

Solvent nucleophilicities of hexafluoroisopropanol/water mixtures

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First-order rate constants k_1 for the trapping of various donor- and acceptor-substituted benzhydrylium ions in mixtures of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and water ranging from 50 to 99% HFIP (w/w) were determined by laser flash photolytic generation of benzhydrylium ions from benzhydryl triarylphosphonium salts in these solvents. From these rate constants, we derived the solvent-specific reactivity parameters N_1 and s_N for HFIP/water mixtures as defined by the linear free energy relationship $\lg k_1(20^\circ\text{C}) = s_N(N_1 + E)$. Copyright © 2012 John Wiley & Sons, Ltd. Supporting information may be found in the online version of this paper.

INTRODUCTION

Because of their unique solvating properties, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and HFIP/water mixtures have been employed as solvents for synthetic transformations^[1–7] and for the study of protein structures.^[8,9] HFIP/water mixtures have also played a key role in solvolytic studies due to their high ionizing powers and low nucleophilicities,^[10–14] which allowed one to investigate S_N1 reactions of substrates which solvolyze with nucleophilic solvent assistance in other media.^[15] However, also in HFIP/water mixtures, a change from S_N1 to S_N2 processes is occurring, when the S_N1 process would lead to poorly stabilized carbocations. In order to predict this change of mechanism from S_N1 to S_N2 , the nucleophilic reactivity of the solvent must be known.^[16]

We have recently reported that highly reactive acceptor-substituted benzhydrylium ions can be generated by laser flash photolysis of phosphonium salts^[17] and employed this method to determine the empirical electrophilicity parameters E of these benzhydrylium ions^[18] as defined by Eqn 1. This linear free energy relationship relates the second-order rate constants k_2 ($\text{M}^{-1} \text{s}^{-1}$) of bimolecular reactions of electrophiles with nucleophiles to the electrophile-specific parameter E and the nucleophile-specific parameters N and s_N .^[19–21]

$$\lg k_2(20^\circ\text{C}) = s_N(N + E) \quad (1)$$

Equation 1 can also be used to predict the first-order rate constants k_1 (s^{-1}) for the reactions of electrophiles with solvents, when the solvent-specific parameters N_1 and s_N are employed (Eqn 1a).^[22]

$$\lg k_1(20^\circ\text{C}) = s_N(N_1 + E) \quad (1a)$$

With the aid of our recently determined electrophilicity parameters E for the highly reactive acceptor-substituted benzhydrylium ions,^[18] we can now provide quantitative reactivity parameters for the weakly nucleophilic HFIP/water mixtures.

RESULTS AND DISCUSSION

Irradiation of ca. 10^{-4} M solutions of the phosphonium salts **E(1–13)**– $\text{PAR}_3^+ \text{BF}_4^-$ ($\text{Ar} = \text{Ph}$ or $p\text{-Cl-C}_6\text{H}_4$) in mixtures of HFIP and water (W) ranging from 50HFIP50W to 99HFIP1W (w/w) yielded the benzhydrylium ions **E(1–13)**⁺ (Scheme 1 and Table 1).

In those cases where the reactions of **E(1–13)**⁺ with the solvent were faster than the recombination with the photo-leaving group PAR_3 , exponential decays of the UV/Vis absorbances of **E(1–13)**⁺ can be observed, as illustrated in Fig. 1a for the decay of the most electrophilic carbocation in our series, **E13**⁺, in 99HFIP1W. From the exponential decays, we derived the first-order rate constants k_1 (s^{-1}) listed in Table 2 for the reactions of **E**⁺ with the HFIP/water mixtures.

Reactions which proceed with rate constants lower than ca. 10^4 s^{-1} were not investigated, because the kinetics of these reactions are complicated by the recombination of **E**⁺ with the photo-leaving group PAR_3 which proceeds on a similar time scale.^[17] To determine the rate constants of slower reactions, one might employ anionic photo-leaving groups such as p -cyanophenolate, which can be expected to undergo significantly slower recombination reactions with the photogenerated carbocations due to the exceptionally good solvation of anions by fluorinated alcohols.^[23] Since a major goal of this investigation was the characterization of the electrophilic reactivities of acceptor-substituted benzhydrylium ions towards relatively weak nucleophiles such as HFIP/water mixtures, we have not included p -cyanophenolates in this study.

Plots of $\lg k_1$ for the reactions of **E**⁺ with the HFIP/water mixtures versus the E parameters of **E**⁺ were linear (Fig. 2) and allowed us to derive the solvent nucleophilicity parameters N_1 and s_N listed in Table 2. Figure 2 illustrates the excellent correlations of k_1 with the E parameters that were derived from reactions of **E**⁺ with

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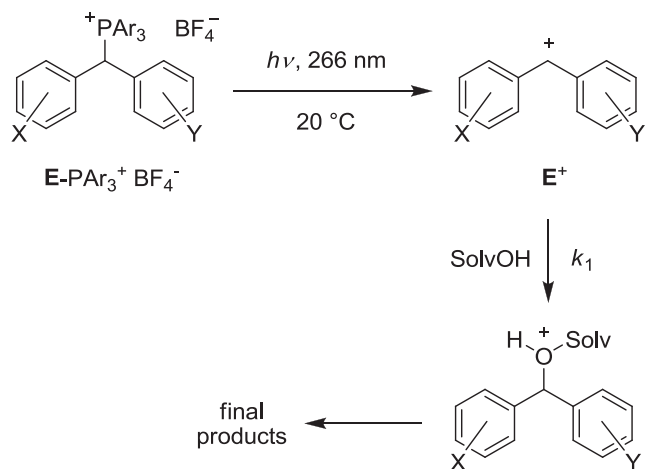
π -nucleophiles in CH_2Cl_2 . Only very small deviations are found for the most electrophilic benzhydrylium ion in the series, E13^+ , although the electrophilicity parameter of this carbocation had been derived from only one rate constant because of its extremely high reactivity.^[18] The kinetic data from this work thus corroborate the electrophilicity parameter $E = 8.02^{[18]}$ for E13^+ .

The 4,4-dichlorobenzhydrylium ion E7^+ deviates slightly from these correlations. Although E7^+ has the same electrophilicity as E6^+ in CH_2Cl_2 , the rate constants for reactions of E7^+ in trifluoroethanol and HFIP/water mixtures are lower than those of E6^+ by a factor of 1.5 to 2.2 (Fig. 2).

The nucleophilic reactivities of the HFIP/water mixtures increase with increasing water content, which is particularly pronounced for the mixtures with low water content. Figure 3 compares $\lg k_1$

for the reaction of E8^+ with HFIP/water mixtures of varying water content, which is similar to a N_1 versus % H_2O plot as the s_N parameters are closely similar.

It has been reported that the microscopic structures of HFIP/water mixtures change when the water content is varied. The structures of the solvent mixtures investigated in this work range from micelle-like assemblies of HFIP molecules in water (50HFIP50W; 38.5 vol.-% HFIP, $x_{\text{HFIP}} = 0.097$) over a poorly characterized complex intermediate structure of small HFIP associates (70HFIP30W to 95HFIP5W; 59–92 vol.-% HFIP, $0.200 \leq x_{\text{HFIP}} \leq 0.671$) to short helical chains of HFIP molecules as in neat HFIP (97HFIP3W to 99HFIP1W; >95 vol.-% HFIP, $x_{\text{HFIP}} \geq 0.776$).^[24] Despite these large structural variations, $\lg k_1$ for the reactions of E8^+ with the HFIP/water mixtures increases almost linearly with the molar fraction of water over the entire range from 99HFIP1W to 50HFIP50W (Fig. 3b). A similar effect



Scheme 1. Generation of benzhydrylium ions E^+ by laser flash irradiation of the phosphonium salts $\text{E-PAr}_3^+ \text{BF}_4^-$ ($\text{Ar} = \text{Ph}$ or $p\text{-Cl-C}_6\text{H}_4$)

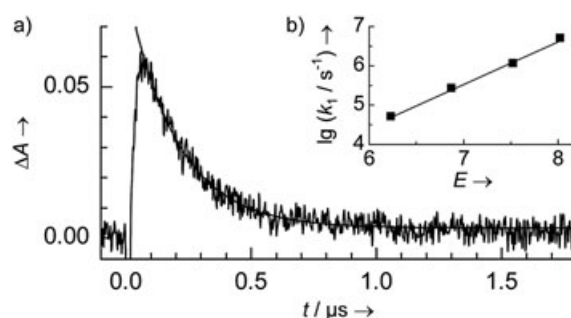
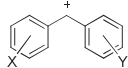


Figure 1. (a) Decay of the absorbance of E13^+ at $\lambda = 439 \text{ nm}$ observed after irradiation of a $8.52 \times 10^{-5} \text{ M}$ solution of $\text{E13-P}(p\text{-Cl-C}_6\text{H}_4)_3^+ \text{BF}_4^-$ in 99HFIP1W and exponential fit of the data ($k_1 = 5.11 \times 10^6 \text{ s}^{-1}$, $R^2 = 0.9685$). (b) Plot of $\lg k_1$ obtained from reactions of E8^+ , E11^+ , E12^+ , and E13^+ with 99HFIP1W against the electrophilicity parameters E of these benzhydrylium ions ($\lg k_1 = 1.09(-1.93 + E)$, $R^2 = 0.9973$)

Table 1. Electrophiles $\text{E}(1\text{--}13)^+$ and their electrophilicity parameters E

no.			E^a
	X	Y	
E1^+	4-MeO	H	2.11
E2^+	4-Me	4-Me	3.63
E3^+	4-Me	H	4.43
E4^+	4-F	4-F	5.01
E5^+	3-F, 4-Me	3-F, 4-Me	5.24
E6^+	H	H	5.47
E7^+	4-Cl	4-Cl	5.48
E8^+	3-F	H	6.23
E9^+	4-(CF_3)	H	6.70
E10^+	3,5- F_2	H	6.74
E11^+	3-F	3-F	6.87
E12^+	3,5- F_2	3-F	7.52
E13^+	3,5- F_2	3,5- F_2	$(8.02)^b$

^aFrom ref.^[18]

^bApproximate value.

Table 2. First-order rate constants k_1 (s^{-1}) for reactions of electrophiles E^+ with HFIP/water mixtures and comparison with rate constants k_{calc} (s^{-1}) calculated from Eqn 1a

Nucleophile solvent ^a	N_1 , s_N	E^+	Electrophile abbreviation	E^b	Experiment k_1^c/s^{-1}	Calculated k_{calc}^d/s^{-1}	k_{calc}/k_1
50HFIP50W 38.5% (v/v) $x_{\text{HFIP}} = 0.097$	$N_1 = 1.50$ $s_N = 1.03$	E1 ⁺	ani(Ph)CH ⁺	2.11	5.56×10^3 ^e	5.23×10^3	0.94
		E2 ⁺	(tol) ₂ CH ⁺	3.63	1.50×10^5	1.92×10^5	1.28
		E3 ⁺	tol(Ph)CH ⁺	4.43	1.20×10^6	1.28×10^6	1.07
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	5.32×10^6	5.07×10^6	0.95
70HFIP30W 59.3% (v/v) $x_{\text{HFIP}} = 0.200$	$N_1 = 1.65$ $s_N = 0.96$	E2 ⁺	(tol) ₂ CH ⁺	3.63	1.13×10^5	1.17×10^5	1.04
		E3 ⁺	tol(Ph)CH ⁺	4.43	8.06×10^5	6.87×10^5	0.85
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	3.25×10^6	2.48×10^6	0.76
		E5 ⁺	–	5.24	3.32×10^6	4.12×10^6	1.24
90HFIP10W 84.9% (v/v) $x_{\text{HFIP}} = 0.491$	$N_1 = 0.96$ $s_N = 0.93$	E6 ⁺	(Ph) ₂ CH ⁺	5.47	7.52×10^6	6.84×10^6	0.91
		E3 ⁺	tol(Ph)CH ⁺	4.43	1.10×10^5	1.03×10^5	0.94
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	3.74×10^5	3.57×10^5	0.95
		E6 ⁺	(Ph) ₂ CH ⁺	5.47	1.01×10^6	9.55×10^5	0.95
		E8 ⁺	mfp(Ph)CH ⁺	6.23	5.21×10^6	4.86×10^6	0.93
		E10 ⁺	dfp(Ph)CH ⁺	6.74	1.55×10^7	1.45×10^7	0.93
93HFIP7W 89.3% (v/v) $x_{\text{HFIP}} = 0.588$	$N_1 = 0.34$ $s_N = 0.96$	E11 ⁺	(mfp) ₂ CH ⁺	6.87	2.10×10^7	1.91×10^7	0.91
		E3 ⁺	tol(Ph)CH ⁺	4.43	3.88×10^4	3.79×10^4	0.98
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	1.39×10^5	1.37×10^5	0.98
		E6 ⁺	(Ph) ₂ CH ⁺	5.47	3.99×10^5	3.78×10^5	0.95
		E7 ⁺	(pcp) ₂ CH ⁺	5.48	2.61×10^5	3.87×10^5	1.48
		E8 ⁺	mfp(Ph)CH ⁺	6.23	1.96×10^6	2.03×10^6	1.04
		E9 ⁺	tfm(Ph)CH ⁺	6.70	6.26×10^6	5.73×10^6	0.92
		E11 ⁺	(mfp) ₂ CH ⁺	6.87	9.10×10^6	8.35×10^6	0.92
95HFIP5W 92.2% (v/v) $x_{\text{HFIP}} = 0.671$	$N_1 = -0.10$ $s_N = 0.97$	E12 ⁺	dfp(mfp)CH ⁺	7.52	2.92×10^7	3.51×10^7	1.20
		E3 ⁺	tol(Ph)CH ⁺	4.43	1.67×10^4	1.59×10^4	0.95
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	5.78×10^4	5.79×10^4	1.00
		E6 ⁺	(Ph) ₂ CH ⁺	5.47	1.70×10^5	1.62×10^5	0.95
		E8 ⁺	mfp(Ph)CH ⁺	6.23	8.61×10^5	8.83×10^5	1.03
		E11 ⁺	(mfp) ₂ CH ⁺	6.87	4.53×10^6	3.69×10^6	0.81
97HFIP3W 95.3% (v/v) $x_{\text{HFIP}} = 0.776$	$N_1 = -1.19$ $s_N = 1.08$	E12 ⁺	dfp(mfp)CH ⁺	7.52	1.55×10^7	1.58×10^7	1.02
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	1.52×10^4	1.34×10^4	0.88
		E6 ⁺	(Ph) ₂ CH ⁺	5.47	5.01×10^4	4.19×10^4	0.84
		E7 ⁺	(pcp) ₂ CH ⁺	5.48	3.00×10^4	4.30×10^4	1.43
		E8 ⁺	mfp(Ph)CH ⁺	6.23	2.68×10^5	2.77×10^5	1.04
		E10 ⁺	dfp(Ph)CH ⁺	6.74	1.11×10^6	9.86×10^5	0.89
		E11 ⁺	(mfp) ₂ CH ⁺	6.87	1.46×10^6	1.36×10^6	0.93
98HFIP2W 96.8% (v/v) $x_{\text{HFIP}} = 0.840$	$N_1 = -1.62$ $s_N = 1.10$	E12 ⁺	dfp(mfp)CH ⁺	7.52	6.48×10^6	6.86×10^6	1.06
		E4 ⁺	(pfp) ₂ CH ⁺	5.01	6.17×10^3	5.36×10^3	0.87
		E6 ⁺	(Ph) ₂ CH ⁺	5.47	2.04×10^4	1.72×10^4	0.84
		E7 ⁺	(pcp) ₂ CH ⁺	5.48	1.24×10^4	1.76×10^4	1.42
		E8 ⁺	mfp(Ph)CH ⁺	6.23	1.14×10^5	1.18×10^5	1.03
		E11 ⁺	(mfp) ₂ CH ⁺	6.87	6.54×10^5	5.96×10^5	0.91
99HFIP1W 98.4% (v/v) $x_{\text{HFIP}} = 0.914$	$N_1 = -1.93$ $s_N = 1.09$	E12 ⁺	dfp(mfp)CH ⁺	7.52	2.60×10^6	3.09×10^6	1.19
		E13 ⁺	(dfp) ₂ CH ⁺	(8.02) ^f	1.20×10^7	1.10×10^7	0.91
		E8 ⁺	mfp(Ph)CH ⁺	6.23	5.18×10^4	4.86×10^4	0.94
		E11 ⁺	(mfp) ₂ CH ⁺	6.87	2.72×10^5	2.42×10^5	0.89
		E12 ⁺	dfp(mfp)CH ⁺	7.52	1.15×10^6	1.24×10^6	1.08
		E13 ⁺	(dfp) ₂ CH ⁺	(8.02) ^f	5.11×10^6	4.35×10^6	0.85

^a) Solvent mixtures are given as w/w. Abbreviations: HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, W = water. To accommodate literature conventions in other fields, we also provide the v/v percentages and molar fractions.

^b) E parameters derived from kinetic data for reactions of E^+ with π -nucleophiles in CH_2Cl_2 ; from ref.^[18]

^c) Laser flash photolysis of triarylphosphonium salts, this work.

^d) Calculated from Eqn 1a.

^e) Determined from a non-exponential decay curve as the reaction of **E1**⁺ with 50HFIP50W does not follow first-order kinetics due to recombination of **E1**⁺ with the photo-leaving group PPh_3 . See Section S1.3 in the Supporting Information for details.

^f) This E parameter is based on only one rate constant.

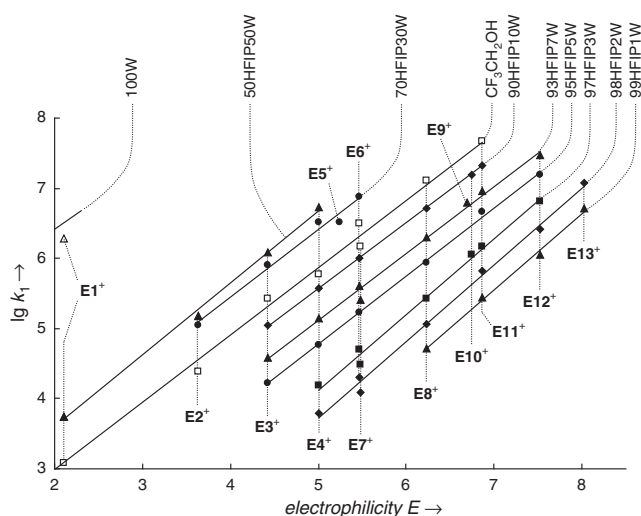


Figure 2. Plot of $\lg k_1$ versus E for the reactions of benzhydryl cations with HFIP/water mixtures (filled symbols). For comparison, data for 100 W and trifluoroethanol are also shown (open symbols; only a part of the correlation lines is shown)^[22]

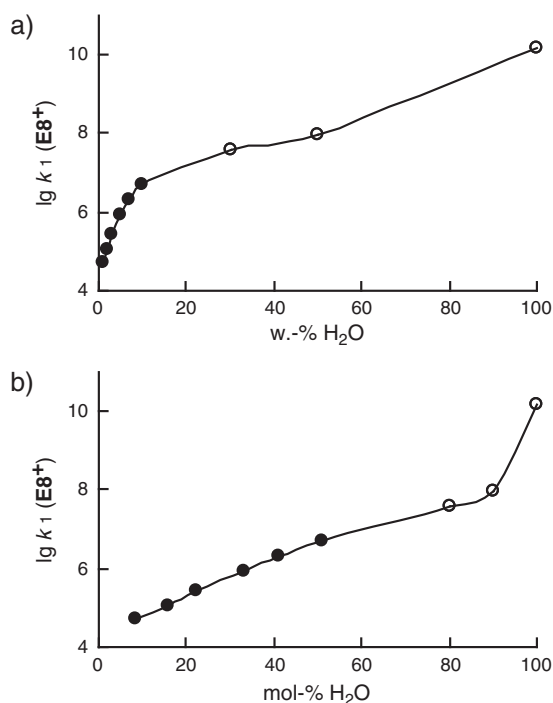


Figure 3. Plots of $\lg k_1$ for the decay of $E8^+$ in HFIP/water mixtures against the water content of the mixtures in weight-% (a) or mol-% (b). Filled circles: experimental data; open circles: calculated from Eqn 1a

is also found for the ionizing powers Y_{OTs} of the HFIP/water mixtures, which decrease almost linearly with increasing water content for compositions with 0–90 mol-% water.^[12] The inverse linear correlation between $\lg k_1$ ($E8^+$) and Y_{OTs} in this range indicates that nucleophilicity as well as solvent ionizing power of HFIP/water mixtures are affected in a similar manner by changes in solvent structure.

Between 90 mol-% water (50HFIP50W) and 100 mol-% water, however, there is a further substantial increase in nucleophilicity

(Fig 3b), indicating that the nucleophilicity of pure water is reduced significantly by the presence of only 10 mol-% of the good hydrogen bond donor HFIP. A sharp increase between 90 and 100 mol-% water is also found in the ionizing powers Y_{OTs} of the HFIP/water mixtures.^[12] These observations are in agreement with another structural transition of the binary solvent system, which exists as dilute single HFIP molecules in water for compositions with more than ~95 mol-% water (35HFIP65W, 25 vol-% HFIP).^[24] Large water clusters that are not influenced by HFIP may also explain why we could not observe $E3^+$ after irradiation of $E3$ - $PAr_3^+ BF_4^-$ in 25HFIP75W (calculated lifetime of $E3^+$ in pure water: 2.7 ns).

As the nucleophilicity parameters for mixtures with low water content are highly sensitive to the water content (Fig. 3a), we did not attempt to determine N_1 and s_N of pure HFIP. Literature values of k_1 for the decay of $E6^+$ in HFIP range from “around $10^2 s^{-1}$ ” (meticulously dried HFIP but inaccurate measurement)^[25] to $2.2 \times 10^4 s^{-1}$ (commercial HFIP, >99.8%, used as received).^[26] The latter value is slightly larger than the calculated rate constant for the reaction of $E6^+$ with HFIP containing 1% water ($k_{calc} = 7.2 \times 10^3 s^{-1}$). It thus seems problematic to derive accurate quantitative information about the electrophilic reactivities of carbocations from their decay rate constants in neat HFIP as traces of water may strongly affect the results.

The N_1 parameters for HFIP/water mixtures determined in this work (Table 2) agree within 1.5 units with our previous estimates for some of these solvents that were derived from a correlation with Kevill's N_T parameters.^[22] However, the s_N parameters of the HFIP/water mixtures are somewhat larger than for other alcoholic and aqueous solvents.^[22]

The low nucleophilicity of HFIP/water mixtures has previously been utilized to study solvolysis reactions under conditions where nucleophilic solvent assistance is reduced. For example, the solvolysis of 2-propyl tosylate in 97% aqueous HFIP proceeds by an S_N1 mechanism, whereas the same reaction in 97% aqueous trifluoroethanol already proceeds with measurable nucleophilic solvent assistance (factor 15).^[15] It has been argued that an intermediate can only exist if its lifetime is at least as long as the duration of a bond vibration ($\sim 10^{-13} s$).^[27–30] Thus, S_N1 reactions leading to carbocations with lifetimes shorter than ca. $10^{-13} s$ cannot occur, and only S_N2 reactions are possible in these cases.

We have previously investigated the borderline between S_N1 and S_N2 mechanisms for nucleophilic substitution reactions in DMSO ($N_1 = 11.3$, $s_N = 0.74$).^[16] Equation 1a predicts a lifetime near the theoretical limit ($5 \times 10^{-14} s$) for $E9^+$ ($E = 6.70$) in DMSO, and no significant nucleophilic solvent participation was observed for reactions of the corresponding bromide (i.e., DMSO only reacts via S_N1 and not via S_N2 mechanism).^[16] On the other hand, significant nucleophilic solvent participation was found for reactions of bis[4-(trifluoromethyl)phenyl]methyl bromide,^[16] in agreement with a calculated lifetime of $6 \times 10^{-15} s$ for the corresponding carbocation ($E = 7.96$)^[18] in DMSO, which is shorter than the period of a bond vibration ($\sim 10^{-13} s$).

The N_1 and s_N parameters for the HFIP/water mixtures from Table 2 can now be employed to predict when a change from S_N1 to S_N2 mechanism can be expected in these solvents. The limiting lifetime of ca. $10^{-13} s$ will thus be reached for carbocations with $E \geq 11$ in 50HFIP50W and for carbocations with $E \geq 12$ in 70HFIP30W. Carbocations with higher electrophilicity parameters cannot exist in these solvents. As the decreasing N_1 parameters are

compensated by slightly increasing s_N parameters in the series 90HFIP10W to 99HFIP1W, we calculate a limiting value of $E \approx (13 \text{ to } 14)$ for all HFIP/water mixtures with $\leq 10\%$ water content. These limiting E parameters are well beyond those of the most electrophilic carbocations which have so far been characterized by Eqn 1.^[18] It can thus be concluded that nucleophilic solvent assistance will generally not be observed in HFIP/water mixtures with $\leq 10\%$ water content.

EXPERIMENTAL SECTION

Solvents

HFIP (Apollo, 99%) was refluxed with CaH_2 for 30 min and then distilled under nitrogen (CAUTION: oil bath temperature $\leq 80^\circ\text{C}$).^[31] Doubly distilled water (Impedance 18.2 Ω) was prepared with a water purification system (Milli-Q Plus machine from Millipore). The appropriate amounts of HFIP and water were combined to obtain the HFIP/water mixtures.

Laser flash photolysis experiments

Solutions of the precursor phosphonium salts **E(1–13)**- $\text{PAR}_3^+\text{BF}_4^-$ ($\text{Ar} = \text{Ph}$ or $p\text{-Cl-C}_6\text{H}_4$) with $A_{266\text{ nm}} \approx 0.2$ to 0.9 (ca. 10^{-4} M) were irradiated with a 7-ns laser pulse (fourth harmonic of Nd:YAG laser, $\lambda_{\text{exc}} = 266\text{ nm}$, 40–60 mJ/pulse).^[17] Kinetics were measured by following the decay of the UV/Vis absorbances of the benzhydryl cations in the HFIP/water solvent mixtures. The rate constants k_1 (s^{-1}) were obtained by least-squares fitting of the absorbance decays of the benzhydryl cations to the single exponential curve $A_t = A_0 e^{-k_1 t} + C$. Non-exponential kinetics were evaluated using the software Gepasi.^[32–35]

CONCLUSION

The excellent linear correlations of $\lg k_1$ for the reactions of benzhydrylium ions with HFIP/water mixtures with the electrophilicity parameters E of these benzhydrylium ions (Fig. 2) once again demonstrate that Eqn 1 adequately describes the decay rate constants of benzhydrylium ions in nucleophilic solvents and solvent mixtures.^[18,22]

In the future, the reactivity parameters of the HFIP/water mixtures may be of interest for characterizing the electrophilic reactivities of further highly reactive electrophiles ($E > 7$) which cannot be studied in trifluoroethanol or acetonitrile due to the high nucleophilicity of these solvents.^[17] The decay rate constants of carbocations in many less nucleophilic solvents such as CH_2Cl_2 , on the other hand, do not reflect the reactivities of these solvents but result from reactions with impurities or with the precursor molecules.^[17] Mixtures of HFIP and water with $\geq 90\%$ (w/w) HFIP combine the two advantages that they are less nucleophilic than trifluoroethanol and acetonitrile but still have a clearly defined nucleophilic reactivity.

SUPPORTING INFORMATION

Details of the kinetic experiments.

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