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Excess thermodynamic functions of mixtures of fluorocarbons with fluorocarbon-hydrocarbon compounds

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A study of excess thermodynamic functions is undertaken with mixtures of perfluoro(octyl) bromide (PFOB) and $C_nF_{2n+1}C_mH_{2m+1}$ (F*n*H*m*) diblock molecules and of bis-1,2-(F-butyl)ethene (F-44E) with F*n*H*m* at 25 °C in order to better understand the dramatic stabilization of fluorocarbon–egg yolk phospholipid (EYP) emulsions achieved by adding mixed fluorocarbon/hydrocarbon diblock compounds. We establish here that such mixtures behave differently from fluorocarbon/fluorocarbon and hydrocarbon/hydrocarbon mixtures. The fluorine/hydrogen ratio in mixed F*n*H*m* compounds and the length of their fluorocarbon chain have a large impact on the excess thermodynamic functions.

Introduction

Fluorocarbons (FC) have a range of specific properties[1,2] in which the biomedical field is interested.[3–7] They have a high solubilizing capacity for respiratory gases at 37 °C (40–50% v/v of dioxygen *versus* only 2.3% v/v for water) and they are remarkably chemically and biologically inert. These two features led to the development of injectable oxygen carriers.[5,6] For example, concentrated emulsions of perfluoro(octyl) bromide ($C_8F_{17}Br$, PFOB) or bis-1,2-(F-butyl)ethene ($C_4F_9CH{=}CHC_4F_9$, F-44E) with egg yolk phospholipids (EYP) as the surfactant have been investigated. FCs are also characterized by extreme hydrophobicity and therefore by low water solubility. This is to be related to fluorine's lower polarizability and larger size when compared to hydrogen.[1] This feature was a key to the development of injectable FC-loaded micron-size gas bubbles, which are now used as contrast agents for ultrasound diagnostic imaging.[7] The presently investigated FC emulsions, though more concentrated and more stable than the first generation emulsions using F-decalin as the fluorocarbon and Pluronic F-68 as the surfactant, suffer from instability over time. Indeed, perfluorocarbon chains (F-chains) have little affinity with the hydrocarbon chains (H-chains) of EYP. It has been established that the main mechanism of droplet size increase over time in FC emulsions is governed by Ostwald ripening, that is, molecular diffusion, rather than by droplet coalescence.[8–11]

We have also found that dramatic stabilization of concentrated FC/EYP emulsions can be obtained by incorporating small quantities (*e.g.*, 2–3% v/v) of $C_nF_{2n+1}C_mH_{2m+1}$ (F*n*H*m*) or $C_nF_{2n+1}CH{=}CHC_mH_{2m+1}$ (F*n*H*m*E) diblock molecules.[12] The amphiphilic structure of these molecules is believed to intervene at the EYP/FC interface and provides a better cohesion between the fluorous phase (lipophobic) consisting of the FC and the hydrocarbon (HC) phase (fluorophobic) made of the fatty chains of EYP. The F*n*H*m* molecules provide a co-surfactant effect[11] and may play the role of molecular dowels between FC and EYP.[5,12,13] Although the amphiphilic structure of F*n*H*m* molecules appears to be an essential factor for the stabilization of fluorocarbon emulsions, statements on the exact mechanism remain controversial. Biological investigations on such F*n*H*m* diblock-stabilized emulsions are ongoing.[6,14]

Literature shows that mixtures of different FCs usually have an almost ideal behaviour.[15,16] Likewise, mixtures of different HCs with similar structures have an ideal behaviour. When the structures are different, regular solutions[17] are obtained and display negative excess volumes and negative deviations of vapour pressures with respect to Raoult's law. Mixtures of linear FCs + HCs (C_4 + C_7) were found to display positive deviations with respect to Raoult's law, with large domains of demixing and excess volumes varying from 1 to 5 ml mol^{-1}.[18,19] These deviations increased with the length of both F-chains and H-chains. These general results may be explained by the fact that the attractive interactions between F-chains are weaker than the ones between H-chains, and that F-chains have little affinity for H-chains.[20] In FC + F*n*H*m* mixtures, the interactions between the F-chains of the FC and the ones of the fluorocarbon moiety coming from the diblock molecule occur simultaneously with interactions between F-chains of the FC and H-chains from the hydrocarbon moiety from the F*n*H*m* diblock. Moreover, the amphiphilic structure of the diblock molecules may lead to their aggregation within the fluorocarbon phase. Such aggregates have been described in perfluoro(octane) for F*n*H*m* mixed compounds with *n* varying from 4 to 14 and *m* = 12.[20,21]

The Lifshitz–Slyozov molecular diffusion theory[10] states that the mean volume of the droplets of the dispersed phase of an emulsion varies linearly with time and with the solubility of the dispersed phase (FC) in water:

$$da^3/dt = (8/9)D\sigma V_m{}^2C/RT \qquad (1)$$

where da^3/dt is the variation of the mean volume of the droplets with time, D the diffusion coefficient of the solute molecules in the solvent phase, σ the interfacial tension between the solvent and the solute, V_m the molar volume of the solute, C the solute solubility in the solvent, R the ideal gas constant and T the absolute temperature.

In the vapour–liquid equilibrium achieved by an FC + F*n*H*m* mixture, where F*n*H*m* is slightly volatile, the vapour pressure

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P_{FC} of the FC is lower than the vapour pressure of the pure FC, P_{FC}*. P_{FC} is proportional to the activity of FC in the liquid; if the FC vapour is itself in equilibrium with an aqueous solution of FC, Henry's law is relevant because the solubility of FC in water is very low:

$$P_{FC} = K_H X_{FC}(H_2O) \qquad (2)$$

where $X_{FC}(H_2O)$ is the molar fraction of FC in solution in the water phase and K_H is Henry's constant. Hence, the solubility of FC in water is proportional to the vapour pressure P_{FC} in the FC + F*n*H*m* mixture and depends on the mixture composition. If the mixture is considered ideal, $X_{FC}(H_2O)$ obeys the relation:

$$X_{FC}(H_2O) = (P_{FC}^*/K_H)X_{FC}(M) \qquad (3)$$

which is obtained from Raoult's law, and where $X_{FC}(M)$ is the molar fraction of FC in the ideal mixture.

The present paper aims to study the behaviour of mixtures of F*n*H*m* diblock compounds with FCs through vapour pressure measurements. This allows excess thermodynamic functions to be calculated. Our study clearly shows the role of the addition of a F*n*H*m* diblock on the solubility of FCs in water and thus on the molecular diffusion in FC-in-water emulsions.

Experimental

The mixed fluorocarbon–hydrocarbon diblocks $C_nF_{2n+1}CH{=}CHC_mH_{2m+1}$ (F*n*H*m*E; $n = 6$, $m = 10$; $n = 8$, $m = 6$; $n = 8$, $m = 10$) and $C_6F_{13}C_{12}H_{25}$ (F*n*H*m*) have been synthesized by previously described methods.[22] Their purity exceeded 99% (GC, FID) and, for F*n*H*m*E, the *Z*:*E* ratio was superior to 75:25. The FCs (PFOB and F-44E, *Z*:*E* < 2:98) used in this study, were generously provided by Atochem.

Vapour pressures were measured using a static method.[23] The whole apparatus (sample-containing vessel and mercury manometer) was placed in a thermostatted bath regulated at 25 ± 0.1 °C. The manometer consisted of a U tube with an internal diameter of 20 mm in order to minimize capillarity errors. One arm of the tube was connected to the vessel *via* a three-way vacuum tap to allow sample degassing. The other arm was connected to a vacuum line ($p \sim 10^{-5}$ torr). The difference between mercury levels in the manometer was measured by a cathetometer. The manometer was tested by measuring the vapour pressure of butan-1-ol (Carlo Erba; 99%) at 30.2 ± 0.1 °C. Mean values and standard deviations for six measurements were $p = 9.96 \pm 0.08$ torr *versus* the reported value of $p = 10.0$ torr.[24]

An indirect method[25] allowed us to measure the vapour pressures of diblock compounds F*n*H*m*E and F*n*H*m*. The values obtained for the compounds investigated ranged between 8×10^{-2} torr (for F8H10E at 90 °C) and 1.6×10^{-2} torr (for F8H6E at 25 °C). These values being very small with respect to the vapour pressures of F-44E (9.2 torr, 25 °C) and PFOB (8.7 torr, 25 °C), their contribution to the total vapour pressure was neglected in the temperature range considered in this study (25–35 °C).

Results and discussion

Vapour pressures of PFOB/F*n*H*m* (or F*n*H*m*E) and F-44E/F*n*H*m* (or F*n*H*m*E) mixtures at 25 °C

Depending on the mixtures' constituents and their proportions, the variations of vapour pressures for mixtures of FCs and F*n*H*m* present either positive deviations with respect to Raoult's law, or both positive and negative deviations (Figs. 1 and 2). These results, which depend on the amphiphilic nature of the F*n*H*m* diblocks, clearly differentiate FC + F*n*H*m* mixtures from FC + HC mixtures.[15] A similar behaviour is found in some polar mixtures such as pyridine + water binary systems, which generate hydrogen bonds.[16] It may also be noted that no demixing was observed.

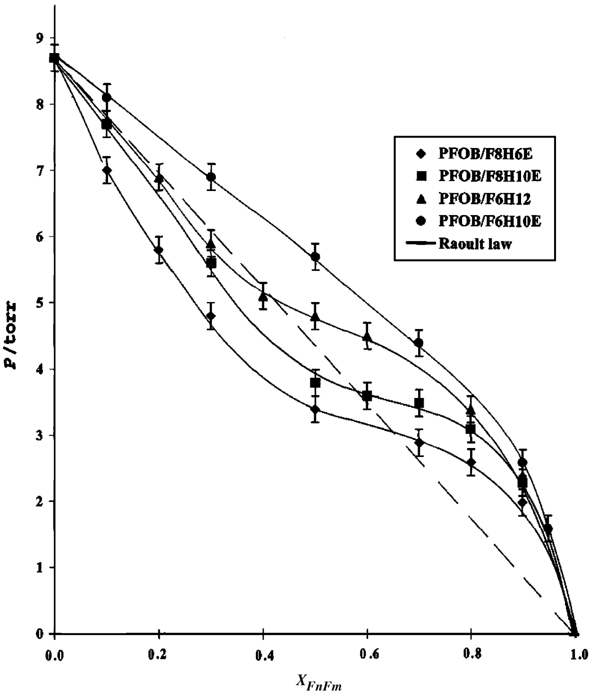

Fig. 1 Vapour pressures of PFOB/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

Small quantities (1–3% v/v) of mixed diblocks are sufficient to strongly stabilize injectable FC emulsions.[5,12] For this reason, we can focus on mixtures poor in F*n*H*m*. For a given diblock molar fraction, we observe that the decrease of the vapour pressure becomes all the more important as the fluorine atoms content of the F*n*H*m* diblock increases. This indicates that a better stabilization of FC-in-water emulsions should be

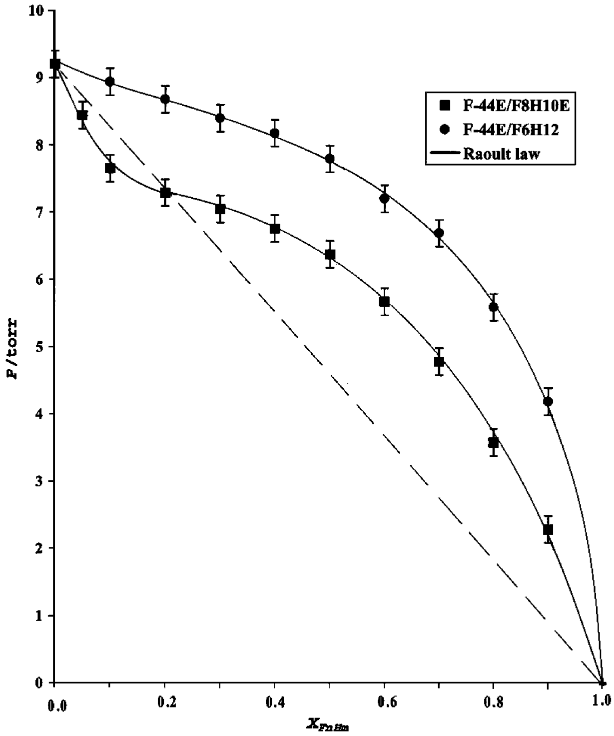

Fig. 2 Vapour pressures of F-44E/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

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favoured by using a fluorine-rich F*n*H*m* diblock. In addition, when the F/H ratio equalled 0.56 (PFOB + F6H10E) or 0.52 (F-44E + F6H12), the HC moiety of the diblock increased the vapour pressure of the FC phase with respect to Raoult's law. These results reflect the competition between the repulsive interactions between FC and HC chains and the attractive interactions between FC and FC or HC and HC chains, the latter being stronger than the former.

Regarding the vapour pressures of PFOB + F8H10E and PFOB + F8H6E mixtures, for which the F/H ratios are 0.74 and 1.1, respectively, one notices that the deviations with respect to Raoult's law are reversed for molar fractions $X_{\mathrm{F}n\mathrm{H}m\mathrm{E}}$ of the diblock around 0.6 and 0.67, respectively. This confirms the importance of the F/H ratio. For PFOB + F6H12 mixtures where this ratio is only 0.52, the decrease of the vapour pressure is even weaker, which is in good relation with the above trend.

Comparing PFOB + F6H12 (Fig. 1) and F-44E + F6H12 (Fig. 2) mixtures, one sees that, in the region of interest, the deviation with respect to ideality is somewhat negative for the first mixture and definitely positive for the second. The F-44E molecule being predominantly in the *E* configuration (*Z*:*E* < 2:98), the two FCs have similar fluorine chain structures. Consequently, the presence of a bromine atom in PFOB appears as an essential factor in lowering the vapour pressure with respect to Raoult's law. Bromine being more lipophilic than fluorine, PFOB has a better affinity towards the HC chains of F*n*H*m* diblock molecules.

Excess Gibbs energy in PFOB/F*n*H*m* (or F*n*H*m*E) and F-44E/F*n*H*m* (or F*n*H*m*E) mixtures

The molar excess Gibbs energy is obtained through measurements of the total vapour pressure of a mixture using the relation:

$$G^e = X_1RT\ln(P_1/P_1^{i}) + X_2RT\ln(P_2/P_2^{i}) \qquad (4)$$

where X_1 and X_2 are the molar fractions of FC and F*n*H*m*, respectively, P_1 and P_2 their experimental vapour pressures and P_1^{i} and P_2^{i} their ideal vapour pressures according to Raoult's law. *R* is the constant of ideal gases and *T* the absolute temperature in Kelvins. The contribution to the total vapour pressure of F*n*H*m* was deemed low enough to be neglected.

For PFOB (Fig. 3), and with the exception of mixtures containing F6H10E, the excess Gibbs energy for PFOB + F*n*H*m*E mixtures is negative when the mixture is rich in FC ($0 < X_{\mathrm{F}m\mathrm{H}n\mathrm{E}} < 0.2$), which corresponds to the most thermodynamically stable mixtures. Maximum stability is reached with F8H6E, which has the highest F/H ratio. When these mixtures become richer in F*n*H*m*, or F*n*H*m*E, the excess Gibbs free energy becomes positive. For all compositions of PFOB + F6H10E mixtures, the excess Gibbs free energy remains positive.

The excess Gibbs free energy is known to be positive for FC + HC mixtures in which the carbon content varies between C_4 and C_7[26]. In these mixtures, the maxima of the excess Gibbs free energy are high and vary between 1000 and 1500 J mol^{-1}. The mixtures that we have studied show maxima that are smaller than the above mentioned, ranging between 200 and 700 J mol^{-1}. The F-44E + F*n*H*m* or F*n*H*m*E mixtures (Fig. 4) behave similarly, and the absence of a lipophilic bromine atom in F6H12 may be the reason for no negative excess of G^e in this case.

Excess enthalpy in PFOB/F*n*H*m* (or F*n*H*m*E) and F-44E/F*n*H*m* (or F*n*H*m*E) mixtures

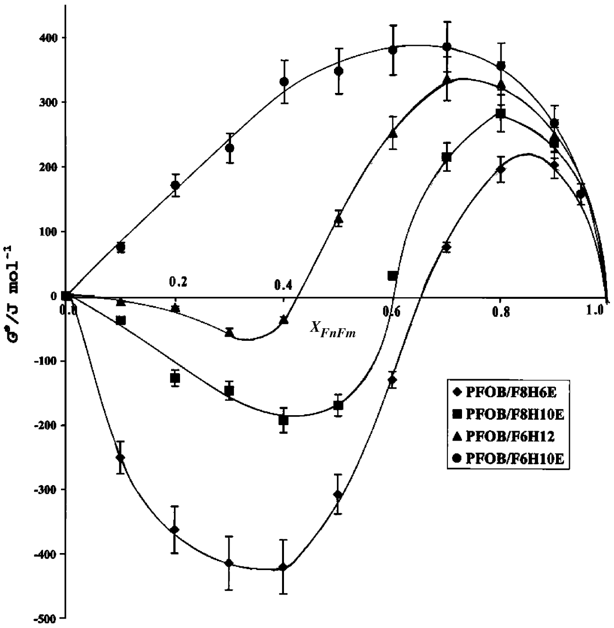

Fig. 3 Excess Gibbs energy of PFOB/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

Excess enthalpy H^e was deducted from the relation $H^e = G^e + TS^e$, the excess entropy being obtained from the relation $S^e = -(\partial G^e/\partial T)_p$ using vapour pressure measurements recorded at three different temperatures (25, 30 and 35 °C).

When mixtures were poor in F*n*H*m*, the excess enthalpy was found to be positive except for F-44E + F6H12 mixtures (Figs. 5 and 6). The excess enthalpy, which is the same as the mixture enthalpy, is, in a way, an estimate of the number of van der Waals interactions between F*n*H*m* molecules that are broken when the mixture is formed. The relatively high enthalpy found indicates that a large number of such interactions are broken upon mixing. This facilitates the insertion of molecular diblocks between FC molecules, such an insertion being responsible for the observed decrease in the vapour pressure. The fact that the enthalpy increases with the number of C–H bonds present in the F*n*H*m* molecules indicates that the HC chains play an essential role in the cohesion of the mixture. These

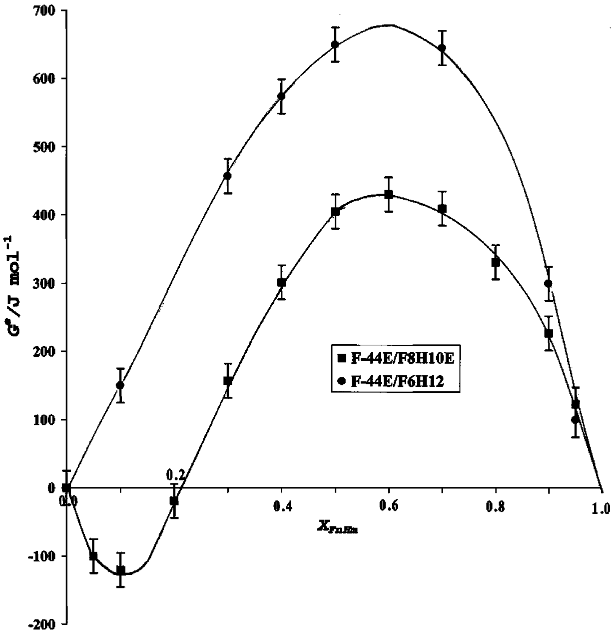

Fig. 4 Excess Gibbs energy of F-44E/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

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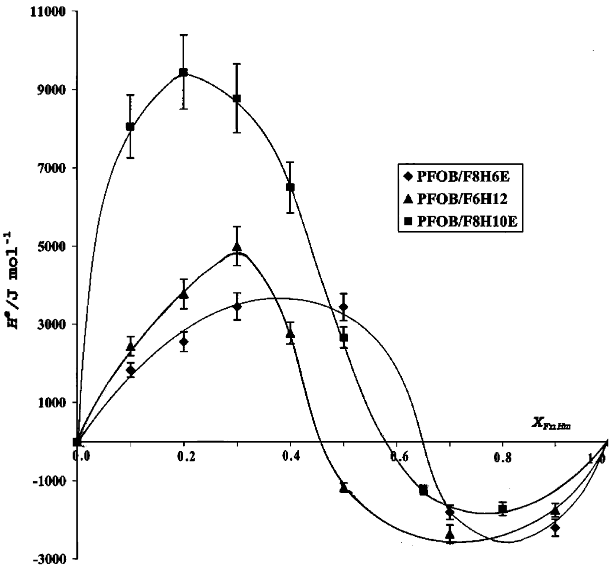

Fig. 5 Excess enthalpy of PFOB/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

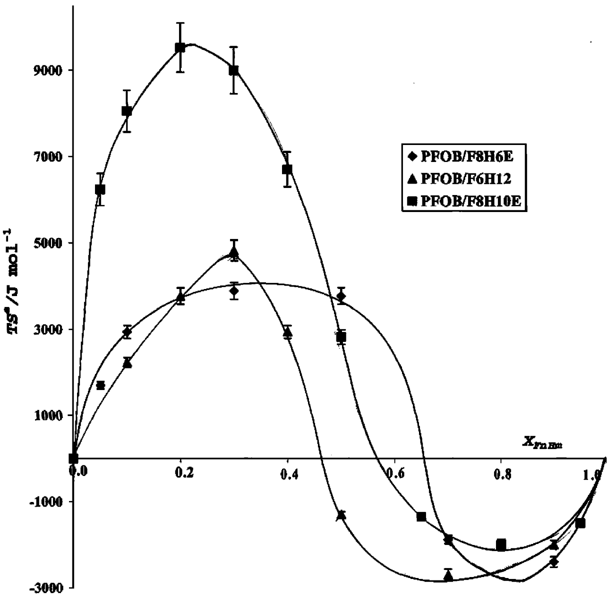

Fig. 7 Excess entropy (TS^e) of PFOB/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

results are compatible with the formation of F*n*H*m* micelles in the FC phase.[21]

High H^e values with respect to G^e values have also been observed for FC + HC mixtures poor in FC, as well as in mixtures of ethanol + HC poor in ethanol.[15] In the latter mixtures, hydrogen bonds play the role attributed to van der Waals interactions between the F*n*H*m* molecules investigated in this paper.

Excess entropy of PFOB/F*n*H*m* (or F*n*H*m*E) and F-44E/F*n*H*m* (or F*n*H*m*E) mixtures

Except for the previously considered F-44E + F6H12 mixtures, excess entropy was found to be positive when the mixtures contained only small amounts of the F*n*H*m* compound (Figs. 7 and 8). As a matter of fact, the diblock molecules lose their orientational order on forming the mixture. On the other hand, the entropy becomes negative when the F*n*H*m* concentration increases because an arrangement is being imposed in terms of orientation and position of the F*n*H*m* molecules. The asymmetry observed for the TS^e function is similar to the one observed for the H^e function.

When comparing the cases of the PFOB + F8H6E and PFOB + F8H10E mixtures, it will be noticed that lengthening the H-chain results in an increase of excess entropy of the system. This is consistent with micelle formation, which is a substantially positive entropic process.

On the other hand, F6H12 causes less disorder than F8H10E, although the H-chain of the former compound is longer—the geometry of the molecule is then to be considered—the overall chain lengths of the two compounds are almost equivalent, but the predominance of the *Z* configuration in F8H10E may lead to higher disorder in the mixture. The very weak insertion of F6H12 molecules into the F-44E phase leads to negative values of excess entropy over the whole range of compositions; the curve is symmetric and the minimum value is −3500 J mol^{-1} for $X_{F6H12} = 0.5$.

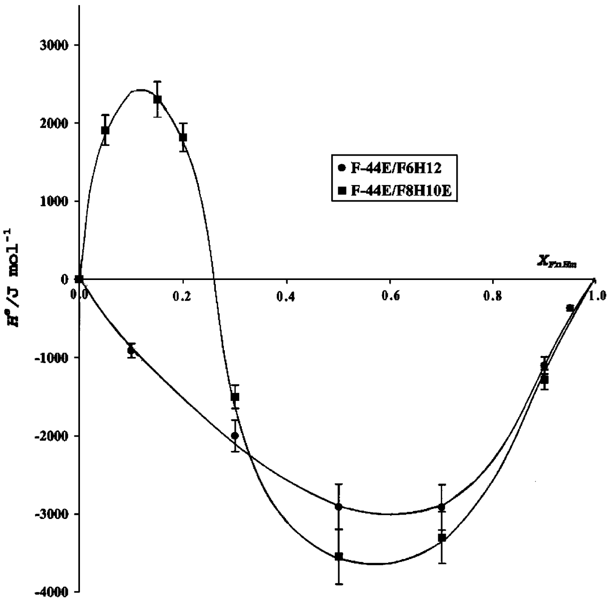

Fig. 6 Excess enthalpy of F-44E/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

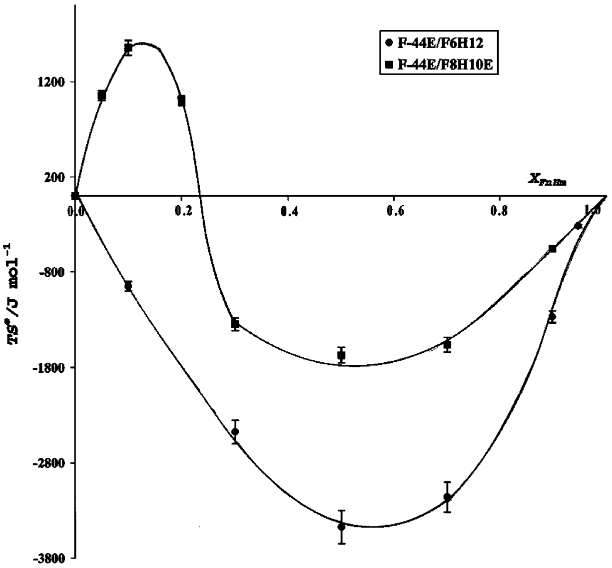

Fig. 8 Excess entropy (TS^e) of F-44E/F*n*H*m* (or F*n*H*m*E) mixtures as a function of molar fraction *X* of mixed fluorocarbon/hydrocarbon diblock compounds at 25 °C.

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Conclusions

The data show that the behaviour of FC + F*n*H*m* (or F*n*H*m*E) mixtures is different from that of FC + FC, FC + HC and HC + HC mixtures.[20] Most of the FC + F*n*H*m* or F*n*H*m*E mixtures are ideal for a given composition ratio and show opposite deviations with respect to ideality on either side of this composition ratio.

The introduction of mixed FC/HC diblock compounds in small amounts into an FC phase generally produces a thermodynamic stabilization of the system with respect to ideality. The F/H ratio in the diblock molecules plays a dominant role in this stabilization. Thermodynamic stabilization, with respect to ideality, increases when the F/H ratio increases. It has also been noticed that the presence of a lipophilic atom, such as bromine, within the dispersed FC molecule favours stabilization.

The addition of a F*n*H*m* diblock compound to a FC phase decreases the vapour pressure of the FC; if we consider the case where the liquid mixture (FC + F*n*H*m*) is in contact with an aqueous phase, the solubility of the FC in this phase decreases. In the submicronic FC-in-water emulsions used as oxygen delivery media, the liquid interface is curved rather than planar; the vapour pressure of the FC is larger than in bulk FC in accordance with Kelvin's equation.[27] The addition of F*n*H*m* diblock molecules in the dispersed FC phase also influences the vapour pressure of the FC. This addition is expected to diminish the rate of Ostwald ripening since this rate is proportional to the solubility of FC in the aqueous phase, according to the Lifshits–Slyozov equation.[5,10] The decrease of vapour pressure, and therefore of the water solubility, of the FC phase is expected to depend on temperature. Experimental evidence indicates that for a PFOB–EYP–F8H8E (90 : 4 : 2.8% w/v) emulsion, the droplet size does not vary in a significant way with temperature over time.[12] This suggests that the observed lowering of the vapour pressure of the FC phase by addition of a small amount of F*n*H*m* or F*n*H*m*E diblock is not the only factor responsible for the stabilization of injectable FC emulsions. The decrease of FC–water interfacial tension in the presence of phospholipids obtained upon addition of diblock molecules, hence the involvement of these diblock molecules at the interface,[11] is also likely to contribute to the stabilization of FC-in-water emulsions observed when F*n*H*m* diblocks are present.

Acknowledgements

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References

1 J. G. Riess, *Tetrahedron*, 2000, **58**, 4113–4131.
2 M. P. Krafft, *Curr. Opin. Colloid Interface Sci.*, 2003, **8**, 213–214.
3 M. P. Krafft, *Adv. Drug Delivery Rev.*, 2001, **47**, 209–228.
4 J. G. Riess, *J. Fluorine Chem.*, 2002, **114**, 119–126.
5 J. G. Riess, *Chem. Rev.*, 2001, **101**, 2797.
6 M. P. Krafft, A. Chittofrati and J. G. Riess, *Curr. Opin. Colloid Interface Sci.*, 2003, **8**, 251–258.
7 E. S. Schutt, D. S. Klein, R. M. Mattrey and J. G. Riess, *Angew. Chem., Int. Ed.*, 2003, **42**, 3218–3235.
8 L. Trevino, L. Solé-Violan, P. Daumur, B. Devallez, M. Postel and J. G. Riess, *New J. Chem.*, 1993, **17**, 275–278.
9 C. Varescon, C. Arlen, M. Le Blanc and J. G. Riess, *J. Chim. Phys.*, 1989, **86**, 2111–2117.
10 A. S. Kabal'nov, K. N. Makarov, O. V. Shcherbakova and A. N. Nesmeyanov, *J. Fluorine Chem.*, 1990, **50**, 271–284.
11 S. M. Bertilla, J. L. Thomas, P. Marie and M. P. Krafft, *Langmuir*, 2004, **20**, 3920.
12 J. G. Riess, L. Solé-Violan and M. Postel, *J. Disp. Sci. Technol.*, 1992, **13**, 349–355.
13 L. Solé-Violan, B. Devallez and J. G. Riess, *New J. Chem.*, 1993, **17**, 581–583.
14 A. DeRoover, M. P. Krafft, G. Deby-Dupont, J. G. Riess, N. Jacquet, M. Lamy, M. Meurisse and M. D'Silva, *Artif. Cells Blood Subst., Immob. Biotech.*, 2001, **29**, 225–234.
15 J. S. Rowlinson, *Liquids and Liquid Mixtures*, Butterworth Scientific, London, 2nd edn., 1969.
16 M. M. Newcome and G. H. Cady, *J. Am. Chem. Soc.*, 1956, **78**, 5216–5218.
17 H. J. Hildebrand, J. M. Prausnitz and R. L. Scott, *Regular and Related Solutions*, Van Nostrand Reinhold Co., New York, 1970.
18 D. E. L. Dyke, J. S. Rowlinson and B. Thacker, *Trans. Faraday Soc.*, 1959, **55**, 111–189.
19 C. McCabe, A. Galindo, A. Gil-Villegas and G. Jackson, *J. Phys. Chem. B*, 1998, **102**, 8060–8069.
20 P. Lo Nostro, *Adv. Colloid Interface Sci.*, 1995, **56**, 245–287.
21 M. P. Turberg and J. E. Brady, *J. Am. Chem. Soc.*, 1988, **110**, 7797–7801.
22 N. O. Brace, *J. Org. Chem.*, 1972, **37**, 2429–2433.
23 A. Weisberger, in *Techniques of Organic Chemistry. Part 1: Physical Methods*, Interscience, New York, 3rd edn., 1961, vol. **1**.
24 *Handbook of Chemistry and Physics*, CRC Press, Boca Raton, FL, USA, 62nd edn., 1981–1982, D-178.
25 R. Sabbah and S. J. Komorowski, *Thermochim. Acta*, 1980, **41**, 379–381.
26 J. D. Cox and G. Fischer, *Thermochemistry of Organic and Organometallic Compounds*, Academic Press, London, 1970.
27 A. W. Adamson, *Physical Chemistry of Surfaces*, J. W. and Sons, Inc., Los Angeles, 5th edn., 1990.