Nucleofugality of pentafluorophenolate in various solvents: solvolytic behavior of phenolates

Matić, Mirela; Bebek, Nives; Denegri, Bernard; Kronja, Olga

Source / Izvornik: **Croatica Chemica Acta, 2016, 89, 355 - 362**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.5562/cca3040

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:163:523575

Rights / Prava: In copyright / Zaštićeno autorskim pravom.

Download date / Datum preuzimanja: **2024-12-04**

Repository / Repozitorij:

Repository of Faculty of Pharmacy and Biochemistry University of Zagreb

DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

ORIGINAL SCIENTIFIC PAPER

CROATICA CHEMICA ACTA

Croat. Chem. Acta **2016**, *89*(3), 355–362

Published online: January 4, 2016

DOI: 10.5562/cca3040

HKD 1926

Nucleofugality of Pentafluorophenolate in Various Solvents: Solvolytic Behavior of Phenolates

Mirela Matić, Nives Bebek, Bernard Denegri,* Olga Kronja**

University of Zagreb, Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, HR-10000 Zagreb, Croatia
* Corresponding author's e-mail address: bdenegri@pharma.hr
** Corresponding author's e-mail address: okronja@pharma.hr

RECEIVED: November 29, 2016 ★ REVISED: December 7, 2016 ★ ACCEPTED: December 12, 2016

Abstract: The leaving group ability (nucleofugality) of the pentafluorophenolate anion has been determined from first order solvolytic rate constants (k) of X,Y-substituted benzhydryl pentafluorophenolates measured in a series of solvents, by using the three parameter LFER equation: log $k = s_f (E_f + N_f)$. Comparison with other leaving groups reveals that pentafluorophenolate is a moderate leaving group, whose nucleofugality (N_f value) is between the nucleofugalities of phenyl carbonate and 3,5-dinitrobenzoate leaving groups. However, due to its high reaction constant (s_f = 1.29 in 80 % aq. ethanol), relative reactivities of benzhydryl pentafluorophenolates and corresponding benzhydryl carboxylates vary with the electrofugality of a carbocation formed in the heterolytic step, *i.e.*, inversion of the reactivity of benzhydryl series with different leaving groups occurs. The plots of $\Delta^{\ddagger}G°$ *vs.* $\Delta_r G°$ for solvolysis of benzhydryl phenolates and carboxylates reveal that phenolates solvolyze over the lower Marcus intrinsic barrier than corresponding carboxylates.

Keywords: nucleofugality, leaving group, LFER, phenolate, intrinsic barrier, solvolysis.

INTRODUCTION

THE reactivity of leaving groups (nucleofugality) has a crucial influence on the rate of the heterolytic bond cleavage, which is the slow step of numerous organic reactions. Consequently, this topic is well-represented in most general textbooks on organic chemistry as well as of mechanistically oriented textbooks.[1] For comparing the reactivities of various leaving groups, their abilities are, by a general qualitative rule of thumb, arranged in the same order as the acidities of their conjugate Brönsted acids. The basic shortcoming of such approach is that the variability of the intrinsic barriers in heterolysis of substrates with different types of leaving groups is neglected.[2,3] Furthermore, such comparison does not have any practical application as the reactivity of leaving groups is not quantified.

In order to develop a comprehensive leaving group ability scale, which would be limited by using a single type of substrate,[4] an electrofugality scale based on 39 benzhydrylium carbocations that covers 18 orders of magnitude in reactivity has been established.[5] Employing that scale and Equation (1), which represents LFER, abilities of structurally diverse leaving groups have been determined in the range of 12 orders of magnitude in a particular solvent.[3–7] In this equation, the contributions of an electrofuge (alkyl/aryl part of a substrate that in heterolytic process gives carbocation) and a nucleofuge to the overall solvolytic reactivity of a substrate are separated. This approach enables the main practical application of the scales, the estimation of reactivities of substrates constituted from any combination of an electrofuge and a nucleofuge in a given solvent at 25 °C.[5]

$$\log k\ (25\ °\mathrm{C}) = s_f (E_f + N_f) \qquad (1)$$

Parameters in Equation (1) are: the solvolytic rate constant of a substrate at 25 °C (k), the nucleofuge-specific parameters N_f (nucleofugality; the negative intercept on the abscissa of the log k *vs.* E_f correlation line) and s_f (the slope of the correlation line), and the electrofugality parameter E_f (the independent variable that quantifies the solvolytic reactivity of a certain electrofuge).[5] The nucleofuge-specific parameters for the certain combination of a leaving group and a solvent can be determined from the log k *vs.* E_f correlation line using solvolytic rate constants in a given solvent of a series of benzhydrylium derivatives and the reference E_f values.[3–7]

This work is licensed under a Creative Commons Attribution 4.0 International License.

In this LFER model, influences of solvation effects are associated to nucleofugality only, defined by two nucleofuge-specific parameters (N_f and s_f), which specify the reactivity of some leaving group in a given solvent.[5] In fact, the N_f parameter determines the basic reactivity of the certain leaving group/solvent combination, while the reaction constant (s_f parameter) varies within a limited range and slightly decreases as reactivity of leaving groups increases.[7]

In our previous study, we have investigated the solvolytic behavior of the series of benzhydryl 2,4-dinitrophenolates and observed that the log k/E_f lines that belong to 2,4-dinitrophenolate and phenyl carbonate are approaching each other as electrofugality decreases, and, finally intersect after a short extrapolation in experimental region of reactivity.[3] This means that the relative reactivities of some pair of leaving groups depend on electrofuges, and more importantly, that inversion of their reactivities can occur. This case additionally demonstrate flaws in determining relative reactivities of leaving groups based on the rate constants for substrates with a common electrofuge. In this study we have examined the solvolytic behavior and nucleofugality of another phenolate leaving group, pentafluorophenolate, and compared the results with the ones obtained previously for carboxylates,[7a] in order to examine the inversion of relative reactivities of leaving groups with variation of the electrofuges and also to rationalize such phenomena.

EXPERIMENTAL

Substrate Preparation

4,4'-Dimethylbenzhydrol, 4-Methoxybenzhydrol, 4,4'-Dimethoxybenzhydrol were prepared by reduction of the commercially available substituted benzophenones with sodium borohydride in methanol.

4-Methoxy-4'-methylbenzhydrol and 4-Methoxy-4'-phenoxybenzhydrol were prepared according to the procedure given in Ref. [8].

The substrates were prepared from the corresponding benzhydrols according to the substantially modified procedure for the preparation of other phenolates given in Refs. [3] and [9].

4,4'-Dimethylbenzhydryl Pentafluorophenyl Ether. Freshly cut potassium (0.15 g; 3.8 mmol) was added to the previously prepared stirring solution of hexafluorobenzene (0.70 g, 3.8 mmol) in anhydrous tetrahydrofurane (15 ml), and the solution was stirred at 60 °C for few minutes under an atmosphere of argon. The solution of 4,4'-dimethylbenzhydrol (0.80 g, 3.8 mmol) in tetrahydrofurane (10 ml) was then added dropwise with vigorously stirring, and the reaction mixture was heated further for 1.5 h. A brown precipitate was filtered off, excess of potassium was removed, and then 15 ml of benzene was added in the solution. After that, the organic layer was washed with water (3 × 15 ml) and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was then left in a freezer with 10 ml of hexane for 12 h. After removal of white crystals, 0.30 g of pale-yellow oil was obtained (49.0 %); ^{1}H NMR (400 MHz, CDCl$_3$, 20 °C): δ/ppm = 2.32 (s, 6H; Ar–CH$_3$), 6.31 (s, 1H; Ar$_2$CH), 7.13 (d, J = 7.9 Hz, 4H; ArH), 7.29 (d, J = 8.1 Hz, 4H; ArH); ^{13}C NMR (150 MHz, CDCl$_3$, 20 °C): δ/ppm = 21.2 (Ar–CH$_3$), 87.0 (Ar$_2$CH), 127.1, 129.2, 136.7, 138.3 (Ar); ^{19}F NMR (282 MHz, CDCl$_3$, 20 °C): δ/ppm = −154.2 (d, J_FF = 25.4 Hz, 2F; F$_5$Ar), −163.0 (t, J_FF = 44.1 Hz, 1F; F$_5$Ar), −163.6 (t, J_FF = 40.1 Hz, 2F; F$_5$Ar).

4-Methoxybenzhydryl Pentafluorophenyl Ether. It was prepared as pale-yellow oil, according to the procedure described for 4,4'-dimethylbenzhydryl pentafluorophenyl ether, from 4-methoxybenzhydrol (1.0 g; 4.6 mmol), potassium (0.17 g; 4.6 mmol), and hexafluorobenzene (0.87 g; 4.7 mmol); yield 0.98 g, 54.7 %; ^{1}H NMR (300 MHz, CDCl$_3$, 20 °C): δ/ppm = 3.74 (s, 3H; Ar–OCH$_3$), 6.30 (s, 1H; Ar$_2$CH), 6.81 (d, J = 8.8 Hz, 2H; ArH), 7.26–7.41 (m, 7H; ArH); ^{13}C NMR (150 MHz, CDCl$_3$, 20 °C): δ/ppm = 52.4 (Ar–OCH$_3$), 84.1 (Ar$_2$CH), 111.0, 124.2, 125.5, 125.7, 126.1, 128.6, 137.0, 140.9, 157.0 (Ar). ^{19}F NMR (282 MHz, CDCl$_3$, 20 °C): δ/ppm = –157.3 (d, J_FF = 21.2 Hz, 2F; F$_5$Ar), −165.9 (t, J_FF = 41.8 Hz, 1F; F$_5$Ar), –166.7 (t, J_FF = 45.4 Hz, 2F; F$_5$Ar).

4-Methoxy-4'-Methylbenzhydryl Pentafluorophenyl Ether. It was prepared as pale-yellow oil, also according to the procedure previously described, from 4-methoxy-4'-methylbenzhydrol (1.0 g; 4.4 mmol), potassium (0.17 g; 4.4 mmol), and hexafluorobenzene (0.82 g; 4.4 mmol); yield 0.85 g, 48.9 %; ^{1}H NMR (300 MHz, CDCl$_3$, 20 °C): δ/ppm = 2.32 (s, 3H; Ar–CH$_3$), 3.77 (s, 3H; Ar–OCH$_3$), 6.30 (s, 1H; Ar$_2$CH), 6.85 (d, J = 8.7 Hz, 2H; ArH), 7.13–7.32 (m, 7H; ArH); ^{13}C NMR (150 MHz, CDCl$_3$, 20 °C): δ/ppm = 21.2 (Ar–CH$_3$), 55.2 (Ar–OCH$_3$), 86.9 (Ar$_2$CH), 113.8, 126.4, 127.0, 128.7, 129.2, 131.7, 136.8, 138.2, 159.7 (Ar); ^{19}F NMR (282 MHz, CDCl$_3$, 20 °C): δ/ppm = −154.4 (d, J_FF = 20.6 Hz, 2F; F$_5$Ar), −163.2 (t, J_FF = 43.6 Hz, 1F; F$_5$Ar), −163.8 (t, J_FF = 40.3 Hz, 2F; F$_5$Ar).

4-Methoxy-4'-Phenoxybenzhydryl Pentafluorophenyl Ether. This compound was prepared according to the procedure previously described, from 4-methoxy-4'-phenoxybenzhydrol (0.80 g; 2.6 mmol), potassium (0.10 g; 2.6 mmol), and hexafluorobenzene (0.49 g; 2.6 mmol); yield 0.61 g, 51.3 %; ^{1}H NMR (300 MHz, CDCl$_3$, 20 °C): δ/ppm = 3.78 (s, 3H; Ar–OCH$_3$), 6.21 (s, 1H; Ar$_2$CH), 6.82–7.35 (m, 13H; ArH); ^{13}C NMR (150 MHz, CDCl$_3$, 20 °C): δ/ppm = 55.2 (Ar–OCH$_3$), 86.3 (Ar$_2$CH), 100.0, 113.7, 118.4, 119.1, 123.5, 128.7, 128.8, 129.8, 131.6, 134.6, 134.7, 156.8, 157.3, 159.6 (Ar); ^{19}F NMR (282 MHz, CDCl$_3$, 20 °C): δ/ppm = −154.4 (d, J_FF = 20.6 Hz, 2F; F$_5$Ar), −162.8 (t, J_FF = 44.0 Hz, 1F; F$_5$Ar), −163.6 (t, J_FF = 43.6 Hz, 2F; F$_5$Ar).

4,4'-Dimethoxybenzhydryl Pentafluorophenyl Ether. Freshly cut potassium (0.16 g; 4.1 mmol) was added to the previously prepared stirring solution of the 4,4'-dimethoxybenzhydrol (1.0 g, 4.1 mmol) in anhydrous tetrahydrofurane (15 ml), and the solution was heated 5 hours under an atmosphere of argon. After that, excess of the potassium was removed and the solution of hexafluorobenzene (0.76 g, 4.1 mmol) in tetrahydrofurane (10 ml) was added dropwise with vigorously stirring, and the reaction mixture was heated further for 30 min. A brown precipitate was filtered off and then 15 ml of benzene was added in the solution. The organic layer was then washed with water (3 × 15 ml) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue was then left in a freezer with 10 ml of hexane for 12 h. After removal of white crystals, 0.90 g of pale-yellow oil was obtained (49.0 %); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ/ppm = 3.79 (s, 6H; Ar–OCH_3), 6.29 (s, 1H; Ar_2CH), 6.86 (d, J = 8.8 Hz, 4H; ArH), 7.32 (d, J = 8.7 Hz, 4H; ArH); ^{13}C NMR (150 MHz, $CDCl_3$, 20 °C): δ/ppm = 55.4 ($ArOCH_3$), 86.8 (Ar_2CH), 114.0, 128.8, 131.9, 159.8 (Ar); ^{19}F NMR (282 MHz, $CDCl_3$, 20 °C): δ/ppm = −154.4 (d, J_{FF} = 25.4 Hz, 2F; F_5Ar), −163.1 (t, J_{FF} = 44.1 Hz, 1F; F_5Ar), −163.8 (t, J_{FF} = 40.1 Hz, 2F; F_5Ar).

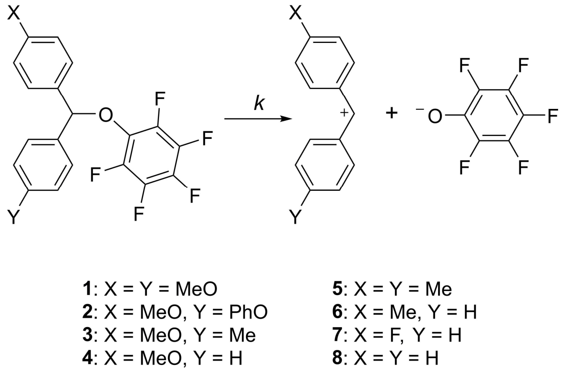
Kinetic Methods

Solvolysis rate constants were measured conductometrically. Freshly prepared solvents (30 mL) were thermostated (± 0.1 °C) at a given temperature for several minutes prior to addition of a substrate. 20–40 mg of a substrate was dissolved in 0.10 mL of dichloromethane and injected into a solvent. An increase of the conductivity during solvolysis was monitored automatically by means of the WTW LF 530 conductometer, using the Radiometer 2-pole Conductivity Cell (CDC641T). Individual rate constants were obtained by least-squares fitting of the conductivity data to the first-order kinetic equation for 3–4 half-lives. The rate constants were averaged from at least three measurements. In order to achieve a complete ionization of a liberated acid, the proton sponge base [1,8-bis(dimethylamino) naphthalene] was added. The typical molar ratio between the base and a substrate was between 3.0 and 40.

RESULTS AND DISCUSSION

Nucleofugality of Pentafluorophenolate

A series of benzhydryl pentafluorophenolates (**1**-PFPh–**5**-PFPh), which were prepared from corresponding benzhydrols, were subjected to solvolysis in pure ethanol, aqueous 90 %, 80 %, 70 % ethanol, aqueous 90 %, 80%, 70 %, 60 % acetone, and 60 % aqueous acetonitrile. The solvolysis rates were measured conductometrically at 25 °C (details are given in Kinetic methods). In a few cases the rates were measured at three different temperatures and extrapolated to 25 °C. First-order rate constants (measured and extrapolated) are presented in Table 1.



Scheme 1. Solvolysis of X,Y-substituted benzhydryl pentafluorophenolates.

The logarithms of first-order rate constants in the given solvents were plotted against E_f, taken from the established electrofugality scale for benzhydryls,[5] and nucleofugality parameters for pentafluorophenolate in the all mentioned solvents were determined (N_f is the negative intercept on the abscissa, whereas s_f is the slope of the plot). For the sake of clarity, only some of the plots are presented in Figure 1. However, all N_f and s_f values obtained along with corresponding standard errors and correlation coefficients, which confirm the high quality of the plots, are shown in Table 2.

The nucleofugalities obtained can be utilized for estimating the reactivities of pentafluorophenolates with different electrofuges according to Equation (1).[5,10] Furthermore, nucleofugality of pentafluorophenolate can now be compared with nucleofugalities of a large number of other leaving groups, as it is presented in Figure 2. By analyzing the N_f values presented in Figure 2, the shortcomings in using pK_a values for qualitative predicting the reactivities of leaving groups can clearly be established. For instance, despite the lower acidity of *p*-toluenesulfonic acid than hydrochloric or hydrobromic acid, tosylate is noticeably better leaving group than both bromide and chloride.[5] Furthermore, 2,4-dinitrophenolate[3] and pentafluorophenolate leaving groups are in a middle of the scales despite the highest pK_a values of their conjugate acids in the series presented.

Another outstanding feature of the PFPh leaving group is that it produces the highest s_f value in the series (parentheses in Figure 2). Therefore, expectedly, its log k/E_f correlation line intersects the lines of other leaving groups that are close enough in nucleofugality. Figure 3 demonstrates such intersections in the region of kinetic

Table 1. Solvolysis Rate Constants of X,Y-substituted Benzhydryl Pentafluorophenolates in Various Solvents at 25 °C

Solvent (a)	Substrate (X, Y)	E_f (b)	k/s^{-1} (c)
100E	**1** (4-OMe, 4'-OMe)	0.00	$(3.47 \pm 0.02) \times 10^{-3}$
	2 (4-OMe, 4'-OPh)	−0.86	$(2.89 \pm 0.02) \times 10^{-4}$
	3 (4-OMe, 4'-Me)	−1.32	$(5.24 \pm 0.03) \times 10^{-5}$
	4 (4-OMe, H)	−2.09	5.41×10^{-6} (d,e)
90E10W	**1** (4-OMe, 4'-OMe)	0.00	$(2.24 \pm 0.06) \times 10^{-2}$
	2 (4-OMe, 4'-OPh)	−0.86	$(1.88 \pm 0.02) \times 10^{-3}$
	3 (4-OMe, 4'-Me)	−1.32	$(3.65 \pm 0.06) \times 10^{-4}$
	4 (4-OMe, H)	−2.09	$(4.01 \pm 0.04) \times 10^{-5}$
80E20W	**1** (4-OMe, 4'-OMe)	0.00	$(5.44 \pm 0.01) \times 10^{-2}$
	2 (4-OMe, 4'-OPh)	−0.86	$(4.92 \pm 0.09) \times 10^{-3}$
	3 (4-OMe, 4'-Me)	−1.32	$(1.08 \pm 0.01) \times 10^{-3}$
	4 (4-OMe, H)	−2.09	$(1.15 \pm 0.02) \times 10^{-4}$
70E30W	**2** (4-OMe, 4'-OPh)	−0.86	$(7.42 \pm 0.10) \times 10^{-3}$
	3 (4-OMe, 4'-Me)	−1.32	$(2.19 \pm 0.04) \times 10^{-3}$
	4 (4-OMe, H)	−2.09	$(2.49 \pm 0.05) \times 10^{-4}$
90A10W	**1** (4-OMe, 4'-OMe)	0.00	$(8.91 \pm 0.11) \times 10^{-4}$
	2 (4-OMe, 4'-OPh)	−0.86	$(6.05 \pm 0.03) \times 10^{-5}$
	3 (4-OMe, 4'-Me)	−1.32	1.52×10^{-5} (d,f)
80A20W	**1** (4-OMe, 4'-OMe)	0.00	$(5.78 \pm 0.09) \times 10^{-3}$
	2 (4-OMe, 4'-OPh)	−0.86	$(4.22 \pm 0.04) \times 10^{-4}$
	3 (4-OMe, 4'-Me)	−1.32	$(9.76 \pm 0.07) \times 10^{-5}$
	4 (4-OMe, H)	−2.09	9.13×10^{-6} (d,g)
70A30W	**1** (4-OMe, 4'-OMe)	0.00	$(1.74 \pm 0.02) \times 10^{-2}$
	2 (4-OMe, 4'-OPh)	−0.86	$(1.38 \pm 0.03) \times 10^{-3}$
	3 (4-OMe, 4'-Me)	−1.32	$(3.45 \pm 0.08) \times 10^{-4}$
	4 (4-OMe, H)	−2.09	$(4.08 \pm 0.02) \times 10^{-5}$
60A40W	**1** (4-OMe, 4'-OMe)	0.00	$(4.44 \pm 0.07) \times 10^{-2}$
	2 (4-OMe, 4'-OPh)	−0.86	$(4.10 \pm 0.07) \times 10^{-3}$
	3 (4-OMe, 4'-Me)	−1.32	$(1.12 \pm 0.02) \times 10^{-3}$
	4 (4-OMe, H)	−2.09	$(1.30 \pm 0.04) \times 10^{-4}$
60AN40W	**2** (4-OMe, 4'-OPh)	−0.86	$(9.82 \pm 0.14) \times 10^{-3}$
	3 (4-OMe, 4'-Me)	−1.32	$(2.43 \pm 0.09) \times 10^{-3}$
	4 (4-OMe, H)	−2.09	$(2.50 \pm 0.07) \times 10^{-4}$
	5 (4-Me, 4'-Me)	−3.44	3.46×10^{-6} (d,h)

(a) Binary solvents are *v*/*v* at 25 °C. A = acetone, AN = acetonitrile, E = ethanol, W = water.

(b) Electrofugality parameters are taken from Ref. [5].

(c) Average rate constants from at least three runs at 25 °C. Errors shown are standard deviations.

(d) Extrapolated from data at higher temperatures by using the Eyring equation.

(e) $\Delta^{\ddagger}H° = 87.1 \pm 1.7$ kJ mol^{-1}, $\Delta^{\ddagger}S° = -53.7 \pm 5.0$ J K^{-1} mol^{-1}.

(f) $\Delta^{\ddagger}H° = 78.9 \pm 1.1$ kJ mol^{-1}, $\Delta^{\ddagger}S° = -72.5 \pm 3.4$ J K^{-1} mol^{-1}.

(g) $\Delta^{\ddagger}H° = 86.6 \pm 1.1$ kJ mol^{-1}, $\Delta^{\ddagger}S° = -51.0 \pm 3.5$ J K^{-1} mol^{-1}.

(h) $\Delta^{\ddagger}H° = 109.0 \pm 5.6$ kJ mol^{-1}, $\Delta^{\ddagger}S° = 16.3 \pm 1.7$ J K^{-1} mol^{-1}.

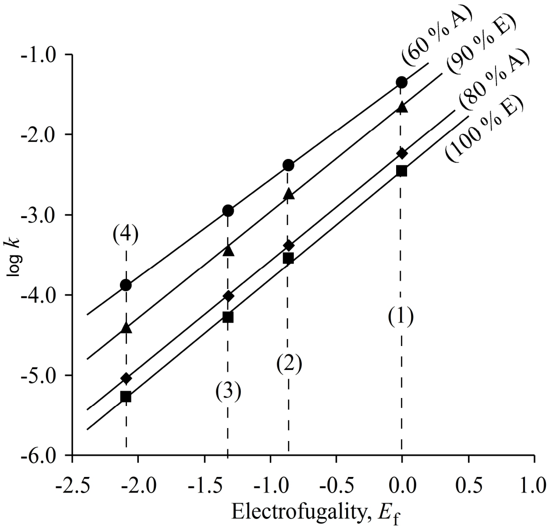


Figure 1. Plots of log *k* (25 °C) *vs.* E_f for solvolysis of substituted benzhydryl pentafluorophenolates in ethanol (E) and aqueous ethanol (E) and acetone (A).

Table 2. Nucleofugality parameters N_f and s_f for pentafluorophenolate in various solvents

Solvent (a)	N_f (b)	s_f (b)	R (c)
70E30W	-0.91 ± 0.04	1.20 ± 0.02	1.0000
80E20W	-0.97 ± 0.04	1.29 ± 0.02	0.9995
90E10W	-1.23 ± 0.06	1.33 ± 0.03	0.9995
100E	-1.79 ± 0.09	1.36 ± 0.04	0.9990
60A40W	-1.12 ± 0.01	1.21 ± 0.01	1.0000
70A30W	-1.40 ± 0.03	1.26 ± 0.02	1.0000
80A20W	-1.66 ± 0.01	1.34 ± 0.01	1.0000
90A10W	-2.28 ± 0.03	1.34 ± 0.01	1.0000
60AN40W	-0.63 ± 0.03	1.34 ± 0.02	1.0000

(a) Binary solvents (*v*/*v*) at 25 °C.
A = acetone, AN = acetonitrile, E = ethanol, W = water.

(b) Errors shown are standard errors.

(c) Correlation coefficient.

measurements, indicating that for numerous pairs of nucleofuges, relative reactivities can vary with variation of the electrofuges. Such behavior is not surprising when comparing electrofuges with various steric demands adjacent to the carbocation center,[11] but it is quite unexpected with the benzhydryl series, since only electronic effects determine their relative reactivities in a certain solvent. Figure 3 further demonstrates the intersection of the line for dinitrophenolate (DNPh)[3] with the line for dichloroacetate (DClAc)[7a] after a short extrapolation. The same has been observed for pentafluorobenzoate (PFB),[6a] but that line is not shown in Figure 3 as it completely overlaps with the line for DClAc. Accordingly, beside the basic application of Equation (1) to estimate solvolytic reactivities of various substrates,[5] the model can also be used for predicting variations of relative reactivities of leaving groups with electrofugality.

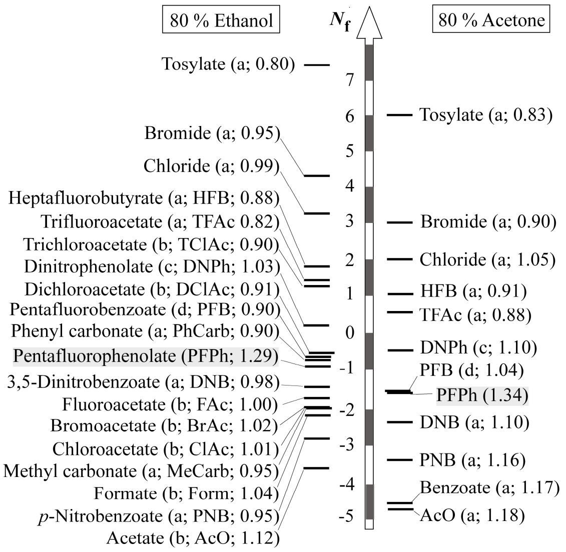


Figure 2. Pentafluorophenolate leaving group in the nucleofugality scale for 80 % aqueous ethanol and 80 % aqueous acetone. Nucleofuge-specific slope parameters are given in parentheses. Data for a, b, c and d are taken from Refs. [5], [7a], [3], and [6a], respectively.

Influences of Intrinsic Barriers on Relative Reactivities

In order to investigate the effect of an electrofuge on solvolytic behavior, we correlated in Figure 4 activation free energies for solvolysis of 4,4'-dimethoxybenzhydryl carboxylates (X = Y = MeO) and phenolates in 80 % ethanol with activation free energies for solvolysis of corresponding benzhydryl carboxylates (X = Y = H) and phenolates. The 4,4'-dimethoxybenzhydrylium cation is by six orders of magnitude a more reactive electrofuge than the benzhydrylium cation ($E_f = 0$ *vs.* $E_f = -6.03$).[5]

A very good linear plot is obtained for carboxylates, whereas the two phenolates deviate substantially. To analyze this correlation, reversible reactions must be taken into consideration. Unfortunately, nucleophilicities of the given anions in 80 % ethanol have not been determined, but it is known that the differences in reactivities between the best nucleophile in the series, the acetate anion, and the chloride anion are within an order of magnitude in acetonitrile, aqueous acetonitrile and acetone.[12] Therefore, the combination rates of other less nucleophilic carboxylate anions with carbocations are expected to be close to the rates of chloride or lower. As the chloride anion in 80 % ethanol recombines with the 4,4'-dimethoxybenzhydrylium cation ($E = 0.00$)[13] *via* a barrier,[12a] it can be presumed that all the carboxylate anions in the series recombine with this carbocation *via* barrier as well (Scheme 2a).

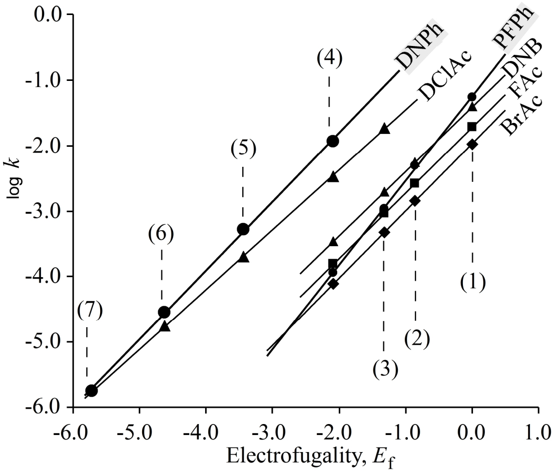


Figure 3. Plots of log k (25 °C) *vs.* E_f for solvolysis of substituted benzhydryl phenolates (PFPh and DNPh[3]) and carboxylates (DNB[5], FAc[7a] and BrAc[7a]) in 80 % ethanol (*v*/*v*).

It is not possible to predict exactly which of the given carboxylates recombine with the six orders of magnitude more reactive benzhydrylium cation ($E = 5.90$)[13] without a barrier, but a fair estimation can be done. If acetate reacts with 3.5 orders of magnitude more reactive 4,4'-dimethylbenzhydrylium cation ($E = 3.63$) without a barrier (diffusion controlled process),[13] as the chloride anion does,[12a] then, based on nucleophilicities in acetonitrile,[12b] it can be presumed that 3,5-dinitrobenzoate and more reactive anions (Figure 4a) recombine with the benzhydrylium cation without a barrier. Accordingly, most of the substrates (higher activation free energies given on the abscissa in Figure 4a), with exception of the fastest ones, undoubtedly solvolyze without a barrier according to the principle of microscopic reversibility (Scheme 2b).[5] Activation free energies for those substrates correspond to their heterolytic free energies.[5] This assumption is supported with the slope of the correlation line in Figure 4a which reveals a noticeably stronger ion-pair character of transition states for solvolysis of benzhydryl carboxylates than of those for solvolysis of 4,4'-dimethoxybenzhydryl carboxylates. Consequently, the range of solvolysis activation free energies in the case of the weaker benzhydrylium electrofuge is closer to the range of Lewis basicity of the given series of carboxylates, *i.e.* better describes the relative stabilities of the anions than the range of reactivities when the 4,4'-dimethoxybenzhydrylium electrofuge is employed.

Due to the barrierless reverse combination reaction of most carboxylates with the benzhydrylium electrofuge, the slope of the correlation plot presented in

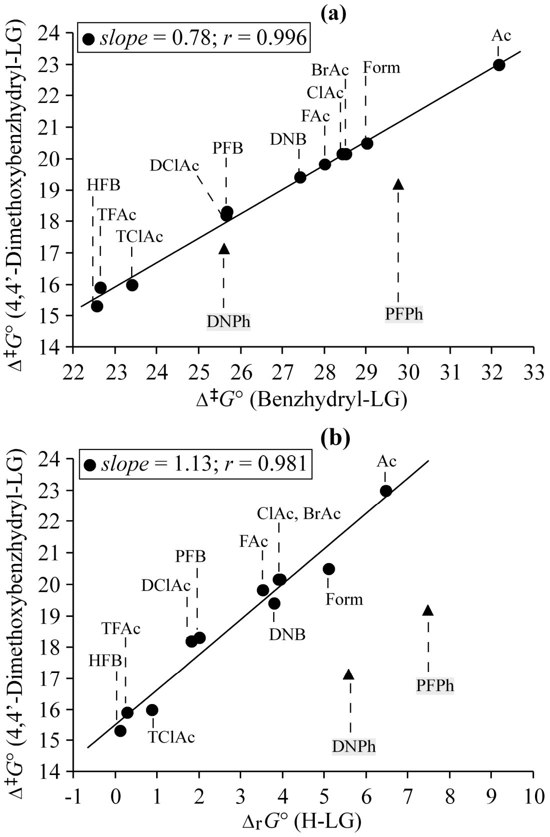
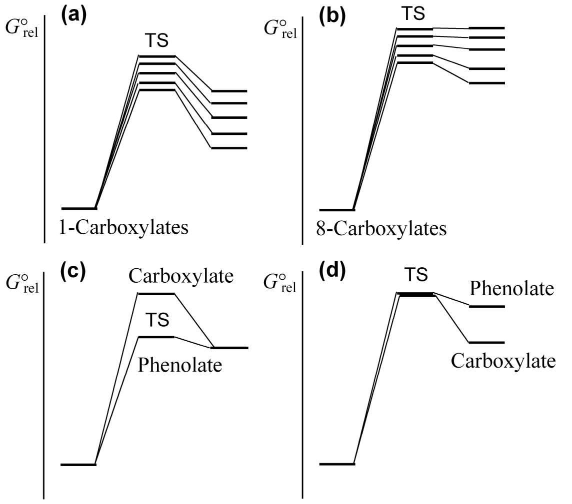


Figure 4. Correlation of activation free energies (in kcal mol^{-1}) for solvolysis of 4,4'-dimethoxybenzhydryl carboxylates and phenolates in 80 % ethanol at 25 °C against activation free energies for solvolysis of corresponding benzhydryl carboxylates and phenolates (a), and standard free energies for heterolysis of corresponding carboxylic acids and phenols in water (b). Values of free energies and references for the literature data are given in the Supplementary Materials.

Figure 4a is close in magnitude to the Hammond-Leffler α-parameter. Its value as well as the high quality of the correlation confirms the applicability of the Hammond postulate[14] and the Bell-Evans-Polanyi principle[15] for carboxylates, *i.e.*, the series of substrates with the same class of leaving groups, which are stabilized in both transition states and free anions with the same type of electronic effects.

The two points on the correlation plot shown in Figure 4a that correspond to phenolates, appreciably deviate from the line, indicating that if 4,4'-dimethoxybenzhydryl carboxylate and phenolate produce anions of the similar relative stability (the abscissa), the solvolysis of a carboxylate occurs over a higher free energy barrier (the ordinate), that is, carboxylates have the higher Marcus intrinsic barrier[16] than phenolates for both heterolysis and the reversible recombination reaction (Scheme 2c). Also, when carboxylate and phenolate solvolyze *via* the same free energy barrier, the former generates the more stable anion, confirming its higher intrinsic barrier (Scheme 2d).



Scheme 2. Schematic presentation of free energy profiles of benzhydryl carboxylates and phenolates.

The correlation of the activation free energies for solvolysis of 4,4'-dimethoxybenzhydryl carboxylates and phenolates in 80 % ethanol with standard free energies for heterolysis of corresponding Brönsted acids in water (obtained from literature pK_a values given in Supplementary Materials), which represent the relative stabilities of the anions toward a proton, qualitatively confirms the above given relations in energies. The slope of the correlation larger than unity with the substrates that solvolyze over barriers is attributed to an appreciably wider energy range of the Lewis basicity of both carboxylate and phenolate anions toward benzhydrylium carbocations than in the case of their Brönsted basicity.[7a]

In general, relative reactivities in the series of carboxylate leaving groups are determined with the stabilities of the free anions produced in solvolysis. The same phenomenon can also be observed with the two phenolates. However, the Hammond postulate and the Bell-Evans-Polanyi principle cannot be applied for interpretation of reactivity-stability relationships for the two classes of substrates, carboxylates and phenolates, due to different stabilization effects that occur in both transition states and free anions. The higher intrinsic barriers and more reactant-like transition states for carboxylates might be rationalized with a lag of resonance in the carboxylate moiety, leaving the polar effects from the aryl/alkyl moiety to dominate and determine the relative stabilities of the transition states. The Hammond postulate is still valid for carboxylates because the stabilizing contribution of resonance in a series of free carboxylate anions is the same. The nonsynchronized onset of the resonance and the polar substituent effects in the TS has already been observed for benzoates[7a] as well as for other substrates.[17] On the other hand, the resonance in both transition states of phenolates and free phenolate anions is a dominant effect, whose contribution in stabilizing free anions determines their relative stabilities and consequently relative solvolytic reactivities of the series of phenolates.

Comparison of the activation free energies on the diagram given in Figure 4a indicates that in the series of the 4,4'-dimethoxybenzhydrylium electrofuge (the ordinate), pentafluorophenolate (PFPh) is a better leaving group than 3,5-dinitrobenzoate (DNB), monosubstututed fluoro-, chloro- and bromoacetates (Fac, ClAc and BrAc), and formate (Form). On the contrary, PFPh is a poorer leaving group than the mentioned carboxylates in the series of substrates with the benzhydrylium electrofuge (the abscisa). Available data presented in the same correlation (Figure 4a) reveal a similar behavior of 2,4-dinitrophenolate (DNPh). It is indicative that the enhancement of the solvolytic reactivity of the phenolates in comparison to some carboxylates occurs in the combination with a better electrofuge, *i.e.* in the series of substrates that solvolyze *via* a barrier. Obviously, the higher intrinsic barrier is the rate determining variable for carboxylates, so phenolates solvolyze faster despite a higher relative stability of the free carboxylate anions (up to 2.5 kcal mol^{-1}). On the other hand, for the series of benzhydryl substrates, solvolysis is either barrierless or close to be barrierless, and consequently, the impact of the intrinsic barrier at carboxylates is minimized. In this case, the carboxylates that yield more stable anions than phenolates, also solvolyze faster than the phenolates, *i.e.*, the relative stabilities of anions control the kinetics.

The variability in contributions of the intrinsic barrier and the relative stabilities of free anions (produced in solvolysis) on relative reactivities of leaving groups with electrofugality accounts for the intersections of the log k/E_f lines shown in Figure 3. The intersections represent the points of the inversion in relative reactivity of two leaving groups. The line for PFPh intersects the three lines for carboxylate at different values of electrofugality in the experimental range. On the right side from an intersection of the lines is the region in which the intrinsic barrier for a certain carboxylate is the rate determining variable, causing that phenolates solvolyze faster than carboxylates. On the left side from the intersections, the intrinsic barrier for the carboxylates is not a dominant variable anymore and the stability of the corresponding anions determine their reactivities; so the carboxylates solvolyze faster than the phenolates, producing more stable anions. Analogously, the log k/E_f lines for phenyl carbonate and DNPh intersect in the experimental region ($E_f \approx -6$, log $k \approx -6$), *i.e.*, inversion in relative reactivities ocurs.[3,18] Figure 4 also demonstrates approaching and intersecting the lines for DClAc and DNPh almost identically as it occurs in the previous case with phenyl carbonate. Expectedly, the inversion in reactivity of the DNPh leaving group occurs with more reactive carboxylates, whose free anions are also closer in stability with DNPh anion.

Importance of the Reaction Constant

In our previous study we showed that the foundations of the s_f and Hammett ρ^+ parameters are the same, *i.e.* both represent the reaction constants.[18] It has also been demonstrated that s_f parameter increases with decreasing reactivity of the leaving group which is in the line with the Hammond postulate.[7a] In the series of leaving groups of the same type, having the same stabilization effects that occur in TS and free anions, a decrease in nucleofugality is followed by an increase of both endergonicity and s_f parameter. Comparison of the two phenolate leaving groups validates the trend; the pentafluorophenolate leaving group has a larger s_f value than more reactive 2,4-dinitrophenolate for a certain solvent in all the cases.

It has already been mentioned that the Hammond postulate cannot be applied to a series of different types of substrates which can be proved by comparison of s_f values of phenolates and carboxylates of similar reactivity. Thus, PFPh in a certain solvent has an appreciably higher s_f value than any carboxylate, including the least reactive ones (Table 2, Figure 2). Similarly, the s_f value for DNPh in a given solvent is larger than s_f values of carboxylates that are several orders of magnitude less reactive (Figure 2). These differences arise from the variability in intrinsic barriers between the two classes of substrates, that is, unusual high s_f values indicate noticeably lower intrinsic barriers for phenolates. Consequently, unusual high s_f values give rise to intersections of the phenolate and carboxylate log k/E_f correlation lines (Figure 3), *i.e.* relative reactivities of some leaving groups vary with electrofugality. This behavior clearly indicates that reactivities of leaving groups, *i.e.* nucleofugalities, cannot be correctly defined with solvolysis rate constants obtained from a series of substrates with a common electrofuge. Along with technical difficulties for collecting experimental data due to limited range of reactivity of such substrates, the results do not give information on variability in intrinsic barriers of different types of leaving groups. On the other hand, this information is preserved in s_f parameters in Equation (1), rendering this method appropriate for both determining the nucleofugality of any type of leaving group and estimating heterolytic reactivity.

Acknowledgment. The authors gratefully acknowledge financial support of this research by the Croatian Science Foundation (under the project number IP-1021).

Supplementary Information. Supporting information to the paper is enclosed to the electronic version of the article at: http://dx.doi.org/10.5562/cca3040.

REFERENCES

[1] (a) T. H. Lowry, K. S. Richardson in: *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, **1987**. (b) E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*; University Science Books, Sausalito, California, **2006**. (c) M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 6th ed.; Wiley, New York, **2007**.

[2] M. Horn, C. Metz, and H. Mayr, *Eur. J. Org. Chem.* **2011**, 6476.

[3] M. Matić, B. Denegri, O. Kronja, *Eur. J. Org. Chem.* **2010**, 6019.

[4] (a) B. Denegri, A. Streiter, S. Jurić, A. R. Ofial, O. Kronja, H. Mayr, *Chem. Eur. J.* **2006**, *12*, 1648. (b) Correction: B. Denegri, A. Streiter, S. Jurić, A. R. Ofial, O. Kronja, H. Mayr, *Chem. Eur. J.* **2006**, *12*, 5415.

[5] N. Streidl, B. Denegri, O. Kronja, H. Mayr, *Acc. Chem. Res.* **2010**, *43*, 1537.

[6] (a) M. Matić, B. Denegri, O. Kronja, *J. Org. Chem.* **2012**, *77*, 8986. (b) M. Matić, B. Denegri, O. Kronja, *Croat. Chem. Acta.* **2012**, *85*, 585.

[7] (a) M. Matić, B. Denegri, O. Kronja, *Eur. J. Org. Chem.* **2014**, 1477. (b) B. Denegri, M. Matić, O. Kronja, *Org. Biomol. Chem.* **2014**, *12*, 5698. (c) M. Matić, B. Denegri, O. Kronja, *Croat. Chem. Acta.* **2014**, *87*, 375.

[8] B. Denegri, O. Kronja, *J. Org. Chem.* **2007**, *72*, 8427.

[9] I. D. Page, J. R. Pritt, M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2* **1972**, 906.

[10] B. Denegri, A. R. Ofial, S. Jurić, A. Streiter, O. Kronja, H. Mayr, *Chem. Eur. J.* **2006**, *12*, 1657.

[11] (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1970**, *92*, 2538. (b) R. C. Bingham, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1971**, *93*, 3189. (c) J. Slutsky, R. C. Bingham, P. v. R. Schleyer, W. C. Dickason, H. C. Brown, *J. Am. Chem. Soc.* **1974**, *96*, 1969. (d) J. S. Lomas, J. E. Dubois, *J. Org. Chem.* **1975**, *40*, 3303. (e) J. S. Lomas, *Tetrahedron Lett.* **1978**, *20*, 1783.

[12] (a) S. Minegishi, R. Loos, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2005**, *127*, 2641. (b) H. F. Schaller, A. A. Tishkov, X. Feng, H. Mayr, *J. Am. Chem. Soc.* **2008**, *130*, 3012.

[13] H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66.

[14] (a) J. E. Leffler, *Science* **1953**, *117*, 340. (b) J. E. Leffler, E. Grunwald, *Rates and Equilibria of Organic Reactions*, Wiley, New York, **1963**. (c) G. S. Hammond, *J. Am. Chem. Soc.* **1955**, *77*, 334.

[15] M. J. S. Dewar, R. C. Dougherty, *The PMO Theory of Organic Chemistry*, Plenum Press, New York, **1975**.

[16] R. A. Marcus, *J. Phys. Chem.* **1968**, *72*, 891.

[17] (a) C. F. Bernasconi, *Adv. Phys. Org. Chem.* **1992**, *27*, 119. (b) C. F. Bernasconi, *Acc. Chem. Res.* **1992**, *25*, 9. (c) T. L. Amyes, I. W. Stevens, J. P. Richard, *J. Org. Chem*. **1993**, *58*, 6057. (d) J. P. Richard, T. L. Amyes, L. Bei, V. Stubblefield, *J. Am. Chem. Soc.* **1990**, *112*, 9513. (e) M. Horn, H. Mayr, *Chem. Eur. J.* **2010**, *16*, 7469.

[18] M. Matić, S. Jurić, B. Denegri, O. Kronja, *Int. J. Mol. Sci.* **2012**, *13*, 2012.

SUPPLEMENTARY MATERIALS

Nucleofugality of Pentafluorophenolate in Various Solvents: Solvolytic Behavior of Phenolates

Mirela Matić, Nives Bebek, Bernard Denegri* and Olga Kronja*

Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, 10000 Zagreb, Croatia

Table S1. Rate Constants and Corresponding Activation Free Energies for Solvolysis of some Benzhydryl Carboxylates and Phenolates in 80 % Ethanol at 25 °C Estimated Using Equation (1)[(a)] and Corresponding Electrofugality and Nuclefugality Parameters

Substrate	E_f[(b)]	N_f	s_f	k/s^{-1} estimated	$\Delta^{\ddagger}G°$/kcal mol^{-1} estimated	Reference for N_f and s_f
1-HFB	0.00	1.80	0.88	3.84×10^{1}	15.29	1
1-TFAc	0.00	1.42	0.82	1.46×10^{1}	15.86	1
1-TClAc	0.00	1.21	0.90	1.23×10^{1}	15.97	2
1-DClAc	0.00	−0.59	0.91	2.90×10^{-1}	18.19	2
1-PFB	0.00	−0.68	0.90	2.44×10^{-1}	18.29	3
1-DNPh	0.00	0.22	1.03	1.69	17.14	4
8-DClAc	−6.03	−0.59	0.91	9.46×10^{-7}	25.67	2
8-FAc	−6.03	−1.72	1.00	1.78×10^{-8}	28.03	2
8-ClAc	−6.03	−1.95	1.01	8.71×10^{-9}	28.45	2
8-BrAc	−6.03	−1.93	1.02	7.60×10^{-9}	28.53	2
8-Form	−6.03	−2.13	1.04	3.26×10^{-9}	29.03	2
8-Ac	−6.03	−3.61	1.12	1.60×10^{-11}	32.18	2
8-PFB	−6.03	−0.68	0.90	9.14×10^{-7}	25.69	3
8-DNB	−6.03	−1.43	0.98	4.89×10^{-8}	27.43	1
8-DNPh	−6.03	0.22	1.03	1.04×10^{-6}	25.62	4
8-PFPh	−6.03	−0.97	1.29	9.33×10^{-10}	29.77	this work

[(a)] $\log k\ (25\ °\mathrm{C}) = s_f(E_f + N_f)$. [(b)] Values are taken from reference 1.

Table S2. Rate Constants and Corresponding Activation Free Energies for Solvolysis of some Benzhydryl Carboxylates Measured in 80 % Ethanol at 25 °C

Substrate	k/s^{-1}	$\Delta^{\ddagger}G°$/kcal mol^{-1}	Reference
1-FAc	1.93×10^{-2}	19.79	2
1-ClAc	1.06×10^{-2}	20.15	2
1-BrAc	1.07×10^{-2}	20.14	2
1-Form	6.11×10^{-3}	20.47	2
1-Ac	9.06×10^{-5}	22.97	5
1-DNB	3.93×10^{-2}	19.37	6
8-HFB	1.70×10^{-4}	22.60	7

8-TFAc	1.49×10^{-4}	22.67	7
8-TClAc	4.24×10^{-5}	23.42	2

Table S3. Literature pK_a Values and Corresponding Standard Free Energies for heterolysis of some Brönsted Acids

Acid	pK_a	$\Delta_r G°$ (kcal/mol)	Reference
Heptafluorobutyric (HFB) acid	0.10	0.14	8
Trifluoroacetic (TFAc) acid	0.23	0.31	9
Trichloroacetic (TClAc) acid	0.66	0.90	10
Dichloroacetic (DClAc) acid	1.35	1.84	10
Fluoroacetic (FAc) acid	2.59	3.53	10
Chloroacetic (ClAc) acid	2.87	3.92	10
Bromoacetic (BrAc) acid	2.90	3.96	10
Formic (Form) acid	3.75	5.12	10
Acetic (Ac) acid	4.76	6.49	10
3,5-Dinitrobenzoic (DNB) acid	2.80	3.82	11
2,4-Dinitrophenol (DNPh) acid	4.09	5.58	12
Pentafluorophenol (PFPh) acid	5.41	7.38	13

Table S4. Experimental Concentrations (c_o) of 1,8–bis(dimethylamino)naphthalene (Proton Sponge Base) and Substrates in Kinetic Measurements of Solvolysis Rate Constants for Substituted Benzhydryl Pentafluorophenolates

Solvent (a)	c_o(PSB)/ mmol dm^{-3} (b)	c_o(PSB)/c_o(S) (b)
100E	52.9–101.4	25.0–40.0
90E10W	25.4–87.6	15.0–30.0
80E20W	14.1–39.4	10.0–15.0
70E30W	7.1–25.4	5.0–10.0
90A10W	52.9–88.8	25.0–35.0
80A20W	31.7–85.3	15.0–35.0
70A30W	8.8–60.9	5.0–25.0
60A40W	4.2–20.3	3.0–10.0
60AN40W	8.5–20.3	5.0–12.0

(a) Binary solvents are v/v at 25 °C; A = aceton, AN = acetonitrile, E = ethanol, W = water. (b) PSB = 1,8–bis(dimethylamino)naphthalene (Proton Sponge Base); S = substrate (substituted benzhydryl pentafluorophenolates)

REFERENCES

1. N. Streidl, B. Denegri, O. Kronja, and H. Mayr, *Acc. Chem. Res.* **43** (2010) 1537–1549.
2. M. Matić, B. Denegri, and O. Kronja, *Eur. J. Org. Chem.* (2014) 1477–1486.
3. M. Matić, B. Denegri, and O. Kronja, *J. Org. Chem.* **77** (2012) 8986−8998.
4. M. Matić, B. Denegri, and O. Kronja, *Eur. J. Org. Chem.* (2010) 6019–6024.
5. B. Denegri and O. Kronja, *Croat. Chem. Acta*, **83** (2010), 223–226.
6. B. Denegri, A. Streiter, S. Jurić, A. R. Ofial, O. Kronja, and H. Mayr, *Chem. Eur. J.* **12** (2006) 1648–1656.
7. B. Denegri and O. Kronja, *J. Org. Chem.* **74** (2009) 5927–5933.
8. R. J. P. Cannell, *Natural Products Isolation*, Humana Press Inc., New Jersey, 1998, p.180.
9. W. P. Jencks and J. Regenstein, *Ionization Constants of Acids and Bases* in *Handbook of Biochemistry and MolecularBiology*, Fasman, G. D. ed., CRC Press, Cleveland. 1976, p. 305–351.
10. CRC *Handbook of Chemistry and Physics*, 87th ed., CRC Press; 2006–2007.
11. C. B. Aakeröy, J. Desper, and J. F. Urbina, *Chem. Commun.* (2005) 2820–2822
12. B. G. Tehan, E. J. Lloyd, M. G. Wong, W. R. Pitt, J. G. Montana, D. T. Manallack, and E. Gancia, *Quant. Struct.-Act. Relat.,* **21** (2002) 457–472.
13. K. Kipper, K. Herodes, and I. Leito, *J. Chromatogr. A*, (2011) 8175–8180.