Diastereoselectivity in the Protonation of Ester Enolates. The Importance of Aggregation with LDA

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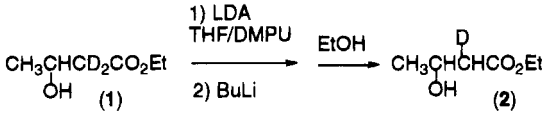
The effect of aggregation on the stereochemistry of electrophilic attack on ester enolate anions has been studied by comparing the diastereoselectivity of protonation of the LDA-generated dianion of **1** in THF/DMPU with the H/D exchange of **3** under non-ion-pairing conditions. The LDA results are consistent with proton transfer to the enolate occurring preferentially from the tightly complexed secondary amine. Proton sources of varying steric requirements produced the same diastereomeric ratio, 63:37 2*R**,3*R**/2*R**,3*S** of **2**. Added BuLi and the omission of DMPU gave the same diastereomeric mixture. In contrast to the LDA results, ethyl β-hydroxy- and β-alkoxybutyrates undergo base-catalyzed H/D exchange largely through antiperiplanar transition states, with diastereoselectivity opposite of that found in the LDA–enolate protonation. Thus, the geometry of the LDA–enolate aggregate, rather than steric and electronic factors in the monomer, is responsible for the stereochemistry of enolate anion protonation. The lower diastereoselectivity in the H/D exchange of **6** in THF is accounted for by ion-pairing effects, as the use of Me_4NOD produced 92% of the 2*R**,3*R** diastereomer. Use of polar solvents in the H/D exchange also raised the diastereoselectivity to a 10:1 ratio or higher.

Stereocontrol in the reactions of acyclic compounds continues to be a major goal of synthetic organic chemistry, and the chemistry of enolate anions has occupied an important part of this effort.[1,2] The generation of enolates with lithium diisopropylamide (LDA), in particular, has provided a powerful and popular methodology. Yet the mechanisms of the reactions of electrophiles with lithium enolates are complex and often ambiguous.[3–6] As part of our studies on the stereochemistry of proton-transfer reactions,[7] we have investigated the protonation of the ester enolate of ethyl 3-hydroxy[2,2-$^2H_2$]butanoate (**1**), as well as solvent effects on the H/D exchange of a variety of β-substituted butyrates, in order to ascertain the effect of aggregation on the stereochemistry of proton transfer.



In addition to the inherent mechanistic interest of this study, we were attracted by the high diastereoselectivities observed in the alkylation of LDA-generated acyclic ester enolates,[8,9] thinking that perhaps this methodology could be applied to the synthesis of stereospecifically deuterated substrates necessary for our studies of elimination reactions of β-substituted esters and thioesters.[10] However, in the attempted synthesis of ethyl 3-hydroxy-[2-$^2H_1$]butanoate (**2**) by deuteration of the dianion of ethyl β-hydroxybutyrate (**3**), we observed the same incomplete deuteration that has been reported previously.[11,12] Approximately 30% of one deuteron was incorporated at the α-position of **2** by reaction of the dianion with ethanol-*d*. Seebach has suggested that this occurs because the external electrophile transfers its deuteron first to the R_2NH species within the aggregate, before it is transferred to the enolate itself, a kind of "conducted-tour" mechanism.[3] He has shown that using BuLi to remove this NH proton leads to completely deuterated product. However, in the case of enantioselective protonation of lithium enolates, it has been suggested that proton transfer occurs directly from the chiral acid to the enolate.[13]

It is well-known that aggregation can dramatically affect chemical reactivity, even though the causal connection is not always clear-cut.[6,14] The possible roles of aggregated, supramolecular species in the chemical behavior of lithium enolates have been cited by many authors.[3,15] In view of the ambiguity of mechanistic details in the reactions of lithium enolates, it is important to ascertain how the aggregate affects stereochemistry.[2] If the bound R_2NH provides the direct transfer of the proton to the ester dianion, does this also control the

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Table 1. Diastereoselectivity and Protium Incorporation from Reaction of Various Alcohols and 4 with the Lithium Enolate of Ethyl 3-Hydroxy[2,2-$^2H_2$]butanoate (1) in 5:2 THF/DMPU

proton source (no.of reactions)	% H incorporation	% 2*R**,3*R** product	added BuLi
EtOH (5)	52	64.6 ± 2.2	no
EtOH (3)	100	64.5 ± 0.8	yes
EtOH (1), no DMPU	57	65.8	no
Et_3COH (2)	51	59.7 ± 0.4	no
Et_3COH (1)	106	62.6	yes
$(C_6H_{11})_3COH$ (2)	33	63.8 ± 2.1	no
$(C_6H_{11})_3COH$ (1)	105	61.9	yes
4 (6)	58	60.7 ± 1.9	no
4 (2)	95	62.6 ± 0.2	yes

diastereoselectivity of the protonation? We decided to investigate this question by determining the diastereoselectivity of protonation of the LDA-generated dianion of **1** with proton donors of various steric requirements and comparing the results with base-catalyzed H/D exchange under nonaggregating conditions.

Results and Discussion

Substrate **1** was readily obtainable by sodium borohydride reduction of ethyl acetoacetate deuterated at C-2 (≥98%). Reaction of 2.2 mol of LDA with **1** in THF/DMPU (1,3-dimethyl-2-oxohexahydropyrimidine)[16] at −78 °C, followed by addition of EtOH at −50 °C, gave only 52% protonation. The transfer of a proton to the enolate was not complete even though the H/D ratio available for proton transfer was 1:1 in the reaction mixture; this lends further credence to Seebach's suggestion that incomplete electrophilic transfer of a deuteron cannot be due to an abnormally large kinetic isotope effect. With the addition of 2 mol of BuLi, to completely remove the deuteron from the bound R_2ND in the aggregate, the reaction of the ester enolate with EtOH gave 100% (±5%) of **2**. In no case was there evidence of diprotonation if the reaction mixture was quenched below −10 °C; use of aqueous H_2SO_4 or D_2SO_4 as quenching agents gave the same deuterium content in **2**.

Table 1 shows the stereochemistry in the protonation of the lithium enolate dianion of **1** with a variety of proton sources of varying steric bulk. Although the percentage of protium incorporation varies widely in these reactions, the ratio of the two diastereomers of **2** is remarkably constant, even with substantial changes in the steric requirements of the electrophilic proton donor. The percentage of the 2*R**,3*R** diastereomer of **2** is 62.8 ± 1.7% over the range from ethanol to 2,2,6,6-tetramethylpiperidinium *p*-toluenesulfonate (**4**); the error is within the limits of our NMR integration precision. In two quite different systems, the protonation of β-silyl ester enolates[4] and the enolate of methyl 4-*tert*-butylcyclohexanecarboxylate,[6] relatively small changes in the diastereoselectivity have been observed when the protonating agent was varied.

Given the lack of information on the structure of LDA–ester enolate complexes, it was difficult to predict how the use of BuLi to deprotonate the amine would affect the structure and properties of the aggregate.[3] However, the results of Table 1 clearly show that the stereochemistry of electrophilic transfer to the enolate carbon is not affected by removal of the deuteron on nitrogen. There is a 63:37 ratio of the 2*R**,3*R**/2*R**,3*S** diastereomers of **2** produced with or without the addition of BuLi. In order to verify this stereochemical preference, a deuteration experiment was carried out using EtOD and nondeuterated **3**, along with the addition of BuLi. Deuteration was complete, yielding 39% 2*R**,3*R** and 61% 2*R**,3*S** **2**. Thus, there is virtually the same preference for the stereochemistry of electrophilic attack on the enolates involved in protonation and deuteration. In addition, the presence of the polar aprotic solvent DMPU does not change the diastereoselectivity. If DMPU converts the trans enolate to the cis enolate within the aggregate, both enolate geometries produce the same diastereoselectivity upon protonation.[16-18] This is consistent with the alkylation of *E* and *Z* β-silyl ester enolates, which also give the same products in the same ratio.[4]

The configurational assignments for **2** were made unambiguously through NMR correlation with the known (2*R**,3*R**)-3-hydroxy[2-$^2H_1$]butanoic acid, whose relative configurations at C-2 and C-3 had been proven earlier by stereospecific synthesis.[19,20] Reaction of its conjugate base with iodoethane in DMPU gave **2** with the C-2 deuteron at δ 2.10 ppm (C_6D_6 = δ 7.15). The two diastereotopic protons at C-2 are separated by 0.12 ppm in benzene; in the 2*R**,3*S** isomer, the C-2 deuteron is at δ 2.22, easily separable by ^1H NMR.

The protonation of the ester enolate of **1** is not highly diastereoselective, much less so than its selectivity in alkylation which is approximately 97:3 2*R**,3*R**/2*R**,3*S**.[8] It is interesting to note that, in this case, the preferred electrophilic attack of a proton is opposite to that of alkylation. There are a number of systems in which alkylation and protonation occur from the same face of an ester enolate, even though alkylation is almost always more diastereoselective.[4,12] However, these have not involved dianions. Presumably, the diastereoselectivity of protonation is dictated largely by the structural requirements within the aggregate, in particular the relative orientation of the lithium enolate and the ligand which transfers the proton to it.

With little precise information available on the structures of ester enolate dianions produced with LDA, one can only speculate on what produces this diastereoselectivity, but it is not unreasonable that the R_2NH is complexed to a lithium cation also coordinated to both oxygen atoms of the enolate.[21] The coordinated amine or another coordinated ligand could then transfer a proton to produce preferentially the favored 2*R**,3*R** diastereomer of **2**. This seems entirely consistent with Seebach's suggestion of preferred internal return of the H-bonded proton attached to the secondary amine. Of course, within the aggregate, it is entirely possible that the proton is shuttled from a ligand coordinated to another nearby lithium. In combination with more precise X-ray and NMR structural results, this could be an important observation in understanding stereocontrol in LDA–enolate complexes.

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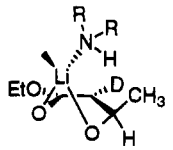
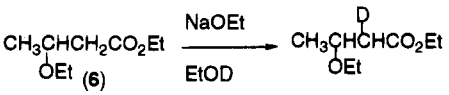


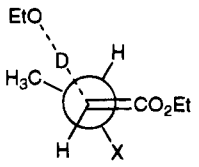
Figure 1.

When LDA is used to generate the enolate of **1**, we have seen that the geometry of the lithium–enolate aggregate controls the diastereoselectivity of protonation and that there is a small stereochemical preference for syn electrophilic attack of the enolate with respect to the hydroxyl substituent at C-3. By contrast, we earlier observed a 91:9 ratio of 2*R**,3*R**/2*R**,3*S** diastereomers in the H/D exchange of ethyl β-ethoxybutyrate (**6**) with NaOEt/EtOD under non-ion-pairing conditions, showing a clear preference for antiperiplanar electrophilic attack.[7]



Is there also different diastereoselectivity for protonation of the enolate of **3** under nonaggregating conditions? This is an important question in that the diastereoselectivities observed in reactions of aggregated substrates are often rationalized in terms of more simple structures. In nucleophilic addition to aldehydes and ketones, as well as in alkylation of β-hydroxy lactone dianions, polar groups that allow for the formation of stable chelates strongly influence diastereoselection.[2,22] Does chelation also change the stereochemistry of enolate protonation? To help answer these questions, we have used a variety of solvents for the base-catalyzed H/D exchange of butyrate esters with heteroatoms substituted at the β-position. The results are compiled in Table 2.

The result of every experiment in Table 2 demonstrates the dominant antiperiplanar electrophilic attack on ester enolate anions that we reported earlier. With oxygen substituents at the C-3 stereocenter, the diastereoselectivity seems to result from an electronic stabilization of the antiperiplanar transition state, with the larger methyl group occupying the "outside" position away from C-1 of the enolate in order to avoid the allylic 1,3-strain between the "inside" group and the groups syn to it on the enolate double bond.[4,7]



Deuteration of **3** in NaOEt/EtOD produces a 59:41 2*R**,3*R**/2*R**,3*S** ratio, a much lower diastereoselectivity than that observed with **5** and **6** under the same reaction conditions. It looks as if the conformational population of the enolate of **3** is perturbed by H bonding of the hydroxyl group with the enolate moiety. Intramolecular H bonding perturbs the diastereoselectivity in water to a far smaller extent, and deuteration of **3** in KOD/D_2O produces 85% of the 2*R**,3*R** isomer, not far from that produced from **5** in EtOD. The limited solubility of **6** in water precludes a direct comparison with **3**; however, **5** is quite water-soluble. In EtOD, a β-methoxy group is not quite as effective as β ethoxy in producing antiperiplanar electrophilic attack on the enolate, although the difference is close to our NMR integration limits; in D_2O, there is a small but real increase in diastereoselectivity in the H/D exchange of **5**.

Table 2. Diastereoselectivity of Base-Catalyzed H/D Exchange at the α-Position of β-Substituted Butyrates[a]

substrate	% 2*R**,3*R** product	solvent
ethyl β-hydroxybutyrate (**3**)	59	EtOD
	85	D_2O (KOD)
ethyl β-methoxybutyrate (**5**)	87	EtOD
	94	D_2O (KOD)
ethyl β-ethoxybutyrate (**6**)	91	EtOD
	72	THF
	72	THF (KOEt)
	92	THF (Me_4NOD)
	93	DMF
	93	DMF (Me_4NOD)

[a] Duplicate reactions were carried out to <10% exchange with <±2% error in the 2*R**,3*R** percentage. Reactions used NaOEt unless otherwise noted.

Electrophilic protonation of the enolate anion of **3** under non-ion-pairing conditions takes place with diastereoselectivity opposite of that found in the LDA–enolate reaction of **1**. To be sure, the diastereoselectivities are low, but without question, they are opposite. This result again shows that one must be quite careful in holding steric and electronic factors in the monomer entirely responsible for the stereocontrol of electrophilic reactions within the supramolecular aggregates of LDA–ester enolates.

To further understand the role of ion pairing and chelation in the protonation of acyclic ester enolates, we investigated different solvents for the H/D exchange of **6**. There is a substantial lowering of the diastereoselectivity on moving from a more polar (EtOD and DMF) to a less polar (THF) solvent. The difference seems due entirely to ion pairing and chelation.

It is not unexpected that the diastereoselectivity would be lowered in the less polar solvent because, in THF, the Na^+ that is ion-paired with the enolate anion can also coordinate both with the β-ethoxy group and with EtOD, thereby reducing the preference for antiperiplanar deuteration. Use of the potassium cation gave the same result, but when a noncoordinating cation, NMe_4^+, was used in THF, the diastereoselectivity returned to the usual 92% 2*R**,3*R** range observed in polar solvents. There was also a monotonic increase in the diastereoselectivity of H/D exchange of **6** from 7:1 THF/EtOD to pure EtOD. Below 15% EtOD, the stereoselectivity remained constant at 72% of the 2*R**,3*R** isomer. Not surprisingly, the rates of H/D exchange in THF and DMF were substantially faster than those in EtOD.

Experimental Section

General Procedures. NMR spectra were run on 200–500 MHz spectrometers using C_6D_6 (Aldrich, 99.5 atom % D) solutions (C_6H_6 for ^2H spectra). Multiple ^1H and ^2H NMR integrations were performed for the determination of reaction diastereoselectivities. For H/D exchanges, glassware was soaked in $NaHCO_3$ solution and then rinsed with H_2O; all glassware was oven-dried. Capillary GC analyses were done on a 25 m methyl silicone column. Ethyl β-hydroxybutyrate was distilled, and tetrahydrofuran (THF) and 1,3-dimethyl-

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2-oxohexahydropyrimidine (DMPU) were distilled from CaH_2 under N_2 before use. Lithium diisopropylamide (Aldrich) and its THF solutions were handled only under N_2. Sodium ethoxide (NaOEt) in ethanol-*d* (EtOD) solutions were prepared from Na metal and stored under N_2 or Ar. Tetramethylpiperidinium *p*-toluenesulfonate (**4**) was synthesized from 2,2,6,6-tetramethylpiperidine (Aldrich) and *p*-toluenesulfonic acid monohydrate in ethyl acetate and recrystallized from EtOH/ethyl acetate, mp 218–219 °C.[23] Tetramethylammonium deuteroxide (Me_4NOD) was made by three exchanges in D_2O of $Me_4NOH \cdot 5\ H_2O$ (Aldrich). The silica gel used in chromatography was Merck Kieselgel 60, 70–230 mesh. EtOD (99+ atom % D), butyllithium (BuLi, 1.6 M in hexane), sodium borohydride ($NaBH_4$, 98+%), ethyl crotonate, methyl crotonate, *N,N*-dimethylformamide (DMF), 3-ethyl-3-pentanol (Et_3COH, 97%), and tricyclohexylmethanol ($[C_6H_{11}]_3COH$) were purchased from Aldrich and used without further purification.

Synthesis of Ethyl 3-Hydroxy[2,2-$^2H_2$]butanoate (1). Ethyl acetoacetate[2-$^2H_2$] was produced by three H/D exchanges as before,[20] giving 97% deuteration at C-2 and 12% at C-4. Reduction of the deuterated keto ester (35.2 g, 0.27 mol) was done by dropwise addition of its solution in 40 mL of EtOD over 10 min to a stirred slurry of 3.3 g of $NaBH_4$ (0.088 mol) in 80 mL of EtOD at 25 °C. After 5 h, excess $NaBH_4$ was destroyed with 5 mL of acetic acid, bringing the pH to 7. Dilution with 100 mL of brine and solid NaCl produced a clear solution, which was extracted with 4 × 80 mL of ether. The extracts were dried with $MgSO_4$ and then $CaSO_4$, and the solvent was evaporated. Separation of unreacted keto ester was done by flash chromatography on 20 g of silica per gram of **1**, using hexane/ether gradients up to 60% Et_2O. NMR integrations of vacuum-distilled **1** (80 °C at 0.1 Torr) showed ≤2% ^1H at C-2.

Protonation of the Enolate Dianion of 1. Using a N_2 glovebag, a solution of 0.10 g of **1** (0.745 mmol) in 1.0 mL of THF was added to a stirred solution of 0.176 g of LDA (1.64 mmol) in 3.0 mL of THF at −78 °C. After 40 min, a DMPU (2.0 mL)/THF (1.0 mL) solution was added. When BuLi was used, 1.0 mL of a 1.6 M solution in hexane (1.59 mmol) was added in one portion and the reaction mixture stirred for 45 min prior to the addition of the DMPU/THF mixture. The reaction mixture was stirred at approximately −50 °C for 10 min, at which time 1.64 mmol of the protonating agent was added, and it was stirred further for 45 min to 1.75 h, depending on the protonating agent. Reaction mixtures were brought to pH 7 with H_2SO_4 (6 M) or D_2SO_4 (10.5 M) at ≤−20 °C when ethanol was the protonating agent, at 0 °C for Me_3COH, and at 10 °C for tricyclohexylmethanol. The protonating agent **4** dissolved in 2.0 mL of THF or DMPU was added at 0 °C, and the reaction was quenched at rt.

The reaction mixture was diluted with 25 mL of brine and extracted with 5 × 25 mL of ether. The combined extracts were extracted four times with 25 mL of brine to remove DMPU when it was present, dried with $MgSO_4$ and $CaSO_4$, and evaporated. Pure ethyl 3-hydroxy[2-$^2H_1$]butanoate (**2**) was recovered by preparatory GC (Varian Aerograph 90-P, 8 ft × $^3/_8$ in. Carbowax 20 M column). To find the percentage of deuteration, the C-2 protons were integrated against the ester methylene quartet. In benzene, the C-2 diastereotopic protons are cleanly resolved at 200 MHz; integrations on the diastereomeric composition of **2** were done using ^2H NMR.

Synthesis of Ethyl (2*R,3*R**)-3-Hydroxy[2-$^2H_1$]butanoate.** To 0.50 g of sodium (2*R**,3*R**)-3-hydroxy[2-$^2H_1$]butanoate (4.0 mmol)[19] dissolved in 10 mL of DMPU was added 2.5 g of iodoethane (16.0 mmol). After stirring for 1.3 h, the mixture was diluted with 50 mL of brine and extracted with 5 × 25 mL of ether, and the combined extracts were washed four times with 25 mL of brine. After being dried ($MgSO_4$, then $CaSO_4$), the ether was evaporated and the product recovered by preparatory GC. The C-2 proton appeared at δ 2.22 ppm in C_6D_6 and the C-2 deuteron at δ 2.10 in C_6H_6.

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Synthesis of Ethyl 3-Methoxybutanoate (5).[24] To 100 mL of 1.2 M NaOMe in methanol was added 50 g of methyl crotonate (0.5 mol), and the mixture was refluxed for 4 h. The reaction was quenched with acid, and 50 mL of brine was added. Five extractions with 25 mL of hexane, followed by a standard workup, produced 31 g (47%) of methyl 3-methoxybutanoate, **7** (bp 148–149 °C).[25] Two transesterification reactions on 22.3 g (0.17 mol) of **7** at rt for 25 min each with 80 mL of 0.06 M NaOEt in ethanol, followed by acid quenching, addition of 50 mL of brine, five extractions with 50 mL of hexane, washing with brine, drying, and solvent removal, led to 10.6 g (43%) of **5** (bp 167–168 °C, 98% purity).

Synthesis of Ethyl 3-Ethoxybutanoate (6).[26] A 15.0 g sample of ethyl crotonate (0.13 mol) was reacted with a 0.16 M solution of NaOEt in ethanol under N_2 at rt for 3 d and neutralized with acetic acid, and the solvent was removed by evaporation. Ether and water were added to dissolve the residue which was extracted three times with ether. After brine washings, drying, and removal of the ether, **6** was distilled at 20 Torr (bp 70 °C, >99% purity).

General Method for H/D Exchanges. Using syringe techniques, exchanges of **3** and **6** were done under N_2 with 0.05 M NaOEt or KOD and 0.5 M substrate. Exchanges of **5** were done with 0.2 M substrate. To 4.0 mL of stirred solvent was added 2 mmol of the ester, and the reaction was initiated with 0.3 mL of 0.8 M base. When the reaction had proceeded to 3–10% exchange as determined by ^1H NMR, it was quenched with 0.06 mL of 2 M D_2SO_4 which brought the pH to 5–6. After quenching, the reaction mixture was chromatographed on 30 g of silica gel (ether). Upon evaporation of the ether, the typical recovery of the ester was over 80%. Reactions were carried out for 1–15 min at rt except for the exchanges of **6** in DMF which were done at −15 °C; Me_4NOD reactions were done for 5–30 s at rt. A 15 min exchange on **6** in EtOD gave incorporation of 10% of one deuteron at C-2, with the 2*R**,3*R** product at δ 2.13 ppm and the 2*R**,3*S** product at δ 2.45, while a 1 min reaction in THF gave 2% exchange. A 10 min exchange on **3** in EtOD produced 8% of one deuteron at C-2. The deuteron of the 2*R**,3*R** product from **5** was at δ 2.11, with the 2*R**,3*S** product at δ 2.43.

Exchanges in D_2O were accompanied by ester hydrolysis, which resulted in a decrease of the reaction pD to approximately 8 over 0.5–1 h for **3** and 5 h for **5**, at which time the exchanges were worked up without quenching; no chromatography was necessary as the carboxylate salt was completely removed by using anhyd K_2CO_3 as the drying agent. Before ^2H NMR analysis of **3** from H/D exchanges in D_2O, an H_2O back exchange was done to remove all of the deuterium from the hydroxyl group.

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