Effect of Electron-Withdrawing α-Substituents on Nucleophile Selectivity toward 4-Methoxybenzyl Carbocations: Selectivities That Are Independent of Carbocation Stability

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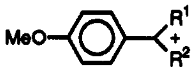
Nucleophile selectivities were determined for partitioning of the following 4-$MeOC_6H_4CR^1(R^2)^+$ (1-$R^1(R^2)$) between reaction with trifluoroethanol and alkyl alcohols in $X/(50 - X)/50$ (v/v/v) alcohol/trifluoroethanol/water: 1-$H(CH_2F)$; 1-$H(CHF_2)$; 1-$CH_3(CF_3)$; 1-$H(CO_2Et)$; 1-$(CF_3)_2$. These were combined with selectivities measured in earlier work to give an extended set of data for the reactions of 1-$R^1(R^2)$. Destabilization of 1-$R^1(R^2)^+$ by electron-withdrawing α-substituents leads to a marked increase in nucleophilic selectivity as measured by the rate constant ratio k_{MeOH}/k_{TFE} for partitioning between reaction with methanol and trifluoroethanol (1-$R^1(R^2)$, k_{MeOH}/k_{TFE}): 1-$H(CH_3)$, 41;[3] 1-$H(CH_2F)$, 40; 1-$H(CHF_2)$, 44; 1-$H(CF_3)$, 80;[4] 1-$CH_3(CF_3)$, 94; 1-$H(CO_2Et)$, 115; 1-$(CF_3)_2$, 180. By contrast, destabilization of α-substituted benzyl carbocations by electron-withdrawing aromatic ring substituents leads to sharp decreases in k_{MeOH}/k_{TFE} and in the selectivities for reaction with other nucleophilic reagents.[2] Two factors are proposed to contribute to the difference in the effects of *meta* ring substituents and α-substituents on nucleophile selectivity toward benzylic carbocations: (1) differential steric/electrostatic interactions of bulky, electron-withdrawing, α-substituents with electron-donating and electron-withdrawing substituents on the alkyl alcohol, and (2) the tendency of electron-withdrawing α-substituents to cause an increase in the intrinsic reaction barrier which leads to an increase in nucleophile selectivity that offsets the decrease in selectivity due to the changing thermodynamic driving force for the carbocation addition reaction.

Introduction

The development of theories to explain the effects of changing carbocation stability on carbocation selectivity for reaction with nucleophilic reagents has been among the most intractable problems in organic chemistry.[1] There have been a number of reports in recent years that destabilization of benzylic carbocations by electron-withdrawing ring substituents leads to marked decreases in the selectivities of these electrophiles toward anionic and neutral nucleophiles.[2-4] These results are in agreement with simple theory which predicts that increasing the thermodynamic driving force for conversion of a carbocation to a neutral adduct should cause a Hammond-type shift in the position of the transition state toward the carbocation reactant.[5,6]

By contrast, destabilization of ring-substituted 1-phenylethyl carbocations by an α-CF_3 for α-CH_3 substitution leads to *small increases* in carbocation selectivity toward alkyl alcohols.[4] The observation that electron-withdrawing ring substituents and α-substituents cause very different changes in the selectivity of benzyl carbocations toward nucleophilic reagents shows that the Hammond postulate alone is insufficient to rationalize these reactivity–selectivity effects.

This paper reports the effect of a large set of electron-withdrawing α-substituents on the selectivity of 4-methoxybenzyl carbocations (1-$R^1(R^2)$) toward alkyl alcohols.


1–$R^1(R^2)$

R^1,R^2 = H, CF_3 $\quad$ CF_3, CF_3
H, CH_2F $\quad$ H, CO_2Et
H, CHF_2 $\quad$ CH_3, CF_3
H,CF_3

The results confirm and extend our initial observation that strongly electron-withdrawing α-substituents cause an increase in the selectivity of 1-$R^1(R^2)$ between reaction with strongly and weakly basic alkyl alcohols.

There are at least two effects of the direct attachment of strongly electron-withdrawing α-substituents at 1-$R^1(R^2)$ which will tend to increase the selectivities of these highly destabilized carbocations in addition reactions of nucleophiles.

(1) A relatively high reactivity of strongly basic alcohols that bear small electron-donating alkyl substituents compared with weakly basic alcohols that bear larger electron-withdrawing haloalkyl substituents might be explained by differential steric and/or electrostatic interactions in the transition state between these nucleophiles and the electron-withdrawing α-substituents.

(2) There is good evidence that the destabilizing inductive effect of strongly electron-withdrawing α-substituents at 1-$R^1(R^2)$ is attenuated by increased resonance

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[1] (a) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348–354. (b) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239–2250.

[2] Hammond effects[5] have been reported for the following carbocation–nucleophile combination reactions: (a) Nucleophilic addition of substituted alkyl alcohols to ring-substituted 1-phenylethyl carbocations (ref 3). (b) Nucleophilic addition of substituted alkyl alcohols, alkylamines, and alkyl carboxylate ions to ring-substituted 1-phenyl-2,2,2-trifluoroethyl carbocations (ref 4). (c) Nucleophilic addition of anions to the trityl carbocation (McClelland, R. A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1986**, *108*, 7023–7027) and the xanthylium carbocation (McClelland, R. A.; Banait, N.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 2929–2935). (d) Nucleophilic addition of azide ion and solvent (ref 13) and alkylamines (McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1992**, *114*, 1816–1823) to diarylmethyl and triarylmethyl carbocations. (e) Nucleophilic addition of halide ions to $XC_6H_4C(CF_3)_2^+$ (Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 4588–4595).

[3] Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383.

[4] Richard, J. P.; Amyes, T. L.; Vontor, T. *J. Am. Chem. Soc.* **1992**, *114*, 5626–5634.

[5] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.

[6] Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511–527.

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Table 1. Nucleophile Selectivities for Reactions of $4\text{-}MeOC_6H_4CR^1(R^2)Y$ with Alkyl Alcohols and Water[a]

		k_{ROH}/k_{TFE},[b] R^1,R^2 =						
ROH	pK_a[c]	H,CH_3[d,e]	H,CH_2F[d,f]	H,CHF_2[d,f]	H,CF_3[d,g]	CH_3,CF_3[h,i]	H,CO_2Et[i,j]	CF_3,CF_3[k]
CH_3OH	15.5	41	40^{j}	44	80	94	115	180^{l}
CH_3CH_2OH	16.0	30	28^{j}	29	55			
$HOCH_2CH_2OH$	15.1	21	20	22	37			
$CH_3OCH_2CH_2OH$	14.8	15	13	15	17			25^{m}
$ClCH_2CH_2OH$	14.3	9.8	9.0	10	12.5			14.6^{m}
$NCCH_2CH_2OH$	14.0	5.1	6.0	4.4	6.4			
$HC{\equiv}CCH_2OH$	13.5	10.7	10.5	10.3	14.5			
Cl_2CHCH_2OH	12.9	3.2	3.3	3.1	3.5			
HOH[n]	15.7	1.9	2.3	2.9	3.8	4.0	2.6	9.0
K_{az}[o] (M)		3×10^{-17}	4×10^{-20}	1×10^{-22}	3×10^{-24}	4×10^{-22}	2×10^{-21}	2×10^{-27}
k_s[p] (s^{-1})		5×10^{7}	1×10^{8}	1×10^{8}	5×10^{7}	3×10^{7}	2×10^{7}	5×10^{6}
k_{MeOH}[q] ($M^{-1}\,s^{-1}$)		3×10^{7}	6×10^{7}	5×10^{7}	4×10^{7}	2×10^{7}	2×10^{7}	4×10^{6}

[a] In $X/(50 - X)/50$ (v/v/v) alcohol/trifluoroethanol/water at 25 °C and constant ionic strength of 0.50 ($NaClO_4$). [b] Dimensionless ratio of second-order rate constants determined from product analysis. [c] Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*, 3rd ed.; Fasman, G. D., Ed.; CRC Press: Cleveland, 1976; Vol. 1, pp 305–351. [d] For reactions in 5/45/50 (v/v/v) alcohol/trifluoroethanol/water. [e] Data from ref 3. [f] Y = Cl and where indicated $F_5C_6CO_2$. [g] Data from ref 4. [h] Y = Br. [i] For reactions in 2/48/50 (v/v/v) alcohol/trifluoroethanol/water. [j] Y = $F_5C_6CO_2$. [k] Y = $CH_3C_6H_4SO_3$. [l] For a reaction in 0.25/49.75/50 methanol/trifluoroethanol/water. [m] For a reaction in 2.5/47.5/50 (v/v/v) alcohol/trifluoroethanol/water. [n] For reactions in 50/50 (v/v) trifluoroethanol/water. [o] Equilibrium constants for formation of $1\text{-}R^1(R^2)$ from the neutral azide ion adducts in 50/50 (v/v) trifluoroethanol/water (ref 11). [p] Pseudo-first-order rate constants for reaction of $1\text{-}R^1(R^2)$ with a solvent of 50/50 (v/v) trifluoroethanol/water (ref 11). [q] Second-order rate constants for the reaction of $1\text{-}R^1(R^2)$ with methanol, calculated as described in the text.

delocalization of positive charge onto the 4-methoxyphenyl ring.[7-12] This increase in resonance stabilization of the carbocation is expected to cause an acceleration of the change in energy with developing covalent bond formation (steeper curvature) along the reaction coordinate for a two-dimensional energy diagram for the carbocation addition reaction, an increase in the intrinsic barrier for the reaction, and a shift to a more product-like transition state that opposes the Hammond-type shift to a more reactant-like transition state.

It is suggested that these two effects are sufficiently large to overwhelm the Hammond effect of α-substituents on the selectivity of $1\text{-}R^1(R^2)$ toward alkyl alcohols.

Experimental Section

Materials. Reagent-grade inorganic salts and organic chemicals for synthesis, trifluoroethanol (Aldrich), and methanol (HPLC grade, Fisher) were used without further purification. The water used for kinetic studies was distilled and then passed through a Milli-Q water purification system.

Syntheses of Substrates. The following substrates used in this work were synthesized by published procedures: $4\text{-}MeOC_6H_4CH(CH_2F)Cl$,[8] $4\text{-}MeOC_6H_4CH(CHF_2)Cl$,[8] $4\text{-}MeOC_6H_4(CF_3)_2OTs$,[10b] $4\text{-}MeOC_6H_4CH(CO_2Et)O_2CC_6F_5$,[11] and $4\text{-}MeOC_6H_4CCH_3(CF_3)Br$.[11]

HPLC Analysis. Reaction products were separated by HPLC as described previously[3,4,7b] and were detected by the UV absorbance of the respective aromatic rings at the following wavelengths: $4\text{-}MeOC_6H_4CH(CH_2F)Y$, 271 nm; $4\text{-}MeOC_6H_4CH(CHF_2)Y$, 271 nm; $4\text{-}MeOC_6H_4C(CF_3)_2Y$, 263 nm; $4\text{-}MeOC_6H_4CCH_3(CF_3)Y$, 271 nm; and $4\text{-}MeOC_6H_4CH(CO_2Et)Y$, 273 nm. The nucleophile adducts to these substrates were identified as described in previous work.[3,4,7b,8]

Procedures for Product Studies. Product studies were performed at room temperature (22 ± 2 °C) in solutions of $X/(50 - X)/50$ (v/v/v) alcohol/trifluoroethanol/water ($I = 0.50$, $NaClO_4$) that were prepared as described in previous work.[4] The reactions were initiated by making a 100-fold dilution of a solution of substrate in acetonitrile into the reaction mixture to give a final substrate concentration of *ca.* 10^{-4} M. The alcohol adducts were shown to be stable to the reaction conditions by determination of product ratios over extended periods of time.

The reactions of $4\text{-}MeOC_6H_4C(CF_3)_2OTs$ and $4\text{-}MeOC_6H_4CH(CO_2Et)O_2CC_6F_5$ were carried out in dilute solutions of perchloric acid in order to eliminate products arising from the reaction of trifluoroethoxide ion. Identical product selectivities were observed for reaction of these substrates in the presence of 0.33 and 1 mM perchloric acid.

The procedure for determination of product yields from the reaction of $4\text{-}MeOC_6H_4C(CF_3)_2OTs$ was modified to remove the quinone methide product of aromatic substitution at $1\text{-}(CF_3)_2$ because the quinone methide interferes with analysis of the yield of the aliphatic substitution products.[8] After a 5-min reaction time (*ca.* 15 half-lives) a sufficient volume of aqueous 1.0 M NaN_3 was added to give a final azide ion concentration of 3.3 mM, which quantitatively converts the quinone methide to $4\text{-}HOC_6H_4C(CF_3)_2N_3$. The product ratios were then determined by HPLC analysis.

Calculation of Nucleophile Selectivities. Nucleophile selectivities for the reactions of $4\text{-}MeOC_6H_4CR^1(R^2)Y$ were calculated from the ratios of the areas of the product peaks determined by HPLC analyses, according to eq 1. Equation 1

$$k_{Nu1}/k_{Nu2} = [\text{area}]_{RNu1}[Nu_2]/[\text{area}]_{RNu2}[Nu_1] \quad (1)$$

holds when the two nucleophile adducts have identical extinction coefficients at the wavelength used for HPLC analysis. It was shown in previous work that the water and alkyl alcohol adducts to $1\text{-}H(CH_3)$[3] and $1\text{-}H(CF_3)$[4] have identical extinction coefficients (±10%), and it is assumed that the relative extinction coefficients of other $1\text{-}R^1(R^2)OR^3$ studied in the present work are independent of the R^3 substituent.

Results

Nucleophile selectivities, k_{ROH}/k_{TFE}, determined from the ratio of product yields for the reactions of $4\text{-}MeOC_6H_4CR^1(R^2)Y$ in $X/(50 - X)/50$ (v/v/v) alcohol/trifluoroethanol/water ($I = 0.50$, $NaClO_4$) are reported in Table 1. The alcohol content of the solvents used for these experiments range from 5% ($X = 5$) to 0.25% ($X = 0.25$).

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(7) (a) Richard, J. P. *J. Am. Chem. Soc.* **1986,** *108,* 6819–6820; (b) *Ibid.* **1989,** *111,* 1455–1465.

(8) Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990,** *112,* 9513–9519.

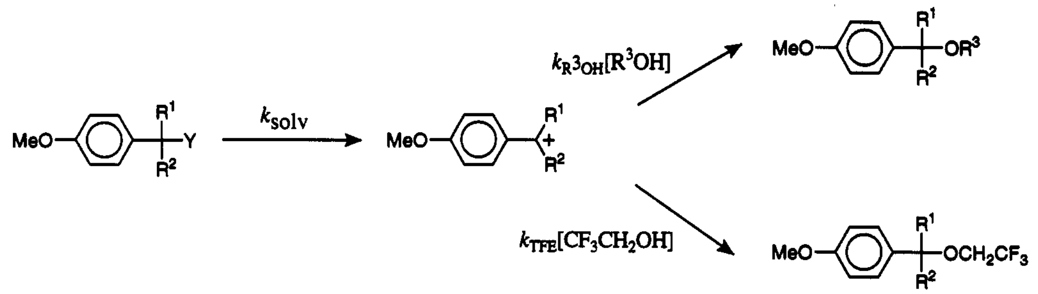
(9) Richard, J. P. *J. Am. Chem. Soc.* **1989,** *112,* 6735–6744.

(10) (a) Allen, A. D.; Ambidge, C; Che, C.; Michael, H.; Muir, R. J.; Tidwell, T. T. *J. Am. Chem. Soc.* **1983,** *105,* 2343–2350. (b) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *Ibid.* **1986,** *108,* 3470–3474. (c) Tidwell, T. T. In *Advances in Carbocation Chemistry*; Creary, X., Ed; JAI Press, Inc.: Greenwich, CT, 1989; Vol. 1, pp 1–44.

(11) Amyes, T. L.; Stevens, I. W.; Richard, J. P. *J. Org. Chem.* **1993,** *58,* 6057–6066.

(12) (a) Richard, J. P., Amyes, T. L.; Stevens, I. W. *Tetrahedron Lett.* **1991,** *32,* 4255–4258. (b) Johnson, L. J.; Kwong, P.; Shelemay, A; Lee-Ruff, E. *J. Am. Chem. Soc.* **1993,** *115,* 1664–1669.

Scheme I



It has been shown in earlier work that the values of k_{MeOH}/k_{TFE} for reaction of 4-$Me_2NC_6H_4CH(CF_3)Y$ do not change over this small variation in solvent composition.[4]

Discussion

The substrates 4-$MeOC_6H_4CR^1(R^2)Y$ studied in this work have been shown to undergo reaction by a common $D_N + A_N$ (S_N1)[3,4,7-9,11,12a] mechanism through carbocation intermediates 1-$R^1(R^2)$ which partition between reaction with solvent and added nucleophilic reagents (Scheme 1). Table 1 lists the following rate and equilibrium constants for the formation and reaction of 1-$R^1(R^2)$.

(1) Equilibrium constants K_{az}, summarized in a recent report from this laboratory,[11] for formation of 1-$R^1(R^2)$ from the neutral azide adducts. These were calculated as rate constant ratios k_{solv}/k_{az}, where k_{solv} (s^{-1}) is the rate constant for ionization of the azide ion adduct to give 1-$R^1(R^2)$ and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of 1-$R^1(R^2)$ with azide ion.[13,14]

(2) Pseudo-first-order rate constants, k_s (s^{-1}), for reaction of 1-$R^1(R^2)$ with a solvent of 50/50 (v/v) trifluoroethanol/water, also from ref 11. These were calculated from the product rate constant ratios k_{az}/k_s (M^{-1}) for partitioning of 1-$R^1(R^2)$ between reaction with azide ion and solvent and $k_{az} = 5 \times 10^9$ M^{-1} s^{-1} for the diffusion-limited reaction of 1-$R^1(R^2)$ with azide ion.[13,14] These data show that the solvent reacts with the liberated carbocation intermediates, and not carbocation-leaving group ion pairs, because irreversible diffusional separation of the ion pair to give the free ions ($k_{-d} \approx 10^{10}$ s^{-1})[3] is essentially complete before there is any significant capture of the ion pair by solvent ($k_s \leq 10^8$ s^{-1}, Table 1).

(3) Second-order rate constants for reaction of 1-$R^1(R^2)$ with methanol, calculated from the values of k_s (s^{-1}), k_{HOH}/k_{TFE}, and k_{MeOH}/k_{TFE} in Table 1 and $k_s = k_{HOH}[HOH] + k_{TFE}[CF_3CH_2OH]$ for reaction in 50/50 (v/v) trifluoroethanol/water.

The second-order rate constants for the reactions of 1-$R^1(R^2)$ with methanol are $\leq 6 \times 10^7$ M^{-1} s^{-1} (Table 1), and the rate constants for the less reactive alcohol nucleophiles are smaller still. These rate constants are all well below $k_{MeOH} = 1 \times 10^9$ M^{-1} s^{-1} that was observed for reaction of the 1-(4-methylphenyl)ethyl carbocation, which is close to the limiting rate constant for an encounter-limited reaction of methanol.[3] This shows that the rate-determining step for the reactions of 1-$R^1(R^2)$ with alkyl alcohols is chemical bond formation within the carbocation–nucleophile encounter complex and not the formation of this complex.[3,4] Therefore, changes in nucleophile selectivity for the reactions of 1-$R^1(R^2)$ must reflect changes in the relative barriers to the chemical bond formation step.

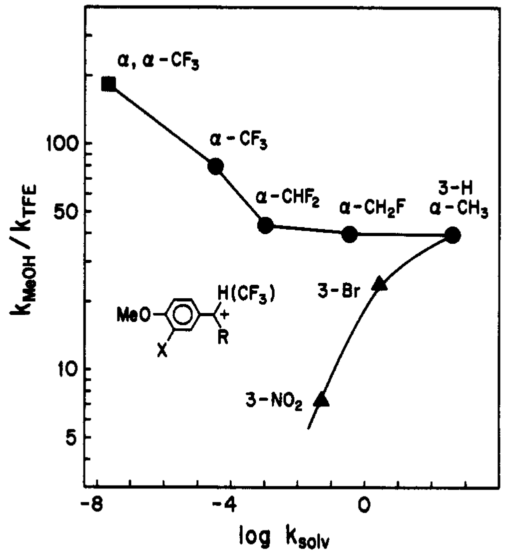


Figure 1. Relationship between log k_{solv} for the ionization of 3-X,4-$MeOC_6H_4CR^1(R^2)Cl$ to give 3-X,4-$MeOC_6H_4CR^1(R^2)^+$ and k_{MeOH}/k_{TFE} (Table 1) for partitioning of these carbocations in 5/45/50 (v/v/v) methanol/trifluoroethanol/water (I = 0.50, $NaClO_4$). The upper and lower lines show, respectively, the effect of addition of β-fluoro and *m*-ring substituents to 4-$MeOC_6H_4$-$CH(CH_3)^+$.

Figure 1 provides still another example of seemingly self-contradictory data which have plagued the development of theories to explain the effect of changing carbocation stability on nucleophile selectivity. The lower line of Figure 1 shows that the addition of electron-withdrawing *meta* ring substituents to 1-$H(CH_3)$ causes large decreases in carbocation stability as measured by rate constants k_{solv} (s^{-1}) for carbocation formation in solvolysis reactions of the chloride ion adducts[15] and large decreases in carbocation selectivity as measured by the rate constant ratio k_{MeOH}/k_{TFE} for partitioning of the carbocation between reaction with methanol and trifluoroethanol.[16a]

By contrast, destabilization of 1-$H(CH_3)$ by the addition of β-fluorine substituents initially has no effect on $k_{MeOH}/$

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(13) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009–1014.

(14) McClelland, R. A.; Cozens, F. L.; Steenken, S.; Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1717–1722.

(15) The values of k_{solv} are taken from ref 8.

(16) (a) The slightly larger rate constants for reaction of methanol than of ethanol (a more basic alcohol) with 1-$R^1(R^2)$ are probably due to a smaller steric barrier to the reaction of methanol.[3,4] (b) Calculated from the slopes of plots of log (k_{ROH}/k_{TFE}) against the pK_a for deprotonation of ROH. A limited range of alkyl alcohols is used for these Brønsted correlations (ROH = CH_3CH_2OH, $CH_3OCH_2CH_2OH$, $ClCH_2CH_2OH$, and Cl_2CHCH_2OH) in order to exclude alcohols which show abnormal reactivity for their pK_as.[3] (c) There is no detectable difference (±10%) in the rate constant ratio k_{MeOH}/k_{EtOH} (Table 1) for the reactions of 1-$H(R^2)$ with R^2 = CH_3, CH_2F, CHF_2, and CF_3.

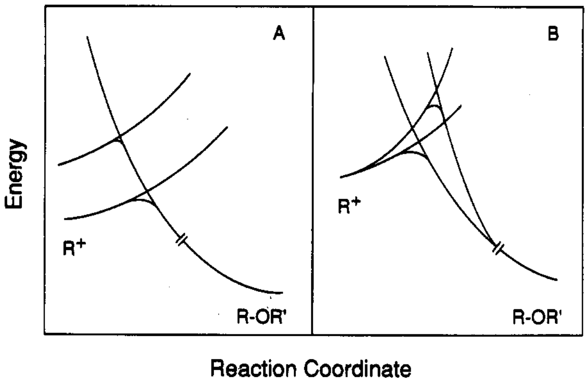


Figure 2. Hypothetical reaction coordinate profiles for the addition of alkyl alcohols to carbocations which show: (A) a simple Hammond effect on the position of the reaction transition state and (B) the effect of changing the intrinsic reaction barrier on the position of the reaction transition state.

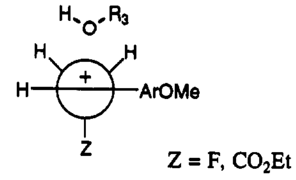
k_{TFE}, but there are marked increases in nucleophile selectivity with the addition of multiple β-fluorine substituents (upper line, Figure 1). The substituent effects on the stability of 1-$R^1(R^2)$ have been estimated from the change in K_{az} (Table 1) for formation of 1-$R^1(R^2)$ from the respective neutral azide ion adducts.[11] In the most extreme case, a 14 kcal/mol *destabilization* of 1-H(CH_3) by a pair of α-CF_3 groups actually causes a 4-fold *increase* in k_{MeOH}/k_{TFE}.

A similar trend is observed for nucleophile selectivities of a larger set of alkyl alcohols (Table 1). Selectivity, as measured by the slopes β_{nuc} of Brønsted plots of rate data for reactions of alkyl alcohols with 3-X-1-H(CH_3), decreases from $\beta_{nuc} = 0.32$ for X = H to $\beta_{nuc} = 0.15$ for X = NO_2,[3] but there is no significant change in β_{nuc} for the reactions of 1-H(R^2) (R^2 = CH_3, CH_2F, CHF_2) and a small increase to $\beta_{nuc} = 0.38$ for reaction of 1-H(CF_3).[16b]

The observed decreasing nucleophile selectivity with decreasing stability of 3-X-1-H(CH_3), and several structurally related carbocations[2] has been attributed to Hammond-type shifts in the position of the reaction transition state on a two-dimensional reaction coordinate diagram (Figure 2A).[5,6] However, this simple model cannot account for both the *changing* selectivity observed when the stability of 1-H(CH_3) is varied by changing the *meta* ring substituent and the *constant* selectivity observed with even larger changes in carbocation stability caused by changing the α-substituents. Therefore, either the model must be expanded and refined to provide an explanation for these anomalous data or it must be abandoned altogether.

There are at least two effects of the direct attachment of strongly electron-withdrawing α-substituents to 1-R^1(R^2) on nucleophile selectivity which will tend to oppose a decrease in selectivity caused by the Hammond effect.

Steric Effects. Differential steric and/or electrostatic interactions of the hydrogen atoms of the methyl group of methanol and the electron-withdrawing trifluoromethyl group of trifluoroethanol with electron-withdrawing α-substituents might cause an increase in the relative reactivity of methanol towards 1-$R^1(R^2)$.[16c] Such steric/electrostatic effects probably contribute to the exceptionally large nucleophile selectivities observed for addition to the relatively congested benzylic carbons at 1-H(CF_3), 1-CH_3-(CF_3), and 1-$(CF_3)_2$ (Figure 1). However, these interactions alone probably cannot account for the large values of k_{MeOH}/k_{TFE} for the reactions of 1-H(CH_2F) and 1-H(CHF_2) (Figure 1) because they may be relieved by rotation of the β-fluorine(s) out of the path of the approaching nucleophilic reagent (see **2**). Furthermore, an α-carbethoxy group should cause relatively modest steric/electrostatic hindrance to the addition of alcohols to 1-H(CO_2Et) (see **2**), but the methanol/trifluoroethanol selectivity for nucleophilic addition to this carbocation (k_{MeOH}/k_{TFE} = 115) is nearly 3-fold larger than that for addition to 1-H(CH_3).



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Resonance Substituent Effects and Intrinsic Reaction Barriers. There is good evidence that the addition of strongly electron-withdrawing α-substituents to 1-H_2 is accompanied by increased delocalization of charge onto the 4-methoxyphenyl ring.[7-12] This serves to attenuate the destabilizing inductive substituent effects by moving the center of positive charge further away from the positive end of the dipole at the benzylic carbon.

An increase in the resonance stabilization of a reactant or product is accompanied by an increase in the intrinsic kinetic barrier for their interconversion, where the intrinsic barrier (Λ) is defined as the kinetic barrier ($\Delta G^\ddagger = \Lambda$) for the reaction when there is no thermodynamic driving force ($\Delta G^\circ = 0$). This increase in Λ has been observed directly for the reactions of carbanions by measurement of decreasing rate constants for thermoneutral protonation with increasing carbanion stabilization by resonance electron-withdrawing substituents.[17] It has been observed indirectly for the reactions of the highly resonance-stabilized carbocations 1-H(CF_3) and 1-$(CF_3)_2$ in 50/50 (v/v) trifluoroethanol/water by the observation of extraordinarily small rate constants for their reactions with solvent (k_s (s^{-1}), Table 1)[7,8,11] and other nucleophilic reagents.[4]

The tendency of increasing resonance stabilization of carbanions and carbocations to increase the intrinsic kinetic barrier for their reaction is due to the requirement for a relatively large fractional loss of these resonance interactions on moving to the reaction transition state.[17-20] This fraction is substantially larger than the fractional loss of the inductive substituent interactions;[3,17-20] the latter change is thought to provide a better measurement of the fractional progress of reactants toward products on moving to the transition state. The difference in the fractional expression of the equilibrium resonance and inductive substituent effects in the transition state has been referred to as an *imbalance* in the change of these interactions,[6,21] or as the *principle of nonperfect synchronization*,[17,18] which implies a lack of synchronization

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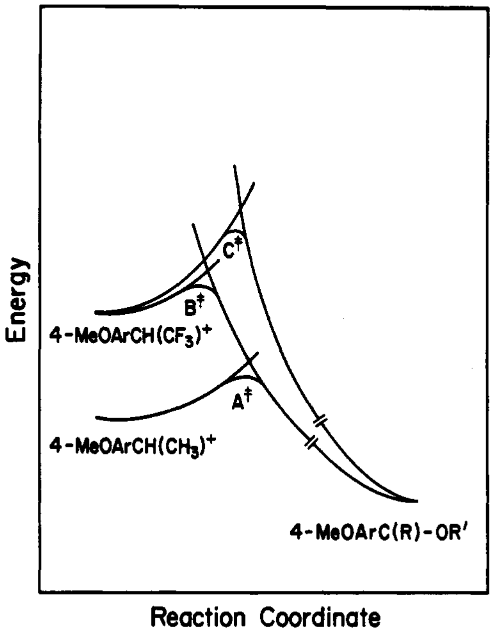

Figure 3. Hypothetical reaction coordinate profiles for the addition of alkyl alcohols to $4\text{-MeOC}_6H_4CH(R^2)^+$ which show the effects of changing the thermodynamic driving force and the intrinsic kinetic barrier on the position of the reaction transition state (see text).

in the loss or development of these interactions[17] on moving from reactant to transition state.

An increase in the intrinsic barrier for a reaction corresponds to a steepening in the curvature of the reaction coordinate (Figure 2B). We now consider the effect of this changing curvature on nucleophile selectivity (Figure 3). A simple Hammond effect of the inductive destabilization of $4\text{-MeOC}_6H_4CH(CH_3)^+$ by an electron-withdrawing α-substituent will cause the reaction transition state to move from *A*‡ to a position *B*‡ which lies closer to the reactants on the *x*-axis. By contrast, the tendency of electron-withdrawing α-substituents to cause an increase in resonance stabilization of $4\text{-MeOC}_6H_4CH(R^2)^+$, a steepening in the curvature of the energy profile, and an increase in the intrinsic barrier for the nucleophile addition reaction, will cause the transition state to shift from *B*‡ to a more central position on the reaction coordinate *C*‡, which lies closer to products. The experimental results reported here for relatively small α-substituents such as α-CH_2F and α-CO_2Et suggest that the resonance and inductive substituent effects cause roughly equal and opposite changes in the nucleophile selectivity, which consequently remains nearly constant.

The above analysis, which is based upon an inspection of the effect of electron-withdrawing α-substituents on the location of the transition state along a two-dimensional reaction coordinate profile for the reactions of $1\text{-}R^1(R^2)$ (Figure 3), is also supported by the Marcus treatment of these profiles.[22] The first derivative of the Marcus equation (eq 2),[23] predicts that nucleophile selectivity will

$$\beta_{\mathrm{nuc}} = \partial \log k_{\mathrm{ROH}}/\partial \mathrm{p}K_{\mathrm{a}} = 0.5 + \Delta G°/8\Lambda \qquad (2)$$

change with changing thermodynamic driving force ($\Delta G°$) and intrinsic barrier (Λ) for the reaction, so that the net substituent effect depends upon the changes in both terms. Resonance electron-donating substituents cause an increase in carbocation selectivity for thermodynamically favorable ($\Delta G° < 0$) reactions with nucleophilic reagents, due to the reinforcing effects of the change to a more positive $\Delta G°$ and increased Λ on nucleophile selectivity (eq 2).[2] However, the change in selectivity may be too small to detect for reactions of highly resonance stabilized carbocations, if Λ has become large relative to the changes in Λ and $\Delta G°$.[1,4] This work provides an unusual and informative example of electron-withdrawing α-substituents that cause $\Delta G°$ to become more negative and Λ to increase. The roughly constant nucleophile selectivities observed for these reactions (Table 1) suggest that the changes in $\Delta G°$ and Λ lead to equal, but opposite, changes in β_{nuc} for eq 2.

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