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On Gas Phase α-Effects. 1. The Gas-Phase Manifestation and Potential SET Character

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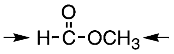
Base	%Yield	%SET
HOO^-	64	39
HO^-	61	0



$\longrightarrow H\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3 \longleftarrow$

Nuc.	%Yield	%SET
HOO^-	8	2.7
HO^-	5	1.6

SET character is greater than 0 for both H^+ and methyl transfer with HOO^-.

The possibility of a gas-phase α-effect has been explored for the methyl transfer from methyl formate to hydroxide, hydroperoxide, and ethoxide by computing barrier heights at the HF/6-311++G(2df,2p) level of theory. The α-nucleophile (hydroperoxide) is found to have a lower barrier than the gas-phase-acidity-matched normal nucleophile (ethoxide) by 3.6 kcal/mol, offering evidence for a gas phase α-effect. A Shi−Boyd analysis for these reactions indicates that there is more single-electron-transfer character in the hydroperoxide transition state than for either hydroxide or ethoxide, further bolstering the existence of a gas-phase α-effect and the appropriateness of the Hoz model for the α-effect.

Introduction and Background

The α-effect is an enhanced nucleophilic reactivity displayed by nucleophiles possessing a lone pair of electrons on the atom (α-atom) neighboring the atom bearing the reactive electron pair, as in the stylized structure **1**.

:XY:

1

This enhanced reactivity has recently been reviewed.[1] The modern quantitative definition of an α-effect includes the idea that two nucleophiles, one an α-nucleophile and one a normal nucleophile without the α lone pair, must be matched in pK_{AH} values for proper definition of the enhanced reactivity.[2,3] Considerable doubt was cast on the existence of a gas-phase α-effect by DePuy et al.[4] following a report on the reaction of hydroxide anion (a normal nucleophile) and hydroperoxide anion (an α-nucleophile) with methyl formate. In this flowing afterglow study, it was found that both nucleophiles gave substantially similar product distributions (Scheme 1). The results of this work were interpreted to demonstrate no α-effect in the gas phase for either methyl transfers or attack at the carbonyl group.

This interpretation can be criticized from two different, but related, bits of data. First, the difference in gas-phase acidity (GPA) between hydrogen peroxide (369.5 kcal/mol) and water (383.7 kcal/mol) is 14 kcal/mol;[5] hence, hydroxide is more basic than hydroperoxide in the gas phase by a substantial margin. On the basis of this difference alone, hydroxide should give significantly more methyl abstraction than hydroperoxide (reaction 3, Scheme 1). However, it is hydroperoxide anion that gives more methyl abstraction, albeit by a modest ratio of 8/5. Thus, hydroperoxide does display a gas-phase α-effect, allowing it to overcome a significant thermodynamic disadvantage in basicity and compete with hydroxide. The conclusion by DePuy et al. that there is no α-effect in this methyl transfer reaction is by no means clear according to the standard definition of the α-effect offered above. A better determination of a gas-phase α-effect should compare hydroperoxide to a more closely GPA-matched normal nucleophile, such as ethoxide (GPA ethanol = 370.8 kcal/mol).[5] This conclusion is supported by the report of Ren and Yamataka, who report $\Delta H^{\ddagger}_{\text{overall}}$ values for α-nucleophiles.[6] That paper reports a small reactivity increase for hydroperoxide vs hydroxide of ca. 1.1 kJ/mol with a methyl chloride substrate. This energy difference amounts to ca. 0.26 kcal/mol, which is similar to the 0.28 kcal/mol computed in this paper (see below) for the 8/5 ratio from the gas-phase experimental results. Table 1 records the difference in $\Delta G^{\ddagger}$ values for hydroxide and hydroperoxide as 0.8 kcal/mol, with hydroxide being the better S_N2 nucleophile in reaction 3. Our more approximate results are thus within ca. 0.56 kcal/mol of

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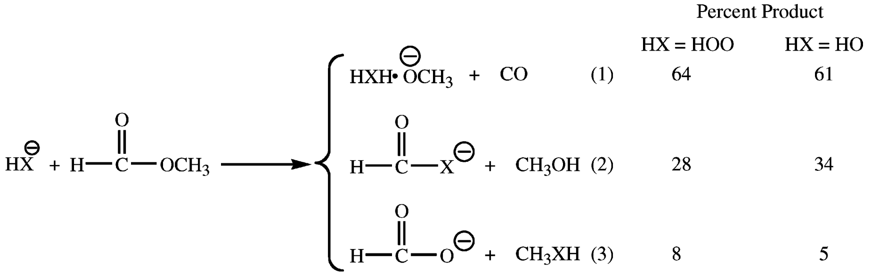
SCHEME 1



the higher level G2(+) results, neglecting the leaving group difference (Cl^- vs $HCOO^-$). The general agreement between the methods is gratifying, despite the slightly higher barrier for hydroperoxide with the simpler model chemistry.

TABLE 1. Activation Free Energies Relative to Reactant Complexes and Gas-Phase Acidities for Normal and α-Nucleophiles

base/nucleophile	reaction 1 $\Delta G^{\ddagger\, a}$	reaction 3 $\Delta G^{\ddagger\, a}$	GPA[a]
HOO^- (config 1)	13.4	15.4	369.5
HOO^- (config 2)	9.5		369.5
HO^-	5.0	14.6	383.7
EtO^-	7.4	19.0	370.8

[a] kcal/mol.

A second criticism of the DePuy et al. conclusion is that the hydroperoxide anion, a much weaker base than hydroxide, actually abstracts slightly more of the formyl protons than hydroxide does. This fact is a strong, unexplained anomaly in this gas-phase experiment and suggests that differences in gas-phase acidity (GPA) are mitigated by some other factor.

Experimental Evidence Consistent with Electronic Effects. Explorations of α-effects, using substituted *N*-methylbenzohydroxamate anions (GNMBH anions, where G represents one or more substitutents) in methyl transfers from arylmethylthioethers in methanol,[7,8] showed that the α-effect could be reduced by increasing electron demand in the GNMBH anions. In fact, the α-effect is completely extinguished in the case of 3,5-dinitroNMBH.[7] Also, the ability of the aryldimethylsulfonium system to accept (electrochemically) a single electron ordered the sizes of the α-effect—the greatest with the easiest single electron transfer (SET).[8] These data seem to argue that at least one component of the α-effect is electronic in nature, and SET character may be very important. Given that the GNMBH data suggest that the α-effect is at least partially electronic in nature, it is difficult to imagine that solvent effects are the sole source, and it seems likely that there is an inherent gas-phase α-effect. Furthermore, absolute methanol was used for every reaction in the GNMBH studies, making it even more unlikely that the observed α-effect is due to solvent alone.

Theoretical Considerations. The state correlation diagram (SCD) model of the S_N2 reaction, due to Shaik et al.[9] and summarized in Figure 1 as a valence bond (VB) formulation, shows a model for inclusion of some SET character in a predominantly polar (two-electron) transfer pathway. The Hoz model for the origin of transition state (TS) stabilization in the α-effect extends the SCD model to suggest that SET is a crucial factor in the α-effect (Figure 2).[10] The transfer of SET character in Figure 2 allows some three-electron bonding character in the transition state, which would confer more stability than a two-electron transfer. Note that these effects would be subtle to explore because both the polar, two-electron transfer pathways and the SET pathway operate on a singlet electronic surface, with the only difference being pairwise (polar) versus single electron transfer (SET). Using instruments to detect this difference, even at femtosecond levels, would be of no use.

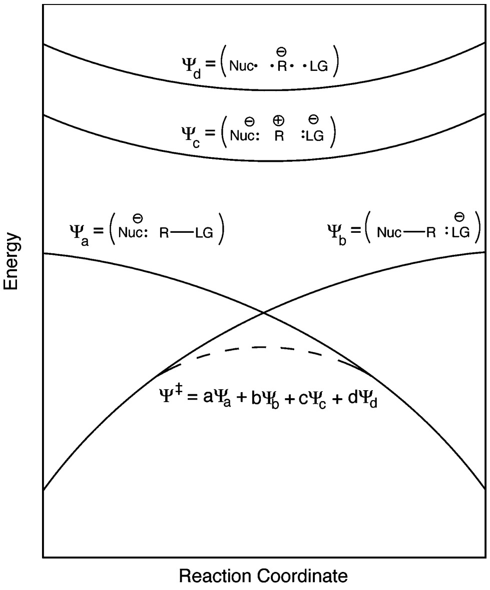


FIGURE 1. State correlation diagram for a general S_N2 or proton transfer.

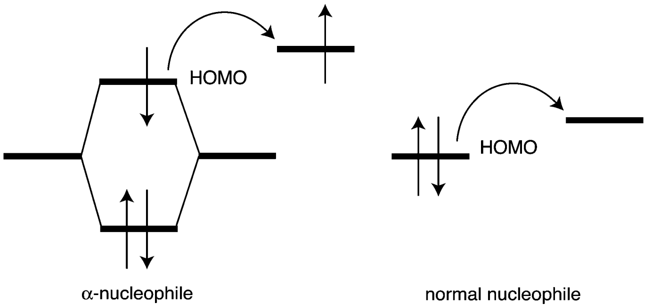


FIGURE 2. Hoz model for the α-effect.

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However, quantum mechanical calculations are well suited for exploring this issue.

A very good example of determination of the quality of charge transfers in S_N2 transition states (TS) comes from a series of papers by Shi and Boyd examining the SCD method by determining the components of the VB wave function as shown in Figure 1 and eq (1).[11−14]

$$Q^{\ddagger}_{x} = a^2Q_x(\Psi_a) + b^2Q_x(\Psi_b) + c^2Q_x(\Psi_c) + d^2Q_x(\Psi_d)$$

$$Q^{\ddagger}_{N} = a^2Q_N(\Psi_a) + b^2Q_N(\Psi_b) + c^2Q_N(\Psi_c) + d^2Q_N(\Psi_d)$$

$$Q^{\ddagger}_{R} = a^2Q_R(\Psi_a) + b^2Q_R(\Psi_b) + c^2Q_R(\Psi_c) + d^2Q_R(\Psi_d) \quad (1)$$

$$a^2 + b^2 + c^2 + d^2 = 1$$

The *Q* values given in eq 1 are charges derived from Bader's topological atoms-in-molecules (AIM) theory.[15] The three simultaneous equations in eq 1 are solved, subject to the normalization condition that the sum of squares of the mixing coefficients $a-d$ be 1.0. With four coefficients yet only three equations, solutions are derived first assuming that $c^2 = 0$, then assuming that $d^2 = 0$ to give upper boundaries for the values of the squares of the mixing coefficients. One of the two assumptions will return unphysical results (e.g., $a^2 + b^2 > 1$), while the other will return a reasonable answer and give a limiting set of coefficients. Following this analysis, Shi and Boyd found that several S_N2-type TSs show modest SET character ($d^2 > 0.0$) at the HF/6-31++G** model chemistry. MP2 corrections to the HF results, or determinations of the TSs at the MP2 level, gave an increase in both the membership of the set of S_N2-type TSs possessing SET character and the sizes of the d^2 coefficients.[11−14]

Support for this approach is provided by Shaik et al.,[16] who suggest that is it possible to couple the above procedure with any charge-partitioning scheme. In fact, partitioning of charges using rudimentary Mulliken populations, cited as unpublished data from ref 16b, report SET character (contributions of the d^2 VB component) for the $F\cdots CH_3\cdots F$ TS of 2.6% and 1% for the $H\cdots CH_3\cdots F$ TS. These numbers agree fairly well, where comparison is possible, with the reported data from Shi and Boyd, using Bader's AIM analysis, with the Mulliken populations giving slightly higher SET character. For example, the $H\cdots CH_3\cdots H$ TS indicates 1% SET using Mulliken populations, but 0% using AIM charges. We can expect then comparable SET character with either population method, with AIM populations giving smaller values of d^2. We choose AIM populations because more systems are reported for comparison by Shi and Boyd to calibrate our computations.

The present paper reports our attempts to study reactions 1 and 3, Scheme 1, in the gas phase using an α-nucleophile (hydroperoxide), a GPA-matched normal nucleophile (ethoxide), and a normal nucleophile that differs greatly in GPA (hydroxide). Through reaction 1, we seek to explain why the weaker base, hydroperoxide, reacts more readily with the formyl proton than hydroxide. Using reaction 3, we seek to examine the magnitude of any gas-phase α-effect in this simple methyl transfer. Comparing both ethoxide and hydroxide with hydroperoxide will allow us to remove issues of gas-phase acidity and focus on the potential role of SET character in the TSs of these reactions.

Computational Methods

Preliminary calculations were used to determine an appropriate level of theory by assuming that the product ratio of 8/5 in reaction 3, Scheme 1,[4] is due to a difference in reaction barrier heights ($\Delta\Delta G^{\ddagger}$) of 0.28 kcal/mol, with the barrier for hydroperoxide attack being lower than that for hydroxide attack. These calculations revealed that the HF/6-311++G(2df,2p) level of theory reproduces the kinetic data reported by DePuy et al.[4] with good accuracy. Inclusion of electron correlation effects at the MP2 level or via density functional theory was found to degrade the quality of the results. As electron correlation is generally required to obtain accurate barrier heights, we can assume that some fortuitous cancellation of errors has occurred. Nonetheless, our results do agree well with the experimental data, and we believe this level of theory to be trustworthy for our purposes. As a further test, we examined the methyl transfer from methyl fluoride to peroxide anion and found that our results compare well to those published previously for hydroxide, with the peroxide anion having a slightly lower barrier (see below).[11−14]

Separated reactants, ion−dipole reactant and product complexes, and transition states were fully optimized at the HF/6-311++G(2df,2p) level of theory. Frequency calculations confirmed the correct number of imaginary vibrational modes (zero for minima, one for transition states) and gave thermodynamic parameters necessary to correct the computed energies to gas-phase Gibbs free energies at 1 atm and 298 K. Intrinsic reaction coordinate (IRC) calculations[17] were used to confirm that the computed transition states do connect to the desired reactant and product complexes. AIM charges were obtained for the optimized transition state structures.

Geometry optimization, frequency, and IRC calculations were performed using Gaussian03W.[18] AIM charges were determined using AIM2000.[19]

Results

Table 1 summarizes the computed activation free energies for reaction 3, Scheme 1, along with the gas-phase acidities of each nucleophile. The activation free energies are relative to the ion−dipole reactant complexes. Table 2 lists AIM charges and coefficients for eq 1 as determined by a Shi−Boyd analysis

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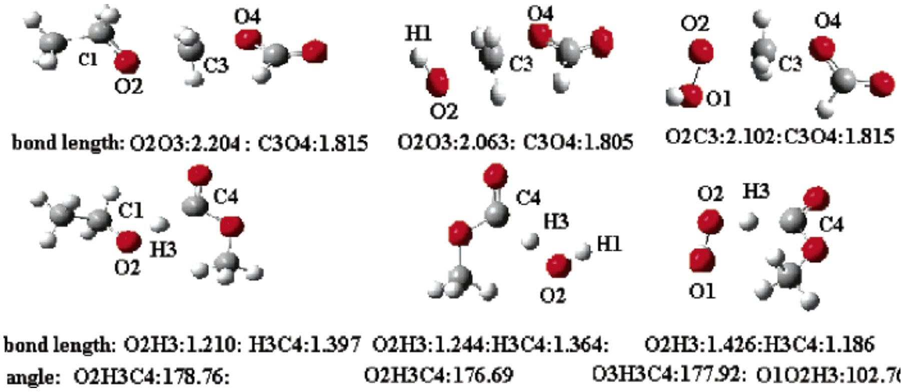
CHART 1. **Transition-State Geometries and Selected Geometric Parameters**



of reactions 1 and 3, Scheme 1. The reaction of hydroperoxide with methyl fluoride is included for comparison. The geometries of the six transition states determined in this study are displayed in Chart 1, along with selected geometric data. The detailed geometries are provided in the Supporting Information.

TABLE 2. Shi−Boyd Analysis of Electronic Configurations in Transition-State Wave Functions

Reaction 1: Abstraction of Formyl Proton

base	$-Q^{\ddagger}_{X}$	$-Q^{\ddagger}_{N}$	$Q^{\ddagger}_{R}$	a^2	b^2	c^2	d^2
HOO^- (conf 1)	0.746	0.850	0.596	0.190	0.245	0.000	0.565
HOO^- (conf 2)	0.734	0.863	0.597	0.258	0.350	0.000	0.394
HO^-	0.725	0.853	0.578	0.277	0.400	0.323	0.000
EtO^-	0.716	0.815	0.591	0.286	0.332	0.382	0.000

Reaction 3: Transfer of Methyl Group

nucleophile	$-Q^{\ddagger}_{X}$	$-Q^{\ddagger}_{N}$	$Q^{\ddagger}_{R}$	a^2	b^2	c^2	d^2
HOO^-	0.814	0.854	0.668	0.378	0.592	0.000	0.027
HO^-	0.804	0.850	0.654	0.584	0.400	0.000	0.016
EtO^-	0.794	0.857	0.651	0.620	0.366	0.000	0.014

Methyl Transfer in Methyl Fluoride

nucleophile	$-Q^{\ddagger}_{X}$	$-Q^{\ddagger}_{N}$	$Q^{\ddagger}_{R}$	a^2	b^2	c^2	d^2
HOO^-	0.827	0.827	0.654	0.524	0.452	0.000	0.024

Discussion

Proton Transfer. The data from the formyl proton transfer reactions (reaction 1, Scheme 1) indicate that hydroxide and ethoxide behave in a very similar fashion, while hydroperoxide is quite different. For instance, two different transition states were found for the proton abstraction with hydroperoxide as the base. The first (conformer 1, Chart 1) has a conformation that suggests a very significant interaction between the alpha oxygen and methyl group of methyl formate. The second (conformer 2, Chart 1) is not substantially different in conformation from the hydroxide attack transition state.

The hydroperoxide transition states gave significantly different results both in terms of relative energy and in terms of degree of electron transfer. From Table 1, it can be seen that conformer 2 is nearly 4 kcal/mol lower in energy than conformer 1, but still 4.5 kcal/mol higher in energy than the hydroxide transition state. From Table 2, it is clear that conformer 1 displays much more SET character than conformer 2 (57% vs 39%). This large SET component follows from Hoz's dictum that substrates having low-lying unoccupied orbitals, such as those in the carbonyl moiety, will show proportionally larger SET character.[10] Conformer 2 is more ionic in character than conformer 1, but still less ionic than the transition states for either normal nucleophile, neither of which displays any SET character.

A recent study of hydroperoxyl radical reacting with formaldehyde[20] also reported that two conformationally related TSs for radical abstraction of the formyl hydrogen atom exist and that both are 10−12 kcal/mol lower in energy than conformationally related TSs for addition to the carbonyl group. This result shows that substantial radical (SET) character will, in fact, favor abstraction of the formyl proton over other modes of reactivity.

It is clear that the model chemistry used in the current paper for the S_N2 reaction (reaction 3, Scheme 1) is not totally adequate for the nucleophiles acting as bases in reaction 1. The rate ratio of 64/61 should have a difference in barrier height of only 0.028 kcal/mol (0.117 kJ/mol), but the most conformationally favorable path for hydroperoxide gives a barrier that is 4.5 kcal/mol higher than for hydroxide. In comparison, the barrier for the GPA-matched ethoxide is only 2.1 kcal/mol (8.8 kJ/mol) higher for the hydroperoxide. Clearly, in this case, a higher level of model chemistry is needed for more quantitative assessment of the role of SET character for α-nucleophiles behaving as bases. Possible model chemistries for refining this qualitative result include the processes recently summarized by Deakyne[21] for predicting thermodynamic properties to "benchmark" (0.25 kcal/mol) or "chemical" (1 kcal/mol) accuracy. That paper points out that addition or removal of a proton is an isogyric process (one where the number of unpaired electrons is identical on both sides of the reaction), and proton affinity is expected to converge more quickly than other thermodynamic properties with respect to level of theory. Nevertheless, Deakyne points out that highly correlated methods and large basis sets are required to reach "benchmark" accuracy. Computation to "chemical" rather than "benchmark" accuracy could employ G2 or G3 theories. Studies at this or similar levels are being considered to more quantitatively assess the SET results of this reaction. The concept that SET transfer is important in α-nucleophile chemistry, indicating that the reactions of α-nucleophiles are not totally polar, but still isogyric, may explain why the model chemistry employed herein is not completely adequate. Even so, it is clear that there is a substantial difference between hydroperoxide and hydroxide concerning the quality of charge transferred in reaction 1. We tentatively conclude that the computed SET character difference between the hydroper-

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oxide and hydroxide acting as bases in reaction 1 accounts at least partly for the anomalous reactivity ratio.

Methyl Transfer. The results presented in Table 1 show that hydroperoxide and hydroxide have very similar activation free energies and should therefore react at similar rates as shown by DePuy et al.[4] However, when hydroperoxide is compared to the gas-phase matched ethoxide it is seen that hydroperoxide has a lower barrier by about 3.6 kcal/mol and should enjoy a rate enhancement of about 400:1 at 298 K. This number is larger than those found in the literature for hydroperoxide versus methoxide in methyl transfers in methanol solution, which range from 3:1 to 10:1.[22] Since methanol has a GPA nearly identical to that of ethanol,[5] one could expect our rate enhancements to better match the experimental values. However, our results are in the gas-phase, so it may be that solvent greatly reduces the α-effect. Furthermore, even a small error in relative free energies of activation will dramatically change the computed rate enhancement. Nonetheless, the data in Table 1 clearly indicate that hydroperoxide should react at a similar rate as the non-GPA-matched normal nucleophile hydroxide and faster than the GPA-matched normal nucleophile ethoxide.

The data in Table 2 show that abstraction of methyl by hydroperoxide exhibits about 68% more SET character than the corresponding abstraction by hydroxide and nearly twice the SET character as in found for ethoxide. The degree of SET character for hydroperoxide in our system (2.7%) is in close agreement with that found for methyl transfer from fluoride to hydroperoxide (2.4%). For comparison, Shi and Boyd obtained 2.0% SET for methyl transfer from methyl fluoride to hydroxide, which is similar to the 1.6% we report for the analogous reaction.[11−14] Since the electron affinities of the leaving groups in these two reactions are similar (3.401 eV for F[5] and 3.498 eV for HCOO[23]), it can be concluded that the observed SET character is due to the nucleophile and is not a function of the leaving group, as has been found in other cases.[24]

The fact that some SET character is seen even for methyl abstraction by hydroxide should not be surprising, as hydroxide is reported to be a good SET donor in the gas phase.[25] This ability is greatly attenuated or even extinguished in solvated reactions, likely due to differential solvation effects and the general reduction in solvated reaction rates compared to those in the gas phase.[26] Thus, our results are consistent with the body of gas-phase data regarding methyl transfers and support the existence of a quantifiable α-effect in the gas phase.

Conclusions

The modern definition of the α-effect requires strict adherence to the requirement that the normal and α-nucleophiles be matched in acidity. We have examined gas-phase proton transfer and methyl transfer reactions from methyl formate to three nucleophiles, hydroperoxide, hydroxide, and ethoxide. Hydroperoxide, an α-nucleophile, has a very different gas-phase acidity than hydroxide but is closely matched with ethoxide. Our results then serve to clarify whether differences in gas-phase reactivity are due to differences in GPA or to a genuine gas-phase α-effect.

We find substantial SET character and with both hydroxide and hydroperoxide in the proton transfer reaction. We also note two conformers exist for the hydroperoxide transition state, one of which is substantially different in geometry from those found with the normal nucleophiles. Exactly what role this plays is the subject of ongoing work. In particular, natural bond orbital (NBO) analysis will be used to determine the specific orbital interaction and their magnitudes.[27]

For the methyl transfer reactions, a small degree of SET character is found with all three nucleophiles, but the enhancement of SET character in the reaction with hydroperoxide relative to the GPA-matched normal nucleophile ethoxide is substantial. This is mirrored by a lower activation free energy for hydroperoxide attack than for ethoxide attack. We further find that hydroperoxide and hydroxide have similar activation free energies despite hydroxide being substantially more basic in the gas phase. Increased SET character is believed to allow hydroperoxide to overcome this inherent difference.

By carefully comparing GPA-matched normal and α-nucleophiles, we have demonstrated a quantifiable α-effect in the gas phase. Continuing work will include additional GPA-matched pairs of nucleophiles and allow us to construct Brønsted-type plots that will help generalize the conclusions of this manuscript for gas-phase reactions.

Acknowledgment. We thank Jon Salmon and Whitermorn Co. for a small grant in support of K.R.F.'s research. We thank Truman State University for office space and some computational facilities.

Supporting Information Available: The geometries for the transition states in Chart 1 are available as .zip files containing the geometries involved as.gjf files capable of visualization with commercially available software. This material is available free of charge via the Internet at http://pubs.acs.org.

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