Supplementary Materials

Experimental Details

1. Materials. Tetramethylsilane, carbon tetrachloride, perfluoro-*t*-butanol and 1,3-di-*t*-butylbenzene were obtained from Sigma-Aldrich. The latter two materials were distilled at atmospheric pressure with a center cut being retained. The other materials were used as received. Densities and molar masses of the fluoroalcohols were taken from the Aldrich Chemical Co. catalog.

2. Preparation of NMR samples. Samples for NMR spectroscopy were approximately 0.10-0.15 M in 1,3-di-*t*-butylbenzene. The solute was weighed into 5 mm J. Young NMR tubes (Wilmad Glass Co.) and the appropriate volume of solvent added. Mixed solvent samples were prepared by addition of equal volumes of the solvents to the NMR tube. A sealed thin capillary tube containing acetone-d6 (lock signal) was placed in the tube and the samples then degassed by 3-5 freeze-thaw cycles before being sealed. Liquid volumes appeared to be additive. For samples containing TMS as a solvent, the sample tube consisted of 1.5 mm capillary attached to the end of a 5mm J. Young tube. In these cases, the sample was inserted into a 5 mm NMR tube containing a mixture of 50% dimethylsulfoxide-d6 (lock signal) and 50% CCl_4.

All NMR spectra were run at a proton frequency of 500 MHz using a Varian INOVA instrument. A Nalorac proton/fluorine probe with a z-axis gradient capability was used. Sample temperatures were regulated by the instrument controller and were calibrated using a standard sample of methanol (Wilmad). All data presented in this paper were collected for samples at 25^{o}. Temperatures are believed to have been stable to better than +/- 0.1^{o} and accurate to better than +/- 0.5^{o}.

Heteronuclear ($^{1}H\{^{19}F\}$) solvent fluorine-solute proton NOEs were determined using the pulse sequence shown below. The combination of field gradient pulses and proton RF pulses at the start of the sequence are used to saturate the proton resonances of the solute. During the mixing time the NOE develops; composite 180 ^{o} pulses in the middle of the mixing time serve to keep the proton magnetization near zero and avoid potential problems with CSA-dipole cross correlation effects.

A complete heteronuclear NOE experiment consists of two scans. When the initial fluorine pulse inverts the fluorine magnetization, the detected signal arises from proton T_1 relaxation as well as the $^{1}H\{^{19}F\}$ NOE. A second scan is collected without initial inversion of the fluorine magnetization; the detected proton fid in this experiment arises only from proton T_1 relaxation during the mixing period. Subtracting the two scan leaves the NOE. It should be noted that the Varian software normalizes the fid collected in a multiple scan experiment by the number of scans. Thus, the observed NOE is this difference experiment if one-half of the true value.

Homonuclear ($^{1}H\{^{1}H\}$) solvent proton-solute proton NOEs were determined using the pulse sequence shown below. A DPFGSE sequence appended to the sequence prior to collection of the fid was used for suppression of the intense solvent signal.[1]

For both heteronuclear and homonuclear experiments, data were collected for 10-15 mixing times that ranged from 0.025 to 1.5 s. It was found that good temperature control and a sharp deuterium lock signal were important to detecting the NOEs, particularly at the shorter mixing

times. Typically, 16 to 64 scans were collected in order to average the effects of instrumental phase instabilities.

Solvent and solute T_1 values were routinely determined to aid in proper set up of experiments. Fluorine T_1s ranged between 2.8 and 4.4 s. Solute proton spins in the heteronuclear NOE experiment remain close to saturation and the recycle rate of the experiment is dependent only on the fluorine T_1. In the homonuclear NOE experiment all spins are near saturation at the end of a scan and a delay of 5-10 x T_1 is needed between scans for the system to return to equilibrium.

Diffusion coefficients were determined by the method of Wu, Chen and Johnson, Jr.[2] using proton and fluorine signals of the sample and 8-12 values for the magnitude of the field gradient pulses that provide coherence defocusing and refocusing. A weak gradient was present during the mixing time to suppress possible effects of radiation damping. A DPFGSE sequence was appended at the end of the basic pulse sequence for suppression of the solvent signal in proton-observe experiments.[1] Field gradients were calibrated using a sample containing a Teflon plug of known dimensions[3] or by using the known diffusion coefficient of the HOD species in D_2O (1.90×10^{-5} cm^2s^{-1} at 25^o).[4] Solute diffusion coefficients were determined using proton NMR signals of the solute methyl group. The samples were equilibrated in the NMR probe for several hours before diffusion experiments were started in order to minimize the effects of thermal gradients. Experiments were then run repetitively until three successive determinations of the diffusion coefficient agreed within ~2%.

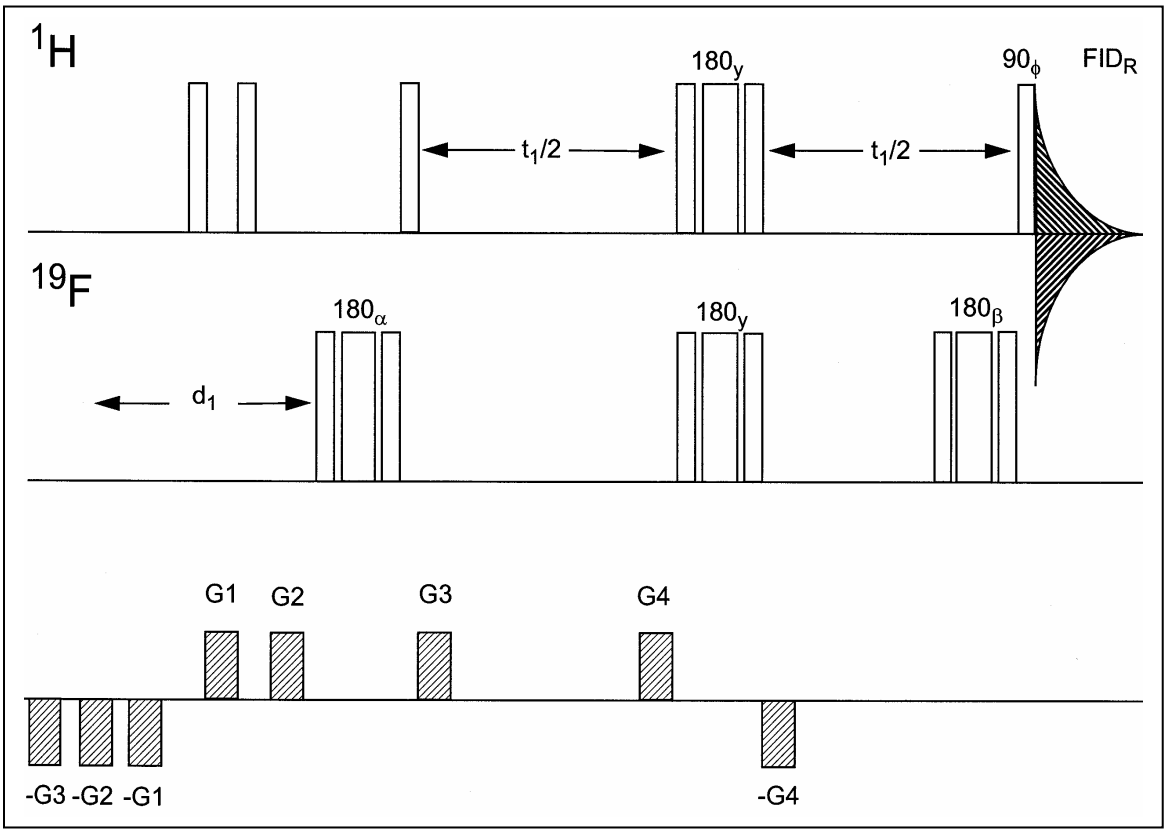
Due to the configuration of the field gradient coil in the probe used, it is expected that plots of signal intensity *vs.* (field gradient)^2 used in the course of diffusion coefficient determinations will be somewhat non-linear with a concave-downward aspect at high values of the square of the field gradient.[5,6] In cases where this behavior was noted we eliminated one or two data points at the end of such data sets one-by-one until a good linear fit ($R > 0.99$) of the remaining data was obtained.

Molecular modeling and dynamics calculations were done with SYBYL (Tripos Associates) and employed the Merck (MMFF94) force field. Molecular surfaces were defined using the notions of Lee and Richards[7] as implemented in Connolly's algorithm (Quantum Chemistry Program Exchange program 429).[8] The van der Waals radii used in the surface calculations for C, N, O were those given by Li and Nussinov.[9] The van der Waals radii used for H and F were 1.2 and 1.35 Å, respectively. [10]For simplicity, anisotropies in the atomic van der Waals radii, while certainly present in real molecules,[11,12] were ignored for these calculations. The dependence of calculated NOEs on coordinate rotation and on the number of dots used to represent a molecular surface was examined.[13,14] Variations of less than 1% in the calculated NOEs were observed when Cartesian coordinates were changed. Typically, molecular surfaces were represented by "Connolly dots" at a density of 200 dots per angstrom^2. Conclusions from calculations based on molecular surfaces were insensitive to the density of these dots as long as the number exceeded 100 dots per angstrom,^{2}.

Heteronuclear $^1H\{^{19}F\}$ NOEs

The pulse sequence used in this work is shown in the first figure below. A set of proton pulses followed by gradient pulses is used to saturate the proton spins. A composite fluorine pulse (90x-180α-90x) is then applied followed by another gradient pulse. The phases of the composite pulse

can be chosen so that the fluorine spins are inverted (phase α 90 degrees different from x) or so that the fluorine magnetization is unchanged (phase α = x). The first set of phases leads to generation of an NOE during the mixing time while the second set of phases would produce the initial conditions for a control experiment. The final composite fluorine pulse is used to control the fluorine magnetization prior to acquisition since the "dipolar field" associated with this is large enough to perturb the proton resonances frequencies.[15,16] When the fluorine T_1 is longer than about 2 sec., it is advantageous to phase this composite pulse so that the residual fluorine Z-magnetization just prior to mixing is returned to the +Z direction if it is not already there.



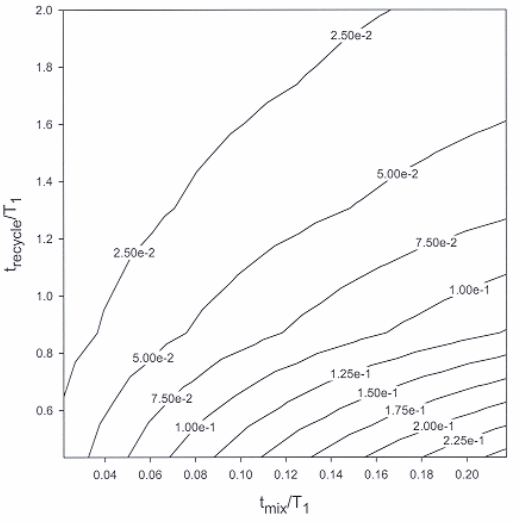
Unless otherwise indicated, the phases of all pulses are x. The phase α is cycled to invert alternately the fluorine Z-magnetization or restore it to the +Z orientation. [x,y,x,y,x,y,x,y]. The phase β is cycled to return the fluorine Z-magnetization to the +Z direction if it is oriented differently at the end of the mixing period: [y,x,y,x,y,x,y,x]. (As discussed below, this can lead to an acceleration of the experiment if the fluorine T_1 is relatively slow when compared to the mixing time. The recycle time is the acquistion time + d_1. The recycle time is adjusted as part of the optimization process.) The last 90° pulse is CYCLOPS cycled: [x,x,y,y,-x,-x,-y,-y]. The phase of the receiver (φ_R) is [-x,x,-y,y,x,-x,y,-y]. If there is a strong proton signal that must be suppressed, a WATERGATE or DPFGSE element can be added after the final 90° pulse.

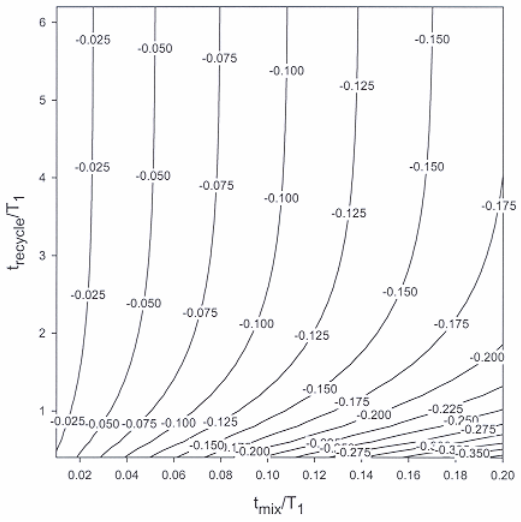
Pulsed field gradients are applied as bipolar pairs to minimize the disturbance of the lock signal by field hysterisis effects. Since the pulsed field gradients are not used for any coherence selection, the values of the gradients used in each pair is largely arbitrary and are adjusted to give the best performance in terms of the difference spectrum which represents the NOE. However, all gradient values (and those of the DPFGSE signal suppression sequence if this is used) should be defined in such a way that gradient recalled echoes are not present.

Accelerating the $^{1}H\{^{19}F\}$ NOE Experiment

The final fluorine pulse of the sequence could be chosen to be a 90 degree pulse and the fluorine dipolar field would be adequately controlled. However, when the composite 180 degree pulse is used as indicated above, the experiment can be somewhat accelerated. Calculations show that after a few times through the sequence (typically 2x [control and NOE]), the system comes to a steady state. The trick is to choose the total recycle time for the experiment such that two criteria are satisfied, namely (1) that the fluorine Z-magnetization at the start of the mixing time be as close (except for sign) to its equilibrium value as possible (say +/- 0.99F0) and (2) that the value of the fluorine Z-magnetization at the start of the fid accumulation be the same value. Since the proton spins are always near saturation during the experiment, their relaxation does not enter into consideration of how rapidly the experiment can be recycled.

The plots below help in determining the conditions for use of the pulse sequence shown in a repetitive scan/signal averaging mode. Both plots assume that two "dummy" runs through the sequence have taken place (Varian parameter SS=2) before data collection begins. The first plot shows the deviation of the fluorine magnetization from its maximal value at the start of the mixing time. One would typically choose a recycle time for the experiment such that the deviation is less than ~0.02 for all values of the mixing time used. With this consideration set, the second plot can be used to estimate how different are the fluorine magnetizations in the NOE and control experiments at the start of acquisition. These two magnetizations should be similar enough that dipolar field effects arising from the fluorine are absent.





If the final fluorine pulse of the sequence is 90 degrees, then one must wait a full 5-6 x the fluorine T_1 for all scans taken. This will typically generate an experiment that runs 2-4 times longer than an optimized, accelerated version.

The plots above are not completely general and were generated using fluorine T_1's (3-5s) that were typical of the work described in the main paper. The FORTRAN program shown below can be used to explore other situations.

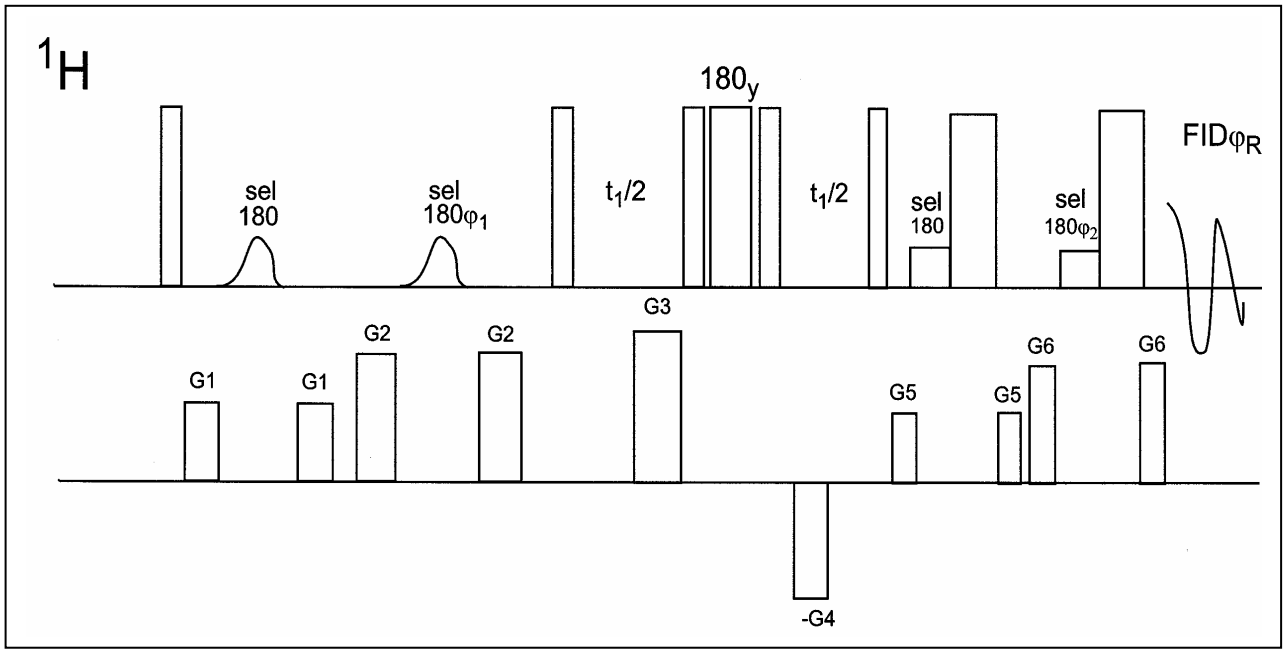
```
C
C  Simulation of HF NOE experiment with restoring 180 pulses
C
C
      WRITE(6,10)
10    FORMAT(1X,' tghnoeG1-180 simulation'/
     & ' Enter the fluorine T1 value-> ',$)
      READ(5,*) FT1
      R1=1./FT1
      WRITE(6,12)
12    FORMAT(' Enter beginning tmix, end tmix, step-> ', $)
      READ(5,*) tmixs, tmixe, tmixst
      WRITE(6,14)
14    FORMAT(' Enter beginning tacq, end tacq, step-> ',$)
      READ(5,*) tacqs,tacqe,tacqst
      WRITE(6,16)
16    FORMAT(' Enter number of ss steps-> ',$)
      READ(5,*) NSS
      WRITE(7,190) FT1,NSS
190   FORMAT(' tghetnoeG1-180 simulation'/5x, 'Fluorine T1=',F10.5
     & /5X, 'NSS=',I5)
      WRITE(7,95)
95    FORMAT(7x,'tmix',7x,'tacq',6x,'Csacq',6x,'Fsacq',4x,'FstartC',
     &8x,'Dev',4x,'FstartN',8x,'Dev',4x,'Exptime')
      WRITE(6,95)
50    CONTINUE
      tmix=tmixs-tmixst
70    CONTINUE
      tmix=tmix+tmixst
      IF(TMIX.gt.TMIXE) GO TO 200
      WRITE(7,89)
89    FORMAT(' ')
      WRITE(6,89)
      tacq=tacqs-tacqst
90    CONTINUE
      tacq=tacq+tacqst
      IF(TACQ.GT.TACQE) GO TO 70
      CALL HF180(R1,TMIX,TACQ,CFACQ,FFACQ,FSTARTC,FSTARTN,NSS)
      DEVC=1.-FSTARTC
      DEVN=1.+FSTARTN
      ETIME=2.*(TMIX+TACQ)
      WRITE(7,100) TMIX,TACQ,CFACQ,FFACQ,FSTARTC,DEVC,FSTARTN,DEVN,ETIME
100   FORMAT(9(1x,F10.6))
      WRITE(6,100) TMIX,TACQ,CFACQ,FFACQ,FSTARTC,DEVC,FSTARTN,DEVN,ETIME
      GO TO 90
200   CONTINUE
      WRITE(7,95)
      WRITE(6,95)
      STOP
      END
C
      SUBROUTINE HF180(R1,TMIX,TACQ,CFACQ,FFACQ,FSTARTC,FSTARTN,NSS)

C
C  R1=1/T1
C  TMIX = mixing time
C  TACQ = acquitisition time + d1
C  CFACQ = F z-component at the start of acquisition (Control)
```

```
C  FFACQ = F z-component at the start of acquisition (NOE)
C  FSTARTC = F z-component at the start of mixing period (Control)
C  FSTARTN = F z-component at the start of the mixing period (NOE)
      KC=0
C start control loop
      CSTARTC=1.
100   CONTINUE
      FSTARTC=CSTARTC
      CMIX=T1(R1,CSTARTC,TMIX/2.)
C 180 pulse mid-tmix
      CMIX=-CMIX
C recovery
      CEND=T1(R1,CMIX,(TMIX/2.))
C 180 pulse restores at end of tmix
      CEND=-CEND
      CFACQ=CEND
      CEND=T1(R1,CEND,TACQ)
C  start NOE loop
      CSTARTN=-CEND
      FSTARTN=CSTARTN
      CMIXN=T1(R1,CSTARTN,TMIX/2.)
C  180 pulse mid-tmix
      CMIXN=-CMIXN
C  recovery
      CENDN=T1(R1,CMIXN,TMIX/2.)
      FFACQ=CENDN
      CENDN=T1(R1,CENDN,TACQ)
      KC=KC+1
      IF(KC.GT.NSS) RETURN
      CSTARTC=CENDN
      GO TO 100
      END
      FUNCTION T1(R1,HINIT,T)
      FAC=EXP(-R1*T)
      T1=(1.-FAC)+HINIT*FAC
c      write(6,6) hinit, t, fac, t1,r1
c6     format(6(1X,f10.6))
      RETURN
      END
```

Homonuclear $^1H\{^1H\}$ NOEs

The pulse sequence used in this work is shown in the figure below. It is basically a combination of ideas due to Scott, *et al*.[17] Dalvit,[18] and Diaz and Berger.[19]



The phases of all pulses are x, except for those indicated. Following Dalvit, φ_1 = 4[x, -y, -x, y], φ_2 = [4[-x],4[y],4x,4[-y]] while the receiver phase (φ_R) is 2[x,-x,x,-x,x,-x,x,-x]. The last DPFGSE part of the sequence is for suppression of the inverted signal prior to detection of the remaining signals. In the case of the experiments with TMS as solvent or cosolvent, this suppression has to be done. If suppression of the inverted signal is not desired or needed, the last DPFGSE part of sequence can be omitted. In that event, the phase of the receiver becomes 4[x,-x,x,-x].

The first DPFGSE in the sequence achieves inversion of the selected signal on alternate scans and restores the selected magnetization to its position along the +Z axis on the other scans. In our experience, and as reported by Liepinsh and Otting,[20] neither of these events is perfect so that it is important to determine what are the +Z or -Z components of the selected spin prior to the start of the mixing period. In our hands, this part of the sequence has 80-82% efficiency. That is, the minus component is about $-0.8*Z_o$. The +Z component produced is usually very slightly larger (81-83% efficient). A correction must be applied to the NOE data which takes these Z-components into account. Presumably the failure to produce full values for +Z or -Z is related to relaxation during the DPFGSE selection and radiation damping effects.

We used G3 pulses (32.5 ms duration, 100 Hz bandwidth, generated by the Pbox software) for the selective 180 degree pulses present during the initial DPFGSE selection part of the sequence.

There is no need (and no ability) to control the dipolar field associated with the intense solvent resonance in these experiment since the last 90 degree pulse of the sequence always leaves this resonance with essentially a zero Z-component at the start of the detection part of the experiment.

Other Considerations

A strong, sharp, well-shimmed, unsaturated deuterium lock signal is critical to the success of both the homonuclear and heteronuclear NOE experiments. In our hands, there also appeared to be a sufficiently large effect of the fluorine dipolar field on the position of the lock signal in the heteronuclear experiments that accumulating reliable difference spectra was not possible. This effect was eliminated by physically separating the deuterated material used for the lock signal from the remainder of the sample. For these reasons, capillaries of acetone-d6 were used for the heteronuclear NOE experiments.

References

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