

Hydrogen Bonding Lowers Intrinsic Nucleophilicity of Solvated Nucleophiles

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Abstract: The relationship between nucleophilicity and the structure/environment of the nucleophile is of fundamental importance in organic chemistry. In this work, we have measured nucleophilicities of a series of substituted alkoxides in the gas phase. The functional group substitutions affect the nucleophiles through ion–dipole, ion-induced dipole interactions and through hydrogen bonding whenever structurally possible. This set of alkoxides serves as an ideal model system for studying nucleophiles under microsolvation settings. Marcus theory was applied to analyze the results. Using Marcus theory, we separate nucleophilicity into two independent components, an intrinsic nucleophilicity and a thermodynamic driving force determined solely by the overall reaction exothermicity. It is found that the apparent nucleophilicities of the substituted alkoxides are always much lower than those of the unsubstituted ones. However, ion–dipole, ion-induced dipole interactions, by themselves, do not significantly affect the intrinsic nucleophilicity; the decrease in the apparent nucleophilicity results from a weaker thermodynamic driving force. On the other hand, hydrogen bonding not only stabilizes the nucleophile but also increases the intrinsic barrier height by 3 to ~4 kcal mol⁻¹. In this regard, the hydrogen bond is not acting as a perturbation in the sense of an external dipole but more directly affects the electronic structure and reactivity of the nucleophilic alkoxide. This finding offers a deeper insight into the solvation effect on nucleophilicity, such as the remarkably lower reactivities in nucleophilic substitution reactions in protic solvents than in aprotic solvents.

Introduction

Nucleophilicity, one of central concepts in organic chemistry, is generally defined as the ability of a nucleophile to attack the carbon atom and replace the leaving group in a bimolecular nucleophilic substitution reaction (S_N2 reaction).^{1,2} Nucleophilicity is largely determined by two major factors: the chemical structure of the reactants and the environment in which the reaction occurs. Many structural chemical properties of the nucleophile, such as basicity, electronegativity, and “hardness”, are strongly correlated with nucleophilicity. Alkyl substitution, depending on the position and bulkiness of the substituent, can slow down the reaction through a steric effect. Beside these intrinsic structural properties, solvation also plays a major role. For example, S_N2 reactivities in polar aprotic solvents are orders of magnitude higher than those in protic solvents. This effect is especially important for “hard” nucleophiles, such as alkoxides.^{1,2}

Solvation effects, although extremely important, are often difficult to study due to the complexity of solvation. One general strategy toward a better understanding of solvation is through gas-phase studies, where, in absence of solvent, only the intrinsic properties are important. On the other hand, the often dramatic differences between the gas phase and solution highlight the importance of solvation, especially when ionic species are involved.^{3–7} Microsolvation in the gas phase, where only one,

or a few, solvent molecules are present, can offer greater insight into solvation.^{8,9} For an S_N2 reaction with microsolvation, the solvent molecules can be placed on the nucleophile and the S_N2 reactivities measured toward an unsolvated substrate, such as methyl halide. Such systems have been investigated in numerous studies, both experimentally and theoretically.^{9–15} A general observation from these studies is that microsolvation significantly raises the activation energy, regardless of the solvent, the nucleophile, and the substrate. Such a result is expected from the kinetics–thermodynamics relationship. During the reaction process, the solvent is “evaporated”. Only the anionic nucleophile is solvated and stabilized, but not the products. Therefore, the exothermicity of the reaction is lowered (less negative) by

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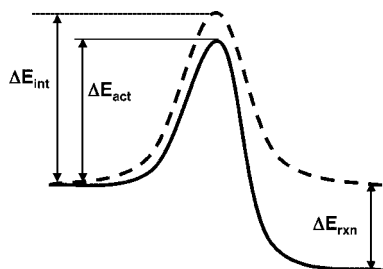


Figure 1. ΔE_{int} and ΔE_{act} in Marcus theory for a single-barrier potential energy surface.

a large amount, typically ~ 20 kcal mol $^{-1}$ for single solvent molecule solvation. A great portion of the thermodynamic driving force is lost, and the reactivity significantly lowered. However, it is not clear how the intrinsic nucleophilicity is affected by microsolvation. To understand this, the contribution from exothermicity must first be excluded.

Marcus theory predicts a simple relationship between the observed activation energy, ΔE_{act} , and the overall exo/endothermicity of the reaction, ΔE_{rxn} . 16,17 ΔE_{act} consists of two components; one is the intrinsic component and the other arises solely from the thermodynamic driving force. The intrinsic activation energy, ΔE_{int} , is defined as the barrier height in absence of a thermodynamic bias, Figure 1. Therefore, ΔE_{act} and ΔE_{int} are equal only in thermoneutral reactions. For nonthermoneutral reactions, ΔE_{int} can be related to ΔE_{act} by eq 1.

$$\Delta E_{\text{act}} = \Delta E_{\text{int}} + \frac{\Delta E_{\text{rxn}}}{2} + \frac{(\Delta E_{\text{rxn}})^2}{16\Delta E_{\text{int}}} \quad (1)$$

Although Marcus theory was originally designed for electron-transfer reactions, the underlying kinetic–thermodynamic relationship goes far beyond, $^{16-19}$ and it has been successfully applied to a variety of organic reactions, $^{20-24}$ including nucleophilic substitution reactions in the gas phase. $^{6,25-30}$ Using Marcus theory, we can analyze how solvent molecules affect intrinsic nucleophilicity without the complications from reaction exothermicity. In this work, we report the gas-phase $S_{\text{N}}2$ reactivities of a set of selected alkoxides toward methyl chloride. These alkoxides were substituted with a variety of functional groups, including polar groups and hydrogen-bond donors. The functional group substitution can introduce ion–dipole, ion–

induced dipole interactions, and/or intramolecular hydrogen bonding. 31,32 This makes the set of the alkoxides a good model system for studying the effect of intramolecular microsolvation on nucleophilicity. 33 The exothermicities of the corresponding $S_{\text{N}}2$ reactions span over a ~ 30 kcal mol $^{-1}$ range, which makes obvious the nonlinear relationship between the exothermicity and the barrier height predicted by Marcus theory. Despite the great difference in the overall exothermicities, the measured intrinsic barrier heights for the alkoxides with various polar group substitutions are essentially the same, ~ 3.8 kcal mol $^{-1}$. Therefore, we conclude that polar group substitution does not significantly affect intrinsic nucleophilicity. On the other hand, hydrogen bonding does lower intrinsic nucleophilicity. For alkoxides, a single hydrogen bond increases the intrinsic barrier height by ~ 3 kcal mol $^{-1}$. Other factors, such as conjugation and steric hindrance, also lower intrinsic nucleophilicity to different extents.

Experimental Section

Materials. All reagents used in this study were commercially available except for 1,3-cyclohexanediols and 1,4-cyclohexanediols, which were purchased as mixtures of cis and trans isomers. Pure samples were obtained by separating the mixtures through previously reported procedures. 32

Ab Initio Calculations. MP2 (second-order Møller–Plesset theory) 34 and DFT (density functional theory) 35,36 calculations were performed. Geometries were optimized at the B3LYP/6-31+G* level of theory. Single-point MP2 energies were calculated on the DFT geometries at the 6-311+(2d,p) basis set. These calculations were used for energetic and structural analysis as well as for input parameters for RRKM (Rice, Ramsperger, Kassel, Marcus) modeling.

Reaction Rates. All reaction rates were measured in the gas phase using an IonSpec OMEGA Fourier transform ion cyclotron resonance spectrometer (FT-ICR). The magnetic field strength was 0.6 T. The temperature of the 2 in. cubic stainless steel cell was estimated to be 350 K. 33 Background pressures ranged from 0.5 to 4.0×10^{-9} Torr, and operating pressures ranged from 0.3 to 5.0×10^{-6} Torr. A Granville Phillips 330 ion gauge was used to obtain pressure readings, which were calibrated against an MKS Baratron 170 capacitance manometer (315BH-1 sensor). Absolute pressure measurements were estimated to have an error of $\pm 20\%$. 33

The rate constants for the $S_{\text{N}}2$ reactions of various alkoxides with methyl chloride are reported in Table 1. Primary ions, fluoride or *tert*-butoxide, were generated from nitrogen trifluoride and di-*tert*-butyl peroxide, respectively. Other alkoxides were produced via proton transfer reactions between the primary ions and corresponding alcohols. Buffer gases were added to ensure that the ions were completely thermalized. The reaction rates measured by monitoring disappearance of the alkoxides as well as appearance of chloride. No pressure dependence on buffer was observed in the reaction rates of most alkoxides except fluoride or *tert*-butoxide. The rates for the two ions were slightly slower under very low buffer pressures ($< 3 \times 10^{-7}$ Torr). The reactivities become pressure-independent under relatively high pressures (3×10^{-6} Torr) or after waiting a few hundred milliseconds. The reported values for these ions were measured in the pressure-independent region.

Accurate measurements of slow reaction rates require extra attention to exclude artifacts introduced from trace amounts of

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Table 1. Gas-Phase Nucleophilicities of Alkoxides (Ranked with Gas-Phase Acidity)

RO-	Rate ^a	Φ	ΔG_a^b	ΔE_{rxn}	$\Delta E_{\text{diff}}^{\text{EXP}}$	$\Delta E_{\text{int}}^{\text{EXP}^c}$	$\Delta E_{\text{diff}}^{\text{MP2}}$	$\Delta E_{\text{int}}^{\text{MP2}^d}$	$\Delta E_{\text{diff}}^{\text{DFT}}$	$\Delta E_{\text{int}}^{\text{DFT}^d}$
	~0.013	~0.0008	338.4	-9.2	-1.0 (-0.5) ^e	3.2 (3.7) ^e	-0.8	3.5	-2.2	2.1
	~0.014	~0.0008	341.5	-12.3	-0.7 (-0.2) ^e	4.8 (5.4) ^e	0.8	6.5	-3.5	2.0
	<0.008	<0.0005	342.3	-13.1	> -0.5	> 5.4	1.7	7.7	-1.2	4.8
	0.71	0.048	348.8	-19.6	-4.8	3.3	-5.0	3.4	-6.8	1.4
	0.096	0.006	352.3	-23.1	-2.5	7.2	-4.3	5.5	-6.5	3.1
	0.045	0.003	353.5	-24.3	-2.1	8.1	-3.0	7.4	-4.5	5.8
	0.63	0.040	353.7	-24.5	-4.6	5.3	-5.8	4.4	-7.3	2.7
	1.3	0.078	354.1	-24.9	-5.8	4.0	-6.2	4.0	-8.3	1.7
	0.038	0.002	354.6	-25.4	-1.9	8.7	-4.0	6.8	-6.7	3.7
	0.025	0.017	355.3	-26.1	-3.4	7.3	-5.5	5.3	-7.9	2.6
	0.035	0.002	355.5	-26.3	-1.9	9.1	-4.2	6.8	-6.6	4.2
	0.50	0.030	355.8	-26.6	-3.8	7.0	-5.8	5.2	-8.3	2.3
	0.025	0.002	356.0	-26.8	-1.7	9.4	-3.9	7.4	-6.3	4.7
	0.63	0.040	356.6	-27.4	-4.6	6.4	-3.8	7.7	-7.2	3.9
	0.5	0.03	356.7	-27.5	-4.0	7.1	-5.0	6.3	-6.9	4.3
	2.5	0.15	359.2	-30.0	-7.0	4.3	-7.6	4.3	-9.5	2.0
	1.4	0.079	360.9	-31.7	-5.9	6.3	-7.0	5.6	-9.3	2.8
	2.2	0.14	361.3	-32.1	-7.2	4.8	-6.9	5.9	-8.2	4.3
	2.6	0.17	363.0	-33.8	-8~9	2.7~4.2	-9.0	3.8	-9.9	2.8
	3.1	0.20	363.4	-34.2	-8~9	2.8~4.3	-7.9	5.4	-9.5	3.4
	3.3	0.21	363.7	-34.5	-8~9	2.9~4.4	-9.0	4.1	-10.2	2.6
	3.1	0.20	364.5	-35.3	-8~9	3.1~4.6	-9.3	3.9	-10.9	1.8
	3.3	0.19	364.6	-35.4	-8~9	3.2~4.7	-9.0	4.4	-10.8	2.0
	2.5	0.15	368.0	-38.8	-7.1	6.9	-7.4	7.5	-9.1	5.4

^a $10^{10} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. ^b Gas-phase acidities (kcal mol^{-1}) of corresponding alcohols. Values are taken from equilibrium measurements (ref 42).

^c Complexation energy is assumed to be $11.0 \text{ kcal mol}^{-1}$, see text. ^d Complexation energy is assumed to be 13.3 and $14.0 \text{ kcal mol}^{-1}$ for MP2 and DFT, respectively, taken from the calculated values for ethoxide–methyl chloride complex with the same theory. ^e The values in parentheses are corrected for possible contaminations, see text.

highly reactive impurities, such as hydrogen chloride, a usual contaminant in methyl chloride. To estimate the degree of contamination in our sample of methyl chloride, we measured the

reaction rate of chloride reacting with our sample. The apparent efficiency of chloride exchange reaction was measured to be 0.0002, which is higher than the widely accepted value according to

literature.³⁷ Therefore, our sample of methyl chloride indeed contained a reactive contaminant, presumably hydrogen chloride. Nevertheless, the experiment set an upper limit for contamination of ~ 0.0004 in the worst-case scenario (assuming the efficiency of the reaction between chloride and hydrogen chloride is 50%). The contamination introduced significant errors for the three least reactive alkoxides we have studied. The measured efficiency for the least reactive species, phenoxide, is ~ 0.0005 ; this value is so close to 0.0004 that we could treat it only as an upper limit. The efficiencies of acetate and 1,1,1,3,3,3-hexafluoro-2-propoxide ($(\text{CF}_3)_2\text{CHO}^-$) are significantly higher, both ~ 0.0008 . We believe that we have measured the $\text{S}_{\text{N}}2$ rates for these two anions, although the actual values might deviate to the lower side by as much as $\sim 50\%$. Other alkoxides are much more reactive and therefore suffer very little from this correction.

The reported rates for most reactions were reproducible within 5% to $\sim 20\%$ on different days. The fluctuations of the measurements were generally smaller for the fast reactions than for the slower ones. The reproducibility of the *trans*-1,3-cyclohexanediol anion and 1,3-difluoro-2-propoxide ($(\text{CH}_2\text{F})_2\text{CHO}^-$) was much worse, $\sim 35\%$, probably because of side reactions and/or contamination.

Some of these reactions, for example, $\text{C}_2\text{F}_5\text{CH}_2\text{O}^-$ and $\text{CF}_3\text{CH}_2\text{O}^-$, have been measured previously in FA-SIFT (flow afterglow-selected ion flow tube).^{37,38} Our values were found to be $\sim 40\%$ lower than those reported earlier. Although the differences were still within the combined error range, we believe that the reactions are indeed slower under our experimental conditions. The ICR instrument in our laboratory worked at a temperature of 350 K, more than 50 K higher than the room temperature, at which those FA-SIFT experiments were performed. Since every reaction in this study has a tight transition state with a significant negative ΔE_{diff} , negative temperature dependence is expected. Such temperature dependence is very common among gas-phase $\text{S}_{\text{N}}2$ reactions and has been reported many times before.^{7,12} The differences in rates measured in the two laboratories can be largely attributed to the difference in temperature. Another possibility was that the alkoxides were not fully thermalized in the ICR. However, we believe this was unlikely since no pressure dependence was observed in those cases.

Obtain ΔE_{diff} Using RRKM Theory. The central $\text{S}_{\text{N}}2$ barrier was determined from the experimentally measured rate constant and statistical modeling of the reaction, through a well-established method.³³ First, the reaction efficiency was calculated as the ratio between the reaction rate and the collision rate, eq 2. Efficiency, defined as the number of productive reactions per collision, is a better parameter to characterize the kinetics than reaction rate constant for ion–molecule reactions in the gas phase.⁷ The collision rates for ion–molecule pairs, k_{coll} , were obtained through the parametrized trajectory model of Su and Chesnavich.³⁹

$$\Phi_{\text{EXP}} = k_{\text{obs}}/k_{\text{coll}} \quad (2)$$

ΔE_{diff} , defined as the difference in energy between the separated reactants and the $\text{S}_{\text{N}}2$ transition state, Figure 2, was then determined by fitting the experimental efficiency with the efficiency calculated by RRKM unimolecular reaction rate theory,⁴⁰ eq 3. The $\text{S}_{\text{N}}2$ reaction was modeled as the unimolecular rearrangement of one ion–molecule complex into another, k_2 , in competition with dissociation of the ion–molecule complex to return to reactants, k_{-1} , Figure 2.

$$\Phi_{\text{RRKM}} = k_2/(k_2 + k_{-1}) \quad (3)$$

For typical reactions a 20% error in reaction rate corresponds to a very small error in barrier height under thermal conditions at 350

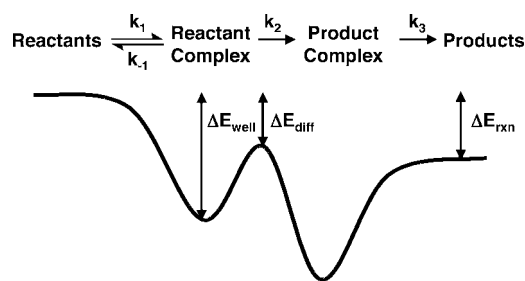


Figure 2. Schematic double-well potential energy surface.

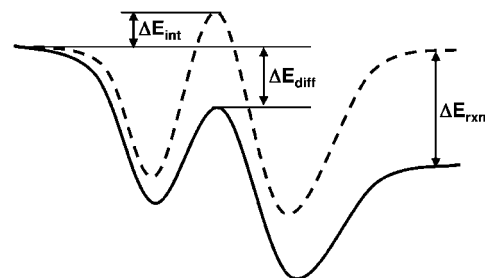


Figure 3. ΔE_{int} and ΔE_{diff} in Marcus theory for a double-well potential energy surface. For the alkoxides, ΔE_{diff} are negative and ΔE_{int} are positive, as shown.

K as long as ΔE_{diff} is not very negative.⁴⁰ However, the sensitivity of RRKM fitting decreases gradually with ΔE_{diff} . A barrier several kilocalories per mole lower than the reactants is hardly felt by the ion–molecule complex. In this limit, the barrier does not affect the complex and the sensitivity of RRKM fitting is completely lost. Typically, when ΔE_{diff} is -7 to ~ -9 kcal mol⁻¹, a 20% error in rate is equivalent to >1 kcal mol⁻¹ error in barrier height. The several most facile reactions in this study fall into this region, and the barrier heights estimated have relatively large errors, Table 1.

Obtain ΔE_{int} Using Marcus Theory. To apply Marcus theory to a gas-phase double-well potential energy surface, Figure 3, Dodd and Brauman redefined the original Marcus expression to be eq 4,²⁷ where ΔE_{rxn} , ΔE_{well} , and ΔE_{diff} are the energies of the product, the reactant complex, and the transition state, respectively. All energies are defined relative to the separated reactants and are usually negative, as shown in Figures 2 and 3. Equation 4 has no mathematical advantage over the original expression but is more convenient, with the complexation energy ΔE_{well} included. ΔE_{well} contributes only to the second-order term, which is usually small. Here, we assume that ΔE_{well} is the same for all alkoxide–methyl chloride complexes. This is a reasonable assumption because the complexation energy consists mostly of ion–dipole and ion-induced dipole interactions. The complexation energy, therefore, is largely determined by the physical properties of the neutral, whereas the detailed structure of the ion is less important. We take the experimental complexation energy of $\text{CH}_3\text{Cl}\cdot\text{Cl}^-$, -11.0 kcal mol⁻¹, to be ΔE_{well} for all of our reactions.⁴¹ The actual value hardly changes the relative ΔE_{int} , as long as the magnitude of ΔE_{well} is greater than ΔE_{diff} .

$$\Delta E_{\text{diff}} = \Delta E_{\text{int}} + \frac{\Delta E_{\text{rxn}}}{2} + \frac{(\Delta E_{\text{rxn}})^2}{16(\Delta E_{\text{int}} - \Delta E_{\text{well}})} \quad (4)$$

Another parameter needed in Marcus theory is the reaction exothermicity. Gas-phase thermodynamic information for the $\text{S}_{\text{N}}2$ product ROCH_3 is unavailable for most alkoxides, especially for diol anions. Instead, we choose the basicities of the alkoxides to represent the reaction exothermicities, assuming the difference in the basicities is the same as the difference in the reaction

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exothermicities. This assumption is equivalent to assuming that the exothermicity of eq 5 is independent of the R group. The experimental exothermicity for the reaction of ethoxide with methyl chloride, $-41.6 \text{ kcal mol}^{-1}$, was taken as a standard. The exothermicities of the other alkoxides were estimated based on their experimental basicities. For example, the reaction of phenoxide, which is $28.5 \text{ kcal mol}^{-1}$ less basic than ethoxide, was estimated to be $-41.6 + 28.5 = -13.1 \text{ kcal mol}^{-1}$ exothermic. This estimated value is 0.0 to $\sim 1.9 \text{ kcal mol}^{-1}$ lower than the experimental value, -11.2 to $\sim -13.1 \text{ kcal mol}^{-1}$.⁴² We took the estimated value instead of experimental to be consistent with other alkoxides.⁴³ All the values are listed in Table 1.



With ΔE_{rxn} , ΔE_{well} , and ΔE_{diff} known, the intrinsic nucleophilicity ΔE_{int} can now be determined using eq 6, which is derived from eq 4, where ΔE_{int} represents the intrinsic barrier height according to Marcus theory. For $\text{S}_{\text{N}}2$ reactions, ΔE_{int} is the intrinsic nucleophilicity, a parameter measuring the nucleophilicity without the bias from reaction exothermicity.

$$\Delta E_{\text{int}} = \frac{1}{2} \left(\Delta E_{\text{diff}} + \Delta E_{\text{well}} - \frac{\Delta E_{\text{rxn}}}{2} + \sqrt{\left(\Delta E_{\text{diff}} - \Delta E_{\text{well}} - \frac{\Delta E_{\text{rxn}}}{2} \right)^2 - \frac{(\Delta E_{\text{rxn}})^2}{4}} \right) \quad (6)$$

Results

The reaction efficiencies of the alkoxides toward methyl chloride are listed in Table 1. Despite the similar structures of all these alkoxides, their $\text{S}_{\text{N}}2$ reactivities are very different. A very large dynamic range is observed; the reaction efficiency varies over 3 orders of magnitude, from almost as high as the collision limit to as low as one in several thousand. The reaction efficiencies were converted to the observed barriers, ΔE_{diff} , through RRKM theory,⁴⁰ and the intrinsic barrier heights, ΔE_{int} , were calculated according to Marcus theory.^{16,17,26,27} All these values are listed in Table 1. Although ΔE_{diff} is always negative, the intrinsic barriers, ΔE_{int} , are significantly positive for all alkoxides we have measured, ranging from 3 to $\sim 9 \text{ kcal mol}^{-1}$. This indicates that alkoxides are not good nucleophiles intrinsically. The thermoneutral reaction of chloride with methyl chloride has a barrier of $\sim 1 \text{ kcal mol}^{-1}$.³⁷ Therefore, chloride is intrinsically more nucleophilic than alkoxides. The apparently high $\text{S}_{\text{N}}2$ reactivities of the alkoxides mostly result from their high exothermicities.

The alkoxides in Table 1 are ranked according to their gas-phase basicities, which is equivalent to the overall exothermicities according to our assumption. From the table, one can easily find a general correlation between basicity and nucleophilicity. For example, in the series of $\text{CFH}_2\text{CH}_2\text{O}^-$, $\text{CF}_2\text{HCH}_2\text{O}^-$, $\text{CF}_3\text{CH}_2\text{O}^-$, $\text{C}_2\text{F}_5\text{CHO}^-$, basicity parallels nucleophilicity very well. This correlation is expected since both basicity and nucleophilicity decrease with the stability of the base/nucleophile. However, many exceptions can be found in Table 1 as well. For example, the intramolecular hydrogen-bonded 1,4-

butanediol anion, $\text{HO}(\text{CH}_2)_4\text{O}^-$, is more basic than $\text{CF}_3\text{CH}_2\text{O}^-$. The basicity–nucleophilicity correlation would predict a higher $\text{S}_{\text{N}}2$ reactivity for the diol anion, whereas it is actually 40 times less reactive. This suggests that the hydrogen bonding in the diol anion is more effective in lowering nucleophilicity than the ion–dipole interactions in the fluoro-substituted anion when they lower the basicity to similar degrees. The pair of $\text{CF}_3\text{C}(\text{CH}_3)_2\text{O}^-$ and $\text{C}_2\text{F}_5\text{CHO}^-$ is another exception. The basicity of $\text{CF}_3\text{C}(\text{CH}_3)_2\text{O}^-$ is $\sim 5 \text{ kcal mol}^{-1}$ higher than $\text{C}_2\text{F}_5\text{CHO}^-$, but the reactivity is 16 times lower. Again, the orders for basicity and nucleophilicity are just opposite. From these exceptions and many other similar cases, we can generalize several rules: hydrogen bonding, steric hindrance, and conjugation lower the $\text{S}_{\text{N}}2$ reactivities greater than expected from the basicity. These effects will be discussed further in the following sections.

Discussion

Effect of Polar Group Substitution on Intrinsic Nucleophilicity. A series of fluoro-substituted linear alkoxides is listed in Table 1, including $\text{CFH}_2\text{CH}_2\text{O}^-$, $\text{CF}_2\text{HCH}_2\text{O}^-$, $\text{CF}_3\text{CH}_2\text{O}^-$, $\text{C}_2\text{F}_5\text{CHO}^-$, and $(\text{CF}_3)_2\text{CHO}^-$. It is clear that both the basicity and the nucleophilicity are greatly lowered by the substitution. For example, $\text{CFH}_2\text{CH}_2\text{O}^-$ is $\sim 26 \text{ kcal mol}^{-1}$ more basic than $\text{C}_2\text{F}_5\text{CHO}^-$ and the $\text{S}_{\text{N}}2$ reaction barrier is about 4 kcal mol^{-1} lower. This is expected since the ion–dipole and ion-induced dipole interactions greatly stabilize the anions and therefore lower the overall reaction exothermicity. However, all of the alkoxides have very similar intrinsic barrier heights, 3 to $\sim 4 \text{ kcal mol}^{-1}$, Figure 6. This strongly suggests that ion–dipole and ion-induced dipole interactions, in general, do not affect the intrinsic nucleophilicity significantly.

It is of great interest to measure the intrinsic nucleophilicity of the unsubstituted anion, methoxide. However, the reaction efficiency of methoxide with methyl chloride is so high, $> 60\%$,³⁷ that the barrier height cannot be determined accurately by the experimental reaction rate through RRKM fitting. Instead, we estimated the reaction barrier theoretically. G2 calculation was performed for this reaction.³⁴ ΔE_{well} and ΔE_{diff} were calculated to be -14.0 and $-11.9 \text{ kcal mol}^{-1}$, respectively. Together with the exothermicity of $-44.8 \text{ kcal mol}^{-1}$, the intrinsic barrier can be estimated to be $3.2 \text{ kcal mol}^{-1}$. This value is very similar to those of the fluoro-substituted alkoxides. The result further strengthens the conclusion that polar group substitution does not significantly affect the intrinsic nucleophilicity.

Effect of Hydrogen Bonding on Intrinsic Nucleophilicity. Table 1 also includes 10 hydroxyl-substituted alkoxides, i.e., diol anions. Some of them possess an intermolecular hydrogen bond and some do not, depending on the geometry and the position of the substitution, Figure 4. Unlike fluoro-substituted alkoxides, these diol anions have very different intrinsic barrier heights, ranging from ~ 3 to $\sim 9 \text{ kcal mol}^{-1}$. Obviously, the intramolecular hydrogen bonding has a significantly impact on the intrinsic nucleophilicity. To understand the nucleophilicity of the diol anions, we have to understand the hydrogen bonding first.

In a previous study,³² we investigated hydrogen bonding in diols and diol anions by measuring gas-phase acidity of a series of diols. According to the strength of the hydrogen bonding in the anions, we categorized the 10 diols, including 6 cyclohexanediol isomers and 4 linear α,ω -diols, 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, and 1,5-pentanediol,³¹ into three groups, Figure 4. Group I consists of those anions that have

(42) NIST Webbook. <http://webbook.nist.gov>.

(43) Since the overall exothermicity is reaction enthalpy, proton affinity (ΔH°) should be used instead of basicity (ΔG°). However, the relative acidities of many alcohols are determined with the equilibrium method without temperature-dependent measurements. The corresponding proton affinities are estimated or calculated. To avoid artifacts, we choose to use the experimental basicities directly, assuming $T\Delta S^\circ$ are the same for all alkoxides. To be consistent, all basicities are taken from equilibrium measurements. We also assume that ΔH° is the same as ΔE .

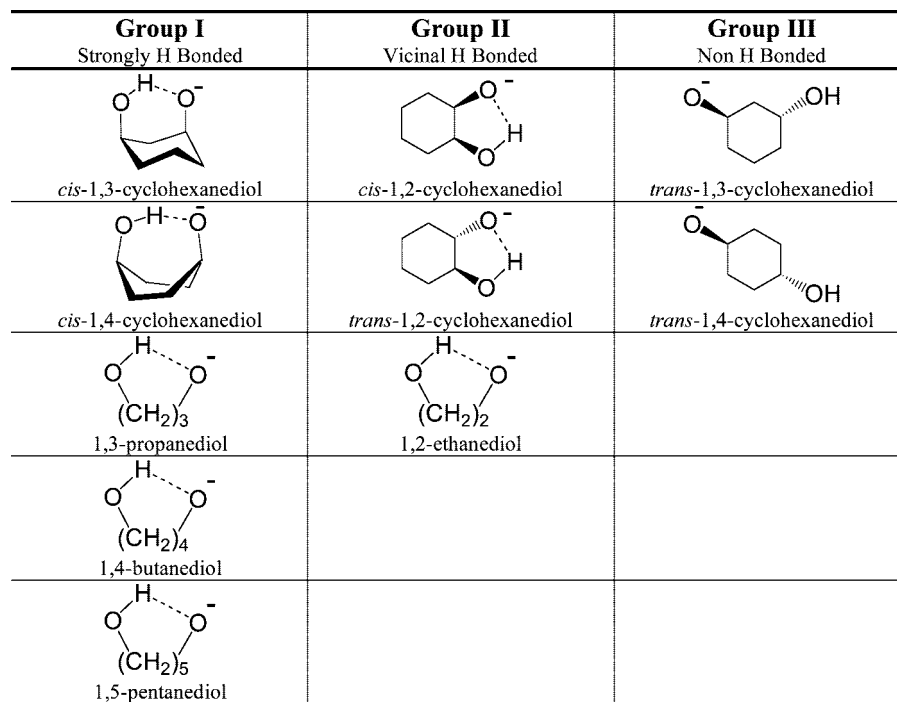


Figure 4. Structure and hydrogen bonding in diol anions.

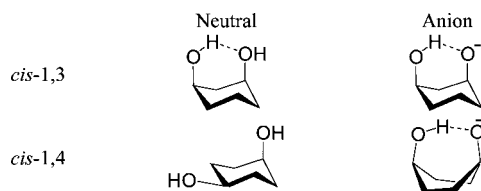


Figure 5. Conformations of *cis*-1,3- and *cis*-1,4-cyclohexanediol and their anions.

strong intramolecular hydrogen bonds. Five diol anions belong to this group, including *cis*-1,3-cyclohexanediol, *cis*-1,4-cyclohexanediol, 1,3-propanediol, 1,4-butanediol, and 1,5-pentanediol. *cis*-1,3-Cyclohexanediol anion has both hydroxyl groups in axial positions, and a hydrogen bond is formed between them, Figure 5. *cis*-1,4-Cyclohexanediol anion allows an hydrogen bond by adopting a twisted boat conformation, Figure 5. The three linear α,ω -diol anions can cyclize to make an intramolecular hydrogen bond. The strength of hydrogen bonds in these anions were estimated to be very close to that in methanol–methoxide complex.³² Group II consists of three vicinal diol anions, *cis*-1,2-, *trans*-1,2-cyclohexanediol, and 1,2-ethanediol. The members of group II have distorted hydrogen bonds in the corresponding anions because of the geometric constraints. Group III has two members, *trans*-1,3-cyclohexanediol and *trans*-1,4-cyclohexanediol, where no hydrogen bond can form because of the limitation of their geometries.

Both the non-hydrogen-bonded diol anions, *trans*-1,3- and *trans*-1,4-cyclohexanediol anions (group III), are very reactive toward methyl chloride. Although the RRKM fittings have relatively large errors for fast reactions, we can estimate the intrinsic barriers to be 2.5 to ~ 4.5 kcal mol⁻¹ for both anions, similar to that in the fluoro-substituted alkoxides, 3 to ~ 4 kcal mol⁻¹. This result is expected, since there should not be any fundamental difference between a fluoro group and a hydroxyl group that is not hydrogen-bonded.

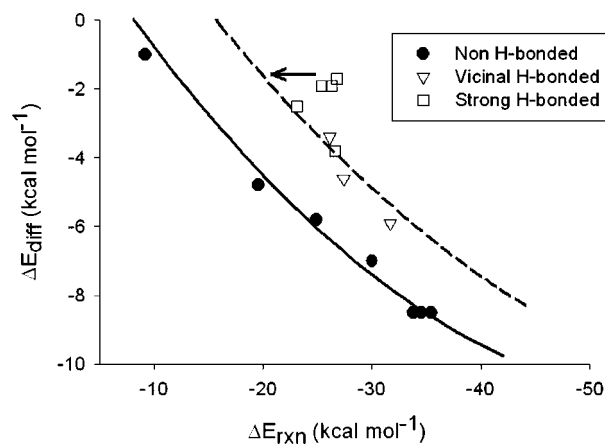


Figure 6. Effect of hydrogen bonding on nucleophilicities of alkoxides. The solid circles are non-hydrogen-bonded alkoxides (group III in Figure 4 and the four fluoro-substituted linear alkoxides). The vicinal hydrogen-bonded diol anions (group II in Figure 4) and strongly hydrogen-bonded diol anions (group I in Figure 4) are represented by triangles and squares, respectively. The solid line and the dashed lines are Marcus theory predictions with intrinsic barriers of 3.8 and 7.0 kcal mol⁻¹, respectively. The arrow represents a possible correction as discussed in the text.

However, when intramolecular hydrogen bonding is present, the intrinsic nucleophilicity is significantly lower. The intrinsic barriers obtained for three vicinal diol anions (group II) are 6.2 to ~ 7.2 kcal mol⁻¹, clearly higher than that of the non-hydrogen-bonded ones. The intrinsic barriers of the five strongly hydrogen-bonded species (group I) are 7.0 to ~ 9.4 kcal mol⁻¹, which appear to be even higher. Hydrogen bonding in these diol anions not only lowers the nucleophilicity by stabilizing the nucleophile but also increases the intrinsic S_N2 barrier directly. The effect seems to be more important in more strongly hydrogen-bonded species.

Some of these strongly hydrogen-bonded species undergo conformational changes from neutral to anion. For example, *cis*-

1,3-cyclohexanediol anion, which has the highest intrinsic barrier, $9.4 \text{ kcal mol}^{-1}$, adopts a boat conformation, whereas the corresponding neutral (the protonated form) is a chair,³² Figure 5. We believe that the boat conformation is maintained in the transition state as suggested by our DFT calculation. The hydrogen bonding in the transition state is still significant, $\sim 10 \text{ kcal mol}^{-1}$ according to DFT. Since the conformation change happens after the transition state, its contribution to the reaction exothermicity should more properly be excluded when Marcus theory is applied. The “effective” exothermicity, therefore, ought to be slightly smaller (less negative), and the intrinsic barrier determined by Marcus theory should be slightly lower. The “effective” exothermicity may be taken as the exothermicity of the hypothetical reaction in which the anion with a boat conformation generates the product also with a boat conformation. Therefore, the exothermicity difference between the hypothetical reaction and the real reaction is the same as the relative stability of the boat and chair conformations in neutral. This value is not experimentally available, but it has been calculated to be $\sim 4 \text{ kcal mol}^{-1}$ with DFT.³² This correction adjusts the “effective” intrinsic barrier to be $7.9 \text{ kcal mol}^{-1}$, $1.5 \text{ kcal mol}^{-1}$ lower than the original value. Similar corrections may apply to the linear diol anions with very high intrinsic barriers as well.⁴⁴ Other diol anions are not significantly affected by this correction.

Figure 6 summarizes the results by plotting the observed barrier heights (ΔE_{diff}) of these diol anions, together with some fluoro-substituted alkoxides, against their exothermicities (ΔE_{rxn}). From the plot, it is clear that both fluoro-substituted alkoxides and non-hydrogen-bonded diol anions, represented as solid circles in Figure 6, are predicted accurately by Marcus theory with an intrinsic barrier of $3.8 \text{ kcal mol}^{-1}$ (solid line). Hydrogen-bonded diol anions, on the other hand, have much higher barriers. As shown in the plot, a Marcus theory prediction with an intrinsic barrier (ΔE_{diff}) of $7.0 \text{ kcal mol}^{-1}$ (dashed line) fits most of such anions. The several anions with even higher intrinsic barriers undergo conformation changes from the nucleophile to the product. If this correction is applied, the data points should be moved toward the left by 1 to $\sim 4 \text{ kcal mol}^{-1}$ and fit better with the dashed line (illustrated by the arrow in Figure 6). Overall, the difference in the intrinsic barrier for the hydrogen-bonded species and the non-hydrogen-bonded ones is 3 to $\sim 4 \text{ kcal mol}^{-1}$, which appears to be the increase of the intrinsic barrier introduced by a single hydrogen bond.

Why does hydrogen bonding lower intrinsic nucleophilicity? We suggest that it is a consequence of the charge distribution in the nucleophile and in the transition state. There are two complementary ways of looking at the consequences. First, it is well-known that hydrogen bonding is much stronger when the charge is more concentrated on the hydrogen-bond acceptor. For example, F^- is much better proton acceptor than Cl^- and the trend extends to the whole family. CF_3^- , an anion with a very dispersed charge distribution, forms very weak hydrogen

bonds.⁴⁵ The $\text{S}_{\text{N}}2$ transition state has much less charge concentrated on the alkoxide oxygen than in the nucleophile. Therefore, the strength of the intramolecular hydrogen bond is much weaker, which directly lowers the intrinsic nucleophilicity. On the other hand, the ion–dipole interactions are not nearly as sensitive to the charge distribution. As the result, the hydrogen bonding is more effective in lowering nucleophilicity.⁴⁶ Alternatively, whereas a “typical” polar group substituent effect on an alkoxide is simply an electrostatic perturbation, the hydrogen-bonded alkoxide is electronically affected to a much greater extent in terms of electron distribution and charge. The diminished charge makes the alkoxide significantly less reactive kinetically. In any case, the overall effect of hydrogen bonding on nucleophilicity, is twofold. First, hydrogen bonding stabilizes the nucleophile and weakens the overall thermodynamic driving force. Second, it increases the intrinsic $\text{S}_{\text{N}}2$ barrier height and slows down the reaction “kinetically”. This offers new insight into the solvation effect on nucleophilicity. The polar group substitution presented earlier can be regarded as a microsolvation model for solvation with polar aprotic solvents while the hydroxyl substitution for protic solvents. It is well-known that polar aprotic solvents can accelerate $\text{S}_{\text{N}}2$ reactivities by several orders of magnitude when compared with protic solvents. The widely accepted explanation in textbooks is that the nucleophile is more effectively solvated and stabilized in protic solvents.^{1,2} Besides this thermodynamic reason, we believe that the hydrogen bonding, which can lower the intrinsic nucleophilicity directly in a pure “kinetic” sense, also contributes to the extremely low $\text{S}_{\text{N}}2$ reactivities in protic solvents. We have estimated that single hydrogen bonding on the nucleophile only can increase the barrier by $\sim 3 \text{ kcal mol}^{-1}$ (Figure 6). In protic solvents, we expect the effect to be even greater because both the nucleophile and the leaving group are hydrogen-bonded, possibly with multiple hydrogen-bond donors at the same time. The overall effect may contribute significantly or even dominate the retardation of the $\text{S}_{\text{N}}2$ reactivities observed in those solvents when compared with polar, aprotic solvents.

The barrier heights of the alkoxides were also calculated with two theoretical methods, DFT and MP2, Table 1. When compared with experimental values, DFT underestimates the barrier by 2 to $\sim 5 \text{ kcal mol}^{-1}$ and the MP2 predictions deviate -3 to $\sim +1 \text{ kcal mol}^{-1}$ relative to the experimental values. It is consistent with previous observations that DFT tends to severely underestimate the transition state, particularly for $\text{S}_{\text{N}}2$ reactions.⁴⁷ The intrinsic barrier heights can also be obtained using calculated barrier heights; these values are listed in Table 1 as well. In general, DFT predicts that hydrogen bonding lowers the intrinsic nucleophilicity by only about 1 to $\sim 2 \text{ kcal mol}^{-1}$, somewhat smaller than the experimental results. MP2 predictions agree with experiments much better, although relatively large differences can be found for some individual nucleophiles. Overall, both the theoretical methods predict similar trends observed in the experiments although quantitative differences remain.

(45) Chabinyk, M. L.; Brauman, J. I. *J. Am. Chem. Soc.* **1998**, *120*, 10863–10870.

(46) This can also be considered in the context of the principle of nonperfect synchronization (PNS): Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301–308. PNS associates large intrinsic barriers with situations in which electronic structure changes are not synchronized with other measures of a reaction progress variable. Here, the hydrogen-bond strength at the transition state must be diminished relative to the bond forming progress variable.

(47) Gronert, S.; Pratt, L. M.; Mogali, S. *J. Am. Chem. Soc.* **2001**, *123*, 3081–3091.

(44) It is not clear whether 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol are cyclic in the gas phase. If so, no correction is needed. According to DFT-calculated ΔH° and estimated ΔS° by Crowder and Bartmess (*J. Am. Soc. Mass Spectrom.* **1993**, *4*, 723) the free energy differences between the cyclic conformations and the extended ones are about ~ 2 , ~ 3 , $\sim 4 \text{ kcal mol}^{-1}$ for the three diols, respectively. The intrinsic barriers after this correction are 6.3, 7.6, 7.6 kcal mol^{-1} , respectively. The original values are 7.0, 8.7, 9.1 kcal mol^{-1} , respectively, Table 1.

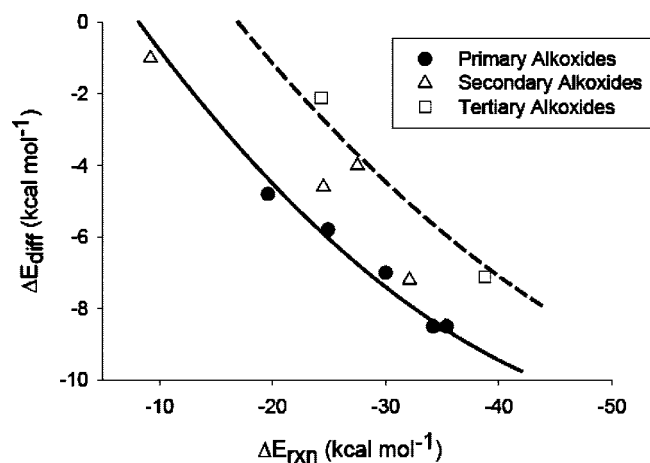


Figure 7. Nucleophilicities of alkoxides with steric effects. The circles, triangles, and squares are primary, secondary, and tertiary alkoxides, respectively. The solid and dashed lines are Marcus theory with 3.8 and 7.5 kcal mol⁻¹, respectively. The intrinsic barrier heights of all 1° alkoxides are ~3.8 kcal mol⁻¹, and those of the 3° alkoxides are ~7.5 kcal mol⁻¹. The intrinsic barrier heights of the 2° alkoxides vary between the two values.

Effect of Conjugation on Intrinsic Nucleophilicity. We have also measured the S_N2 reactivities of acetate anion and phenoxide anion. These two anions are fundamentally different from the other alkoxides we have discussed earlier because of the conjugation in these two species. The intrinsic barrier of acetate is determined to be ~5 kcal mol⁻¹. The intrinsic barrier of phenoxide is even higher; only a lower limit can be estimated, which is 5.4 kcal mol⁻¹, Table 1. The values are both much higher than the simple alkoxides, suggesting that conjugation not only stabilizes the nucleophile but also lowers the intrinsic nucleophilicity. The charge distribution is probably responsible for this observation as well. The conjugation is more important in the nucleophile where the charge is more concentrated than in the transition state where the charge is widely dispersed. This is essentially the same argument we employed for the effect of hydrogen bonding on the intrinsic nucleophilicity. Both the hydrogen bonding and conjugation prefer highly concentrated charge densities on the alkoxide oxygen.

Steric Effect on Intrinsic Nucleophilicity. Steric effects were observed for the branched alkoxides. For example, in the series of CF₃CH₂O⁻, CF₃CH(CH₃)O⁻, CF₃C(CH₃)₂O⁻, the basicities are almost the same, Table 1. However, the secondary alkoxide is about half as reactive as the primary alkoxide and the tertiary alkoxide more than 1 order of magnitude lower than the secondary. All primary (non-hydrogen-bonded) alkoxides have very similar ΔE_{int}, ~3.8 kcal mol⁻¹, and the ΔE_{int} values for tertiary alkoxides are ~7.5 kcal mol⁻¹; ΔE_{int} of the secondary alkoxides vary between the two values. Figure 7 summarizes the results.

The steric effect seems to be strongly correlated with geometry in the corresponding transition states. According to our DFT calculations, the three reaction-center atoms, the

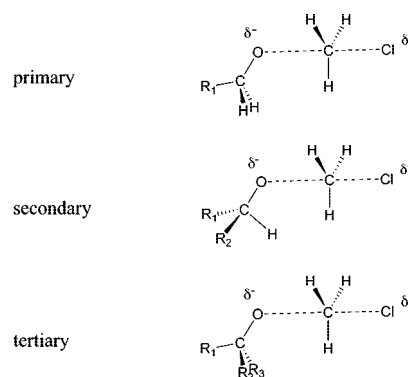


Figure 8. Schematic geometries of the S_N2 transition states of primary, secondary, and tertiary alkoxides, calculated by DFT. The C–O–C–Cl are almost coplanar in all cases. For the primary and tertiary alkoxides, the largest substitute, R₁, shares the same plane and is pointing away from the reaction center. For the secondary alkoxides, the H shares the same plane and is pointing toward the reaction center.

nucleophile oxygen, the central carbon, and the leaving group chloride, are almost collinear. The O–C–Cl angle is ~178° in all cases, Figure 8. The α-carbon on the nucleophile is tilted away from the centerline. The C–O–C angle is ~113°, very close to the tetrahedral angle 109°28', suggesting that the nucleophile oxygen is close to sp³ hybridized. The more interesting feature is the rotational conformation of the α-groups on the nucleophile. For all primary alkoxides in this study, the bulky substituent always points away from the reaction center while the two α-hydrogen atoms face the other way, as illustrated in Figure 8. For secondary alkoxides, there are two substitutions on the α-carbon. Both of them can be turned away from the reaction center by a 60° rotation so that the smallest α-hydrogen points toward the reaction center, Figure 8. For tertiary alkoxides where all three α-groups are bulky, the steric interactions between the substituents and the reaction center seem inevitable. We investigated two tertiary alkoxides, the *tert*-butoxide and CF₃C(CH₃)₂O⁻. The optimized structures for both alkoxides have the largest group pointing away from the center carbon, Figure 8. Interestingly, the tertiary alkoxides adopt the similar rotational conformation as the primary alkoxides, whereas the secondary alkoxides is off by 180° (or 60°). Overall, the system seems to minimize the steric hindrance by placing fewest groups possible and the smallest group possible toward the reaction center.

The magnitude of the steric effect we have observed here in the gas phase is greater than in solution. A possible explanation is that the intrinsic steric effect could be more or less compensated by solvation. A highly substituted nucleophile should be more poorly solvated relative to the unsubstituted one, because of the shielding effect from the extra alkyl groups. In the S_N2 transition state in solution, the nucleophile has to be partially desolvated.^{4,5,7} Therefore, a smaller penalty is paid to desolvate such a bulky nucleophile. This effectively lowers the S_N2 reaction barrier in solution, making the steric effect apparently smaller than in the gas phase. In other words, nucleophiles larger in size should be apparently more nucleophilic in solution. This is probably a general phenomenon regarding the relationship between steric effects and solvation effects when bulky substitution is located on an ionic reactant, such as an anionic nucleophile in S_N2 reactions.⁴⁸ A similar argument based on size of the nucleophile has previously been

(48) We note that solvation affects the steric effect differently if the substitution is located on the neutral substrate. In those cases, the bulky substitution close to the reaction center can induce substantial geometrical changes in the transition state which is not significant in this study. See: Vayner, G.; Houk, K. N.; Jorgensen, W. L.; Brauman, J. I. *J. Am. Chem. Soc.* **2004**, *126*, 9054–9058. Regan, C. K.; Craig, S. L.; Brauman, J. I. *Science* **2002**, *296*, 2245–2247.

suggested to explain the extraordinary high nucleophilicity of sulfides relative to alkoxides in solution.³⁷

Summary

In summary, we have measured the S_N2 reactivities of variously substituted alkoxides as model systems to study the effect of intramolecular microsolvation on nucleophilicity. Marcus theory was used to determine their intrinsic nucleophilicities. It is found that hydrogen bonding significantly increases the intrinsic barrier. On the other hand, the substitution by polar groups does not seem to affect the intrinsic nucleophilicity very much. Other factors including conjugation and steric effects, especially in case of tertiary alkoxides, also lower the intrinsic

nucleophilicity. These findings offer new insight and explanations for the observed nucleophilicities in aprotic and protic solutions.

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Supporting Information Available: Geometries and energies of the S_N2 transition states. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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