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HEXAFLUOROISOPROPANOL - A SOLVENT OF HIGH IONIZING POWER AND LOW NUCLEOPHILICITY

Frank L. Schadt and Paul v.R. Schleyer*
Department of Chemistry, Princeton University, Princeton, New Jersey 08540 U.S.A.
T. William Bentley
Department of Chemistry, University College Swansea, Singleton Park,
Swansea, Glamorgan SA2 8PP, Great Britain

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Although fluorinated alcohols and carboxylic acids are increasingly used in solvolytic studies, attention has mainly been devoted to 2,2,2-trifluoroethanol[1] and to trifluoroacetic acid[2]. We now report that hexafluoroisopropanol,[3] $(CF_3)_2CHOH$, possesses advantages over both these solvents, because it has a higher ionizing power and a lower nucleophilicity than trifluoroethanol and is much less acidic than trifluoroacetic acid. Also, the kinetics of reactions in $(CF_3)_2CHOH$ can be followed conveniently and accurately by conductivity techniques,[4] whereas rate studies in trifluoroacetic acid require less convenient and less reliable u.v. spectroscopic methods.[2a] Table I summarizes data in the two fluorinated alcohol solvents.

We recently defined a solvent nucleophilicity scale based on solvolysis data (equation 1)[5] which agrees well with an independent scale derived from rates of displacement on cyclic halonium ions in liquid SO_2.[6] Calculation of N for any solvent requires the rate constant of methyl

$$\underline{N} = \log\,(\underline{k}/\underline{k}_o)_{CH_3OTs} - 0.3\,\underline{Y} \qquad (1)$$

tosylate in that solvent ($\underline{k}$) relative to that in 80% aq. ethanol ($\underline{k}_o$), and values of $\underline{Y}$ determined from t-butyl chloride[5,7] or 2-adamantyl tosylate.[5,8] The latter appears to be the more appropriate standard over a widened solvent range, since t-butyl chloride shows anomalous behavior in fluorinated solvents.[1c,e,3a,9] We find (Table 2) that 97% aq. hexafluoroisopropanol is 1.5 $\underline{N}$ units less nucleophilic than 97% trifluoroethanol, 0.6 $\underline{Y}$ units more ionizing than formic acid, and only about one unit removed from trifluoroacetic acid in each of these solvent properties! Hexafluoroisopropanol should be a particularly useful solvent for synthetic cyclization reactions[1a,b,d,g,2b] and for mechanistic studies of neighboring group participation.[1f,2c]

Table 1. Rate Constants For Solvolyses of Alkyl Tosylates (ROTs)[a]

Substrate (ROTs) R	10^5<u>k</u> 97 wt % $(CF_3)_2CHOH/H_2O$	10^5<u>k</u> 97 wt % CF_3CH_2OH/H_2O
Methyl	0.0018[b,c]	0.013[b,c,d]
2-Propyl	0.155[c]	0.064[c,e]
Cyclohexyl	1.81	0.14 [f]
2-Adamantyl	9.75	0.164

[a] Determined conductimetrically at 25°, except where otherwise noted. [b] 50°. [c] Calculated from data at other temperatures. [d] Ref. 1d. [e] Corrected from 97 vol % aq. CF_3CH_2OH, R.E. Hall, A.B. Thesis, Princeton University, 1970. [f] Estimated from reference 11.

Table 2. Estimates of Nucleophilicity (<u>N</u>) and Ionizing Power (<u>Y</u>) of Solvents

Solvent	$\underline{Y}^a$(OTs)	<u>N</u> (eq. 1)
CF_3CO_2H	4.57	-5.56
97 wt. %$(CF_3)_2CHOH/H_2O$	3.61	-4.18
97 wt. % CF_3CH_2OH/H_2O	1.83	-2.79
HCO_2H	3.04	-2.35
CH_3CO_2H	-0.61	-2.35
80% CH_3CH_2OH/H_2O	0.00	0.00

[a] From $\log(\underline{k}/\underline{k}_o) = \underline{Y}_{(OTs)}$, where <u>k</u> is the rate constant of 2-AdOTs in any solvent and $\underline{k}_o$ is the rate constant in 80% <u>v/v</u> ethanol/water. Data from ref. 5 and Table 1.

Hexafluoroisopropanol fills the "gap" between formic and trifluoroacetic acids and allows further insight into the mechanism of solvolysis of simple secondary substrates.[10,11] We have proposed that the 10^4 variation in the 2-propyl/2-adamantyl rate ratio in going from ethanol to trifluoroacetic acid is caused mainly by varying amounts of nucleophilic solvent assistance.[10,12] The highly hindered 2-adamantyl tosylate solvolyses by a limiting $\underline{k}_c$ ionization,[10,13] while less hindered secondary substrates are accelerated by nucleophilic solvent assistance ($\underline{k}_s > \underline{k}_c$). Estimates of the magnitude of such solvent involvement ($\underline{k}_s/\underline{k}_c$) can be calculated from eq. 2, assuming that the trifluoroacetolyses of all simple secondary tosylates are limiting ($\underline{k}_t \equiv \underline{k}_c$). Eq. 2 was considered[10] to provide minimum values since the possibility that even trifluoroacetic acid was providing weak nucleophilic stabilization for unhindered secondary substrates could not

$$\underline{k}_s/\underline{k}_c = [\underline{k}_t\,(\mathrm{ROTs})/\underline{k}_t\,(\text{2-AdOTs})]_{\text{ANY SOLVENT}} \Big/ [\underline{k}_t(\mathrm{ROTs})/\underline{k}_t\,(\text{2-AdOTs})]_{CF_3COOH} \qquad (2)$$

be excluded. The present results indicate that this is not the case since *the $\underline{k}_s/\underline{k}_c$ ratios for 2-propyl and cyclohexyl tosylates are essentially unity in the range from 97 wt. % hexafluoroisopropanol (N = -4.25, Y = 3.61) to trifluoroacetic acid (N = -5.56, Y = 4.57)*. The fact that the $(CF_3)_2CHOH$ $\underline{k}_s/\underline{k}_c$ values are slightly less than 1 might be due to differing but minor amounts of ion pair return.[11,14]

Our findings confirm that unhindered secondary systems can undergo limiting[15] ionization in solvents of high ionizing power and low nucleophilicity and strengthen our proposal that variations in observed $\underline{k}_s/\underline{k}_c$ ratios are due mainly to changes in the magnitude of nucleophilic solvent assistance.[10,12] In contrast to trifluoroacetic acid, solvolysis rates in hexafluoroisopropanol can be measured easily and accurately. Thus, hexafluoroisopropanol may well be the solvent of choice for studying limiting solvolyses of secondary substrates and these experiments are underway.

Table 3. Relative Rates of Solvolysis - Estimates of Nucleophilic Solvent Assistance ($\underline{k}_s/\underline{k}_c$)[a]

	Solvent				
Substrate (ROTs)	CF_3CO_2H	97 wt. % $(CF_3)_2CHOH$	HCO_2H	97 wt. % CF_3CH_2OH	CH_3CO_2H
2-Adamantyl	1.0	1.0	1.0	1.0	1.0
Cyclohexyl	1.0	0.62	5.0	2.9	28.0
2-Propyl	1.0	0.58	32.0	14.2	472.0

[a] From equation 2.

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15. Prompted by a referee's comment, we wish to make clear that "limiting" in the present context refers to the lack of nucleophilic assistance by solvent (attack on the α-carbon or on a β-hydrogen) in the rate determining step, and does not exclude the possibility of rate enhancement by neighboring group participation. The magnitude of such anchimeric assistance, if present at all in the secondary systems treated here, has yet to be established.