benzoate (5.3 min), 1-phenyl-2-methyl-1,3-pentanedione gave the following: ^{1}H NMR ($CDCl_3$) 1.0 (3 H, t), 1.4 (3 H, d), 2.4 (2 H, q), 4.4 (1 H, q), 7.2–7.5 (3 H, m), 7.85 (2 H, m), no enol seen; IR (neat) 1690, 1720 cm^{-1} (C=O).

2,4-Dimethyl-3,5-heptanedione[5] was prepared from isobutyryl chloride and diethyl ketone trimethylsilyl enol ether by procedures A and B. GC analysis of the crude product identified three components [identity (retention time)]: diethyl ketone enol isobutyrate (2.2 min), 2,4-dimethyl-3,5-heptanedione (3.7 min), dodecane (6.4 min). Spectral analysis of 2,4-dimethyl-3,5-heptanedione gave the following: ^{1}H NMR ($CDCl_3$) 3.8 and 16.5 (1 H, q and s), 2.2–3.0 (3 H, overlapping septet and quartet), 1.8 and 1.15 (3 H, s and d), 0.9–1.1 (9 H, overlapping t and d), spectrum shows keto and enol forms; IR (neat) 1700, 1725 (C=O, keto form), 1580 cm^{-1} (C=C, enol form).

4-Methyl-3,5-heptanedione[14] was prepared by methods A and B from diethyl ketone trimethylsilyl enol ether and propionyl chloride. GC analysis of the crude products showed four components [identity (retention time)]: diethyl ketone (0.8 min), diethyl ketone enol proprionate) (3.9 min), 4-methyl-3,5-heptanedione (6.7 min), undecane (10 min). Spectral analysis of 4-methyl-3,5-heptanedione gave the following: ^{1}H NMR ($CDCl_3$) 3.65 and 16.3 (1 H, q and s), 2.5 (4 H, q), 1.8 and 1.25 (3 H, s and d), 1.05 (6 H, t), spectrum shows keto and enol forms; IR (neat) 1725, 1700 (C=O, keto form), 1600 cm^{-1} (C=C, enol form).

Diethyl ketone enol propionate was prepared by both methods A and B: ^{1}H NMR ($CDCl_3$) 5.0 (1 H, q), 1.9–2.6 (4 H, m), 1.45 (3 H, d), 0.9–1.3 (6 H, m).

2,2,4-Trimethyl-3,5-heptanedione was prepared by both procedures A and B from pivaloyl chloride and diethyl ketone trimethylsilyl enol ether. GC analysis of the crude product showed four major components [identity (retention time)]: diethyl ketone (1.0 min), diethyl ketone enol trimethyl acetate (3.0 min), 2,2,4-trimethyl-3,5-heptanedione (5.2 min), dodecane (6.9 min). Spectral analysis of 2,2,4-trimethyl3,5-heptanedione gave the following: ^{1}H NMR ($CDCl_3$) 4.1 (1 H, q), 2.5 (2 H, q), 1.35 (3 H, d), 0.9–1.1 (12 H, overlapping t and s), no enol seen; IR (neat) 1700, 1725 cm^{-1}; mass spectrum, *m/e* (relative intensity), 41 (13), 57 (100), 85 (15), 86 (34), 99 (6), 114 (4), 142 (0.3), 170 (M^+, 1). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found C, 70.64; H, 10.80.

(14) House, H. O.; Gannon, W. F. *J. Org. Chem.* **1958**, *23*, 879.

Acknowledgment. We thank the National Science Foundation for partial support of this work.

Registry No. Cyclohexanone trimethylsilyl enol ether, 6651-36-1; cyclopentanone trimethylsilyl enol ether, 19980-43-9; 3-pentanone trimethylsilyl enol ether, 17510-47-3; 2,4-dimethyl-3-pentanone trimethylsilyl enol ether, 55339-64-5; isobutyrophenone trimethylsilyl enol ether, 39158-85-5; acetophenone trimethylsilyl enol ether, 13735-81-4; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 3-pentanone, 96-22-0; 2,4-dimethyl-3-pentanone, 565-80-0; acetophenone, 98-86-2; isobutyrophenone, 611-70-1; 2-acetylcyclohexanone, 874-23-7; cyclohexanone enol acetate, 1424-22-2; 2-acetylcyclopentanone, 1670-46-8; cyclopentanone enol acetate, 933-06-2; 3-methyl-2,4-hexanedione, 4220-52-4; diethyl ketone enol acetate, 13893-75-9; 3,3,5-trimethyl-2,4-hexanedione, 42412-60-2; diisopropyl ketone enol acetate, 4007-46-9; 1-phenyl-1,3-butanedione, 93-91-4; acetophenone enol acetate, 2206-94-2; 1-phenyl-2,2-dimethyl-1,3-butanedione, 3815-34-7; isobutyrophenone enol acetate, 5170-76-3; 1-phenyl-2-methyl-1,3-pentanedione, 13618-19-4; diethyl ketone enol benzoate, 13893-94-2; 2,4-dimethyl-3,5-heptanedione, 37484-68-7; diethyl ketone enol isobutyrate, 83710-44-5; 4-methyl-3,5-heptanedione, 1187-04-8; diethyl ketone enol propionate, 83710-42-3; 2,2,4-trimethyl-3,5-heptanedione, 83710-43-4; diethyl ketone enol trimethyl acetate, 83710-45-6; CH_3COCl, 75-36-5; PhCOCl, 98-88-4; CH_3CH_2COCl, 79-03-8; $(CH_3)_2CHCOCl$, 79-30-1; $(CH_3)_3CCOCl$, 3282-30-2; $ZnCl_2$, 7646-85-7; $SbCl_3$, 10025-91-9; $TiCl_4$, 7550-45-0; $SbCl_5$, 7647-18-9; $SnCl_4$, 7646-78-8; BCl_3, 10294-34-5; $FeCl_3$, 7705-08-0; $AlCl_3$, 7446-70-0.

Synthesis and Proton Nuclear Magnetic Resonance Spectra of Diastereomeric β-Hydroxy Esters. An Unusual Hydroxy to Methyl Coupling through Four σ Bonds

Jan B. Wooten and Yoram Houminer*

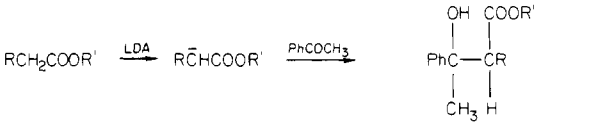
Philip Morris Research Center, Richmond, Virginia 23261

Received April 23, 1982

A series of 3-hydroxy-3-phenyl-2-alkylbutyrate esters has been prepared by the reaction of various ester enolates with acetophenone. A 1:1 mixture of diastereoisomers was obtained in each case which was conveniently separated by HPLC. The two isomers, erythro (e) or threo (t), were identified on the basis of their IR and proton NMR spectra. In $CDCl_3$ solution only the erythro isomers exhibited a 1-Hz coupling constant between the hydroxyl and geminal methyl protons. This coupling is transmitted through four σ bonds which are arranged in a "W" configuration. In Me_2SO solution, the intramolecular hydrogen bond which allows the "W" configuration is disrupted, causing coupling to disappear and the spectra of the erythro and threo isomers to become nearly equivalent.

Compounds with two adjacent asymmetric centers which exist in two diastereomeric forms have frequently been studied by NMR spectroscopy.[1] The stereochemistry of a series of diastereomeric ethyl 3-hydroxy-3-(para-substituted phenyl)butyrates has been previously determined by Balsamo et al. using careful analysis of the proton chemical shifts.[2] We have extended and generalized this early study by applying similar methods to various 3-hydroxy-3-phenyl-2-alkylbutyrate esters. In particular, we report the observation of a long-range spin–spin coupling between the protons of the methyl group and the geminal

Scheme I



1, R = CH_3; R' = CH_3
2, R = $CH_2CH_2CH_3$; R' = CH_2CH_3
3, R = $CH(CH_3)_2$; R' = CH_2CH_3

(1) Spassov, S. L. *Tetrahedron* **1969**, *25*, 3631.
(2) Balsamo, A.; Barili, P. L.; Crotti, P.; Ferretti, M.; Macchia, B.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2548.

0022-3263/82/1947-5102$01.25/0

Table I. Proton Chemical Shifts (ppm) in Several Solvents Relative to Internal Me_4Si

compd	solvent	shift a OH	b CH_3COH	c OCH_3	e CHR	f $CHCH_3$	coupling const, Hz
1t	$CDCl_3$	3.85	1.58	3.80	2.88	0.97	$J_{ab} \simeq 0$
1e	$CDCl_3$	4.05	1.49	3.50	3.05	1.34	$J_{ab} = 0.98$
1t	Me_2SO-d_6	5.05	1.50	3.48	2.76	0.92	$J_{ab} \simeq 0$
1e	Me_2SO-d_6	5.05	1.52	3.45	2.80	0.96	$J_{ab} \simeq 0$
1t	toluene-d_8	3.90	1.46	3.31	2.88	0.93	$J_{ab} \simeq 0$
1e	toluene-d_8	4.04	1.32	3.03	2.80	1.19	$J_{ab} = 0.92$

compd	solvent	shift a OH	b CH_3COH	c OCH_2CH_3	d OCH_2CH_3	e CHR	f $CH(CH_2)_2CH_3$	coupling const, Hz
2t	$CDCl_3$	3.79	1.54	4.26	1.33	2.78	0.75	$J_{ab} \simeq 0$
2e	$CDCl_3$	3.98	1.49	3.88	0.89	2.88	0.95	$J_{ab} = 0.98$
2t	Me_2SO-d_6	5.11	1.51	3.94	0.99	*a*	0.78	$J_{ab} \simeq 0$
2e	Me_2SO-d_6	5.04	1.52	3.93	1.02	*a*	0.75	$J_{ab} \simeq 0$

compd	solvent	shift a OH	b CH_3COH	c OCH_2CH_3	d OCH_2CH_3	e CHR	f $CH(CH_3)_2$	coupling, const, Hz
3t	$CDCl_3$	4.33	1.55	4.33	1.36	2.76	0.92, 0.71	$J_{ab} \simeq 0$
3e	$CDCl_3$	4.39	1.53	3.92	0.94	2.88	1.12, 1.10	$J_{ab} = 1.10$
3t	Me_2SO-d_6	4.88	1.54	3.906,[b] 3.909[b]	1.02	2.57	0.85, 0.84	$J_{ab} \simeq 0$
3e	Me_2SO-d_6	4.88	1.55	3.917,[b] 3.926[b]	1.02	2.71	0.84, 0.80	$J_{ab} \simeq 0$
3t	toluene-d_8	4.49	1.51	4.01	1.03	2.70	1.03, 0.70	$J_{ab} \simeq 0$
3e	toluene-d_8	4.51	1.45	3.605,[b] 3.593	0.64	2.81	1.14, 1.04	$J_{ab} = 1.10$

[a] Partially obscured by solvent. [b] In some solvents the methylene quartet was doubled due to a slight nonequivalence between the two protons.

hydroxy group proton which occur in the NMR spectra of these β-hydroxy esters. This four-bond coupling may prove to be a valuable tool in making stereochemical assignments in similar systems.

Results and Discussion

Synthesis and Stereochemical Assignments of β-Hydroxy Esters. The β-hydroxy esters were easily prepared by reacting the appropriate ester enolate with acetophenone (Scheme I). In each case an approximately 1:1 mixture of diastereoisomers was obtained (regardless of the size of R or R′) which were easily separated by high-pressure liquid chromatography. The two isomers were designated either e (erythro) or t (threo), depending on their stereochemical assignment which will be discussed in detail below. The e and t structures are shown in Figure 1 and correspond to the erythro and threo isomers, respectively.[3] Compounds **1–3** were analyzed by proton NMR in different solvents, and the chemical shifts are reported in Table I with the exception of the phenyl group which appeared as broad multiplets having similar chemical shifts.

Each diastereoisomer can exist in three different conformations as shown in Figure 1. It is reasonable to expect that the most stable conformation in both isomers is the one that permits intramolecular hydrogen bonding, unless nonbonded interactions preclude it. Before an attempt was made to make the stereochemical assignments, it was first established by IR spectroscopy that hydrogen bonding exists in **1–3**. For example, both **2e** and **2t** in CCl_4 exhibit hydroxyl absorptions at 3500 and 3520 cm^{-1}, which do not shift with dilution. These frequencies are characteristic in general for acyclic β-hydroxy esters which form internal hydrogen bonds predominantly between the hydroxy group and the ester carbonyl group.[4] Our IR data show the same shifts in absorption frequencies from the values for free hydroxyl and carbonyls, thus indicating hydrogen bonding in **1–3**. On the basis of these data, conformation e-II and t-III are ruled out since in both cases the hydroxyl group

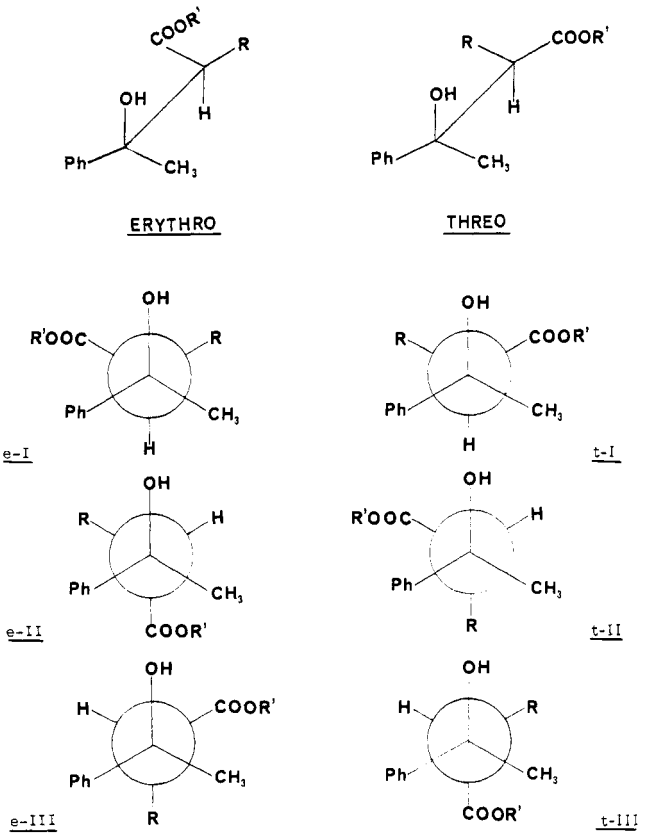


Figure 1. Erythro and threo conformations of 1–3.

(3) The erythro isomer is the one in which the two oxygen functionalities (OH and COOR′) and the two alkyl groups (CH_3 and R) are both cis. This definition makes the stereochemical assignment of **1–3** consistent with the convention used in ref 2.

(4) Aaron, H. S. *Top. Stereochem.* **1979**, *11*, 1–52.

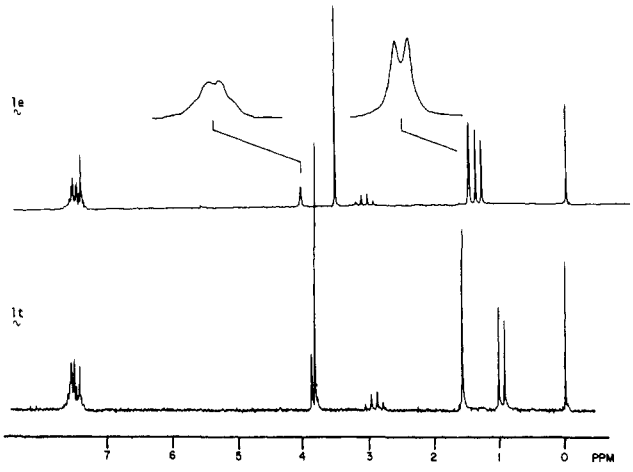


Figure 2. 80-MHz NMR spectra of **1e** and **1t** in $CDCl_3$.

and ester group are trans which does not permit hydrogen bonding. The preferred conformation must then be either I or III in the case of the erythro isomers, and either I or II in the case of the threo isomers.

The chemical shifts are very useful in the stereochemical determination as will be demonstrated for the case of **1**. Only data obtained from $CDCl_3$ solutions were employed for this purpose since this solvent does not exhibit unusual solvent effects on the chemical shifts. The chemical shift of the ester methyl group of the **1t** isomer occurs at 3.8 ppm, which is a typical shift value for methyl esters. The same group of **1e**, however, is shielded, and its resonance appears at 3.5 ppm. Similarly, the $CHCH_3$ methyl group of **1t** is strongly shielded compared to the same methyl group in **1e** (column f in Table I and also Figure 2). These data strongly suggest that both the **1e** and **1t** isomers exist predominately in the e-I and t-I conformations, respectively. In e-I, the ester group is cis to the phenyl group and therefore is strongly shielded whereas the $CHCH_3$ methyl group is trans and therefore is not affected by interaction with the phenyl group. In t-I the ester group is now trans to the phenyl group, and its chemical shift is not influenced by that group, and the $CHCH_3$ methyl group being cis to the phenyl is now strongly shielded. It should be noted that if t-II represents the stable conformation of the threo isomer, both the ester and the $CHCH_3$ methyl group should be shielded. On consideration of nonbonded interactions also, the I conformation is expected to be the most stable one for both the erythro and threo isomers.[2] Consequently, both the erythro and threo rotamer populations should be averaged predominately in favor of the I conformer. A similar approach was taken by Balsamo et al., who made the same assignments for their series of β-hydroxy esters.[2] By extension of the above analysis to compounds **2** and **3**, the stereochemistry of each pair of isomers can be determined. It can be seen from Table I that **2** and **3** also exhibit the same effects on their chemical shifts, therefore implying that the e-I and t-I conformation assignments are general for the three different compounds. The same stereochemical assignments are also obtained by analysis of the relative chemical shifts in toluene-d_8 for the cases of **1** and **3**. However, in this solvent all the resonance lines are shifted to higher field due to the shielding effect of the solvent itself.

Long-Range Coupling between Methyl and Hydroxyl Protons. Perhaps the most interesting feature in the NMR spectra of the β-hydroxy esters is the appearance of a long-range coupling transmitted through four σ bonds between the OH and the adjacent methyl group protons in only the erythro isomers of **1–3**. As shown in Figure 2

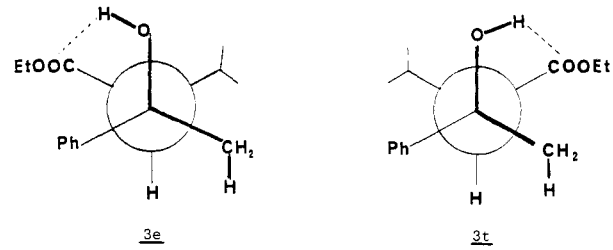


Figure 3. Intramolecular hydrogen bonding in the stable conformations of **3e** and **3t**.

for the case of **1**, the OH resonance appears as a quartet and the CH_3 resonance as a doublet only in the **1e** isomer. This coupling was carefully verified by selective decoupling as well as by D_2O-exchange experiments. The four-bond coupling was observed in $CDCl_3$ and toluene, but not in Me_2SO-d_6. It is also important to note that this coupling was usually observed only at relatively low concentrations. In the case of **1** the coupling was not observed at concentrations higher than 0.1 M. This concentration effect, as discussed below, probably results from intermolecular hydrogen bonding which becomes minimal at lower concentrations.

Although numerous examples of four-bond coupling constants (^4J) involving hydroxyl groups are known, most of these examples occur in aromatic molecules such as intramolecularly hydrogen bonded phenols[5] in which the coupling is transmitted through π bonds. Four-bond coupling over single bonds to a hydroxyl proton is not uncommon in some monosaccharides[6] and has been reported also in cyclic hydroxy ketones.[7] The involvement of CH_3 groups in long-range coupling over single bonds has also been observed in a variety of systems such as steroids[8] and rigid cyclic hydrocarbons.[9] By contrast, an appreciable value for ^4J (>0.4 Hz) between the protons of a methyl group and the proton of a geminal hydroxyl group is exceedingly rare. The long-range coupling in the β-hydroxy esters reported here is further distinguished by the fact that it occurs in a conformationally mobile system rather than in a rigid structure.

Since geminal methyl and hydroxyl groups occur very frequently, it is somewhat surprising that long-range coupling between them has not been reported more often. The explanation for this paucity of data lies both in the experimental details of their observation and in the dependence of spin–spin coupling on the orientation of the bonds involved and, consequently, on the effects of motional averaging. First of all, it is clear that in many cases where this type of coupling might have been observed,[2,7] the presence of a trace of water which would cause proton exchange, or self-association due to intramolecular hydrogen bonding at high concentrations resulting in broader line widths, would foil attempts to directly measure a coupling constant. More pervasively, however, the maximum coupling is observed only when the four-σ-bond system assumes a "W" configuration in a conformationally rigid system.[9] Therefore, it is not surprising that in all the above-reported examples at least one of the coupled protons is fixed in space. In the case of the β-hydroxy esters,

(5) Schaefer, T.; Chum, K. *Can. J. Chem.* **1978**, *56*, 1788 and references cited therein.
(6) Gillet, B.; Nicole, D.; Delpuech, J.-J.; Gross, B. *Org. Magn. Reson.* **1981**, *17*, 28.
(7) O'Loane, J. K.; Combs C. M.; Griffith, R. L. *J. Org. Chem.* **1964**, *29*, 1730.
(8) Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, CA, 1964; p 115.
(9) Barfield, M.; Dean, A. M.; Fallick, C. J.; Spear, R. J.; Sternhell, S.; Westerman, P. W. *J. Am. Chem. Soc.* **1975**, *97*, 1482.

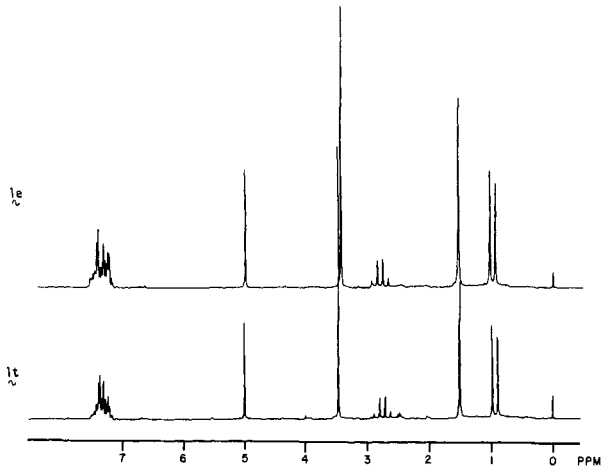


Figure 4. 80-MHz NMR spectra of **1e** and **1t** in Me_2SO-d_6.

both the OH and methyl groups are free to rotate, but the existence of a strong internal hydrogen bonding makes it possible for part of the four-σ-bond structure to become immobilized and thus, on a time average, exhibit a long-range coupling. As shown in Figure 3, it is only the erythro isomer that can form the favorable configuration required for maximal coupling, thus explaining the 1-Hz coupling observed for **1e–3e** in nonhydrogen bonding solvents. A value of ^4J = 1.0 Hz is consistent with a dihedral angle for the Me–C–O–H system of 180° as discussed by Barfield et al.[9]

The fact that all erythro isomers exhibited the same coupling provided further support for our stereochemical assignment, and the long-range coupling through four σ bonds reported here can be taken as a valuable tool for *stereochemical assignments in systems that exhibit the* same phenomenon. The only other example which we have found of a value of ^4J = 1.0 Hz for coupling between geminal methyl and hydroxyl protons has recently been reported by Huffman and Desai.[10] They describe an agarofuran which has a hydroxyl intramolecularly hydrogen bonded to an cyclic ether oxygen which stabilizes the unusual "W" configuration between the hydroxyl proton and a geminal methyl proton, thus allowing the observed coupling.

Solvent Dependence of Chemical Shifts and Coupling Constants. The β-hydroxy esters were also studied in Me_2SO since this solvent forms strong hydrogen bonds to alcohols[11] and would be expected to disrupt the intramolecular hydrogen bond between the hydroxyl proton and ester carbonyl oxygen, thereby permitting free rotation about the C–C bond of the ethanic fragment. The results in Table I show that in Me_2SO both the erythro and threo isomers of each compound have very similar chemical shifts. This result is further illustrated in figure 4 for the case of **1e** and **1t**. The chemical shifts of groups c–f (Table I) appear to be shifted to slightly higher field than would be expected in Me_2SO, indicating that the anisotropic *shielding effects of the phenyl group are averaged equally* over each rotational conformation in both erythro and threo isomers of **1–3**. In addition, the coupling between OH and adjacent methyl protons in all the erythro isomers disappears, and both groups resonate as sharp singlets. The disappearance of the long-range coupling can be attributed to the disruption of the stable internal hydrogen bond. Solvent effects on coupling constants frequently signify a conformational change and have been observed, for example, in *syn*-hydroxy epoxides in which hydrogen bonding solvents disrupt an internal hydrogen bond, as in the present case, resulting in an altered conformation.[12]

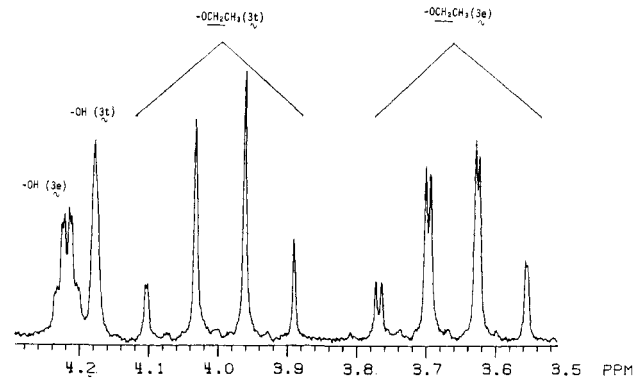


Figure 5. 100-MHz NMR spectrum of 1:1 mixture of **3e** and **3t** in toluene-d_8 at 75 °C.

Table II. Long-Range Spin–Spin Coupling Constants (in Hertz) for 3e and 3t Obtained in Toluene-d_8 at 75 °C with Selective Decoupling

	^4J(OH,CH)	^4J(OH,CH_3)	^4J(CH,CH_3)
3e	0.27	1.01	<0.1
3t	0.32	0.27	<0.1

In a 100-MHz spectrum of a 1:1 mixture of **3e** and **3t** in toluene-d_8 at 75 °C the resolution was improved sufficiently to reveal two additional features in these hydroxy esters. First, the two methylene protons of the ethyl group of the ester have slightly different chemical shifts and different coupling constants with the ester methyl group as shown in Figure 5. This effect, which results from the prochirality of these protons, exists in both isomers but is more pronounced in the erythro isomer. A spectrum run at 300 MHz showed clearly the small splitting observed in toluene at 100 MHz was the result of an ABX_3-coupled spin system in the ethyl group. Interestingly, the 300-MHz spectra of **3e** and **3t** in $CDCl_3$ showed no chemical shift difference for the ethyl group methylene protons, indicating that this effect results from associative shielding from toluene. The second feature in the spectra of toluene solutions is the resolution of additional long-range coupling through four σ bonds between the methine and hydroxyl protons in both isomers. The spectra run at higher temperature afforded better resolution because the greater molecular mobility results in more narrow line widths. By selective decoupling experiments each of the four bond coupling constants was obtained as given in Table II. No resolved splitting was observed between the methine and methyl protons, suggesting a very small H–C–C–Me dihedral angle.[9]

Experimental Section

All reactions involving organometallic reagents were carried out under an N_2 atmosphere. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 621 spectrophotometer. NMR spectra were recorded at ambient temperature (ca. 28 °C) with a Varian XL-100 or a Bruker WP-80 spectrometer, and the chemical shifts are given in δ units downfield from internal Me_4Si. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN. TLC was carried out on silica gel GF plates with hexane containing 15–40% acetone as the eluent. HPLC was conducted on silica gel by using Waters

(10) Huffman, J. W.; Desai, R. C., manuscript submitted for publication. We thank Professor Huffman for providing us with his manuscript prior to publication.

(11) Sehgal, R. K.; Koenigsberger, R. U.; Howard, T. J. *Tetrahedron Lett.* **1974**, *47* 4173.

(12) Rasletter, W. H.; Adams, J. *J. Org. Chem.* **1980**, *45*, 3534.

Associates 206 and 500 instruments.

(2*RS*,3*RS*)- and (2*SR*,3*RS*)-Methyl 2-Methyl-3-hydroxy-3-phenylbutyrate (1e and 1t). To a solution of diisopropylamine (5 g, 0.05 mol) in anhydrous Et_2O (100 mL) at −78 °C was added with stirring a solution of BuLi (0.05 mol) in hexane (20 mL). The resulting mixture was stirred at −78 °C for 15 min. A solution of methyl propionate (4.4 g, 0.05 mol) in Et_2O (20 mL) was added rapidly with stirring. After 20 min of additional stirring at −78 °C, a solution of acetophenone (6.0 g, 0.05 mol) in Et_2O (25 mL) was added, and the mixture was stirred for 15 min. A 10% HCl solution (35 mL) was added, and the mixture was allowed to warm to room temperature. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The liquid so obtained was distilled in a Kugelrohr apparatus to yield 5.3 g (51%) of pure **1** as a 1:1 mixture of **1e** and **1t**: bp 55 °C (air-bath temperature; 0.025 mmHg); IR (neat) 3505, 1715, 1448, 1350, 1205, 1070, 765, 700 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.02; H, 7.96.

The two diastereoisomers were separated by preparative HPLC with 1:19 EtOAc–hexane as the eluent. Pure samples of the less polar (assigned **1t**, solid, mp 52–54 °C) and the more polar (assigned **1e**, liquid) isomers were obtained.

(2*RS*,3*RS*)- and (2*SR*,3*RS*)-Ethyl 2-Propyl-3-hydroxy-3-phenylbutyrate (2e and 2t). To a solution of LDA (0.11 mol), prepared as above, in anhydrous Et_2O (200 mL) at −78 °C was added with stirring a solution of ethyl valerate (13.0 g, 0.1 mol) in Et_2O (40 mL) over a period of about 2 min. The mixture was stirred at −78 °C for 20 min. A solution of acetophenone (12.0 g, 0.1 mol) in Et_2O (50 mL) was added, and the mixture was stirred at −78 °C for 15 min. The workup as in the case of **1** afforded a liquid which was distilled in a Kugelrohr apparatus to yield 12.4 g (50%) of pure **2** as a 1:1 mixture of **2e** and **2t**: bp 80 °C (air-bath temperature; 0.05 mmHg); IR (neat) 3500, 1710, 1445, 1375, 1345, 1185, 1028, 712, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.01; H, 8.99.

The two diastereoisomers were separated by preparative HPLC with 1.5% EtOAc in hexane as the eluent. Pure samples of the less polar (assigned **2t**) and the more polar (assigned **2e**) isomers both as liquids were obtained. The IR spectra of the two isomers in CCl_4 are slightly different. The OH in **2t** absorbs at 3520 cm^{-1} whereas that of **2e** absorbs at 3500 cm^{-1}. Some other small differences exist mainly in the fingerprint area.

(2*RS*,3*RS*)- and (2*SR*,3*RS*)-Ethyl 2-(2-Propyl)-3-hydroxy-3-phenylbutyrate (3e and 3t). To a solution of LDA (0.05 mol), prepared as above, in anhydrous Et_2O (100 mL) at −78 °C, was added with stirring a solution of ethyl 3-methylbutyrate (6.5 g, 0.05 mol) over a period of about 2 min. The mixture was stirred at −78 °C for 20 min. A solution of acetophenone (6.0 g, 0.05 mol) in Et_2O (25 mL) was added, and the mixture was stirred at −78 °C for 15 min. The workup as in the case of **1** afforded a liquid which was distilled in a Kugelrohr apparatus to yield 6.8 g (54%) of pure **3** as a 1:1 mixture of **3e** and **3t**: bp 65–70 °C (air-bath temperature; 0.025 mmHg); IR (neat) 3495, 1708, 1448, 1380, 1190, 1028, 762, 698 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.06; H, 8.88.

The two diastereoisomers were separated by preparative HPLC with 2.5% EtOAc in hexane as the eluent. Pure samples of the less polar (assigned **3t**, a solid; mp 37–39 °C) and the more polar (assigned **3e**, liquid) isomers were obtained.

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Registry No. **1e**, 14366-99-5; **1t**, 14366-98-4; **2e**, 83633-71-0; **2t**, 83633-72-1; **3e**, 83633-73-2; **3t**, 83633-74-3; diisopropylamine, 75-31-0; butyllithium, 109-72-8; lithium diisopropylamide, 4111-54-0; methyl propionate, 554-12-1; ethyl valerate, 539-82-2; ethyl 3-methylbutyrate, 108-64-5; acetophenone, 98-86-2.

Structure and Selectivity in Anodic and Metal Ion Oxidations of Polyalkylbenzenes[1a]

Enrico Baciocchi,*[1b] Lennart Eberson,*[1c] and Cesare Rol[1b]

Dipartimento di Chimica, Università di Perugia, 06100 Perugia, Italy, and Division of Organic Chemistry 3, Chemical Center, University of Lund, S-220 07 Lund, Sweden

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Positional selectivity and the partition deuterium isotope effect (k_H/k_D) have been determined in the chemical [with cerium(IV) ammonium nitrate (CAN), cobalt(III) acetate, and *N*-bromosuccinimide (NBS)] and electrochemical side-chain oxidation of alkyl aromatics by using 5-R-hemimellitenes (R = H, *t*-Bu) and 1,3-dimethyl-2-(trideuteriomethyl)-5-*tert*-butylbenzene as the substrates. Considering also the already available data for isodurene, it has been found that the positional selectivity is strongly influenced by the substrate structure in the anodic and CAN-promoted oxidations, both reactions exhibiting a very similar pattern. In contrast, $Co(OAc)_3$ selectivities do not correlate with those of the anodic oxidation but with the selectivities of the side-chain bromination promoted by NBS. These results have been interpreted by suggesting that, as in the anodic oxidations, CAN-induced reactions involve first the formation of a radical cation intermediate which then loses a proton to give a benzylic free radical in the selectivity-determining step. The data for Co^{III} would instead suggest a mechanism involving a hydrogen atom transfer, but this conclusion cannot yet be considered definitive. No simple correlation exists between selectivity data and the k_H/k_D values.

A recent study has shown that the isomeric product distribution (intramolecular selectivity) in the side-chain oxidation of isodurene and *p*-ethyltoluene by metal ion (Ce^{IV}, Co^{III}, Mn^{III}) reagents is strongly influenced by the nature of the metal.[2] This result has been accommodated to what is at present the more generally accepted mechanism for the reactions of alkyl aromatic compounds with one-electron oxidants (eq 1–3)[3,4] by suggesting that in the

$$ArCH_3 + M^{n+} \rightleftharpoons ArCH_3^{+\cdot} + M^{(n-1)+} \quad (1)$$

$$ArCH_3^{+\cdot} + B \rightarrow ArCH_2\cdot + BH^+ \quad (2)$$

$$ArCH_2\cdot + M^{n+} \rightarrow ArCH_2B + M^{(n-1)+} \quad (3)$$

B = conjugate base of the solvent or ligand of the metal ion

(1) (a) Part 8 of the series "Oxidation of Aromatic Compounds by Metal Ions". Part 7: Baciocchi, E.; Rol, C.; Mandolini, L. *J. Am. Chem. Soc.* **1980**, *102*, 7597. (b) Università di Perugia. (c) University of Lund.

(2) Baciocchi, E.; Mandolini, L.; Rol, C. *J. Org. Chem.* **1980**, *45*, 3906.

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