Received: 21 September 2023 | Revised: 30 October 2023 | Accepted: 31 October 2023

DOI: 10.1002/poc.4600

RESEARCH ARTICLE

Journal of Physical Organic Chemistry WILEY

Changes in mechanism and transition state structure for solvolysis reactions of ring substituted benzyl chlorides in aqueous solution

Paul E. Yeary[1] | **John P. Richard**[2]

[1]Division of Science & Mathematics, Alice Lloyd College, Pippa Passes, Kentucky, USA

[2]Department of Chemistry, SUNY Buffalo, Buffalo, New York, USA

Correspondence
John P. Richard, Department of Chemistry, University at Buffalo, SUNY, Buffalo, NY 14260-3000, USA.
Email: jrichard@buffalo.edu

Funding information
This work was supported by National Institutes of Health Grant GM39754.

Abstract

Rate and product data are reported for the solvolysis reactions of 27 mono, di [3,4] and tri [3,4,5] ring-substituted benzyl chlorides. The first order rate constant for solvolysis in 20% acetonitrile in water decrease from $k_{solv} = 2.2\ s^{-1}$ for 4-methoxybenzyl chloride to $1.1 \times 10^{-8}\ s^{-1}$ for 3,4-dinitrobenzyl chloride. The product rate constant ratios k_{MeOH}/k_{TFE} for solvolysis in 70/27/3 (v/v/v) HOH/TFE/MeOH range from a minimum of $k_{MeOH}/k_{TFE} = 8$ to a maximum of 110. The rate data were fit to a four-parameter Hammett equation that separates the resonance ($\rho_r\sigma_r$) and polar ($\rho_n\sigma_n$) effects of the aromatic ring substituents on the reaction rate. Increases in the values of the Hammett reaction constants ρ_r and ρ_n are observed as the substituent constants σ_r or σ_n are increased. A sharp decrease in the product selectivity $k_{MeOH}/k_{TFE} = 26$ for stepwise solvolysis of 4-methoxybenzyl chloride is observed as electron-withdrawing *meta*-substituents are added to 4-methoxybenzyl ring due to a Hammond-effect on the position of the transition state for solvent addition to the substituted 4-methoxybenzyl carbocation reaction intermediates. Sharp increases in the selectivity k_{MeOH}/k_{TFE} are observed with decreasing reactivity of other 3,4,5-subsituted benzyl chlorides due to anti-Hammond shifts, on a two-dimensional More–O'Ferrall reaction coordinate diagram, in the position of the transition state for a concerted solvolysis reaction.

KEYWORDS

anti-Hammond effect, carbocation, concerted reaction, Hammond effect, Hammett relationship, product selectivity, solvolysis, stepwise reaction

1 | INTRODUCTION

We are interested in understanding relationships between the mechanism for nucleophilic substitution at aliphatic carbon and the lifetime of the carbocation intermediate of the stepwise solvolysis reaction.[1–5]

There is extensive evidence that solvolysis reactions in water proceed by a stepwise $D_N + A_N$ reaction mechanism when the lifetime for the reaction intermediate is sufficiently long to allow for diffusional encounter with solvent; and, that the change from a stepwise $D_N + A_N$ to a concerted A_ND_N reaction mechanism occurs as the lifetime of the stepwise carbocation reaction intermediate in the presence of the reacting nucleophile approaches the limit of $\approx 10^{-13}$ s for the lifetime of the transition state for a concerted reaction.[6] For example, the mechanism for nucleophilic substitution reactions of 1-phenylethyl derivatives in aqueous solvents show systematic changes

from $D_N + A_N$ to A_ND_N as the lifetime of the carbocation intermediate of the stepwise reaction is caused to approach this limiting value by changing the aromatic ring-substituent from strongly electron-donating 4-N-$(CH_3)_2$ to the strongly electron-withdrawing 4-NO_2.[4,5] The substitution reactions of neutral and anionic nucleophiles at secondary aliphatic carbon in water proceed by a concerted A_ND_N mechanism that is enforced because there is no significant barrier for addition of water and more reactive nucleophiles to secondary aliphatic carbocations.[7–9] Finally, substrates at the borderline region between stepwise and concerted reaction mechanisms have been identified that undergo competing stepwise $D_N + A_N$ solvolysis with addition of solvent to a liberated carbocation intermediate, and concerted A_ND_N substitution of azide anion which is proposed to be enforced by the absence of significant barrier for addition of azide anion to the carbocation intermediate of the stepwise reaction.[5,10,11]

This paper reports the results of experiments that examine the relationship between reaction mechanism and the stability of the putative carbocation intermediates of nucleophilic substitution reactions at ring-substituted benzyl derivatives (Scheme 1).[10] The previously upward curvature in the Hammett plot of the correlation between log k_{solv} and $\Sigma\sigma^+$ for the phenyl ring substituents for the solvolysis reactions of 3,4-disubsituted benzyl chlorides in 50% ethanol/water at 60°C[9] is consistent with a change from a $D_N + A_N$ mechanism for substrates with electron-donating ring-substituents that strongly stabilize the carbocation reaction intermediate (large negative Hammett reaction constant ρ) to a A_ND_N mechanism[12] for substrates with electron-withdrawing ring-substituents.[13] Other explanations for this curvature that were discussed in a paper by Young and Jencks are examined in this study.[14]

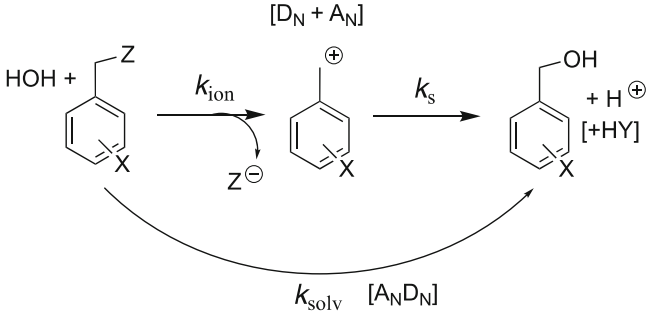
We report first-order rate constants k_{solv} for solvolysis of a broad series of mono-, di-, and trisubstituted benzyl chlorides (Scheme 2), where 3 and 5-ring substituents are varied for reactions of benzyl chlorides with different fixed 4 substituents. These rate data were fit to the Hammett-type equation favored by Young and Jencks, that formally separates polar ($\rho_n\sigma_n$) from resonance ($\rho_r\sigma_r$) interactions between the aromatic ring substituent and the reaction center.[4,14] The Hammett reaction constants ρ_n and ρ_r, respectively, show sharp changes with changing 3,5- or 4-ring substituents. These changes are consistent with an increase in transition state bonding of the nucleophile and leaving group with the central benzylic carbon as the lifetime of the putative carbocation intermediate of the stepwise solvolysis reaction is decreased.

We also report rate constant ratios k_{MeOH}/k_{TFE} determined from the ratio of yields of the products of these reactions (Scheme 2) in the mixed solvent of 70/27/3 (v/v/v) water/trifluoroethanol/methanol. The changes in product selectivity with changing 3,5-substituents at 4-methoxybenzyl chloride are consistent with a Hammond-effect on the position of the transition state for solvent addition to 3,5 substituted 4-methoxybenzyl carbocation intermediates of stepwise reactions.[15] The changes in product selectivity with changing 3,5-substituents at other benzyl chlorides are consistent with anti-Hammond effects on the structure of the transition state for a concerted bimolecular displacement reaction.[16]

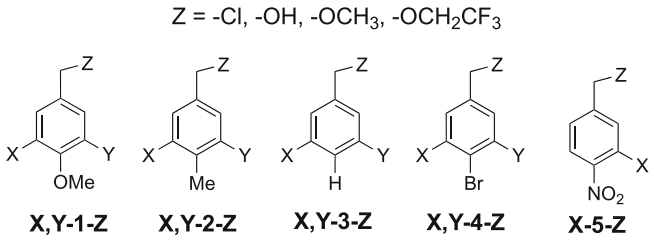
2 | EXPERIMENTAL

2.1 | Materials

The following organic compounds used for syntheses were purchased from Aldrich and used without further purification: 3-cyanobenzoic acid, 3-bromobenzyl alcohol, 4-bromobenzyl alcohol, 3,4-dimethoxybenzyl alcohol, 3,4-dimethylbenzyl alcohol, 3,4-dinitrobenzyl alcohol, 4-bromobenzaldehyde, 3-nitrobenzoic acid, 3-nitrobenzaldehyde, 4-methyl-3-nitrobenzaldehyde,



SCHEME 1 Stepwise $D_N + A_N$ solvolysis of a ring-substituted benzyl derivative in water through a benzyl carbocation intermediate and the concerted A_ND_N solvolysis reaction mechanism that avoids formation of this intermediate.



X,Y: H,H; MeO,H; Br, H; CN,H; NO_2,H; Br, NO_2; NO_2, NO_2

SCHEME 2 Nomenclature for the ring-substituted benzyl derivatives examined in this work.

3-amino-4-methylbenzoic acid, 1-bromo-2-methoxybenzene, 1-cyano-2-methoxybenzene, and 1-methoxy-2-nitrobenzene, trifluoroacetic acid and paraformaldehyde. 4-Methyl-3,5-dinitro benzoic acid was purchased from Chem Services. Concentrated nitric and sulfuric acids were reagent grade from Fisher. Hydrogen chloride gas was generated by addition of concentrated hydrochloric acid to concentrated sulfuric acid and was dried by passage through concentrated H_2SO_4. Silica-gel for column chromatography was Silica-Gel 60 (0.063–0.2 mm, 70–130 mesh) purchased from Brinkmann. The following reagent grade substrates were purchased from Aldrich and used without further purification for kinetic and product studies: **1-Cl** and **2-Cl**. **3-NO_2-3-Cl** and **5-Cl** were purchased from Aldrich and purified by column chromatography, eluting with 2:1 (v/v) hexanes: ethyl acetate.

Inorganic salts for kinetic and product studies were reagent grade from Aldrich and were used without further purification. Organic and inorganic reagents for chemical syntheses and column chromatography were reagent grade and were used without further purification. Water used for kinetic and HPLC analyses was passed through a Milli-Q water purification system. Methanol and acetonitrile used for kinetic and HPLC analyses was HPLC grade from Fisher. 2,2,2-Trifluoroethanol was Gold Label grade from Aldrich.

2.2 | Chemical syntheses

All NMR spectra were obtained using a Gemini 200 MHz instrument. All chemical shifts are reported relative to a value of 0 for tetramethylsilane.

2.2.1 | Electrophilic aromatic substitution reactions

4-Bromo-3-nitrobenzaldehyde. 4-Bromobenzaldehyde (8 g, 43 mmole) was dissolved in 25 mL of concentrated sulfuric acid at room temperature, and this was followed by the addition of 2.5 mL fuming nitric acid. This mixture was stirred at room temperature for 45 min and poured onto ice to give a crystalline product that was used without further purification (90% yield); mp 100°C. ^{1}H NMR ($CDCl_3$): 7.96 (2H, s, Ar), 8.33 (1H, s, Ar), 10.05 (1H, s, CHO).

4-Bromo-3,5-dinitrobenzaldehyde. 4-Bromo-3-nitrobenzaldehyde (5 g, 18 mmole) was dissolved in 25 mL concentrated sulfuric acid, the mixture was cooled to 0-5°C and fuming nitric acid (2.5 mL) was added. The solution was slowly heated to 75°C and this temperature was maintained for 1 h. Quenching over ice gave a crystalline product which was purified by column chromatography over silica gel, eluting with a 5/1/3 hexanes/ethyl acetate/chloroform solvent system (75% yield), mp 124-125°C. ^{1}H NMR ($CDCl_3$): 8.39 (2H, s, Ar), 10.09 (1H, s, CHO).

2.2.2 | Bromination reactions

The following general procedure was followed for bromination of ring-substituted benzyaldehydes.[17] The substituted benzaldehyde was suspended in 25–50 mL 1/1 sulfuric acid/water and 3 mol equivalents of $KBrO_3$ were added over a period of 15 min. The reaction mixture was stirred vigorously at room temperature for a specified period of time. The solid product was collected by filtration and redissolved in ether. The ether was extracted twice with saturated $NaHCO_3$, and the aqueous layers combined and acidified with concentrated HCl to give a solid product which was collected by filtration and used without further purification.

3-Bromo-4-methoxy-5-nitrobenzoic acid was synthesized from 4-methoxy-3-nitrobenzaldehyde (1 g, 6 mmole) by the above procedure with a reaction time of 4.5 h (60% yield); mp 172-174°C. ^{1}H NMR (d-6 acetone): 4.06 (3H, s, OCH_3), 8.42 (1H, d, $J = 2$ Hz, Ar), 8.44 (1H, d, $J = 2$ Hz, Ar).

3-Bromo-4-methyl-5-nitrobenzoic acid was synthesized from 4-methyl-3-nitrobenzoic acid (3.7 g, 28 mmole) by the above procedure with a reaction time of 48 h (85% yield); mp 175-177°C. ^{1}H NMR (d-6 Acetone): 2.60 (3H, s, CH_3), 8.37 (1H, d, $J = 2$ Hz, Ar), 8.42 (1H, d, $J = 2$ Hz, Ar).

3-Bromo-5-nitrobenzoic acid was synthesized from 3-nitrobenzaldehyde (5 g, 33 mmole) by the above procedure with a reaction time of 48 h (80% yield); mp 158-159°C. ^{1}H NMR (d-6 Acetone): 8.51, 8.63, 8.71 (3H, m, Ar).

3,4-Dibromo-5-nitrobenzoic acid was prepared from 4-bromo-3-nitrobenzaldehyde (1.5 g, 6.5 mmole) the above procedure with a reaction time of 50 h. The product was extracted into diethyl ether. The ether was washed with saturated $NaHCO_3$, dried with $MgSO_4$, and evaporated to yield the crude product which was used without further purification.

2.2.3 | Chloromethylation reactions

The following general procedure was followed for addition of a chloromethylene group to substituted anisoles. The substituted anisole and 1.5 mol equivalents of paraformaldehyde were dissolved in 100 mL of chloroform. The solution was saturated with dry hydrogen chloride

gas and then stirred at a specified temperature and for a specified length of time. The reaction was quenched by careful addition of water at 0°C and the chloroform layer was extracted with 5% $NaHCO_3$ (two times) and dried over $MgSO_4$ and evaporated.

3-Bromo-4-methoxybenzyl chloride was synthesized by chloromethylation of 2-bromoanisole (18.5 g, 100 mmole) by the above procedure with a four-hour reaction time at room temperature. The product was purified by vacuum distillation (30% yield); bp 118-120°C/0.7 mmHg (135-138°C/4 mmHg[8]), mp 47.5-49°C (48-49°C).[8] ^{1}H NMR ($CDCl_3$): 3.95 (3H, s, OCH_3), 4.55 (2H, s, CH_2), 6.86 (1H, d, $J = 8$ Hz, Ar), 7.30 (1H, dd, $J = 2$, 8 Hz, Ar), 7.60 (1H, d, $J = 2$ Hz, Ar).

4-Methoxy-3-nitrobenzyl chloride was synthesized by chloromethylation of 2-nitroanisole (15.3 g, 100 mmol) by the above procedure with refluxing for 14 h. The product was purified by column chromatography over silica gel eluting with a 2/1 (v/v) hexanes/ethyl acetate (40% yield); mp 83.5-84.5°C. ^{1}H NMR ($CDCl_3$): 3.98 (3H, s, OCH_3), 4.58 (2H, s, CH_2), 7.20 (1H, d, $J = 10$ Hz, Ar), 7.60 (1H, dd, $J = 2$, 9 Hz, Ar), 7.90 (1H, d, $J = 2$ Hz, Ar).

3-Cyano-4-methoxybenzyl chloride was prepared by adaptation of a published procedure.[18] 2-Methoxybenzonitrile (0.016 mol) and $AlCl_3$ (0.024 mol) were dissolved in 30 mL of CS_2 and methoxyacetyl chloride (0.015 mol in 2 mL CS_2) was added over a period of 20 min. This mixture was stirred at room temperature for 40 min and then quenched by addition of 20 mL water. The organic and aqueous layers were separated, and the aqueous layer was extracted three times with ether. The ether and carbon disulfide layers were combined and dried with dried over $MgSO_4$ and the solid product was recrystallized from 100% ethanol. The first crop of crop of crystals was collected and product was further purified by column chromatography over silica gel eluting with 35% (v/v) ethyl acetate/hexanes (40% yield); mp 90-92°C. ^{1}H NMR ($CDCl_3$): 3.96 (3H, s, OCH_3), 4.54 (2H, s, CH_2), 6.95, 7.55, 7.50 (3H, m, Ar). Anal. calculated: C (59.52), H (4.44), Cl (19.52). Found: C (59.59), H (4.48), Cl (19.60).

2.2.4 | Nucleophilic aromatic substitution reactions

The following general procedure was followed for conversion of 4-bromobenzaldehydes to the corresponding 4-methoxybenzaldehydes. Substituted 4-bromobenzaldehyde (ca. 1 g) and 100 mg of copper dust were added to 25 mL of methanol. Next, 3 mol equivalents of sodium methoxide were added, and the reaction mixture stirred at a specified temperature for a specified length of time. Excess sodium methoxide was neutralized with 6.0 M HCl, and the product extracted into ether. The ether was washed twice with saturated $NaHCO_3$, once with water, dried over $MgSO_4$ and evaporated.

4-Methoxy-3-nitrobenzaldehyde was synthesized from 4-bromo-3-nitrobenzaldehyde (3 g, 13 mmole) by the above procedure with refluxing for 24 h. The product (70% yield) was used without further purification. ^{1}H NMR ($CDCl_3$): 4.08 (3H, s, OCH_3), 7.23 (1H, d, $J = 8$ Hz, Ar), 8.10 (1H, dd, $J = 2$, 8 Hz, Ar), 8.37 (1H, d, $J = 2$ Hz, Ar), 9.96 (1H, s, CHO).

4-Methoxy-3,5-dinitrobenzaldehyde was synthesized from 4-bromo-3,5-di-nitrobenzaldehyde (1 g, 3.6 mmole) by the above procedure at room temperature with a 26-h reaction time and in a vessel wrapped in aluminum foil to inhibit light-initiated radical reactions. The product was purified by column chromatography over silica gel eluting with 5:1:3 hexanes/ethyl acetate/chloroform (60% yield); mp 80-81°C. ^{1}H NMR ($CDCl_3$): 4.16 (3H, s, OCH_3), 8.54 (2H, s, Ar), 10.04 (1H, s, CHO).

3-Bromo-4-methylbenzoic acid was synthesized from 3-amino-4-methylbenzoic acid (15 g, 100 mmole) by adaptation of a published procedure. The crude product obtained from reaction of the diazonium ion with CuBr was recrystallized from 50% ethanol (65% yield), mp 206-208°C. ^{1}H NMR (d^6 Acetone): 2.47 (3H, s, CH_3), 7.50 (1H, d, $J = 8$ Hz, Ar), 7.92 (1H, dd, $J = 2$, 8 Hz, Ar), 8.17 (1H, d, $J = 2$ Hz, Ar).

2.2.5 | Reductions by sodium borohydride

The following general procedure was used to convert ring-substituted benzaldehydes to the corresponding benzyl alcohols. The benzaldehyde was dissolved in methanol or ethyl ether, and one mole equivalent of $NaBH_4$ was added. The mixture was stirred for a specified time at room temperature and the reaction quenched by addition aqueous 6.0 M HCl. The aqueous layer was washed twice with ether and the combined ether layers were dried over $MgSO_4$ and evaporated. The products of these reactions were converted directly to the corresponding benzyl chlorides, without further purification.

4-Bromo-3-nitrobenzyl alcohol was synthesized from 4-bromo-3-nitrobenzaldehyde (0.5 g, 2.2 mmole) by the above procedure in ethyl ether and with a reaction time of 30 min (95% yield). ^{1}H NMR ($CDCl_3$): 1.80 (1H, s, OH), 4.77 (2H, s, CH_2), 7.44 (1H, dd, $J = 2$, 8 Hz, Ar), 7.73 (1H, d, $J = 8$ Hz, Ar), 7.87 (1H, d, $J = 2$ Hz, Ar).

4-Methoxy-3,5-dinitrobenzyl alcohol was synthesized from 4-methoxy-3,5-di-nitrobenzaldehyde (0.2 g, 0.90 mmole) by the above procedure in methanol and with a reaction time of 45 min (90% yield). ^{1}H NMR ($CDCl_3$): 4.08 (3H, s, OCH_3), 4.83 (2H, s, CH_2), 8.08 (2H, s, Ar).

2.2.6 | Reductions using diborane/THF

The following general procedure was followed to carry out diborane reduction of ring-substituted benzoic acids to the corresponding benzyl alcohols.[19] The benzoic acid was dissolved in tetrahydrofuran under argon and the solution was cooled to the specified temperature. A specified amount of diborane solution was added over 15 min and the reaction was allowed to proceed at a specified temperature for a specified length of time. The excess diborane was destroyed with 1/1 water/trifluoroethanol. The aqueous phase was saturated with solid K_2CO_3 and the product extracted into ether. The organic layer was dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the solvent was evaporated to yield the product, which was converted directly to the corresponding benzyl chloride.

3-Cyanobenzyl alcohol was synthesized from 3-cyanobenzoic acid (7.4 g, 50.3 mmole). A solution of substrate was cooled to −15°C, 1 mol equivalent of diborane was added, and the mixture was stirred at room temperature for 12 h. ^{1}H NMR ($CDCl_3$): 2.2 (1H, s, OH), 4.8 (2H, s, CH_2), 7.60 (4H, m, Ar).

3-Bromo-4-methylbenzyl alcohol was synthesized from 3-bromo-4-methylbenzoic acid (2.7 g, 12.5 mmole). A solution of substrate was cooled to -5°C in an ice/salt bath, 1.33 mol equivalents of diborane were added and the mixture was stirred at room temperature for 12 h. ^{1}H NMR ($CDCl_3$): 1.63 (1H, s, OH), 2.39 (3H, s, CH_3), 4.64 (2H, s, CH_2), 7.20 (2H, s, Ar), 7.55 (1H, s, Ar).

4-Methyl-3,5-dinitrobenzyl alcohol was prepared from 4-methyl-3,5-dinitrobenzoic acid (5.7 g, 25 mmole) by the above procedure, using 1.33 mol equivalents of diborane solution and with vigorous stirring at room temperature for 3 h. ^{1}H NMR ($CDCl_3$): 2.05 (1H, s, OH), 2.56 (3H, s, CH_3), 4.86 (2H, s, CH_2), 8.02 (2H, s, Ar).

3-Bromo-4-methyl-5-nitrobenzyl alcohol was synthesized from 3-bromo-4-methyl-5-nitrobenzoic acid (1.5 g, 5.8 mmole) by the above procedure using 1.5 mol equivalents of diborane solution and with stirring at room temperature for 5 h. ^{1}H NMR ($CDCl_3$): 2.55 (3H, s, CH_3), 4.74 (2H, s, CH_2), 7.73 (1H, s, Ar), 7.81 (1H, s, Ar).

3-Bromo-4-methoxy-5-nitrobenzyl alcohol was synthesized from 3-bromo-4-methoxy-5-nitrobenzoic acid (0.65 g, 2.3 mmole) using 1.33 equivalents of diborane and with stirring at room temperature for 4 h. ^{1}H NMR ($CDCl_3$): 2.01 (1H, s, OH), 4.02 (3H, s, OCH_3), 4.73 (2H, s, CH_2), 7.77 (1H, d, $J = 2$ Hz, Ar), 7.83 (1H, d, $J = 2$ Hz, Ar).

3,4-Dibromo-5-nitrobenzyl alcohol was synthesized from 3,4-dibromo-5-nitrobenzoic acid (0.50 g, 1.5 mmole) by the above procedure using 1.5 mol equivalents of diborane and with stirring for 18 h at room temperature. ^{1}H NMR ($CDCl_3$): 4.75 (2H, s, CH_2), 7.66 (1H, d, $J = 2$ Hz, Ar), 7.86 (1H, d, $J = 2$ Hz, Ar).

3-Bromo-5-nitrobenzyl alcohol was synthesized from 3-bromo-5-nitrobenzoic acid (2.0 g, 8.1 mmole) using 1.5 mol equivalents of diborane solution and with stirring overnight at room temperature. ^{1}H NMR ($CDCl_3$): 2.10 (1H, s, br, OH), 4.85 (2H, s, CH_2), 7.87 (1H, m, Ar), 8.18 (1H, m, Ar), 8.30 (1H, m, Ar).

2.2.7 | Chlorination by thionyl chloride

Procedure 1. The ring-substituted benzyl alcohol was dissolved in either dry dichloromethane or ether. Pyridine (*ca* 300 mg) and thionyl chloride (1.5 mol equivalent) were added and the mixture was stirred at a specified temperature for a specified length of time. The excess thionyl chloride was destroyed by addition of water and the product was extracted into ether. The ether was washed with water (one time) and with saturated $NaHCO_3$ (two times) and dried over $MgSO_4$ and the product purified by distillation, recrystallization, or column chromatography.

3-Bromobenzyl chloride was synthesized from 3-bromobenzyl alcohol (11.1 g, 60 mmole) by the above procedure with refluxing for thirty min in dichloromethane. The product was purified by vacuum distillation (80% yield), bp 87-89°C/3 mmHg. ^{1}H NMR ($CDCl_3$): 4.54 (2H, s, CH_2), 7.40 (4H, m, Ar). Anal. calculated for C_7H_6BrCl: C (40.92), H (2.94). Found: C (41.04), H (2.96).

4-Bromobenzyl chloride was synthesized from 4-bromobenzyl alcohol (2.5 g, 13.4 mmole) by the above procedure with refluxing for 2 h in dichloromethane. The product was purified by column chromatography over silica gel eluting with a 5/1/3 (v/v/v) hexanes/ethyl acetate/chloroform solvent system (83% yield), mp 34-35°C. ^{1}H NMR ($CDCl_3$): 4.54 (2H, s, CH_2), 7.27 (2H, d, $J = 8$ Hz, Ar), 7.50 (2H, d, $J = 8$ Hz, Ar). Anal. calculated for C_7H_6BrCl: C (40.92), H (2.94). Found: C (40.93), H (2.95).

3,4-Dimethylbenzyl chloride was synthesized from 3,4-dimethylbenzyl alcohol following the above procedure with stirring overnight at room temperature. The product was purified by column chromatography over silica gel eluting with 20:1 (v/v) hexanes/ethyl acetate and was found to be 99% pure by HPLC analyses. ^{1}H NMR ($CDCl_3$): 2.26 (6H, s, $2CH_3$), 4.55 (2H, s, CH_2), 7.15 (3H, m, Ar). Anal. calculated for $C_9H_{11}Cl$: C (69.9), H (7.17) Cl (22.93). Found: C (69.8), H (2.95) Cl (22.85).

3,4-Dimethoxybenzyl chloride was synthesized from 3,4-dimethoxybenzyl alcohol (15 g, 89 mmole) in ether following the above procedure with a twenty-minute reaction time. The product was recrystallized from hexanes (80% yield), mp 50-51°C. ^{1}H NMR ($CDCl_3$): 3.89 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.58 (2H, s, CH_2), 6.90 (3H, m, Ar). Anal. calculated for $C_9H_{11}ClO_2$: C (57.9), H (5.96), Cl (19.0). Found: C (58.09), H (5.99), Cl (18.9).

3-Cyanobenzyl chloride was synthesized from 3-cyanobenzyl alcohol (7.9 g, 60 mmole) in dichloromethane following the above procedure with refluxing for 1.5 h. The product from the initial workup was > 98% pure by HPLC analysis and was not further purified (90% yield), mp 63–65°C. ^{1}H NMR ($CDCl_3$): 4.60 (2H, s, CH_2), 7.60 (4H, m, Ar). Anal. calculated for C_8H_6ClN: C (63.38), H (3.99), Cl (23.38). Found: C (63.38), H (4.02), Cl (23.37).

3-Bromo-4-methylbenzyl chloride was synthesized from 3-bromo-4-methylbenzyl alcohol (12 g, 60 mmole) in dichloromethane following the above procedure with refluxing for 45 min. The product from the initial workup was >98% pure by HPLC analysis and was not further purified (80% yield). ^{1}H NMR ($CDCl_3$): 2.40 (3H, s, CH_3), 4.53 (2H, s, CH_2), 7.23 (2H, s, Ar), 7.57 (1H, s, Ar). Anal. calculated for C_8H_8BrCl: C (43.77), H (3.67). Found: C (43.49), H (3.61).

3-Bromo-4-methoxy-5-nitrobenzyl chloride was synthesized from 3-bromo-4-methoxy-5-nitrobenzyl alcohol (0.1 g, 0.4 mmole) in dichloromethane following the above procedure with refluxing for 2 h. The product was purified by column chromatography over silica gel eluting with 2/1 (v/v) hexanes/ethyl acetate (72% yield), mp 43-44.5°C. ^{1}H NMR ($CDCl_3$): 4.03 (3H, s, OCH_3), 4.56 (2H, s, CH_2), 7.81 (1H, d, $J = 2$ Hz, Ar), 7.85 (1H, d, $J = 2$ Hz, Ar). Anal. calculated for $C_8H_7BrClNO_3$: C (34.25), H (2.52), N (4.99). Found: C (34.10), H (2.66), N (4.85).

3,4-Dibromo 5-nitrobenzyl chloride was synthesized from 3,4-dibromo-5-nitrobenzyl alcohol (0.50 g, 1.6 mol) following the above procedure with refluxing for 2 h in dichloromethane. The product was purified by column chromatography over silica gel eluting with 5:1 (v/v) hexanes/ethyl acetate (74% yield), mp 66-67°C. ^{1}H NMR ($CDCl_3$): 4.55 (2H, s, CH_2), 7.68 (1H, d, $J = 2$ Hz, Ar), 7.88 (1H, d, $J = 2$ Hz, Ar). Anal. calculated for $C_7H_5ClBr_2$: C (25.53), H (1.22), N (4.25). Found: C (25.60), H (1.26), N (4.28).

4-Bromo-3-nitrobenzyl chloride was synthesized from 4-bromo-3-nitrobenzyl alcohol (0.20 g, 0.90 mmole) following the above procedure refluxing for 1 h in dichloromethane. After extraction the product was >98% pure by HPLC analysis and was not further purified (81% yield), mp 37-39°C. ^{1}H NMR ($CDCl_3$): 4.59 (2H, s, CH_2), 7.48 (1H, dd, $J = 2$, 8 Hz, Ar), 7.76 (1H, d, $J = 8$ Hz, Ar), 7.90 (1H, d, $J = 2$ Hz, Ar). Anal. calculated for $C_7H_5BrClNO_2$: C (33.57), H (2.01), N (5.59). Found: C (33.67), H (2.01), N (5.56).

3-Bromo-4-methyl-5-nitrobenzyl chloride was synthesized from 3-bromo-4-methyl-5-nitrobenzyl alcohol (0.50 g, 2 mmole) following the above procedure with refluxing for 2 h in dichloromethane. The product was purified by column chromatography over silica gel eluting with 1/1 hexanes/chloroform (70% yield), mp 70-71°C. ^{1}H NMR ($CDCl_3$): 2.57 (3H, s, CH_3), 4.56 (2H, s, CH_2), 7.77 (1H, d, $J = 2$ Hz, Ar), 7.84 (1H, d, $J = 2$ Hz, Ar). Anal. calculated for $C_8H_7ClBrNO_2$: C (36.33), H (2.67), N (5.30), found: C (36.43), H (2.68), N (5.35).

3-Bromo-5-nitrobenzyl chloride was synthesized from 3-bromo-5-nitrobenzyl alcohol (0.95 g, 4.1 mmole) following the above procedure with refluxing for 4 h in dichloromethane. The product was purified by column chromatography over silica gel eluting with 1:1 hexanes/chloroform (65% yield), mp 72-74°C. ^{1}H NMR ($CDCl_3$): 4.63 (2H, s, CH_2), 7.89 (1H, m, Ar), 8.22 (1H, m, Ar), 8.35 (1H, m, Ar). Anal. calculated for $C_7H_5ClBrNO_2$: C (33.57), H (2.01), N (5.59). Found: C(33.65), H (2.04), N (5.61).

Procedure 2,[9] The alcohol was dissolved in neat thionyl chloride and the mixture was refluxed for a specified length of time. After cooling, the mixture was diluted into ether which was washed with water (once), saturated $NaHCO_3$ (twice) and dried over $MgSO_4$ and evaporated.

3,4-Dinitrobenzyl chloride was synthesized from 3,4-dinitrobenzyl alcohol (1.9 g, 9 mmole) with refluxing in 5 mL neat thionyl chloride for 3 h. The product was purified by column chromatography over silica gel eluting with 2:1 (v/v) hexanes/ethyl acetate (57% yield), mp 55-56°C. MS, found M^+ 215.9938, $C_7H_5ClN_2O_4$ required 215.9939. ^{1}H NMR ($CDCl_3$): 4.69 (2H, s, CH_2), 7.80, 7.87 (3H, m, Ar).

4-Methyl-3,5-dinitrobenzyl chloride was synthesized from 4-methyl-3,5-dinitrobenzyl alcohol (0.33 g, 1.5 mmole) with refluxing overnight in 2 mL neat thionyl chloride. The product was purified by column chromatography over silica gel eluting with 2:1 (v/v) hexanes/ethyl acetate (65% yield), mp 60.5-61.5°C. ^{1}H NMR ($CDCl_3$): 2.59 (3H, s, CH_3), 4.65 (2H, s, CH_2), 8.05 (2H, s, Ar). Anal. calculated for $C_8H_7ClN_2O_4$: C (41.67), H (3.06), N (12.15). Found: C (41.77), H (3.08), N (12.06).

4-Methoxy-3,5-dinitrobenzyl chloride was synthesized from 4-methoxy-3,5-dinitrobenzyl alcohol (0.25 g, 1.1 mmole) with refluxing in 2 mL neat thionyl chloride for 3 h. The product was purified by column chromatography over silica gel eluting with 2:1 (v/v) hexanes/ethyl acetate (40% yield), mp 54-55°C. ^{1}H NMR ($CDCl_3$): 4.09 (3H, s, OCH_3), 4.63 (2H, s, CH_2), 8.10 (2H, s, Ar). Anal. calculated for $C_8H_7ClN_2O_6$: C (38.96), H (2.86), Cl (14.38), found: C (39.14), H (2.91), Cl (14.24).

2.3 | Preparation of solutions

Solvents of 20% acetonitrile in water were prepared by adding a measured amount of the organic cosolvent to a volumetric flask and diluting to the final volume with the appropriate aqueous salt solution (I = 1.00, $NaClO_4$). Solvents containing 70/27/3 (v/v/v) water/trifluoroethanol/

methanol (I = 0.70, $NaClO_4$) were prepared by mixing seven parts of a 1.00 M solution of $NaClO_4$ in water and three parts of a 9/1 (v/v) solution of trifluoroethanol/methanol.

2.4 | HPLC analyses

HPLC analyses were performed as described in previous work,[4,20] using a Waters Associates reverse-phase 10 μM octadecylsilane chromatography column which was pressurized inside a Waters Radial Compression Module. The components of the reaction mixture were separated by either isocratic or gradient elution with mixtures of MeOH/HOH. The reactants and products were detected by the UV absorbance of the aromatic ring at the following wavelengths: **1-Z**, 265 nm; **3-OMe-1-Z**, 290 nm; **3-Br-1-Z**, 278 nm; **3-CN-1-Z**, 300 nm; **3-NO_2-1-Z**, 250 nm; **3-Br**, **5-NO_2-1-Z**, 264 nm; **3,5-di-NO_2-1-Z**, 250 nm; **3-Me-2-Z**, 270 nm; **2-Z**, 263 nm; **3-Br-2-Z**, 270 nm; **3-NO_2-2-Z**, 263 nm; **3-Br,5-NO_2-2-Z**, 263 nm; **3,5-di-NO_2-2-Z**, 250 nm; **3-Z**; 260 mn; **3-Me-3-Z**, 270 nm; **3-MeO-3-Z**, 280 nm; **3-Br-3-Z**, 270 nm; **3-CN-3-Z**, 275 nm; **3-NO_2-3-Z**, 250 nm; **3-Br,5-NO_2-3-Z**, 267 nm; **3,5-di-NO_2.-3-Z**, 250 nm; **4-Z**, 250 nm; **3-NO_2-4-Z**, 250 nm; **3-Br,-5-NO_2-4-Z**, 250 nm; **3,5-di-NO_2-4-Z**, 250 nm; **5-Z**, 250 nm; **3-NO_2-5-Z**, 250 nm.

2.5 | Kinetic methods

The solvolysis reactions in 20% acetonitrile in water at 25°C were initiated by making a 100-fold dilution of to give a final substrate concentration of 0.25–0.70 mM in a volume of 1.0 mL. The reaction progress for faster reactions of the following substrates was monitored by following the change in UV absorbance at the following wavelengths: **1-Cl**, 265 nm; **3-OMe-1-Cl**, 290 nm; **3-Br-1-Cl**, 278 nm; **3-CN-1-Cl**, 255 nm; **3-NO_2-1-Cl**, 250 nm. Pseudo first-order rate constants k_{obs} were obtained as the slopes of semilogarithmic plots of reaction progress against time which were linear for at least 3 reaction halftimes. The rate constants were reproducible to ±5 %.

The progress of slower reactions was monitored by HPLC analyses in solutions that contain 5 μL of a 0.30 M solution of 1-(4-methoxyphenyl)-1-propanol in acetonitrile. This served as a stable internal standard that was used to correct for small variations in the volume of the sample injected onto the HPLC. The solvolysis reactions with halftimes of shorter than 30 days were monitored by following the appearance of the benzyl alcohol product for >10% reaction. Pseudo first-order rate constants k_{obs} were obtained as the slopes of semilogarithmic plots of reaction progress against time. Reactions with halftimes of longer than 30 days were monitored for the appearance of the benzyl alcohol product by HPLC over the first 3%–5% of the reaction. The first-order rate constants were determined from the slopes of linear plots of $(A_{ROH})_{obs}/(A_{RCl})_o$ versus time, where $(A_{ROH})_{obs}$ is the observed peak area of the alcohol reaction product, and $(A_{RCl})_o$ is the peak area of the parent benzyl chloride. This analysis assumes that the extinction coefficients for the substrate and product are the same at the wavelength used for the analysis. This was confirmed for **3,5-di-NO_2-1-Z**, **3-Me,5-NO_2-1-Z**, and **3-NO_2-5-Z** by showing that identical (±10%) peak areas from HPLC analysis were observed for injection of equal molar amounts of authentic standard solutions of the ring-substituted benzyl chloride and the corresponding benzyl alcohol.

2.6 | Product studies

The reactions were initiated by making a 100-fold dilution of the ring-substituted benzyl chloride in acetonitrile into 70/27/3 HOH/TFE/MeOH (v/v/v) at 25°C or 70°C to give a final substrate concentration of 0.25–0.70 mM. HPLC product analyses during the reactions of ring-substituted benzyl chlorides in 20% acetonitrile showed a single product peak which was identified as the ring-substituted benzyl alcohol by comparison with an authentic standard. The methyl and trifluoroethyl ether products from reactions in mixed HOH/TFE/MeOH solvents were identified as the additional product peaks observed for the reaction in the mixed alcohol solvent and with the earlier determination that the methyl ethers of ring substituted 1-phenylethyl derivatives elutes well before the trifluoroethyl ether from our Water reverse phase HPLC column.[4,21]

The product yields were determined by HPLC analyses as described in previous work.[4,20] Rate constant ratios for partitioning of substrate between reaction with methanol and trifluoroethanol were determined using Equation (1) or (2), where A_{ROMe}, A_{ROTFE} and A_{ROH} are the areas for the respective product peaks from HPLC analyses. Equations (1) and (2) hold when the extinction coefficients for the two nucleophile adducts are the same. This has been shown to be the case studies on the solvolysis reactions of 4-$MeOC_6H_4CH_2OH$,[10] $XC_6H_4CH(CH_3)Y$,[21] and $XC_6H_4CH(CF_3)Y$.[22]

$$\frac{k_{MeOH}}{k_{TFE}} = \frac{A_{ROMe}[TFE]}{A_{ROTFE}[MeOH]} \quad (1)$$

$$\frac{k_{HOH}}{k_{TFE}} = \frac{A_{ROMe}[TFE]}{A_{ROH}[HOH]} \quad (2)$$

3 | RESULTS

The monosubstituted benzyl chlorides studied in this work were commercially available. The 3-substituted-4-methoxybenzyl chlorides were prepared by direct chloromethylation of the *ortho*-substituted methoxybenzenes using either paraformaldehyde and HCl gas (3-Br and 3-NO_2) or $AlCl_3$ and methoxyacetyl chloride in CS_2 (3-CN).[23] Figure 1 summarizes the methods used for the preparation of many of the other ring-substituted benzyl chlorides studied in this work. Standard protocols were followed for the synthesis of the remaining benzyl chlorides.

Table 1 reports first-order rate constants k_{solv} determined for the solvolysis of ring-substituted benzyl chlorides in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$). The solvolysis of **1-Cl** in this solvent was too fast to be monitored by our methods. This rate constant was estimated by assuming that the rate constant ratio of 390 determined for the solvolysis **3-Br-1-Cl** and **1-Cl** in 50% methanol at 25°C is also observed for solvolysis in 20% acetonitrile in water.

Table 2 reports the rate constant ratios k_{MeOH}/k_{TFE}, k_{MeOH}/k_{HOH}, and k_{HOH}/k_{TFE} for the solvolysis of ring-substituted benzyl chlorides in 70/27/3 (v/v/v) HOH/TFE/MeOH at $I = 0.70$ ($NaClO_4$), and at either 25°C, or at 70°C when the reactions were too slow to be conveniently monitored at the lower temperature. The rate constant ratios were calculated from the ratio of the yields of the alcohol, methyl ether and trifluoroethyl ether products using Equation (1) or (2). It was shown for the reactions of **3-NO_2-1-Cl** and **3-NO_2-2-Cl** in 70/27/3 (v/v/v) HOH/TFE/MeOH that the product rate constant ratios determined for reactions at 25°C and 70°C agree to better than ±5%.

4 | DISCUSSION

4.1 | Solvolysis in 20% acetonitrile in water

The first-order rate constants k_{solv} (Table 1) determined for the solvolysis of 27 mono-, di-, and trisubstituted

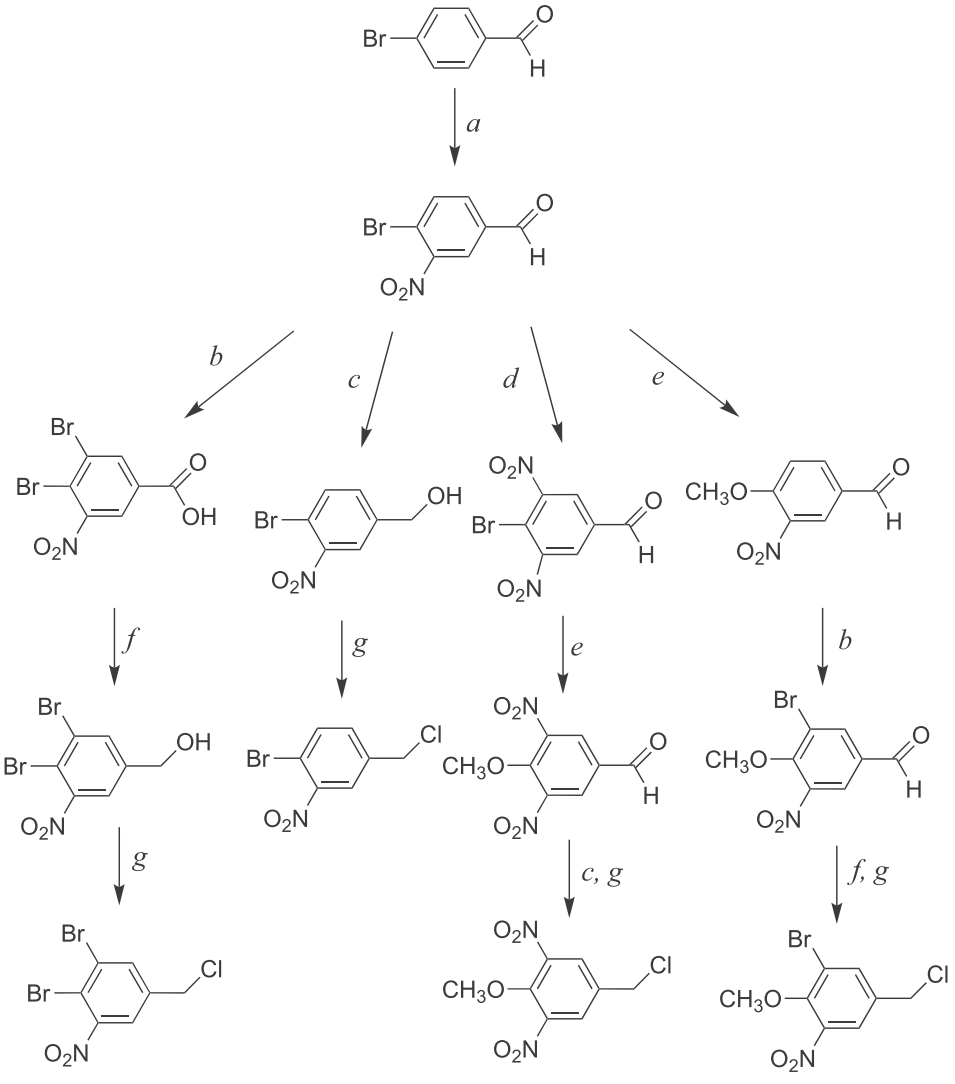


FIGURE 1 Summary of methods used for the synthesis of ring-substituted benzyl chlorides. Key: *a*, 1/1 H_2SO_4/HNO_3 at room temperature; *b*, $KBrO_3/H_2SO_4$; *c*, $NaBH_4$ in methanol; *d*, 1/1 H_2SO_4/HNO_3 with slow warming to 75°C; *e*, NaOMe in methanol; *f*, Diborane in tetrahydrofuran; g, $SOCl_2$ in dichloromethane.

TABLE 1 First-order rate constants k_{solv} for the solvolysis of ring-substituted benzyl chlorides in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$).

Substrate	k_{solv} (s^{-1})	Substrate	k_{solv} (s^{-1})
1-Cl[a]	2.2	**Br-3-Cl**[c]	6.0×10^{-7}
MeO-1-Cl[b]	0.72	**CN-3-Cl**[d]	1.6×10^{-7}
Br-1-Cl[b]	5.7×10^{-3}	**NO_2-3-Cl**[d]	7.3×10^{-8}
CN-1-Cl[b]	5.9×10^{-5}	**Br,NO_2-3-Cl**[d]	2.7×10^{-8}
NO_2-1-Cl[b]	1.4×10^{-5}	**di-NO_2-3-Cl**[d]	1.5×10^{-8}
Br,NO_2-1-Cl[c]	5.8×10^{-8}	**4-Cl**[c]	2.2×10^{-6}
di-NO_2-1-Cl[c]	2.2×10^{-8}	**NO_2-4-Cl**[d]	3.9×10^{-8}
Me-2-Cl[b]	1.7×10^{-4}	**Br,NO_2-4-Cl**[d]	1.8×10^{-8}
2-Cl[b]	6.0×10^{-5}	**di-NO_2-4-Cl**[d]	8.3×10^{-9}
Br-2-Cl[b]	3.0×10^{-6}	**5-Cl**[d]	4.3×10^{-8}
NO_2-2-Cl[d]	2.0×10^{-7}	**NO_2-5-Cl**[d]	1.1×10^{-8}
Br,NO_2-2-Cl[d]	5.1×10^{-8}		
di-NO_2-2-Cl[d]	2.2×10^{-8}		
Me-3-Cl[c]	5.3×10^{-6}		
3-Cl[c]	4.9×10^{-6}		
MeO-3-Cl[c]	1.8×10^{-6}		

[a]Estimated as described in the text.
[b]Rate constant determined by monitoring the reaction by UV-Vis spectroscopy.
[c]First-order rate constant determined by monitoring the reaction progress by HPLC for >10%.
[d]Rate constant determined by method of initial rates over <10% of the reaction.

TABLE 2 Rate constant ratios from product analyses for the reactions of ring-substituted benzyl chlorides with 70/27/3 (v/v/v) HOH/TFE/MeOH at $I = 0.70$ ($NaClO_4$).[a]

Compound	k_{MeOH}/k_{TFE}	k_{MeOH}/k_{HOH}	k_{HOH}/k_{TFE}
1-Cl	26	13	2.0
MeO-1-Cl	26	16	1.6
Br-1-Cl	16	8.2	1.9
CN-1-Cl	8.7	3.8	2.3
NO_2-1-Cl[b]	8.7	3.6	2.4
Br,NO_2-1-Cl[c]	41	6.2	6.5
di-NO_2-1-Cl[c]	82	5.5	14.8
Me-2-Cl	5.8	4.5	1.3
2-Cl	7.3	3.5	2.1
Br-2-Cl	26	6.6	3.9
NO_2-2-Cl[b]	52	9.4	5.5
Br,NO_2-2-Cl[c]	61	6.9	8.8
di-NO_2-2-Cl[c]	82	5.8	14.1
Me-3-Cl	16	8.3	1.9
3-Cl	22	7.5	2.9
MeO-3-Cl	18	10.5	1.7
Br-3-Cl	33	8.2	4.0
CN-3-Cl[c]	56	7.1	7.9
NO_2-3-Cl[c]	56	7.2	7.8
Br,NO_2-3-Cl[c]	77	6.3	12.2
di-NO_2-3-Cl[c]	111	5.1	22
4-Cl[c]	22	8.4	2.6
NO_2-4-Cl[c]	47	10.1	4.7
Br,NO_2-4-Cl[c]	79	6.5	12.2
di-NO_2-4-Cl[c]	84	6.4	13.1
5-Cl[c]	58	8.1	7.2
NO_2-5-Cl[c]	110	6.3	17

[a]The reaction temperature was 25°C, unless stated otherwise.
[b]The product ratios determined at 25 and 70°C agree to better than ±5%.
[c]Product ratios determined at 70°C.

benzyl chlorides in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$) decrease from 2.2 s^{-1} for **1-Cl** to 8.3×10^{-9} s^{-1} for **di-NO_2-4-Cl**. These rate data cannot be fit to a single parameter Hammett equation. We have used the following protocol to fit these data to the 4-parameter Hammett Equation (3),[4,14] which partitions the total interaction between ring substituents and the reaction center into a polar component ($\rho_n\sigma_n$) and a resonance component for 4-substituents ($\rho_r\sigma_r$), where σ_n and σ_r are published substituent constants.[24]

$$\log k_{solv} = C + \rho_n\sigma_n + \rho_r\sigma_r \quad (3)$$

$$\log k_{solv} = C + \rho_n\Sigma\sigma_m \quad (\sigma_n = \sigma_m) \quad (4)$$

$$\log k_{solv} - \rho_n\sigma_n = C + \rho_r\sigma_r \quad (5)$$

Figure 2A shows the fits of data from Table 1 to Equation (4) for solvolysis reactions where the 4-ring substituent is held constant as the 3,5-substituents are varied.[24] The slope determined over the linear region of each plot ($\sigma_n = \sigma_m \leq 0.71$) is equal to the polar reaction constant ρ_n (Table 3). This parameter provides a measure for the interaction between the 3,5-substituents and positive charge at the transition state for reactions where the resonance electron-donating 4-substituent is held constant. By comparison, the smaller absolute value of $\rho_n = -4.9$ reported for the solvolysis of 3-substituted 1-(4-methoxyphenyl)ethyl chlorides in 50/50 (v:v) water/trifluoroethanol compared with $\rho_n = -8.3$ for solvolysis of 3,5 disubstituted methoxybenzyl chlorides (Table 3) is consistent with a reduction in the transition state positive charge at the secondary benzylic carbon compared with the primary benzylic carbon of **X,Y-1-Cl**.[4] We propose that this is due to the competing delocalization of positive

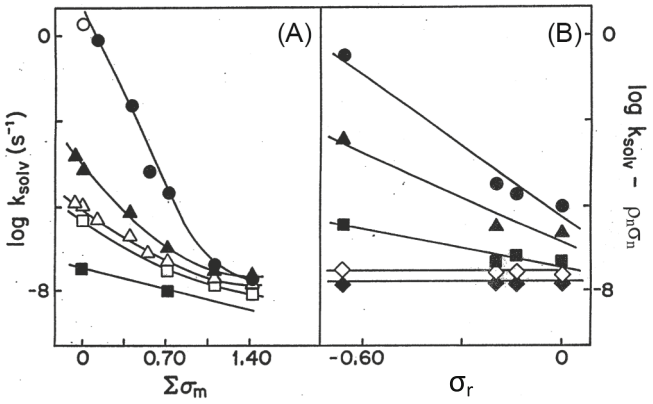


FIGURE 2 Hammett correlations of rate constants k_{solv} for the solvolysis of ring-substituted benzyl chlorides in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$). (A) Reactions where the 4-ring substituent is held constant as the 3,5-substituents are varied. The slopes of the linear regions ($\sigma_n = \sigma_m \leq 0.71$) of the individual correlations are the Hammett reaction constants ρ_n (Equation 4). Key: solid circle, constant 4-OMe; solid triangle, constant 4-Me; open triangles; constant 4-H; open squares, constant 4-Br; solid squares; constant 4-NO_2. (B) Reactions where the 3,5-ring substituents are held constant as the 4-substituent is varied. The slopes of the individual correlations are equal to the Hammett reaction constants ρ_r (Equation 5). Key: solid circles, constant 3, 5-H; solid triangle, constant 3-Me, 5-H; solid squares, constant 3-NO_2, 5-H; open diamonds, constant 3-Br, 5-NO_2; closed diamonds, constant 3, 5-NO_2.

charge [hyperconjugation] onto the methyl group that is attached to the benzylic carbon.

The decrease in ρ_n with increasing 4-substituent constant σ_r at 3,5 disubstituted benzyl chlorides (Table 3) shows that the magnitude of the interaction between the 3,5 ring-substituents and the reaction center decrease as positive charge at the benzylic carbon is destabilized by the change from electron-donating to electron-withdrawing 4-substituents. This is consistent with a tightening in the transition state bonding at the reacting benzylic carbon that results in a decrease in positive charge at this carbon.

Figure 2B shows the fits of the data from Table 1 to Equation (5) for reactions where the 3,5-substituents are held constant as the 4-substituent is varied. Several of these 4-substituents (-OMe, -Me, -Br) show both polar and resonance interactions with the reaction center. In these cases the value for the resonance substituent constant σ_r was calculated as the difference between the Brown substituent constant σ^+ and the polar substituent constant σ_n; $(\sigma_r = \sigma^+ - \sigma_n)$.[24] The term $\rho_n\sigma_n$ from Equation (4) corrects the value of k_{solv} for small differences in the polar interaction of the *para*-substituents with the transition state.[25] The slopes of the plots of log $k_{solv} - \rho_n\sigma_n$ against σ_r from Figure 2B are equal to the

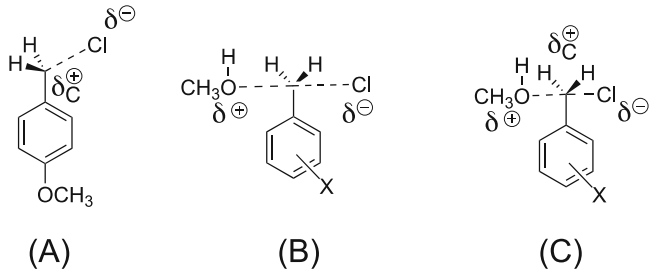
TABLE 3 Values for the Hammett reaction constants ρ_n and ρ_R for the solvolysis reactions of ring-subsituted benzyl chlorides in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$) determined, respectively, from the fits of the data from Figure 2A,B to Equations (3) and (4).

Constant 4-Substituent	ρ_n	Constant 3,5-substituents	ρ_r
MeO- $\sigma_r = -0.66$	−8.3	H, H $\sigma_m = 0$	−7.2
Me- $\sigma_r = -0.20$	−3.6	H, Br $\sigma_m = 0.28$	−4.7
H- $\sigma_r = 0$	−2.4	H, NO_2 $\sigma_m = 0.71$	−1.9
Br- $\sigma_r = -0.14$	−2.0	Br, NO_2 $\Sigma\sigma_m = 0.99$	−0.2
NO_2 $\sigma_r = 0$	−0.9	NO_2, NO_2 $\Sigma\sigma_m = 1.42$	≈0

values of the resonance reaction constants ρ_r (Table 3). By comparison, a value of $\rho_r = -4.4$ was determined for the solvolysis reactions of ring-substituted 1-phenylethyl chlorides in 50/50 (v:v) water trifluoroethanol.[4]

Table 3 shows that there is sharp decrease in the values of ρ_r and ρ_n for increasing values of σ_r and σ_n. There are two possible causes for the changes in Hammett reaction constant ρ_n and ρ_r shown in Figure 2.

1. The plots of values of log k_{solv} against $\Sigma\sigma_m$ for the solvolysis reactions of **X,Y-1-Cl** (Figure 2A) are linear for $\Sigma\sigma_m \leq 0.71$, and then show upward breaks to smaller negative slopes for $\Sigma\sigma_m > 0.71$. The solvolysis reaction of **1-Cl** in aqueous solvents has been shown to proceed by a stepwise $D_N + A_N$ reaction mechanism with a rate-determining transition state for heterolytic bond cleavage to form the 4-methoxybenzyl carbocation intermediate (Scheme 3A).[10,11] The large negative value of ρ_n = -8.3 is for the stepwise solvolysis reactions of **X,Y-1-Cl** to form **X,Y-1**$^+$; and, the decrease in slope for $\Sigma\sigma_m > 0.71$ is due to a change to a concerted A_ND_N reaction mechanism.
2. The values of $\rho_n \geq$ -3.6 determined for the reactions of the remaining 4-substituted benzyl chlorides (Table 3) are for solvolysis by a concerted A_ND_N reaction mechanism. The individual plots from Figure 2A each show upward curvature, which corresponds to an increase in the value of ρ_n as electron-withdrawing 3,5-substituents are added to the different 4-substituted substrates. This change in ρ_n is consistent with an anti-Hammond shift in the structure of the transition state for this concerted solvolysis reaction from a loose, or exploded,[2,26] structure for the fast solvolysis reactions through transition states that are



SCHEME 3 Hypothetical transition states for solvolysis reactions of ring substituted benzyl derivatives. (A) Transition state for stepwise $D_N + A_N$ reactions of **X,Y-1-cl**. (B) Open transition state for A_ND_N reactions of methanol. (C) Tight transition state for A_nD_n reactions of methanol.

strongly stabilized by resonance interactions between aromatic ring and the benzylic carbon (Scheme 3B), to a tighter structure with stronger bonding interactions to the benzylic carbon (Scheme 3C).[16] A similar anti-Hammond-shift in the structure of the transition state will also account for the decreasing values of ρ_r (Table 3) determined for solvolysis of ring-substituted benzyl chlorides with different constant 3,5-ring substituents (Table 3).

4.2 | Solvolysis reactions in 70/27/3 water/trifluoroethanol/methanol

Figure 3 shows a superposition of plots of values of log k_{solv} from Figure 2A for solvolysis ring-substituted benzyl chlorides in 20% acetonitrile in water at 25°C (right hand axis) and of values of the product selectivity log (k_{MeOH}/k_{TFE}) for solvolysis in 70/27/3 (v/v/v) HOH/TFE/MeOH (left hand axis) against the sum of the 3,5-ring substituent constants for solvolysis of **X,Y-1-Cl** (4-MeO-, Figure 3A) and **X,Y-2-Cl** (4-Me, Figure 3B).

The values of log (k_{MeOH}/k_{TFE}) for solvolysis of X,Y-**1**-Cl define an open V shaped plot similar to that observed in studies on the solvolysis reaction of ring-substituted 1-phenylethyl derivative in 50/45/5 (v/v/v) HOH:TFE:MeOH.[5] Large values of k_{MeOH}/k_{TFE} are observed for solvolysis of **X,Y-1-Cl** when X,Y are weakly (X = H) or strongly (X = 3,5-NO_2) electron-withdrawing. The minimum selectivity is observed for solvolysis of **4-NO_2-1-Cl**. The large values of log (k_{MeOH}/k_{TFE}) on the left-hand side of Figure 3A are for partitioning of the **X,Y-1**$^+$ carbocation reaction intermediate between addition of methanol and trifluoroethanol (Scheme 4).[10] This selectivity decreases as the carbocation intermediate is destabilized by 3,5-ring substituents due to a Hammond-effect[15] on the position of the transition state for solvent addition to the carbocation. Similar Hammond effects have been reported for addition of alcohols to ring-substituted 1-phenylethyl[21] and 1-phenyl-2,2,2-trifluroethyl carbocations.[20,22] The upward break in the values of log (k_{MeOH}/k_{TFE}) is due to a change from a stepwise to a concerted solvolysis reaction mechanism, in which the alcohol provides nucleophilic push to displacement of the leaving group (Scheme 3B).[5]

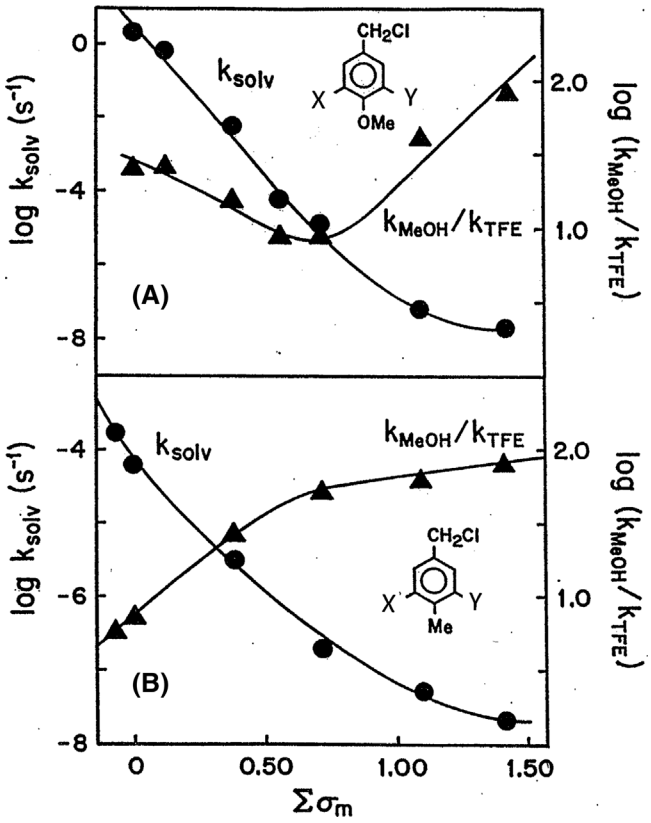
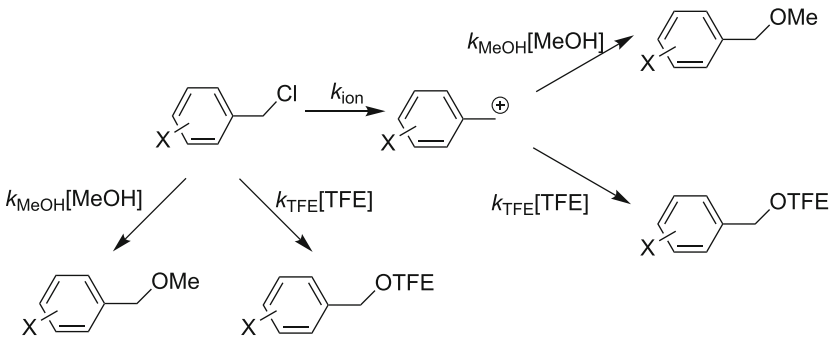


FIGURE 3 Structure-reactivity plots of log k_{solv} (closed circles) against $\Sigma\sigma_m$ for solvolysis in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$) superimposed on plots of the methanol selectivity log (k_{MeOH}/k_{TFE}) for reactions in 70/27/3 (v/v/v) HOH/TFE/MeOH at $I = 0.70$ ($NaClO_4$). (A) Solvolysis of **X,Y-1-Cl**. (B) Solvolysis of **X,Y-2-Cl**.

The upward breaks in the plots of log k_{solv} and log (k_{MeOH}/k_{TFE}) for solvolysis of **X,Y-1-Cl** occur at similar positions on Figure 3A. This provides strong support for the conclusion that the change from a stepwise to concerted reaction mechanism accounts for both breaks. The increase in the alcohol selectivity log (k_{MeOH}/k_{TFE}) for the solvolysis reactions of **X,Y-1-Cl** when $\Sigma\sigma > 0.71$ is consistent with an anti-Hammond shift from an exploded (Scheme 3B)[2,26] to a tight (Scheme 3C) reaction transition state.[5,16]

The superposition of Hammett correlations of values of log k_{solv} and log (k_{MeOH}/k_{TFE}) for the solvolysis of **X,Y-2-Cl** (Figure 3B), **X,Y-3-Cl** (Figure 4A), or **X,Y-4-Cl** (Figure 4B) show in all cases a good correlation between



SCHEME 4 Solvolysis reactions of **X,Y-1-Cl** by concurrent stepwise $D_N + A_N$ and concerted A_ND_N reactions mechanisms.

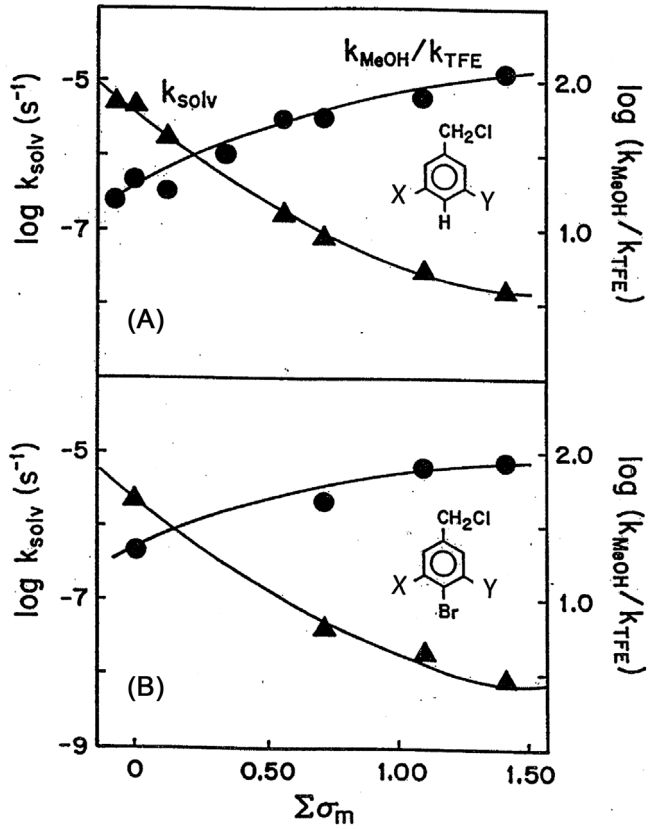


FIGURE 4 Structure-reactivity correlations of values of log k_{solv} (closed circles) against $\Sigma\sigma_m$ for solvolysis in 20% acetonitrile in water at 25°C and $I = 0.80$ ($NaClO_4$) superimposed on correlations of the methanol selectivity log (k_{MeOH}/k_{TFE}) (closed triangles) for reactions in 70/27/3 (v/v/v) HOH/TFE/MeOH at $I = 0.70$ ($NaClO_4$). (A) Solvolysis of **X,Y-3-Cl**. (B) Solvolysis of **X,Y-4-Cl**.

the upward curvature observed for plots of log k_{solv} and the downward curvature observed for plots of log (k_{MeOH}/k_{TFE}) on moving from the left- to the right-hand side of these correlations. This reflects the approach to limiting values of log $k_{solv} \approx$ -8 and log (k_{MeOH}/k_{TFE}) $\approx$ 2.1 at the right-hand side of these correlations. These limits are consistent with the approach to an invariant reaction transition state as the 3,5-ring substituents are changed from 3,5-H to strongly electron-withdrawing 3,5-di-NO_2.

4.3 | Reaction energy profile

The structure-reactivity correlations for solvolysis of ring-substituted benzyl chlorides shown in Figures 2–4 may be rationalized using a two-dimensional More–O'Ferrall reaction-coordinate diagram (Figure 5).[16,27] This profile assigns separate coordinates to cleavage of the carbon-chloride bond to the leaving group and to formation of the bond to nucleophilic solvent. The fully stepwise solvolysis reaction is shown to run along the top and outside right borders of Figure 5. The solvolysis of **1-Cl** proceeds by this stepwise mechanism through the solvent-equilibrated carbocation intermediate $\mathbf{1}^+$ that partitions between addition of different ROH. The liberated intermediate forms because the carbocation lifetime $1/k_s$ for solvent addition is sufficiently long to allow for the diffusional separation of the leaving group by k_{-d}.

The sharp upward break in the value of log k_{MeOH}/k_{TFE} observed for the reactions of **3,5-1-Cl** (Figure 3A) is due to a change to a concerted bimolecular solvolysis reaction through the transition state A that lies on the interior of the More O'Ferrall diagram. The position of this transition state then shifts on the interior of the diagram from A to D, due to an anti-Hammond effect, as the energy of the carbocation intermediate in the upper right-hand corner is increased relative to the hypothetical pentavalent species (not shown) in the lower left-hand corner.[16,27]

Combining $\rho_n = 2.5$ for addition of solvent to ring-substituted phenylethyl carbocations,[4] $\Sigma\sigma_m = 0.99$ for the 3-Br and 5-NO_2 substituents, and $k_s = 2 \times 10^8\ s^{-1}$ for addition of solvent to $\mathbf{1}^+$, gives $k_s \approx 6 \times 10^{10}\ s^{-1}$ for addition of solvent to **3-Br**, **5-NO_2-1**$^+$, which is longer than the vibrational rate constant of $\approx 10^{13}$ s that is proposed as a limit for carbocation nucleophile addition reactions.[5,6] This provides evidence that the change to the concerted solvolysis reaction mechanism for **3-Br**, **5-NO_2-1-Cl** is not enforced by the absence of a significant lifetime for the carbocation intermediate of the stepwise reaction.[6]

A rate constant of $k_s = 2 \times 10^{10}\ s^{-1}$ for addition of solvent to the 4-methylbenzyl carbocation ($\mathbf{2}^+$) in a mostly aqueous solvent can be calculated from

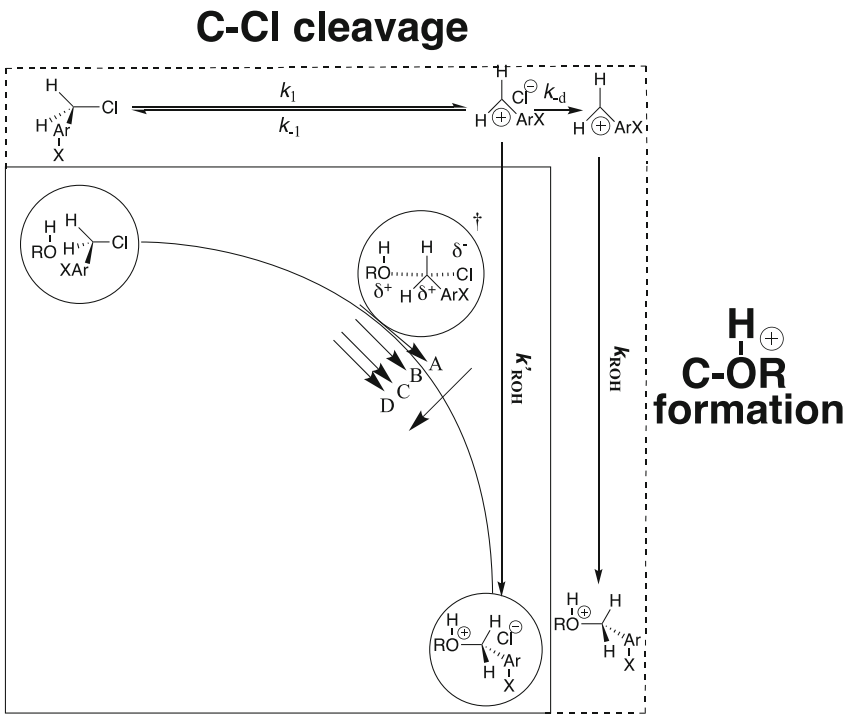


FIGURE 5 Two-dimensional More–O'Ferrall reaction coordinate diagram for the solvolysis reactions of ring-substituted benzyl chlorides. An anti-Hammond shift in the position of the transition state for a concerted reaction, from A to D, is observed for a change from electron-donating to electron-withdrawing 3,5-ring substituents.

$k_s = 6 \times 10^9\ s^{-1}$ for addition of a solvent of 50/50 water/trifluoroethanol to the 1-(4-methylphenyl)ethyl carbocation,[21] and the 4-fold larger rate constant for addition of this solvent to the 4-methoxybenzyl carbocation ($\mathbf{1}^+$) compared with the 1-(4-methoxyphenyl)ethyl carbocation.[10] We conclude that $\mathbf{2}^+$ has a finite lifetime in 70/27/3 (v/v/v) HOH:TFE:MeOH, but reacts with solvent (k'_{MeOH}, Figure 5) before there is significant escape of chloride anion from the ion pair (k_{-d}) to form the liberated carbocation intermediate. The value of $k_{MeOH}/k_{TFE} = 7.3$ (Table 2) determined for the reaction of **2-Cl** is larger than the limiting value of $k_{MeOH}/k_{TFE} \approx 3$ determined for the partitioning of short-lived ion-pair intermediates.[21] This analysis suggests that **2-Cl** reacts by concurrent stepwise solvolysis through a carbocation-anion reaction intermediate, and concerted bimolecular solvolysis that avoids formation of this intermediate.

The small barrier estimated above for addition of solvent to the **3-Br-5-NO$_2$-1**$^+$ ($k_s \approx 6 \times 10^{10}\ s^{-1}$) suggests that this 4-methoxy substituted carbocation may form as an intermediate of a stepwise solvolysis reaction. However, the nucleophile selectivity of $k_{MeOH}/k_{TFE} = 41$ determined for solvolysis of **3-Br-5-NO$_2$-1-Cl** is larger than expected for trapping of the short-lived intermediate **3-Br-5-NO$_2$-1**$^+$. The results are consistent with a concerted A_ND_N solvolysis reaction for **3-Br-5-NO$_2$-1-Cl**, where there is a significant advantage to the coupling of bond cleavage and bond formation at the pentavalent reaction transition state for reaction the primary carbon for this substrate.[28] There is good evidence that the advantage from this coupling is much smaller for substitution reactions at the secondary carbon of ring-substituted 1-phenylethyl derivatives due to steric hindrance to formation of the more crowded pentavalent reaction transition state.[5] The large methanol selectivity observed for reactions of ring-substituted benzyl chlorides that proceed through putative carbocation intermediates more unstable than $\mathbf{2}^+$ are consistent with concerted bimolecular displacement reactions that in many or most cases are enforced because there is no significant barrier for addition of nucleophile to the intermediate of the stepwise reaction.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

John P. Richard https://orcid.org/0000-0002-0440-2387

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How to cite this article: P. E. Yeary, J. P. Richard, *J Phys Org Chem* **2024**, *37*(7), e4600. https://doi.org/10.1002/poc.4600