The kinetic assay procedure was as described[10] except for the following points: (a) the capillary tubes used as kinetics vessels were not silylated before use; (b) buffer A used in the phosphodiesterase digestion was made 50 mM in $MgCl_2$, not 18.8 mM; (c) the pH electrode monitored pH adjustment of the reaction mixture and pH correction solutions required by the assay[10] were avoided by adjusting the state of protonation of the catalyst for the reaction mixture, and by making the correction solution from the calculated amounts of acid or base required to titrate 1 μL of each reaction mixture back to pH 7.00.

Imidazole, half-protonated imidazole, and imidazole hydrochloride were all prepared as 6 M stock solutions from recrystallized imidazole and freshly titrated concentrated HCl and used to make up the kinetic reaction mixtures.

Cleavage of poly-U by Imidazole Buffers. The data are listed in sections A, B, and C of Table I. For section A, 140 μL of solution was prepared 62.3 mM in poly-U, 1.03 mM in potassium *p*-nitrobenzenesulfonate hplc standard, and imidazole catalyst as listed. Each solution was divided into 10 melting point capillary tubes which were sealed and incubated at 80.0 ± 0.2 °C. For section B, 95 μL of solution was divided among 8 tubes. For section C, only 7 points per run were done.

Cryoscopy of the Buffer. A solution 0.99 M in total imidazole, half each imidazole and imidazole hydrochloride in H_2O, gave a melting point depression of 2.501 °C for H_2O. This corresponds to 1.358 molal independent solute particles (calcd 1.484). At half the concentration it gave a 1.302 °C depression, corresponding to 0.70 molal particles (calcd 0.74). For calibration, 0.1 N NaOH in H_2O gave ΔT 0.395 °C, corresponding to 0.212 molal particles (calcd 0.020).

Registry No. Im, 288-32-4; ImCl, 1467-16-9; poly-U, 27416-86-0; ribonuclease, 9001-99-4.

Transition Structures for C- and O-Alkylation of Acetaldehyde Enolate. Stereoelectronic Effects and C/O Alkylation Ratios

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Abstract: The transition structures for the gas-phase C- and O-alkylations of acetaldehyde enolate with methyl fluoride have been located with ab initio RHF calculations and the 3-21G basis set. Single point calculations have been carried out with the 6-31G* basis set. The activation energy for O-alkylation is lower than that for C-alkylation, even though the latter is favored thermodynamically. These results parallel those found for the reactions of Me^- and HO^- with MeF and arise from the lower intrinsic barrier for reactions of oxygen-centered nucleophiles (or leaving groups) than carbon-centered nucleophiles in S_N2 reactions. The geometries of the transition structures indicate that stereoelectronic factors favor product-like conformations, even for relatively early transition states.

Alkylations of enolates are synthetically valuable and mechanistically intriguing processes.[1,2] Many hypotheses have been advanced about the factors which control the ratios of C- and O-alkylation[1-5] and the stereoelectronic factors controlling the direction of attack of the alkylating agent on the enolate.[6-9] We report insights into both of these phenomena obtained from ab initio transition structures for the C- and O-alkylation of acetaldehyde enolate by methyl fluoride.

Results and Discussion

Transition structures were located with ab initio molecular orbital calculations using the 3-21G basis set.[10] Anion–neutral complexes formed between the two reactants and the two products were also optimized at this level, since these anion–molecule complexes are known to be intermediates in gas-phase S_N2[11-13] and enolate reactions.[12,14] Reactions of the methyl anion and the hydroxide ion with methyl fluoride were also studied, in order to compare the C- and O-alkylation of enolates to the analogous reactions of localized species. Single point calculations on reactants and transition structures were also carried out at the 6-31G* level with use of the 3-21G optimized geometries. These calculations are designated as 6-31G*//3-21G.[15]

The relative energies of the stationary points on these surfaces are summarized in Figure 1, while salient geometrical features are summarized in Figures 2 and 3.[16-17] In the gas phase, as in solution, the C-alkylated product is more stable than the O-alkylated. At the 6-31G*//3-21G level, propionaldehyde is 23 kcal/mol more stable than methyl vinyl ether, whereas this difference is 18 kcal/mol from Benson's group equivalents.[18] Ac-

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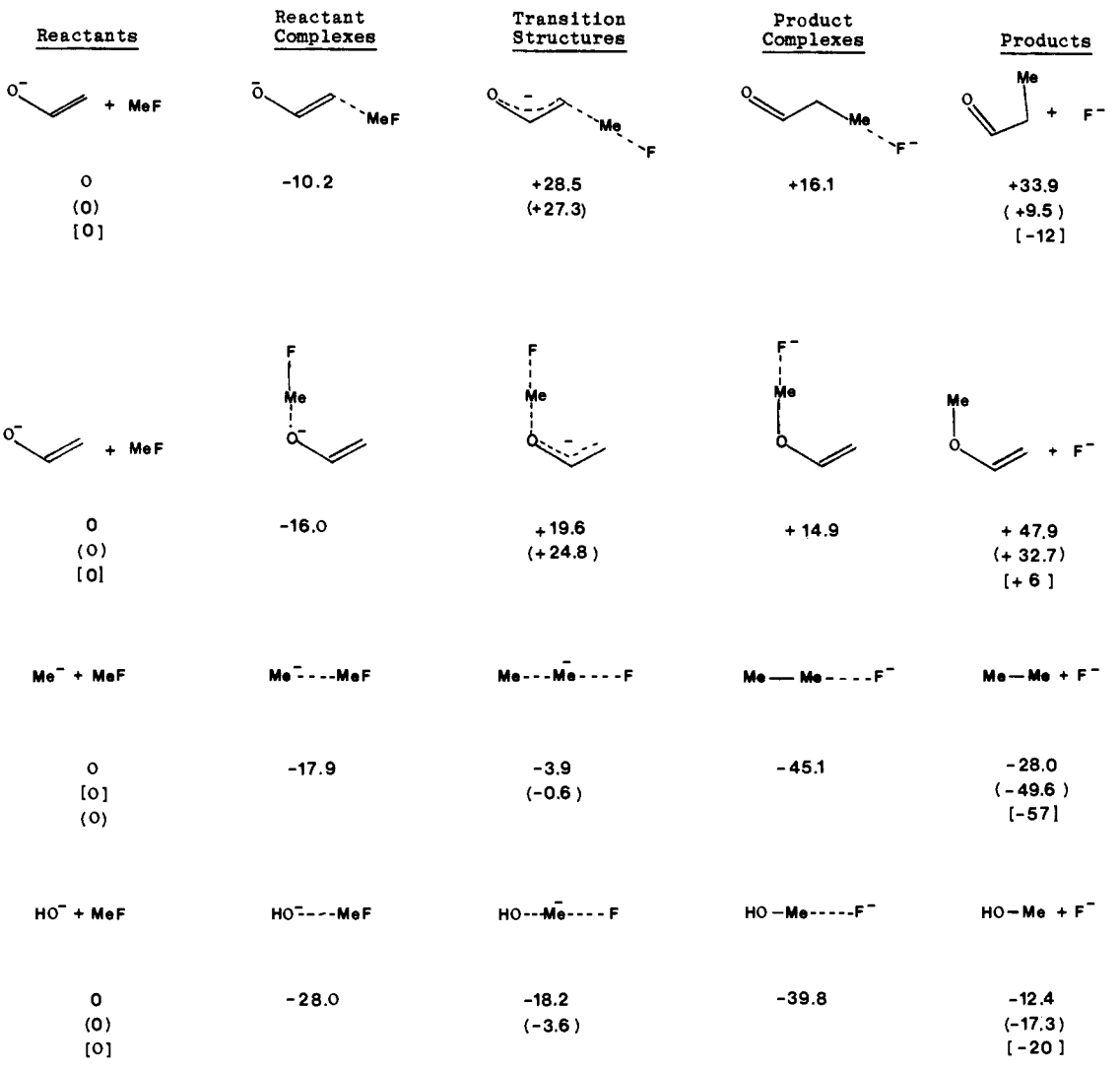
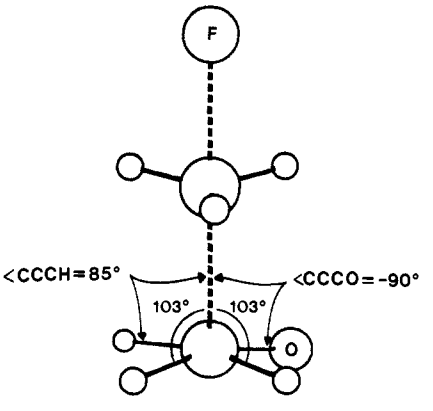


Figure 1. 3-21G relative energies (kcal/mol) of stationary points for reaction of acetaldehyde enolate, hydroxide, and methyl anion with methyl fluoride. 6-31G* energies are given in parentheses, and the estimated experimental heats of reaction (see text) are given in brackets.

cording to the calculations carried out here, both the C- and O-alkylation of acetaldehyde enolate by methyl fluoride are endothermic in the gas phase, while experimental estimates indicate that O-alkylation is endothermic by 6 kcal/mol and C-alkylation is exothermic by 12 kcal/mol.[19] We attribute the considerable underestimation of product stabilities in our calculations to the fact that localized anions such as fluoride are treated poorly with small basis sets lacking diffuse functions. Although the polarization functions in the 6-31G* basis set lead to some improvement, there is still considerable error in the absolute energies of the reactions. However, the relative energies of products and the relative energies of transition structures are reasonable, so that these results are useful for qualitative interpretations.



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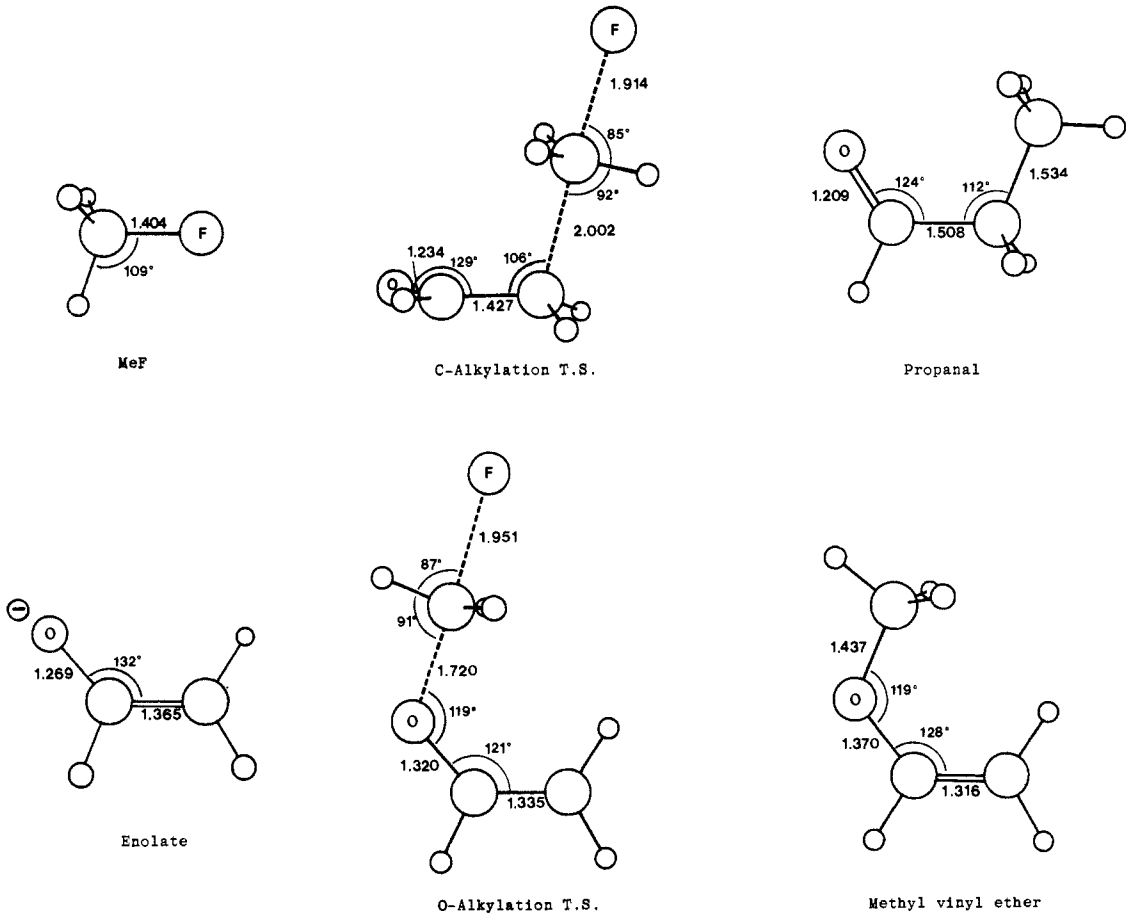

Figure 2. 3-21G geometrical parameters of heavy atoms in reactants, transition structures, and products for the reactions of acetaldehyde enolate with methyl fluoride.

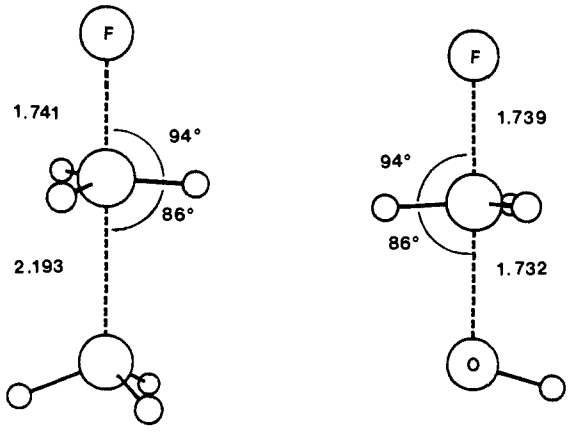

Figure 3. Transition structures for the reactions of methyl anion and hydroxide with methyl fluoride.

In spite of the relative lateness of the transition structures of these reactions, the thermodynamically unfavored O-alkylation of the enolate anion is predicted to occur with a 3–9 kcal/mol lower activation energy than C-alkylation. The results are parallel to those found for the reactions of the localized anions. Alkylation of methyl anion by methyl fluoride is favored by 30 kcal/mol by the estimated reaction thermochemistry,[18,19] or by 16–32 kcal/mol computationally, but the activation energy for alkylation of hydroxide by methyl fluoride is 3–14 kcal/mol lower than that for the reaction of the methyl anion. The theoretical prediction that O-alkylation is strongly favored kinetically in the gas phase is in agreement with the fact that cyclohexanone enolate undergoes only O-alkylation by methyl bromide in the gas phase.[5] O-Alkylation has also been inferred for alkylation of acetone enolate by methyl chloride and bromide.[12] On the other hand, enolates are believed to react at carbon with carbonyl compounds in the gas phase.[14]

Our calculations, on a relatively "hard" and unreactive electrophile, MeF, combined with experimental gas-phase data on alkylations with softer electrophiles,[5,12] imply that a free enolate reacts exclusively at O, regardless of the hardness or softness of the alkylating agent, or whether the transition state is early or late. C-Alkylation of metal enolates is often favored in solution, but this preference must arise from coordination of the enolate oxygen by metal cations, which decreases the reactivity of O relative to C.[4] O-Alkylation is found to dominate even in solution with very reactive alkylating agents in dipolar aprotic solvents, and in general the less tightly coordinated the anion in solution the smaller the C/O alkylation ratio.[2-4] Our calculations and gas-phase experimental studies indicate that O-alkylation of enolates is favored with all electrophiles. Changes in C/O alkylation ratios with the nature of the alkyl halide are probably not related to the "hardness" or "softness" of the alkyl halide but to the ability of the halide to influence the structures of metal enolate aggregates.[4]

The inherent preference for O-alkylation can be attributed to the lower intrinsic barrier for the reaction $HO^- + CH_3OH \rightarrow HOCH_3 + OH^-$ than for the reaction $CH_3^- + CH_3CH_3 \rightarrow CH_3{-}CH_3 + CH_3^-$. In these identity reactions, the transition structure with the negative charge distributed over two oxygens is clearly more stable than that in that where negative charge is shared only by carbons. This greater inherent superiority of negative oxygen over negative carbon as a nucleophile (and leaving group) more than overcomes the thermodynamic preference for reaction of the negative carbon of the methyl anion or the carbon terminus of the enolate.

The transition structures shown in Figure 2 reveal interesting features about the relationship between reaction progress and reactivity. The more endothermic O-alkylation of the enolate has a more advanced transition structure than found for the C-alkylation, both in terms of extent of bonding to the methyl group

and the extent of CF bond breaking. In general, the more exothermic the reaction the less advanced the transition structure, in accord with the Hammond postulate. Nevertheless, the reactions of oxygen nucleophiles have lower activation energies than those of carbon nucleophiles. The extent of distortion of the enolate system is slightly larger during C-alkylation than during O-alkylation, but in both transition structures, the enolate moiety is distorted about 50% from the geometry of the reactant to that of a product. Analysis of the Mulliken charges indicates that a similar extent of charge transfer (35%) from enolate to methyl fluoride occurs in the transition structures for both C- and O-alkylation, whereas qualitative arguments predict a constant 50% charge transfer.[20]

There are obvious similarities between the transition structures of the enolate alkylations and the geometries of the products. The angle of approach of the electrophilic methyl fluoride on the enolate carbon is 106°, only slightly smaller than the corresponding CCC angle in the product. Attack occurs in a plane perpendicular to the enolate plane as shown in A. This agrees with the empirical deductions by Corey about the stereoelectronic factors controlling the direction of attack of electrophiles on enolates.[6,7] None of the deviation from perpendicular attack proposed by Agami[8] is observed, but it is possible that the earlier transition states for MeI reactions could have such distortions.

Attack on oxygen occurs in the plane of the enolate, syn to the double bond, and with a CO—C angle of 119°. These geometrical features are identical with those of the product of O-alkylation, and the energetic preference for this geometry is similar to that found in the product.[21] The reactant complex (not shown) has a CO—C angle of 134°, which places the electrophilic methyl fluoride at the site of the largest negative electrostatic potential. The stereoelectronic preference for syn-O-alkylation is related to the suggestion by Gandour that syn-attack of electrophiles such as a proton will be favored for carboxylates.[22] In both cases, the electrophile approaches the oxygen in such a manner as to minimize internal electrostatic repulsions between oxygen lone pairs and the π electron density at the other terminus of the π system. Similarly, stereoelectronic effects generally favor product-like conformations in transition structures of a variety of organic reactions.[23,24] In general, reactions with activation barriers, even those with early transition states, have conformational preferences resembling those of products.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this research.

Registry No. CH_2=CH—O^-, 35731-40-9; CH_3F, 593-53-3.

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Milbemycin–Avermectin Studies. 5. Total Synthesis of Milbemycin β_3 and Its C(12) Epimer[1]

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Abstract: The total synthesis of milbemycin β_3 (**1**) and its epimer, 12-epimilbemycin β_3, is described. The central features of the synthetic strategy are (a) construction of the spiro ketal unit by nitrile oxide dipolar addition, (b) introduction of the requisite C(12) methyl center via a chelation-controlled cuprate addition in tandem with a stereocontrolled Ireland–Claisen rearrangement, and (c) construction of the southern hemisphere via a novel S_N2' reaction of lithium diphenylphosphide with a γ-vinyl-γ-lactone (i.e., **10**).

In 1974, Mishima et al.[3] announced the isolation and structure elucidation of the milbemycins, a new family of architecturally novel antibiotics, the simplest member of which is milbemycin β_3 (**1**). Now numbering 20 members, the milbemycins possess remarkably potent insecticidal activity.[4] Contemporary with this discovery, the Merck group, led by Albers-Schonberg, uncovered

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