

Kinetics of the Solvolyses of Fluoro-Substituted Benzhydryl Derivatives: Reference Electrofuges for the Development of a Comprehensive Nucleofugality Scale

Christoph Nolte^[a] and Herbert Mayr^{*[a]}

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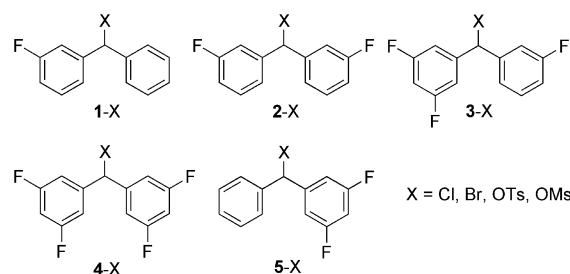
A series of *m*-fluoro-substituted benzhydryl chlorides, bromides, mesylates, and tosylates **1-X** to **5-X** were prepared and subjected to solvolysis reactions in various solvents. The observed first-order rate constants k_s (25 °C) were found to follow the correlation equation $\log k_s(25\text{ °C}) = s_f(N_f + E_f)$,

which allowed us to determine the electrofugality parameters E_f for these destabilized benzhydrylium cations and the nucleofugality parameters N_f , s_f for a series of leaving group/solvent combinations.

Introduction

The stabilization of benzhydryl cations (diarylcarbenium ions)^[1] can be modified widely by variation of substituents in *p*- and *m*-position, while the steric shielding of the carbocation center is kept constant. For that reason, benzhydrylium ions have not only been used to construct the most comprehensive nucleophilicity scale presently available,^[2] but also for the development of a nucleofugality scale.^[3] In order to compare the leaving group abilities of tosylate and bromide in solvents of high ionizing power, we had studied the solvolyses of mono- to tetra(*m*-chloro)-substituted benzhydrylium derivatives.^[3a,3b] However, as mentioned in a previous report,^[3a] several researchers were suffering from severe skin irritations when working in a laboratory where these compounds were used. For that reason we had to abandon the *m*-chloro-substituted compounds as references and replace them by the corresponding fluoro derivatives **1-X** to **4-X** with one to four *m*-fluoro substituents (Scheme 1).

The highly electrophilic benzhydrylium ions generated from these precursors have recently been employed to study the fastest bimolecular reactions in the electronic ground state we are aware of, i.e., the reaction of **4**⁺ with methanol, which proceeds with a reaction time of 2.6 ps, corresponding to a time in which light propagates less than 1 mm.^[4] We now report on the synthesis and characterization of compounds **1-X** to **5-X** and the kinetics of their solvolysis reactions in order to determine the electrofugality parameters of **1**⁺–**4**⁺.



Scheme 1. Benzhydrylium derivatives employed in this study.

Results and Discussion

Synthesis of the Precursors

The fluoro-substituted benzhydrols (**1**–**3**)-OH and **5**-OH were synthesized by the reactions of the fluorinated phenylmagnesium bromides with fluorinated benzaldehydes (Table 1) as described in detail in the Supporting Information. For the synthesis of the symmetrical tetrafluoro-substituted benzhydrol **4**-OH, 3,5-difluorophenylmagnesium bromide was combined with 0.5 equiv. of ethyl formate.

Table 1. Synthesis of the fluoro substituted benzhydrols (**1**–**5**)-OH.

Product	Grignard reagent	Aldehyde reagent
1 -OH	PhMgBr	(3-FC ₆ H ₄)CHO
2 -OH	(3-FC ₆ H ₄)MgBr	(3-FC ₆ H ₄)CHO
3 -OH	(3,5-F ₂ C ₆ H ₃)MgBr	(3-FC ₆ H ₄)CHO
4 -OH	(3,5-F ₂ C ₆ H ₃)MgBr	0.5 HC(O)(OEt)
5 -OH	(3,5-F ₂ C ₆ H ₃)MgBr	PhCHO

Standard reagents (SOCl₂, PBr₃) were used to convert the benzhydrols (**1**–**5**)-OH into the benzhydryl chlorides (**1**–**2**)-Cl and benzhydryl bromides (**1**–**5**)-Br. Attempts to convert the benzhydrols (**1**–**4**)-OH to the corresponding tosyl-

[a] Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5-13 (Haus F), 81377 München, Germany
Fax: +49-89-21807717
E-mail: herbert.mayr@cup.uni-muenchen.de

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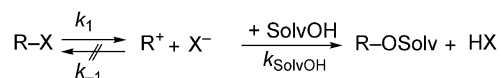
ates with *p*-toluenesulfonyl chloride/pyridine, *p*-toluenesulfonyl anhydride/triethylamine, or *p*-toluenesulfonyl anhydride/sodium hydride were unsuccessful.^[5] Therefore, the benzhydryl tosylates (**1–4**)-OTs were synthesized according to a procedure by Cheeseman and Poller^[6] by treatment of the corresponding benzhydryl bromides (**1–4**)-Br with silver tosylate in dichloromethane. The benzhydryl mesylates (**1–4**)-OMs were synthesized in the same manner by treatment of the corresponding benzhydryl bromides with silver mesylate. Only the tetrafluorinated benzhydryl mesylate **4**-OMs was obtained as a pure solid. The other mesylates (**1–3**)-OMs could not be isolated as pure substances and were obtained as yellowish oils that could neither be distilled nor brought to crystallization. Nevertheless, it was possible to investigate their solvolysis reactions by using diluted solutions, in analogy to a procedure by Bentley.^[7] The benzhydryl sulfonates used in this study are sensitive to moisture, and great care has to be taken to exclude traces of moisture during synthesis and handling of these compounds.

Kinetics

When compounds (**1–5**)-X were dissolved in aqueous or alcoholic media, an increase of conductivity due to the generation of HX was observed. Because calibration experiments showed a proportionality between conductivity (*G*) and the concentration of HX in the concentration range investigated, the observed monoexponential increase of conductivity (*G*) [Equation (1)] indicated the operation of a first-order rate law.

$$G = G_{\infty}(1 - e^{-k_s t}) + C \quad (1)$$

The first-order rate constants k_s were obtained by fitting the time-dependent conductivities *G* to the monoexponential function (1). Because all solvolyses studied in this work follow first-order rate laws, common-ion return^[8] (k_{-1} in Scheme 2) obviously does not occur, and the k_s values listed in Table 2 correspond to the ionization rate constants k_1 defined in Scheme 2.



Scheme 2. Simplified solvolysis scheme.

The Eyring and Arrhenius activation energies were determined for **1**-Br and **3**-OTs in 80E20W as representative systems (Table 3). Both compounds exhibit activation parameters, which are typical for solvolysis reactions.^[3,9]

Correlation Analysis

In previous work we have demonstrated that Equation (2) can be used to correlate solvolysis rates of substrates, which differ widely in reactivity.^[3] In this equation, carbocations are characterized by the electrofugality parameter E_f , while the nucleofuge-specific parameters N_f and s_f refer to combinations of leaving groups and solvents.

Table 2. Solvolysis rate constants (25 °C) of the benzhydryl derivatives (**1–5**)-X in different solvents.

Solvent ^[a]	X	Electrofuge	k_s [s ⁻¹]
90A10W	TsO	1	1.16×10^{-2}
		2	4.24×10^{-4}
80A20W	TsO	1	$5.59 \times 10^{-2[b]}$
		2	2.42×10^{-3}
		3	1.10×10^{-4}
80A20W	OMs	1	3.87×10^{-2}
		2	1.37×10^{-3}
		3	5.92×10^{-5}
60A40W	Br	1	1.47×10^{-3}
50A50W	Br	2	1.59×10^{-4}
60AN40W	OTs	1	$2.14^{[b]}$
		2	9.53×10^{-2}
		3	4.26×10^{-3}
		4	1.45×10^{-4}
60AN40W	OMs	2	4.82×10^{-2}
		3	2.52×10^{-3}
		4	8.04×10^{-5}
60AN40W	Br	4-Me ^[c]	$4.57^{[b]}$
		H ^[d]	$1.44 \times 10^{-1[b]}$
		1	4.59×10^{-3}
		2	1.18×10^{-4}
		5	1.59×10^{-4}
60AN40W	Cl	1	2.67×10^{-4}
100E	OTs	1	8.22×10^{-2}
		2	3.35×10^{-3}
		3	1.88×10^{-4}
100E	OMs	1	4.34×10^{-2}
		2	1.70×10^{-3}
		3	9.12×10^{-5}
80E20W	OTs	2	4.07×10^{-2}
		3	1.94×10^{-3}
		4	8.15×10^{-5}
80E20W	OMs	2	3.37×10^{-2}
		3	1.35×10^{-3}
		4	5.27×10^{-5}
80E20W	Br	1	9.47×10^{-4}
		2	2.30×10^{-5}
		5	3.98×10^{-5}
100M	OTs	1	8.33×10^{-1}
		2	2.07×10^{-2}
		3	1.13×10^{-3}
		4	5.51×10^{-5}
100M	Br	1	5.75×10^{-4}
80M20W	Br	2	1.90×10^{-4}
100TFE	OTs	3	7.99×10^{-2}
		4	1.73×10^{-3}
100TFE	OMs	3	9.21×10^{-2}
		4	1.78×10^{-3}
100TFE	Br	1	7.27×10^{-2}
		2	1.49×10^{-3}
		5	2.36×10^{-3}
		3	2.54×10^{-5}
100TFE	Cl	1	2.10×10^{-2}
		2	3.87×10^{-4}

[a] Mixtures of solvents are given as (v/v); solvents: A = acetone, AN = MeCN, E = ethanol, M = methanol, TFE = 2,2,2-trifluoroethanol, W = water. [b] Stopped-flow kinetics. [c] 4-Methylbenzhydryl. [d] Benzhydryl.

$$\log k_s(25^\circ\text{C}) = s_f(N_f + E_f) \quad (2)$$

s_f , N_f : nucleofuge-specific parameters

E_f : electrofuge-specific parameter

Table 3. Activation parameters for the solvolyses of **1-Br** and **3-OTs** in 80E20W.

	1-Br	3-OTs
ΔH^\ddagger [kJ mol ⁻¹]	84.2 ± 0.7	79.8 ± 0.8
ΔS^\ddagger [J mol ⁻¹ K ⁻¹]	-20.2 ± 2.4	-28.9 ± 2.7
E_a [kJ mol ⁻¹]	86.6 ± 2.4	82.2 ± 0.8
lg <i>A</i>	12.2 ± 0.1	11.7 ± 0.1

The solvolysis rate constants k_s in Table 2 and previously reported solvolysis rate constants for benzhydryl derivatives were subjected to a least-squares minimization according to Equation (3), where E_f for (4-MeOC₆H₄)₂CH⁺ was set to 0.00, and s_f for the leaving group/solvent combination chloride/ethanol was set to 1.00.

$$\Sigma \Delta^2 = \Sigma (\log k_s - \log k_{\text{calcd.}})^2 = \Sigma [\log k_s - s_f(N_f + E_f)]^2 \quad (3)$$

Minimization of the deviation between calculated and experimental rate constants, i.e., $\Sigma \Delta^2$ as defined by Equation (3), yielded the electrofugality parameters for the benzhydrylium ions **1**⁺–**4**⁺ (Table 4) and the nucleofuge-specific parameters N_f/s_f for OTs, OMs, and Br in solvents of high ionizing power (Table 5).

Table 4. Electrofugality (E_f) parameters of fluoro-substituted benzhydryl cations.

Benzhydryl cation	Substituents	E_f
1	3-fluoro	-7.53
2	3,3'-difluoro	-9.25
3	3,3',5-trifluoro	-10.88
4	3,3',5,5'-tetrafluoro	-12.60

Table 5. Nucleofugality parameters N_f/s_f for leaving groups X in various solvents.

Solvent	X = OTs	OMs	Br
TFE	9.73/0.94 ^[a]	9.84/1.00 ^[b]	6.19/0.95 ^[a]
60AN40W	7.97/0.82	7.69/0.83	5.23/0.99
80E20W	7.44/0.80 ^[a]	7.48/0.82	4.36/0.95 ^[a]
100M	7.33/0.82	—	4.23/0.99 ^[a]
100E	6.08/0.78 ^[a]	5.81/0.80	[c]
80A20W	5.99/0.83 ^[a]	5.85/0.84	[c]
90A10W	5.38/0.89 ^[a]	—	[c]

[a] These parameters revise previously published values from ref.^[3a]
 [b] Solvolysis data not included into the total correlation as only two rate constants were available for this leaving group/solvent system. [c] See ref.^[3a]

Figure 1 illustrates the high quality of these correlations for benzhydryl bromides (a), tosylates (b) and mesylates (c).

Some of the nucleofuge-specific parameters N_f/s_f in Table 5 have previously been reported. The small deviation of the new parameters, which are based on a larger set of experimental data, confirms the solidity of the previously reported set of nucleofugality parameters.^[3a,3b] From the electrofugality parameters in Table 4 and the nucleofugality parameters for Cl⁻ in MeOH ($N_f = 2.95$, $s_f = 0.98$)^[3a] and EtOH ($N_f = 1.87$, $s_f = 1.00$)^[3a] one can calculate the methanolysis rate constant for **1-Cl** ($3.18 \times 10^{-5} \text{ s}^{-1}$) and the ethanolysis rate constant for **1-Cl** ($2.14 \times 10^{-6} \text{ s}^{-1}$), which agree

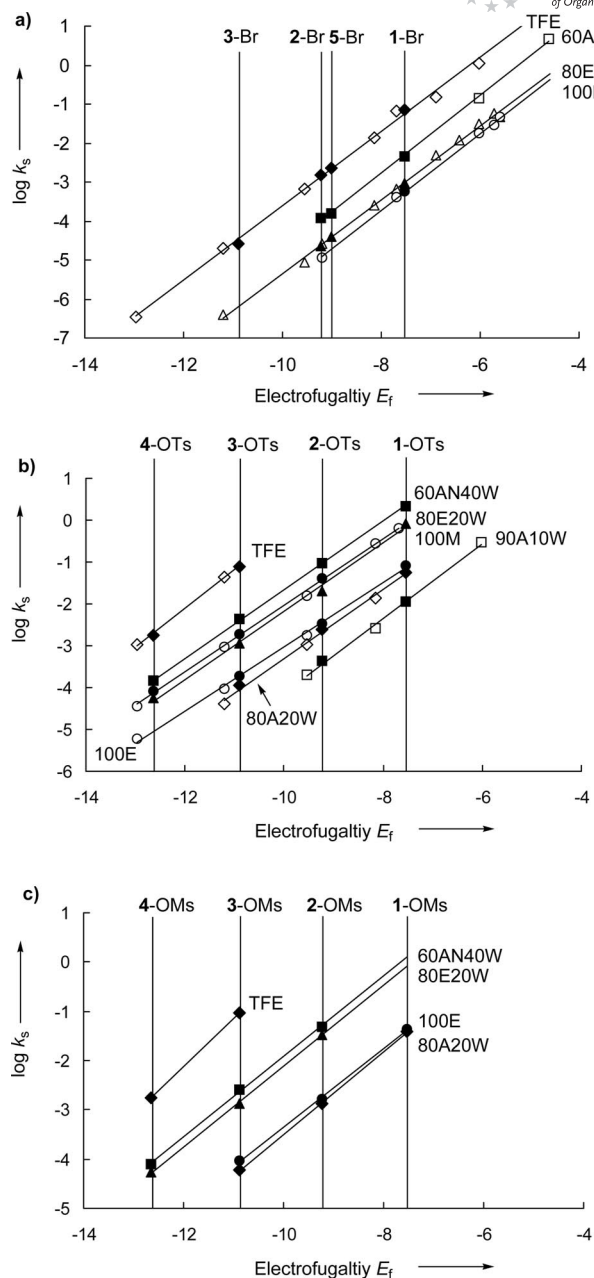


Figure 1. Plot of $\log k_s$ for the solvolysis reaction of various substituted benzhydryl derivatives vs. electrofugality E_f : (a) bromides, (b) tosylates, (c) mesylates. Data points with filling were taken from Table 2, data points without filling were taken from previously published data.^[3a,3b] Mixtures of solvents are given as (v/v); solvents: A = acetone, AN = MeCN, E = ethanol, M = methanol, TFE = 2,2,2-trifluoroethanol, W = water.

nicely with the experimental values of $2.97 \times 10^{-5} \text{ s}^{-1}$ and $1.74 \times 10^{-6} \text{ s}^{-1}$, respectively, reported by Nishida.^[10b] The closely similar nucleofugalities of TsO and MsO in different solvents is in line with the previously reported similar magnitude of the leaving-group abilities of these two sulfonate groups.^[7] The slightly lower nucleofugality of mesylate can be explained by the better delocalization of negative charge by tosylate. Depending on the solvent, the nucleofugality of bromide is 2.5–3.8 orders of magnitude smaller than that of TsO or MsO.

In line with the similar magnitude of Hammett's σ_m constants for Cl (0.37) and F (0.34),^[11] the *m*-fluoro-substituted benzhydrylium ions **1**⁺–**4**⁺ have similar electrofugalities as the corresponding chloro-substituted benzhydrylium ions.^[3a] Remarkable is the almost constant increment of -1.7 per *m*-F substituent on the electrofugality E_f of the benzhydrylium ions (Table 4). In accord with this observation, Figure 2 shows a linear correlation between E_f and $\Sigma\sigma$ with a slope of -4.91 , which corresponds to Hammett ρ values from -4.06 to -5.08 for reaction series with $0.78 < s_f < 0.99$ (Table 5). From the three different rate constants for the reaction of **5**-Br in TFE, 60AN40W and 80E20W an electrofugality of $E_f = -9.00$ was calculated. The almost identical E_f values of the symmetrical (**2**) and unsymmetrical difluoro-substituted system (**5**) also illustrates the additivity of substituent effects. This behavior contrasts that of donor substituents, where a levelling effect is observed,^[10e,12] i.e., the second electron-donor group has generally a smaller cation-stabilizing effect than the first donor group. From the observation that replacement of one H by F has a similar effect in the comparison **3**⁺ \rightarrow **4**⁺ as in the comparison $\text{Ph}_2\text{CH}^+ \rightarrow \text{1}^+$ one may conclude that nonadditivity of substituent effects in benzhydrylium systems is specific for substituents with +M effects.^[10] The unsymmetrical difluoro-substituted system **5**, which exhibits a similar reactivity as the symmetrical difluoro-substituted system **2**, was not included into the series of reference electrofuges.

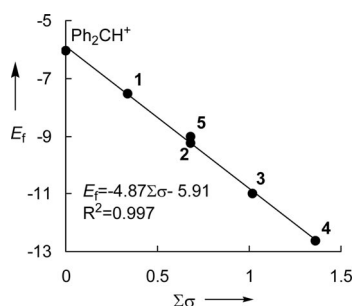


Figure 2. Correlation of the electrofugality parameters E_f of benzhydrylium ions (Table 4) with Hammett σ constants (from ref.^[11]).

Conclusions

The solvolyses of the fluoro-substituted benzhydryl bromides, tosylates and mesylates (**1**–**5**)-X in various aqueous and alcoholic solutions follow first-order kinetics with rate-determining ionization and no common-ion return.^[8] All rate constants follow the correlation $\log k_s = s_f(N_f + E_f)$ [Equation (2)], which confirms previously reported nucleofugality parameters N_f , s_f for bromide and tosylate in various solvents and allows to determine nucleofugalities for mesylate as well as electrofugalities E_f of the fluoro-substituted benzhydrylium ions **1**⁺–**5**⁺. The fluorine effects are roughly additive, and the solvolysis rates are retarded by a factor of 18 to 59 per *m*-fluorine. Because the E_f values of **1**⁺–**4**⁺ (Table 4) are similar to those of the corresponding chloro-substituted benzhydrylium ions,^[3a] the fluoro-substi-

tuted benzhydryl cations **1**⁺–**4**⁺ are suggested to replace the skin-irritating chloro-substituted analogues as references in the high electrophilicity and low electrofugality range for quantifying weak nucleophiles and strong nucleofuges, respectively.

Experimental Section

Benzhydryl Derivatives: Syntheses and characterization of the substrates (**1**–**5**)-X are described in the Supporting Information.

Kinetics: Hydrolysis or alcoholysis of the benzhydryl derivatives (**1**–**5**)-X with X = Cl, Br, OM, OTs led to the formation of the benzhydrols [(**1**–**5**)-OH] or benzhydryl ethers (**1**–**5**-OR) along with the strong acids HX. The generation of HX resulted in an increase of conductivity. Calibration experiments for two representative systems showed that the initial concentration of benzhydryl bromide or tosylate correlates linearly with the final conductance, in agreement with previous results. Therefore, the solvolysis rate constants can be determined reliably by conductimetry. Most reactions were monitored with a conventional conductimeter. The temperature of the solutions during all kinetic studies was kept constant at 25.0 °C (± 0.1 °C) by using a circulating bath thermostat. Fast solvolysis reactions, e.g., solvolysis of **1**-OTs in 80% aqueous acetone, have been measured in a stopped-flow conductometer by mixing 1 equiv. of the benzhydryl derivative in acetone or MeCN with 10 equiv. of aq. acetone or MeCN to give solvent mixtures of the desired composition. Details of the kinetic measurements are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Preparative procedures, product characterization, details of the kinetic experiments.

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