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# The importance of the *ortho* effect in the solvolyses of 2,6-difluorobenzoyl chloride<sup>†</sup>

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The *ortho* effect of the chloro substituents in 2,6-dichlorobenzoyl chloride sufficiently hindered attack on the acyl carbon such that an ionization mechanism was observed over the full range of solvents studied. We now compare this behavior with that of 2,6-difluorobenzoyl chloride. The smaller fluoro substituents allow the dominant pathway to be addition–elimination (association–dissociation) in all solvents except those rich in fluoroalcohol, where ionization is dominant. Ranges of operation for both mechanisms had previously been observed for the parent benzoyl chloride but with a wider ionization range than for the 2,6-difluoro derivative. This indicates that, relative to the parent, the electronic destabilizing influence of the fluorines on acyl cation formation outweighs the steric retardation to attack because of the presence of the two *ortho*-fluorine atoms. An extended (two-term) Grunwald–Winstein equation treatment of the solvolyses of 2,6-difluorobenzoyl chloride is reported. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: fluorine substituents; Grunwald-Winstein equation; ortho effect; solvolysis

#### INTRODUCTION

Recently, we reported on the solvolyses of 2,6-dichlorobenzoyl chloride (**1**) and isomeric dichlorobenzoyl chlorides.<sup>[1]</sup> It was possible to compare the solvolytic behavior with that of the earlier studied<sup>[2,3]</sup> 2,6-dimethylbenzoyl chloride (**2**). Compound **2** was found, because of the steric hindrance on the attack on the acyl carbon from the presence of the two *ortho*-methyl groups, coupled with their electron supplying influence, to undergo solvolysis by an ionization (unimolecular) mechanism.

Because of favorable electronic influences, **2** underwent solvolyses very rapidly and, even with a rapid-response conductivity bridge, rates at 25.0°C could be determined only in ethanol and 97–70% acetone.<sup>[3]</sup> The solvolyses of **1** were retarded because the *ortho* substituents were now electron-withdrawing, and elevated temperatures (mainly 55.0°C) were required and specific rates could now be conveniently determined over the full range of solvents usually included in studies of solvolytic displacement reactions.<sup>[4–7]</sup>

In particular, the wide range of solvents studied for the solvolyses of **1** allowed for the application of the original (one-term) Grunwald–Winstein Eqn (1)<sup>[8]</sup> and the extended (two-term) Eqn (2).<sup>[5,9]</sup> In Eqns (1) and (2), *k* and  $k_o$  are the specific rates (first-order rate coefficients) for the solvolysis of a substrate in a given solvent and in the standard solvent (80% ethanol), respectively, *m* is the measure of the sensitivity to changes in solvent ionizing power (Y),<sup>[4–11]</sup> *I* is the measure of the sensitivity to changes in solvent nucleophilicity (N),<sup>[5–7,9]</sup> and *c* is the constant (residual) term.

$$\log(k/k_{\rm o}) = mY + c \tag{1}$$

$$\log(k/k_{\rm o}) = IN + mY + c \tag{2}$$

It was found<sup>[1]</sup> that over the full range of 30 well-chosen solvents, a reasonably good correlation was obtained on application of Eqn (1) and this correlation was improved when Eqn (2)

was applied, with a moderate *l* value of  $0.29 \pm 0.07$ . It was postulated, consistent with earlier studies, <sup>[6,11-13]</sup> that this *l* value arose from a stabilization of a developing carbocation by nucleophilic solvation. Application of Eqn (2) to other dichlorobenzoyl chlorides showed for the 2,4-derivative, a balance between addition–elimination (Scheme 1) and ionization (Scheme 2) mechanisms. Other derivatives (3,4- and 3,5-) with no *ortho* substituents showed a wide range of solvents for which solvolyses occurred by the addition–elimination mechanism, and only in the high ionizing and low nucleophilic solvents, containing an appreciable fluoroalcohol component, could evidence for the ionization pathway be found.

In the present study, the chlorines of **1** are replaced by fluorines to give 2,6-difluorobenzoyl chloride (**3**). With regard to the changes in electronic effects in the *meta* position, the Hammett  $\sigma$  values are essentially identical at 0.34 for fluorine and 0.37 for chlorine.  $^{[14,15]}$  Differences are larger in the *para* position, where resonance interactions also come into play with values of 0.06 for fluorine and 0.22 for chlorine,  $^{[14,15]}$  indicative of a larger electron-supplying resonance contribution from the fluorine. Probably more relevant are the  $\sigma_{\rm p}$  + values based on the solvolysis of *t*-cumyl chloride,  $^{[15,16]}$  where values of -0.07 and 0.11, respectively, are obtained. The difference in values of 0.16 for  $\sigma_{\rm p}$  values and 0.18 for  $\sigma_{\rm p}^+$  values are, however, essentially identical.

When the introduction of substituents is in the *ortho* position relative to the reaction center, the "peculiar effects"<sup>[17]</sup> are largely because of the steric phenomenon and are considered to

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$$\begin{array}{cccccccccccc} R-C-CI & \xrightarrow{S \cup O_{+}^{-}H} & \xrightarrow{S \cup O} & \xrightarrow{S \cup O_{+}^{-}H} & \xrightarrow{S \cup O} & \xrightarrow{S \cup O_{+}} & \xrightarrow{S \cup O_{+} & \xrightarrow{S \cup & \xrightarrow{S \cup O_{+} & \xrightarrow{S \cup & \xrightarrow{S \cup & \xrightarrow{S \cup & \xrightarrow{S \cup$$

Scheme 1. Addition-Elimination (Association-Dissociation) Pathway



involve, in addition to primary effects, steric hindrance to solvation and secondary steric effects. To evaluate the steric effects one must be able to quantify the accompanying polar effects. The earlier attempts involved the assumption that polar effects at the *ortho* position would mirror those at the *para* position and several examples of the application of this approach have been discussed.<sup>[18,19]</sup> Charton has suggested that it is unlikely that  $\sigma_o$  scales of wide applicability can be developed.<sup>[20,21]</sup> Charton developed a steric parameter (u), which is based on hydrogen as the standard (u=o), with the result that all values are positive.<sup>[22]</sup> The halogens have values of 0.27, 0.55, 0.65, and 0.78 for F, Cl, Br, and I, respectively, with the u value for fluorine being half-way between those for hydrogen and chlorine.

### RESULTS

The specific rates of solvolysis were determined by a rapid response conductivity technique for **3** in 31 pure and binary solvents at 55.0°C. The specific rates (first-order rate coefficients) are reported in Table 1. Also listed in the table are the required  $N_{\rm T}^{61}$  and  $Y_{\rm CI}^{[4,10,11]}$  values from the literature. The solvents used in the study consisted of ethanol, methanol, and 2,2,2-trifluoroethanol (TFE) and, for each, a series of mixtures with water. Determinations of the specific rates of solvolysis in binary mixtures of water with 1,1,1, 3,3,3-hexafluoro-2-propanol (HFIP) and acetone and in mixtures of TFE with ethanol are also reported.

Also contained in Table 1 are the ratios, for each solvent, of the specific rate of solvolysis of **3** relative to that of **1**. These values vary widely from 947 in 80% acetone to 0.062 in 97% HFIP.

## DISCUSSION

The important thing to consider is the establishment of the solvolytic behavior of **3**, with two *ortho*-fluoro substituents. Included in the study is a comparison with **1** (with larger chlorine atoms) and with the parent benzoyl chloride (with smaller hydrogen atoms in the *ortho* positions).<sup>[23–28]</sup> The behavior of **3** for most solvents was found to be very different to that of 2,6-dichlorobenzoyl chloride (**1**). The ( $k_3/k_1$ ) specific rate ratios given in Table 1 for the solvolyses of **3** and **1** are extremely illuminating in this regard. The compound **1** has been shown to solvolyze by an ionization mechanism over the full range of solvents.<sup>[11]</sup> If this was also the case for the 2,6-difluorobenzoyl chloride (**3**), a similar behavior and a fairly constant ratio would be expected.

In the aqueous fluoroalcohols, favoring ionization, the ratios are below unity for TFE (0.11) and all the binary mixtures of water with TFE or HFIP that were studied, but the range is not

extremely large (0.06 to 0.83). This is consistent with the general consensus, discussed in the introduction, that fluorine is slightly more electron-withdrawing than chlorine, coupled with the

**Table 1.** Specific rates of solvolysis (*k*) of 2,6-difluorobenzoyl chloride (**3**) in a wide variety of hydroxylic solvents at  $55.0^{\circ}$ C and a comparison, k(3)/k(1) ratios, with corresponding values for the solvolyses of 2,6-dichlorobenzoyl chloride (**1**)

Solvent <sup>a</sup>	$10^3 k (s^{-1})^b$	Ν <sub>T</sub> <sup>c</sup>	$Y^{\rm d}_{\rm CI}$	<i>k</i> (3)/ <i>k</i> (1)
100% EtOH	6.65±0.01	0.37	-2.52	724
90% EtOH	15.7±0.1	0.16	-0.94	339
80% EtOH	$24.1 \pm 0.3$	0.00	0.00	163
70% EtOH	34.0±0.1	-0.20	0.78	74
60% EtOH	$48.4 \pm 0.8$	-0.38	1.38	35
50% EtOH	66.1±3.4	-0.58	2.02	15
100% MeOH	37.5±0.4	0.17	-1.17	367
90% MeOH	70.6±0.1	-0.01	-0.18	212
80% MeOH	112. $\pm$ 1.0	-0.06	0.67	108
70% MeOH	159. $\pm$ 1.0	-0.40	1.46	56
60% MeOH	$211.\pm3.0$	-0.54	2.07	28
50% MeOH	308. $\pm$ 2.0	-0.75	2.70	20
90% Acetone	$3.16 \pm 0.01$	-0.35	2.39	
80% Acetone	$8.29 \pm 0.01$	-0.37	-0.83	947
70% Acetone	$14.9 \pm 0.1$	-0.42	0.17	329
60% Acetone	$28.5 \pm 0.2$	-0.52	0.95	73
50% Acetone	$42.7\pm0.4$	-0.70	1.73	33
100% TFE	$0.389 \pm 0.001$	-3.93	2.81	0.11
97% TFE	$0.371 \pm 0.001$	-3.30	2.83	0.17
90% TFE	$0.934 \pm 0.001$	-2.55	2.85	0.32
80% TFE	$3.56 \pm 0.09$	-2.22	2.90	0.60
70% TFE	$6.10 \pm 0.01$	-1.98	2.96	0.72
60% TFE	$11.9 \pm 0.1$	-1.85	3.06	0.82
50% TFE	$22.2 \pm 0.1$	-1.73	3.16	0.83
80T-20E	$0.624 \pm 0.005$	-1.76	1.89	1.31
60T-40E	$1.66 \pm 0.01$	-0.94	0.63	12
40T–60E	$3.39 \pm 0.01$	-0.34	-0.48	53
20T-80E	$5.35 \pm 0.01$	0.08	-1.42	262
97% HFIP	$3.46 \pm 0.01$	-5.26	5.17	0.062
90% HFIP	$2.48 \pm 0.02$	-3.84	4.31	0.103
70% HFIP	6.84±0.01	-2.94	3.83	0.294

<sup>a</sup>Prepared on a v/v basis at 25.0 °C with other component water, except that T–E represents TFE–ethanol mixtures and TFE–H<sub>2</sub>0 and HFIP–H<sub>2</sub>0 mixtures are prepared on a w/w basis. <sup>b</sup>With associated standard deviation.

<sup>c</sup>Solvent nucleophilicity values from Ref. <sup>[6]</sup>

<sup>d</sup>Solvent ionizing power values from Ref. <sup>[4,10,11]</sup>.

operation of the mechanism of Scheme 2 as the dominant mechanism for both **1** and **3** in these solvents.

In ethanol (724) and methanol (367) and binary mixtures with water of these two alcohols and acetone, the values are above unity and they fall as the water component is increased, reaching values of 15 for 50% EtOH, 20 for 50% MeOH, and 33 for 50% acetone. For **3**, these values are best explained by an addition– elimination mechanism (Scheme 1) accompanying the ionization mechanism in these solvents, in contrast to the operation of only the ionization mechanism in the presence of the two *ortho*-chloro-substituents of **1**. Accordingly, the drop off in the specific rate values as one goes to the less ionizing and more nucleo-philic solvents will be much less for **3** than for **1**, leading to the observation of increased ( $k_3/k_1$ ) ratios.

A more sophisticated approach involves the application of the Grunwald–Winstein equation<sup>[8,9]</sup> (Eqns (1) and (2)). Applying Eqn (1) to the data in Table 1 leads to what at first appears to be a scatter plot (Fig. 1). There are, however, fairly linear plots for each individual binary system. This is in stark contrast to the corresponding plot for **1** where a good linear plot was obtained<sup>[11]</sup> with all solvents included, with a slope of 0.55  $\pm$  0.04 and a correlation coefficient of 0.943. The behavior for solvolyses of **3** is typical for what is observed when a bimolecular mechanism, involving nucleophilic attack by a solvent molecule, is operative for all or a large fraction of the solvents.<sup>[6,29–32]</sup>

When the extended (two-term) Grunwald–Winstein equation is applied, a poor correlation is again obtained when all 31 solvents are included. The *I* value is  $0.80\pm0.10$ , the *m* value is  $0.42\pm0.07$ , the *c* value is  $0.07\pm0.10$  and the multiple correlation coefficient is at a low value of 0.839. One can divide up the solvolyses into two groups, as was achieved previously for the majority of monosubstituted benzoyl chlorides studied.<sup>[28]</sup> One group is dominated by the addition–elimination pathway (Scheme 1) and the other by the ionization pathway (Scheme 2).

A listing of some typical correlation values for mono-substituted and di-substituted benzoyl chloride has recently been presented.<sup>[1]</sup> For the parent benzoyl chloride (*ortho* hydrogens),



**Figure 1.** Plot of log ( $k/k_o$ ) for the solvolyses of 2,6-difluorobenzoyl chloride (**3**) in 31 pure and binary solvents at 55.0°C against  $Y_{CI}$  values. Solvents: E, EtOH–H<sub>2</sub>O; M, MeOH–H<sub>2</sub>O; A, Acetone–H<sub>2</sub>O; TFE, TFE–H<sub>2</sub>O; HFIP, HFIP–H<sub>2</sub>O; T–E, TFE–EtOH

the 47 solvents were divided into 32 proceeding by the ionization mechanism ( $l=0.47\pm0.03$ ;  $m=0.79\pm0.02$ ; correlation coefficient (R) of 0.990) and 12 proceeding by the bimolecular mechanism ( $l=1.27\pm0.29$ ;  $m=0.46\pm0.07$ ; R value of 0.917), with three borderline solvents showing intermediate behavior.<sup>[28]</sup> For **3**, the relative importance of the two pathways, in terms of the number of solvolyses assigned to each, is reversed, with ethanol–water, methanol–water, acetone–water, and TFE–ethanol solvents assigned to the addition–elimination pathway. For these 20 solvents, values are obtained of  $l=1.80\pm0.18$ ;  $m=0.66\pm0.06$ ; R value of 0.940. The plot is shown in Fig. 2. For the nine TFE–H<sub>2</sub>0 and HFIP–H<sub>2</sub>0 solvents the ionization pathway dominates, with values of 0.88±0.10 for l;  $1.12\pm0.14$  for m, and with an R value of 0.964. This plot is shown in Fig. 3.



**Figure 2.** Plot of log  $(k/k_o)$  for the solvolyses of 2,6-difluorobenzoyl chloride (**3**) in 20 pure and binary solvents at 55.0°C against  $(1.80N_T + 0.66Y_{Cl})$ . Solvents: See caption of Fig. 1



**Figure 3.** Plot of log  $(k/k_o)$  for the solvolyses of 2,6-difluorobenzoyl chloride (**3**) in nine binary solvents at 55.0 °C against  $(0.88N_T + 1.12Y_{CI})$ . Solvents: See caption of Fig. 1

# CONCLUSIONS

The reduction in the size of the halogen substituents in going from 2,6-dichlorobenzoyl chloride (1) to 2,6-difluorobenzoyl chloride (3) has a profound effect upon the mechanism of solvolyses in the commonly used hydroxylic pure and binary solvents. For 1, an ionization mechanism over the full range of the solvents was previously established and it was proposed that this was observed by default, despite the acyl cation-destabilizing influence of the chlorine substituents, because of an appreciable steric hindrance towards the approach of the nucleophile to the acyl carbon.

In contrast, for **3**, with the chlorine substituents being replaced by considerably smaller fluorines, there is a reduced hindrance to the approach of the nucleophile. It is now observed that the addition–elimination pathway is dominant in all solvents, except those rich in fluoroalcohol (TFE or HFIP). For these solvents, the ionization pathway continues to be the dominant one.

#### EXPERIMENTAL

2,6-Difluorobenzoyl chloride (**3**, 99%) was used as received from Sigma-Aldrich Chemical Company (St. Louis, Missouri 63178, USA). Solvents were purified as previously described.<sup>[7]</sup> The kinetic experiments were carried out in a conductivity cell containing 5.00mL of the appropriate solvent to which 1 µL of a 1.00M stock solution of **3** in acetonitrile was added (substrate concentration of  $2 \times 10^{-4}$  M). Data were collected until a constant conductivity value was observed, after which the data were subjected to curve fitting using the ORIGIN 3.0 (Microsoft Corporation, Redmond, Washington 98052, USA) program. The monitoring procedure and the procedure for calculation of the first-order rate coefficients (specific rates) were as previously reported.<sup>[33]</sup>

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