

## THEORETICAL STUDIES OF SN<sup>2</sup> TRANSITION STATES. THE ALPHA EFFECT

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*Summary:* The qualitative HOMO-LUMO orbital interaction interpretation of the alpha effect is found to be invalid for anionic nucleophiles. In any event, gas phase SN<sup>2</sup> reactions of HOO<sup>-</sup> and FO<sup>-</sup> show no evidence of the effect. The role of a hydroxylic solvent requires greater consideration as the source of positive deviations from rate-equilibrium plots.

The frontier molecular orbital (FMO) treatment<sup>1</sup> of the reaction  $X^- + CH_3Y \rightarrow XCH_3 + Y^-$  focuses upon the charge transfer from the HOMO of  $X^-$  to the LUMO of  $CH_3Y$ . In the qualitative argument, the efficiency of the reaction is inversely proportional to the HOMO-LUMO energy gap. Therefore, the process will proceed more rapidly the higher-lying the HOMO or the lower-lying the LUMO. For X or Y = halogen, the HOMO levels are expected to follow electronegativity trends,<sup>2</sup> i.e.,  $I^- > Br^- > Cl^- > F^-$ , and the LUMO levels are  $\sigma_{CI}^* < \sigma_{CBr}^* < \sigma_{CCl}^* < \sigma_{CF}^*$ .<sup>3</sup>

The theory seems to conform to the concepts of nucleophilicity and leaving group ability, since iodide is thus predicted to be the best nucleophile, and also the best leaving group, as is observed experimentally in hydroxylic solvents.<sup>4</sup> However, it has long been known<sup>5</sup> that, in acetone solvent, the reactivities of the halide ions towards several p-toluenesulfonates and alkyl bromides are  $Cl^- > Br^- > I^-$ , the reverse of the usual order.

Extension of the FMO method to incorporate solvent effects is not straightforward,<sup>6</sup> so that the relevance of predicted nucleophilicity and leaving group ability trends to any particular experimental result in solution is uncertain. It is also uncertain that the theory is strictly applicable to the treatment of gas phase SN<sup>2</sup> reactions, because the formation of stable ion-molecule clusters under such conditions<sup>7</sup> changes the nature of the reaction coordinate. Moreover, the rates (efficiencies) of gas phase SN<sup>2</sup> reactions can be correlated with heats of reaction<sup>8</sup> in the manner suggested by Marcus theory,<sup>9</sup> and the concepts of nucleophilicity and leaving group ability then lose their distinction<sup>10</sup> in a treatment based upon intrinsic barriers<sup>11</sup> and overall energy change. The same conclusion follows from the Marcus treatment of SN<sup>2</sup> reactions conducted in hydroxylic solvents.<sup>12</sup>

A variety of data indicate that the enthalpies of transfer of inorganic anions from the gas phase to water solvent are large,<sup>13</sup> and that differences in heats of solvation between different anions are also large. As discussed recently by Bohme,<sup>14</sup> addition of three water molecules to a gas phase SN<sup>2</sup> reaction causes the disappearance of the ion-molecule complexes and restoration of the usual bell-shaped reaction coordinate. Clearly, solvation of anions, and the different solvation characteristics of different anions, have profound effects upon the rates, and, therefore, the quantitative treatment of SN<sup>2</sup> reactions in solution.<sup>15</sup>

It is common to correlate the rates of nucleophilic substitution or addition reactions in solution with Brönsted basicities of the nucleophiles.<sup>16</sup> Typically, a plot of the logarithm of the rate constant versus  $\text{p}K_a$ , where  $K_a$  refers to the conjugate acid of the nucleophile, is linear, provided that the nucleophiles in question share the same nucleophilic centre, i.e., all  $\text{RO}^-$ , or all  $\text{RS}^-$ , or all  $\text{RNH}_2$ , etc. Even within a given family, e.g.,  $\text{RNH}_2$ , different Brönsted correlations may be needed to describe R = primary carbon, secondary carbon, or tertiary carbon.<sup>17</sup> One reason for these restrictions is that a Brönsted correlation is now known to be a special case of a more general rate-equilibrium relationship in which the rate depends upon both thermodynamic (equilibrium) and kinetic (intrinsic activation barrier) factors.<sup>9,18</sup> With closely related members of a family of nucleophiles, the intrinsic barriers are relatively invariant,<sup>11</sup> and the effect of the kinetic term diminishes.

The alpha-effect<sup>19</sup> refers to the enhanced reactivity of nucleophilic reagents containing a heteroatom adjacent to the reaction centre, and is normally manifested as a positive deviation on a Brönsted plot. The origin of this effect has been discussed extensively,<sup>20</sup> and usually in terms of one or more of the following factors: (i) destabilization of the ground state of the alpha-nucleophile; (ii) stabilization of the transition state; (iii) stabilization of the products; (iv) reduced solvation of alpha-nucleophiles.

According to FMO theory, ground state destabilization is the result of orbital interaction between the adjacent electron pairs of an alpha-nucleophile.<sup>21</sup> This leads to a HOMO comprised of an out-of-phase combination of these electron pairs, which lies higher than the HOMO of a normal nucleophile. A lower HOMO-LUMO energy difference results, and is considered to be the cause of the increased reactivity.

This argument is incorrect for anions. The out-of-phase combination observed for the HOMO of an alpha-nucleophile represents the second order perturbational effect of the heteroatom attached to the reacting centre. When the first order (i.e., electronegativity<sup>22</sup>) effect of the adjacent heteroatom is also taken into account, the out-of-phase HOMOs of  $\text{HOO}^-$ ,  $\text{ClO}^-$  and  $\text{FO}^-$  are found to lie substantially *lower* than the HOMO of  $\text{HO}^-$ , as seen from the data presented in the Table. Therefore, if FMO theory is valid, a *decrease* in reactivity is predicted for alpha-nucleophiles in the gas phase. The FMO rationalization of (i) thus becomes ambiguous.

TABLE. Calculated HOMO Energies of Oxyanions<sup>a,b</sup>

Anion	HOMO Energy (au)	Anion	HOMO Energy (au)
$\text{HO}^-$	-0.0340	$\text{HOO}^-$	-0.0868
$\text{CH}_3\text{O}^-$	-0.0635	$\text{FO}^-$	-0.1372

<sup>a</sup>At the 4-31G level, with full geometry optimization (1 au = 627.5 kcal/mol); <sup>b</sup>In the computations of M.M. Heaton, *J. Am. Chem. Soc.*, **100**, 2004 (1978), the HOMO of  $\text{ClO}^-$  was found to lie 19.9 kcal/mol below the HOMO of  $\text{HO}^-$ , but the HOMO of  $\text{HOO}^-$  was 6.3 kcal/mol *above* that of  $\text{HO}^-$ . The latter is a result of Heaton's use of the geometry of the hydroperoxyl radical rather than the anion. Recomputation of  $\text{HOO}^-$ , using Heaton's basis set and the fully optimized geometry, lowers the energy of the HOMO by 35.0 kcal/mol.

In terms of the Marcus treatment of reactivity, (i), (ii) and (iii) do not constitute independent interpretations, because these factors are interrelated when the more general rate-

equilibrium correlation is employed to probe for the alpha-effect. We have found recently<sup>8</sup> that a Marcus-type relationship (eq [1]) exists in the gas phase for methyl transfer reactions involving fifteen independent combinations of X and Y, in which the entering and leaving groups are any of hydrogen, carbon, nitrogen, oxygen, fluorine or sulfur, and in which  $\text{HOO}^-$  and  $\text{FO}^-$  have been included.

$$[1] \quad \Delta E_{XY} = \frac{1}{2}(\Delta E_{XX} + \Delta E_{YY}) + \frac{1}{2}\Delta E^\circ + \left\{ \frac{\Delta E^{\circ 2}}{8}(\Delta E_{XX}^\ddagger + \Delta E_{YY}^\ddagger) \right\}$$

In eq [1],  $\Delta E_{XY}$  is the ab initio<sup>2,3</sup> energy difference between the transition state and the separated reactants,  $\Delta E^\circ$  is the potential energy change for the reaction, and  $\Delta E_{XX}^\ddagger$  and  $\Delta E_{YY}^\ddagger$  are the intrinsic barriers for the degenerate reactions. As shown by Brauman,<sup>10</sup>  $\Delta E_{XY}$  is a good measure of the efficiency of a gas phase  $\text{SN}_2$  reaction.

Thus, in terms of eq [1], the gas phase  $\text{SN}_2$  behavior of the alpha-nucleophiles  $\text{HOO}^-$  and  $\text{FO}^-$  is completely normal. However, since no experimental Marcus-type relationship incorporating alpha-nucleophiles yet exists for reactions in hydroxylic solvents, it could be argued that eq [1] does not conform to the accepted definition of the alpha-effect, which is based solely on thermodynamic rather than a combination of thermodynamic and kinetic effects. Figure 1 demonstrates that this caveat is not valid. This Figure shows a plot of  $\Delta E_{XY}$  versus  $\Delta E^\circ$  for four reactions of the type  $\text{RO}^- + \text{CH}_3\text{F} \rightarrow \text{ROCH}_3 + \text{F}^-$ , and now does conform to the accepted test for the existence of the alpha-effect. A linear relationship ( $r = 0.99$ ) exists, because the  $\text{RO}^-$  intrinsic barriers<sup>11</sup> are clustered around a single value ( $\sim 20$  kcal/mol).

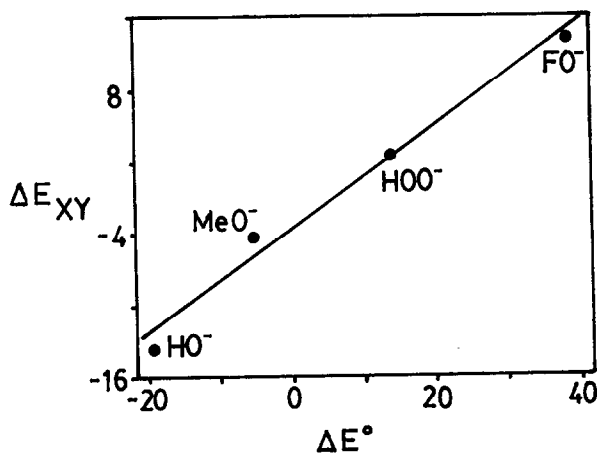


Figure 1. A plot of  $\Delta E_{XY}$  versus  $\Delta E^\circ$  for ab initio reactions of  $\text{HO}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{HOO}^-$  and  $\text{FO}^-$  with  $\text{CH}_3\text{F}$ . Data are in kcal/mol<sup>3</sup> from 4-31G level computations with full geometry optimization.

Unfortunately, all experimental data relating to the alpha-effect refer to hydroxylic solvents, in which the role of (iv) is expected to be maximal. According to recent work by Benson,<sup>24</sup> the difference in the heats of aquation of HO<sup>-</sup> and HOO<sup>-</sup> is 21.5 kcal/mol. Although the existence of such a large solvation effect is not surprising,<sup>13</sup> the possibility that this factor alone may be responsible for the alpha-effect seems generally to have been discounted, despite the recognition otherwise given to the important role of solvation effects.

It is known that the magnitude of the alpha-effect depends upon the reaction type, and is smallest in an SN2 reaction.<sup>25</sup> Clearly, it is necessary to extend the theoretical treatment of rate-equilibrium relationships from SN2 reactions to the more complex problems of additions to sp and sp<sup>2</sup> centres. It is also necessary to extend experimental investigations of the rate-equilibrium behavior of alpha-nucleophiles to a range of dipolar non-hydroxylic solvents. Finally, it appears that the validity of the FMO treatment of certain bimolecular reactions requires reevaluation.

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