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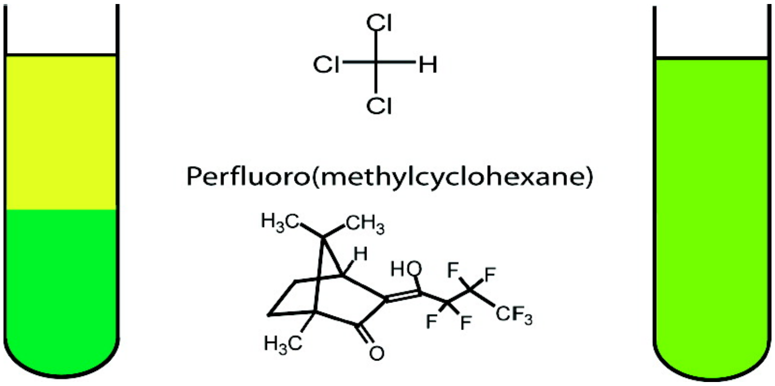

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Selective Solvent Interactions in a Fluorous Reaction System

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Abstract: Mixtures of chloroform and perfluoro(methylcyclohexane) can be used as solvents for “fluorous” biphase reactions since they exist as two separate phases at low temperature but become a single phase at higher temperatures. Intermolecular nuclear Overhauser effects have been used to investigate the interactions of solvent components with the protons and fluorines of 3-heptafluorobutyrylcamphor in both phases of this biphasic system at 25 °C as well as the single phase at 54 °C. The results indicate that at 25 °C in the perfluorocarbon-rich phase, both solvent components interact with the solute selectively. There are no indications of unusual solute interactions of either solvent component in the chloroform-rich phase and only weak suggestions of selective interactions in the high-temperature phase. Various mechanisms for the enhancement of solute spin-solvent spin cross relaxation rates in the perfluoro(methylcyclohexane)-rich phase are considered. It is suggested that the solvation layer around the solute has a composition and possibly hydrodynamic properties different from those of the bulk solution in this phase. There are indications of appreciable regioselectivity of chloroform interactions with the hydrocarbon part of the solute in all phases.

Liquid perfluorocarbons have high densities, low surface tensions, low polarizabilities, and low dielectric constants. They generally are immiscible with hydrocarbons, although some fluorocarbon−hydrocarbon systems become miscible at temperatures conveniently achieved in the laboratory. The ability of such nonaqueous systems to exist as two phases at low temperature but as a single phase at higher temperature has led to development of strategies for doing chemical synthesis that rely on the temperature-dependent phase behavior to achieve separation of reactants from products and reaction catalysts. These so-called “fluorous” methodologies have received much attention and have been reviewed recently by a number of authors.[1−9] For fluorous approaches to be effective, reactant molecules with a high degree of hydrocarbon character must be rendered compatible with a perfluorocarbon-rich environment. This is typically accomplished by derivatizing them with highly fluorinated groups. An area of active research seeks to determine how much perfluorocarbon character needs to be added to a molecule of interest in order to render a given structure soluble in a perfluorocarbon-containing phase.

Compared to alkanes, perfluoroalkanes are distinctly more inert and more weakly interacting with a dissolved species.[10] Interactions between hydrocarbons and perfluorocarbons are largely the result of dispersion (London) forces.[11] However, the C−F bond is highly polarized, and solute molecules adjacent to fluorocarbons must also feel the influence of the strong local C−F dipoles.[12] In addition to solvent−solute dispersion energies, dipole−dipole interactions and dipole-induced dipole interactions may need to be considered when describing perfluorocarbon−hydrocarbon interactions.

Several groups have attempted to predict the phasephilicity of molecules that have both perfluorocarbon and hydrocarbon parts by statistical or linear free energy methods, and there has been some success in this regard.[13−15] Such methods attempt to correlate properties of a solute molecule, such as solvent accessible surface, polarizability, or atomic composition, with quantitative measures of fluorophilicity, defined as the tendency of a molecule to dissolve in a perfluorinated solvent in preference to a hydrocarbon. All such efforts to date appear to have ignored possible specific interactions of a solute with either the perfluorocarbon or hydrocarbon solvent components of fluorous reaction mixture as contributors to fluorophilicity.

It was the purpose of the present work to provide experimental information about the interactions between a molecule with distinct hydrocarbon and perfluorocarbon parts and the solvent components of a fluorous reaction system. The experimental tool used was detection of solvent spin-solute spin dipolar interactions as reflected in intermolecular nuclear Overhauser

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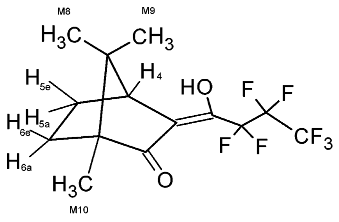
effects.[16−21] Specifically, we have examined interactions of 3-heptafluorobutyrylcamphor (**I**) with the solvent components of a mixture of perfluoro(methylcyclohexane) and chloroform. Given equal volumes of the two components, this solvent system is biphasic at room temperature but becomes a single phase at 51.5 °C.[22] Chloroform is the polar component (solvent polarity index $P_s = 7.93$) in this system, while perfluoro(methylcyclohexane) is essentially nonpolar ($P_s = 0.46$).[23]



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The results provide evidence for preferential solvent interactions of both solvent components with **I** under conditions where the perfluorocarbon is the major solvent component.

Experimental Section

Materials. 3-Heptafluorobutyryl-(+)-camphor (96%) was supplied by Aldrich and was used as received. Perfluoro(methylcyclohexane) (Aldrich, 90%) was extracted three times with an equal volume of reagent chloroform at room temperature, then chilled to 4 °C overnight. The lower layer was withdrawn and used for preparation of samples. Chloroform (Merck) containing 0.75% ethanol as a stabilizer was used as received. Deuterium oxide (99.9%) was from Aldrich.

NMR Sample Preparation. One milliliter each of chloroform and perfluoro(methylcyclohexane) was added to a small vial; the mass of each aliquot was determined after its addition. A known mass (~20 mg) of 3-heptafluorobutyryl-(+)-camphor was added. The sample was gently warmed until it became a single phase. An aliquot of the single-phase solution was added to a 3 mm J. Young NMR tube (Wilmad) and sealed. The remainder of the solution was allowed to cool to 25 °C in a water bath. An aliquot of the top layer was drawn off with a pipet and placed in a 3 mm J. Young tube. A small amount of the bottom layer was added such that a detectable amount of lower layer was present (column height ~3 mm) but not to such an extent that it came close to the transmitter−receiver coil of the probe used. Similarly, a sample that was mostly lower layer, but in contact with a small amount of the upper layer, was placed in a third J. Young tube. The upper layer was ~3 mm in length and situated well away from the transmitter−receiver coil of the probe. All three samples were sealed but, because of the facile sublimation of the fluorinated compounds, were not degassed. The 3 mm sample tubes were centered inside a 5 mm NMR tube containing 99.9% deuterium oxide to provide a lock signal.

Instrumentation. All NMR spectra were collected using a Varian INOVA instrument operating at a proton frequency of 500 MHz. A Nalorac H/F probe equipped with a *z*-axis gradient coil was used. All data presented in this paper were collected for samples at 25 or 54 °C. Sample temperatures were determined using a standard sample of methanol (Wilmad) and are believed to have been constant to better than ±0.1 °C and accurate to better than ±0.5 °C. Care was taken to avoid the effects of radiation damping, which were typically present when ^{1}H observations were undertaken, unless the ^{1}H (inner) coil of the probe was significantly detuned. Pulse sequences used for determination of intermolecular NOEs were local adaptations of published sequences and are described in the Supporting Information. The experiments for NOE determinations involve difference methods and were extensively signal-averaged to minimize the effects of instrumental instabilities.

Determination of Diffusion Coefficients. Samples were allowed to equilibrate in the probe at the regulated temperature at least 3 h before attempting diffusion measurements. Self-diffusion coefficients were determined by bipolar pulse pair-longitudinal eddy current delay (BPP-LED),[24] bipolar double-stimulated echo (DSTE),[25] and double multiple spin−echo (DMSE)[26] pulsed field gradient methods. The latter two methods suppress the effects of convection within the sample on the measured diffusion coefficient. It has been pointed out that determinations of translational diffusion coefficients in high-resolution NMR probes with pulsed field gradient coils are limited by the linearity of gradient pulses over the volume of the sample.[27] Any such limitations are compounded by the nature of our samples—a 3 mm tube of low dielectric material inserted into a 5 mm tube containing a high dielectric (deuterium oxide). A 3 mm sample of reagent grade cyclohexane (Mallinckrodt) in a 5 mm tube containing D_2O was used to calibrate field gradient pulses using the published diffusion coefficients of cyclohexane.[28] Gradient values and timing parameters for a pulse sequence which led to ~2 orders of magnitude change of the signals of interest were used. The estimated experimental uncertainty for the diffusion coefficients reported is ±5%.

Determination of Cross Relaxation Rates (σ_{XY}). NOEs were determined for a range of mixing times (t_{mix}). Observed peak intensities were fit to the empirical function $A \times t_{mix} + B \times t_{mix}^2$, with the coefficient A being taken as the initial slope of the data. Investigations using synthetic data suggested that this procedure gives values for the initial slopes that are reliable to better than 5% when the signal-to-noise ratio is good. Initial slopes were less reliably determined when the concentration of solvent species is low. All data were corrected for the extent of inversion of the solvent signal (see Supporting Information for more details). The largest NOE was typically less than 0.2% at a mixing time of 1 s.

Molecular Radii. The apparent radii of the molecules used in this work were estimated by constructing a model in SYBYL using standard bond lengths and angles. After minimizing the conformational energy, a van der Waals surface for the model was calculated using the Connolly method.[29] The radius of the sphere "rolled" over the surface of the model in these calculations was 1.2 or 1.35 Å, corresponding to the van der Waals radii of a covalent hydrogen atom or covalent fluorine, respectively.[30] Distances from the surface defined by the probing spheres to the center of the molecule were calculated and averaged. Using this approach, it was estimated that the average radii of chloroform and of perfluoro(methylcyclohexane) are 2.40 and 3.43 Å, respectively. Marcus has recently discussed various methods for estimating a molecular radius when the molecule is to be approximated by a sphere[31] and indicates that the radius of a sphere representing a chloroform molecule would

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Table 1. Proton Chemical Shifts (ppm) of 3-Heptafluorobutyryl-(+)-camphor[a]

proton	lower layer (25 °C)	upper layer (25 °C)	single phase (54 °C)
H4	2.955	2.850	2.913
H5e	2.165	2.076	2.127
H6e	1.848	1.772	1.813
H5a[b]	1.565	1.456	1.520
H6a[b]	1.565	1.456	1.529
methyl 10	1.097	1.007	1.060
methyl 9	1.047	0.959	1.012
methyl 8	0.922	0.817	0.873

[a] The chloroform signal in each phase was used as a reference and set to 7.27 ppm. [b] Signals for these spins overlap. No attempt was made to determine the shifts for the individual spin; the reported data are for the center of the groups of signals arising from the spins.

Table 2. Composition of Phases

component	lower layer (25 °C) (M)	upper layer (25 °C) (M)	single phase (54 °C) (M)
chloroform	1.87 ± 0.2	11.6 ± 0.3	5.81 ± 0.3
perfluoro(methylcyclohexane)	3.85 ± 0.02	0.93 ± 0.02	2.37 ± 0.1
3-heptafluorobutyryl-(+)-camphor	0.14 ± 0.01	0.88 ± 0.02	0.44 ± 0.02

Table 3. Diffusion Coefficients of Components ($\times 10^9$ m^2 s^{-1})

component	lower layer (25 °C)	upper layer (25 °C)	single phase (54 °C)
chloroform	1.72	2.04	3.10
perfluoro(methylcyclohexane)	0.94	0.95	1.63
3-heptafluorobutyryl-(+)-camphor	0.74	0.98	1.45

be between 2.30 and 2.71 Å, while a sphere representing perfluoro(methylcyclohexane) would have a radius between 3.34 and 3.54 Å, both radii in agreement with the estimates produced by our method. The radius of a sphere representing 3-heptafluorobutyryl-(+)-camphor was estimated to be 4.24 Å.

Calculation of Cross Relaxation Rates. Expected cross relaxation rates due to intermolecular dipolar interactions were calculated as previously described.[32] The method takes into account the shape of a solute molecule (represented by its Connolly surface) but approximates solvent molecules as spheres. It has been shown that for any reasonable set of conditions, the interacting spins of a solvent molecule behave as if they are positioned at the center of its representative sphere.[33] Experimental self-diffusion coefficients are used in the calculations.

Estimated Rotational Correlation Times. Rotational correlation times (τ_R) were estimated from hydrodynamic theory.[34] Neglecting microviscosity considerations and assuming that the molecule of interest can be represented by a sphere of radius r, the rotational correlation time for a solution species was estimated from $\tau_R \approx 2 \times r^2/9 \times D_{\text{trans}}$, where D_{trans} is the experimental translational diffusion coefficient.[34]

Results

Identification of Solute Spins. Assignments of the proton signals for **I** were accomplished by consideration of double quantum filtered COSY and ROESY spectra and are collected in Table 1. Fluorine signals were readily assigned based on considerations of electronegativity effects and the structure of multiplets. Fluorine-19 spectra for perfluoro(methylcyclohexane) consisted of multiplets spread over a ~120 ppm range. Because of the difficulty in uniformly exciting this range by RF pulses on our instrumentation, fluorine experiments were primarily focused on the CF_3 group of perfluoro(methylcyclohexane) and the CF_3 group of the solute. These two multiplets were separated by ~11.5 ppm.

Layer Compositions. The compositions of the upper and lower layers (Table 2) were estimated from the known amounts of material present and the relative intensities of signals from sample components in proton and fluorine-19 spectra. The volumes of the solvent components appeared to be additive within an error of about 1%. The expansion of the single-phase sample at 54 °C was estimated to be 15% and was taken into account in calculating the molar concentrations of sample components at this temperature.

Intermolecular Cross Relaxation. The intensity of an NMR signal from solute spin X depends on the z-component of its corresponding magnetization prior to application of the RF pulse that produces the signal. Following a perturbation of a spin Y associated with a solvent molecule, the initial change in the solute signal intensity with time is described by eq 1.[34]

$$\frac{dX_Z}{dt} = -\sigma_{XY}(Y_Z(0) - Y_Z{}^0) \tag{1}$$

Here, X_Z is proportional to the intensity of the solute signal of interest; $Y_Z(0)$ is the initial value of the solvent spin z-magnetization; $Y_Z{}^0$ is the z-component of the solvent magnetization when the system is at equilibrium, and σ_{XY} is the cross relaxation rate due to the dipole−dipole interactions of the solvent and solute spins. If the gyromagnetic ratios of solute spins and solvent spins are γ_X and γ_Y, respectively, then $X_Z{}^0/\gamma_X = Y_Z{}^0/\gamma_Y$, where $X_Z{}^0$ is the z-component of the solute spin z-magnetization at equilibrium.[35] The initial slope of a plot of the intensity of the solute signal after perturbation of the solvent as a function of time after the perturbation (the mixing time) is $2\sigma_{XY}$, assuming that the solvent magnetization was completely inverted at the start of the experiment.

The dipolar cross relaxation rate σ_{XY} is given by

$$\sigma_{XY} = \frac{1}{10}\gamma_X{}^2\,\gamma_Y{}^2 h^2[6J_2(\omega_X + \omega_Y) - J_2(\omega_X - \omega_Y)] \tag{2}$$

where ω_X and ω_Y are the Larmor frequencies of the spins of interest, and J_2 is a spectral density function that, for intermolecular interactions, depends on the sum of the diffusion coefficients for the molecules containing the X and the Y spins ($D = D_X + D_Y$), their distance of closest approach, r_{XY}, and N_Y, the number of solvent spins per milliliter.[35,36] In the extreme narrowing limit ($\omega r_{XY}{}^2/D \ll 1$), the cross relaxation rate is proportional to $N_Y/r_{XY}D$ if the solvent has a constant composition from the distance of closest approach to the edge of the sample. Thus, prediction of an experimental σ_{XY} requires knowledge of the concentration of solvent spins, the mutual diffusion coefficient for solute and solvent, and an estimate of the distance of closest approach of solute and solvent spins.

Diffusion coefficients for the components of each phase were determined by a variety of pulsed field gradient methods (Table 3). Results from all methods were similar at 25 °C. Determinations made by the DSTE and DMSE methods at 54 °C agreed well with each other but not with the results of BPP-LED

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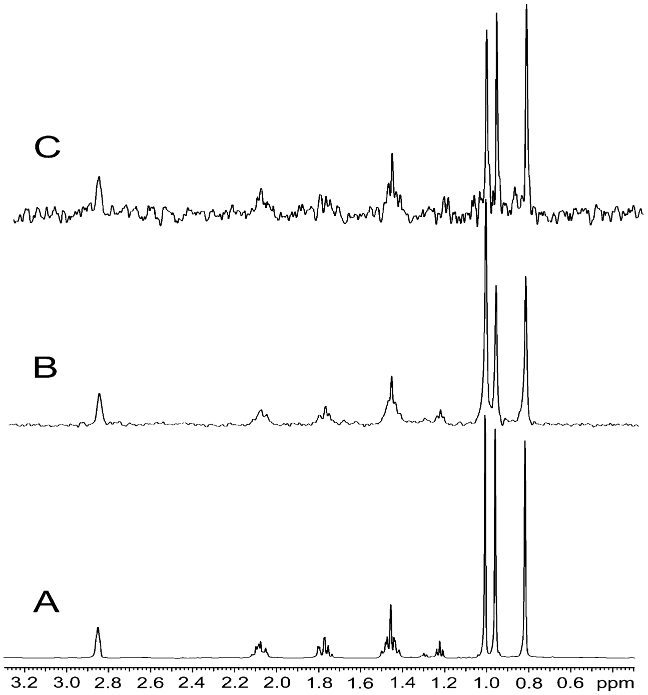

Figure 1. ^{1}H{^{1}H} and ^{1}H{^{19}F} solvent−solute NOEs for 3-heptafluorobutyryl-(+)camphor (**I**) dissolved in chloroform−perfluoro(methylcyclohexane) upper layer at 25 °C: (A) control spectrum; (B) chloroform proton magnetization inverted; (C) perfluoro(methylcyclohexane) CF_3 magnetization inverted. The mixing time for both experiments was 800 ms. The vertical scale factor for spectrum B is approximately 1000-fold larger than that for the control spectrum. The vertical scale factor for spectrum C is approximately 5000-fold larger than that of the control.

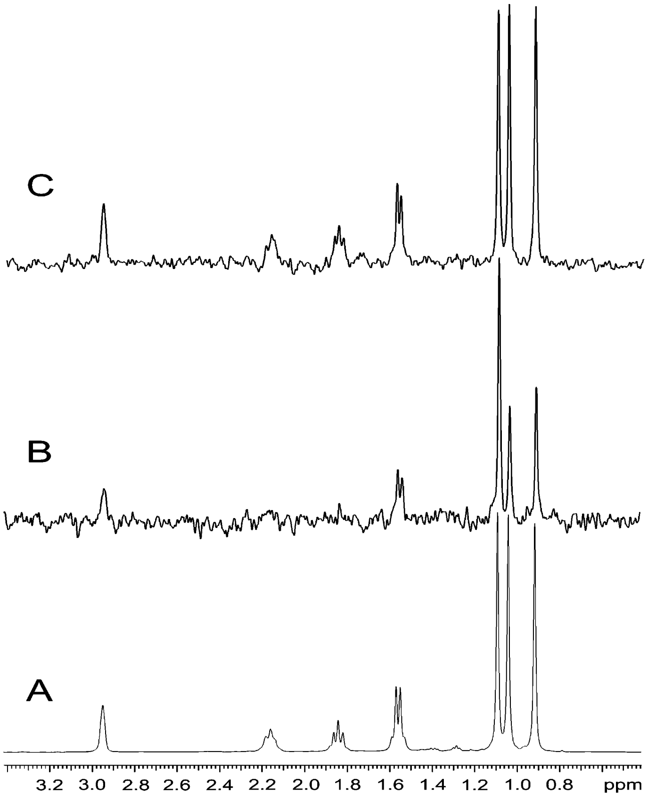

Figure 2. ^{1}H{^{1}H} and ^{1}H{^{19}F} solvent−solute NOEs for 3-heptafluorobutyryl-(+)camphor (**I**) dissolved in chloroform−perfluoro(methylcyclohexane) lower layer at 25 °C: (A) control spectrum; (B) chloroform proton magnetization inverted; (C) perfluoro(methylcyclohexane) CF_3 magnetization inverted. The mixing time for both experiments was 800 ms. The vertical scale factor for the NOE spectra is approximately 2000-fold larger than that for the control spectrum.

experiments, indicating the presence of convection effects at this temperature.[25]

Upper Layer. At 25 °C, a mixture of chloroform and perfluoro(methylcyclohexane) exists as two phases. The lighter, upper layer consists mostly of chloroform (Table 1); most of the solute **I** is also distributed into this layer. Intermolecular cross relaxation rates for the protons and fluorine spins of the solute (σ_{HH}, σ_{FH}) that are produced by interaction with the hydrogens of the chloroform molecules in this phase were determined (Figure 1, Table 4). The ^{19}F{^{1}H} effects shown are for the trifluoromethyl group of the solute only. Intermolecular ^{1}H{^{19}F} and ^{19}F{^{19}F} NOEs produced by inversion of the signal for the trifluoromethyl group of perfluoro(methylcyclohexane) in the solvent were also determined for the upper layer (Table 4).

The experimental diffusion coefficients for the components of the upper layer and the composition of this layer (Table 1) were used to compute the intermolecular cross relaxation rates expected in these experiments. The estimated uncertainty for the cross relaxation rate constants (σ_{XY}) produced by the experiments with the upper layer is about ±10%, a bit less than that for the CH_3 and CF_3 groups since their signals are more intense. Calculated values for the cross relaxation rate constants are subject to the experimental uncertainty of the diffusion coefficients and the molar concentration of each component in this layer as well as any uncertainties introduced by the approximations used in forming the theoretical basis for the calculations. Considering these factors, it is estimated that the uncertainties in the calculated values for the cross relaxation rates are about ±10%. Thus, ratios of the observed to calculated

Table 4. Intermolecular Cross Relaxation Rates in the Upper Layer (25 °C)

	Invert $CHCl_3$			Invert CF_3 of Perfluoro-(methylcyclohexane)		
	$\sigma_{HH} \times 10^3$ exp.	$\sigma_{HH} \times 10^3$ calcd	σ_{HH}(exp.)/σ_{HH}(calcd)	$\sigma_{HF} \times 10^3$ exp.	$\sigma_{HF} \times 10^3$ calcd	σ_{HF}(exp.)/σ_{HF}(calcd)
			Observe ^{1}H			
H4	1.5	1.4	1.1	0.41	0.27	1.5
H5e	1.7	1.6	1.1	0.34	0.31	1.1
H6e	1.6	1.6	1.0	0.31	0.32	0.97
H5a	2.1	1.6	1.3	0.33	0.32	1.0
H6a	2.1	1.6	1.3	0.33	0.32	1.0
methyl 10	2.4	1.7	1.4	0.24	0.33	0.73
methyl 9	1.5	1.6	0.94	0.29	0.31	0.94
methyl 8	1.6	1.6	1.0	0.32	0.32	1.0
			Observe ^{19}F			
	$\sigma_{FH} \times 10^3$ exp.	$\sigma_{FH} \times 10^3$ calcd	σ_{FH}(exp.)/σ_{FH}(calcd)	$\sigma_{FF} \times 10^3$ exp.	$\sigma_{FF} \times 10^3$ calcd	σ_{FF}(exp.)/σ_{FF}(calcd)
solute CF_3	0.15	0.16	0.94	0.36	0.30	1.2

Table 5. Intermolecular Cross Relaxation Rates in the Lower Layer (25 °C)

	Invert $CHCl_3$			Invert CF_3 of Perfluoro(methylcyclohexane)		
	$\sigma_{HH} \times 10^3$ exp.	$\sigma_{HH} \times 10^3$ calcd	σ_{HH}(exp.)/σ_{HH}(calcd)	$\sigma_{HF} \times 10^3$ exp.	$\sigma_{HF} \times 10^3$ calcd	σ_{HF}(exp.)/σ_{HF}(calcd)
			Observe ^{1}H			
H4	0.65	0.26	2.5	2.1	1.2	1.8
H5e	<0.65[a]	0.30	<2.2	2.3	1.4	1.6
H6e	<0.65[a]	0.30	<2.2	1.9	1.4	1.4
H5a	0.83	0.29	2.9	2.0	1.4	1.4
H6a	0.83	0.30	2.8	2.0	1.4	1.4
methyl 10	0.99	0.31	3.2	1.7	1.5	1.1
methyl 9	0.53	0.30	1.8	1.7	1.4	1.2
methyl 8	0.66	0.29	2.2	1.8	1.4	1.3
			Observe ^{19}F			
	$\sigma_{FH} \times 10^3$ exp.	$\sigma_{FH} \times 10^3$ calcd	σ_{FH}(exp.)/σ_{FH}(calcd)	$\sigma_{FF} \times 10^3$ exp.	$\sigma_{FF} \times 10^3$ calcd	σ_{FF}(exp.)/σ_{FF}(calcd)
solute CF_3	0.42	0.30	1.4	2.3	1.3	1.8

[a] Signal-to-noise considerations limited evaluation of this cross relaxation rate. The value given probably represents an upper limit. See Figure 2.

Table 6. Intermolecular Cross Relaxation Rates in the Single Phase (54 °C)

	Invert $CHCl_3$			Invert CF_3 of Perfluoro(methylcyclohexane)		
	$\sigma_{HH} \times 10^3$ exp.	$\sigma_{HH} \times 10^3$ calcd	σ_{HH}(exp.)/σ_{HH}(calcd)	$\sigma_{HF} \times 10^4$ exp.	$\sigma_{HF} \times 10^4$ calcd	σ_{HF}(exp.)/σ_{HF}(calcd)
			Observe ^{1}H			
H4	0.84	0.52	1.6	0.77	0.54	1.4
H5e	0.87	0.60	1.5	0.77	0.63	1.2
H6e	0.90	0.59	1.5	0.48	0.62	0.77
H5a	0.88	0.58	1.5	0.62	0.61	1.0
H6a	0.88	0.60	1.5	0.62	0.63	0.98
methyl 10	1.1	0.61	1.8	0.47	0.64	0.73
methyl 9	0.72	0.59	1.2	0.58	0.61	0.95
methyl 8	0.79	0.60	1.3	0.57	0.63	0.90
			Observe ^{19}F			
	$\sigma_{FH} \times 10^4$ exp.	$\sigma_{FH} \times 10^3$ calcd	σ_{FH}(exp.)/σ_{FH}(calcd)	$\sigma_{FF} \times 10^3$ exp.	$\sigma_{FF} \times 10^3$ calcd	σ_{FF}(exp.)/σ_{FF}(calcd)
solute CF_3	0.60	0.58	1.0	0.54	0.59	0.92

cross relaxation rates (σ_{XY}(exp.)/σ_{XY}(calcd)) shown in Table 4 could range from about 0.8 to 1.2 just because of experimental uncertainties. Overall, the observed σ_{XY} are in good agreement with the corresponding calculated cross relaxation rates. This indicates that the computational procedure used for estimating the intermolecular NOEs is reliable and suggests that the experimental results for the upper layer are consistent with the conclusion that all solvent−solute interactions in this layer are understandable in terms of the diffusion behavior and bulk composition of this phase.

Lower Layer. The heavier, lower layer produced when chloroform and perfluoro(methylcyclohexane) are mixed is rich in the perfluorinated hydrocarbon. It dissolves less of the solute **I**. Figure 2 present some typical results of ^{1}H{^{1}H} and ^{1}H{^{19}F} NOE experiments, while Table 5 summarizes the cross relaxation data produced.

Calculated intermolecular cross relaxation rates for the lower layer are compared to the observed cross relaxation rates in Table 5. The experimental uncertainties in the proton-observe NOEs are higher than those for upper layer because of the lower concentration of chloroform and solute in this layer. On the basis of the results of several replicate experiments, it is estimated that these uncertainties are as high as ±25% in the case of the NOEs for single protons. The uncertainty of the calculated cross relaxation terms is about the same as that of the case for the upper layer. Thus, the ratio of observed to calculated σ_{XY} values for the lower layer could range from 0.7 to 1.3 just because of experimental uncertainties. Considering all of the data in Table 5 in this light, it is apparent that there are appreciable differences between the observed and calculated cross relaxation rates in the lower layer.

Single Phase. Proton and fluorine solute−solvent intermolecular NOEs were determined for a homogeneous system at a sample temperature of 54 °C. Table 6 compares the experimental cross relaxation rates at this temperature to values calculated by the same methodology as used for the separate layers.

Unfortunately, reproducibility of cross relaxation rates was poorer at the higher temperature, and we estimate that ratios of σ_{XY}(exp.)/σ_{XY}(calcd) could range from 0.6 to 1.4 because of experimental uncertainties. Thus, most of the intermolecular cross relaxation rates observed under single-phase conditions are within experimental error of those predicted by the computational method. However, reminiscent of what was found for the perfluorocarbon-rich layer at 25 °C, it appears that chloroform proton−solute proton interactions lead to cross relaxation effects that are somewhat larger than expected on the basis of calculations.

Solvent−Solvent Cross Relaxation. Cross relaxation between the chloroform and perfluoro(methylcyclohexane) components of the solvent mixture can be detected by inverting the fluorine spins of the perfluorocarbon and observing the effect on the intensity of the chloroform proton signal (σ_{HF}) or by the opposite experiment in which the protons of chloroform are inverted (σ_{FH}). The ratio σ_{HF}(exp.)/σ_{FH}(exp.) should be dependent only on the ratio $N_{perfluoro(methylcyclohexane)}/N_{chloroform}$ since all other factors in the theoretical expression for the cross relaxation rate should cancel. Table 7 records cross relaxation rates for interaction of the two solvent components and compares their

Table 7. Chloroform−Perfluoro(methylcyclohexane) Cross Relaxation Rates[a]

	observe solvent ^{1}H, invert solvent CF$_3$ σ_{HF}, $\times 10^3$	observe solvent CF$_3$, invert solvent ^{1}H σ_{FH}, $\times 10^3$	σ_{HF}(obs)/σ_{FH}(obs)	[perFMCH]/[chloroform]
upper layer (25 °C)	0.25 ± 0.09 (0.23)	0.99 ± 0.10 (0.95)	0.25 ± 0.1	0.24 ± 0.02
lower layer (25 °C)	1.9 ± 0.05 (1.0)	0.19[b] ± 0.05 (0.16)	10.0 ± 4.	6.2 ± 0.7
single phase (54 °C)	0.56 ± 0.03 (0.45)	0.47 ± 0.05 (0.37)	1.2 ± 0.2	1.2 ± 0.1

[a] NOEs were determined between the protons of chloroform and the CF$_3$ spins of perfluoro(methylcyclohexane). Values in parentheses are theoretical cross relaxation rates calculated by regarding the solvent interactions as involving spheres with radii indicated in the text. [b] In a series of experiments, NOEs on signals for the CF$_2$ groups of perfluoro(methylcyclohexane) were determined in turn. The cross relaxation rates (σ_{FH}) were essentially the same as that obtained for the CF$_3$ group. There, thus, is no evidence for structure-selective interactions between chloroform and perfluoro(methylcyclohexane).

ratio to the ratio of the fluorine and proton spin concentrations. The table includes the cross relaxation rates calculated by assuming that both solvent components are spheres of the radii mentioned earlier. For the upper layer and the single phase, the ratios of the experimental cross relaxation rates for interaction of the solvent components generally agree well with the concentration ratios when experimental uncertainties are taken into account. However, the cross relaxation rates (and their ratio) for the lower layer appear to be larger than expected based on the bulk diffusion constants of the chloroform and perfluoro(methylcyclohexane) components of this phase.

Discussion

The assumptions used in predicting solvent−solute cross relaxation rates include (1) the solvent composition is the same throughout the sample, including solvent near a solute molecule; (2) the diffusive behavior of all species in the solution is faithfully represented by the measured bulk diffusion coefficient; (3) solute molecules can be represented by spheres which tumble rapidly enough that their spins can be regarded as being present at the center of the sphere; and (4) the distance of closest approach of solvent molecules to a solute molecule, averaged over all approach pathways, is correctly accounted for by the numerical method used. We take the agreement found in most instances between observed and calculated cross relaxation rates to mean that the basic assumptions used to obtain the calculated rates is correct, rather than being the result of a cancellation of errors. A significant disagreement between observed and calculated cross relaxation rates thus likely indicates a breakdown in one or more of these assumptions.

It should be recognized that solute−solvent Overhauser effects have a relatively weak dependence on the solute spin-solvent spin distance and that an appreciable part of an observed NOE depends on solution conditions far from the solute spin. This point has been made in the context of water proton−protein proton NOEs by Halle and co-workers.[37,38] For example, presuming the solvent composition is homogeneous, about 18% of an observed solute proton−chloroform solvent proton dipolar interaction is due to the chloroform molecules beyond the second layer of solvent molecules that are clustered around the solute proton.

The largest disagreements between observed and calculated solute−solvent cross relaxation rates found in the present work were for the lower layer of the chloroform−perfluoro(methylcyclohexane) system (Table 5). We find that σ_{HH} for most interactions of the chloroform protons and the protons of the camphor derivative **I** are 2−3 times larger than the corresponding predicted cross relaxation rates; σ_{FF} for interactions of the perfluoro(methylcyclohexane) CF$_3$ spins with the fluorines of **I** is similarly enhanced. Fluorine−proton interactions, as reflected by σ_{HF} and σ_{FH}, are also somewhat larger than predicted, although the effects in these cases are barely beyond experimental uncertainty. Interactions between the protons and fluorines of the solvent components in the lower phase are also characterized by cross relaxation rates larger than those predicted (Table 7).

Enhancement of a cross relaxation rate (σ_{XY}) could arise because (1) the number density (N_Y) of solvent spins near the solute protons is higher than that of the bulk solvent due to preferential interactions of **I** with the solvent molecules, (2) the diffusion of solute and solvent in the vicinity of the solute is not well represented by the bulk relative diffusion coefficient D ($D_{\mathrm{chloroform}} + D_{\mathrm{solute}}$), or (3) the distance of closest approach averaged over the shape of the solvent molecule is incorrect. The last consideration is unlikely to be the reason that a cross relaxation rate σ_{XY} is larger than expected. In the event that chloroform always interacts with a solute proton so that the chloroform proton is oriented toward the solute, coming within van der Waals contact ($r_{HH} \sim 2.4$ Å), the computed σ_{HH} would only be increased by 150% over the value expected if rapid rotation makes the chloroform proton appear to be on average at the center of the sphere representing it. When modulation of the solute proton−chloroform proton distance by rotational diffusion of chloroform (correlation time $\tau_R \sim 7$ ps) is taken into account using the interacting spheres model of Ayant et al.,[36] the calculated σ_{HH} is only about 11% larger than what is calculated assuming the chloroform is located at the center of its representative sphere.

Preferential solvation of camphor derivative **I** in the lower layer by the solvent components is consistent with our observation that solute proton−chloroform proton (σ_{HH}) and solute fluorine−perfluorocarbon fluorine (σ_{FF}) cross relaxation rates are larger than expected. This would have the effect of making the concentration of chloroform or perfluoro(methylcyclohexane) dependent on the distance from the solute protons, with a concentration higher than the bulk concentration near the solute spin, tapering toward the bulk concentration as one moves away from the solute molecule. It is shown in the Supporting Information that if the solvent component concentration is large relative to the concentration of the solute, if the diffusion of the solvent molecules is everywhere the same as the diffusion

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of the bulk, and if the solvent component concentration changes from ($N_{\text{solvent}}^{\text{dca}} + N_{\text{solvent}}^{\text{bulk}}$) at the distance of closest approach to the concentration in the bulk of the sample $N_{\text{solvent}}^{\text{bulk}}$ according to $1/r$, where r is the distance from the solute spin, then the cross relaxation rate σ_{HH} for the chloroform proton−solute proton interactions would be increased by the factor

$$\frac{\frac{N_{\text{chloroform}}^{\text{dca}}}{2} + N_{\text{chloroform}}^{\text{bulk}}}{N_{\text{chloroform}}^{\text{bulk}}}$$

The treatment used to arrive at this result is crude but suggests that the local concentration of chloroform near a solute hydrogens would have to be about 3 times as large as the concentration of this solvent component in the bulk to be consistent with our observations. Similarly, an increase in perfluoro(methylcyclohexane) concentration near the perfluoroalkyl part of **I** would be consistent with the observed σ_{FF}.

A local increase in the concentration of chloroform molecules near solute protons implies that the local concentration of perfluoro(methylcyclohexane), the other solvent component, near those protons would be reduced by mutual exclusion. This should lead to experimental cross relaxation rates involving the CF_3 group (σ_{HF}) of perfluoro(methylcyclohexane) that are smaller than those predicted. It seems clear that dipolar interactions between the solute protons and the fluorines of the solvent mixture lead to cross relaxation rates that are, if anything, larger than expected. It may be that the apparently increased concentrations of perfluoro(methylcyclohexane) near the perfluoroalkyl part of the solute, indicated by our results, compensate to some extent for the “missing” fluorocarbon molecules in the immediate vicinity of the solute protons.

It is possible that chloroform or perfluoro(methylcyclohexane) molecules interact strongly enough with camphor derivative **I** in the lower layer that dipolar interactions between the solvent spins and spins of the solute are modulated by the rotational motion of the solute−solvent molecule complex rather than by diffusive encounter. That is, the cross relaxation arising from solvent spin-solute spin interaction becomes, in essence, an intramolecular process. The contribution of such a long-lived interaction to the observed dipolar cross relaxation rate is given by[37]

$$(\gamma_X \gamma_Y \hbar)^2 \sum_{k=1}^{N} \frac{1}{r_k^6} \left(\frac{6\tau_{\text{C},k}}{1 + (w_X + \omega_Y)^2 \tau_{\text{C},k}^2} - \frac{\tau_{\text{C},k}}{1 + (w_X - \omega_Y)^2 \tau_{\text{C},k}^2} \right) \tag{3}$$

where N is the number of solvent molecules interacting with the solute in this way; r_k is the solvent spin-solute spin distance for the kth interaction; $\tau_{\text{M},k}$ is the mean residence time for that interaction, and the correlation time, $\tau_{\text{C},k}$, is given by

$$\frac{1}{\tau_{\text{C},k}} = \frac{1}{\tau_{\text{R}}} + \frac{1}{\tau_{\text{M},k}}$$

A mean residence time for a solvent molecule in association with the solute would be have to be at least one rotational correlation time of the complex for the relaxation interaction to be effective. The rotational correlation time (τ_{R}) of **I** is estimated to be ∼42 ps in the lower layer; τ_{R} for a complex would not be shorter. A sufficiently long-lived interaction with the solvent molecule at a distance of 3.6 Å (van der Waals contact of a chloroform molecule with a solute proton), with a mean residence time $\tau_{\text{M},k} \geq \tau_{\text{R}}$ would produce a cross relaxation effect an order of magnitude too large. A cross relaxation effect of the correct magnitude would be produced if the solute spin-solvent molecule interaction distance r_k were increased to about 5 Å, but such an increase to well beyond the van der Waals interaction distance seems inconsistent with the notion that solute−solvent interactions are strong enough to produce a long-lived complex of solute and solvent.

Alternatively, it could be the case that interactions of solvent molecules with the camphor derivative **I** lead to alterations in diffusive behaviors such that bulk diffusion constants are not reliable descriptors of the encounters of these species. In an important paper, Halle presented several extensions of the usual treatment of intermolecular long-range dipole−dipole interactions, including a model in which the relative translational diffusion coefficient for solute and solvent molecules is allowed to take a value in the solvation layer around the solute that differs from that of the bulk medium.[37] The cross relaxation rate estimated by this treatment depends on the thickness of the solvation layer as well as the diffusion coefficients in the layer and in the bulk solution. An examination of the predictions of this model (Supporting Information) suggests that a layer of solvent molecules about 2 molecules thick in which the local mutual diffusion coefficient is reduced by a factor of 2 or 3 compared to its value in the bulk would be consistent with our observations. While is it clear that attractive interactions between solute and solvent can reduce the observed translational diffusion coefficient,[39] it is difficult to know what would be reasonable expectations for the thickness of the solvent layer or the extent of slowing of diffusion within this layer. However, infrared evidence indicates that chloroform in a fluorous solvent does not behave as it does in bulk chloroform,[40] and there appears to be no reason to dismiss such considerations as part or all of the source of the augmented cross relaxation rates for all solvent−solute and solvent−solvent interactions in the lower layer.

In contrast to what is observed for solvent−solute interactions in the lower layer of the chloroform−perfluoro(methylcyclohexane) system, there is good agreement between observed and calculated solute−solvent cross relaxation rates for the upper layer of this fluorous solvent system (Table 4). Solvent−solute and solvent−solvent interactions in this phase thus appear to be consistent with the model in which all dipolar interactions can be described simply in terms of the bulk properties of the solvent mixture.

At 54 °C, the chloroform−perfluoro(methylcyclohexane) system becomes homogeneous. As was the case for the lower layer, there may be enhancements of some cross relaxation rates in this phase, although the effects are not as large as was found with the lower layer. Beyond temperature, the major difference between the lower layer system and the single-phase system is the ratio of the concentration of perfluoro(methylcyclohexane) to that of chloroform. The special solute−solvent interactions that appear to be present in the lower layer and possibly to a

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lesser extent in the single phase, appear to be dependent on the amount of the nonpolar component (perfluoro(methylcyclohexane)) relative to the amount of chloroform.

The experimental cross relaxation rates suggest that there is regiospecificity in the interactions of chloroform with the protons of 3-heptafluorobutyrylcamphor (**I**). Methyl group 10 appears to be an especially favored site of interaction in all systems examined; equatorial protons at carbons 5 and 6 appear to be selectively avoided in the lower layer (Figure 2). Presumably steric accessibility to these sites is taken into account by our method for calculating the cross relaxation rates, so some electronic factor(s) must be present that favors the orientation or duration of the encounters with chloroform molecules in these regions of **I**. Electric dipolar or hydrogen-bonding interactions of chloroform in the vicinity of the oxygen function at carbon 2 of **I** may account for the observed regioselectivity.

Given the hydrocarbon−perfluorocarbon aspects of camphor derivative **I**, it is possible that the molecule is aggregated in one or more of the phases studied in this work.[41−45] There is no direct information that refutes this possibility. However, if it is assumed that the viscosity of the chloroform-rich upper layer is the same as that of pure chloroform, it can be estimated that the translational diffusion coefficient for the solute should be about 0.95×10^{-9} m^2 s^{-1}, which compares well with the experimental value for the upper layer (0.98×10^{-9} m^2 s^{-1}). Extensive aggregation would be expected to reduce the observed translational diffusion coefficient compared to the predicted value. Solute aggregation would have the effect of protecting parts of the solute molecules from interactions with solvent species, thereby reducing solvent−solute cross relaxation rates. The effects on cross relaxation rates observed in this work, when present, are in the direction of enhancement.

Summary. Intermolecular NOE studies presented are consistent with the conclusion that the hydrocarbon part of 3-heptafluorobutyrylcamphor is selectively solvated by the chloroform component of the fluorous biphasic mixture of chloroform/perfluoro(methylcyclohexane) when the perfluorocarbon is the major component of the solvent mixture. Simultaneously, the perfluoroalkyl part of this solute is selectively solvated by the perfluorocarbon. Alternatively, or perhaps concurrently, solvent molecules around the solute may have hydrodynamic properties different from those characteristic of the bulk solution. Either explanation points to unusual interactions between the solvent components and the solute in this phase. There are no indications of such selective interactions with either part of the solute in the phase where chloroform is the major component.

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Supporting Information Available: Pulse sequences used for the homonuclear and heteronuclear NOE experiments, other experimental considerations, discussion of cross relaxation when a solvent component selectively associates with a solute or when the diffusion behavior near the solute is different from that of the bulk solvent, and proton and fluorine T_1 values for the systems studied. This material is available free of charge via the Internet at http://pubs.acs.org.

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