Importance of Electronic Geminal Interactions in Solvolysis Reactions. Application to the Determination of the α-Silyl Effect on Carbenium Ion Stability

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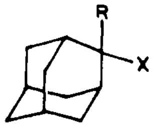
The relative stabilities of carbenium ions, e.g., R_1^+ and R_2^+, are often deduced from the solvolysis rates of the corresponding R_1X and R_2X.[1] In doing so, it is often assumed that relative to the energy difference between the carbenium ions the energy difference between the reactants is insignificant.[1] While it is clear that the presence of large steric or electronic interactions in the precursors must be manifested in their solvolysis rate, this effect has been demonstrated mostly for steric interactions.[1,2] Despite substantial recent evidence from experiment and from ab initio calculations that electronic geminal interactions can be very large even in neutral molecules (e.g., 17.4 kcal/mol in $CH_2(OH)_2$,[3] their significance to organic reactivity was discussed only in a few cases.[4,5] In particular, one of us has argued that the nearly identical solvolysis rates of **1a** and **1b**, X = *p*-nitrobenzoate (OPNB), are not due to the similar stabilities of the corresponding carbenium ions (calculations show that Me_3C^+ is more stable than $(H_3Si)Me_2C^+$ by 6 kcal/mol) but rather it reflects the fact that α-silyl alcohols (models for the OPNB) are electronically destabilized relative to the corresponding alkyl alcohols by 6–8 kcal/mol (eq 1, X = OH, R = H, CH_3).[4a] This conclusion was questioned

$$\mathrm{R_3SiCH_2X + R_3CCH_3 \rightarrow R_3SiCH_3 + R_3CCH_2X} \qquad (1)$$

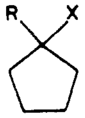
recently on the basis of the relatively fast solvolysis rate of **1**, R = CF_3, X = OTs, which was attributed in part to relief of ground-state strain,[6] suggesting that the solvolysis of **1b** is also accelerated sterically,[6] not electronically as we have argued.[4a]

In this paper we present new experimental and computational evidence showing that electronic interactions in the reactants, between the leaving group (X) and a geminal substituent (R), can affect strongly the solvolysis rates and can alter significantly the relative nucleofugality of leaving groups, even when R is not electronegative, as for the comparison of alkyl and silyl groups. Furthermore, we demonstrate that the size of the geminal interactions depends on the identity of the leaving group, as is manifested in the following Me_3CX/Me_3SiMe_2CX solvolysis rate ratios: 3 for X = OPNB, 792 for X = Cl, and 3010 for X = Br. Failure to include the geminal interactions between R and X in interpretations of solvolysis rates may lead to wrong conclusions regarding the relative stabilities of carbocations.

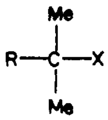
If the solvolysis of **1b** is significantly accelerated by the relief of ground-state steric congestion,[6] then the $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ rate ratio for **2** and **3** is expected to be much larger than for **1**.[7] In contrast, we find that $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ is nearly the same for all three *p*-nitrobenzoates: i.e., 0.92, 1.0, and 3.1, for **1**, **2**, and **3**, respectively, ruling out the presence of significant steric acceleration in **1b**.



1a, R = Me
1b, R = Me_3Si



2a, R = Me
2b, R = Me_3Si



3a, R = Me
3b, R = Me_3Si

How can one demonstrate experimentally the theoretical prediction[4a,b] that *electronic* geminal interactions *destabilize* the ground state of α-silyl *p*-nitrobenzoates relative to that of the corresponding α-methyl OPNB? Geminal interactions are strongly dependent on the electronic characteristics of the interacting groups,[3a,b] and they should therefore be dependent on the leaving group. Ab initio calculations[8a,b] at the MP2/3-21G(*)//3-21G(*) level[8c] indeed show that the exothermicity of eq 1 (R = H), which measures the geminal interactions in H_3SiCH_2X relative to CH_3CH_2X, decreases from 7.8 kcal/mol for X = formate (a model for benzoate), to 5.6 kcal/mol for X = OSO_2H (a model for sulfonate), to 4.4 kcal/mol for X = Cl, to 1.9 kcal/mol for X = Br, and to only 1.0 kcal/mol for X = I.[9] These energy differences imply that geminal effects in the reactants can enhance the solvolysis rates of α-silyl derivatives relative to the analogous α-methyl derivatives by a factor of 4.8×10^5 for *p*-nitrobenzoates but only by a factor of 24 and 5 for the corresponding bromides and iodides, respectively (at 25 °C).

To test these theoretical predictions, we have measured the solvolysis rates in 97% TFE of **3** where R = Me or Me_3Si, varying the leaving group from OPNB to Cl and Br, and found them to be fully consistent with the computational conclusions. Thus, the $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ rate ratio for **3** increases from 3 for X = OPNB to 792 for X = Cl and to 3010 for X = Br. Similarly, this ratio is 0.92 for **1**, X = OPNB, but 70 for **1**, X = Cl. These are among the largest known variations in solvolytic rate ratios of two compounds as a function of the leaving group.[10] The low $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ rate ratios found for the *p*-nitrobenzoates (e.g., **1b**) do not result from similar stabilities of the corresponding carbenium ions. They reflect the enhanced solvolysis rates of the α-silyl OPNBs (relative to the corresponding alkyl OPNBs), due to electronic destabilization of their precursors,[11] which is the largest

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(1) See, for example: (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; 3rd ed.; Harper & Row: New York, 1987; Chapter 4. (b) Vogel, P. *Carbenium Ions*; Elsevier: Amsterdam, 1985.

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(3) (a) For a review, see: Kirby, A. G. *The Anomeric Effect and Related Stereoelectronic Effects in Organic Chemistry*; Springer-Verlag: Berlin, 1983. (b) For more recent theoretical calculations, see: Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393. Reed, A. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 7362. (c) For recent experimental evidence, see: More O'Ferrall, R. A.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1098. Verevkin, S.; Dogan, B.; Beckhaus, H.-D.; Ruchardt, C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 674.

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(6) Allen, A. D.; Krishnamurti, R.; Surya Prakash, G. K.; Tidwell, T. T. *J. Am. Chem. Soc.* **1990**, *112*, 1291.

(7) (a) In contrast to **1**, in **2** and **3** R is not locked in an axial position, and steric effects are therefore expected to be much smaller.[2b] This is manifested in the following $k(t\text{-Bu})/k(\mathrm{Me})$ rate ratio: For **1**, X = OPNB = 2.2×10^4,[2b] for **2**, X = OPNB = 112,[7b] for **2**, X = Cl = 2.8,[7c] and for **3**, X = Cl = 1.3.[2b] (b) Peters, E. N.; Brown, H. C. *J. Am. Chem. Soc.* **1975**, *97*, 2892. (c) Ranganayakulu, K.; Vasumathi Devi M.; Balaji Rao, R.; Rajeswari, K. *Can. J. Chem.* **1980**, *58*, 1484.

(8) (a) For a general description of the method, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986. (b) Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, B. L.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. *Gaussian 88*; Gaussian Inc., Pittsburgh, PA, 1988. (c) Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039. 3-21G(*) basis-set for Br: Dobbs, K. D.; Hehre, W. J. *J. Comput. Chem.* **1986**, *7*, 359.

(9) (a) The 3-21G(*) basis set was used because a 6-31G(*) basis set is not available for Br and I. However, calculations for X = OH, OSO_2H, OC(=O)H, and Cl at 6-31G(*) and 3-21G(*) gave very similar results. Calculations for X = Br which used the LANL1DZ pseudopotentials to describe the inner electrons[9b] gave very similar results to those obtained with 3-21G(*). (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 284.

(10) A similar dependence of $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ on the leaving group was reported recently, but no commentary or interpretation was given. Thus, $k(\mathrm{Me})/k(\mathrm{Me_3Si})$ for PhCHRX in 97% TFE (25 °C) is 0.66 for X = OTs and 1.6×10^4 for X = Br. See: Shimizu, N.; Osajima, E.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1145.

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for the *p*-nitrobenzoates and the smallest for the bromides. The $k(Me)/k(Me_3Si)$ of 3010 measured for **3**, X = Br, translates into an energy difference of 4.8 kcal/mol between Me_3C^+ and $(Me_3Si)Me_2C^+$, in very good agreement with the computational predictions[4a] (taking into account the residual difference of 1.9 kcal/mol between the two bromides).

Another dramatic manifestation of these ground-state geminal effects is found in the Br/OPNB rate ratios. While $k(Br)/k(OPNB)$ for **3a** is 7.6×10^5,[12] it is only 44.8 for **3b**. The latter value is, to the best of our knowledge, the lowest known $k(Br)/k(OPNB)$ rate ratio in a k_c process.[1,13]

In conclusion, *geminal interactions even for nonpolar substituent groups such as alkyl and silyl groups must be included in the interpretation of solvolysis rates*,[14] as well as for other reactions in which a C–X bond is broken in a rate-determining step (e.g., radical and anionic processes). Geminal effects are significant for benzoates and sulfonates but are relatively small for Br and I. The latter should therefore be preferred for comparing solvolysis rates. Finally, this study reinforces our previous conclusion[4a] that substitution of a Me by a Me_3Si group destabilizes tertiary carbenium ions[15] by ca. 6 kcal/mol.

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(11) In agreement, the ionization energy of the oxygen lone pair in α-silicon-substituted ethers is lower by ca. 1 eV relative to those of alkyl-substituted ethers. See: Matsunaga, S.; Isoe, S.; Yoshida, J.; Maekawa, T.; Murata, T. *J. Am. Chem. Soc.* **1990**, *112*, 1962.

(12) This value is close to other reported $k(Br)/k(OPNB)$ rate ratios, e.g., 5×10^5 for Ph_2CHX. See: Goering, H. L.; Hopf, H. *J. Am. Chem. Soc.* **1971**, *93*, 1224.

(13) For examples of the common situation, where the relative nucleofugalities of leaving groups in solvolysis reactions are nearly independent of the substrate, see: Bentley, T. W.; Roberts, K. *J. Org. Chem.* **1985**, *50*, 5852; **1985**, *50*, 4821.

(14) Richard, J. P.; Amyes, T. L.; Rice, D. J. *J. Am. Chem. Soc.*, following paper in this issue. The authors reach similar conclusions regarding the rates of solvolysis of $MeOCH_2X$, X = F, Cl, OCH_3. Note that in this case *polar* geminal groups are involved.

(15) For recent support, see: Soderquist, J. A.; Hassner, A. *Tetrahedron Lett.* **1988**, 1899. See also ref 10.

Effects of Electronic Geminal Interactions on the Solvolytic Reactivity of Methoxymethyl Derivatives

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We report that compounds with strong stabilizing geminal interactions, methoxymethyl fluoride and methoxymethyl methyl ether, are strongly stabilized toward hydrolysis in comparison with methoxymethyl chloride, a compound with a much weaker stabilizing geminal interaction.

There is extensive evidence from thermochemical measurements,[1] ab initio calculations,[2] and experiment[3] that geminal interactions between electronegative substituents across a methylene group are stabilizing by up to 17.4 kcal/mol for formaldehyde hydrate.[2] These stabilizing geminal interactions are responsible for the anomeric effect.[4] It is evident from first principles that the presence of geminal interactions must be manifested in the rate constants for reactions in which they are lost.[5,6] However, this fact has not gained wide recognition because of the absence of quantitative evaluations of the effect of ground-state geminal interactions on the reactivity of classical substrates for nucleophilic substitution reactions such as 4-methoxybenzyl and methoxymethyl derivatives.

Table I. Rate Constants for the Hydrolysis of 4-Methoxybenzyl Derivatives and Methoxymethyl Derivatives^{a}

X	$MeOCH_2X$	$4\text{-}MeOC_6H_4CH_2X$
$MeO/H^{+\,b}$	1.3×10^{-5} M^{-1} $s^{-1\,c}$	3.7×10^{-5} M^{-1} $s^{-1\,d}$
F^{e}	1.6×10^{-3} $s^{-1\,f,g}$	8.0×10^{-3} $s^{-1\,f,h}$
Cl^{e}	5×10^{4} $s^{-1\,i}$	4 $s^{-1\,j}$
k_{Cl}/k_F	3.1×10^{7}	5.0×10^{2}
k_{Cl}/k_{MeOH}	3.8×10^{9} M	1.1×10^{5} M

^{a}In aqueous solution at 25 °C. ^{b}Second-order rate constants for specific-acid-catalyzed cleavage of the methyl ethers. ^{c}Reference 7. A statistical correction was made by dividing the reported rate constants by 2. ^{d}At $I = 0.30$ (KCl), this work. Pseudo-first-order rate constants, k_{obsd}, in the presence of 0.10, 0.20, and 0.30 M HCl were determined by following the disappearance of the substrate by HPLC. The second-order rate constant was obtained from the slope of a plot of k_{obsd} against $[H^+]$. ^{e}The first-order rate constant for the hydrolysis reaction. ^{f}For a reaction in the presence of 0.10 M NaOH and 0.10 M $NaClO_4$. ^{g}Reference 9. ^{h}This work. Determined spectrophotometrically by following the disappearance of the substrate at 240 nm. ^{i}Estimated by extrapolation of a plot of log *k* for solvolysis of $MeOCH_2Cl$ in acetone/water mixtures at 25 °C (ref 8) against *Y* to $Y = 3.49$ for 100% water.[17] ^{j}Estimated by extrapolation of log *k* for solvolysis of $4\text{-}MeOC_6H_4CH_2Cl$ in 70% and 80% acetone in water at 25 °C (ref 12) using $m = 1.08$ (Graczyk, D. G.; Taylor, J. W.; Turnquist, C. R. *J. Am. Chem. Soc.* **1978**, *100*, 7333–7339) and $Y = 3.49$ for 100% water.[17]

Table I compares rate constants obtained from the literature for the acid-catalyzed hydrolysis of methoxymethyl methyl ether[7] and the uncatalyzed hydrolysis reactions of methoxymethyl chloride[8] and fluoride[9] with rate constants for the hydrolysis of the corresponding 4-methoxybenzyl derivatives that were determined in this work.[10]

X = Cl, F, MeO/H$^+$

The data in Table I show that there are large differences between the relative nucleofugalities of leaving groups at methoxymethyl derivatives and at the corresponding 4-methoxybenzyl derivatives. The difference in the reactivities of a chloride ion and a fluoride ion as leaving groups is 60 000-fold larger for the reactions of $MeOCH_2X$, for which $k_{Cl}/k_F = 3.1 \times 10^7$, than for the reactions of $4\text{-}MeOC_6H_4CH_2X$, for which $k_{Cl}/k_F = 500$. That is, fluoride ion is a *much worse leaving group* compared with chloride ion when it is attached to a $MeOCH_2$- moiety than when it is attached to a $4\text{-}MeOC_6H_4CH_2$- moiety. Assuming that geminal interactions in $4\text{-}MeOC_6H_4CH_2X$ are negligible, then the 60 000-fold larger value of k_{Cl}/k_F for the reaction of $MeOCH_2X$ can be explained by a ≥ 6.4 kcal/mol larger geminal ground-state stabilization of $MeOCH_2F$ than of $MeOCH_2Cl$ and

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(10) 4-Methoxybenzyl fluoride was synthesized by a literature procedure.[11] 4-Methoxybenzyl methyl ether was prepared by reaction of 4-methoxybenzyl chloride with sodium methoxide in methanol at room temperature for 22 h.

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