Nucleophilic Substitution Reactions of *p*-Nitrobenzyl Chloroformate

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The reactions of aromatic and aliphatic acyl halides with hydroxylic molecules under solvolytic condition or with low concentrations of reactant in aprotic solvent have been studied extensively.[1,2] However, the reaction mechanism is not well established.

Bentley and co-workers[3,4] have proposed initially that *p*-substituted benzoyl chlorides react by concurrent addition-elimination and concerted S_N2 processes (a loose transition state). Lee[5] has proposed that these solvolyses proceed by a combined S_N1-S_N2 and carbonyl addition pathway. Hudson and Moss[6] proposed that the reaction with moderate concentration of a hydroxylic species in low polar aprotic solvent favored an addition-elimination mechanism, or a possible mechanism with a tight S_N2 transition state.

We previously reported that the methanolysis of benzoyl halides[7] and a series of aliphatic acyl halides[8] in acetonitrile proceed through either an addition-elimination (tetrahedral intermediate) or a loose S_N2 transition state (carbocation character) with the substrate structure, reactant, and solvent conditions. Also, kinetic order for methanolyses of carboxylic acid chlorides[7a,8] and bromides[7b] in acetonitrile have been analysed in terms of both first- and second-order in methanol (second- and third-order overall). The term of second-order in methanol was proposed to involve general-base catalysis, and the term of first-order to involve nucleophilic attack without general-base catalysis.

In particular, the simple[9] and extended[10] Grunwald-Winstein equations [Eqs. (1) and (2)] have been applied to a very useful mechanistic tool for solvolysis reactions. In Eqs. (1) and (2), k and k_o are the specific rate constants of solvolysis in a given solvent and in 80% ethanol, respectively; l is the sensitivity to changes in solvent nucleophilicity (N_T);[11] m is the sensitivity to changes in ionizing power (Y_{Cl});[12] and c is a residual term.

$$\log(k/k_o) = mY_{\text{Cl}} + c \qquad (1)$$

$$\log(k/k_o) = lN_T + mY_{\text{Cl}} + c \qquad (2)$$

Recently, we reported that the l-values (bond making) in the range 1.5-1.7 and m-values (bond breaking) in the range 0.5-0.6 for the solvolyses of several chloroformate esters[13-15] will be typical values for the operation of an addition-elimination pathway with addition being rate-determining (or possibly an enfored concerted variant).

In the present study, we analize the specific rate constants of solvolysis of *p*-nitrobenzyl chloroformate in a wide range of solvent type using the simple and extended Grunwald-Winstein equations, and also report concerning the methanolysis of this substrate in a series of haloformates in acetone.

Results and Discussion

The specific rate constants of solvolysis of *p*-nitrobenzyl chloroformate (*p*-NBC; *p*-$NO_2C_6H_4CH_2OCOCl$) studied at 25.0 °C are reported in Table 1 for a variety of pure and binary solvent mixtures.

The products from the solvolyses of the substrate in EtOH, 80%EtOH, 80%TFE, and 80TFE-20EtOH have been determined by gas chromatography after reaction at 25.0 °C. These results are reported in the footnote to Table 1.

An analysis in terms of the simple Grunwald-Winstein equation [Eq. (1)] leads to an extremely poor correlation with values of 3.6 for the *F*-test value and 0.498 for the correlation coefficient. Clearly, this equation doesn't correlate the data. Again, analysis of the data using the extended Grunwald-Winstein equation [Eq. (2)] leads to a good linear correlation with values of 1.66 ± 0.12 for l, 0.47 ± 0.07 for m, 0.08 ± 0.09 for c, 0.980 for the correlation coefficient, and 119 for the *F*-test value (Figure 1).

Table 1. Specific rate constants of solvolysis of *p*-nitrobenzyl chloroformate[a] in pure and mixed solvents at 25.0 °C, and the N_T and Y_{Cl} values for the solvents

solvent[b]	$10^4 k$ (sec^{-1})	N_T[c]	Y_{Cl}[c]
100%MeOH[e,g]	6.24 ± 0.03	0.17	-1.17
90%MeOH	13.2 ± 0.1	-0.01	-0.18
80%MeOH	18.7 ± 0.2	-0.06	0.67
100%EtOH[f,g]	1.86 ± 0.01	0.37	-2.52
80%EtOH[f,g]	7.47 ± 0.03	0.00	0.00
60%EtOH	10.6 ± 0.4	-0.38	1.38
90%Me_2CO	0.0292 ± 0.002	-0.35	-2.22
80%Me_2CO	0.907 ± 0.006	-0.37	-0.80
70%Me_2CO	1.72 ± 0.01	-0.42	0.17
90%TFE	0.0191 ± 0.0010	-2.55	2.83
80%TFE[f]	0.0792 ± 0.020	-2.19	2.91
80T-20E[f,h]	0.0362 ± 0.0012	-1.76	1.89
60T-40E[h]	0.216 ± 0.004	-0.94	0.63

[a]Substrate concentration of *ca*. 5.00×10^{-3} M. [b]Volume/volume basis at 25.0 °C, except for TFE-H_2O mixture, which are on a weight/weight basis. [c]From ref. 11. [d]From ref. 12. [e]Rate constant of MeOD, $k_{\text{Me3OD}} = (2.58 \pm 0.03) \times 10^{-4}$ sec^{-1} at 25.0 °C, kinetic solvent isotope effect value, $k_{\text{MeOH}}/k_{\text{MeOD}} = 2.42$. [f]Percentage of products for the solvolysis of this substrate; 100%EtOH: *p*-$NO_2C_6H_4CH_2OCOEt$ (retention time (r.t), 10.58 min., 100%), 80% EtOH: *p*-$NO_2C_6H_4CH_2OH$ (r.t., 8.95 min., 16.5%) and *p*-$NO_2C_6H_4CH_2OCOEt$ (r.t., 10.58 min, 83.5%), 80%TFE: *p*-$NO_2C_6H_4CH_2OH$ (r.t., 8.95 min., 89.8%) and *p*-$NO_2C_6H_4CH_2OTfe$ (r.t., 9.42 min., 10.2%), 80T-20E: *p*-$NO_2C_6H_4CH_2OTfe$ (r.t., 9.42 min., 1.10%) and *p*-$NO_2C_6H_4CH_2OCOEt$ (r.t., 10.58 min., 98.9%). [g]100% MeOH; $\Delta H^{\neq}_{298}$ = 50 kJ · mol^{-1}, $\Delta S^{\neq}_{298}$ = -137 J · mol^{-1}K^{-1}, 100% EtOH; $\Delta H^{\neq}_{298}$ = 59 kJ · mol^{-1}, $\Delta S^{\neq}_{298}$ = -125 J · mol^{-1}K^{-1}, 80%EtOH; $\Delta H^{\neq}_{298}$ = 50 kJ · mol^{-1}, $\Delta S^{\neq}_{298}$ = -138 J · mol^{-1}K^{-1}. [h]T-E are trifluoroethanol (TFE)-ethanol mixtures (EtOH).

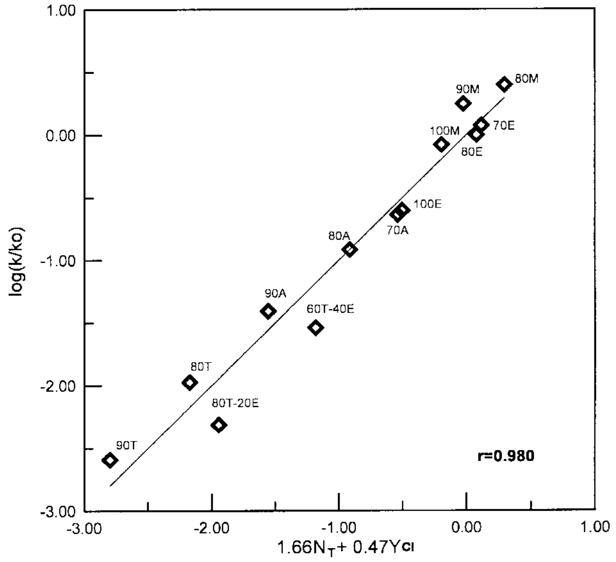

Figure 1. Plot of log(k/k_o) for solvolyses of *p*-nitrobenzyl chloroformate at 25.0 °C against (1.66N_T + 0.47 Y_{Cl}).

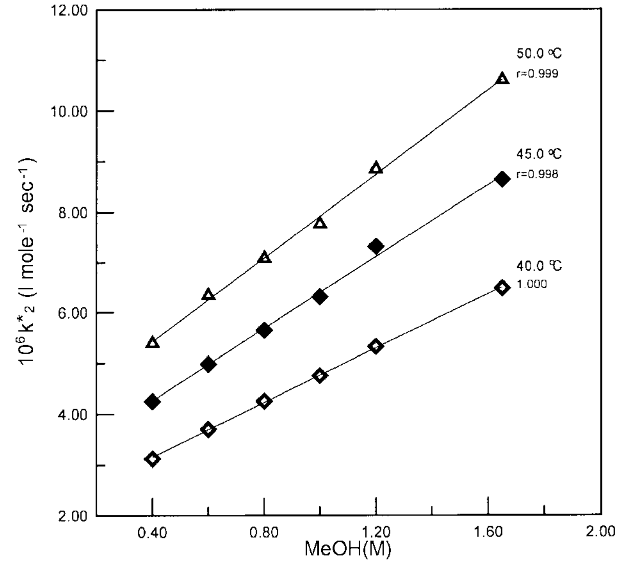

Figure 2. Plots k_2* *vs*. the initial methanol concentrations for the methanolysis of *p*-nitrobenzyl chloroformate in acetone at various temperatures.

The very large sensitivity (*l*-value) to changes in solvent nucleophilicity suggests a very pronounced involvement of the solvent as a nucleophile in the rate-determining step, consistent with the first step of an addition-elimination mechanism being rate-determining. These *l* and *m*-value are similar to those previously obtained for solvolyses of phenyl-(l=1.68 ± 0.10, m=0.57 ± 0.06)[13a] and methyl chloroformate (l=1.59 ± 0.09, m=0.58 ± 0.05)[15a] over the full range of solvent, and ethyl chloroformate (l=1.56 ± 0.09, m=0.55 ± 0.03)[13b] in more nucleophilic and least ionizing solvents, suggesting that the addition-elimination pathway, well established for solvolyses of these chloroformates also applies to *p*-nitrobenzyl chloroformate solvolysis in this range of solvents.

The kinetic solvent isotope effect value (k_{MeOH}/k_{MeOD}) for *p*-nitrobenzyl chloroformate in methanol showed 2.42. This value is within the range 1.8-2.8 predicted for a general-base catalysed and/or addition-elimination pathway.[16-19] But the values for isopropyl chloroformate, *p*-methoxybenzoyl and *p*-methoxybenzyl chlorides, which are known to solvolyze by a unimolecular pathway, are close to unity, being in the range 1.1-1.2.[17,20]

The partitioning between solvolysis (with acid formation) and decomposition (without acid formation) has been studied for four solvents. All of the reaction in four solvents obtained the products of mixed carbonate esters (p-$NO_2C_6H_4CH_2OCO_2Tfe$ and p-$NO_2C_6H_4CH_2OCO_2Et$) and *p*-nitrobenzyl alcohol (p-$NO_2C_6H_4CH_2OH$) formed by loss of carbon dioxide from the unstable hydrogen carbonate ester solvolized by attack of water at the acyl carbon. However, the *p*-nitrobenzyl chloride (p-$NO_2C_6H_4CH_2Cl$) formed by decomposition (with loss of carbon dioxide) was not obtained.

This observation suggests that the solvolysis of the substrate is a bimolecular attack at the acyl carbon, rather than a competition between decomposition and capture by four solvents for a preformed free or ion-paired carboxylium ion. As previously reported,[14,21] the product studies for the solvolyses of *p*-nitrobenzyl chloroformate are consistent with an addition-elimination pathway.

The methanolysis of *p*-nitrobenzyl chloroformate in acetone was studied at several temperatures and over a wide range of methanol concentration. Experimental second-order rate constants, calculated according to Eq. (3), are reported in Table 2.

$$d[HCl]/dt = k_2^*[p\text{-NBC}][MeOH] \qquad (3)$$

Plots of the experimental second-order rate constant against the initial methanol concentrations are linear (correlation coefficient $\geq$ 0.998) and show positive intercepts on the Y-axis (k_2^*) (Figure 2).

From these results, the kinetics for *p*-nitrobenzyl chloroformate was found to be represented by Eq. (4), and the values of the second-order (k_2) and third-order (k_3) rate constants in Table 3 were obtained from the intercepts and slopes, respectively.

$$d[HCl]/dt = k_2[p\text{-NBC}][MeOH] + k_3[p\text{-NBC}][MeOH]^2$$
$$(k_2^* = k_2 + k_3[MeOH]) \qquad (4)$$

Briody[22] and Ross[23] had assumed that acyl halides would react with traces of water within the acetone or acetonitrile but not with the solvent itself. Therefore, the rates of background solvolysis in the absence of methanol were negligible relation to the rates with the lowest alcohol concentration.

As in the case of the reaction of alcohol with *p*-nitrobenzoyl chloride,[7a,22-24] the third-order rate constant (k_3) is believed to be associated with general-base catalysis to involve the deprotonation of a first formed tetrahedral intermediate to give a second intermediate. Regeneration of the carbonyl group from the first intermediate would favour loss

Table 2. Experimental second-order rate constants[a] for the reaction of 0.0285 M *p*-nitrobenzyl chloroformate with methanol in acetone at various temperatures

MeOH (M)	$10^6 k_2^*$ (l · mole^{-1}sec^{-1})		
	40.0 °C	45.0 °C	50.0 °C
1.65	6.48 ± 0.05	8.64 ± 0.03	10.6 ± 0.11
1.20	5.32 ± 0.01	7.31 ± 0.01	8.85 ± 0.05
1.00	4.75 ± 0.04	6.31 ± 0.002	7.76 ± 0.02
0.80	4.25 ± 0.002	5.65 ± 0.001	7.08 ± 0.003
0.60	3.70 ± 0.02	4.98 ± 0.001	6.34 ± 0.04
0.40	3.12 ± 0.01	4.25 ± 0.01	5.39 ± 0.01

[a] Average of all points from duplicated runs, with standard deviation.

Table 3. Second- and third-order rate constants[a] at various temperatures

	Temp. (°C)		
	40.0	45.0	50.0
$10^6 k_2$ (l · mole^{-1} · sec^{-1})[b]	2.08	2.83	3.75
$10^6 k_3$ (l^2 · mole^{-2} · sec^{-1})[c]	2.68	3.56	4.17
r[d]	0.9998	0.9976	0.9969
k_3/k_2 (l · mole^{-1})	1.29	1.26	1.11

[a] Calculated from $k_2^* = k_2 + k_3$[MeOH], using the data of Table 2. [b] $\Delta H^{\neq}_{313}$ = 47 kJ · mol^{-1}, $\Delta S^{\neq}_{313}$ = -205 J · mol^{-1}K^{-1}, [c] $\Delta H^{\neq}_{313}$ = 35 kJ · mol^{-1}, $\Delta S^{\neq}_{313}$ = -241 J · mol^{-1}K^{-1}. [d] Correlation coefficient for the plot.

of methanol rather than chloride ion, and regeneration from the second intermediate loss of chloride ion rather than methoxide ion.

The k_3/k_2 ratios are summarized in Table 3. These values (k_3/k_2 = 1.1-1.3) are similar to the values of 1.1-1.4 for methanolysis of benzoyl chlorides in acetone.[23] The close similarity in k_3/k_2 ratios suggests that similar reaction pathways are involved in these studies. Therefore, the methanolysis of this substrate in acetone is believed to react by an addition-elimination pathway as previously reported.[23]

Also, the values of the enthalpy and entropy of activation for the methanolysis of *p*-nitrobenzyl chloroformate are reported in the footnotes to Table 1 and Table 3. These values are consistent with the finding by Orlov[25] and our previous study[7a,21] of similar activation parameters for the alcoholyses of acyl halides, with a very negative entropy of activation, and with the bimolecular nature of the proposed rate-determining step.

In conclusion, the solvolysis of *p*-nitrobenzyl chloroformate in all the solvents studied and the methanolysis of the substrate in acetone give no evidence for mechanistic change. This substrate (l = 1.66, m = 0.47, l/m = 3.53), where bond making (l-value) is more progressed than bond breaking (m-value), is indicated to proceed by a dominant addition-elimination pathway in which the rate determining step involves nucleophilic addition. This behaviour is very similar to those previously reported for solvolyses of other chloroformate esters[13,15a] over the full range of solvents. Also, these pathway are assisted by general-base catalysis, either by a second methanol molecule or by an acetone solvent molecule. The second-order kinetics pathway can represent nucleophilic attack by methanol without general-base catalysis.

Experimental Section

p-Nitrobenzyl chloroformate (Aldrich, p-$NO_2C_6H_4CH_2O$-COCl) was recrystallized from petroleum ether, mp 32-34 °C (lit.[26] 33.5-34 °C). Solvents were purified and the kinetic runs carried out as previously described.[7,14] The products were directly analyzed by gas chromatography as previously described.[14] All determinations were carried out at least in duplicate.

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