1}H-NMR and ^{19}F-NMR spectra were recorded on a Bruker DRX 300 spectrometer, at 20 °C. The water (HDO) chemical shift, $\delta = 4.83$ ppm, was used as internal reference for ^{1}H-NMR spectra [26, 27]. Its sensitivity to pH changes has been reported to be –2 ppb per pH unit [28], that is, two orders of magnitude below the recorded chemical shift changes (for example, the chemical shift change observed for the βCD H3 protons and $r = 0.5$ is 0.16 ppm). For ^{19}F-NMR spectra C_6F_6 was used as reference. The NMR spectra were always recorded using freshly prepared and unbuffered D_2O solutions [29]. This precaution was taken in order to avoid any effect resulting from possible inclusion of buffer anions in βCD [30].

Concerning the inclusion of PFH in βCD, guest size in relation with cavity dimension constraints were assessed by model calculations carried out with the Gaussian 03 set of programs [31]. The PFH and βCD geometries were fully optimized with the B3LYP/6-31G(d) and semi-empirical PM3 calculations, respectively. The geometry for the βCD·PFH inclusion complex was optimized at the semi-empirical PM3 level, keeping as constants all the previously optimized PFH intramolecular geometric parameters. The optimized geometry for the 1:1 inclusion complex is shown in Fig. 1.

The stoichiometry of the inclusion complexes in aqueous solution was experimentally determined by a method due to Job, generally known as the continuous variation method or Job's method [32, 33]. This method, applied to the chemical shift variations of the βCD H5 and H3 protons located in the cyclodextrin cavity interior, yielded a 1:1 stoichiometry for the

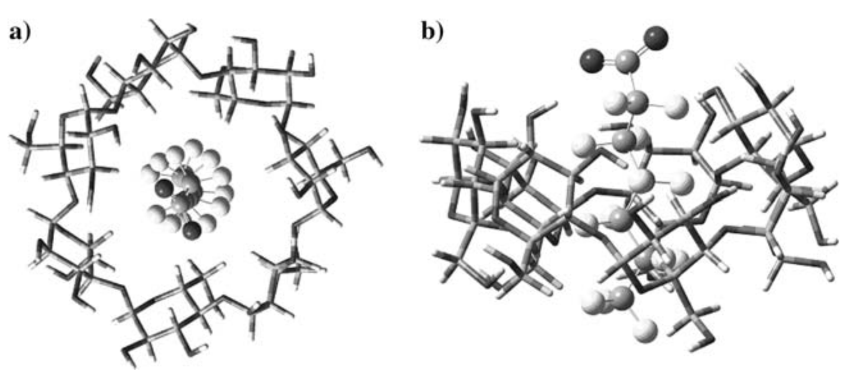

Fig. 1 Side and top *GaussView* images for the inclusion complex βCD·PFH. *GaussView* is a graphical user interface for Gaussian produces

βCD·PFH inclusion complex (Fig. 2). The first five points of the Job's plot can be fitted with a straight line whose $R^2 = 0.9996$. This experimental result can be used to estimate a minimum value for the apparent inclusion constant ($K_{HG} = [HG]/([H][G])$, where $[H]=[H]_o–[HG]$ and $[G]=[G]_o–[HG]$) found to be of the order of magnitude of 10^4 M^{-1}.

Results and discussion

The model

In order to interpret the chemical shift variations observed for the PFH fluorine atoms, we assume a monodisperse PFH aqueous solution containing βCD (in this work, $[\beta CD]_o$=15 mM) and, above the PFH CMC, a single self-associated state for PFH, PFH_n. These assumptions lead to the consideration of three distinct PFH fluorine atom states: in the free PFH monomer, in the 1:1 host–guest βCD·PFH inclusion complex and, above the PFH CMC, in the self-associated PFH_n state. Since no distinct ^{19}F NMR resonances were observed for these distinct states (fast exchange regime), the recorded chemical shifts change linearly with the mole fractions of the distinct states [24],

$$\delta = x_{PFH}\,\delta^o_{PFH} + x_{\beta CD\cdot PFH}\,\delta^o_{\beta CD\cdot PFH} + x_{PFHn}\,\delta^o_{PFHn} \quad (1)$$

where x stands for mole fraction and δ^o represents the chemical shift when the corresponding mole fraction equals 1 (the remaining mole fractions are zero). As

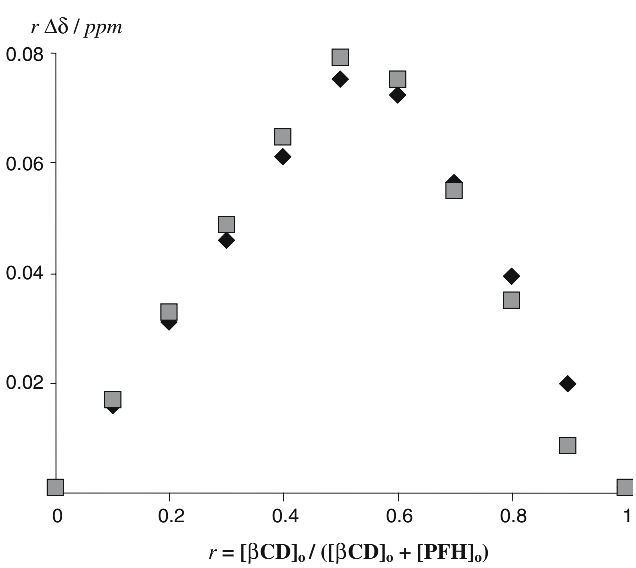

Fig. 2 Job's plot for D_2O solutions of βCD and PFH, at 20 °C. Chemical shifts variations refer to H3 (♦) and H5 (■) protons of βCD

the mole fractions add to unity ($x_{PFH} + x_{\beta CD\cdot PFH} + x_{PFHn} = 1$), substitution of $x_{PFH} = 1–x_{\beta CD\cdot PFH} - x_{PFHn}$ in (1) leads to

$$\delta = \delta^o_{PFH} + x_{\beta CD\cdot PFH}\,(\delta^o_{\beta CD\cdot PFH} - \delta^o_{PFH}) + x_{PFHn}\,(\delta^o_{PFHn} - \delta^o_{PFH}) \quad (2)$$

If general Eq. 1 is written for the solution with the lowest concentration of PFH (this solution, herein indicated by subscript "i", has $[PFH]_o$=5 mM and $[\beta CD]_o$=15 mM), one obtains $\delta_i \approx \delta^o_{\beta CD\cdot PFH}$, as $x_{PFHn,i} = 0$ ($[PFH]_o$ is well below the PFH CMC) and $x_{\beta CD\cdot PFH,i} \approx 1$ ($[\beta CD\cdot PFH] \approx [PFH]_o$, as there is an excess of βCD over PFH). Subtracting δ_i to δ in (2) and rearranging the resulting equation yields

$$\Delta\delta = \delta - \delta_i \approx (x_{\beta CD\cdot PFH} - 1)\,(\delta^o_{\beta CD\cdot PFH} - \delta^o_{PFH}) + xP_{FFn}\,(\delta^o_{PFHn} - \delta^o_{PFH}) \quad (3)$$

that is, the subscript "i" refers to the zero-$\Delta\delta$ solution. This expression is not in a convenient form for analysis of chemical shift variations, since the experimental variable (in this work, $[PFH]_o$) appears in the second member as denominator of the mole fraction variables (in the most general case, $[PFH]_o = [PFH] + [\beta CD\cdot PFH] + n[PFH_n]$). A more convenient expression can be obtained by multiplying both members of (3) by $[PFH]_o$, yielding

$$\Delta\delta[PFH]_o \approx ([\beta\,CD\cdot PFH] - [PFH]_o) \times (\delta^o_{\beta CD\cdot PFH} - \delta^o_{PFH}) + n\,[PFHn]\,(\delta^o_{PFH}) \quad (4)$$

The plot of $\Delta\delta\cdot[PFH]_o$ vs. $[PFH]_o$ can be easily interpreted using (4), as the second member terms essentially indicate how $[\beta CD\cdot PFH]$ and $[PFH_n]$ vary with $[PFH]_o$. Note that the recorded chemical shift variations, $\Delta\delta$, refer to specific sets of magnetically equivalent fluorine atoms. In the second member of (4), this specificity is conveyed by the $\Delta\delta^o$ coefficients.

For $[PFH]_o <$ CMC, the second term of the second member of (4) is zero, and two concentration regions need to be considered:

(i) $[PFH]_o \leq [\beta CD]_o$ (=15 mM), where the first term is approximately zero, as the estimated value for the apparent inclusion constant ($K_{\beta CD\cdot PFH} \geq 10^4$, see Methods) is high and, consequently, $[\beta CD\cdot PFH] \approx [PFH]_o$;
(ii) $[PFH]_o > [\beta CD]_o$, where the first term can be approximated by $([\beta CD]_o–[PFH]_o)(\delta^o_{\beta CD\cdot PFH}– \delta^o_{PFH})$, with a negative concentration factor ($[\beta CD]_o < [PFH]_o$).

Only for $[PFH]_o$ above the CMC, does the second term of (4) become significant.

In the absence of βCD, the concentration factor ($x_{\beta CD \cdot PFH}$–1) in Eq. 3 is zero, as both $x_{\beta CD \cdot PFH}$ and $x_{\beta CD \cdot PFH,i}$ are zero. Hence, Eq. 4 takes the simpler form

$$\Delta\delta\ [PFH]_o \approx n\ [PFHn]\ (\delta^o_{PFHn} - \delta^o_{PFH}) \quad (5)$$

^{19}F NMR chemical shift variations

Figure 3 plots $\Delta\delta\cdot[PFH]_o$ vs. $[PFH]_o$, in the absence of βCD, where the chemical shift variations refer to fluorine atoms bonded to C2, C4, C6 and C7 of PFH. The zero-$\Delta\delta$ solution has $[PFH]_o = 5$ mM. These plots essentially show two straight lines intercepting at the PFH CMC and can be easily interpreted using Eq. 5. In fact, for $[PFH]_o$ below the CMC, $[PFH_n] \approx 0$ and $\Delta\delta\cdot[PFH]_o \approx 0$, for all the fluorine atoms. In turn, for $[PFH]_o >$ CMC, $n[PFH_n] = [PFH]_o$–CMC and $\Delta\delta\cdot[PFH]_o = ([PFH]_o\text{–CMC})(\delta^o_{PFHn}\text{–}\delta^o_{PFH})$. This equation expresses a linear variation with slope $\delta^o_{PFHn}\text{–}\delta^o_{PFH}$. At higher values of $[PFH]_o$, $\Delta\delta\cdot[PFH]_o$ decreases linearly with different slopes (C7: –2.3326 ppm; C6: –1.6624 ppm; C4: –1.0835 ppm; C2: –0.5323 ppm) corresponding to different $\delta^o_{PFHn}\text{–}\delta^o_{PFH}$ values. The common intercept with the $[PFH]_o$ axis (104–105 mM) can be ascribed to the PFH CMC in these media. The absolute values of the slopes increase as the fluorine atoms become more distant from the carboxylate group, thus reflecting the distance from this group (the average Mulliken charge on the fluorine atoms of the CF_3 group is ≈20% smaller than for the

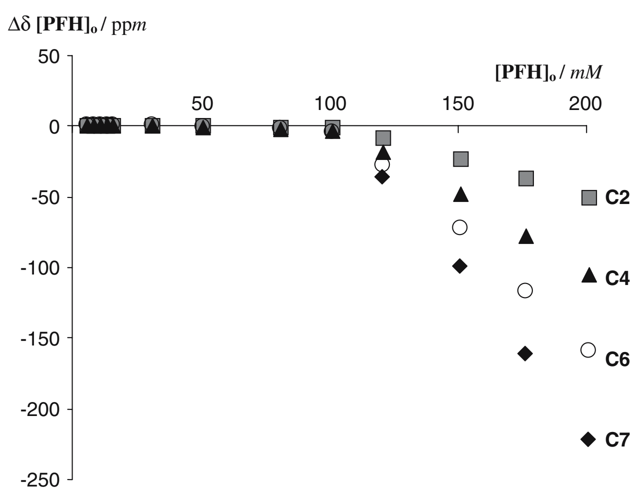

Fig. 3 $\Delta\delta[PFH]_o$ vs. $[PFH]_o$: chemical shifts changes for fluorine atoms bonded to carbon atoms C2, C4, C6 and C7 of PFH, multiplied by the initial concentration of PFH, $[PFH]_o$, for defined values of $[PFH]_o$, in D_2O

fluorine atoms bonded to C2; see Methods for details of the calculation). Being negative ($\delta^o_{PFHn} < \delta^o_{PFH}$), one can conclude that the self-association of PFH leads to shielding of the fluorine atoms, as expected.

When βCD is present in solution, interpretation of the $\Delta\delta\cdot[PFH]_o$ vs. $[PFH]_o$ plots requires Eq. 4. Figure 4 presents $\Delta\delta\cdot[PFH]_o$ vs. $[PFH]_o$ plots for the fluorine atoms bonded to carbon atoms C7 (Fig. 4a), C6 (Fig. 4b) and C4 (Fig. 4c), in the presence of βCD ($[\beta CD]_o$=15 mM). The corresponding plots in the absence of βCD are also shown, for comparison.

For $[PFH]_o$ values up to 15 mM (this is the stoichiometric point for the 1:1 inclusion in βCD), the first term of (4) is approximately zero because $[\beta CD \cdot PFH] \approx [PFH]_o$.

From $[PFH]_o = 15$ mM up to the PFH CMC, $\Delta\delta\cdot[PFH]_o$ values are approximately zero for the fluorine atoms bonded to C7 (Fig. 4a), thus suggesting that the corresponding $\delta^o_{\beta CD \cdot PFH}\text{–}\delta^o_{PFH}$ coefficient is close to zero, i.e., the CF_3 group of the included PFH anion stays outside the βCD cavity, a result which is consonant with the calculated geometry for the inclusion complex (see Fig. 1). A similar experimental result is found, to a smaller extent, that is, for a slightly higher $\Delta\delta^o$ coefficient, for the fluorine atoms bonded to C6 (Fig. 4b), as these fluorine atoms are near the βCD narrower rim (see Fig. 1).

In turn, for the fluorine atoms bonded to C4 (Fig. 4c) in the range of concentrations from 15 mM up to the PFH CMC, it can be seen that $\Delta\delta\cdot[PFH]_o$ values are negative and decrease linearly with $[PFH]_o$ (fitting of the $\Delta\delta\cdot[PFH]_o$ values at $[PFH]_o = 30$, 50, 80 and 100 mM yields a slope equal to –0,6045 with $R^2 = 0.9984$; for $\Delta\delta = 0$, this straight line yields $[PFH]_o = 16$ mM, that is, slightly above $[\beta CD]_o$).

Since the $\Delta\delta\cdot[PFH]_o$ values and the concentration factor for the first term of Eq. 4 are both negative ($[\beta CD \cdot PFH] \approx [\beta CD]_o < [PFH]_o$), one concludes that the $\delta^o_{\beta CD \cdot PFH}\text{–}\delta^o_{PFH}$ coefficient, if significant, is positive, that is, $\delta^o_{\beta CD \cdot PFH} > \delta^o_{PFH}$. This result (the inclusion of PFH in βCD leads to deshielding of the fluorine atoms) suggests that, for a PFH molecule, the βCD cavity provides a more polar environment than the cage of water molecules around the perfluorinated fragment of PFH in the bulk solvent.

In the range of concentrations above CMC, $\Delta\delta\cdot[PFH]_o$ decrease linearly with $[PFH]_o$ (fitting of the $\Delta\delta\cdot[PFH]_o$ values at $[PFH]_o = 150$, 175 and 200 mM yields the slope –1.6083). Taking into consideration the non-zero slope in the previous range of concentrations, from 15 mM up to the CMC, one can easily arrive at the CMC value in the presence of βCD, 116 mM. This value should be compared with 104 mM, in the absence

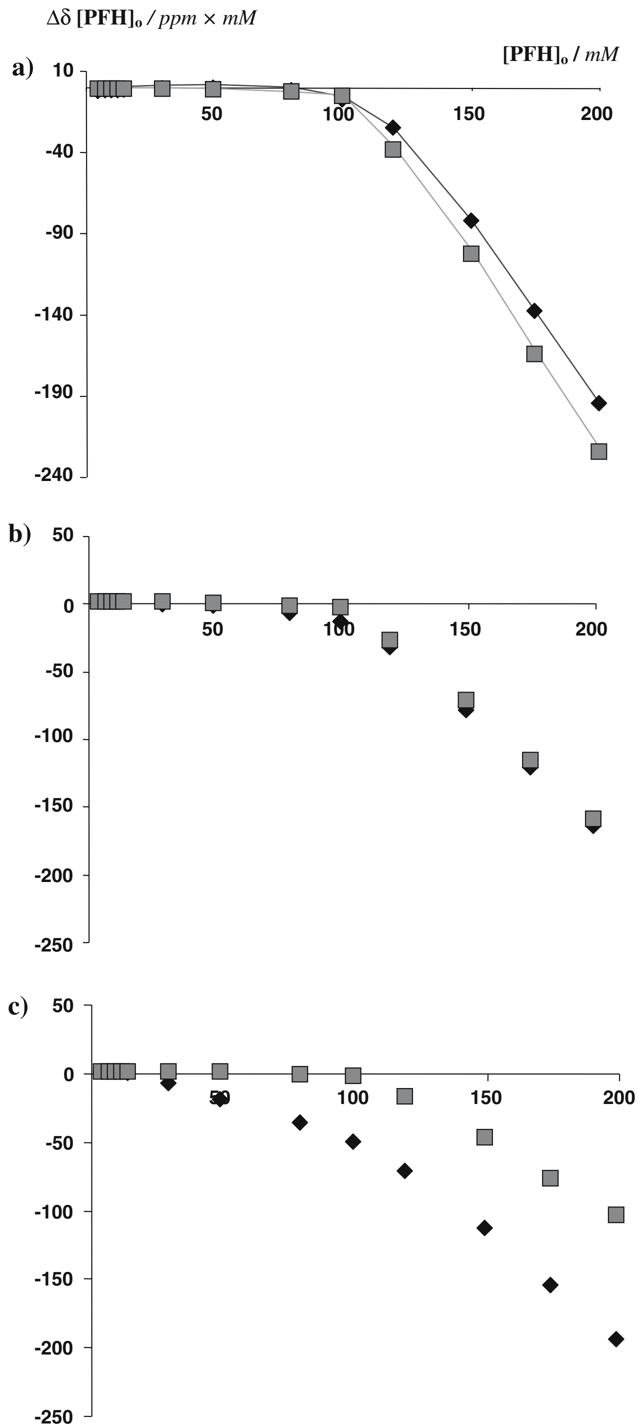

Fig. 4 $\Delta\delta[PFH]_o$ vs. $[PFH]_o$: ^{19}F chemical shift variations multiplied by the initial concentration of PFH, in D_2O, in the absence (■) and presence (♦) of βCD, for fluorine atoms bonded to (**a**) C7; (**b**) C6; (**c**) C4

of βCD, as mentioned above. The difference in these CMC values can be reasonably accounted for by the inclusion of PFH in βCD. In addition, these CMC values closely agree with those obtained from chemical shift data for other PFH fluorine atoms, thus supporting the assumptions, which led to model Eq. 4.

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