Reactivity of Acetates in Aqueous Alcohols

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Abstract. A series of X,Y-substituted benzhydryl acetates (**1-3**) were subjected to solvolysis in various binary methanol/water and ethanol/water mixtures at 25 °C. The LFER equation $\log k = s_f(E_f + N_f)$ was used to derive the nucleofuge-specific parameters (N_f and s_f) for an S_N1 type reaction in 60 % and 80 % aqueous methanol. It has been established that X,Y-substituted benzhydryl acetates produce almost parallel correlation lines, so the average $s_f = 0.9$ has been taken for calculation of the nucleofugality parameters from a single rate constant in some solvent mixtures. In comparison with other leaving groups for which the nucleofugality has already been determined, acetates are the poorest nucleofuges.

Keywords: acetate, nucleofugality, electrofugality, solvolysis, nucleophilic substitution

INTRODUCTION

Carboxylic esters react with strong nucleophiles in a second-order reaction yielding substitution products. The initial step is addition to the carbonyl carbon atom and formation of the tetrahedral intermediate. With weaker nucleophiles esters react only in the presence of acids or bases as catalyst. However, if stabilized carbocation intermediates are produced by cleavage of the alkyl-oxygen bond of carboxylic esters, the carboxylate ion acts as a leaving group and the carbocation intermediate is formed, which in the second step reacts with a solvent or other nucleophile present. Such S_N1 type reactions occur under mild conditions.[1]

Acetates are frequent products or intermediates in organic syntheses. They are also used as hydroxyl protective groups.[2] Even though it is well accepted that acetates are "weak" leaving groups in displacement reactions, in everyday laboratory practice the question often arises if it is possible to transform, purify or crystallize a given acetate in aqueous or alcoholic solutions without being solvolyzed. Therefore, it is important to be able to estimate quantitatively their S_N1 reactivities.

According the comprehensive nucleofugality scale developed for benzhydryl derivatives,[3] because of the linear relationship between the logarithms of the first-order rate constants and the electrofugalities of substrates in a given solvent, the reaction rate can be determined semiquantitatively, according to the following three-parameter LFER equation (1):

$$\log k \left(25\,°C \right) = s_f \left(E_f + N_f \right) \qquad (1)$$

in which: k is the first order rate constant (s^{-1}), s_f is the nucleofuge specific slope parameter, N_f is the nucleofugality parameter, E_f is electrofugality parameter. Electrofuges are characterized with a single parameter (E_f), while two parameters N_f and s_f define the combination of the leaving group and a given solvent. The E_f values of the series of benzhydrylium ions are given in Ref. 3a. The strongest electrofuge for which E_f has yet been determined according to equation (1) is the dianisylcarbenium ion (carbocation of **1**, $E_f = 0$).

EXPERIMENTAL

General procedure for preparation of X,Y-substituted benzhydryl acetates **1-3**, – X,Y-Substituted benzhydrol (1 eq.) was heated with acetanhydride in the presence of sodium acetate (3 eq.) at 60−70 °C for 5 h. After evaporation the reaction mixture, the crude product was dissolved in benzene and washed with aq. NaHCO$_3$ and water. The benzene layer was dried over Na$_2$SO$_3$, and the solvent was evaporated and the product was precipitated with petroleum ether, yielding 45−70 % of pure product.

Bis(4-methoxyphenyl)methyl acetate (**1**), – ^{1}H NMR (600 MHz; CDCl$_3$): δ/ppm: 2,08 (s; 3H; O=C-CH$_3$); 3,73 (s; 6H; Ar-OCH$_3$); 6,77 (s; 1H; Ar$_2$CH); 6,82 (d; 4H; J = 8,7 Hz; ArH); 7,20 (d; 4H; J = 8,5 Hz; ArH);

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Table 1. Solvolysis Rate Constants of X,Y-Substituted Benzhydryl Acetates in Aqueous Alcohols at 25 °C

Substrate (X,Y)	Solvent [a]	E_f [b]	k/s^{-1} [c]
1 (MeO, MeO)	M 100 %	0.00	$(5.21 \pm 0.07) \times 10^{-5}$ [d]
1 (MeO, MeO)	M 90 %, W 10 %	0.00	$(1.41 \pm 0.02) \times 10^{-4}$ [d]
1 (MeO, MeO)	M 80 %, W 20 %	0.00	$(2.73 \pm 0.05) \times 10^{-4}$ [d]
2 (MeO, PhO)		−0.81	$(4.19 \pm 0.05) \times 10^{-5}$ [d]
3 (MeO, Me)		−1.29	$(1.74 \pm 0.01) \times 10^{-5}$ [d]
1 (MeO, MeO)	M 70 %, W 30 %	0.00	$(4.71 \pm 0.07) \times 10^{-4}$ [e]
1 (MeO, MeO)	M 60 %, W 40 %	0.00	$(7.64 \pm 0.10) \times 10^{-4}$ [e]
2 (MeO, PhO)		−0.81	$(1.21 \pm 0.02) \times 10^{-4}$ [e]
3 (MeO, Me)		−1.29	$(5.53 \pm 0.05) \times 10^{-5}$ [e]
1 (MeO, MeO)	E 90 %, W 10 %	0.00	$(4.41 \pm 0.07) \times 10^{-5}$ [d]
1 (MeO, MeO)	E 80 %, W 20 %	0.00	$(9.06 \pm 0.15) \times 10^{-5}$ [d]
1 (MeO, MeO)	E 70 %, W 30 %	0.00	$(1.50 \pm 0.03) \times 10^{-4}$ [d]
1 (MeO, MeO)	E 60 %, W 40 %	0.00	$(2.34 \pm 0.04) \times 10^{-4}$ [e]

[a] Binary solvents are defined with volume fraction at 25 °C. E = ethanol, M = methanol, W = water.
[b] Electrofugality parameters are taken from Ref. 3a.
[c] Average rate constants from at least three runs performed at 25 °C. Errors shown are standard deviations.
[d] Buffered with Proton sponge base [1,8-bis(dimethylamino)naphthalene].
[e] Buffered with triethylamine.

^{13}C NMR (150 MHz; CDCl$_3$): δ/ppm: 20,9 (O=C-<u>C</u>H$_3$); 54,8 (Ar-O<u>C</u>H$_3$); 75,8 (Ar$_2$<u>C</u>H); 113,4; 127,9; 132,2; 158,7 (Ar); 169,6 (C=O).

(4-methoxy-4'-phenoxydiphenyl)methyl acetate (**2**), – ^{1}H NMR (300 MHz; CDCl$_3$): δ/ppm: 2,28 (s; 3H; O=C-CH$_3$); 3,92 (s; 3H; Ar-OCH$_3$); 6,98 (s; 1H; Ar$_2$CH); 7,01 (d; 2H; J = 8,8 Hz; ArH); 7,08–7,16 (m; 4H; ArH); 7,24 (t; 1H; J = 14,8 Hz; ArH); 7,39–7,49 (m; 6H; ArH); ^{13}C NMR (75 MHz; CDCl$_3$): δ/ppm: 21,7 (O=C-<u>C</u>H$_3$); 55,6 (Ar-O<u>C</u>H$_3$); 76,5 (Ar$_2$<u>C</u>H); 114,3; 118,9; 119,5; 123,8; 128,9; 128,9; 130,1; 132,7; 135,5; 157,3; 159,6 (Ar); 170,4 (C=O).

(4-methoxy-4'-methyldiphenyl)methyl acetate (**3**), – ^{1}H NMR (300 MHz; CDCl$_3$): δ/ppm: 2,27 (s; 3H; O=C-CH$_3$); 2,47 (s; 3H; Ar-CH$_3$); 3,91 (s; 3H; Ar-OCH$_3$); 6,98–7,02 (m; 3H; Ar$_2$CH + ArH); 7,26–7,41 (m; 6H; ArH); ^{13}C NMR (75 MHz; CDCl$_3$): δ/ppm: 21,5 (O=C-<u>C</u>H$_3$); 21,7 (Ar-<u>C</u>H$_3$); 55,6 (Ar-O<u>C</u>H$_3$); 76,9 (Ar$_2$<u>C</u>H); 114,2; 127,3; 128,9; 129,5; 133,0; 137,8; 138,9; 159,6 (Ar); 170,4 (C=O).

Kinetic measurements, – Solvolysis rates of **1-3** were measured conductometrically in the series of aqueous ethanol and methanol at 25 °C. Typically, 10−30 mg of substrate was dissolved in 0.10−0.15 mL of dichloromethane and injected into the solvent (30 mL). In order to achieve a complete ionization of a liberated weak acid, either a proton sponge base [1,8-(dimethylamino)-naphthalene] or triethylamine was added. The typical molar ratio between the base and the substrate was between 2 and 10. An increase of the conductivity during solvolysis was monitored automatically by means of a WTW LF 530 conductometer using a Pt electrode LTA 1/NS. Rate constants were averaged from at least three

measurements. The first order rate constants obtained are presented in Table 1.

RESULTS AND DISCUSSION

X,Y-Substituted benzhydryl acetates **1-3** were chosen because it was necessary to combine acetate, which is a poor nucleofuge, with good electrofuges, to obtain substrates that react with the rates appropriate for conventional kinetic measurements. Low solubility of the substrates and too low reactivity are the two major reasons why the measurements have not been performed with all substrates in more aqueous solvents. Nevertheless, data collected are sufficient for determining the reactivities of acetates in aqueous alcohols in the alcohol-rich solvents.

In order to calculate the nucleofugality parameters (N_f) and the slope parameters (s_f) for acetate in 80 % and 60 % aqueous methanol, logarithms of the first-order rate constants were plotted against E_f (Figure 1). The nucleofuge specific parameters are presented in Table 2.

With respect to slope parameters, due to solvation effects there are generally two groups of nucleofuges: those which s_f parameters in binary aqueous solvent depend only marginally on the solvent content, and those which s_f parameters are strongly influenced with the solvent. The former produce practically parallel log k *vs.* E_f plots, while the slopes of log k *vs.* E_f plots of later decrease as the fraction of the water increases.[4] Nucleofuges that belong to first group are those which delocalize the developing negative charge moderately (*e.g.* trifluoroacetates, heptafluorobutyrates, chlorides, *etc.*),[5] while those in the second group substantially
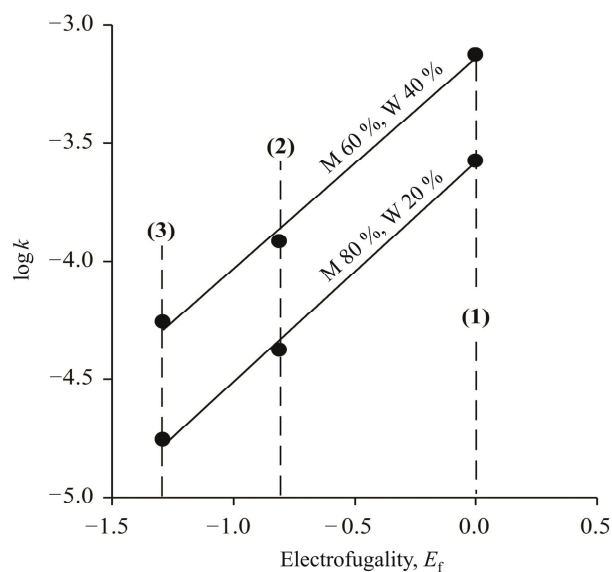
Figure 1. Plots of log k *vs.* E_f for the solvolysis of X,Y-substituted benzhydryl acetates **1-3** in binary methanol-water solvents at 25 °C.

delocalize the negative charge to more than two atoms causing diminished solvation in the TS (*e.g.* the negative charge in carbonates is delocalized to three oxygen atoms almost equally).[6] The question arises here if it is justified to apply the average value of the s_f parameters obtained in 60 % and 80 % methanol to equation (1) and calculate the nucleofugality of acetate in other solvents. The experimental s_f obtained in 60 % and 80 % aqueous methanol are the same in the limits of experimental error, indicating that, as expected, acetates belong to the first group along with the above mentioned esters. Also, the s_f parameters previously measured in aqueous ethanol and methanol for various leaving groups (*e.g.* chloride, trifluoroacetate, heptafluorobutyrate, *etc.*) differ

Table 2. Nucleofuge specific parameters for acetates in aqueous alcohols

Solvent [a]	N_f [b]	s_f [b]
M 100 %	−4.8	0.9 [c]
M 90 %, W 10 %	−4.3	0.9 [c]
M 80 %, W 20 %	−3.83 ± 0.27	0.94 ± 0.06
M 70 %, W 30 %	−3.7	0.9 [c]
M 60 %, W 40 %	−3.51 ± 0.35	0.89 ± 0.07
E 90 %, W 10 %	−4.8	0.9 [c]
E 80 %, W 20 %	−4.5	0.9 [c]
E 70 %, W 30 %	−4.3	0.9 [c]
E 60 %, W 40 %	−4.0	0.9 [c]

[a] Binary solvents are defined with volume fraction at 25 °C. E = ethanol, M = methanol, W = water.

[b] Errors shown are standard errors; the values without standard error are calculated according to equation (1) applying the solvolytic rate of **1** and the estimated $s_f = 0.9$.

[c] Estimated value.
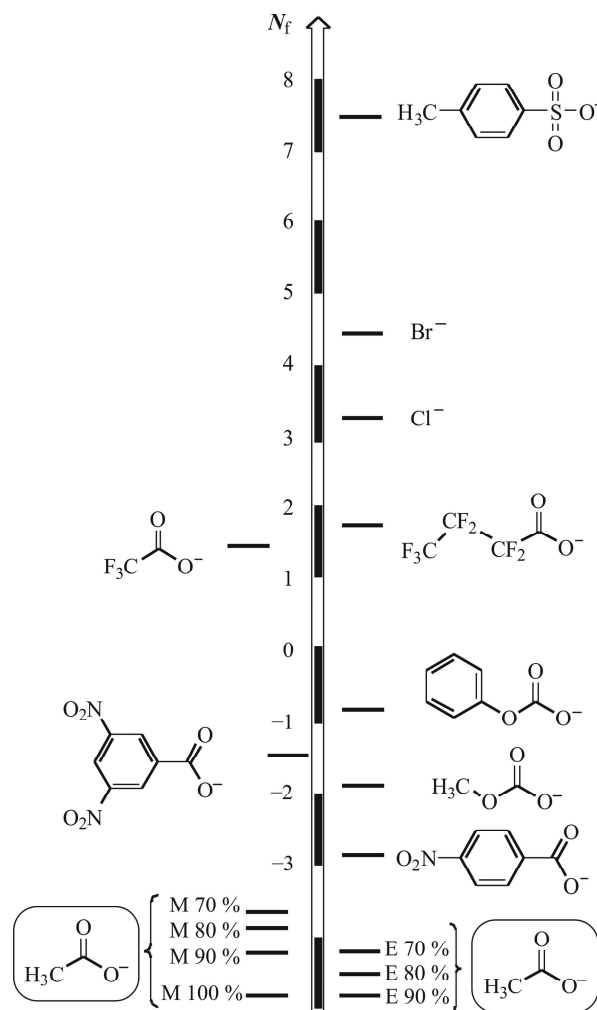
Figure 2. Comparison of the nucleofugality values (N_f) for some leaving groups in 80 % aqueous ethanol with the nucleofugalities of acetate in aqueous alcohols (E = ethanol, M = methanol).

only in the limits of the error.[3,5] Therefore the average $s_f = 0.9$ has been applied to equation (1) and the nucleofugalities of acetates in other aqueous alcohols have been calculated from a single rate constant. The solvolysis rate constants have been systematically determined for substrate **1** in all the solvents used, so according to equation (1) the nucleofugality parameters equal: $N_f =$ log $k/0.9$ since $E_f = 0$ for **1**. The results are presented in Table 2.

Since one unit of nucleofugality corresponds to approximately one order of magnitude in reactivity, by using the N_f parameters it is possible to quantitatively compare the abilities of acetate nucleofuge in various solvents with other leaving groups (Figure 2). Clearly, acetates are so far the poorest leaving group on the scale. For example, acetates solvolyze almost two orders of magnitude slower than the corresponding *p*-nitrobenzoate and almost three orders of magnitude slower than the corresponding methyl carbonate.

In conclusion, it is easy now to estimate the S_N1 reactivity of various acetates in different solvents semi-quantitatively by applying the previously determined electrofugality parameters of various electrofuges and the here presented nucleofuge specific parameters to equation (1).[3] For example, calculated rate constants show that brief handling of *p*-anisylphenylmethyl acetate (X = MeO, Y = H in Scheme 1) at room temperature in 90 % ethanol is safe, since the solvolysis half-life is about 13 days ($E_f = -2.1$). However, the same substrate will solvolyze in 60 % aqueous methanol with the half-life of about 20 h, so 60 % methanol should not be a solvent of choice for *e.g.* purification of the compound.

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SAŽETAK

Reaktivnost acetata u vodenim otopinama alkohola

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Serija X,Y-supstituiranih benzhidril-acetata (**1-3**) je podvrgnuta solvolizi u različitim binarnim smjesama vode i metanola te vode i etanola pri 25 °C. Za izračunavanje parametara specifičnih za nukleofuge (N_f i s_f) u S_N1 tipu reakcije, korištena je sljedeća jednadžba linearnog odnosa slobodne energije: $\log k = s_f(E_f + N_f)$. Pokazano je da X,Y-supstituirani benzhidril-acetati daju gotovo paralelne korelacijske pravce, pa je za izračunavanje nukleofugalnosti acetata u nekim smjesama otapala korišten prosječni $s_f = 0.9$. U usporedbi s drugim odlazećim skupinama kojima je nukleofugalnost do sada određena, acetati su najlošiji nukleofuzi.