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Reactions of Charged Substrates. 6. The Methoxymethyl Carbenium Ion Problem. 1. A Semiempirical Study of the Kinetic and Thermodynamic Stabilities of Linear and Cyclic Oxo- and Thiocarbenium Ions Generated from Pyridinium and Dimethylanilinium Ions

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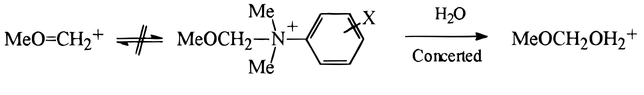
AM1-calculated energy profiles for dissociation of (methoxymethyl)pyridinium and dimethylanilinium ion substrates show that the methoxymethyl carbenium ion is not sufficiently stable to exist as an intermediate on the reaction coordinate for this model reaction. [(Thiomethoxy)methyl]-pyridinium ion, however, has a distinct transition state because of the stability of the resulting ion−neutral complex. The complete potential energy surfaces for water displacement on the methoxymethyl substrate with either pyridine or dimethylaniline as the leaving group show distinct transition states and very flat surfaces for the ion−neutral complexes in which interaction of the carbenium ion with both leaving group and nucleophile is stabilizing. Secondary systems studied, including linear methoxy and thiomethoxy substrates, 5- and 6-membered cyclic oxo and thio substrates, and ribosyl-, xylopyranosyl-, and glucopyranosylpyridinium ions yield ion−neutral complexes with sufficient intrinsic stability to exist as intermediates. Comparison with solution data, primarily activation entropy and Brønsted coefficients, suggests that the sugar oxocarbenium ions, either as distinct, solvent-equilibrated intermediates or elements of ion−neutral complexes, are formed by unimolecular dissociation of the respective substrates in solution.

Introduction

On the basis of an extrapolation of the results of a sulfite "clock" trapping reaction during the hydrolysis of ketals and acetals, in 1977 Young and Jencks[1] suggested that the methoxymethyl carbenium ion ($MeO{=}CH_2^+$) was too unstable to exist as a solvent-equilibrated intermediate on the reaction coordinate for simple dissociative reactions. The fact that the rate constants for acid-catalyzed cleavage of formaldehyde acetals were much greater than those for cleavage of methyl glucosides led Young and Jencks to propose that the glucosyloxocarbenium ion could not exist as an intermediate. Knier and Jencks[2] studied the reactions of neutral and negative nucleophiles with $MeOCH_2NMe_2Ar^+$. The borderline kinetic behavior found and the use of various LFERs led Knier and Jencks to conclude that the original estimate of the lifetime of $MeO{=}CH_2^+$ was valid. They also made the bold suggestion that substrates will undergo an S_N2 reaction "simply because" the incipient carbenium ion is too unstable to exist as a solvent-equilibrated intermediate; inherent in this statement is the assumption that substitution reactions must occur through a single mechanism. Because of these rationales, the mechanism of the hydrolysis reactions of $MeOCH_2NMe_2Ar^+$ was attributed to direct solvent displacement. Using these and other results, Jencks[3] has formulated a scheme for substitution reactions that has important implications for an understanding of the mechanisms used by enzymes such as lysozyme and the glycosyl hydrolases. In particular, Sinnott and Jencks[4] have suggested that the "exploded" transition state is important for enzymatic cleavage of bonds at the anomeric carbon of glycosyl substrates.



The original estimate of the lifetimes in solution of both $MeO{=}CH_2^+$ (10^{-15} s) and the glucosyl oxocarbenium ion (10^{-11} to 10^{-15} s *or less*) have been revised upward over the years and now stand near the diffusion limit at 10^{-12} s.[5] Despite these estimates, there are extensive experimental data, including Taft and Brønsted coefficients and activation values for solution and enzyme-catalyzed reactions, that are consistent with unimolecular dissociative reactions of pyranosyl- and ribosylpyridinium substrates. Schröder et al.[6] have challenged the view that ribosylpyridiniums such as nicotinamide−adenosine dinucleotide (NAD^+) react via the "exploded" transition state, and Tarnus et al.,[7] Johnson et al.,[8] Handlon and Oppenheimer,[9] and Buckley et al.[10] have published experimental and computational results that strongly

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(1) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238−8248.

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(3) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161−169. Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345−375.

(4) Sinnott, M. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2026−2032.

(5) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900. Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951−7958, 7958−7963.

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(10) Buckley,N.; Handlon, A. L.; Maltby, D.; Burlingame, A. L.; Oppenheimer, N. J. *J. Org. Chem.* **1994**, *59*, 3609−3615.

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suggest NAD^+ analogs dissociate to ion–neutral complexes in solution and the gas phase. The excellent correlation of experimental and computational results found for the gas-phase dissociation of β-nicotinamide arabinosides[10] prompted us to perform the computational study reported here.

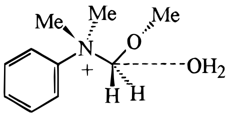
We calculated the energy profiles in AM1 for a series of pyridinium and dimethylanilinium substrates that can undergo heterolytic cleavage to give oxocarbenium ions. The relative stabilities of the oxocarbenium ions formed were evaluated in terms of $\Delta H^{\ddagger}$ and ΔH_R and compared with experimental data from the literature and from our own work. In brief, our results are consistent with the original suggestion that $MeO{=}CH_2^+$ is too unstable to exist as an intermediate *for the model reaction of a charged pyridinium or dimethylanilinium substrate* and that displacement by water is a reasonable mechanism. The results also suggest, however, that use of the lifetime of this species to estimate the lifetime of cyclic oxocarbenium ions such as ribosyl or glucosyl carbocations is not justified.

Computational Methods

Calculations in AM1[11] and PM3[12] were performed on a 486 (16MB RAM) using Release 4.0 of the Hyperchem software. Initial structures were built using the default model building routine and then minimized with MM+ (Hyperchem's version of MM2) using the partial charge option, after which the force-field minimized structure was fully minimized with the appropriate semiempirical method. The Polak–Ribiere block diagonal algorithm was used for all MM+ and semiempirical minimizations to a root mean square gradient of <0.1 kcal/(Å mol). All semiempirical calculations were restricted Hartree–Fock with the wavefunction calculated to a convergence limit of <0.001.

To construct the energy profiles, the leaving group bond length was increased in steps from the initial length using the restraint function to a final restraint force constant of 10^5 employing the stepped method we have described.[10] Each structure was minimized completely with no constraint other than the reaction coordinate. Values of ΔH_f for each structure were used to construct energy profiles and locate the approximate energy of the transition state; structures were refined until the criterion of a single negative (imaginary) frequency[13] was confirmed by force constant diagonalization. In all cases, the first normal (negative) mode corresponded to the reaction coordinate. ΔH_R was calculated as (ΔH_f cation + ΔH_f leaving group) − ΔH_f starting structure.

The complete potential energy surface for the displacement reaction of water on **2** was computed in AM1. The unconstrained complex between the reactants was fully minimized in AM1 to produce the initial structure from which the relative energies were measured. The C–N (initial value of 1.5 Å) and C–O (initial value of 2.74 Å) bonds were varied in 0.25 Å steps and the structures at each value minimized with no constraints other than the reaction coordinates. A 36-point matrix of relative energies was used to construct the potential energy surface.



Results

Reaction Profiles for Heterolytic Bond Cleavage. Values of $\Delta H^{\ddagger}$ were determined from energy profiles such as those shown in Figure 1 for **1**–**3** and in Figure 2 for **4** and **5**. Results of the AM1 calculations for all model compounds studied are listed in Table 1. Values of $\Delta H^{\ddagger}$ and ΔH_R for **10**–**12** have been reported.[10,14] Katritzky et al.[15] have shown, and we[10] have confirmed, that benzylpyridiniums do not give a transition state in PM3 but they do in AM1. In accord with this finding, $\Delta H^{\ddagger}$ for the β-nicotinamide arabinosides gave consistent results in AM1[10] but not in PM3. Because of the need to compare our results with the arabinoside results, the AM1 Hamiltonian was used for all reactions even though the control computations (see below) suggest that the PM3 Hamiltonian produces more consistent results. As a check on the method, we generated energy profiles for **1** and **3** in PM3, AM1, and MNDO; the PM3 and AM1 results are shown in Figures 1 and 2. **1** did not give a transition state in any method, but **3** gave a transition state in all methods.

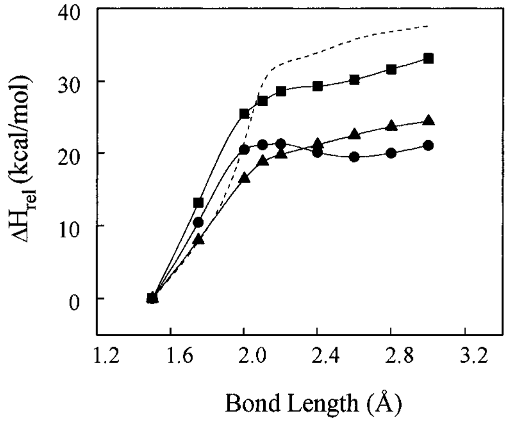


Figure 1. AM1 energy profiles for the dissociation of $MeOCH_2Py^+$ (**1**, ■), $MeOCHMePy^+$ (**3**, ●), and $MeOCH_2NMe_2Ph^+$ (**2**, ▲). The dashed line is the PM3 energy profile for **1**.

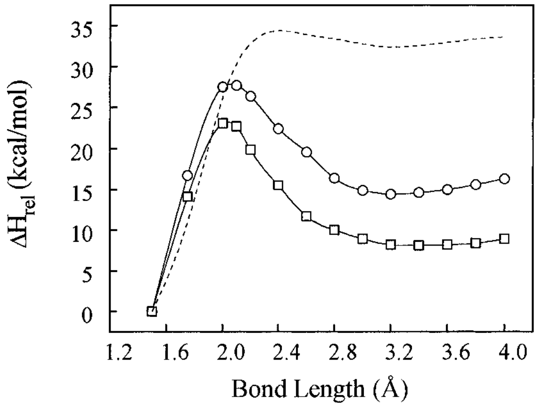


Figure 2. AM1 energy profiles for the dissociation of $MeSCH_2Py^+$ (**4**, ○), and $MeSCHMePy^+$ (**5**, □). The dashed line is the PM3 energy profile for **4**. This very deep well may be an artifact of the AM1 method (see text).

Stability of the Intermediates. In the gas phase,[16] $MeO{=}CH_2^+$ is a stable species. Vibrational analysis of the AM1-minimized structure (ΔH_f = 157.9 kcal/mol) gives no negative roots in the Hessian and no negative normal modes. There are two strong stretches, C–O and

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(12) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220.

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(15) Katritzky, A. R.; Malhotra, N.; Ford, G. P.; Anders, E.; Tropsch, J. G. *J. Org. Chem.* **1991**, *56*, 5039–5044.

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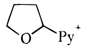
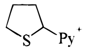
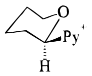
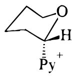
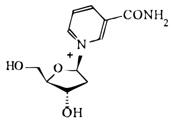
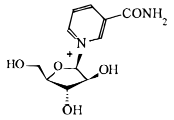
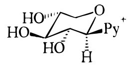
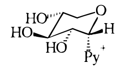
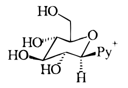
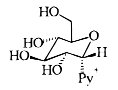
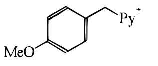
Table 1. AM1 Enthalpies of Activation ($\Delta H^{\ddagger}$) and Reaction (ΔH_R) for the Dissociation of Methoxymethyl and 1-Oxa-Cyclic Pyridinium Substrates[a]

Entry	Substrate	$\Delta H^{\ddagger}$	ΔH_R
1	$MeOCH_2Py+$	No transition state	46.7
2	$MeOCH_2NMe_2Ph+$	No transition state	38.3
3	MeOCHMePy+	21.3	33.3
4	$MeSCH_2Py+$	27.7	29.1
5	MeSCHMePy+	23.1	20.3
6		22.7	34.1
7		24.1	21.6
8		19.0	26.7
9		19.3	28.6
10		20.7	27.5
11		23.3	32.7
12		22.5	29.8
13		25.7	33.0
14		23.6	31.0
15		26.3	30.6
16		30.7	34.6

[a] All energies in kcal/mol. Py = pyridine. Entries **10** and **11** are from ref 10, entry **16** from ref 14.

C–H, for the conjugated and hyperconjugated resonance forms, respectively. Dissociation of **1** and **2** into completely separated reactants is highly exothermic (ΔH_R = 46.7 and 38.3 kcal/mol, respectively), and ΔH_R are the highest values for any substrates studied (Table 1).

For gas-phase heterolytic cleavage of RX^+, however, it is the stability of the ion–neutral complex and not the individual stabilities of the separated species that determines the shape of the reaction profile. Release of the reaction coordinate restraint for any of the structures generated by stretching the C–N bond in **1** and **2** followed by complete minimization led to collapse of the structures directly back to the starting structure. (4-Substituted benzyl-SMe_2^+ structures show the same behavior.[14]) Performing the same maneuver for any structure with a bond length greater than the transition state bond length of 2.1Å in **3**, however, gave stable intermediates. The same is true for the linear sulfur compounds **4** and **5** and all the cyclic compounds, including the β-nicotinamide arabinosides,[10] and for the intermediates that exist on the flat portion of the potential energy surface for the displacement reaction of water on **2** (see below). (4-Substituted benzylpyridinium$^+$ ion–neutral complexes show the same behavior.[14])

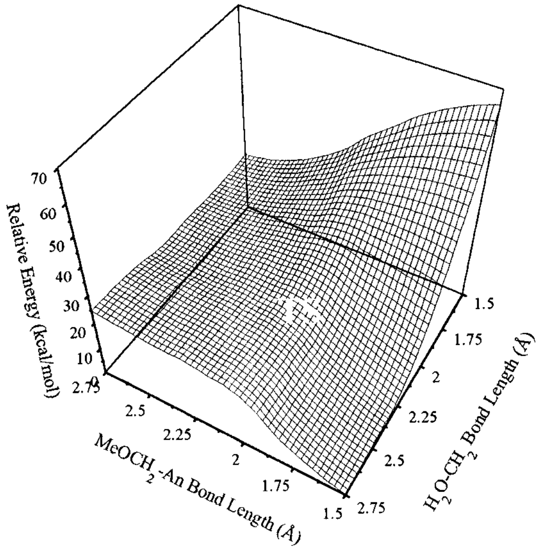


Figure 3. AM1 potential energy surface for the displacement by water on **2**. The reaction begins in the lower corner of the plot.

Potential Energy Surface for Displacement of Dimethyaniline from 2 By Water. For the water displacement reaction on **2**, the separated reactants formed the initial complex with a release of 10 kcal/mol of energy. The potential energy surface is shown in Figure 3. Stretching the C–N bond with the water constrained to the initial value of 2.75 Å produced a two-dimensional profile essentially indistinguishable from the profile shown in Figure 1 in the absence of water. The full displacement reaction, however, has a distinct transition state. On force constant diagonalization, the activated complex gave a single negative first normal mode that corresponded to the reaction coordinate. There was a strong vibration for the C–OMe stretch in the vibrational spectrum. The potential energy surface has almost precisely the same shape as found for water displacement on **1** (see Figure 7) and β-nicotinamide riboside (see Figure 5 of ref 6).

Control Studies. Apeloig and Karni[17] have published the results of *ab initio* calculations on the relative stabilities of linear α-oxy and α-thio carbenium ions. They found that the energies depended on the basis set used, with the "best" energies obtained at the MP3/6-31G* level. As a check on our methods, many of the reactions studied by Apeloig and Karni were calculated in AM1 and PM3; the results are listed in Table 2 with the available gas-phase experimental values. In most instances, the *ab initio* and semiempirical energies are in good agreement and show the same trends in stability; in fact, the 6-31G* and PM3 values are often in very close agreement, although both are lower than the MP3/6-31G*

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[17] Apeloig, Y.; Karni, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 625–636. These authors provide an excellent summary of the gas-phase and solution data for these compounds.

Table 2. Comparison of the 6-31G*, MP3/6-31G*, AM1, and PM3 $\Delta H'_R$ and the Experimental Values for Hydride and Chloride Exchange for α-Oxo and α-Thio Methyl Carbenium Ions in the Gas Phase[a]

reaction	6-31G*[b]	MP3/6-31G*[b]	AM1[c]	PM3[c]	Expt[d]
$CH_3^+ + MeOH \rightarrow CH_4 + {}^+CH_2OH$	−51.7	−62.1	−42.7	−51.4	−65.6
$CH_3^+ + MeSH \rightarrow CH_4 + {}^+CH_2SH$	−45.0	−59.7	−56.5	−50.8	−64.0
$CH_3^+ + MeOMe \rightarrow CH_4 + {}^+CH_2OMe$	−64.6	−72.7	−49.9	−56.2	−71.0
$CH_3^+ + MeSMe \rightarrow CH_4 + {}^+CH_2SMe$	−57.8	−73.4	−67.1	−57.4	−74.0
$HOCH_2^+ + MeSH \rightarrow HOMe + {}^+CH_2SH$	8.4	2.4	−13.8	0.6	1.5
$MeOCH_2^+ + MeSH \rightarrow MeOMe + {}^+CH_2SH$	7.4	−0.7	−17.2	−1.5	
$MeSCH_2Cl + {}^+CH_2OMe \rightarrow MeSCH_2^+ + ClCH_2OMe$	2.3	−3.9[e]	−17.8	−7.2	

[a] Energies in kcal/mol. $\Delta H'_R = \Sigma\Delta H_f$ products − $\Sigma\Delta H_f$ reactants. [b] *Ab initio* values from ref 17. [c] Semiempirical values from this study. [d] Experimental values: Taft, R. W.; Martin, R. H.; Lampe, F. W. *J. Am. Chem. Soc.* **1965**, *87*, 2490−2497 (cited in ref 17). [e] At the MP2/6-31G* level.

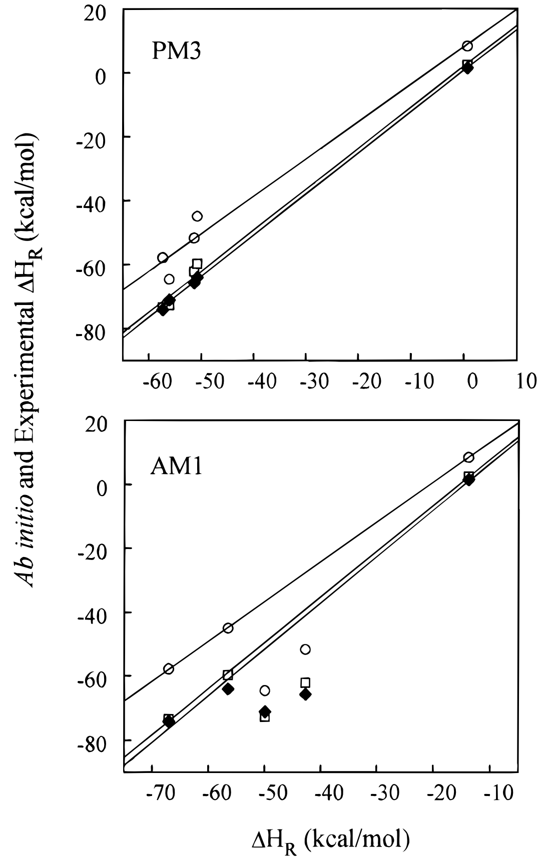
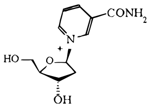
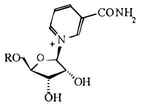
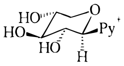
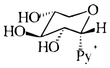
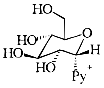


Figure 4. Plots of the 6-31G* (○), MP3/6-31G* (□), and experimental (◆) ΔH_R values from ref 17 vs the PM3 and AM1 ΔH_R computed for the reactions in Table 2. For PM3, the respective slopes and correlation coefficients are as follows: 1.17, $r = 0.987$; 1.28, $r = 0.997$; 1.29, $r = 0.9998$. For AM1, the sets of outlying points are for the oxygen compounds. The respective slopes and correlation coefficients for the sulfur compounds are as follows: 1.24, $r = 0.9999$; 1.43, $r = 0.9998$; 1.43, $r = 0.9977$.

and experimental values. Correlations between the PM3 and AM1 ΔH_R and the 6-31G*, 6-31G*/MP3, and experimental ΔH_R are shown in Figure 4. While the PM3 values are 30% lower than MP3/6-31G* and experimental values, the correlations are excellent. The AM1 values, however, show an anomaly: for the sulfur compounds they are 45% lower than the *ab initio* values, but all correlate well with Apeloig's computed values and the experimental values; values for the two oxygen compounds, however, are off the correlation line (Figure 4). The difference in the AM1 ΔH_R between the α-oxy and α-thio compounds is consistent at 13 kcal/mol (Table 1), but the results in Table 2 and the reaction profiles in Figure 2 suggest that AM1 overestimates the stabilities of the thiocarbenium ions by a factor of 2−3.

Table 3. Values of $\Delta S^‡$ for the Hydrolysis of Pyridinium Substrates

Entry	Compound	$\Delta S^‡$ (gibbs/mol)	Ref.
2	$MeOCH_2NMe_2Ar^+$	-1.2	
		(-9.2 for $k_{obsd}/55.5$)	2
16	$MeOCH_2OAr$	-6.7	
	($MeOCH_2OAr + I^-$	-8.5)	31
10		9.5 ± 2.5	33
17		6.2 ± 2.5	34
12		31 ± 3	28
13		24 ± 6	28
15		15.2 ± 3.3	28

Discussion

Values of $\Delta H^‡$ and ΔH_R obtained from the AM1 energy profiles (Figure 1 for **1**−**3**, Figure 2 for **4** and **5**) are listed in Table 1. There are Taft ρ values, $\Delta S^‡$ values (Table 3), and Brønsted β_{LG} values available for the solution reactions of many of the substrates studied. In the sections that follow, we will discuss the computational results in light of these solution values. There is a consistent match of the computational stabilities and reactivities with the solution values.

Linear Oxygen Compounds. Of the 15 compounds studied, only $MeOCH_2Py^+$ (**1**) and $MeOCH_2NMe_2Ph^+$ (**2**) failed to give a distinct transition state for simple heterolytic bond cleavage (Figure 1). As we have argued elsewhere,[10] the fact that a mechanism occurs in the gas phase is not proof that the same mechanism will occur in solution. For heterolytic cleavage of charged substrates in the gas phase, dissociation can occur directly (generally for substrates such as $MePy^+$ containing a *very* unstable incipient carbenium ion,[15] although there are exceptions in which proton abstraction can occur simultaneously with bond cleavage for species with excellent oxocarbenium ions[18]) or, a common occurrence, with bond

Figure 5. Stereoview of structures for the ion−neutral complexes for **4** (left) and **7** (right) showing a bridged structure between the carbon and sulfur. The energy before bridging begins is much lower than energy of the ion−neutral complexes for the oxo compounds; bridging alone is not responsible for the stability.

cleavage and formation of an ion−neutral complex.[10,14,19] In all systems we have studied, $\Delta H^{\ddagger}$ for the return reaction from the ion−neutral complex to the starting material or for diffusion apart of the elements of the ion−neutral complexes are lower than $\Delta H^{\ddagger}$ for bond cleavage.[10,14]

If a simple heterolytic cleavage occurs by direct dissociation in the gas phase without the formation of an ion−neutral complex, there is good reason to suppose that dissociation will not occur in solution under more energetically demanding conditions. The two main restraints to reaction in solution are electrostriction[20] and the loss of entropy of solvation of either or both the transition state or the leaving group;[21] we have shown[22] for benzyl substrates that solvation of the leaving group has a striking effect on $\Delta S^{\ddagger}$. While time is said to be the quantity that keeps everything from happening at once, solvent keeps things from falling apart all at once (or nearly so), or at all.[23] Thus, the computational results for **1** and **2** suggest that the $MeO{=}CH_2^{+}{\cdot}X$ ion−neutral complex is too unstable to exist as an intermediate for the model reaction of a charged substrate.

Replacing a methylene proton by a methyl, however, produces a substrate (**3**) that gives a distinct transition state. This is not the result of relief of strain; the compound obtained by replacing a methylene proton in **1** with CF_3, a group that will destabilize the activated complex by withdrawal of electron density, does not give a distinct transition state. Thus, the oxocarbenium ion derived from a secondary alkyl system, presumably because of inductive or hyperconjugative effects, or both, is sufficiently stable that the ion−neutral complex is stable. Indeed, the stability of the ion−neutral complexes formed from arabinosyl nicotinamides is directly related to the intrinsic stability of the carbenium ion.[10]

Knier and Jencks[2] argued that the reaction of **2** and the other anilinium ions with water was S_N2, consistent with the finding that formaldehyde was a product of the reaction that would arise by displacement on the methylene to give directly protonated formaldehyde methyl hemiacetal, which would rapidly hydrolyze to formaldehyde. Isolation and characterization of $MeOCH_2{-}NMe_3^{+}$ from the reaction with NMe_3 supported the supposition that displacement for the other neutral, hard nucleophiles occurred on the methylene.

The computed AM1 potential energy surface for the S_N2 reaction of **2** with water shows a distinct transition state (Figure 3) and a large, flat surface that is close in energy to the complex of dimethylaniline with the protonated methyl hemiacetal. (A very similar surface is found for displacement on **1**; see Figure 7.) The back-reaction (well-to-well) is exothermic by ca. 20.3 kcal/mol, consistent with water being a better leaving group than dimethylaniline ($\Delta pK_a \sim 7$). This result, which does not include the effects of solvation, electrostriction, or proton transfer[24] from the neutral hemiacetal to water, is nonetheless fully consistent with the Knier−Jencks proposal for an S_N2 hydrolysis reaction for these substrates and with the measured $\Delta S^{\ddagger}$ values (see below).

Linear Sulfur Compounds. The importance of the stability of the carbenium ion in the ion−neutral complex is illustrated for the sulfur analogs **4** and **5**. Using pulsed ICR techniques, Caserio[16] has shown that $MeS{=}CH_2^{+}$ is more thermodynamically stable than $MeO{=}CH_2^{+}$ in the gas phase both in terms of chloride affinity ($MeO{=}CH_2^{+} + MeSCH_2Cl \rightleftharpoons MeOCH_2Cl + MeS{=}CH_2^{+}$) and hydride transfer reactions ($MeO{=}CH_2^{+} + MeSMe \rightleftharpoons MeOMe + MeS{=}CH_2^{+}$). Accordingly $MeSCH_2Py^{+}$ (**4**) and $MeSCHMePy^{+}$ (**5**) give distinct transition states in AM1 (Figure 2) because the ion−neutral complexes are stable. In the AM1-minimized ion−neutral complexes for both compounds, the pyridine has moved away from a direct line with the positive carbon center and is interacting with the sulfur in a bridged structure very much like phenonium ions; the same structure forms for **7** (Figure 5). The extra stability afforded by this structure can be seen clearly in the energy profiles shown in Figure 2. Because AM1 appears to overestimate the stabilities of sulfur compounds (see Figure 4), however, this difference may be an artifact of parameterization; the ion−neutral complex for the PM3-calculated energy profile is not in as deep a well (Figure 2). The differences in AM1 energies between **4** and **5** suggests that changing from a primary to a secondary system is worth 4.2 kcal/mol in $\Delta H^{\ddagger}$ and 8.7 kcal/mol in ΔH_R; the difference in ΔH_R between **4** and **5** in PM3 is 7.4 kcal/mol.

Because Caserio's hydride transfer results[16] showed that thio analogs are favored kinetically over oxo analogs, she argued that the hydrolysis of the chlorides, for which the oxo compound reacts faster than the thio compound, is the result of solvation effects. Apeloig and Karni[17] have shown that the predominance of the thiocarbenium

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[21] Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1−34.

[22] Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1994**, *59*, 5717−5723.

[23] For instance, we found that 4-Me-, 4-H-, and 4-Cl-benzylpyridinium dissociate readily in the gas phase (ref 14) but that they failed to react with either water or 1.7 M azide *after 6 months at 96 °C* (ref 40).

[24] In an attempt to "solvate" the displacement reaction and check for possible water base-catalyzed addition of water, two waters were hydrogen bonded to the "nucleophilic" water interacting with the reaction center. While the total energy was lowered, there was no effect on the relative energy, and no proton transfer took place from the "nucleophilic" water to the "general base" waters.

ion in the chloride exchange reaction with the oxocarbenium ion is the result of substantial ground-state stabilization of the oxo compound, which agrees with the semiempirical results reported here (Table 2). They also showed that, relative to the hydrocarbons, $HO{=}CH_2^+$ is 2.4 kcal/mol more stable than $HS{=}CH_2^+$ at the MP3/6-31G* level of theory (and by 1.5 kcal/mol in the gas phase, Table 2), and we found it to be 0.6 kcal/mol more stable in PM3. Nonetheless, relative to the hydrocarbons, $MeS{=}CH_2^+$ is more stable than $MeO{=}CH_2^+$ by 0.7 kcal/mol at the MP3/6-31G* level of theory and 1.5 kcal/mol in PM3 (Table 2), which must reflect the inductive effect of the Me. It is doubtful that there is a substantial hyperconjugative effect, given Bordwell's finding[25] that there is no resonance interaction between ring substituents and the sulfur atom in the solvolysis of chloromethyl aryl sulfides.

In the model pyridinium dissociative reaction, the sulfur compounds are more stable thermodynamically (by 12.6−13 kcal/mol in AM1 ΔH_R and 7.4 kcal/mol in PM3 ΔH_R), but the oxygen compounds have lower values of $\Delta H^\ddagger$ (by 1.6−1.8 kcal/mol), which matches the relative rates for solution dissociation of alkyl chloroethers and thioethers.[25] Recently, Richard[26] found that the rate constants for hydrolysis of α-MeO-benzyl azides are greater than those for α-MeS-benzyl azides, despite the greater thermodynamic stability of the sulfur compound as measured by the product ratios in a "clock" reaction. While we are great champions of the effects of solvation, it is clear that in this case intrinsic factors control rates and thermodynamic factors differently, and the usual supposition inherent in the Leffler−Hammond postulate[27] that reactivity follows thermodynamic stability is not true in this series.

Unsubstituted Cyclic Compounds. The simple unsubstituted tetrahydrofuran (**6**), tetrahydrothiophene (**7**), and tetrahydropyran (**8**, **9**) substrates have distinct transition states in AM1 (Table 1). The six-membered systems **8** and **9** are more stable than **6** and have lower values of $\Delta H^\ddagger$, which reflects the greater flexibility—and therefore the smaller number of nonbonded interactions upon reaching the activated complex—of the six-membered system. Dissociation of the equatorial pyridine (**8**) is slightly favored over the axial (**9**), in contrast to the solution reactions for the corresponding xylopyranosylpyridiniums **12** and **13** in which the rate for the axial is favored by a modest amount.[28] The oxygen and sulfur compounds **6** and **7** show the same trends in AM1 $\Delta H^\ddagger$ and ΔH_R as found for the linear analogs.

Arabinosyl-, Xylopyranosyl-, and Glucopyranosylpyridiniums. These compounds have secondary structures at the reaction center and give distinct transition states in AM1 (Table 1). The 2′-deoxyarabinosyl compound **10** has a lower $\Delta H^\ddagger$ than the THF compound **6**, which is the result of the stability afforded by the 5′-hydroxymethyl group.[6] The xylopyranosyl (**12** and **13**) and glucopyranosyl (**14** and **15**) compounds have lower values of $\Delta H^\ddagger$ than the arabinosyl compounds bearing the same 2′ substituent (compare **11** and **12**). As found for the THP compounds **8** and **9**, the equatorial pyridine is favored over the axial pyridine by 3.2 kcal/mol in $\Delta H^\ddagger$, which is the reverse of the relative rates in solution.[28] We assume that this difference reflects differential solvation of the ground and transition states for the anomers[6] and that the gas-phase values more accurately reflect the *intrinsic* reactivity, including a stereoelectronic preference for expulsion of the axial pyridine,[29] but we have no proof for this assumption. While of interest, this difference is inconsequential to our main concern, which is that *both* classes of compounds give distinct transition states and react faster than the arabionsyl compounds. They are well-behaved systems that undergo unambiguous heterolytic cleavage of the carbon−pyridine bond.

The Estimation of the Stability of Glucosyl and Ribosyl Oxocarbenium Ions. Because of vast differences in solvation of the ground and transition states of formaldehyde acetals and methyl glucosides, we believe that the kinetic comparison used by Jencks[1,5] to estimate the lifetime of the glucosyl oxocarbenium ion is unwarranted *a priori*. Without making assumptions, we can compare directly the relative gas-phase stabilities of the oxocarbenium ions generated from our substrates. The extent of gas-phase dissociation is far greater for *β*-nicotinamide arabinosides[10] (e.g., **10** and **11**) than for benzylsulfoniums or -pyridiniums[14] (e.g., **16**) under identical conditions; the computed values favor **10** over **16** by 10 kcal/mol in $\Delta H^\ddagger$ and by 7.1 kcal/mol in ΔH_R. Thus, for the standard reaction, the ribosyl oxocarbenium ion is kinetically and thermodynamically more stable than the 4-methoxybenzyl carbenium ion, which is a solvent-equilibrated intermediate in water.[22,30] As noted above, *β*-nicotinamide arabinosides dissociate through the same mechanism in the gas phase and in solution,[10] which with the results for the other compounds reported here supports our contention that a cyclic oxocarbenium ion can exist in solution either as a distinct solvent-equilibrated intermediate or as an element of a contact or solvent-separated ion−dipole complex.

Activation Values and Linear Free Energy Relations (LFERs) For the Model Reactions. Because it reflects a large change in translational entropy, $\Delta S^\ddagger$ is the activation value most often used to differentiate between uni- and bimolecular mechanisms.[21] In systems containing the same (or very similar) leaving groups that would be solvated in the same way, this seems to be an appropriate measure. Among the various LFERs used in attempts to define the structure of activated complexes are Hammett, Taft, and Brønsted correlations. Secondary deuterium isotope effects have been measured for many of the reactions studied here, but Kirby[31] has argued cogently that use of apparently disparate values from many different studies to define structures of the activated complex for either solution or enzyme-catalyzed reactions is fraught with difficulty; therefore, we will not discuss the extensive and contradictory data here.

(a) Activation Entropy. Values of $\Delta S^\ddagger$ (Table 2) are available for the hydrolysis reactions of some of the

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[25] See: Bordwell, F. G.; Cooper, G. D.; Morita, H. *J. Am. Chem. Soc.* **1957**, *79*, 376−378. For a very detailed study of the hydrolysis of methyl chloromethyl ether also see: Jones, T. C.; Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 4863−4867.

[26] Jagannadham, V.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 8465−8466.

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[29] Kirby, A. J. *Acc. Chem. Res.* **1984**, *17*, 305−311. This author champions the stereoelectronic argument, while Sinnott (ref 28) opposes it.

[30] Kevill, D. N.; Ismail, N. H. J.; D'Sousa, M. J. *J. Org. Chem.* **1994**, *59*, 6303−6312.

[31] Craze, G.-A.; Kirby, A. J.; Osborne, R. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 357−368.

compounds studied computationally. The $\Delta S^\ddagger$ for **2** is -1.2 gibbs/mol for k_{obsd} or -9.2 for the second-order rate constant ($k_{obsd}/55.5$), and the value for the reaction of **2** with *n*-propylamine is -2.1 gibbs/mol. The equivalent 2,5-dinitrophenol derivative **16** has values of -6.7 gibbs/mol for the pH-independent hydrolysis and -8.5 gibbs/mol for the reaction with iodide.[32] The negative entropies, and especially the correspondence of the values for reactions with neutral and negative nucleophiles, are consistent with reaction by direct solvent displacement (see Figure 3). Unlike the cyclic compounds, however, the linear substrates may lose rotational entropy between the ground state and activated complex because of the resonance interaction of the methoxy with the reaction center. While this loss of entropy may be important in these systems, it is difficult to assess its relative contribution to the total entropy of activation. It should be noted, however, that in minimized ground-state structures the methoxy group has assumed the position expected for conjugation and loss of rotational entropy, and there will be little or no change in entropy between the ground and transition states. A solvated methoxy may have a different geometry, however.

The high, positive $\Delta S^\ddagger$ values for the pyridine arabinosyl, xylopyranosyl, and glucopyranosyl compounds, which are in the range for tertiary and aryl compounds known to undergo unimolecular solvolysis,[21] are clearly consistent with a dissociative reaction, especially the extremely high values[28] for the xylopyranosyl compounds **11** and **12**. The value for pH-independent hydrolysis of β-nicotinamide deoxyribose[33] (**10**) is 9.5 ± 2.5 gibbs/mol and for NAD$^+$ (**17**) is 6.2 ± 2.4 gibbs/mol.[34] These values are consistent with the energy profiles calculated for this class of compounds.[10] Indeed, Bennet and colleagues[35] recently reported that solvolysis of 2′-deoxyglucosylpyridiniums produces ion−dipole complexes, a finding that bolsters the claim made by some years ago by Schuber[7] and recently by Richard[36] that ribosyl or galactosyl oxocarbenium ions are stable intermediates in enzyme active sites.

There are correlations ($r = 0.90-0.92$) between the AM1 values of $\Delta H^\ddagger$ and the experimental $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the hydrolysis of 2′-substituted β-nicotinamide arabinosides[33] (Figure 6) and the xylopyranosyl- and glucopyranosylpyridiniums[28] (not shown). The rate constants for hydrolysis of the three six-membered compounds also correlate with the AM1-calculated $\Delta H^\ddagger$ (not shown; $r = 0.90$); the correlation for the arabinosyl compounds, which is measurably better, has been reported.[10] As expected from the relative stabilities and computed $\Delta H^\ddagger$, the 5- and 6-membered compounds fall on two distinct lines.

(b) Taft Correlations. The effects of 2′-substituents on the acid-catalyzed dissociation of glucosides[37] and purine nucleosides[38] are consistent with a dissociative mechanism. To our knowledge, the only systematic study of the effect of substituents on the rates for the uncatalyzed hydrolysis of compounds studied here is Handlon's study[9] of the hydrolysis of 2′-substituted β-nicotinamide arabinosides and ribosides, both of which give $\rho_I = -6.7$, a value consistent with an S_N1 mechanism. Relative rates for the gas-phase dissociation of the arabino series follow the Taft equation ($\rho_F = -0.75$), and the computed values of $\Delta H^\ddagger$ correlate well with the relative rates.[10] In fact, scaling the gas-phase value to the solution value using a conversion factor[39] gives $\rho = -6.4$, a very satisfying result.

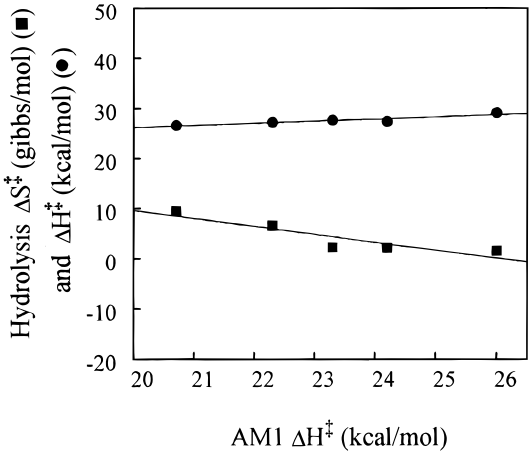

Figure 6. Correlations between the AM1-calculated $\Delta H^\ddagger$ and the experimental values of $\Delta H^\ddagger$ (■) and $\Delta S^\ddagger$ (●) for the hydrolysis of 2′-substituted β-nicotinamide arabinosides (ref 10 for AM1, ref 33 for experimental values).

(c) Brønsted Correlations. The Brønsted coefficient β_{LG} is often taken as a measure of the leaving group effect on the progress of the reaction. Values are available for some of the model reactions studied here. The β_{LG} for the reaction of $MeOCH_2NMe_2Ar^+$ with water is -0.89 and is -0.70 for *n*-propylamine;[2] values for hydroxide and acetate estimated from data for two substrates are in the same range. For the hydrolysis of **12**, **13**, and **15** the values are -1.20, -1.28, and -1.06, respectively.[28] Schuber and his colleagues[7] report a value of -1.12 for the hydrolysis of NAD$^+$ analogs and a value of -0.98 for enzyme-catalyzed bond cleavage. All of these values are consistent with a "late," "loose" transition state structure for bond cleavage.

Brønsted values must be used with caution to describe transition state structures, however. For instance, it is generally assumed that large negative β_{LG} values for nucleophilic substitution reactions of compounds containing incipient, stable carbenium ions indicate a large amount of "carbenium ion character" in the activated complex. Recently, we[40] found, however, that β_{LG} for the azide reaction of 4-substituted benzyl- *and* methylpyridiniums were of essentially the same large, negative

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[32] Craze, G.-A.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 354−356.

[33] Handlon, A. L. Ph.D. Dissertation, University of California, San Francisco, 1991.

[34] Note that the value reported in ref 8 is erroneous. Using the rate constants in the range 37−95 °C, an Eyring plot of ln [$k_{obsd}h/Tk_B$], where h is Planck's constant and k_B is the Boltzmann constant, vs $1/T$ gives $\Delta S^\ddagger = 6.2 \pm 2.4$ gibbs/mol and $\Delta H^\ddagger = 26.5$ kcal/mol ($r = 0.998$).

[35] Huang, X.; Surry, C.; Hiebert, T.; Bennet, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10614−10621.

[36] Richard, J. P.; Westerfeld, J. G.; Lin, S.; Beard, J. *Biochemistry* **1995**, *34*, 11713−11724.

[37] Marshall, R. D. *Nature* **1963**, *199*, 998−999. Withers, S. G.; Pervival, M. D.; Street, I. P. *Carbohydr. Res.* **1989**, *187*, 43−66.

[38] York, J. L. *J. Org. Chem.* **1981**, *46*, 2171−2173. Zielonacka-Lis, E. *Nucleosides Nucleotides* **1989**, *8*, 383−405.

[39] The normalization was calculated in the following way. The values of $\delta\Delta G°_{t-cumyl}$ for the gas-phase reaction 4-Y-$C_6H_4C(Me){=}CH_2 + H^+ \rightleftharpoons$ 4-Y-$C_6H_4CMe_2^+$ (Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 2−83) and σ^+ scales correlate with a slope of 14. Dividing this slope by 1.65, the conversion factor for σ to σ_I scales, gives a factor of 8.5 that can be used to convert the gas-phase ρ values to an equivalent solution value.

[40] Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 7360−7372.

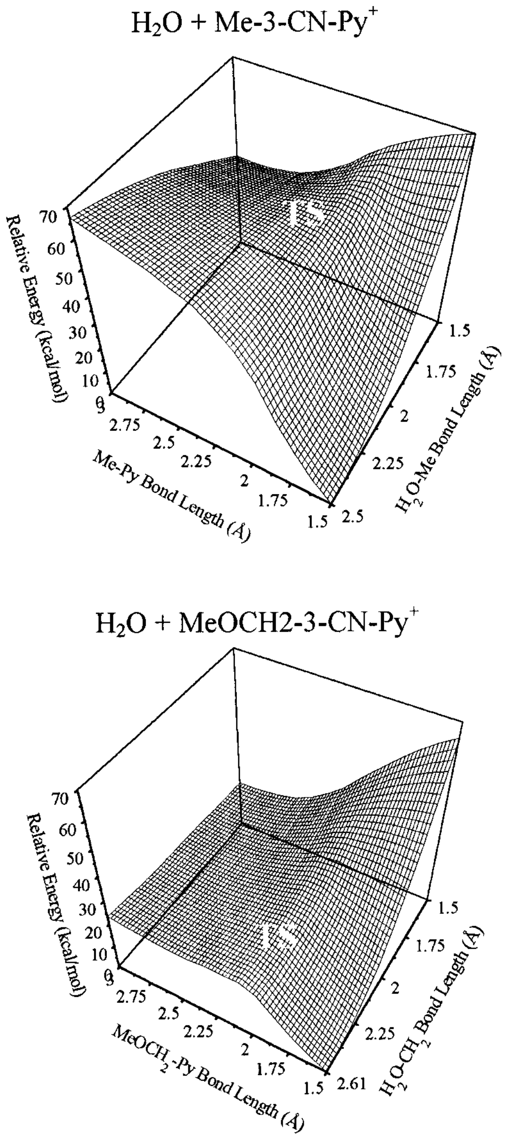

Figure 7. Complete AM1 reaction surfaces for the water displacement reactions of Me-3-CNPy$^+$ and MeOCH$_2$-3-CNPy$^+$. Contour plots corresponding to these surfaces are given in ref 40.

values of −1.4 to −1.6. Other data for the reactions of methylpyridiniums with iodide[41] ($\beta_{LG} = -1.13$) or triphenylphosphine[42] ($\beta_{LG} = -0.4$) show a relatively large range of values.

We have computed the complete energy surfaces[43] for displacement of 3-cyanopyridine by water from Me- and MeOCH$_2$ substrates and have reported some results elsewhere.[40] Both reactions give surfaces with distinct transition states that lie close in energy to the initial complex for the back-reaction, displacement of protonated water by the pyridine (Figure 7). $\Delta H^\ddagger$ for the Me substrate is much greater—by ca. 40 kcal/mol—than that for the MeOCH$_2$− substrate because of resonance stabilization in the latter. This pattern is opposite that predicted by Dewar and Dougherty[44] for reactions of these substrates. While the C−Py bond lengths at the transition state are approximately the same in both reactions, the C−O bond lengths are quite different, being much longer for the MeOCH$_2$− substrate because of charge repulsion between the incoming water and the MeO− group that is building up positive charge as the reaction proceeds. After the transition state is achieved, the energy of the substrate−water complex after the transition state is relatively constant for a wide range of C−O and C−Py bond lengths. In this regard, the surface closely resembles the PM3 surface computed by Schröder et al.[6] for the water displacement of nicotinamide from β-nicotinamide riboside. Thus, the presence of a water coordinated with the reaction center is sufficient to lower the energy by ca. 10 kcal/mol and produce a distinct transition state, unlike the reaction profile for the purely dissociative reaction (Figure 1). This computational result, and the result for water displacement on **2** given above, confirms the suggestion of Knier and Jencks[2] that the hydrolysis reactions of their substrates occurs by direct solvent displacement.

The AM1 computed transition state bond lengths to the nicotinamide leaving group[10] for Handlon's arabinoside series[9] are relatively constant at ca. 2.1 Å, despite Shuber's finding of a large β_{LG} for dissociation of analogs of **17** with different pyridine leaving groups in solution.[7] The AM1 bond lengths to the pyridine leaving group for the xylopyranosyl and glucopyranosyl substrates are in the range 2.1−2.2 Å. The AM1 bond lengths for dissociation of benzylpyridiniums in the gas-phase[18] are relatively constant at 2.1 Å. The computed $\Delta H^\ddagger$ and the experimental relative rates for gas-phase dissociation correlate very well.[10,14] Because these gas-phase dissociative reactions may follow RRKM kinetics and dissociation may take place independent of a potential energy surface,[14,19] use of Hammond concepts[27] may not be warranted. It is noteworthy, however, that while all the benzylpyridinium and benzyldimethylsulfonium substrates dissociate in the gas phase, only the (4-methoxybenzyl)dimethylsulfonium substrate undergoes an S$_N$1 reaction in water;[22,30] the others all react by direct solvent displacement.[40,45]

Thus, the lack of any pattern that is predictive of the structure of the activated complex between the gas phase and solution emphasizes the importance of solvation of both the ground and transition states. Solvation effects can be very subtle. We found, for instance, that $\Delta S^\ddagger$ for solvolysis of (4-methoxybenzyl) dimethylsulfonium is 7 gibbs/mol in D_2O[22] but is 13.7 gibbs/mol in H_2O,[30] an astonishing difference that may be related to the hydrophobic effect for solvation of SMe$_2$ at the transition state. The much shorter computed bond lengths found for the arabinosyl, xylopyranosyl, and glucopyranosyl substrates compared with the relatively large β_{LG} values for dissociation in water may reflect stabilizing effects of solvent. It is also possible that β_{LG} values have entirely different physical meanings that depend on the mechanism. Both of these suggestions are of course the rawest kind of speculation. Nonetheless, all of these factors suggest that β_{LG} values as measures of geometry and charge development must be used with caution and that solvation may be the most important factor that deter-

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[41] Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892−5902.

[42] Berg, U.; Gallo, R.; Metzger, J. *J. Org. Chem.* **1976**, *41*, 2621−2624.

[43] Surfaces were computed in AM1 using the reaction coordinate method as described in ref 40 and in the Computational Methods section. Activated complexes gave single negative eigenvalues upon diagonialization of the force constant matrix, and the first normal (negative) mode corresponded to the reaction coordinate.

[44] Dewar, M. J. S.; Dougherty, R. J. *PMO Theory of Organic Chemistry*; New York: Plenum, 1975; pp 262−263.

[45] Friedberger, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1976**, *98*, 2861−2865.

mines a particular value. Thornton[46] and Pross[47] have pointed out that there is no particular reason to suppose that charge development and geometry are explicitly linked, and the computational results (Figure 7) are consistent with this view.

Conclusions. The computational results reported here are consistent with the idea first suggested by Young and Jencks[1] that $MeO{=}CH_2^+$ is too unstable to exist as an isolated intermediate on the reaction coordinate for the model reaction. Our finding that linear and cyclic secondary systems give distinct transition states by dissociating to stable ion−neutral complexes suggests that there is no *intrinsic* limit to the stability of glucosyl and ribosyl oxocarbenium ions. In fact, arabinosyl, xylopyranosyl, and glucpyranosyl compounds dissociate with lower values of $\Delta H^\ddagger$ than benzyl compounds (Table 1), and the oxocarbenium ions are more stable than substituted benzyl carbenium ions in the gas phase.[10,14] There are also sufficient data for solution reactions to suggest that reactions of $MeOCH_2X^+$ substrates, including hydrolysis, are bimolecular, but that hydrolysis reactions for ribosyl-, xylopyranosyl-, and glucopyranosylpyridiniums are dissociative, which is consistent with the computational results. Reactions in which the LGs are either protonated water or a variety of protonated alcohols are considered in the companion paper.[48] For a number of reasons, these reactions are much more complex.

Acknowledgment. Supported in part by NIH Grant No. GM-22982. We thank Dr. James Caldwell (UCSF) and Dr. James Fishbein (Wake Forest) for their comments on the manuscript.

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[46] Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915−2927. “There is no reason why geometry and charge separation should parallel one another precisely” (p 2922).

[47] Pross, A. *Adv. Phys. Org. Chem.* **1985**, *21*, 99−196. “[T]he Brønsted parameter does not constitute a measure of transition state charge development, and it is unlikely to represent a meaningful measure of transition state geometry” (p 151).

[48] Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 8048.