

# Diastereoselectivity of Enolate Anion Protonation. Reaction of HCN with the Enolate of 3-Fluorobutanoic Acid. An ab Initio Molecular Orbital Study

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**Abstract:** The protonation of the enolate of 3-fluorobutanoic acid by hydrogen cyanide was chosen as a suitable computational model for the H/D exchange reaction of ethyl 3-ethoxybutanoate in ethanol-*d*. A diastereomeric excess of 82% is found in the experimental system, compared to calculated selectivities which range from 84 to 91%, dependent on the level of theory used. Both *cis* and *trans* enolates yield similar diastereomeric ratios. In the lowest energy transition state for each diastereomeric pathway the C–F bond is oriented *anti* to the incipient C–H bond. These two transition states are differentiated by steric forces, the higher energy diastereomer having a *gauche* interaction between the CH<sub>3</sub> and CO<sub>2</sub>H groups. The orientation of the C–F bond in these two transition states is rationalized as a stabilizing orbital interaction between the electron rich  $\sigma$  orbital of the enolate–HCN bond and the low-lying  $\sigma^*$  orbital of the C–F bond, an interaction also proposed by Anh to explain the selectivity of nucleophilic addition to chiral carbonyl compounds. Alternatively, an electrostatic argument can account for the data. When the C–F bond is *anti* to the incipient C–H bond, the dipole moment, and hence the electrostatic energy, is at a minimum.

## Introduction

The protonation of enolate anions is a reaction of great importance in chemistry and biochemistry, but the stereochemistry of this reaction has not been well studied under non-ion-pairing conditions. In the preceding manuscript, Mohrig *et al.* describe the diastereoselectivity of H/D exchange in ethoxide/ethanol-*d* of various ethyl 3-X-butanoate derivatives.<sup>1</sup> A combination of electronic and steric effects are used to explain the observed diastereoselectivity. In this article, ab initio molecular orbital theory will be used to model the experimental system with two goals in mind: reproducing the experimental results and further examining the mechanism of selectivity.

From a computational viewpoint, much attention has been paid to the diastereoselectivity of addition of nucleophiles to carbonyl compounds.<sup>2</sup> Far fewer papers have looked at the selectivity of addition of electrophiles to alkenes. Houk *et al.* calculated the energies of the diastereomeric transition states for addition of boranes to alkenes and successfully reproduced experimental selectivities.<sup>3</sup> Surprisingly, there is no work at this level of sophistication for the important case of stereoselective addition of a proton to an unsaturated carbon center. Several studies have been published on proton transfer,<sup>4</sup> though

only recently has proton transfer to an enolate been examined.<sup>5</sup> While the facial selectivity of proton addition to allylic alcohols has been examined by Hehre *et al.*, diastereomeric transition states were not calculated.<sup>6</sup> Other workers have looked at the addition of nucleophiles to  $\alpha,\beta$  unsaturated carbonyl compounds, a reaction which generates an enolate as an intermediate.<sup>7</sup> The minimum energy conformation of this enolate was used to rationalize the selectivity of protonation, but transition states for this step were not calculated. This paper presents the first complete computational study of stereoselective protonation of an unsaturated carbon center.

Our computational model was chosen with several factors in mind. Mohrig *et al.* found that the selectivity of protonation was relatively insensitive to a surprisingly large amount of structural variation. Specifically, diastereoselectivity was constant with changes in (a) the nature of the electronegative substituent, (b) the alkyl group of the ester, and (c) the steric bulk of the protonating agent. In order to minimize the computer time needed, computational parameters were varied so as to produce a model of minimum size, 3-fluorobutanoic acid. An additional constraint was placed on the protonating agent: it had to have approximately the same gas-phase  $pK_a$  as the C<sub>2</sub> proton of 3-fluorobutanoic acid. Otherwise a transition state for proton transfer would not exist. HCN was chosen. Finally, since selectivity in the experimental system has been

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shown to be invariant to the solvent polarity,<sup>8</sup> we felt that ab initio work done in the gas phase would provide data relevant to the experimental system.

### Computational Methods

Ab initio calculations were performed using the Gaussian 90<sup>9</sup> and Gaussian 92<sup>10</sup> program suites. Structures were optimized using 3-21G or 6-31G\* basis sets at the Hartree–Fock level. All basis sets were used as implemented in Gaussian.<sup>11</sup> All stationary points were confirmed with analytical second derivatives. All transition states had a single imaginary frequency in the vibrational analysis. Electron correlation was accounted for by using Moeller–Plesset perturbation theory.<sup>12</sup> Standard notation was employed, i.e. HF/6-31G\*//HF/3-21G is equivalent to a HF/6-31G\* single-point calculation at the optimized HF/3-21G geometry.

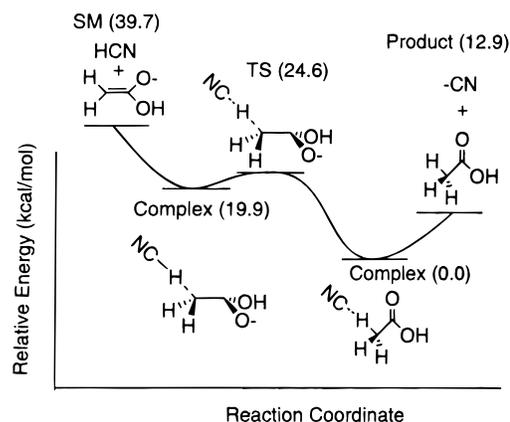
In single-point calculations involving the diastereomeric transition states, diffuse functions<sup>13</sup> and large basis sets such as 6-311++G\*\* were used to offset the dual problems of describing localized anions and of basis set superposition error (BSSE),<sup>14</sup> respectively. No correction for BSSE was employed.<sup>15</sup> Since the diastereomeric transition states have very similar structures, a cancellation of errors should result when calculating relative energies.<sup>16</sup>

Gaussian calculations were performed on a Cray X-EA-MP/4-64 at the Minnesota Supercomputer Institute and on a Cray Y-MP832 and a Cray C-90 at the NSF Pittsburgh Supercomputer Center (Grant No. CHE920022P).

### Results

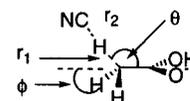
#### Proton Transfer Reaction of Acetic Acid and Cyanide Ion.

Before examining the potential energy surface of the enolate of 3-fluorobutanoic acid, it is worthwhile to explore a much simpler surface, that of proton transfer between the enolate of acetic acid and cyanide ion. This system has the same general features as the larger system (optimized at HF/3-21G and HF/6-31G\*) but has the advantage that much higher levels of theory can be used in the calculations (optimized at HF/6-31++G\*\* and MP2/6-31G\*). Figure 1, below, illustrates the five stationary points on this potential energy surface: starting materials (enolate, HCN), complex, transition state, complex, and products (acetic acid, cyanide ion). The complexes arise from the strong attraction between the charge of the anion and the permanent dipole of the neutral partner and is typical of ionic gas-phase



**Figure 1.** Potential energy surface for the protonation of the enolate of acetic acid by HCN. Energies listed in parentheses are from an HF/6-31G\* optimization and are relative to the cyanide ion-dipole complex with acetic acid set to 0.00 kcal/mol. Absolute energy of this species is  $-245.222\ 25$  Hartrees.

**Table 1.** Geometric Parameters for the Potential Energy Surface for the Protonation of the Enolate of Acetic Acid by Hydrogen Cyanide



		HF/ 3-21G	HF/ 6-31G*		HF/ 3-21G	HF/ 6-31G*
enolate	$r_1$	$\infty$	$\infty$	$\theta$	NA	NA
complex		1.999	2.090		101.1	103.1
TS		1.521	1.548		108.6	110.0
complex		1.107	1.094		109.9	110.0
acetic acid		1.078	1.079		109.3	109.6
enolate	$r_2$	1.137 <sup>a</sup>	1.132 <sup>a</sup>	$\phi$	0.0	0.0
complex		1.102	1.105		12.4	25.9
TS		1.309	1.308		22.9	40.3
complex		2.098	2.335		28.8	22.9
acetic acid		$\infty$	$\infty$		31.1	31.0
		HF/ 6-31++G**	MP2/ 6-31G*		HF/ 6-31++G**	MP2/ 6-31G*
acetic acid	$r_1$	1.079	1.089	$\theta$	109.5	109.3
TS		1.557	1.548		107.6	108.9
acetic acid	$r_2$	1.127 <sup>a</sup>	1.177 <sup>a</sup>	$\phi$	31.0	30.9
TS		1.303	1.297		36.3	22.1

<sup>a</sup> Geometries for HCN.

reactions.<sup>17</sup> In solution, ions are stabilized by the solvent, and complexes are not seen. Since the transition state (TS) is only 5 kcal/mol higher in energy than the starting material complex and nearly 25 kcal/mol higher than the product complex, it should have structural features similar to the starting material complex in accord with the Hammond postulate. However, an examination of the geometric data in Table 1 shows that this assumption is incorrect.

The following discussion will focus on the geometric parameters for the TS found in Table 1. Both the distance from C<sub>2</sub> to the transferred proton ( $r_1$ ) and the distance from the cyanide anion to the proton ( $r_2$ ) are significantly larger in the TS than the corresponding values in the product and starting material. This suggests that there is a substantial amount of both bond making and bond breaking in the TS. Interestingly, the H–C<sub>2</sub>–C<sub>1</sub> angle ( $\theta$ ) in the TS is very close to the tetrahedral value, a result consistent with the findings of Burgi and Dunitz

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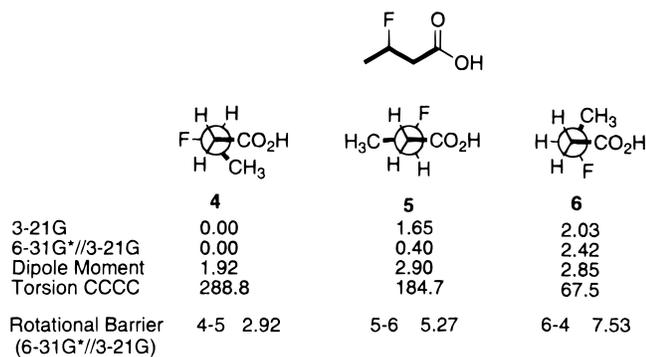
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**Figure 2.** Rotamers and rotational barriers of 3-fluorobutanoic acid. All structures are optimized using the HF/3-21G basis set. Energies and rotational barriers are relative to **4**, which is set to 0.00 kcal/mol. The absolute energy for **4** is  $-492.499\ 27$  Hartrees (HF/3-21G) and  $-494.731\ 59$  Hartrees (HF/6-31G\*). Dipole moments are in Debye.

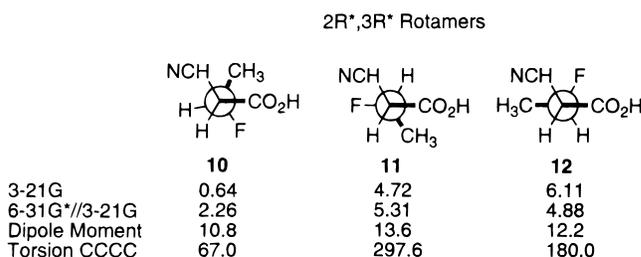
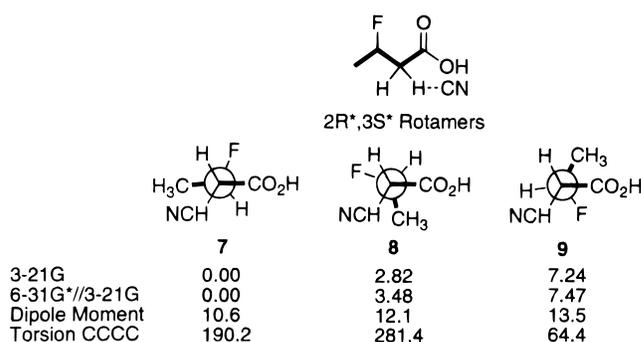
for nucleophilic attack on an unsaturated center.<sup>18</sup> Finally, the degree of pyramidalization ( $\phi$ ) in the TS shows that the carbon accepting the proton is almost fully  $sp^3$  hybridized. The fact that all of these geometric features are independent of basis set suggests that the modest basis sets used to optimize the structures for the 3-fluorobutanoate reaction also provide reasonably accurate geometries for the higher level single-point calculations.

The protonation of the enolate of 3-fluorobutanoic acid by HCN was carried out at the HF/3-21G and HF/6-31G\* levels. The five important points on this potential energy surface are analyzed in the following sections.

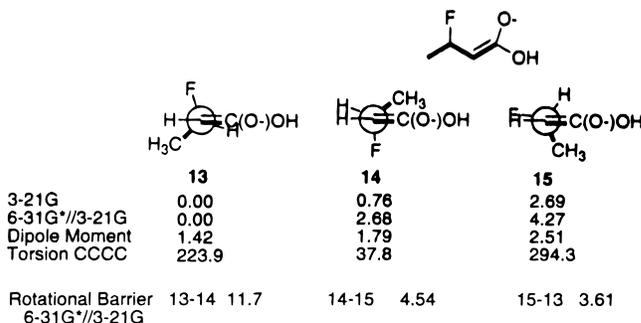
### 3-Fluorobutanoic Acid and Complexes with Cyanide Ion.

The three minimum energy rotamers of 3-fluorobutanoic acid are shown in Figure 2. Since cyanide ion can complex with either the *pro-R* or the *pro-S* hydrogen at  $C_2$  in each fluorobutanoic acid conformer, there are a total of six rotamers of the complex, which are shown in Figure 3. In both the acid and its cyanide complexes, electronic forces play the primary role in determining the relative energies. The rotamers having the smallest dipole moments are lowest in energy. In the acid, this conformation is achieved when the C–F bond is *anti* to the  $CO_2H$  group, **4**, while in the acid complexes it is achieved when the C–F bond lies *anti* to the  $H\cdots CN$  bond, **7** and **10**. In the gas phase it is not unusual for the conformer with the lowest dipole moment to also be lowest in energy, though this ordering can change when a polar solvent is introduced.<sup>19</sup> For the acid complexes there are three cases where the dipole moments are comparable {(7,10), (8,12), and (9,11)}. In these instances steric forces determine the relative energy ordering. In particular, **10** has a gauche interaction between  $CH_3$  and  $CO_2H$  which is absent in **7**, a factor which will recur in the examination of the transition states.

**Enolate of 3-Fluorobutanoic Acid and Complexes with HCN.** The rotamers of the enolate of 3-fluorobutanoic acid are shown in Figure 4. Again, the relative energies decrease with decreasing dipole moment. Unlike the acid complexes, only four enolate complexes are formed and are shown in Figure 5. The HCN can complex to either the *re* or the *si* face at  $C_2$  of the enolate. It is difficult to rationalize the energy ordering, especially since there are large changes in relative energies in going from the HF/3-21G to the HF/6-31G\*\*/HF/3-21G levels of theory. Since the TS geometries are structurally similar to the acid complexes, a more complete study of the enolate complexes was not carried out.



**Figure 3.** Rotamers of 3-fluorobutanoic acid complexed to cyanide ion. All structures are optimized using the HF/3-21G basis set. The *2S,3R* and *2R,3R* stereoisomers are depicted. Energies are relative to **7**, which is set to 0.00 kcal/mol. The absolute energy for **7** is  $-494.281\ 98$  Hartrees (HF/3-21G) and  $-497.040\ 71$  Hartrees (HF/6-31G\*). Dipole moments are in Debye.



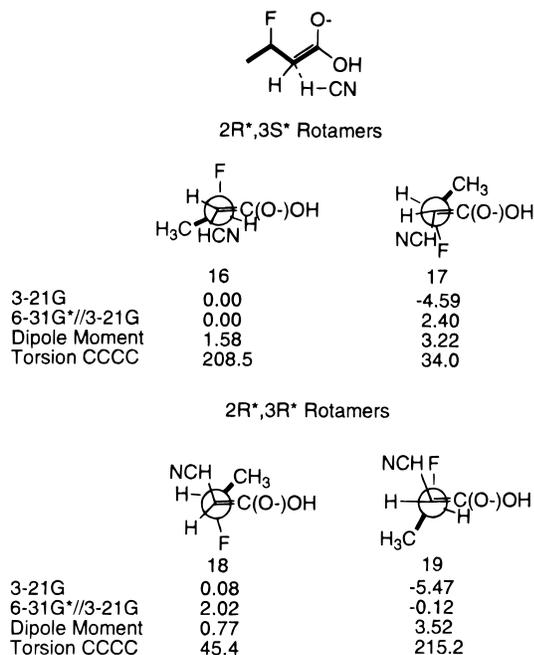
**Figure 4.** Rotamers and rotational barriers of the enolate of 3-fluorobutanoic acid. All structures are optimized using the HF/3-21G basis set. Energies and rotational barriers are relative to **13**, which is set to 0.00 kcal/mol. The absolute energy for **13** is  $-491.886\ 83$  Hartrees (HF/3-21G) and  $-494.117\ 13$  Hartrees (HF/6-31G\*). Dipole moments are in Debye.

**Transition States.** The six diastereomeric transition states (**20**–**25**) for the reaction of HCN with the enolate of 3-fluorobutanoic acid are shown in Figure 6. If the protonating agent were DCN, the TS's **20**–**22** lead to  $2R^*,3S^*$  products while the TS's **23**–**25** lead to  $2R^*,3R^*$  products. Each TS connects an enolate $\cdots$ HCN complex with an acid $\cdots$ cyanide ion complex. Two TS's, **20** and **23**, were found by first locating the maximum energy for proton transfer from the enolate complexes **16** and **18** to the acid complexes **7** and **10**, respectively. The other TS's were located by maximizing the energy with respect to proton transfer while minimizing the energy of the torsion about  $C_2$ – $C_3$ . Despite numerous attempts, the sixth structure **25**, connecting **12** and **19**, could not be found at the 3-21G level of theory. However, a lower limit of the energy for **25** is provided.

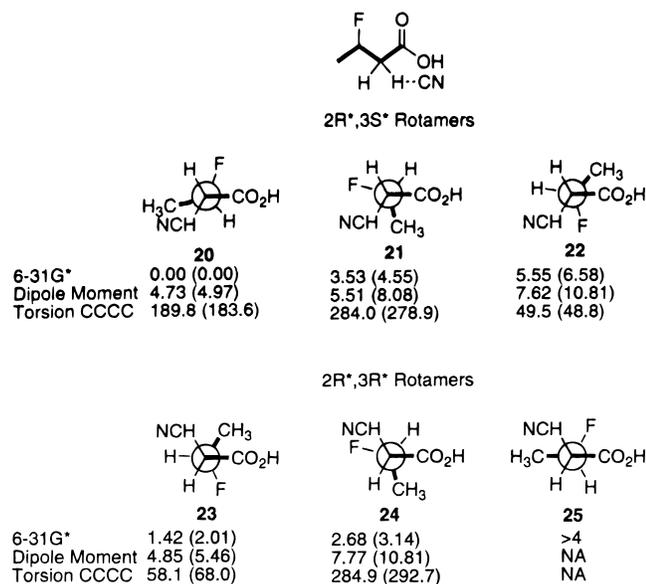
As was the case for the acid, enolate, and acid complex rotamers, the TS with the lowest dipole moment for each diastereomer is also lowest in energy (**20**,  $2R^*,3S^*$  and **23**,  $2R^*,3R^*$ ). In both of these TS's, the C–F bond is aligned *anti* to the incipient  $C_2$ –H bond. The relative energies of **20** and **23**, which have similar dipole moments, are determined by steric

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**Figure 5.** Rotamers of the enolate of 3-fluorobutanoic acid complexed to HCN. All structures are optimized using the HF/3-21G basis set. The 2*S*,3*R* and 2*R*,3*R* stereoisomers are depicted. Energies are relative to **16**, which is set to 0.00 kcal/mol. The absolute energy for **16** is -494.269 56 Hartrees (HF/3-21G) and -497.017 86 Hartrees (HF/6-31G\*). Dipole moments are in Debye.



**Figure 6.** Transition states for the addition of HCN to the enolate of 3-fluorobutanoic acid optimized at the HF/6-31G\* geometry. The 2*S*,3*R* and 2*R*,3*R* stereoisomers are depicted. Values in parentheses refer to the trans isomer at the HF/6-31G\*/HF/3-21G level of theory. Energies are relative to **20**, which is set to 0.00 kcal/mol. As **25** was never located, an estimate of the relative energy is provided. The absolute energy for **20** is -497.011 24 Hartrees (HF/6-31G\*). Dipole moments are in Debye.

forces. Gauche interactions between the CH<sub>3</sub> and CO<sub>2</sub>H groups of **23**, not present in **20**, account for the higher energy of the former. While it is clear that the relative energies of the other TS's are higher than **20,23** due to less favorable electronic interactions, we will not attempt to rationalize their ordering.

Diastereomeric excesses (de's) are calculated using a Boltzmann weighted sum of TS's for each diastereomer and are shown in Table 2. Since contributions to the stereoselectivity decrease exponentially with increasing energy, only the lowest

**Table 2.** Diastereomeric Excesses (%) Calculated at 298 K<sup>a</sup>

	HF/3-21G geometry		HF/6-31G* geometry	
	HF/3-21G	HF/6-31G*	HF/6-31G*	MP2/6-311++G**
cis enolate	19.8	91.1	83.6	86.8
trans enolate	93.4	97.6	97.1 <sup>b</sup>	97.2 <sup>b</sup>

<sup>a</sup> A scaled correction which includes zero-point and thermal energy corrections is applied to the energy at 0 K. Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*; Gaussian, Inc.: Pittsburgh, PA, 1996; pp 63-69. <sup>b</sup> Only the lowest energy isomer for each diastereomer is used for this calculation.

energy TS for each diastereomer, **20** and **23**, figures significantly in the calculation. While there is little selectivity predicted at the HF/3-21G level of theory, de's favoring the 2*R*\*,3*S*\* isomer of 84% and 87% were found at higher levels of theory, HF/6-31G\*/HF/6-31G\* and MP2/6-311++G\*\*/HF/6-31G\*, respectively. The small changes in the energy difference between **20** and **23** on going from the HF/6-31G\* to the MP2/6-311++G\*\*/HF/6-31G\* level of theory suggest that similar results would be obtained using geometries optimized with correlated wave functions. The calculated de is remarkably close to the experimental de of 82% in favor of the 2*R*\*,3*R*\* diastereomer found for the H/D exchange of ethyl 3-ethoxybutanoate in ethanol-*d*. Note that the 2*R*\*,3*S*\* isomer in this work corresponds to the 2*R*\*,3*R*\* isomer in the experimental study due to a change in the priority ordering for the assignment of C<sub>2</sub>.

**Enolate Geometry.** The computational work above used the cis enolate exclusively to reproduce the experimental results of Mohrig *et al.*<sup>1</sup> The deprotonation of esters in tetrahydrofuran



(THF) leads primarily to the trans enolate, though addition of polar additives such as hexamethylphosphoric triamide (HMPT) reverses this selectivity.<sup>20</sup> The situation in ethanol, which was used by Mohrig *et al.*, is less clear. While the more stable enolate is probably cis, it is reasonable to assume that in ethanol the kinetic enolate will react faster than it isomerizes. Clearly it is important to determine the diastereoselectivity of the trans enolate.

The lowest energy conformation of the trans enolate was calculated to be 1.5 kcal/mol less stable than the cis enolate. Similar to the results found for the cis enolate, five TS's corresponding to **20-24** were found at the HF/3-21G level of theory. Energies, dipole moments, and the torsional angles of the carbon skeleton for the trans isomer are listed in parentheses in Figure 6, next to the values for the cis isomer. As with the cis enolates, the orientation of the C-F bond in the trans enolates is *anti* to the incipient C-H bond in the lowest energy TS for each diastereomer. Moreover, the isomer corresponding to **20** was nearly 2 kcal/mol more stable than that corresponding to **23** at every level of theory which was studied. Indeed, if selectivity is calculated using only the lowest energy TS for each diastereomer, the de of the trans enolates favoring the 2*R*\*,3*S*\* isomer is 93%, 98%, and 97% at the HF/3-21G, HF/6-31G\*/HF/3-21G, and MP2/6-311++G\*\*/HF/6-31G\* levels of theory, respectively. The de is slightly higher than that predicted for the cis enolate. The important point, however, is that in this system the enolate geometry does not significantly affect the diastereoselectivity of electrophilic attack.

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## Discussion

**Orbital Explanations of the Diastereoselectivity.** The computational results from this work can be analyzed in light of several existing theories of stereoselectivity. In the addition of nucleophiles to chiral carbonyl compounds, Felkin postulated that the incipient bond between the nucleophile and carbonyl carbon would be staggered with respect to the bonds of the  $\alpha$  carbon in order to avoid unfavorable torsional interactions.<sup>21</sup> To minimize steric interactions, the carbonyl carbon– $\alpha$  carbon bond would rotate so as to orient the large group *anti* to the incoming nucleophile. The medium group would preferentially be oriented “inside”, *gauche* to the carbonyl group. Later, Houk generalized Felkin’s model to include the addition of radicals and electrophiles to unsaturated centers.<sup>22</sup> He suggested that the preferred orientation of the medium group would vary depending on the specifics of the system. While these ideas are well accepted, the effects of electron-donating and electron-withdrawing groups attached to the  $\alpha$  carbon are still controversial. For nucleophilic addition to carbonyls, Anh suggested that favorable orbital interactions between the  $\sigma^*$  orbital of the substituent– $\alpha$  carbon bond and the  $\sigma$  orbital of the forming nucleophile–carbonyl carbon bond would be maximized with the strongest electron-withdrawing group *anti*.<sup>23</sup> This idea was again generalized by Houk to electrophilic attack.<sup>24</sup> In this case, the strongest electron donor at the  $\alpha$  carbon would lie *anti* to the incoming electrophile in order to maximize favorable orbital interactions between the  $\sigma$  orbital of the donor and the  $\sigma^*$  orbital of the incipient bond. Arguing that incipient bonds are inherently electron deficient, Cieplak reasoned that the dominant stabilizing interaction should be between the  $\sigma$  orbital of the substituent– $\alpha$  carbon bond and the  $\sigma^*$  orbital of the nucleophile–carbonyl carbon bond.<sup>25</sup> Thus, the orbital stabilization is maximized when the strongest electron donating group lies *anti* to the incoming reagent for both electrophilic and nucleophilic addition.

The computational work from this study is very much in accord with the generalized Felkin model of Houk. Indeed, all of the calculated transition states are staggered with respect to the incoming electrophile. However, the lowest energy transition states have F, an electron-withdrawing group, *anti* to the incoming electrophile, HCN, in seeming violation of both the Anh–Houk and Cieplak models for electrophilic addition. These theories were designed for a general electrophile,  $E^+$ , adding to a weakly nucleophilic alkene, such as allyl alcohol. In our system, the alkene component is the ester enolate while the electrophile is HCN. The highly nucleophilic enolate anion donates a large amount of electron density into the forming  $C\cdots H$  bond. Hence, stabilization should result from donation by the  $\sigma$  orbital of the incipient bond into the  $\sigma^*$  orbital of the antiperiplanar electron-withdrawing group. This is identical to the explanation used by Anh to account for nucleophilic addition to carbonyls. Thus, electronic effects are not necessarily governed by whether an electrophile or a nucleophile adds to an unsaturated center, but whether the incipient bond is electron

rich or electron poor in the transition state. Since the Cieplak model assumes that this bond is electron poor, it has no bearing on our study.

It is worthwhile to see how these ideas fit with the experimental data of Mohrig *et al.*<sup>1</sup> Let us assume that the transition state for reaction of ethanol-*d* with ethyl 3-X-butanoates has a staggered conformation in accord with Houk’s generalization of the Felkin model. Clearly, when X is *tert*-butyl, it will be large and lie *anti* to the electrophile. Selectivity will arise from the energy difference between two rotamers: (1) the methyl group lies on the inside and the hydrogen on the outside and (2) the hydrogen lies on the inside and the methyl group on the outside. The major product is consistent with the second case being lower in energy. This assumption is reasonable, since *gauche* interactions between the methyl group and ester functionality are absent in the second case. When X is methoxy, ethoxy, *tert*-butoxy, cyano, trifluoromethyl, and fluoro (computationally), it acts as the large group since the direction of the selectivity is the same as when X is *tert*-butyl. The electron-withdrawing nature of the X group at carbon-3 through the  $\sigma$  system seems to be the primary stereochemical determinant, as this feature is common to all these groups. Interactions of the  $\pi$ -system in X play little or no role, since donating (alkoxy), withdrawing (cyano), and neutral (trifluoromethyl) X groups all lead to the same diastereomer as the major product. It might be argued that when X is electron withdrawing, methyl lies *anti*, X *inside*, and hydrogen *outside*. While giving the observed major products, this alternative hypothesis is at odds with our computational results, which successfully reproduce both the magnitude and direction of the observed selectivity.

**Electrostatic Explanations of Diastereoselectivity.** An alternative viewpoint, independent of orbital interactions, is that the most energetically favored pathway in the protonation of the enolate of 3-fluorobutanoic acid will minimize electrostatic repulsion in the transition state. This can be viewed in two ways. The partially negative F atom should be kept at a maximum distance from the partially negative N atom to minimize electrostatic repulsion. Alternatively, the C–F and H–CN dipoles should be aligned so as to minimize the overall dipole moment. Either formulation correctly predicts that transition states where the C–F bond is *anti* to the incipient C–H bond, i.e. **20** and **23**, will be lowest in energy. This argument is not unique to our system. Hehre used electrostatic arguments in an *ab initio* study of electrophilic addition to chiral allylic alcohols.<sup>6</sup> Recently, in two unrelated studies on the aldol reaction, the Evans laboratories<sup>26</sup> and the Boeckman laboratories,<sup>27</sup> argued that transition state conformations where the dipole–dipole interactions were lowest led to the major observed products.

Two “experiments” were used to help support this argument.<sup>28</sup> First, the cyanide anion was removed from the transition state structures and the resulting energies were recalculated. The relative energies became scrambled relative to the parent system, as shown in Table 3. Interestingly, the **20,23** energy difference remains constant at just above 1 kcal/mol, even though these two conformers are no longer the minimum energy structures.

In the second experiment, the cyanide ion was replaced by a negative charge of 0.5 e at 4 Å from  $C_2$  along the  $C_2$ –H bond vector. The magnitude and position of this charge was chosen

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**Table 3.** Simulation of Stereoselectivity Using a Point Charge

isomer	20	21	22	23	24
dipole moment (Debye)	4.73	6.08	7.61	4.85	7.76
MP2/6-311++G**//HF/6-31G*	0.00	4.51	6.36	1.49	3.58
experiment 1, deletion of cyanide <sup>a</sup>	0.00	-0.97	-1.16	1.18	-4.80
experiment 2, charge inserted <sup>a</sup>	0.00	2.73	7.35	1.22	-0.97
stabilization on adding charge <sup>b</sup>	6.35	2.65	-2.16	6.31	2.52

<sup>a</sup> See text for a description of experiments 1 and 2. Energies are relative to **20**, set to 0.00 kcal/mol. Energies calculated using the HF/6-31G\* basis set at the HF/6-31G\* optimized geometry. Absolute energy for **20** in Hartrees is -404.666 38 for experiment 1 and -404.676 50 Hartrees for experiment 2. <sup>b</sup> Equals absolute energy (experiment 1) - absolute energy (experiment 2) in kcal/mol.

to coincide with the calculated charge<sup>29</sup> and position of the N atom. Compared to the results of the first experiment, the resulting relative energies in Table 3 have several features of note. With the exception of **24**, the crude ordering seen in the parent system is recovered: isomer **20** is more stable than **23**, which, in turn, is significantly more stable than **21** and **22**. The change on going from experiment 1 to experiment 2 is most stabilizing to **20,23**, suggesting that these structures are situated optimally to interact with either a negative charge or cyanide ion. Presumably, if the charge had been placed closer to the ester or increased in magnitude, isomer **20** not **24** would be the global minimum.

However, the quantitative merits of these "experiments" are secondary. Importantly, the cyanide anion is critical in the gas phase for determining the relative energies of the diastereomers. Moreover, the effects of the counterion can be mimicked to a great extent by a test charge with an appropriate magnitude and position.

As in the previous section, it is worthwhile to compare the calculated results with experimental data. Mohrig *et al.* have shown that there is little or no effect of the solvent on the experimentally observed diastereoselectivity of H/D exchange, once ion-pairing effects are removed.<sup>8</sup> Therefore, it is reasonable to assume that the calculated results, which are in the gas phase and are thus relevant to solution studies in nonpolar solvents, are also applicable to results in ethanol-*d*. However, electrostatic effects, and hence the selectivity, should decrease as the dielectric constant of the medium increases, which is not seen. Though attenuated in ethanol, the electrostatic effect may still be strong enough to orient the polar group at the  $\alpha$  carbon *anti* to the incoming electrophile. Attempts at modeling the effect of the solvent computationally led to inconclusive results.<sup>30</sup> These data are contained in the Supporting Information.

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## Conclusions

The diastereoselectivity of H/D exchange of ethyl 3-X-butanoate derivatives in ethoxide/ethanol-*o-d*, studied by Mohrig *et al.*,<sup>1</sup> has been modeled by ab initio calculations of the transition states for addition of HCN to the enolate of 3-fluorobutanoic acid. This work is the first complete computational study of stereoselective protonation of an unsaturated carbon center.

The C-F bond is oriented *anti* to the incipient C-H bond in the lowest energy transition state for each diastereomer. In a comparison of the lowest energy transition state conformers, it was found that a gauche interaction between the CH<sub>3</sub> and CO<sub>2</sub>H groups raises the energy of the *2R\*,3R\** relative to the *2R\*,3S\** transition state.

A Boltzman distribution of the five transition structures located shows that the diastereomeric excess (de) is 84-91%, favoring the *2R\*,3S\** isomer at all but the lowest level of theory studied. This compares well with the de of 82% found in ethanol solution for the H/D exchange of ethyl 3-ethoxybutanoate. Both *cis* and *trans* enolates led to similar de's.

The energetic preference for the C-F bond to lie *anti* to the incoming electrophile is rationalized as a stabilizing orbital interaction between the electron rich  $\sigma$  orbital of the enolate-HCN bond and the low-lying  $\sigma^*$  orbital of the C-F bond, an interaction proposed by Anh to explain the selectivity of nucleophilic addition to chiral carbonyl compounds. It is concluded that electronic effects are not necessarily governed by whether an electrophile or a nucleophile adds to an unsaturated center but whether the incipient bond is electron rich or electron poor in the transition state.

An electrostatic argument is advanced which also supports the data. The cyanide anion and partially negative fluorine are situated *anti* to minimize electrostatic energy. Replacement of the cyanide ion by a realistic test charge reproduces many of the features of the parent system. Since selectivity in the experimental system is solvent independent, the calculated gas phase results should be highly relevant to the solution studies.

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**Supporting Information Available:** Tables of the SCRF calculations and the archive files for all optimized structures. (23 pages). See any current masthead page for ordering and Internet access instructions.

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