When Is a Trifluoromethyl Group More Lipophilic than a Methyl Group? Partition Coefficients and Selected Chemical Shifts of Aliphatic Alcohols and Trifluoroalcohols

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Abstract □ Octanol–water partition coefficients were determined for 12 trifluoromethylated aliphatic alcohols and their unfluorinated counterparts. The latter values were derived from measurements using the benzyl alcohol–water solvent system after developing an appropriate correlation equation. Incidentally, an empirical equation was found which allows the partition coefficient of an unsubstituted alcohol to be estimated given the molecular formula and boiling point. Trifluorination strongly enhances lipophilicity *only* when the trifluoromethyl group is in the α-position. The enhancement is barely measurable for the β- and γ-(trifluoromethyl) alcohols, while the δ- and ϵ-(trifluoromethyl) compounds are considerably more hydrophilic than their parent compounds. Chemical shift comparisons suggest that the changes in relative lipophilicity are controlled primarily by the inductive effect of the trifluoromethyl group on the acidity–basicity of the hydroxyl group. New synthetic procedures for obtaining some of the alcohols are presented.

When a biochemically or pharmacologically active "parent" compound is modified by substituting a trifluoromethyl group for a methyl group, the resulting "analogue" is often found to have similar, though not identical, activity.[1,2] The physicochemical behavior of the analogue, e.g. its binding to proteins or membranes, may conveniently be studied by ^{19}F NMR spectrometry. Information thus obtained may help to elucidate the behavior of the parent compound, but only if the factors governing differences between the interactions of the parent and the analogue with solvents or ligands are well understood. One effect often associated with the introduction of a trifluoromethyl group is a decrease of hydrophilicity; for example, values of the hydrophobic substituent parameter, π, derived from observations with substituted phenylacetic acids, include 0.54 for the 3-methyl and 1.21 for the 3-trifluoromethyl groups.[3] This is somewhat paradoxical in light of the fact that trifluoromethylation of a hydrocarbon moiety introduces a sizable electric dipole moment which should interact favorably with the medium having a high dielectric constant. The crucial question, what circumstances determine the relative lipophilicities of the parent and analogue, cannot be fully answered on the basis of existing data.

Systematic studies of the effects of trifluoromethyl groups on lipophilicity for families of structurally related, aliphatic compounds have not previously been made, probably because the required materials have not been easily available. Such a study, which takes advantage of the fact that electrochemical trifluoromethylation[4,5] makes it fairly simple to obtain an appropriate collection of trifluorinated alcohols with up to six carbon atoms, is reported here. Using ^{19}F NMR spectrometry, the octanol–water partition coefficient, P_{oct}, of each alcohol could readily be determined. The quantity $\log P_{oct}$ is directly proportional to the standard free energy of transfer of the material from water-saturated octanol to octanol-saturated water and is an accepted measure of lipophilicity.[2,3]

For comparison, values of P_{oct} for the parent alcohols were also needed. The work of Leo et al.[3] provided some, but not all, of these. The missing values could not be measured directly with ^1H NMR because the signals of the solutes are obscured by those of octanol. Use of the benzyl alcohol–water solvent system is much more attractive, since this alcohol shows no absorption in the region of $\delta < 3.5$ ppm. Accordingly, the benzyl alcohol–water partition coefficients, P_{bzal}, were determined for 15 aliphatic alcohols, including the 12 whose analogues were available. The known values of P_{oct} for 10 of these compounds were used to find a correlation equation which allowed the needed values of P_{oct} to be calculated.

Selected ^1H NMR and ^{19}F NMR chemical shifts were determined in a variety of media to provide additional clues concerning the interactions of these materials with solvents.

Results and Discussion

The measured values of $\log P_{bzal}$ (benzyl alcohol–water partition coefficient) for the unfluorinated alcohols are given in Table I together with values of $\log P_{oct}$ (octanol–water partition coefficient) from Leo et al.[3] Only values which represent direct measurements, rather than results derived from correlation equations, were selected. The empirical equation:

$$\log P^c_{oct} = 1.210 \log P_{bzal} - 0.14 \qquad (1)$$

gave the values listed in the fourth column of Table I. The agreement between $\log P_{oct}$ and $\log P^c_{oct}$ is within 0.07 units for most of the alcohols but is slightly worse for 3-methyl-1-butanol, *tert*-amyl alcohol, and neopentyl alcohol. For isobutyl alcohol, two "direct" values are cited in Leo et al.[3] Neither was used in deriving eq. 1, but the value calculated with eq. 1 is near the average of these two "direct" values.

Two considerations suggest that where there is disagreement, values of $\log P^c_{oct}$ are preferred over those of $\log P_{oct}$, especially when systematic comparisons are to be made. Most importantly, $\log P^c_{oct}$ values represent a complete set and they were all obtained by the same method in the same laboratory. In addition, they reveal a consistent tendency for the partition coefficients within a family of isomers to increase rather uniformly as the boiling points increase. This tendency is much more evident when $\log P^c_{oct}$ values, rather than the available values of $\log P_{oct}$, are examined. Indeed, it appears that in the absence of any other data, $\log P_{oct}$ for a new, monohydric, aliphatic alcohol could be estimated with reasonable reliability from the relation:

$$\log P_{oct} = 0.58\, n_C - 1.44 - 0.0158\, \Delta T \qquad (2)$$

where n_C is the number of carbon atoms and ΔT is the difference in boiling points between the *n*-alkanol (with the same n_C) and the alcohol in question. As shown in Table I, eq. 2 reproduces $\log P^c_{oct}$ with an error of ≤ 0.06 for all but two of the alcohols; even for *tert*-amyl and neopentyl alcohol the

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Table I—Benzyl Alcohol–Water and Octanol–Water Partition Coefficients for Aliphatic Alcohols

ROH	log P_{bzal} [a]	log P_{oct} [b]	log P^c_{oct} [c]	(log P_{oct})$_{calc}$ [d]
Ethanol	−0.11	−0.32	−0.27	−0.28
1-Propanol	0.39	0.34	0.33	0.30
2-Propanol	0.19	—	0.09	0.06
1-Butanol	0.84	0.88	0.88	0.88
2-Butanol	0.66	0.61	0.66	0.60
2-Methyl-1-propanol	0.76	0.65, 0.83	0.78	0.74
2-Methyl-2-propanol	0.39	0.37	0.33	0.33
1-Pentanol	1.33	1.40	1.47	1.46
2-Methyl-1-butanol	1.24	—	1.36	1.31
3-Methyl-1-butanol	1.20	1.16	1.31	1.32
2-Methyl-2-butanol	0.76	0.89	0.78	0.90
2,2-Dimethyl-1-propanol	1.12	1.36	1.22	1.08
1-Hexanol	1.77	2.03	2.00	2.04
3-Hexanol	1.51	—	1.69	1.68
3-Methyl-1-pentanol	1.68	—	1.89	1.95

[a] Benzyl alcohol–water partition coefficient. [b] Octanol–water partition coefficient taken from Ref. 3. [c] Octanol–water partition coefficient calculated using eq. 1 from log P_{bzal}. [d] Octanol–water partition coefficient calculated according to eq. 2.

errors (0.12 and 0.14) are no larger than discrepancies often found when values measured in different laboratories are compared.[3] This kind of behavior apparently has not been noted before, but it might have been anticipated for compounds containing only a single reactive group. Here, the contributions to P_{oct} from hydrogen-bonding or hydrophobic effects should vary little from one isomer to another. Thus, P_{oct} will be determined by variables that also control the enthalpy of vaporization and, hence, the boiling point. When there is more than one reactive group, isomerization is apt to change their mutual interaction, and a simple correlation such as eq. 2 is no longer expected. No correlation was found for the trifluorinated alcohols.

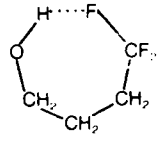
Table II contains the values of log P_{oct} for the fluorinated alcohols. The only comparable data from Leo et al.[3] are for trifluoroethanol, for which the values 0.32 and 0.41 are listed. It is satisfying that the value determined in this study lies nearly midway between these. Table II also includes the boiling points, the quantity $\Delta \log P = (\log P_{oct})_{analogue} - (\log P^c_{oct})_{parent}$, and a Greek letter designating the relative positions of the trifluoromethyl and hydroxyl groups. It is immediately apparent that $\Delta \log P$ is markedly dependent on the number of bonds between the trifluoromethyl and hydroxyl groups, and nearly independent of whether the alcohol is primary, secondary, or tertiary, and of whether the chain is straight or branched. Only the three α-(trifluoromethyl) alcohols are markedly more lipophilic than their parent compounds, with nearly equal values of $\Delta \log P$. The six β- and γ-(trifluoromethyl) alcohols all have nearly the same value of $\Delta \log P$ (slightly positive but only slightly larger than the experimental uncertainty). The two δ-(trifluoromethyl) alcohols have similar and definitely negative values of $\Delta \log P$, while the single ϵ-derivative has a slightly more negative value. The fact that 6,6,6-trifluoro-1-hexanol is about twice as hydrophilic as its parent is in harmony with the observation that replacing the terminal methyl group of a long-chain soap or surfactant by a trifluoromethyl group *increases* the critical concentration for micelle formation by nearly a factor of two.[6,7]

Table II—Boiling Points, Octanol–Water Partition Coefficients, and Related Quantities for Trifluorinated Alcohols

ROH	bp, °C	log P_{oct} [a]	$\Delta \log P$ [b]	CF_3 Site
1. CF_3CH_2OH	74	0.36	0.63	α
2. $CF_3CH_2CH_2OH$	99–100	0.39	0.06	β
3. $CF_3CH(OH)CH_3$	75–76	0.70	0.61	α
4. $CF_3(CH_2)_3OH$	125	0.90	0.02	γ
5. $CF_3CH_2CH(OH)CH_3$	99.8–99.9	0.71	0.05	β
6. $CF_3(CH_3)_2COH$	81	1.04	0.71	α
7. $CF_3(CH_2)_4OH$	147.5–148.0	1.15	−0.32	δ
8. $CF_3CH_2CH(CH_3)CH_2OH$	132–133	1.39	0.03	γ
9. $CF_3CH(CH_3)CH_2CH_2OH$	139–140	1.37	0.06	γ
10. $CF_3(CH_2)_5OH$	165.5–166.0	1.64	−0.36	ϵ
11. $CF_3CH_2CH_2CH(OH)CH_2CH_3$	140.4–140.9	1.70	0.01	γ
12. $CF_3CH_2CH(CH_3)CH_2CH_2OH$	158.7	1.61	−0.28	δ

[a] Octanol–water partition coefficient. [b] $\Delta \log P = (\log P_{oct})_{analogue} - (\log P^c_{oct})_{parent}$.

This pattern of behavior suggests that the intrinsic effect of an isolated trifluoromethyl group is to increase the hydrophilicity of a saturated hydrocarbon chain by a factor of 2 to 2.5. When the trifluoromethyl group is near a solubilizing group such as hydroxyl, this effect may be reversed, probably through the joint action of two factors. First, the inductive effect of the trifluoromethyl group is expected to increase the acidity (or lower the basicity) of the hydroxyl group, so that ROH − − − B hydrogen bonds with a base, B, are strengthened while RO − − − HA bonds with an acid, HA, are weakened. The net result should be to make the alcohol less hydrophilic, and the effect should be progressively attenuated as the number of intervening bonds increases. Second, it is possible that the presence of the hydroxyl group, or other changes in molecular structure, can modify the details of the solvation of the trifluoromethyl groups in a way that would cause $\Delta \log P$ to vary. For example, it might be suggested that γ-(trifluoromethyl) alcohols can be stabilized in a lipoid environment because of their ability to adopt internally hydrogen-bonded conformations such as:



To try to ascertain which of these effects is dominant, two sets of NMR experiments were performed.

First, the ^{19}F chemical shift of each fluoroalcohol was determined for dilute solutions in heptane, dry octanol, octanol-free water (each at 1% by volume), and Me_2SO-d_6 containing 1% Me_4Si (2.5% alcohol by volume). The shifts in heptane, given in the first columns of Table III, show that for the linear alcohols, $CF_3(CH_2)_nOH$ with n >2, the peak position is nearly independent of chain length and near the value of 10.58 found for the "inert" solute, 1,1,1,10,10,10-

hexafluorodecane. A β-methyl side chain or a β-hydroxyl group shifts the signal to a lower applied field, while an α-methyl or α-hydroxyl group produces a large upfield shift.

The remaining columns of Table III show shift *differences*, $\Delta\delta$ = δ(solvent) − δ(heptane), found when another liquid replaces heptane. Although the solvent effects are large, it is striking that there are only minor changes from one alcohol to another. The only definite trend is that $\Delta\delta$ tends to be larger for the α-(trifluoromethyl) alcohols than for the others. This suggests that the large upfield shift caused by the hydroxyl group (see above) may be diminished by a few percent when ROH − − − B hydrogen bonds form. Apart from this, changes in the molecular structure leave the solvent dependence of the fluorine shift virtually invariant, implying that there are no large changes in the character of the solvation of the trifluoromethyl groups.

The second set of NMR measurements consisted of ^1H chemical shift determinations for the hydroxyl proton of each trifluoroalcohol and its parent compound in Me_2SO-d_6. In this solvent, proton exchange between alcohol and any water that may be present is so slow that separate signals are observed. The peak at the lowest field represents the complex, ROH − − − $OSMe_2$. Strengthening the hydrogen bond in the complex by enhancing the acidity of the hydroxyl group should shift the peak even farther downfield. Indeed, as shown in Table IV, it is at δ 6.01 ppm for trifluoroethanol and δ 4.30 ppm for ethanol. Data for the remaining alcohols are also given, together with the difference, D, between analogue and parent [$\delta(OH)_{analogue} - \delta(OH)_{parent}$]. These results dramatically reveal changes in the acidity of the hydroxyl protons that arise from the inductive effect of the trifluoromethyl groups and that run roughly parallel with the changes in acid strength of the related ω,ω,ω-trifluorocarboxylic acids.[8] The difference, D, lies near 1.65 for the three α-(trifluoromethyl) alcohols and falls progressively to a value that approaches zero for the ε-derivative.

Table III—Fluorine Chemical Shifts for Trifluorinated Alcohols and their Solvent Dependence

ROH	δ(Heptane)[a]	Shift Differences[b]		
		Me_2SO-d_6	H_2O	Octanol
CF_3CH_2OH	−0.48	3.49	2.25	1.21
$CF_3CH_2CH_2OH$	12.28	3.07	1.88	0.62
$CF_3CH(OH)CH_3$	−4.72	3.43	2.29	1.30
$CF_3(CH_2)_3OH$	10.64	2.87	1.86	0.68
$CF_3CH_2CH(OH)CH_3$	13.24	3.22	1.91	0.91
$CF_3(CH_3)_2COH$	−7.38	3.10	2.14	1.19
$CF_3(CH_2)_4OH$	10.54	2.87	1.90	0.67
$CF_3CH_2CH(CH_3)CH_2OH$	13.47	2.89	1.84	0.85
$CF_3CH(CH_3)CH_2CH_2OH$	3.61	2.66	1.87	0.59
$CF_3(CH_2)_5OH$	10.55	2.96	1.99	0.64
$CF_3CH_2CH_2CH(OH)CH_2CH_3$	10.61	2.87	1.82	0.71
$CF_3CH_2CH(CH_3)CH_2CH_2OH$	13.77	2.84	1.78	0.77

[a] Shifts in ppm downfield from external trifluoroacetic acid, corrected for bulk susceptibility. [b] $\Delta\delta$ = δ(solvent) - δ(heptane).

Table IV—Hydroxyl Proton Chemical Shifts for Trifluorinated and Parent Alcohols[a]

ROH	$\delta(OH)_{analogue}$	$\delta(OH)_{parent}$	D[b]
CF_3CH_2OH	6.01	4.30	1.71
$CF_3CH_2CH_2OH$	4.81	4.31	0.50
$CF_3CH(OH)CH_3$	6.00	4.30	1.70
$CF_3(CH_2)_3OH$	4.60	4.28	0.32
$CF_3CH_2CH(OH)CH_3$	4.83	4.26	0.57
$CF_3(CH_3)_2COH$	5.76	4.14	1.62
$CF_3(CH_2)_4OH$	4.42	4.27	0.15
$CF_3CH_2CH(CH_3)CH_2OH$	4.70	4.31	0.39
$CF_3CH(CH_3)CH_2CH_2OH$	4.57	4.25	0.32
$CF_3(CH_2)_5OH$	4.34	4.28	0.06
$CF_3CH_2CH_2CH(OH)CH_2CH_3$	4.56	4.16	0.40
$CF_3CH_2CH(CH_3)CH_2CH_2OH$	4.39	4.23	0.16

[a] In Me_2SO-d_6:Me_4Si. [b] D = $\delta(OH)_{analogue} - \delta(OH)_{parent}$.

It may be argued that, in addition to changes in hydrogen-bond strength, D could include a contribution reflecting a "direct" effect of the trifluoromethyl group on the hydroxyl proton shift, i.e., one which would occur even in an isolated molecule. The magnitude of such an effect may be estimated by examining the spectra of molecules which contain methyl protons that are just as far from the trifluoromethyl group as the hydroxyl protons, since methyl protons are not involved in hydrogen bonding. One example is 1,1,1-trifluoro-2-propanol, where the methyl shift differs from that in 2-propanol by only 0.16, while for the hydroxyl protons, D = 1.70. Again, for 2-butanol and 4,4,4-trifluoro-2-butanol, trifluorination shifts the $-CH(OH)CH_3$ methyl signal by just 0.13, while D = 0.57. One may conclude that the direct effect and hydrogen-bond strengthening make contributions to D which agree in sign, with the direct effect accounting for only a small fraction of the total.

As shown in Fig. 1, the quantities D and Δ log *P* are well enough correlated to suggest that whenever Δ log *P* is more positive than ~−0.4, this mainly reflects the change in the acidity–basicity of the hydroxyl group due to trifluorination. A single clue points to the possibility that other effects may not be entirely negligible: instead of a smooth decrease of Δ log *P* with increasing distance between the trifluoromethyl and hydroxyl groups, Table II shows nearly equal values for the β- and γ-(trifluoromethyl) alcohols. That the Δ log *P* value is "too high" for the γ-derivatives is also suggested by the fact that the corresponding data points lie farther than any others above the dashed line in Fig. 1. There is, then, a suggestion that the lipophilicities of the γ-(trifluoromethyl) alcohols, and perhaps to an even lesser extent the β-derivatives, may be a little enhanced through the participation of cyclic, intramolecularly hydrogen-bonded conformations, as shown. However, the fluorine chemical shifts in heptane, which might have been expected to give some indication of the occurrence of such structures, do not show a discernible trend which could support this suggestion.

It has been pointed out before that trifluoromethyl groups which can interact with atoms having lone-pair electrons "raise the partition coefficients by an increment greater than simple additivity,"[3] but little quantitative information was provided. It seems likely that the large positive values

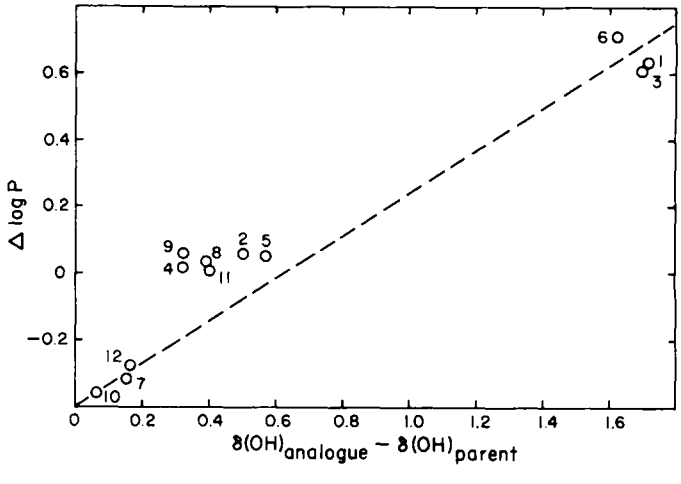


Figure 1—*Plot of Δ log P against the shift difference, D, between parent and analogue [$\delta(OH)_{analogue} - \delta(OH)_{parent}$] for the alcohols listed in Tables II and IV. The dashed line is provided primarily as a visual aid.*

assigned to the hydrophobic substituent parameters for the trifluoromethyl groups in various trifluoromethyl-aromatic compounds[1,3] arise in a manner similar to that proposed here. That is, the π electrons may be presumed to participate in a favorable interaction with water which is largely quenched upon trifluorination of the methyl side chain, and the resulting change again overwhelms the intrinsic tendency of the trifluoromethyl group to enhance hydrophilicity.

Conclusions

Aliphatic α-(trifluoromethyl) alcohols are more lipophilic than their parents by a factor of 4 or 5. However, β- and γ-(trifluoromethyl) alcohols are only marginally more lipophilic than their parents, and δ- or ϵ-(trifluoromethyl) alcohols are less lipophilic by a factor of ~2. Other structural features, i.e., chain branching or changing from a primary to a secondary or tertiary alcohol, have little effect on the relative lipophilicities. These findings imply that a trifluoromethyl group is *less* lipophilic than a methyl group, unless it is able to interact with an atom or group having lone-pair electrons (or π electrons). When such a group is near, the inductive effect of the trifluoromethyl substituent may so sharply reduce the basicity of the lone-pair or π electrons that a drastic increase in lipophilicity ensues. The influence of the inductive effect diminishes with increasing distance, but it does not become negligible until there are at least five carbon atoms between the trifluoromethyl and hydroxyl groups.

Experimental Section

Materials—The unfluorinated alcohols were the best available commercial samples, used without further purification, as were trifluoroethanol, 1,1,1-trifluoro-2-propanol, and 1,1,1-trifluoro-2-methyl-2-propanol. The other fluorinated alcohols were prepared in this laboratory as described below. All boiling points are uncorrected. Analytical results obtained for compounds were within ± 0.4 % of the theoretical values. Nuclear magnetic resonance spectra were recorded at the ambient probe temperature (~34 °C) with a Perkin-Elmer R-32 spectrometer operated at 84.669 MHz (^{19}F) or 90 MHz (^{1}H). Fluorine chemical shifts are reported for one volume percent solutions in heptane with trifluoroacetic acid as external reference. They are corrected for the bulk susceptibility difference, and positive values indicate shifts to a lower field. They are so intricately solvent-dependent that converting them to the Φ^* scale (i.e., one based on the use of fluorotrichloromethane as both solvent and internal reference) by adding a single number is a questionable procedure. If an *approximate* conversion is desired, it can be made by adding −76.5 to the shifts in heptane.

3,3,3-Trifluoro-1-propanol—This compound has been prepared by several methods.[9-11] The sample used here boiled at 99–100 °C [lit.[9] bp 100 °C] and was obtained by reduction with lithium tetrahydroaluminate of 3,3,3-trifluoropropanoic acid (synthesized by electrolyzing partially neutralized trifluoroacetic acid in acetonitrile in the presence of malonic acid[12,13]).

4,4,4-Trifluoro-1-butanol—This previously described material[14] was obtained in excellent yields by the lithium tetrahydroaluminate reduction of 4,4,4-trifluorobutanal;[5] the product boiled at 125 °C [lit.[14] bp 125 °C (755 mm)].

4,4,4-Trifluoro-2-butanol—This compound was prepared by reducing 4,4,4-trifluoro-2-butanone[4] with lithium tetrahydroaluminate to afford the alcohol in yields of 50–60%, bp 99.8 – 99.9 °C; ^{19}F NMR: δ 13.24 (t, J = 10.8 Hz); ^{1}H NMR (2.5%, Me_2SO-d_6:Me_4Si): δ 4.83 (d, J = 6 Hz, 1), 3.91 (septet, J = 6 Hz, 1) 2.29 (quartet of doublets, J_{HF} = 11.5 Hz, J_{HH} = 6 Hz, 2), and 1.14 ppm (d, J = 6 Hz, 3). Anal. ($C_4H_7F_3O$) C,H.

5,5,5-Trifluoro-1-pentanol—4,4,4-Trifluoro-1-butanol was converted to 4,4,4-trifluoro-1-bromobutane by treatment with aqueous hydrobromic and sulfuric acids. The Grignard reagent prepared from this bromide was treated with formaldehyde to give the desired product (bp 147.5–148.0 °C) [lit.[15] bp 146 °C], essentially as described for the corresponding 1-chloro-derivative by Overberger and Khattab.[15]

4,4,4-Trifluoro-2-methyl-1-butanol—Electrolysis of partially neutralized trifluoroacetic acid in methanol in the presence of methyl methacrylate gave, after hydrogenation of the mixture, material (bp 119–121 °C) identified by NMR as nearly pure methyl 4,4,4-trifluoro-2-methyl-butanoate.[13] Reduction of the ester or the corresponding acid with lithium tetrahydroaluminate afforded the alcohol, bp 132–133 °C; ^{19}F NMR: δ 13.47 (t, J = 10.8 Hz); ^{1}H NMR (2.5%, Me_2SO-d_6:Me_4Si): δ 4.70 (t, J = 5.5 Hz, 1), 3.28 (m, 2), 1.65–2.5 (m, 3), and 0.95 ppm (d, J = 6.6 Hz, 3). Anal. ($C_5H_9F_3O$) C,H.

4,4,4-Trifluoro-3-methyl-1-butanol—Electrolysis of trifluoroacetic acid that was co-dissolved with crotonic acid in acetonitrile yielded a mixture of products containing 2,3-bis(trifluoromethyl)butanoic acid as a major component.[13] Treatment of the mixture with aqueous sodium hydroxide hydrolyzed the 2-trifluoromethyl group to produce a substituted malonic acid, as described elsewhere for the analogous 2-(trifluoromethyl)-4,4,4-trifluorobutanoic acid.[16] On distillation, the malonic acid was decarboxylated, affording the known 4,4,4-trifluoro-3-methyl butanoic acid[17] which was contaminated mainly with crotonic acid. Treatment with bromine in carbon tetrachloride, followed by a further distillation, gave the pure acid, which was then reduced with lithium tetrahydroaluminate to the alcohol[18] (bp 139–140 °C) [lit.[18] bp 57–59 °C (30 mm)].

6,6,6-Trifluoro-1-hexanol—6,6,6-Trifluorohexanoic acid was prepared by the reaction between adipic acid and sulfur tetrafluoride.[19] Another batch was obtained by hydrogenating the mixture of unsaturated acids produced in a Knoevenagel condensation of 4,4,4-trifluorobutanal[5] with malonic acid. The alcohol[20] (bp 165.5–166.0 °C) [lit.[21] bp 51.5–53.5 °C (5 mm)] was obtained by reducing the acid with lithium tetrahydroaluminate. ^{19}F NMR: δ 10.55 (t, J = 10.4 Hz); ^{1}H NMR (2.5% Me_2SO-d_6:Me_4Si): δ 4.34 (t, J = 5.3 Hz, 1), 3.39 (br q, 2), 1.9–2.5 (br m, 2), and 1.3–1.6 ppm (br m, 6).

6,6,6-Trifluoro-3-hexanol—This compound was prepared in 72% yield by a Grignard reaction of ethylmagnesium bromide with 4,4,4-trifluorobutanal, using the procedure described by Drake and Cooke.[22] The fraction used in the partition experiments boiled between 140.4 and 140.9 °C; ^{19}F NMR: δ 10.61 (t, J = 10.8 Hz); ^{1}H NMR (2.5%, Me_2SO-d_6:Me_4Si): δ 4.56 (d, J = 5.4 Hz, 1), 3.32 (m, 1), 1.9–2.5 (m, 2), 1.2–1.7 (m, 4), and 0.86 ppm (t, J = 7 Hz, 3). Anal. ($C_6H_{11}F_3O$) C,H.

5,5,5-Trifluoro-3-methyl-1-pentanol—Partially neutralized trifluoroacetic acid was electrolyzed in aqueous 90% methanol in the presence of methallyl cyanide giving, after partial workup, a mixture rich in 5,5,5-trifluoro-3-methyl-pent-2-enonitrile and isomers of this compound.[13] After catalytic hydrogenation (5% Pd/C, methanol 3 atm, 6–8 h), the mixture was distilled and a fraction boiling at 168.5–170.5 °C (mostly at 168.5 °C) was found by NMR to be nearly pure 5,5,5-trifluoro-3-methylpentanonitrile. This was hydrolyzed by refluxing for 4 h with aqueous sulfuric acid to produce the parent acid (bp 200.0–200.5 °C) which was then reduced to the alcohol (bp 158.7 °C) with lithium tetrahydroaluminate. ^{19}F NMR: δ 13.77 (t, J = 10.5 Hz); ^{1}H NMR (2.5%, Me_2SO-d_6:Me_4Si): δ 4.39 (t, J = 5.4 Hz, 1), 3.44 (q, J = 6 Hz, 2), 1.8–2.4 (m, 3H), 1.25–1.6 (m, 2), and 0.97 ppm (d, J = 6 Hz, 3). Anal. ($C_6H_{11}F_3O$) C, H.

Partition Coefficients—For each solute, two or more partitioning mixtures were prepared by weighing the alcohol into glass-stoppered volumetric flasks and adding known amounts of cosolvent-saturated water and water-saturated cosolvent using volumetric pipets. The volumes were so chosen that the amounts of solute in each of the two phases would be similar, with the concentration in the nonaqueous phase within the range of 7–20 mg/mL. The solutions were equilibrated by inverting the flasks ~250 times during a period of ~1 h. Only the nonaqueous layers were analyzed and the partition coefficients calculated with the equation:

$$P = C_{alc}V_{aq}/(M - C_{alc}V_{alc}) \quad (3)$$

where C_{alc} is the concentration in the alcoholic layer, M is the total mass of solute, and V_{aq} and V_{alc} are the volumes of the aqueous and alcoholic layers, respectively.

For analysis of each solution, two samples of ~0.8 mL were placed in NMR tubes with capillaries containing an appropriate material to provide a locking signal for the NMR spectrometer, and the spectra were recorded several times. The concentrations were found by comparing the heights of the most prominent solute ^{1}H or ^{19}F NMR peaks with those of the corresponding peaks in the spectra of three standard solutions, each containing the particular alcohol in water-saturated cosolvent. This procedure tends to cancel any errors due to possible low levels of contaminants in the solutes. The four or more

values of log P obtained for each solute generally differed from their average by ≤0.05 units. The main source of irreproducibility seemed to be small fluctuations in effective sensitivity of the spectrometer.

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