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Stereochemistry of 1,2-Elimination and Proton-Transfer Reactions: Toward a Unified Understanding

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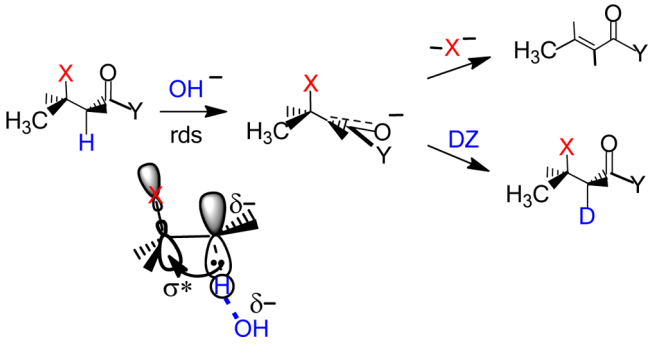
CONSPECTUS



Many mechanistic and stereochemical studies have focused on the breaking of the C—H bond through base-catalyzed elimination reactions. When we began our research, however, chemists knew almost nothing about the stereospecificity of addition—elimination reactions involving conjugated acyclic carbonyl compounds, even though the carbonyl group is a pivotal functional group in organic chemistry. Over the last 25 years, we have studied the addition—elimination reactions of β-substituted acyclic esters, thioesters, and ketones in order to reach a comprehensive understanding of how electronic effects influence their stereochemistry. This Account brings together our understanding of the stereochemistry of 1,2-elimination and proton-transfer reactions, describing how each study has built upon previous work and contributed to our understanding of this field.

When we began, chemists thought that *anti* stereospecificity in base-catalyzed 1,2-elimination reactions occurred via concerted E2 mechanisms, which provide a smooth path for *anti* elimination. Unexpectedly, we discovered that some E1cB$_{irrev}$ reactions produce the same *anti* stereospecificity as E2 reactions even though they proceed through diffusionally equilibrated, "free" enolate-anion intermediates. This result calls into question the conventional wisdom that *anti* stereochemistry must result from a concerted mechanism. While carrying out our research, we developed insights ranging from the role of historical contingency in the evolution of hydratase-dehydratase enzymes to the influence of buffers on the stereochemistry of H/D exchange in D_2O.

Negative hyperconjugation is the most important concept for understanding our results. This idea provides a unifying view for the largely *anti* stereochemistry in E1cB$_{irrev}$ elimination reactions and a basis for understanding the stereoelectronic influence of electron-withdrawing β-substituents on proton-transfer reactions.

Introduction

There are two major pathways in base-catalyzed 1,2-elimination reactions, the familiar concerted second-order elimination pathway (E2), where the chemical bonds are being made and broken at the same time,

$$B^- + H-C-C-X \rightarrow B-H + C{=}C + X^- \qquad \text{(E2)}$$

and first-order elimination from the conjugate base (E1cB).[1]

$$B^- + H-C-C-X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B-H + {}^-C-C-X \xrightarrow{k_2} B-H + C{=}C + X^- \qquad \text{(E1cB)}$$

In the E1cB mechanism, the conjugate base of the substrate expels the nucleofuge. When k_1 is small and

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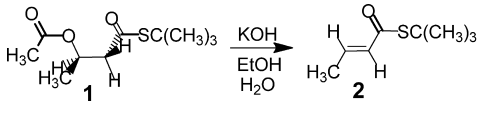
$k_2 \gg k_{-1}$, step 1 is essentially irreversible and the mechanism is called E1cB$_{irrev}$. When the carbanion intermediate is formed reversibly, the mechanism is called E1cB$_R$. In the E2 mechanism, the reaction is concerted but transfer of the proton and dissociation of the nucleofuge need not be completely synchronous; thus, the transition state may be carbanion-like (E1cB-like).

The conventional wisdom has been that *anti* stereospecificity results from a concerted E2 mechanism in which a staggered conformational isomer of the substrate is converted to the product through a smooth low-energy path.[2] The question that sparked our interest came from the observation that enoyl-CoA hydratase (EC 4.2.1.17), a key enzyme in fatty acid metabolism, catalyzes an unusual *syn* elimination of water from stereospecifically tritiated 3-hydroxybutanoyl-CoA.[3] In the 1970s and 1980s, the dominant view of enzyme stereochemistry was that stereospecificity was determined by the most favorable pathway for the substrate, which defines mechanistic efficiency.[4] Thus, enoyl-CoA hydratase could have evolved to use a more efficient *syn* mechanism, even though the *anti* route is normally favored in base-catalyzed 1,2-elimination reactions in the absence of aggregation or the complex conformational constraints of cyclic substrates. The question was whether base-catalyzed eliminations of β-substituted butanethioates inherently produce *syn* elimination or if the enzymatic stereospecificity reflects other aspects of enzyme evolution.

We chose to answer the question of whether base-catalyzed eliminations of β-substituted butanethioates inherently produce *syn* elimination by studying the elimination of acetic acid from *tert*-butyl 3-acetoxybutanethioate (**1**) using KOH in 3:1 v/v EtOH/H_2O. This elimination reaction produced 99% of the (*E*)-alkene (**2**) (eq 1).

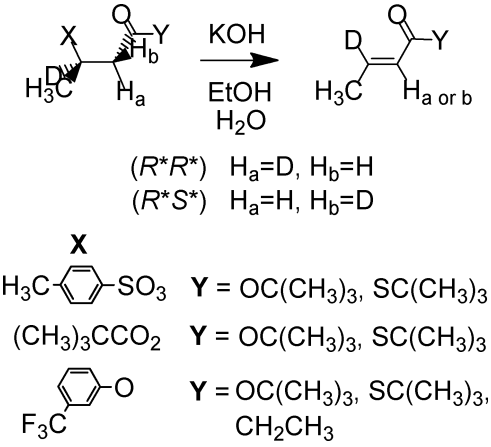


1 **2** (1)

When we discovered that the attack of hydroxide at the acetoxy carbonyl group provided a separate pathway for *syn* elimination, we replaced the β-acetoxy nucleofuge with a trimethylacetoxy nucleofuge.[5]

The α-protons of thioesters are relatively acidic (p$K_a \sim 21$), which could lead to an E1cB-like transition state, and a previous mechanistic study of the elimination reaction of **1** had concluded that the reaction was either E2 or E1cb$_{irrev}$.[6] Transition states that lead to *syn* elimination often have more E1cB character, and it has been suggested that when a molecule is substituted with an electron-withdrawing group that stabilizes a carbanion intermediate, *syn* elimination will often be faster.[7,8] However, Bartsch and Závada suggested that the likelihood of activated *syn* eliminations will generally be low for acyclic substrates.[9]

SCHEME 1



Stereospecific Synthesis of Deuterated Acyclic β-Substituted Carbonyl Substrates

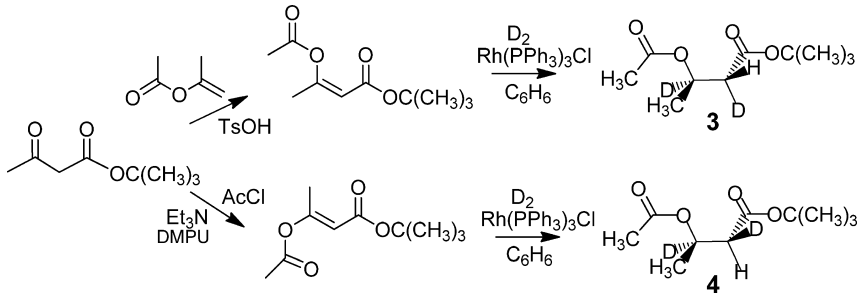
The set of stereospecifically deuterated substrates that we have studied is shown in Scheme 1.

When we began, there were no general methods for the stereospecific synthesis of these isotopically labeled substrates. We had our first success using the $NaBD_4$ cleavage of 2,3-epoxybutanoic acid in alkaline D_2O.[10] Unfortunately, we were unable to produce both of the necessary diastereomers by this methodology. However, using Wilkinson's catalyst, the stereospecific *syn* addition of D_2 to the (*Z*)- and (*E*)-isomers of *tert*-butyl 3-acetoxy-2-butenoate proved to be an excellent method, which we used successfully in our subsequent syntheses of the necessary (2*R**,3*R**)- and (2*R**,3*S**)-diastereomers of the β-acetoxybutanoate substrates, as shown in Scheme 2.[11]

The *tert*-butyl esters **3** and **4** could easily be converted to the thioesters using trifluoroacetic acid, followed by TFAA and 2-methyl-2-propanethiol. The β-trimethylacetoxy and β-tosyloxybutanoates shown in Scheme 1 were synthesized by hydrolysis of **3** and **4** to the β-hydroxybutanoates, followed by esterification with trimethylacetyl chloride and tosyl chloride, respectively.[5,12]

Synthesis of the deuterated 3-trifluoromethylphenoxy substrates was carried out by using Wilkinson's catalyst to produce stereospecific *syn* addition of D_2 to *tert*-butyl (*Z*)- and

SCHEME 2



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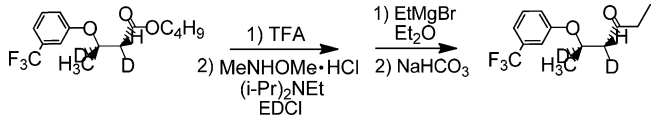


(*E*)-3-(3-trifluoromethylphenoxy)-2-butenoate, which led to the necessary (2*R**,3*R**)- and (2*R**,3*S**)-3-trifluoromethylphenoxy ester and thioester substrates for the elimination studies.[13] With this leaving group it also became feasible to extend our study to a ketone substrate. Before our research, no stereochemical study of a 1,2-elimination reaction that produces a conjugated acyclic ketone had been reported. The synthesis of the necessary ketone substrates without significant H/D exchange or scrambling was made possible by the use of Weinreb amide methodology (Scheme 3).[13,14]

The availability of the necessary substrates and of high-field deuterium NMR allowed us to determine the configurations and stereochemical purity of the isotopically labeled substrates, to calculate k_H/k_D values, and to determine the innate *anti*/*syn* ratio for the elimination reactions of the undeuterated substrates.

Anti Stereospecificity in E1cB Elimination Reactions

A major goal of our research program was to gain a comprehensive understanding of the stereochemistry of 1,2-elimination reactions of acyclic carbonyl compounds where ion pairing and complex conformational issues are excluded as much as possible. We chose to study the elimination reactions of a range of β-substituted *tert*-butyl butanoates (p$K_a \sim 25$), butanethioates (p$K_a \sim 21$), and an analogous ketone (p$K_a \sim 19$), with an excellent β-tosyloxy nucleofuge, a β-trimethylacetoxy nucleofuge, and a poor β-3-trifluoromethylphenoxy nucleofuge (Scheme 1). This latter leaving group was the poorest nucleofuge that did not lead to concurrent H/D exchange at the α-carbon during the elimination reaction.[13] The second-order rate constants for these compounds with NaOH in 3:1 (v/v) EtOH/H_2O covered a range of 2×10^3.[13] Increasing the acidity of the protons α to the carbonyl group and having a better β-leaving group led to larger rate constants.

It is likely that all of our β-trimethylacetoxy and 3-trifluoromethylphenoxy substrates, as well as our β-tosyloxythioester substrate, undergo elimination by E1cB$_{irrev}$ pathways.[13,15] With both acyclic β-phenoxyesters and ketones, there is a substantial body of kinetic evidence that supports the E1cB$_{irrev}$ mechanism, including saturation kinetics at high amine buffer concentrations in general-base catalysis, as well as identical rates for elimination and H/D exchange using hydroxide as the base.[16] Our stereospecifically deuterated β-3-trifluoromethylphenoxyketone substrate produced a small amount of H/D exchange at the C-2 α-carbon while α,β-elimination was proceeding at C-4 and C-5 without H/D exchange. It is unlikely that enolate-anion intermediates are produced at C-2 but not at C-4 of the ketone. Fortunately, for our stereochemical studies, the likelihood of an E1cB$_R$ pathway is lessened by the relatively slow protonation of enolate anions. This slow protonation is thought to result from imperfect synchronization, where part of the electronic delocalization that stabilizes the enolate anion is lost in the transition state for protonation, thereby producing a higher activation energy for protonation at carbon.[17] There is a substantial body of unambiguous evidence that the elimination reactions of our β-3-trifluoromethylphenoxy substrates occur through E1cB$_{irrev}$ pathways (Scheme 4).

The availability of both diastereomers of each stereospecifically deuterated substrate allowed us to calculate the k_H/k_D primary isotope effects for the elimination reactions.[5,12,13] Thus, we were able to calculate the innate percentages of *anti* elimination for the undeuterated substrates, which are shown in Table 1. These percentages are similar to the ~96% *anti* elimination that is generally

SCHEME 4

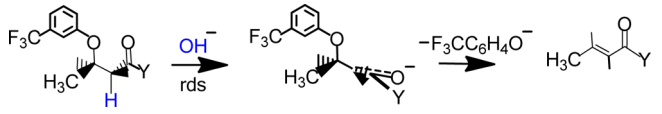
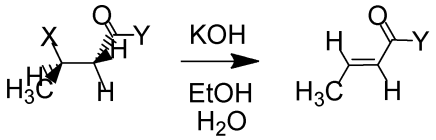


TABLE 1. Innate Stereospecificity of Base-Catalyzed Elimination Reactions



X	% *anti* elimination[a] Y = $OC(CH_3)_3$	Y = $SC(CH_3)_3$	Y = CH_2CH_3
H_3C–SO_3	94	94	--
$(CH_3)_3CCO_2$	94	95	--
F_3C–O	89	89 (87[b])	85[c]

[a]3:1 v/v EtOH/H_2O; [b]6:1 v/v EtOH/ H_2O; [c]5:1 v/v EtOH/H_2O

observed in base-catalyzed E2 reactions of simple acyclic tosylates and halides under non-ion-pairing conditions.[7a,18] The somewhat lower percentages for *anti* elimination of the 3-trifluoromethylphenoxy substrates are minimum values, since it is not unlikely that a component of *syn* elimination of the *R**,*R** diastereomers of these compounds may actually be due to *anti* elimination of a less populated rotomer, which can form the (*E*)-alkene by rotation of the C–C bond of the intermediate enolate anion before the nucleofuge is lost.[13]

Concertedness and *Anti* Stereochemistry: The Role of Negative Hyperconjugation

The E1cB reactions of the 3-trifluoromethylphenoxy substrates have a stepwise mechanism through a "free" enolate anion,[13] and all but one of the other reactions summarized in Table 1 are also likely to be E1cB reactions; yet they all have the same dominant *anti* stereospecificity that is shown in E2 reactions. This forces us to reconsider the connection between concertedness and *anti* stereochemistry. Does the concerted E2 pathway produce *anti* stereospecificity or does some other factor produce it, perhaps the same factor that produces the *anti* stereochemistry in E1cB reactions? Of course E2 reactions are associated with *anti* stereochemistry when aggregation and complex conformational factors are

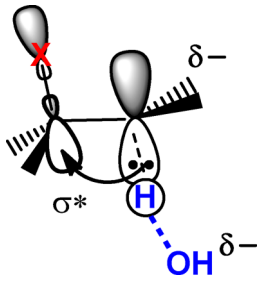


FIGURE 1. Activation of the *anti* proton by negative hyperconjugation.

not present, but now we know that some E1cB reactions also are associated with *anti* stereochemistry. There is a fundamental difference between the correlation of an E2 pathway and *anti* stereochemistry and suggesting that the concerted bond breaking and making in the E2 pathway causes the *anti* stereospecificity. The origin of *anti* stereospecificity in E2 and E1cB reactions is a question that bears consideration by computational chemists using liquid-phase calculations.[15]

A likely cause of the *anti* stereospecificity for the reactions in Table 1 is negative hyperconjugation, where electron transfer occurs from an antiperiplanar σ_{C-H} bond to the vacant σ^*_{C-O} orbital at the adjacent carbon, producing a lowering of the total energy as the result of interaction between the filled donor orbital and the unfilled acceptor orbital.[19] Other examples of antiperiplanar acceptors assisting in bond making and breaking have appeared recently.[20] The interaction of the α-C–H bond with a σ^*_{C-O} orbital activates proton removal as shown in Figure 1, a depiction of the transition state for C–H bond breaking in base-catalyzed E1cB pathways.[13]

Carbon–oxygen bonds have relatively low-lying antibonding σ^*-orbitals, which are capable of accepting electrons from σ-bonds at adjacent carbon atoms. A σ^*-orbital of a C–O bond is an excellent electron acceptor at the carbon end but a poor acceptor at the oxygen end.[20a] This accounts for the importance of the antiperiplanar transition states in 1,2-elimination reactions. Greater electron withdrawal at the oxygen functional group also seems to produce greater polarization of a σ^*_{C-O} orbital toward carbon, which increases its acceptor properties.[21] As the α-C–H bond breaks, the developing electron density makes the σ_{C-H} orbital a good electron donor.

The hyperconjugative interaction of these antiperiplanar orbitals results in C–O bond elongation and C–C bond shortening.[22] We observed these bond length attributes in a solution computational study of the elimination pathways of the methyl esters of 3-acetoxybutanoate, 3-acetoxybutanethioate, and 3-tosyloxybutanethioate.[15] The β-C–O

SCHEME 5

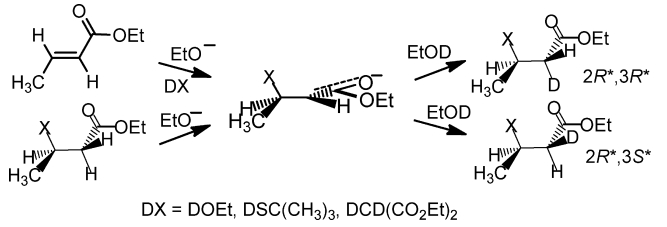


TABLE 2. Stereoselection of H/D Exchange on β-Substituted Ethyl Butanoates

X	% *anti* deuteration (±2%)
OEt, OPh, O*t*-Bu, OMe, S*t*-Bu, CMe_3	89
CF_3	83
$CH(CO_2Et)_2$, Ph, CN	77
$CHMe_2$, CH_2CMe_3	69
CH_2Me	59

bond lengths of the intermediate enolate anions compared to the substrates increase by 0.03−0.08 Å, and the α,β-C−C bond lengths decrease by 0.04−0.05 Å. During gas-phase geometry optimizations of anions where β-C−X is a very good leaving group, such as Cl, the anions can undergo barrierless elimination with the formation of an alkene, showing how a strong hyperconjugative interaction can be "transformed" into a chemical reaction.[21]

Both E2 and E1cB transition states in solution could be stabilized by negative hyperconjugation.[23] This kind of donor−acceptor interaction has been cited as a possible factor in the *anti* stereospecificity of E2 elimination reactions.[2b]

Diastereoselectivity of Enolate Anion Protonation in EtOD

As we investigated the stereospecificity of 1,2-elimination reactions, we were also studying the stereochemistry of base-catalyzed 1,4-conjugate addition. The addition of EtOD to ethyl 2-butenoate produces 89−91% of the 2*R**,3*R** diastereomer of ethyl 3-ethoxy-2-$^2H_1$-butanoate, which is the product of an *anti* addition. This is the same percentage that we obtained in the ethoxide-catalyzed H/D exchange of ethyl 3-ethoxybutanoate in EtOD (Scheme 5). In fact, all of our experimental evidence demonstrates that the diastereoselection of nucleophilic conjugate addition and base-catalyzed H/D exchange result from the protonation of the enolate-anion intermediate and is dependent on the product's β-substituent (Table 2).[24] All of the β-substituents shown in Table 2 are such poor nucleofuges that H/D exchange dominates.

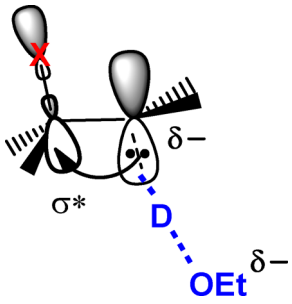


FIGURE 2. Transition state for *anti* deuteration stabilized by negative hyperconjugation.

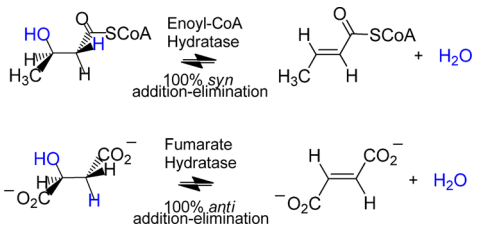
The pattern shown in Table 2 indicates that high diastereoselection leading to the *anti*-deuteration product is determined largely by electronic effects, contrary to the conclusions of Fleming, who stressed the importance of steric effects and suggested that oxygen substituents might be more or less orthogonal rather than periplanar to a bond developing to an electrophile.[25] Except for high stereoselection with a bulky β-*tert*-butyl group, only electronegative β-substituents gave the highest diastereoselectivity. To be sure, the steric effects of other alkyl groups also lead to an excess of *anti*-deuteration, but their effects are smaller. A likely explanation for the high diastereoselection when electronegative β-alkoxy and thioalkoxy substituents are present is the interaction of the electron-rich π-system of the enolate-anion intermediate with the σ^* orbital of the anti-periplanar C−X bond, which will have a substantial amplitude at the β-carbon atom. This electron donation by negative hyperconjugation can stabilize the transition state for *anti* protonation, as shown in Figure 2.[20]

Thus, negative hyperconjugation is the likely stereoelectronic determinant for both *anti* E1cB stereospecificity in the elimination reactions of acyclic carbonyl compounds and for *anti* deuteration in the H/D exchange of β-substituted acyclic esters.

Stereochemistry of Hydratase-Dehydratase Enzymes

Now we can return to the question that was the motivation for our entire research program: Why does the addition−elimination of water, catalyzed by enoyl-CoA hydratase, have *syn* stereospecificity? There are two stereochemical classes of the hydratase-dehydratase enzymes that play fundamental roles in many metabolic pathways. Those that catalyze the addition of water to α,β-unsaturated thioesters, including enoyl-CoA hydratase and seven other enzymes, give *syn* addition−elimination, whereas those that catalyze the addition of water to conjugated carboxylate substrates,

including fumarate hydratase and six other enzymes, proceed with *anti* stereospecificity (eq 2).[4a,26] If these stereospecificities exist because of mechanistic efficiency, it has been suggested that the acidity of the proton attached to the α-carbon might influence which is the most efficient pathway.[4a,26,27]



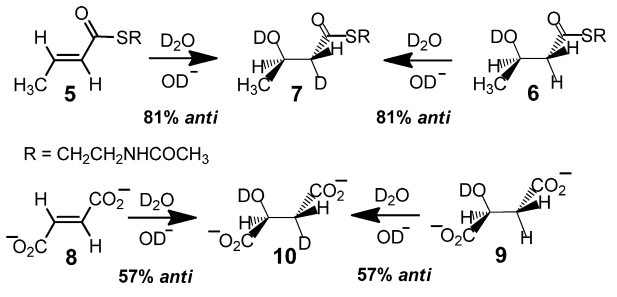
(2)

Determination of the nonenzymatic stereochemistry of the KOD-catalyzed addition of D_2O to *S*-crotonyl *N*-acetylcysteamine (**5**) and to fumarate (**8**), as well as H/D exchange at the prochiral center of the β-hydroxy substrates, **6** and **9**, demonstrated that historical contingency in enzyme evolution, rather than mechanistic efficiency, was responsible for the observed enzymatic stereospecificities (Scheme 6).[28] The argument that mechanistic efficiency is a determining factor in the evolution of the enzymatic mechanisms is belied by the fact that **8**, which is converted to malate with *anti* stereospecificity by fumarate hydratase, gives substantially less *anti* stereoselectivity in simple base-catalyzed conjugate addition than **5**, which proceeds by *syn* addition under enoyl-CoA hydratase catalysis.[28]

Two years after our results were reported, Gerlt demonstrated that glucarate dehydratase catalyzes with equal facility the dehydration of D-glucarate and its stereoisomer D-idarate by a *syn* β-elimination with D-glucarate and an *anti* elimination with L-idarate. These results revealed that a chemical imperative based on the pK_a's of the α-proton of the carboxylate ion substrate has not dominated the evolution of the mechanisms for these β-elimination reactions.[29]

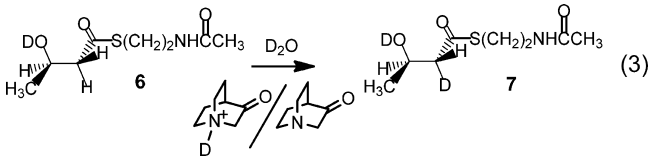
The important discovery of distinct enzyme superfamilies, where enzymes within a superfamily possess common sequence motifs and key active site residues, has placed the importance of historical contingency in the evolution of enzymatic catalysis on a sound basis.[30] In turn, the rapid growth of protein structural data has strengthened the identification of protein superfamilies.[31] We now know that all of the enzymes that produce *syn* addition−elimination of H_2O are in the enoyl-CoA hydratase superfamily and all those that produce *anti* addition−elimination are in the aspartase/fumarase superfamily.[32,33] For the enoyl-CoA hydratase superfamily there is divergent evolution with conservation of an oxyanion hole that stabilizes an enolate anion. For the aspartase/fumarase superfamily there is an active site that stabilizes an *aci*-carboxylate intermediate. It seems clear that although enzymatic catalysis is tremendously efficient, not all enzymes have necessarily reached catalytic perfection.

SCHEME 6



Effect of Buffer Catalysis on Diastereoselectivity of H/D Exchange in D_2O

Determination of the stereospecificities of the KOD-catalyzed conjugate addition of D_2O to *S*-crotonyl *N*-acetylcysteamine (**5**) and H/D exchange at the prochiral center of 3-hydroxybutyryl *N*-acetylcysteamine (**6**) had been carried out in a highly alkaline solution of 0.005−0.5 *M* KOD,[28] whereas the enzymatic studies were done at pH 7−8. In order to ensure that the lower pH would not affect the stereospecificity, we decided to study the H/D exchange of **6** using buffers at a lower pH (eq 3). To my surprise the H/D exchange at pD ∼ 8.6 using a 0.33 *M* 3-quinuclidinone buffer gave 44% *anti*-deuteration, that is 44% of the 2*R**,3*R** diastereomer **7**. The KOD-catalyzed H/D exchange had produced 81% *anti* deuteration.



(3)

This kind of effect had only been reported once before in aqueous solution.[34] In order to discover what was causing this unexpected phenomenon, we studied five buffer systems, each of which has a pK_a of 7.2−8.5, as shown in Table 3.[35]

At lower buffer concentration, the percentage of *anti* product increased, whereas at higher concentration it decreased. The diastereospecificity is produced by the competition of D_2O and the buffer general acid as the deuteron donor, but the data set was too limited to assign with

TABLE 3. Stereospecificity of H/D Exchange of **6** in 0.33 M Buffers

Buffer General Acids	pK_a	pD	% *anti* Product (**7**)
None		12–13	81
HEPES	7.5	8.4	39
3-Quinuclidinone	7.5	8.6	44
Phosphate	7.2	8.0	60
Tris	8.2	8.0	76
4-Hydroxybenzenesulfonate	8.5	9.2	86

confidence an absolute stereospecificity to any of the buffers.

The most dramatic stereochemical changes were produced by HEPES and 3-quinuclidinone buffers, whose general acids have greater steric demands at the tertiary ammonium sites where the labile deuteron is attached. They also have stronger conjugate acids and are presumably stronger hydrogen-bond donors. The buffer with the weakest general acid, 4-hydroxybenzenesulfonate, actually produced a modest increase in the percentage of *anti* deuteration.

The kinetic data of Aymes and Richard have shown that there is a chemical barrier to the transfer of a deuteron within the ion pair $BD^+ \cdot {}^-CH_2COSEt$ in the H/D exchange of ethyl thioacetate in the presence of 3-quinuclidinone buffers.[36] Formation of the ion-pair encounter complex and subsequent slow deuteron transfer from the buffer general acid offer an adequate opportunity for different stereospecificities with different buffers.

Before observing the effect of buffers, we had always been able to interpret the diastereoselectivity of H/D exchange in EtOD and D_2O using electronic and steric factors pertaining to the substrate. However, in the presence of a buffer the transfer of a deuteron to carbon can also depend on the recognition motif in the enolate/buffer acid encounter complex. Perhaps the only surprise is that the effect occurs in water solution, not in less polar organic solvents where the effect of aggregation phenomena on stereochemistry is not uncommon.

Two possible causes for the differing stereochemical outcomes in the presence of a buffer are hydrogen bonding and steric effects. It is not unlikely that hydrogen bonding is responsible, where the buffer general acid is the hydrogen-bond donor and the β-hydroxyl group is the acceptor, thus

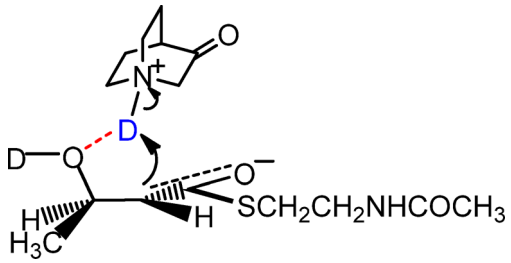


FIGURE 3. Hydrogen bonding in a $BD^+ \cdot$enolate encounter complex that leads to *syn* deuteration.

favoring *syn* deuteration (Figure 3). In retrospect, it should not be surprising that hydrogen bonding, which can be so important at enzyme active sites, can also be important within ion-pair encounter complexes in nonenzymatic reactions. However, it should be pointed out that *syn* addition–elimination is favored by greater than 8 kcal/mol at the active site of enoyl-CoA hydratase,[37] whereas the energy differences we have observed between the diastereotopic transition states are much smaller, generally less than 1 kcal/mol.

This hydrogen-bond model, which in general produces greater *syn* deuteration, may have implications for the mechanism of the *syn* addition–elimination of water that is catalyzed by enoyl-CoA hydratase. One factor that has been cited in favor of a concerted rather than a stepwise mechanism of water in the enzymatic reaction is the 81% *anti* addition of D_2O to **5** that we observed with KOD catalysis.[38] Now that we have shown the potential importance of hydrogen bonding on the stereospecificity of proton transfer, it is clear that the nonenzymatic stereospecificity is consistent with either a concerted or stepwise mechanism for the enoyl CoA-hydratase reaction.

To probe the generality of a buffer's ability to affect the stereospecificity of H/D exchange, we also studied the deuteration in D_2O of a simple acyclic ester, ethyl 3-methoxybutanoate (**11**). Our earlier research had shown that H/D exchange of **11** using D_2O/OD^- produced 93–94% *anti* deuteration.[39] However, 0.33 M 3-quinuclidinone buffer at pD 8.9–9.6 gave 60% *anti* deuteration and 0.45 M 3-quinuclidinone buffer produced 54%. A buffer's effect on the stereospecificity of H/D exchange of acyclic carbonyl compounds seems to be a general phenomenon.

Unlike a β-methoxy group, a hydroxyl group is not only able to act as a hydrogen-bond acceptor but also as a hydrogen bond donor, where OD^- is the acceptor, as shown in Figure 4. This could account for the greater percentage of *syn* deuteration of ethyl 3-hydroxybutanoate in D_2O (15%) than that seen with ethyl 3-methoxybutanoate (6–7%).[39]

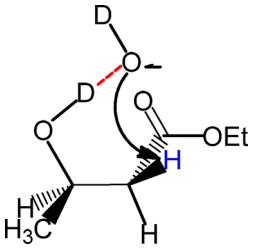
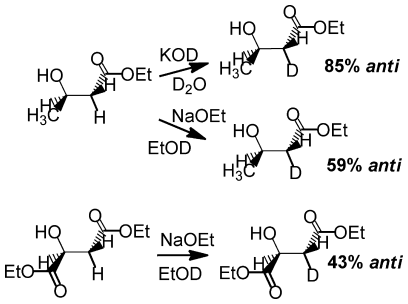


FIGURE 4. Hydrogen bonding with ethyl 3-hydroxybutanoate and OD^- that leads to abstraction of the *syn* proton.

SCHEME 7



The Malate System

Although high *anti* stereoselectivity is the norm for base-catalyzed H/D exchange with butanoate derivatives having electron withdrawing β-substituents, for many years it was a puzzle why the fumarate-malate system shown in Scheme 6 gave such low stereoselection. The base-catalyzed H/D exchange of malate **9** with KOD/D_2O to produce **10** gives only 57% *anti* deuteration, whereas the H/D exchange of 3-hydroxybutyryl *N*-acetylcysteamine **6** gives 81%. It was difficult to understand how negative charge or steric effects, produced by the replacement of a methyl substituent with a carboxylate group, could account for such a change. It was only after we understood the role of negative hyperconjugation that the stereospecificity of malate substrates could be understood. Comparative data for the H/D exchange of ethyl 3-hydroxybutanoate and diethyl malate are shown in Scheme 7.[39,40]

The H/D exchange of both diethyl malate and ethyl 3-hydroxybutanoate have low stereospecificity in EtOD/NaOEt, with diethyl malate even having a modest preference for *syn* deuteration. Part of the *syn* preference in the case of diethyl malate may come from the competition of the σ^* orbitals of the β-C$-$OH and β-C$-CO_2$Et bonds for interaction with the σ_{C-H} donor orbital. The β-CO_2Et group is more electronegative than the $\beta-$OH group as judged by their σ_I values.[41] Therefore, the β-CO_2Et group could compete favorably with the $\beta-$OH group in negative hyperconjugation overlap and produce a greater amount of *syn* deuteration. The β-carboxylate group of malate is also electronegative; thus, the β-C$-CO_2^-$ σ^*-orbital could possibly participate in $\sigma^*-\sigma_{C-H}$ overlap, which would also lead to greater *syn* stereospecificity. In order to evaluate this hypothesis, the acceptor characteristics of the relevant σ^*_{C-X} orbitals will need to confirmed by computational methods.

The hydrogen-bonding effect is also apparent in the different stereoselection between H/D exchange experiments in D_2O and EtOD. Hydrogen bonding between EtO^- and the C-3 hydroxyl group is more important in EtOD than the OD^-/C-3 hydroxyl group interaction is in D_2O. Thus, the transition state for *syn* deuteration in EtOD is stabilized to a greater degree.[35]

Conclusion

In order to understand the electronic factors that determine the stereospecificity of 1,2-elimination and proton-transfer reactions, we have studied acyclic carbonyl compounds under conditions where aggregation is not important. We have shown that contrary to earlier suggestions activation by a carbonyl group has little influence on the stereochemistry of base-catalyzed E1cB reactions. Electronic effects, likely through negative hyperconjugation, produce *anti* elimination in E1cB pathways and *anti* protonation of enolate anions. Hydrogen bonding can also be an important influence on the stereospecificity of proton transfer in hydroxylic solvents.

The research reported in this Account was carried out almost entirely by undergraduates at Carleton College. Involvement in significant research is an important part of any undergraduate chemistry curriculum and mechanistic studies in particular are ideal for crafting research projects for individual students. Undergraduate research offers outstanding mentoring opportunities and provides students with a first-hand view of the process of science.

I gratefully acknowledge my many talented undergraduate colleagues, who over 27 years performed the experimental studies that are described in this Account. We acknowledge generous research funding that came from many sources, chiefly from the National Science Foundation, the National Institutes of Health, the Research Corporation, the Petroleum Research Fund, administered by the American Chemical Society, and the Howard Hughes Medical Institute.

BIOGRAPHICAL INFORMATION

Jerry Mohrig received his B.S. in Chemistry from the University of Michigan in 1957 and his Ph.D. from the University of Colorado in 1963 under the mentorship of Stanley Cristol. After teaching for 3 years at Hope College, he joined the faculty at Carleton College in

1967, retiring in 2003. After his early research on the chemistry of alkanediazonium ions, the stereochemistry of elimination and proton-transfer reactions became the focus of his research program. He was also deeply engaged in chemical education, developing many experiments for the undergraduate organic laboratory, most recently of a guided-inquiry nature, serving on the ACS Committee on Professional Training and as a founding member of the Council on Undergraduate Research. He was awarded the Catalyst Award in 1978 from the Chemical Manufacturers Association, the James Flack Norris Award for Achievement in the Teaching of Chemistry from the Northeastern Section of the ACS in 1989, and the Brasted Award of the Minnesota Section of the ACS for Excellence in Teaching Chemistry in 2008.

FOOTNOTES

The authors declare no competing financial interest.

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