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Destruction of perfluoroalkyl surfactant aggregates by β-cyclodextrin†

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Received (in Cambridge, UK) 2nd December 2003, Accepted 16th February 2004
First published as an Advance Article on the web 27th February 2004

A water ^{1}H NMRD and ^{19}F NMR spectroscopy study has proved, for the first time, that perfluoroalkyl surfactant micelles can be completely destroyed upon addition of β-cyclodextrin to form successively 1:1 and 2:1 (β-CD:R_F) inclusion complexes.

Fluorocarbons have exceptional chemical and physical properties, *e.g.* thermal, chemical and biological inertness, low surface tension, low viscosity and high gas dissolving capacity.[1] Water-soluble materials (surfactants) can be obtained by addition of a hydrophilic part to the molecule. The chemistry of perfluoroalkyl surfactants (abbreviated as R_Fs) has therefore a great potential in the biomedical field and one of the main interests is the use of these surfactants as drug delivery systems such as pulmonary drug delivery or blood substitutes.[2] Since perfluoroalkyl chains are more hydrophobic than their alkyl analogues, the critical micellar concentration (cmc) of perfluoroalkyl surfactants is commonly two to three orders of magnitude lower than for hydrocarbon surfactants of similar length.[2] The current literature indicates that fluorocarbons can now extend the list of organic compounds capable of interacting with β-cyclodextrin (abbreviated as β-CD), with a larger association constant than for the hydrocarbon analogues.[3] Thanks to van der Waals interactions they can thread into the shallow truncated cone of a β-CD and thereby form inclusion complexes within the oligomeric cone. It has been proved that for long perfluoroalkyl chain surfactants (more than 6 carbon atoms) 2:1 (β-CD:R_F) inclusion complexes can be formed, for a concentration of the R_F below the cmc.[4] For R_F concentrations above the cmc, perfluoroalkyl surfactant micelle–CD interaction has been evidenced but destruction of the micelles has not been pointed out.[5] Alkyl surfactants can also interact with cyclodextrin,[6] but the presence of cyclodextrin does not affect the micellisation, *i.e.* the aggregation number and the dissociation degree of the micelles.[7] A recent study evidenced the formation of mixed spherical micelles for concentrations higher than the cmc, with a ratio of β-CD to alkylsurfactants of 1:9 accompanied by changes in their structural and physical properties (*e.g.* aggregation number, cmcs).[8]

For the first time we demonstrate that R_F micelles can be completely and rapidly destroyed by formation of inclusion complexes with β-CD proceeding through a displacement of the equilibrium between the micellar and the monomeric forms (Fig. 1). To serve this purpose, the hydrophilic head of the studied R_F consists of either a Y^{3+}- or a Gd^{3+}-DO3A‡-monoamide complex (this latter complex is named gadofluorine 8 and was provided by Schering AG, Berlin).[9] For all the measurements the concentration of the surfactant was much higher than the cmc [shown to be less than 10 mM by ^{1}H NMRD (nuclear magnetic relaxation dispersion spectroscopy) measurements, see ESI†].[10]

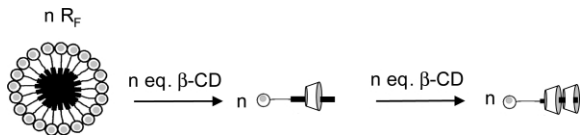

Fig. 1 Scheme of the successive formation of (β-CD:R_F) 1:1 and 2:1 inclusion complexes by addition of β-CD to the perfluoroalkyl micelles. R_F is the abbreviation for one perfluoroalkyl surfactant; *n* corresponds to the aggregation number.

To assert the formation of the host–guest complexes as given in Fig. 1, the relaxivity, r_1, in the presence of gadofluorine 8 has been measured for different ratios of β-CD:R_F at 298.2 K and 40 MHz on a Bruker minispec mq40. The relaxivity r_1 represents the enhancement of the longitudinal relaxation rate of water protons due to the presence of the paramagnetic complex (concentration expressed per mM of Gd^{3+}). The effective r_1 of the solution, for different equivalents of β-CD is presented in Fig. 2 and expressed in eqn. (1), where r_1 is the sum of the contributions of each species present in solution weighted by their mole fraction. x_m, x_1 and x_2 are the mole fractions of Gd^{3+} surfactant in the micelle (such as $x_m + x_1 + x_2 = 1$), the 1:1 inclusion complex and the 2:1 inclusion complex, respectively. r_1^m, r_1^1 and r_1^2 are the corresponding relaxivities (with $r_1^m > r_1^2 > r_1^1$).

$$r_1 = x_m r_1^m + x_1 r_1^1 + x_2 r_1^2 \quad (1)$$

Fig. 2 shows that three domains exist, where r_1 is linearly dependent upon the ratio $C_{\beta\text{–CD}}/C_{Gd}$: (i) for $C_{\beta\text{–CD}}/C_{Gd}$ between 0 and 1, r_1 decreases drastically, which corresponds to eqn. (2); (ii) then r_1 increases slightly until $C_{\beta\text{–CD}}/C_{Gd} = 2$ [eqn. (3)]; and (iii) remains finally constant for higher ratios. This is a proof of the destruction of the micelles ($r_1^m = 16.9$ mM^{-1} s^{-1} at 40 MHz and 298.2 K) through the successive and complete formation of 1:1 ($r_1^1 = 7.2$ mM^{-1} s^{-1}) and 2:1 ($r_1^2 = 7.8$ mM^{-1} s^{-1}) inclusion complexes of R_F surfactants with β-CD. The 3:1 inclusion complex is not formed even with a large excess of β-CD.

$$r_1 = r_1^m + (C_{\beta\text{-CD}}/C_{Gd}) \times (r_1^1 - r_1^m) \quad (2)$$

$$r_1 = 2r_1^1 - r_1^2 + (C_{\beta\text{-CD}}/C_{Gd}) \times (r_1^2 - r_1^1) \quad (3)$$

^{1}H NMRD relaxivity profiles of gadofluorine 8 were also recorded at 298.2 K in the absence and presence of 1 or 2

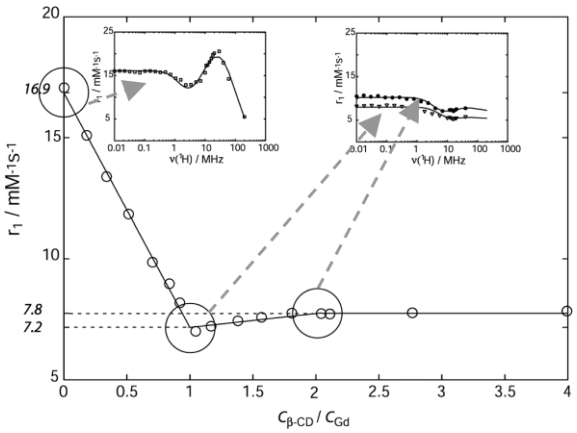

Fig. 2 β-CD concentration dependence of the relaxivity of gadofluorine 8 at 40 MHz and 298.2 K (titration of a 6.75 mM solution of surfactant with a 7.47 mM solution of β-CD). The three straight lines represent the least-squares fit of the data (○) and the dashed horizontal lines are guide lines for the eyes. (Inset) ^{1}H NMRD profiles of gadofluorine 8 in the micelle (□ left; $C_{Gd} = 9.49$ mM), 1:1 (▽ right bottom; $C_{Gd} = 3.23$ mM, $C_{\beta\text{-CD}} = 3.39$ mM), and 2:1 (● right top; $C_{Gd} = 2.16$ mM, $C_{\beta\text{-CD}} = 4.40$ mM) inclusion complexes at 298.2 K.

† Electronic supplementary information (ESI) available: experimental data for the relaxivity measurements, kinetic analysis, exchange matrix, cmc determination data. See http://www.rsc.org/suppdata/cc/b3/b315681h/

DOI: 10.1039/b315681h

equivalents of β-CD (Fig. 2). These profiles can be considered as good fingerprints to obtain information about the water exchange rate on the metal ion, k_{ex}, the electron spin relaxation of Gd^{3+} and the tumbling of the whole molecule or assembly, described by a rotational correlation time, τ_R.[11] The three ^1H NMRD profiles have been described by the Solomon–Bloembergen–Morgan equations (Fig. 2).[11] As shown in previous studies, k_{ex} is not affected by de-aggregation or aggregation of the surfactants.[10] The diffusion parameters of water and k_{ex} at 298.2 K have been fixed to common values to fit the profiles ($k_{ex} = 1.2 \times 10^6$ s^{-1} for Gd^{3+}-DO3A-monoamide complexes).[11] The obtained electronic parameters take typical values but their discussion is not relevant for this study (see ESI†). Indeed, the decrease of r_1 is due to a drastic decrease of the rotational correlation time, τ_R, from 5000 ps for the micelle to 140 ps for the 1:1 (β-CD:R_F) host–guest system: by adding β-CD, the maximum of r_1 (characteristic for a low rotating assembly) at NMR fields (*ca.* 30 MHz) is cancelled (Fig. 2). At these fields, r_1 for the new relaxing agent formed with β-CD is reduced by a factor 3.7 for the 1:1 inclusion complex, which is evidence of the micelle destruction (Fig. 1 and 2). There is no maximum of r_1 at this field for the inclusion complex with β-CD, which is in agreement with a fast rotating complex.[11] By adding more than one equivalent of β-CD the relaxivity increases slightly due to the formation of the 2:1 inclusion complex, for which τ_R is higher (250 ps). The Debye–Stokes equation gives a size factor of about 50 from the micelle to the 1:1 inclusion complex.

The demicellisation of the Y^{3+}–R_F aggregates has been studied by ^{19}F NMR at 376.3 MHz. The spectra, presented in Fig. 3, were recorded for different molar ratios of β-CD:R_F. The spectrum (Fig. 3; $C_{\beta\text{-CD}}/C_Y = 0$) exhibits the characteristic pattern of a $-(CF_2)_7CF_3$ chain and is attributed to the fluorine atoms within the micelle.[12] Addition of β-CD induces a new set of signals; at the ratio β-CD:R_F = 1:1 all ^{19}F NMR signals of the original set disappear, which is in agreement with the previous relaxivity study. For higher ratios no signals from the micellar form are visible but small changes of the spectrum still appear due to the formation of the 2:1 inclusion complex. This successive formation of 1:1 and 2:1 inclusion complexes has already been observed in previous studies, but for R_F concentrations lower than the cmc.[4] The downfield shifting of the new set of peaks is in agreement with van der Waals interactions of β-CD with the fluorine atoms: the distance between the fluorine atoms and their neighbours tends to be maximised, which decreases the intramolecular shielding among them.[4a] For $C_{\beta\text{-CD}}/C_Y = 0.25$, the inverse of the mean lifetime of the η fluorines in the micelle, τ, such that $1/\tau = k$, was extracted from the variable temperature ^{19}F NMR spectra by line shape analysis using the Kubo–Sack formalism with a 2 × 2 exchange matrix (see analysis in ESI†).[13] The reaction is entropically favoured [k(298 K) = 3.8 s^{-1}; $\Delta S^{\ddagger} = +26 \pm 3$ J mol^{-1} K^{-1}; and $\Delta H^{\ddagger} = 75 \pm 8$ kJ mol^{-1}]. Since this is not in accordance with a classic demicellisation process ($\Delta S^{\ddagger} < 0$), the gain in entropy must be a consequence of the 1:1 inclusion complex formation, accompanied by a desolvation of the hydrophobic interior of the β-CD. The typically fast exchange of a surfactant between the micelle and the bulk[14] can be proposed as a first step of the whole process followed by the inclusion of free R_F into the β-CD, which might be the rate-determining step of the demicellisation.

A reaction path through the monomeric form is in agreement with the low k since the cmc of the studied surfactant is very low.

In conclusion, perfluoroalkyl micelles have been proved for the first time to be destroyed upon addition of β-CD to form inclusion complexes. Using this process, the transport of organic molecules, including drug delivery, could be associated with an improved release of the molecule into the targeted zone by the rapid and complete destruction of the micellar carrier.

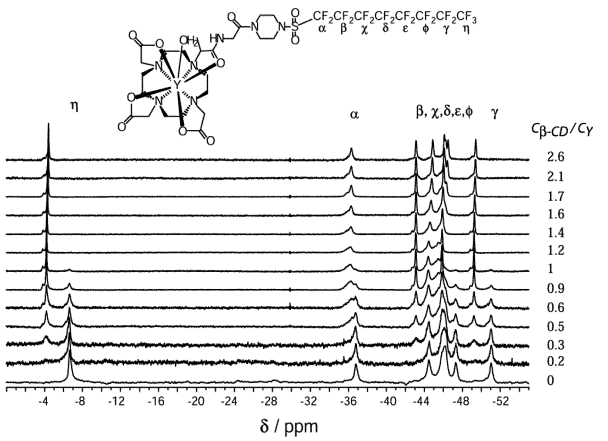

Fig. 3 376.3 MHz ^{19}F NMR spectra of the Y^{3+} perfluoroalkyl surfactant (chemical formula above) recorded at 323.2 K for several molar ratios of β-CD *versus* Y^{3+}. Chemical shifts are referred to CF_3COOH (δ = 0 ppm) as an external reference. The different fluorine atom types of the lipophilic chain have been assigned, from α to η, for the micellar form in the absence of β-CD.

Notes and references

‡ DO3A is 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

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