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Electric Field Facilitated S_N2 Reactions in 7-Bromonorbornanes

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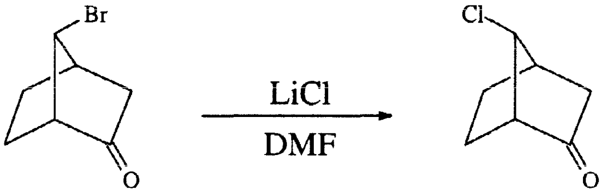
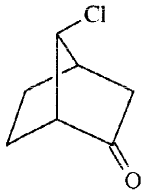
Abstract: *Ab initio* and natural bond orbital calculations on a series of substituted norbornanes show that the nucleophilic displacement of a nucleofuge at C7 can be enhanced when the molecule contains a substituent at C2 or C3 that creates a strong electric field.

Because the C1-C7-C4 bond angle in the rigid norbornyl framework is equal to about 93°, sp^2 hybridization at C7 in the transition state of an S_N2 reaction is difficult to achieve.[1] Moreover, the approach of a nucleophile to C7 is hindered by the presence of *exo*-5 and *exo*-6 substituents.[1a] Thus, S_N2 reactions at C7 in norbornyl derivatives, although not unknown, are extremely rare. For example, Lumb and Whitham reported[1a] the synthesis of *anti*-7-chloro-2-norbornanone (**2**) from *syn*-7-bromo-2-norbornanone (**1**) using LiCl in refluxing dimethylformamide (DMF). The authors suggest that the carbonyl group in **1** plays a role in facilitating the displacement of bromide ion but do not provide any evidence to support this hypothesis. We have successfully used[2] this procedure to prepare **2** and did not find any evidence for the formation of *syn*-7-chloro-2-norbornanone (**3**). Thus, this reaction appears to proceed with complete inversion of configuration at C7.

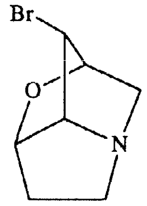


1 **2**



3

Nucleophilic displacement at C7 has been attempted on other 7-bromo norbornyl derivatives, albeit unsuccessfully. For example, Wilson and Sawicki found[3] **4** to be unreactive toward nucleophilic displacement with methylamine in acetonitrile at 100°C. Gassman and coworkers observed[4] that the acetolysis of **5** proceeds with



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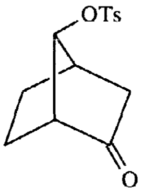

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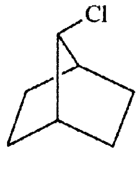
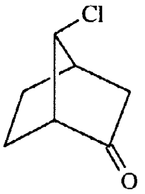
95% inversion of configuration at C7. In this study, the authors suggested that the carbonyl group retards the overall rate of acetolysis by a factor of 10 but "causes a dramatic increase in the S_N2 character of the ionization process".

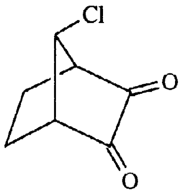
In order to understand the nature of the enhanced reactivity of **1** toward nucleophilic displacement at C7, we have performed a series of *ab initio* molecular orbital (MO) calculations and natural bond orbital[5] (NBO) calculations[6] on the ground states of compounds **6a-6h**.[7] MO calculations were also performed on the S_N2 transition states (at C7) for each of these molecules.



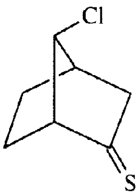
6a



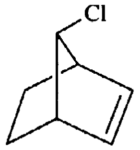
6b



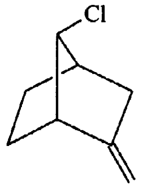
6c



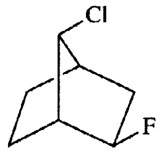
6d



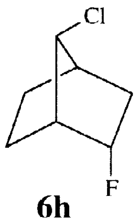
6e



6f



6g



6h

S_N2 reactions can be considered to result from an interaction of the highest occupied molecular orbital (HOMO) of the nucleophile (n orbital of Cl^-) with the σ^* orbital of the electrophile (C-Cl σ^* orbital of **6a-6h**).[7] One might thus anticipate that S_N2 reactions should become more facile as the energy of the σ^* orbital is reduced (or as the energy of the HOMO is raised).[8] The calculated (HF/6-31+G*) activation enthalpy[9] ($\Delta H^{\ddagger}$) for each molecule is plotted as a function of the relative[10] HF/STO-3G[11] C-Cl σ^* orbital energy in Figure 1. There is a nearly linear relationship between $\Delta H^{\ddagger}$ and the C-Cl σ^* orbital energy.

In particular, the calculated $\Delta H^{\ddagger}$ for the parent compound, **6a**, is 22.4 kcal/mol. The value for $\Delta H^{\ddagger}$ drops to 18.2 kcal/mol when a ketone is present at C-2 (**6b**), and there is a further, dramatic drop of $\Delta H^{\ddagger}$ to 10.1 kcal/mol in the dione **6c**. In order to identify the source of the shifts in the C-Cl σ^* orbital energies for these compounds, an NBO analysis was used to "dissect" the interactions[2,12] between the C-Cl σ^* orbital and the $\sigma(\pi)$ orbitals of the substituent group into through-space (TS), through-bond (TB), hyperconjugative and electric field[13] components. For **6b-6h**, TS and TB interactions between the C-Cl σ^* orbital and the $\sigma(\pi)$ orbitals of the substitutent are vanishingly small (the largest shifts due to TS and TB interactions are 0.0005 au and 0.0002 au, respectively). Moreover, the calculated shifts in the C-Cl σ^* orbital due to hyperconjugative interactions with the norbornyl framework are nearly the same in **6a-6h** (the maximum deviation is 0.0011 au).

In fact, *the NBO analysis shows that the shifts in the C-Cl σ^* orbital of **6b-6h** are due almost entirely to the electric field produced by the substituent.* Not surprisingly, the electric field effect is greatest in those molecules where the substituent group possesses a large dipole moment (such as **6b**, **6c**, **6g** and **6h**). There is an excellent linear correlation between the calculated (HF/6-31+G*) activation enthalpy for each molecule and the relative[10] shift in the C-Cl σ^* orbital due to the electric field (see Figure 2).

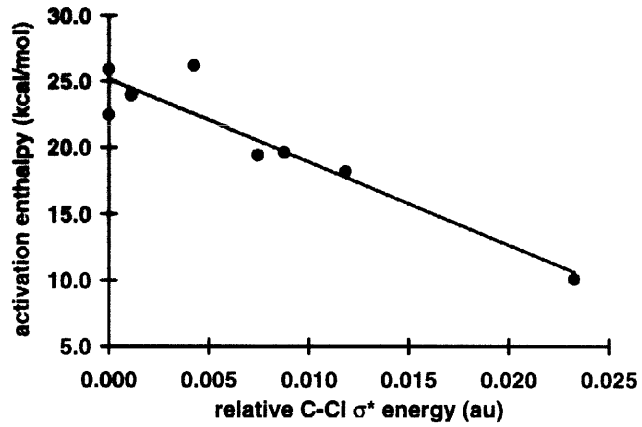


Figure 1. HF/6-31+G* Activation Enthalpy Versus Relative C-Cl σ* Energy. The data points from left to right are for **6a** (lower), **6e** (upper), **6f**, **6g**, **6d**, **6h**, **6b** and **6c**.

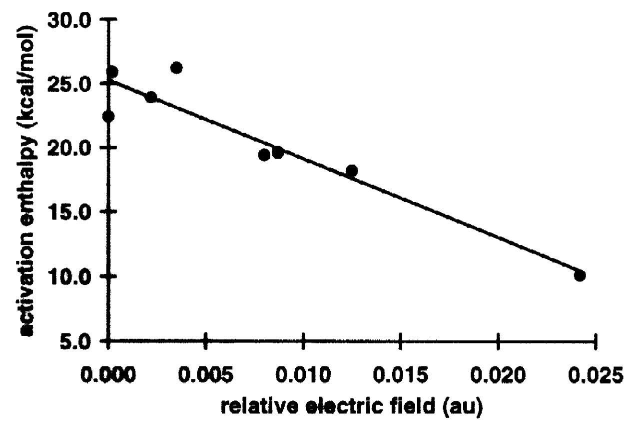


Figure 2. HF/6-31+G* Activation Enthalpy Versus Relative Electric Field. The data points from left to right are for **6a**, **6e**, **6f**, **6g**, **6d**, **6h**, **6b** and **6c**.

A comparison of compounds **6g** and **6h** lends additional support for the relative importance of the electric field effect. The electric field effect is known to depend on the orientation between the substituent dipoles.[13] The shifts in the C-Cl σ* orbitals of **6g** and **6h** due to the presence of the C-F dipole (0.0035 au and 0.0087 au, respectively) are very different and do clearly depend on the orientation of the C-F bond.

We have also performed calculations on the *anti*-7-chloro analogues of **6b**-**6h** to determine whether or not a *syn* relationship between the C-Cl group and the substituent is necessary to facilitate S_N2 chemistry at C7. The calculations show that the activation enthalpies are relatively unaffected by the orientation (*syn* vs. *anti*) of the C-Cl group at C7. In the *anti*-7-chloro molecules, the electric field is again primarily responsible for lowering the C-Cl σ* orbital energies. TS and TB interactions between the C-Cl σ* orbital and the σ(π) orbitals of the substituent are more pronounced in the *anti*-7-chloro systems. Though these interactions do raise the energy of the C-Cl σ* orbital, the net effect is small and one can predict that *anti*-7-halo derivatives which are appropriately substituted at C2 or C3 will also show a disposition toward nucleophilic displacement.

In summary, our calculations suggest that the observed reactivity of **1** toward nucleophilic displacement at

C7 is due to the electric field produced by the carbonyl group. This effect should be particularly important in molecules related to the diketone, **6c**, and we are preparing its *syn*-7-bromo analogue to test this prediction. Our calculations also suggest that *anti*-7-halo substrates will exhibit reaction dynamics similar to those of the *syn* isomers and we will examine the substitution chemistry of *anti*-7-bromo-2-norbornanone to test this prediction. Finally, the enhanced reactivity toward nucleophilic displacement created by the presence of a strong electric field may explain the anomalous observations reported for substituted β-phenethyl chlorides,[14] and compounds of the type $C_6H_5CO(CH_2)_nCl$.[15,16]

Acknowledgment. We are grateful to the National Science Foundation, Grant CHE 9311828, for financial support.

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1. See, for example: (a) Lumb, J. T.; Whitham, G. H. *Chem. Commun.* **1966**, 400. (b) Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 3887.
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6. The Gaussian 94 program was used for all MO and NBO calculations.
7. Chloride, rather than bromide, was used as the nucleofuge to simplify the calculations.
8. In our calculations, we assumed that the energy of the Cl^- n orbital was essentially constant.
9. The calculated enthalpies of activation reported here are for gas-phase reactions corrected to 298K.
10. Energies are relative to those for the parent compound, **6a**.
11. We used the STO-3G basis set to avoid the potential problems associated with the virtual orbitals with diffuse basis sets. See, for example: (a) Falcetta, M. F.; Jordan, K. D. *J. Phys. Chem.* **1990**, *94*, 5666. (b) Falcetta, M. F.; Jordan, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 2903.
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16. Conversely, it is reported that syn-7-bromobenzonorbornanone is unreactive toward LiCl in refluxing DMF; see: Wilt, J. W.; Chenier, P. J. *J. Org. Chem.* **1970**, *35*, 1562.