quaternary CH_3); GC/MS (70 eV), *m/e* (relative intensity) 398 (20, M^+), 383 (13), 369 (1), 191 (100), 177 (36). Anal. ($C_{29}H_{50}$) C, H. The purity of this product by capillary GC analysis was 99%.

30-Nor-17α-moretan-22-one (19). To 33 mg (0.153 mmol) of pyridinium chlorochromate in 0.5 mL of dichloromethane was added 42 mg (0.102 mmol) of alcohol 17 in 1.0 mL of dichloromethane. The mixture was stirred for 2.5 h at 25 °C, diluted with ether, and filtered. The filtrate was concentrated and chromatographed on Macherey-Nagel silica gel F254 in 1:3:5 ether–hexane–dichloromethane to afford 30-nor-17α-moretan-22-one (19): 30 mg (72%); mp 190–191 °C; ^1H NMR ($CDCl_3$) δ 0.80, 0.84, 0.88, 1.00, and 1.04 (6 s, signal at 0.80 consists of two superimposed s, 18, quaternary CH_3), 2.13 (s, 3, $COCH_3$). These NMR data are in agreement with literature values.[14]

30-Nor-17α-hopan-22-one (20). The procedure described for the preparation of **9** was repeated with 5.4 mg (0.131 mmol) of ketone **19** to afford, after chromatography on Merck silica gel F254 in 1:10 ethyl acetate–hexane, 4.7 mg (87%) of 30-nor-17α-hopan-22-one (**20**) having ^1H NMR data in accord with literature values.[14]

30-Nor-17α-hopane (3). A Wolff–Kishner reduction was repeated with 30.5 mg (0.74 mmol) of 30-nor-17α-hopan-22-one (**20**) to afford, after chromatography on Merck silica gel F254 in hexane, 30-nor-17α-hopane (**3**): 15.2 mg (52%); mp 173–174.5 °C; ^1H NMR ($CDCl_3$) δ 0.79, 0.82, 0.85, 0.93, 0.96 and 0.99 (6 s, 18, quaternary CH_3); GC/MS (70 eV), *m/e* (relative intensity) 398 (33, M^+), 383 (22), 369 (2), 191 (100), 177 (42). Anal. ($C_{29}H_{50}$) C, H. The purity of this product by capillary GC analysis was 97.9%. This product was identical by GC coinjection, GC/MS, and ^1H NMR comparison with authentic 30-nor-17α-hopane obtained from P. Albrecht.[2b]

Acknowledgment. We thank Professor P. Albrecht for samples of 30-norhopane and 30-nor-17α-hopane and Professor G. Ourisson for a sample of 22-hydroxyhopan-3-one. We also thank Professor Edward L. Clennan for providing us with the DEPT and GASPE programs used for the ^{13}C NMR studies.

Registry No. **2**, 36728-72-0; **3**, 53584-60-4; **4**, 3258-87-5; **5**, 81600-07-9; **6**, 1981-81-3; **7**, 1615-92-5; **8**, 1615-91-4; **9**, 1172-78-7; **10**, 10379-52-9; **11**, 1253-69-6; **12**, 54352-47-5; **13** (isomer 1), 58239-44-4; **13** (isomer 2), 58239-45-5; **15a** (isomer 1), 87452-77-5; **15b** (isomer 2), 87452-78-6; **16**, 87452-79-7; **17**, 33719-12-9; **18**, 33281-77-5; **19**, 33281-19-5; **20**, 33281-79-7.

Kinetics of Decarboxylation of the Two Epimers of 5-*tert*-Butyl-1-methyl-2-oxocyclohexanecarboxylic Acid: Lack of Stereoelectronic Control in β-Keto Acid Decarboxylation

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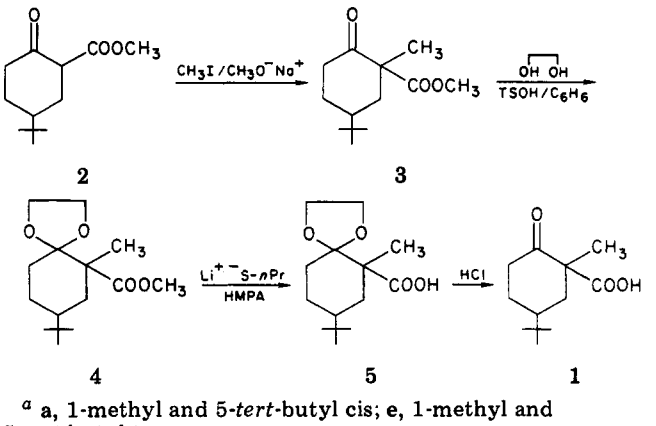
Rates of decarboxylation of the two epimers of 5-*tert*-butyl-1-methyl-2-oxocyclohexanecarboxylic acid have been measured under both acidic and basic conditions at 25 °C. The decomposition of isomer **1e** (methyl and *tert*-butyl trans) is more rapid than that of isomer **1a** (methyl and *tert*-butyl cis) both in acid (about 3-fold) and in base (15- to 20-fold). These results are not in agreement with the principle of stereoelectronic control. Reasons for this discrepancy are discussed.

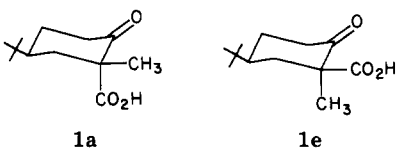
Stereoelectronic control of the enolization of ketones has been the subject of many investigations since the pioneering work of Corey and Sneen.[1] They postulated that, in the absence of large steric effects to the contrary, α axial hydrogens of cyclohexanones will be lost more readily than α equatorial ones since the axial C–H bond is correctly aligned to give continuous overlap with the π orbital of the carbonyl group during enolization. Although this theory is attractive and widely accepted,[2a] actual rate discriminations are often small.[1,3-5] Recently, however, Fraser and Champagne have reported a large selectivity in the base-catalyzed exchange of the protons α to the carbonyl group of a dibenzocycloheptadienone derivative (73:1)[6a] and a twistan-4-one (270:1),[6b] and Spencer[7] has demonstrated the highly selective (>100:1) abstraction of axial α protons from iminium ions of *trans*-decalone derivatives as well as the corresponding ketones.

Scheme I[a]



[a] **a**, 1-methyl and 5-*tert*-butyl cis; **e**, 1-methyl and 5-*tert*-butyl trans.

We wish to report here the relative rates of decarboxylation of the two epimeric 5-*tert*-butyl-1-methyl-2-oxocyclohexanecarboxylic acids **1a** and **1e**, a reaction formally

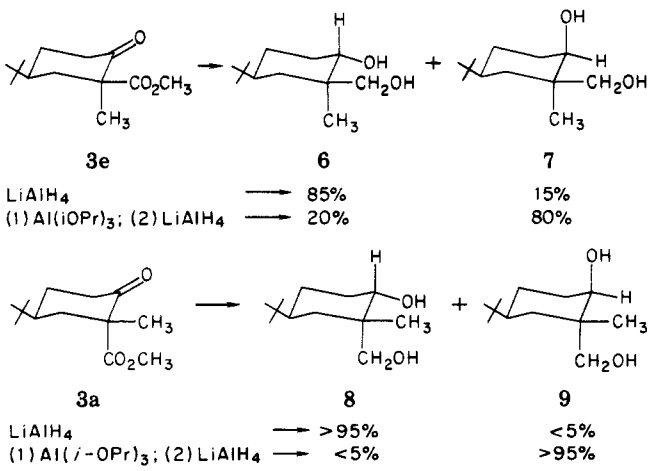


1a **1e**

(1) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.
(2) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin Inc.: Menlo Park, CA, **1972**; p 469. (b) Ibid. pp 60ff.
(3) Trimitsis, G. B.; Van Dam, E. M. *J. Chem. Soc., Chem. Commun.*, **1974**, 610–611.
(4) Metzger, P.; Casadevall, E. *Tetrahedron Lett.* **1973**, 3341–3344.
(5) Lamaty, G. In "Isotope Effects in Organic Chemistry"; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, **1976**; Vol. 2, 33–88.
(6) (a) Fraser, R. R.; Champagne, P. J. *Can. J. Chem.* **1976**, 3809–3811. (b) Fraser, R. R.; Champagne, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 657–658.
(7) Ferran, H. E., Jr.; Roberts, R. D.; Jacob, J. N.; Spencer, T. A.; *J. Chem. Soc., Chem. Commun.* **1978**, 49–50.

0022-3263/83/1948-4497$01.50/0

Scheme II



similar to the enolization of cyclohexanone. Since both enolization and decarboxylation require continuous overlap of the incipient p orbital with the π orbital of the carbonyl, both reactions should be subject to the same type of stereoelectronic control. Surprisingly, we find that **1e** decarboxylates more rapidly than **1a** as both the free acid and as the anion, a result which is not in accord with stereoelectronic predictions.

Results

The synthesis of the two epimers of 5-*tert*-butyl-1-methyl-2-oxocyclohexanecarboxylic acid is outlined in Scheme I. Methylation of methyl 5-*tert*-butyl-2-oxocyclohexanecarboxylate with methyl iodide gave a mixture of the isomeric methylated compounds (**3a** and **3e**), which were separated by column chromatography. Subsequent reactions were carried out starting with either pure **3a** and **3e**; no interconversion of isomers at any stage was observed. The ester groups of the ketals **4a** and **4b** could not be easily hydrolyzed; refluxing in methanolic KOH for three days resulted only in the isolation of unreacted ester. The procedure of Bartlett and Johnson,[8] however, using lithium *n*-propyl sulfide, was satisfactory. The resulting ethylene acetals of the β-keto acids were purified and hydrolyzed in 2 N HCl at room temperature to give the isomeric β-keto acids **1a** and **1e**.

In order to assign structures to the two series, both isomers of **3** were converted to the corresponding diols by reduction (Scheme II). Reduction of **3e** by lithium aluminum hydride gave an 85:15 mixture of two diols, whereas the product from LAH reduction of **3a** consisted of only one detectable isomer. Based upon literature precedent,[2b] the major product from **3e** was tentatively assigned structure **6** and the product from **3a** was assumed to be **8**. Reduction of the keto esters by aluminum isopropoxide followed by lithium aluminum hydride reduction of the ester group gave a 20:80 mixture of **6** and **7** from **3e** and exclusively **9** and **3a**.

Our structure assignment of the configuration at C-2 for **3a** and **3e** (and thus **1a** and **1e**) is based upon the fact that in **6**, **7**, and **8** the hydroxyl group and the hydroxymethylene group are gauche and thus can form an internal hydrogen bond, whereas in **9** these two groups are anti and internal hydrogen bonding cannot occur. At relatively high concentrations (3% to 10%) in carbon tetrachloride solution all four compounds show a broad peak in the infrared spectrum at about 3400 cm^{-1}, corresponding to intermolecular hydrogen bonding,[9] in addition to a small peak at about 3640 cm^{-1} due to free OH. However, dilution to about 0.1% causes the disappearance of the 3400 cm^{-1} band in all cases and the appearance of two sharp peaks at about 3545 and 3650 cm^{-1} for **6**, **7**, and **8** but only one peak at 3645 cm^{-1} for **9**. The 3650 cm^{-1} peak in all four diols is due to free OH, whereas the 3545 cm^{-1} peak is due to intramolecular hydrogen bonding.[9] Since this latter peak is missing in **9**, it must be the diaxial diol (as shown) and **3a** must have the carbomethoxy group trans to the *tert*-butyl group (as shown). Although structures for **6** and **7** cannot be rigorously assigned, it is clear that the structure for **3e** is correct.

Table I. Rate Constants for Decarboxylation of 1a and 1e[a]

solvent	k^{obsd}, s^{-1} 1a	1e
20% dioxane		
0.01 N HCl	1.45×10^{-4}	3.64×10^{-4}
0.03 N HCl		3.60×10^{-4}
0.001 N HCl[b]		3.37×10^{-4}
60% dioxane		
0.01 N HCl	1.22×10^{-4}	3.14×10^{-4}
70% methanol		
0.02 N KOH	9.95×10^{-6}	1.72×10^{-4}
0.10 N KOH	9.97×10^{-6}	1.60×10^{-4}
80% ethanol		
0.02 N KOH	1.81×10^{-5}	3.78×10^{-4}
90% ethanol		
0.02 N KOH		5.86×10^{-4}

[a] Measured spectrophotometrically at 25 °C with no added salts unless otherwise specified. [b] μ = 0.03, NaCl.

Dissociation constants for the keto acids **1a** and **1e** were determined in 70% methanol/water at 0 °C to prevent excessive decarboxylation during the time required for titration. Measured values for the pK_a's of **1a** and **1e** are 5.21 and 5.79, respectively. Because of the large fraction of organic solvent in the solution these values cannot be directly compared to pK_a values measured in water. However, they are still useful as a measure of the relative acidity of **1a** and **1e**.

Both **1a** and **1e** decarboxylate at convenient rates at 25 °C to give 2-methyl-4-*tert*-butylcyclohexanone. Comparison of the NMR and IR spectra of the product mixture with the reported[10] spectra shows that the product consists of about 90–95% cis isomer and only 5–10% trans (starting with either **1a** or **1e**). The reaction was monitored both by NMR and UV, and agreement between the two methods is satisfactory. Spectrophotometric rate measurements are more precise and are reported in Table I.

As expected[11] for β-keto acid decarboxylations, there is little variation of the rate constant with either acid concentration or solvent composition for the undissociated acids. For the anions the rate of decarboxylation is independent of added base, but there is a moderate rate increase as the solvent polarity is lowered. The decomposition of isomer **1e** is faster than **1a** both for the neutral acids (about 3-fold) and in base where the acids exist as the anions (15- to 20-fold).

Discussion

Assignment of Configuration to 1a and 1e. The major methylation product (**3e**) was previously isolated by Kuehne,[12] who assigned it the trans configuration (as

(8) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459–4462.

(9) Nakanishi, K. "Infrared Absorption Spectroscopy"; Holden-Day: San Francisco, 1962; p 146.

(10) Nerdel, F.; Frank, D.; Rehse, K. *Chem. Ber.* **1967**, *100*, 2978–2991.

(11) Pollack, R. M. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; p 467–491.

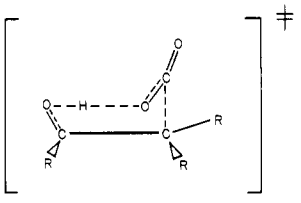
shown in Schemes I and II) on the basis of a higher VPC retention time relative to **3a** and a less shielded methyl for **3e** (δ 1.48) than **3a** (δ 1.28). Kuehne also correlated the configuration of **3e** with the corresponding 5-*tert*-butyl-1-methyl-2-oxocyclohexanenitrile.

The ethyl esters of **1a** and **1e** have been synthesized by two other groups.[10,13] On the basis of physical and spectral properties, Nerdel et al.[10] assigned structures for the ethyl esters which agree with Kuehne's assignment (i.e., the isomer with the less shielded α-methyl has the 1-methyl and 5-*tert*-butyl groups trans). Previously, however, Conia and Briet[13] had assigned the opposite structures to these esters, but apparently they had second thoughts and later decided that "probably the assignments should be reversed".[14]

Although all three groups now seem to be in agreement concerning the configurational assignments on the basis of physical evidence, we felt that the importance of the correct assignments to our work warranted an additional test. Our approach is based upon the fact that reduction of **3e** gives two epimeric diols, *both* of which have the potential for intramolecular hydrogen bonding, whereas reduction of **3a** gives two diols, only *one* of which can form an intramolecular hydrogen bond. Analysis of the infrared spectra of the four diols shows this prediction to be correct and confirms the structural assignments of Kuehne[12] (vide supra).

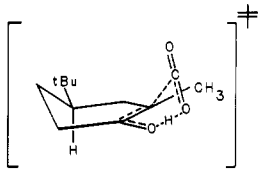
Relative Rates of Decarboxylation. Reactivity of the Free Acids. If stereoelectronic control is a significant factor in the decarboxylation of **1a** and **1e**, then the more reactive isomer should be the one with the axial carboxyl group. On the basis of the structural assignments above, epimer **1a** would be expected to decarboxylate more rapidly than **1e**. In fact, the kinetic data clearly show that the isomer with the *equatorial* carbonyl is more reactive in both acidic and basic solutions, in apparent conflict with the principle of stereoelectronic control.

A critical examination of the nature of the transition states for the decarboxylation of both the free acids and the anions, however, can point the way to a reconciliation of the present results with the need for continuous overlap of the leaving group orbital with the π orbital of the carbonyl group. We have previously suggested[11] that the transition state for the decarboxylation of unionized β-keto acids has a six-membered ring with the newly forming O—H bond nearly in the same plane as the original C—C=O system (**10**). The carbon–carbon bond which

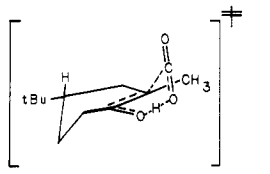


10

is breaking, on the other hand, is perpendicular to this plane in order to allow overlap of the incipient p orbital with the p orbital of the carbonyl carbon. Application of this model to the decarboxylation of **1a** and **1e** produces the transition states **11a** and **11e**. In both cases, the incipient cyclohexene ring should be in a half-chair conformation with the *tert*-butyl group in an equatorial position and the 2-methyl group in the plane of the carbon–carbon double bond. If the energies of the two transition states are similar, as one might expect, then the relative rates of decarboxylation of **1a** and **1e** should only depend on their relative stabilities. Although there is no direct evidence concerning the preference of a carboxyl group for the equatorial vs. axial positions in 2-substituted cyclohexanones, both carboxyl and methyl substituents show a similar preference for the equatorial position in cyclohexanes (1.70 kcal/mol for CH_3 and 1.35 kcal/mol for COOH).[15] If this result can be extrapolated to cyclohexanones, then the slightly greater reactivity of **1e** can be explained by its instability relative to **1a** (axial CH_3/equatorial COOH in **1e** vs. axial COOH/equatorial CH_3 in **1a**).



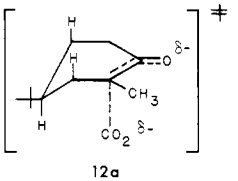
11e



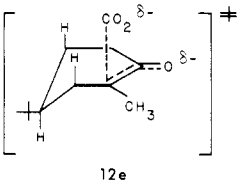
11a

Reactivity of the Anions. The mechanism for decarboxylation of the anions of β-keto acids is generally accepted[11] as being a simple carbon–carbon bond cleavage to give carbon dioxide and the enolate ion. This process is formally similar to base-catalyzed enolization, and this one might expect a similar sensitivity to stereoelectronic control in the two reactions. For 4-*tert*-butylcyclohexanone, Trimitsis and Van Dam[3] found the rate of exchange catalyzed by NaOD in Me_2SO/water to be 5.5-fold faster for the axial α protons than for the equatorial α protons. Similarly, Lamaty[5] found $k_{axial}/k_{equatorial}$ to be 3.3 for cyclohexanone in 50% dioxane with OD^- and 2.2 in 75% acetic acid with acetate ion as the base. *trans*-1-Decalone exchanges its 2-axial proton 3.8-fold faster than the 2-equatorial proton[5] in agreement with the results in the cyclohexanone series. On the other hand, Spencer[7] has observed a rate discrimination of 130-fold favoring axial proton removal vs. equatorial abstraction in the α-deprotonation of 10β-methyl-9α-acetoxydecal-2-one by hydroxide ion. Although the stereoelectronic factor favoring axial over equatorial deprotonation is usually small in cyclohexanones, in every case axial loss of a proton is favored.[16]

How then can we explain the preference for loss of equatorial carbon dioxide in the case of **1a** and **1e**? Available evidence suggests[11] that the transition state for decarboxylation of β-keto acids occurs late on the reaction coordinate, that is, it resembles the enolate ion. The transition state for decarboxylation of the anion of **1a** would then look like **12a** and the transition state for **1e** like **12e**. If steric interactions with the axial hydrogens



12a



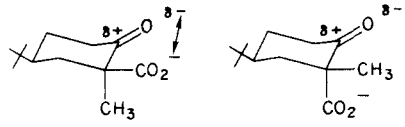
12e

in **12a** and **12e** are unimportant then these two transitions states will have similar energies and the relative rates will

(12) Kuehne, M. *J. Org. Chem.* **1970**, *35*, 171–175.
(13) Conia, J. M.; Briet, P. *Bull. Soc. Chim. Fr.* **1966**, 3881–3888, 3888–3895.
(14) Reference 14 in Huff, B. J.; Tuller, F. N.; Caine, D. *J. Org. Chem.* **1969**, *34*, 3070–3075.
(15) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, **1975**; p 114.
(16) In contrast, Coller et al. have observed a k_{eq}/k_{ax} ratio of 3.8 for the base-catalyzed H-D exchange of the C-3 protons in 4-*tert*-butyl-1-acetylcyclohexene. (a) Coller, B. A. W.; Jackson, W. R.; Stragalinou, A.; Strauss, J. U. G. *Tetrahedron Lett.* **1979**, 2261–2262. (b) Coller, B. A. W.; Jackson, W. R.; Stragalinou, A.; Straus, J. U. G. *Aust. J. Chem.* **1981**, *34*, 171–180.

reflect the differences in energy of **1a** and **1e**, similar to what we postulated for the free acids.

We believe that the anion of **1e** is significantly less stable than the anion of **1a** due to a charge–dipole interaction (**1e**$^-$) which is absent in the anion of **1a** (**1a**$^-$), and that this



1e$^-$ **1a**$^-$

factor causes **1e**$^-$ to decarboxylate more readily than **1a**$^-$. An analogous situation occurs with 2-bromocyclohexanone.[17] Here, the axial conformer is favored over the equatorial one due to dipole–dipole repulsion in the equatorial conformation. Evidence that this interaction is significant can be seen in the pK_a's of **1a** and **1e**. The axial carboxyl group of **1a** is significantly more acidic than the equatorial carboxyl of **1e** (pK_a 5.21 vs. 5.79 in 70% methanol) as would be predicted if a charge–dipole interaction is important in **1e**$^-$. Dissociation constants for *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acids have previously been measured in 66% dimethylformamide–water (pK_a = 8.23 and 7.79, respectively).[18] These results, combined with the pK_a's for **1a** and **1e**, show that an α carbonyl group increases the acidity of an axial carboxyl by about 1.0 pK unit more than it increases the acidity of an equatorial carboxyl, surely indicative of a significant charge–dipole interaction in the equatorial isomer.

Thus, in the case of the epimeric 5-*tert*-butyl-1-methyl-2-oxocyclohexanecarboxylic acids (**1a** and **1e**) the relative rates of loss of axial carbon dioxide and equatorial carbon dioxide can be rationalized in terms of a transition state which still allows continuous overlap of the incipient p orbital with the π-orbital of the carbonyl group. As long as the transition state for decarboxylation resembles the enolate ion, the relative rates of decarboxylation will reflect the relative stabilities of the reactants.

The lack of stereoelectronic control in the decarboxylation of both the free acids and the anions of **1a** and **1e** shows that this factor is not a dominant one in the decarboxylation of β-keto acids. Its effect on most enolization reactions, as well, appears to be only of marginal importance, as the majority of enolizations show only relatively small rate discriminations between axial and equatorial protons.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 257 spectrophotometer (with 0.1-cm or 1.0-cm cells as appropriate), and ^{1}H NMR spectra were obtained on a Hitachi Perkin-Elmer R-20A spectrometer. Chemical shifts are reported relative to internal tetramethylsilane ($CDCl_3$) or internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate (D_2O). Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. pH measurements were made on a Radiometer Model 26 pH meter equipped with a combination electrode and standardized at pH 7 and pH 4 with aqueous buffers. A Waters high-performance liquid chromatograph was used for HPLC analysis.

5-*tert*-Butyl-2-oxocyclohexanecarboxylic Acid. This reaction was carried out in a nitrogen atmosphere. A solution of 28 mL of diisopropylamine (0.2 mol) in 150 mL of anhydrous ether was cooled to 0 °C and a few crystals of 1,10-phenanthroline were added to serve as an indicator. The temperature was kept at 0–2 °C while 120 mL of 1.6 M *n*-butyllithium (0.2 mol) was added dropwise with stirring. Stirring was continued at 0 °C for 30 min. A solution of 30.8 g (0.2 mol) of 4-*tert*-butylcyclohexanone in 50 mL of anhydrous ether was added dropwise while the temperature was maintained at 0–2 °C to the end point (pale yellow solution) and stirring was continued for 1 h. Dry carbon dioxide was bubbled through the reaction mixture vigorously for the first 25 min and more slowly for 10 minutes. Stirring was continued for an additional 30 min while the solution warmed to room temperature. The solution was concentrated to about half-volume by removal of ether on the rotovac (no heat used). The ether solution was added to 400 mL of cold 1.0 N HCl until acid to pH paper. The ether layer was separated and made basic with 400 mL of 1.0 M NaOH. The aqueous layer was added to 400 mL of 1.0 N HCl in ice. The white precipitate was filtered and dried under vacuum. A yield of 16.5 g (42%) of dry acid was obtained, mp 95–96 °C (lit.[2] 97–99 °C). The acid is stable if kept under refrigeration. Care must be taken to avoid keeping the acid in solution since it easily decarboxylates. The acid was used in subsequent steps without further purification.

Methyl 5-*tert*-Butyl-2-oxocyclohexanecarboxylate (2). The methyl ester of 5-*tert*-butyl-2-oxocyclohexanecarboxylic acid was prepared by reaction of the acid with diazomethane.[19] Anhydrous ether (250 mL) was added to 33 mL of 40% aqueous potassium hydroxide and the mixture cooled to 0 °C. Finely powdered nitrosomethylurea (1 g) was added in small portions over 1–2 min with continued cooling and shaking. The yellow ether layer was separated from the aqueous layer and added in small portions to a cooled (0 °C) solution of 22.2 g (0.11 mol) of 5-*tert*-butyl-2-oxocyclohexanecarboxylic acid in 250 mL of anhydrous ether while the solution was kept at 0°. The ether was evaporated under vacuum to yield a pale yellow liquid (NMR δ 3.72 (s)). The crude product was used in subsequent reactions.[20]

Methyl 5-*tert*-Butyl-1-methyl-2-oxocyclohexanecarboxylate (3). A solution of sodium methoxide (90 mL, 1.04 M) in methanol was added dropwise over 15 min with stirring to a mixture of 19.5 g of crude **2** (0.092 mol) and 18.0 g of methyl iodide (0.225 mol) in 150 mL of dry xylene under nitrogen. The solution was heated for 3 h at about 45 °C, stirred at room temperature for 12 h, and then refluxed for 1 h. After the solution was cooled to room temperature, most of the methanol was removed under vacuum. The remaining solution was treated with 1.0 N HCl until acidic, and the aqueous layer extracted with ether (2 × 50 mL). The combined organic layers were extracted with 1.0 N NaOH (50 mL) and water (2 × 25 mL) and dried over $MgSO_4$, and the solvent was removed under vacuum to give 21 g of oil. Analysis by gas chromatography (5% Carbowax, 175 °C) showed, in order of elution: *tert*-butylcyclohexanone (15%), epimer **3a** (18%), **2** (< 2%), and epimer **3e** (65%). The crude oil was then fractionally distilled under vacuum (~5 mm). Early fractions (bp 100–119 °C) contained varying amounts of *tert*-butylcyclohexanone (8 g); the final fraction (bp 120–130 °C), containing a mixture of epimers **3a** and **3e** (11 g), crystallized upon standing. Pure epimer **3e** was obtained by recrystallization of the final fraction from hexane as large prisms (mp 63–65 °C, lit.[12] 67–68 °C). The remaining mother liquor was stripped and chromatographed on silica gel with hexane–ether (96:4). The first product to elute was a liquid (epimer **3a**) and the second product was a solid (epimer **3e**). Earlier fractions from distillation were also chromatographed to give a total of 8.5 g of epimer **2e** and 1.9 g of epimer **2a** of reasonable purity (>98% by GC).

3a: NMR ($CDCl_3$) δ 0.91 (s, 9 H), 1.26 (s, 3 H), 3.70 (s, 3 H), 2.7–1.0 (m, 7 H); IR 1715–1750 cm^{-1} (br).

3b: NMR ($CDCl_3$) δ 0.92 (s, 9 H), 1.42 (s, 3 H), 3.70 (s, 3 H), 2.7–1.0 (m, 7 H); IR 1715, 1735 cm^{-1}.

Methyl 5-*tert*-Butyl-1-methyl-2-oxocyclohexanecarboxylate Ethylene Acetals (4a and 4e). Purified **3a** or **3e** (1.15 g, 0.005 mol), 1.6 g (0.025 mol) of ethylene glycol, and a few crystals of toluenesulfonic acid were refluxed in 10 mL of anhydrous benzene (dried over molecular sieves) so that the condensed vapors passed through molecular sieves and calcium chloride before returning to the flask. This was accomplished by interspersing an equilibrating dropping funnel (filled partway

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(20) A better route to **2** is that of Kuehne.[12]

with molecular sieves and then to the top with calcium chloride) between the flask and the condenser. After being refluxed for 24 h, the benzene solution was cooled to room temperature, neutralized with 3 mL of 5% sodium bicarbonate, and dried ($MgSO_4$). Removal of the solvent gave a product which was greater than 98% pure by gas chromatography (5% Carbowax 150 °C). No interconversion of epimers was observed under these conditions.

4a (ethylene acetal of **3a**): NMR ($CDCl_3$) δ 3.94 (br s, 4 H), 3.65 (s, 3 H), 1.0–2.2 (m, 7 H), 1.18 (s, 3 H), 0.85 (s, 9 H).

4e (ethylene acetal of **3e**): NMR ($CDCl_3$) δ 3.84 (br s, 4 H), 3.61 (s, 3 H), 1.1–1.9 (m, 7 H), 1.31 (s, 3 H), 0.88 (s, 9 H).

5-*tert*-Butyl-1-methyl-2-oxocyclohexanecarboxylic Acid Ethylene Acetals (5a and 5e). The methyl esters of the ethylene acetals were hydrolyzed by using the procedure of Bartlett and Johnson.[8] All operations were conducted under N_2 in a glove bag under an efficient hood.

Lithium hydride (1.8 g) was suspended in 60 mL of distilled hexamethylphosphoramide, and 6.0 mL of distilled *n*-propyl sulfide was added in one portion. The mixture was stirred 1 h at room temperature and the solution was filtered. The filtrate was ca. 0.5 M in lithium *n*-propylmercaptide reagent.

5e. A portion of the *n*-propylmercaptide solution (25 mL) was added to 810 mg of acetal **4e** in one portion and kept under nitrogen for 3 h (longer reaction times did not increase the yield). The solution was slowly poured into 300 mL of ice–water and 1 N HCl was added until the pH was about three. The solution was immediately extracted with ether and dried ($MgSO_4$), and the solvent was evaporated to give a yellow oil. The residue was treated with 100 mL of 1.0 N NaOH and extracted with 30 mL of ether. The aqueous phase was acidified to pH 3 and rapidly extracted with ether (2 × 100 mL). The ether layers were dried over magnesium sulfate and evaporated to give a yellow oil which solidified when triturated with hexane (0.61 g, 80%). Recrystallization from hexane–ether (4:1) gave 520 mg (68%) of **5e**: mp 155–156 °C (in sealed capillary); NMR ($CDCl_3$) δ 10.1 (s, 1 H), 3.90 (s, 4 H), 1.38 (s, 3 H), 2.0–1.1 (m, 7 H), 0.90 (s, 9 H); IR ($CHCl_3$, 3.6%) 3670, 3600–3000, 1754 (monomer COOH), 1700 (dimer COOH, weak) cm^{-1}; IR (dioxane, 4%) 1727 (s), 1680 (w) cm^{-1}. Anal. ($C_{14}H_{24}O_4$) C, H.

5a. The same procedure as for the hydrolysis of **4e** to **5e**, applied to 827 mg of **4a**, yielded 522 mg of **5a** (67%) after recrystallization from hexane-ether: mp 133–134 °C; NMR ($CDCl_3$) δ 10.5 (br s, 1 H), 4.35 (br s, 4 H), 1.30 (s, 3 H), 2.5–1.0 (m, 7 H), 0.93 (s, 9 H); IR ($CHCl_3$, 3%) 3675, 3600–3000, 1750 (monomer COOH), 1700 (dimer COOH, weak) cm^{-1}; IR (dioxane, 4%) 1733 (br s), 1760 (w), 1675 (w) cm^{-1}. Anal. ($C_{14}H_{24}O_4$) C, H.

5-*tert*-Butyl-1-methyl-2-oxocyclohexanecarboxylic Acids (1a and 1e). NMR analysis (acetone-d_6) revealed that the ethylene acetals (**5a** and **5e**) are rapidly hydrolyzed to the ketones upon addition of DCl. Thus, the acetal **5e** hydrolyzed (34 °C, in NMR probe) in acetone-d_6 containing 0.10 mL of concentrated DCl (ca. 2 N DCl) within 3 min (to >95% completion). Under these same conditions, the product β-keto acid **1e** decarboxylated relatively slowly ($t_{1/2} \sim 22$ min). Therefore, the β-keto acids were obtained from the acetals by hydrolysis in HCl.

1e. Concentrated hydrochloric acid (0.6 mL) was added in one portion to 200 mg of **5e** in 2.5 mL acetone. The solution was cooled in a cold water bath to keep the temperature below 25 °C. After 5 min standing at 25 °C the solution was concentrated on a rotary evaporator (no heat) which quickly cooled the solution. After 4 min of evaporation, 2 mL of cold water was added. The crystals were filtered and washed rapidly with cold water (3 × 1 mL) and cold hexane (1 mL). The solid was dried under suction for 1 min (and under vacuum for 2 min longer without any significant weight change) to give 140 mg of white crystals (84%). Total reaction and workup time did not exceed 15 min: mp 104–105 °C with gas evolution after heating apparatus to 90 °C before inserting sample; NMR ($NaOD/D_2O$) δ 2.8–1.1 (m, 7 H), 1.37 (s, 3 H), 0.96 (s, 9 H); IR ($CHCl_3$, 5%) 3500–2500, 1755 (monomer COOH), 1710 (dimer COOH), 1720 (C=O) cm^{-1}; IR ($CHCl_3$ + 10% Et_3N) 2500 (NH^+), 1610 (COO^-) cm^{-1}; IR (dioxane, 3%) 1742 (COOH), 1712 (C=O) cm^{-1}; UV (dioxane–H_2O + KOH) λ_{max} 286 (ε 43).

1a. By the above procedure 60 mg of **5a** yielded 36 mg (72%) of β-keto acid **1a**: mp 106–107 °C with gas evolution when inserted at 90 °C; NMR ($NaOD/D_2O$) δ 3.0–1.0 (m, 7 H), 1.23 (s, 3 H), 0.97 (s, 9 H); IR ($CHCl_3$, 4%) 3500–2500, 1705 (COOH), 1720 (C=O) cm^{-1} IR (dioxane, 3%) 1740 (w), 1714 (C=O) cm^{-1}; UV (dioxane–H_2O, + KOH) λ_m 284 (ε 46); IR ($CHCl_3$ + 8% Et_3N) 2500 (NH^+), 1610 (COO^-) cm^{-1}.

Reduction of 3a and 3e by Lithium Aluminum Hydride. The following general procedure was used for all lithium aluminum hydride reductions. About 6 mmol of lithium aluminum hydride was stirred in 5 mL of ether under nitrogen. The ketone (2 mmol) in 4 mL of ether was added dropwise over 5 min and stirring was continued for 3 h. Workup followed the procedure given by Fieser[21] in which a reduction using *n* grams of lithium aluminum hydride is treated with *n* mL of water, *n* mL of 15% sodium hydroxide, and 3 *n* mL of water. The precipitate was then washed several times with ether. The ether layer was washed with saturated sodium chloride (2 × 15 mL) and saturated sodium bicarbonate (2 × 15 mL) and dried over $MgSO_4$, and the solvent was evaporated.

6. Reduction of **3e** by the above procedure gave 95% yield of product diol. HPLC analysis (70% MeOH/H_2O, 7.8 mm × 30 cm C_{18} reverse phase) showed 85% **6** (retention volume 26.1 mL) and 15% **7** (retention volume 29 mL). Pure **6** was obtained by preparative HPLC: mp 146–147 °C; NMR ($CDCl_3$) δ 3.45 (br s, 3 H), 2.78 (m, 2 H), 1.9–0.8 (m, 7 H), 0.99 (br s, 3 H), 0.83 (s, 9 H). Anal. ($C_{12}H_{24}O_2$), C, H.

8. Reduction of **3a** gave 76% yield of diol. HPLC analysis of a twice recrystallized (hexane) sample showed 96% **8**. Purification was accomplished by preparative HPLC (60% MeOH/H_2O, 7.8 mm × 30 cm C_{18} reverse phase, retention volume 45 mL): mp 69–70 °C; NMR ($CDCl_3$) δ 3.8–3.1 (m, 5 H), 2.0–0.8 (m, 7 H), 1.15 (s, 3 H), 0.83 (s, 9 H). Anal. ($C_{12}H_{24}O_2$), C, H.

Reduction of 3a and 3e by Aluminum Isopropoxide Followed by Reduction with Lithium Aluminum Hydride. About 2.5 mmol of aluminum isopropoxide, 0.9 mmol of ketone, and 75 mL of isopropanol were refluxed for 3 h. The reaction mixture was allowed to cool and carefully poured into 50 mL of ice-cold water and acidified to pH 6 with 0.1 N HCl. Addition of 300 mL of ether produced two phases. The ether layer was separated and combined with ether extractions of the aqueous layer (3 × 50 mL). The combined organic layers were washed with saturated NaCl (50 mL) and dried over $MgSO_4$. Removal of the solvent gave a nearly quantitative yield of crude hydroxy ester which was reduced by lithium aluminum hydride according to the above procedure without further purification.

7. The crude product from reduction of **3e** (55% overall yield) was a mixture of **7** (80%) and **6** (20%) as shown by HPLC (60% MeOH/H_2O, C_{18}). Compound **7** was purified by HPLC (retention volume 34 mL): mp 79 °C; NMR ($CDCl_3$) δ 3.8–3.4 (m, 5 H), 2.9–1.8 (m, 7 H), 0.88 (s, 9 H), 0.82 (s, 3 H). Anal. ($C_{14}H_{24}O_2$) H; C: calcd, 71.95; found 71.20.

9. Reduction of **3a** gave an overall yield of 55% of **9** which was >95% pure by HPLC (70% MeOH/H_2O, C_{18}, retention volume 17.5 mL). IR samples were purified by HPLC: mp 148–150 °C; NMR ($CDCl_3$) δ 3.50 (m, 3 H), 1.9–0.8 (m, 9 H), 1.01 (s, 3 H), 0.83 (s, 9 H). Anal. ($C_{12}H_{24}O_2$) H; C: calcd, 71.95; found 71.50.

Kinetics. The decarboxylation reactions of **1a** and **1e** were monitored by two analytical methods: (1) NMR and (2) spectrophotometry. NMR methods were used to confirm the disappearance of the β-keto acid by monitoring the loss of the methyl singlet and concurrent appearance of the methyl peak due to product (primarily *cis*-2-methyl-4-*tert*-butylcyclohexanone). However, accurate kinetic analysis required large amounts of sample (~40 mg) and other more sensitive methods were sought.

Spectrophotometric analysis was the most satisfactory method of following the reactions of both the β-keto acids and their anions. Large decreases in absorbance during loss of carbon dioxide were observed below 235 nm. The mixed solvents employed were made up by volume. Methanol and ethanol were reagent grade and used as received, while dioxane was purified as described by Vogel.[22] Stock solutions of the β-keto acids were prepared immediately before use by dissolving 4 to 10 mg of the acid in 40 μL of dioxane. Rates of decarboxylation of the acids were monitored at 222–225

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nm by mixing 10 μL of the stock in 3 mL of solvent. In some runs HCl was added, but this had no effect on the rates. The decarboxylation of the anions was monitored at 230–235 nm by first adding KOH to give 0.02 M KOH prior to addition of the β-keto acid. A nonlinear least-squares analysis of the absorbance data usually gave first order rates with standard deviations of 1% of less for absorbance changes of 0.2–0.4. All runs were done at 25.0 ± 0.1 °C and were followed for 3–6 half-lives.

pK_a measurements were performed in 70% methanol/water (v/v at 25 °C) cooled to 0.0 ± 0.1 to minimize decarboxylation. About 5–10 mg of accurately weighed keto acid (**1a** or **1e**) was dissolved in 6 mL of 70% methanol at 0 °C. The pH electrode (previously cooled to 0 °C) was inserted, 20-μL aliquots of cold 0.30 N KOH in 70% methanol were added, and the pH recorded. The entire procedure took no longer than 10–15 min. The pK_a's were calculated from weighted least-squares analysis of a plot of $1/[H^+]$ vs. [anion]/[acid].

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Registry No. **1a**, 87373-02-2; **1e**, 87373-03-3; **2a**, 42031-70-9; **3a**, 87373-04-4; **3e**, 22249-33-8; **4a**, 87373-05-5; **4e**, 87373-06-6; **5a**, 87373-07-7; **5e**, 87373-08-8; **6**, 87373-09-9; **7**, 87373-10-2; **8**, 87373-11-3; **9**, 87373-12-4; 5-*tert*-butyl-2-oxocyclohexanecarboxylic acid, 42031-70-9.

Bromide Ion Promoted β-Elimination in α-Bromo Ester Substrates. Evidence for an Intermediate in the E2C Reaction

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The TDKIE criteria of transition state geometry in H-transfer reactions have been applied in the title reactions; a bent transition state consistent with the geometry of the E2C reaction has been verified by the results of intramolecular and intermolecular competition modes of determining k_H/k_D as a function of temperature. The extraordinary magnitude measured for the α secondary deuterium isotope effect in the E2C mechanism is reconciled with a very loose transition state and an acute angle of H-abstraction in the course of rearward approach to C_α by the promoter base. The virtual identity of the inter- and intramolecular isotope effects can be correlated by the assumption of a reaction intermediate of trigonal-bipyramid structure surrounding C_α and in which the abstractable H and D atoms are equally available to the action of the promoter base. The properties of this intermediate (**4**), by way of contrast with the transition state of an S_N2 process, are discussed in detail.

Since the earliest observations[1-3] of the remarkable efficiency of certain weak bases (thiolate, halide anions, etc.) in bringing about the biomolecular β-elimination of HX, the mechanism of this reaction has been the subject of vigorous controversy. The credibility of the proposed E2C mechanism[4-7] transition state (TS) (Figure 1a) espoused by Winstein and Parker and their co-workers and opposed by Bunnett[8,9] (Figure 1b) has recently been achieved by application of the temperature dependence of the kinetic isotope effect (TDKIE)[10] criteria of the geometry of an H-transfer TS. Thus, it was shown[11] that, in a conventional example of halide ion-promoted elimination of HX from C_6H_5–CH_2–CH_2X in aprotic media, a temperature-independent k_H/k_D was to be observed ($[\Delta E_a]_D^H \approx 0$) over a long temperature range (~70 °C). Values for A_H/A_D of up to 6.6 depending on the leaving group, X, were determined. These A_H/A_D values were greater than the practical limit for linear H-transfer (i.e., 1.2). Such properties of the isotope parameters have been frequently correlated[10] with a bent TS of H-transfer and, in the present instance, have provided strong support for the E2C mechanism, while distinguishing it from the Bunnett E2 process involving linear H-transfer.

Moreover, the magnitude of A_H/A_D has been shown both theoretically and empirically to correspond directly with the angle of H-transfer.[12] On this basis, also, it was concluded that (so-called) tight transition states with little ionic extension of the C_B–$H^{+\delta}$ bond and little sp^2 development at C_α show the larger values of k_H/k_D (large angles of H-transfer), contrary to earlier interpretations[13] based on single-temperature values of k_H/k_D.

Correlating a bent TS with the magnitude and temperature dependency of the primary deuterium kinetic isotope effect may be conducted by using a quantum mechanical treatment within the framework of transition state theory. The concept that a bent TS gives rise to a small, primary deuterium isotope effect was first put forward by Lewis,[14,15] and has since been adopted by

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