Unravelling the behaviour of HFA propellants: Building a case for a halogen bond

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Summary

Despite having been studied intensively for the past 10 years, the properties of HFAs are still a mystery. Solvency, interfacial tensions, and wetting ability for instance cannot be predicted through standard physico-chemical models.

These unusual behaviours are driven by the inherent chemical structure of the HFAs. Evidence for a particular inter- and intra-molecular interaction is shown from excipients' phase behaviour in HFAs, as well as from surface and interfacial tensions.

Faced with this evidence, it is suggested that a form of non contact interaction, akin to a Hydrogen bond, drives the interactions. It is suggested to name this interaction Fluorine bond, by analogy to the halogen bond defined by other chemists in the crystallographic field.

Introduction

Despite having been studied intensively for the past 10 years, the properties of HFAs are still a mystery. Solvency, interfacial tensions, and wetting ability for instance cannot be predicted through standard physico-chemical models. Somehow, HFAs do not follow the expected trends, and do not fit models developed for other organic liquids (1-3).

These unusual behaviours are driven by the inherent chemical structure of the HFAs. The difficulty is to know which aspect of the structure matters: chemical function?, geometry? To develop the right understanding and model is the next challenge. An understanding of the mechanics of this phenomenon is essential to predict the behaviour of fluorinated formulations.

Discussion

The properties of the HFA propellants can be seen in particular in 3 areas:

- -Physical properties of the liquid state
- -Surface and interfacial tension data
- -Phase diagram

-The physical properties of the liquid state

Table 1 summaries and contrasts the properties of HFA propellants vs. their fluorinated and hydrogenated counterparts.

The most striking feature is the difference in boiling points between the different liquids. This is one of the prevalent indicators of the liquid state. The boiling points are systematically the highest for the partially fluorinated compounds, a direct consequence of stronger interactions between the partially fluorinated molecules. A similar tendency can be seen in the values of the melting points, although these result also from the particularities of the corresponding crystal lattices, and therefore can not be related directly to the liquid state.

Table 1: summary and comparison of HFA propellant properties vs. their fully fluorinated and fully hydrogenated homologues.

	Pentane	HPFP	PFPt	Propane	HFA 227	PFPr	Ethane	HFA 134a	PFEt
MW (g.mol^{-1})	72	252	288	44.1	170	188	30.07	102	138
d. (g.cm^{-3})	0.64	1.58^{20}	1.63^{25}	0.49^{25}	1.42^{20}	1.29^{20}	0.55^{-89}	1.21^{25}	1.52^{-76}
B.p. (^{o}C)	36	53.6	29.2	-42.1	-16.5	-36.6	-88.6	-26.3	-78.1
M.p. (^{o}C)	-129.6	-63.6	-10	-187.6	-80	-147.6	-182.8	-101	-100.7

HPFP: 2H, 3H decafluoropentane, PFPt: perfluoropentane, HFA 227: 1,1,1,2,3,3,3-heptafluoropropane, PFPr: perfluoropropane, HFA 134a: 1,1,1,2-tetrafluoroethane, PFEt: perfluoroethane.

-Surface and interfacial data

A second set of evidence comes from surface and interfacial data, as listed on table 2.

The surface tension values probe the inter-molecular forces against the air interface. As such they shed light on the potential strength of the dispersive forces interactions. These interactions are strongest for non fluorinated molecules, and the weakest for fully fluorinated ones (i.e. the higher the surface tension, the higher the cohesive energy). The trends are modulated by the influence of the molecule carbon chain length, as can be expected, but point nevertheless to stronger inter-molecular interactions for this type of molecules.

Table 2: summary of surface and interfacial tensions of HFA propellants, and their fully fluorinated and hydrogenated homologues.

	Surface tension ($mN.m^{-1}$)	Interfacial tension against water ($mN.m^{-1}$)
Pentane	16.05^{20}	47.6^{20}
HPFP	13.59^{20}	35.63^{20}
Perfluoropentane	9.89^{20}	52.72^{20}
Propane	7.49^{20}	10.1^{20}
HFA 227	6.96^{20}	50.0^{20}
Perfluoropropane	6.85^{-4}	NA
Ethane	16.18^{-90}	NA
HFA134a	8.8^{20}	44.9^{20}
Perfluoroethane	NA	NA

The interfacial tension values against water tell a similar story, bar the example of pentane, for which a chain length effect starts to be felt (with the possibility of chain folding, or even screening of strongly binding chemical entities). Higher than expected interfacial tensions are found for partially fluorinated liquids. Interestingly, when attempts are carried out to model the interfacial tension according to the models developed by Fowkes and Good and Girifalco (see equation 1), or as developed by van Oss (see equation 2), these quickly meet with limited success. Simple models that consider a range of surface tension components simply fail. They all underestimate the interfacial tensions, pointing at strong interactions between the interfacial water and the HFAs. This interaction is strongest for HFA 227. This would indicate a preferential chain length, hence an effect that would combine partial fluorination with geometric orientation.

Equation 1[1-4]:

$$\gamma_i = \gamma_i^p + \gamma_i^d$$

$$\gamma_{12} = \gamma_1 + \gamma_2 + 2(\gamma_1^d \cdot \gamma_2^d)^{1/2}$$

Equation 2[5]:

$$\gamma = \gamma^{LW} + 2(\gamma^+ \cdot \gamma^-)^{1/2}$$

$$\gamma_{12} = \gamma_1 + \gamma_2 - 2\sqrt{\gamma_1^{LW}\gamma_2^{LW}} - 2\sqrt{\gamma_1^+\gamma_2^-} - 2\sqrt{\gamma_1^-\gamma_2^+}$$

Other models, such as those relating boiling point, or melting points to surface tension are equally limited. Further decomposition of the surface tension in multiple components are known to equally short fall of predicting the interfacial values.

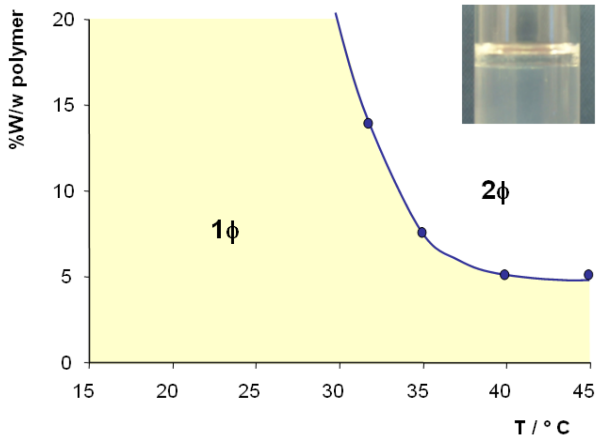

Figure 1: Phase diagram of PEG 600 in HPFP[6].

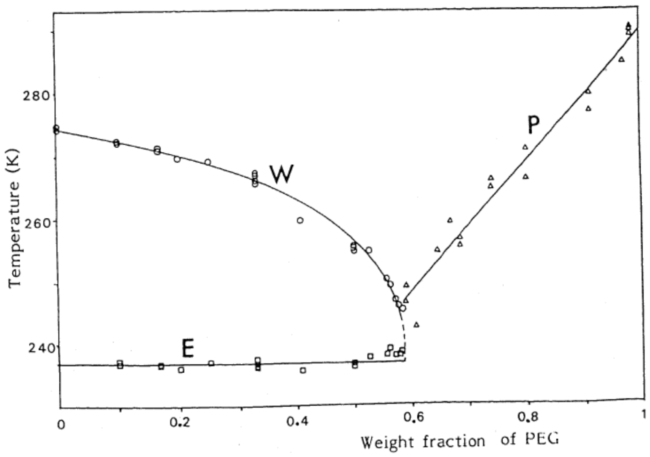

Figure 2: Phase diagram of PEG 600 in water. Phase diagram of PEG 600 in water. E: Eutectic PEG 600 (238 K), W: equilibrium solution-ice crystals, P: equilibrium solution-PEG crystals[7].

-Phase diagram

The phase diagrams of PEG600 in Water and HPFP are presented as further evidence of the unexpected partially polar properties of the partially fluorinated liquids (see Figures 1 and 2).

The monophasic domain in HPFP is more restricted than in water. Its stability is limited by an upper consolute boundary, not observed, or at least not reported, in water. The upper consolute boundary is the phase separation between an homogeneous one phase system to a biphasic system, consisting of a concentrated PEG solution in equilibrium with a very dilute PEG solution. This phase separation happens on heating the solution. The phase separation is driven by weakened solute-solvent interactions, which of course have to be understood in the light of the low boiling point of the HPFP (38 ^{o}C). The nevertheless large monophasic domain points at the relatively good solvent properties of HPFP, unlike pentane or perfluoropentane, thus denoting preferential interactions with HPFP. A similar behaviour is observed in HFA 227 and HFA 134a. The driver of this solubulisation is probably due to the partial fluorination of the alkane, this in turn influences the electronegativity and polar moment of the molecules, and enables a form of polar driving force to solubilise the solutes.

Further evidence can be found in recent publications on the phase behaviour of a range of excipients in fluorinated liquids[8-11].

Conclusions

Fluorinated liquids are usually said to be non-polar. They are therefore expected to behave like other non-polar liquids, to have poor solvent properties, and interact weakly with water. This is however not the case for partially fluorinated molecules.

Evidence from their physical properties, surface and interfacial tensions, as well as the phase behaviour of excipients solubilised in them point at a weakly polar behaviour that needs to be understood.

Faced with the evidence of the unusual behaviour, it is suggested that a form of non contact interaction, akin to the hydrogen bond, drives interactions in HFA liquids. It is dependent on the electronegativity of the fluorine atoms, and partial fluorination, and is directed by the conformation of the fluorinated molecules, their level of fluorination, and the presence in the solute or in the contact phase of reachable and polarisable oxygen rich chemical functions.

As a consequence, it is suggested to name this interaction the Fluorine bond. It is a strong distance interaction, driven by an electronegativity imbalance in the fluorinated molecules, dependent on chemical geometry, and molecular chain conformation (see Figure 3). It is of the same nature as the halogen bond proposed by others[12-13].

This interaction is particularly favourable with oxygen reach chemical function (such as those found at an interface with water, or with alcohol functions, or carboxylic acids). This explains also why oxygen rich excipients are soluble in HFAs, such ethanol, PEG, but also compounds such as peracetylated cyclodextrins. Some of these properties are reminiscent of behaviour seen in supercritical CO_2.

Further work is required to understand the magnitude of the bond, its preferred conformation, and the parameters that would limit its scope.

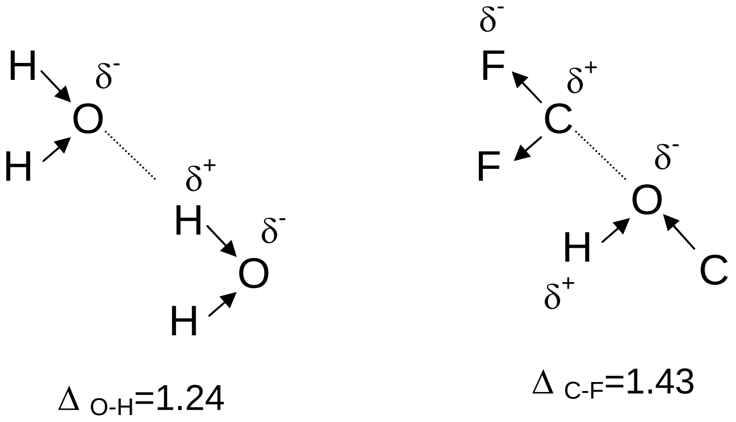

Figure 3: a proposal for the Fluorine bond. ΔC-H and ΔC-F are the differences in the Pauling electronegativity for Carbon, Hydrogen and Fluorine.

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