[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME, NOTRE DAME, IND.]

Conformational Analysis. VIII. The Conformational Equilibrium Constant of the Carbethoxyl Group[1]

BY ERNEST L. ELIEL, H. HAUBENSTOCK AND R. V. ACHARYA

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The conformational equilibrium constant for the carbethoxyl group in ethyl cyclohexanecarboxylate (*i.e.*, the equilibrium constant between the isomers with an axial and equatorial carbethoxyl group, respectively) has been determined by three different methods; namely, (1) by comparison of the rate of saponification of the ester in 70% ethanolic sodium hydroxide at 25.2° with the corresponding rates for ethyl *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylates; (2) by comparison of the rate of saponification of ethyl *cis*-4-methylcyclohexanecarboxylate with those of the corresponding *cis*- and *trans*-4-*t*-butyl compounds; and (3) by a direct equilibration of ethyl *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylate by means of sodium ethoxide and measurement of the equilibrium position by gas chromatographic analysis of the ester mixture. The free energy differences between equatorial and axial carbethoxyl so determined are: (1) −1.0 kcal./mole, (2) −1.0 to −1.2 kcal./mole, (3) −1.2 kcal./mole. The "*A*-value" for the CO_2Et group is thus 1.1 ± 0.1 kcal.

In previous papers[2-4] we have established methods for finding the conformational equilibrium constant for a substituted cyclohexane (Fig. 1).

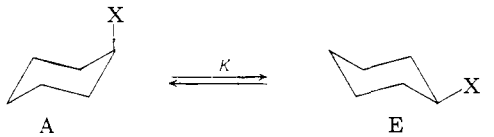

Fig. 1.—Conformational equilibrium in substituted cyclohexane.

One of these methods,[2] first developed by Winstein and Holness,[2b] is kinetic in nature; the desired conformational equilibrium constant K is given by the equation

$$K = (k - k_a)/(k_e - k) \quad \text{(i)}$$

where k is the specific rate for any convenient reaction of the substituted cyclohexane ($C_6H_{11}X$), k_e is the specific rate for the same reaction of the *trans*-4-*t*-butyl derivative, 4-$(CH_3)_3CC_6H_{10}X$, and k_a is the specific rate for the same reaction of the corresponding *cis*-4-*t*-butyl derivative. In another, thermodynamic method,[3] the 4-*t*-butyl derivatives are equilibrated directly by some suitable chemical means and the equilibrium constant (Fig. 2) is determined from the composition of the equilibrium mixture as established by conventional methods of analysis.

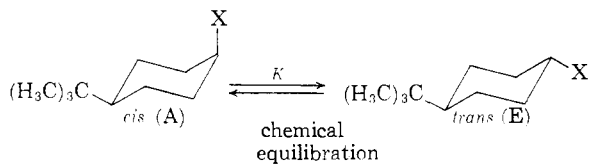

Fig. 2.—Equilibration of 4-*t*-butyl-substituted cyclohexanes.

The present paper reports the determination of the conformational equilibrium constant and the corresponding free energy difference for the carbethoxyl group by means of eq. i applied to saponification rates, since work in the area of natural products (see below) encouraged us to expect rather substantial differences in saponification rates between equatorial and axial carbethoxyl groups. An accurate determination of the equilibrium constant for the carbethoxyl group seemed desirable in order to compare its effective size with that of methyl for which the free energy difference between the equatorial and axial positions is believed to be[5] 1.6–1.8 kcal./mole. It would seem that although the two oxygen atoms attached to the carbethoxyl group are more space-consuming than the three hydrogen atoms in the methyl group, the carbon atom of the carbethoxyl group and the two attached oxygen atoms are planar, and the group could orient itself in the axial position of a cyclohexane ring in such a way as to minimize the interactions between the carbethoxyl oxygens and the axial hydrogen atoms in positions 3 and 5. (The methyl group cannot do this.) In addition, there is a possibility that attractive London forces between the rather polarizable carbethoxyl group and the interfering axial hydrogen atoms counteract the steric repulsion to some extent.[1]

Ethyl cyclohexanecarboxylate was obtained commercially and the corresponding *cis*- and *trans*-4-*t*-butyl homologs were synthesized from the known[6] acids. Alkaline saponification rates of the esters were measured in 70% aqueous ethanol at 25.2°. The averaged measured rate constants (in l. mole^{-1} sec.$^{-1}$ × 10^4) are: ethyl cyclohexanecarboxylate (k), 7.25; ethyl *cis*-4-*t*-butylcyclohexanecarboxylate (k_a), 0.428; ethyl *trans*-4-*t*-butylcyclohexanecarboxylate (k_e), 8.50. From these specific rates, applying eq. i, one can calculate a conformational equilibrium constant of 5.46 corresponding to a free energy difference of −1.0 kcal./mole.

The considerably greater specific rate—by a factor of 20—of saponification of ethyl *trans*-4-*t*-butylcyclohexanecarboxylate (equatorial carbethoxyl group) as compared to the *cis* isomer (axial isomer) is in keeping with examples recorded in the literature. Thus the alkaloid yohimbine, which has an equatorial carbomethoxyl group, is saponified considerably faster than its axial epimer corynanthine.[7] Since the alkaline saponification

(1) Paper VII, E. L. Eliel and R. G. Haber, *J. Am. Chem. Soc.*, **81**, 1249 (1959).

(2) (a) E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957); (b) *cf.* S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

(3) E. L. Eliel and R. S. Ro, *ibid.*, **79**, 5992 (1957).

(4) For a recent review, see E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

(5) W. G. Dauben and K. S. Pitzer in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 18; E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

(6) H. H. Lau and H. Hart, *ibid.*, **81**, 4897 (1959).

(7) M. M. Janot, R. Goutarel, A. LeHir, M. Amin and V. Prelog, *Bull. soc. chim. France*, 1085 (1952).

of corynanthine gives yohimbic acid rather than corynanthic acid,[8] it is not clear whether the recorded rate of saponification of corynanthine is a true saponification rate, or whether it is the rate of epimerization of corynanthine to yohimbine, the latter being saponified rapidly as it is formed. For the purpose of the present investigation it was important to establish that the measured rate of saponification of ethyl *cis*-4-*t*-butylcyclohexanecarboxylate was a true saponification rate and not an epimerization rate (to the *trans* isomer). It was found that the product of saponification of the *cis*-ester was nearly pure *cis*-acid; therefore epimerization did not precede saponification.

Our findings are in contradistinction to a recent report[9] according to which the saponification rate of methyl cyclohexanecarboxylate is greater than that of methyl *trans*-4-*t*-butylcyclohexanecarboxylate despite the fact that the carbomethoxyl group in the latter compound must already be essentially entirely in the equatorial position. The explanation[9] of this anomalous result as being due to a polar effect of the *t*-butyl group is unlikely in view of the present results with the ethyl ester. Furthermore, the dissociation constants of *cis*-3-*t*-butylcyclohexanecarboxylic acid and *trans*-4-*t*-butylcyclohexanecarboxylic acid, measured in 80% methyl Cellosolve at 25°,[10] are identical. This precludes the possibility of an appreciable polar effect attributable to a 4-*t*-butyl group.

As an independent check on the conformational equilibrium constant of the carbethoxyl group, both ethyl *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylate were epimerized, by means of sodium ethoxide in boiling absolute ethanol, to an equilibrium mixture of the two esters. Gas chromatographic analysis indicated that mixtures of the same composition were obtained from either ester containing 84.7 ± 0.6% of the *trans* isomer. Assuming[2] that the *t*-butyl group, because of its very large size (exceeding by far the size of the carbethoxyl group), will occupy the equatorial position in both the *cis*- and *trans*-esters, the carbethoxyl group will be axial in the *cis*-ester and equatorial in the *trans*-ester and equilibration will correspond to the situation depicted in Fig. 2 (X = CO_2Et). Thus the conformational equilibrium constant for carbethoxyl may be calculated directly from the observed composition of the equilibrated mixture of esters as being 84.7/15.3 or 5.54 in absolute ethanol at 80° corresponding to a free energy difference between axial and equatorial carbethoxyl of −1.2 kcal./mole.

Since the carbethoxyl group in ethyl cyclohexanecarboxylate occupies largely the equatorial position, the specific rate of saponification of this ester (k) is rather close to that of the purely equatorial ethyl *trans*-4-*t*-butylcyclohexanecarboxylate (k_e) and application of the eq. i therefore involves a small difference between large numbers in the denominator and is thus apt to give a rather inaccurate result. It was reasoned that this difficulty could be avoided, and that, at the same time, a direct comparison of the size of carbethoxyl and methyl could be obtained by studying the conformational equilibrium for ethyl *cis*-4-methylcyclohexanecarboxylate (Fig. 3). The averaged specific rate of saponification of this ester was found

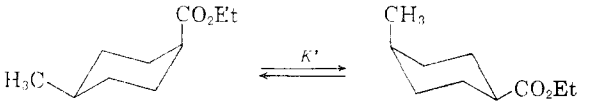

Fig. 3.—Conformational equilibrium for ethyl *cis*-4-methylcyclohexanecarboxylate.

to be 2.65 × 10^{-4} l. $mole^{-1}$ $sec.^{-1}$ in 70% aqueous ethanolic sodium hydroxide at 25.2°, from which K' is calculated to be 0.38. The fact that K' is smaller than unity means (*cf.* Fig. 3) that carbethoxyl is smaller than methyl. The value of $\Delta F'$ for the equation (Fig. 3) as written is 0.6 kcal./mole. Now the process shown in Fig. 3 involves moving a methyl group from the equatorial to the axial position at an expense[5] of 1.6–1.8 kcal./mole and moving a carbethoxyl group from the axial to the equatorial position at a gain of x kcal./mole. Assuming that the free energy changes due to the translocation of the methyl and carbethoxyl groups are additive,[4] and considering, by the usual convention, that ΔF is negative for a favorable change, $\Delta F' = x + 1.6(1.8) = 0.6$ and $x = -1.0(-1.2)$ kcal./mole.

The values as obtained by the three methods (−1.0, −1.2, −1.0 to −1.2 kcal./mole) for the free energy difference between equatorial and axial carbethoxyl are in good agreement, the average value being −1.1 ± 0.1 kcal./mole.

After this work was completed, a paper appeared[11] reporting the equilibration of diethyl cyclohexane-*cis*-1,3-dicarboxylate. The equilibration product contained 71% *cis*- and 29% *trans*-ester. Making allowance for the fact that the *trans* isomer in this case is a *dl*-pair, this gives a ΔF value of −1.05 kcal./mole for the carbethoxyl group which is in excellent agreement with our findings. An identical result was obtained[11] for the equilibration of the corresponding methyl ester.

Stolow[12] and, independently, Tichý, Jonáš and Sicher,[10] recently have calculated the conformational equilibrium constants for the carboxyl group from the dissociation constants for cyclohexanecarboxylic acid and various methylcyclohexanecarboxylic acids in water[13] and in 80% methyl Cellosolve[10] and have concluded that the free energy difference between equatorial and axial carboxyl is −1.7 ± 0.2 kcal./mole[12] (−1.6 ± 0.3 kcal./mole[10]). A calculation[12] based on the dissociation constants of cyclohexanecarboxylic acid and its *cis*- and *trans*-4-*t*-butyl homologs in 66% aqueous dimethylformamide leads to an uncertain value for $-\Delta F_{CO_2H}$ of 1.0–2.0 kcal./mole. Recently, an empirical equation has been described[14] by means of which the pK_a values of acids (where

(8) M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 509 (1949).

(9) E. A. S. Cavell, N. B. Chapman and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960).

(10) M. Tichý, J. Jonáš and J. Sicher, *Coll. Czech. Chem. Comm.*, **24**, 3434 (1959).

(11) N. L. Allinger and R. J. Curby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

(12) R. D. Stolow, *J. Am. Chem. Soc.*, **81**, 5806 (1959).

(13) J. F. Dippy, S. R. C. Hughes and J. W. Laxton, *J. Chem. Soc.*, 4102 (1954).

(14) P. F. Sommer, V. P. Arya and W. Simon, *Tetrahedron Letters*, 18 (1960).

K_a is the apparent dissociation constant of the acid in 80% by weight aqueous methyl Cellosolve) can be estimated as a function of the number of 1,3-diaxial interactions present involving the carboxyl group and the nature of the immediate environment of the carboxyl group.

It appears from these data that the carboxyl group is appreciably larger than either carbethoxyl or carbomethoxyl. It is not entirely clear at the present time, however, whether the difference in ΔF-values is real. Since the dissociation constant of cyclohexanecarboxylic acid is very close to that of *trans*-4-*t*-butylcyclohexanecarboxylic acid, eq. i did not give results of acceptable accuracy when applied to this case and both reported values[10,12] for ΔF_{CO_2H} are essentially based on the dissociation constant of *cis*-4-methylcyclohexanecarboxylic acid. Unfortunately, this acid is very hard to obtain in the pure state. Our own sample, obtained by saponification of the ethyl ester which, in turn, was purified by preparative gas chromatography, melted at 32–33°, whereas Sicher's acid[10] melted at 28–29.5° and Dippy's acid[13] (on whose dissociation constant Stolow's calculations[12] are based) melted at 12–13°. Moreover, values for ΔF_{CO_2H} based on *cis*-4-methylcyclohexanecarboxylic acid depend on ΔF_{CH_3}; if this is taken to be 1.6 kcal./mole instead of 1.8 kcal./mole, Sicher's value becomes 1.4 ± 0.3 kcal./mole instead of 1.6 ± 0.3 and would therefore (within the combined limits of error) fall into the range of our own value for ΔF_{CO_2Et}.

If ΔF_{CO_2H} is indeed larger than ΔF_{CO_2Et}, the difference may be ascribed to hydrogen bonding in the acid (which would tend to stabilize the equatorial isomer because of its better disposition to form a hydrogen bond) or possibly due to complications arising from existence of acid molecules in dimeric form. Such dimers would presumably form more readily when the carboxyl groups are in the equatorial positions.

Experimental

All melting points and boiling points are uncorrected. Microanalyses by Midwest Microlab, Indianapolis, Ind. Infrared spectra were recorded on a Perkin–Elmer model 21 and on a Baird model 4–55 instrument. Gas chromatography was effected by means of a Wilkens Aerograph instrument.

Ethyl cyclohexanecarboxylate was obtained from Eastman Kodak Co. and distilled before use; b.p. 82–83° (16 mm.), $n^{20}D$ 1.4421. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.48; H, 10.60. The ester used in some of the kinetic runs was prepared from the acid and redistilled before use; b.p. 76–77° (10 mm.), $n^{20}D$ 1.4418.

Ethyl *cis*- and *trans*-4-*t*-Butylcyclohexanecarboxylate.—The acids were prepared from 4-*t*-butylbenzoic acid as described elsewhere.[8] Infrared spectra of the acids compared with the spectrum of 4-*t*-butylbenzoic acid confirmed the absence of any detectable amount of the latter.

The *trans*-acid, m.p. 173–175° (11 g., 0.06 mole), was allowed to react at room temperature with 7.5 ml. of thionyl chloride for about 16 hours. The reaction mixture was warmed on a steam-bath for 30 minutes, and the excess thionyl chloride was removed by vacuum distillation. To the acid chloride was added 35 ml. of pyridine followed by a solution of 35 ml. of absolute ethanol in 20 ml. of pyridine. After standing overnight, the reaction mixture was poured into dilute hydrochloric acid, and the ester was recovered by ether extraction, washing of the ether solution with water and sodium bicarbonate solution, drying over magnesium sulfate and distillation of the ether. Distillation of the residue gave 10 g. (79%) of ethyl *trans*-4-*t*-butylcyclohexanecarboxylate, b.p. 74–78° (0.4–0.7 mm.), $n^{20}D$ 1.4522.

The *cis*-acid, m.p. 119.5–121°, similarly yielded ethyl *cis*-4-*t*-butylcyclohexanecarboxylate in 82% yield, b.p. 89–90° (2.5 mm.), $n^{20}D$ 1.4532. In this case the acid chloride was warmed gently only 10 minutes to prevent rearrangement.[8] The isomeric purity of the two esters was established by comparison of infrared spectra and by gas chromatography on a Tide column at 194° and a helium flow rate of 57 ml./min. The *cis* isomer showed no trace of impurity. The *trans* isomer contained a trace of impurity estimated at *ca.* 1%. *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found (*trans*-ester): C, 73.85; H, 11.51; (*cis*-ester): C, 73.81; H, 11.35.

Ethyl *cis*-4-Methylcyclohexanecarboxylate.—*p*-Toluic acid (28 g., 0.2 mole) dissolved in 250 ml. of glacial acetic acid was hydrogenated in the presence of 5 g. of platinum oxide at 50 p.s.i. The hydrogen uptake was rapid, the reaction being completed in about 1 hour. The solutions from the reductions of a total of 73 g. of *p*-toluic acid were combined and the acetic acid was distilled. The residue was fractionally distilled through a helix-packed column giving 61.6 g. of acid in four fractions.

The first three fractions (46 g.) were combined and esterified by refluxing for 12 hours with 400 ml. of absolute ethanol and 12 g. of concentrated sulfuric acid. This yielded 52 g. of crude ethyl ester which was distilled twice through a spinning band column. Although there was an enrichment of the *cis*-ester in the first fractions of each distillation, as shown by gas chromatographic analysis using a Tide column, no fraction was completely free of the other isomer. The best fractions were combined and subjected to further purification by preparative gas chromatography through a Beckman Megachrom, utilizing an Apiezon column. It was assumed that the peak with the lower retention time was the *cis*-ester. This subsequently was verified by the kinetic results as well as saponification and isolation of the acid. The *cis*-ester which was collected contained no detectable amount of *trans*-ester (gas chromatogram on an Apiezon column). *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 71.12; H, 10.69.

A portion of the ester (200 mg., 0.0012 mole) was saponified. On acidification and cooling, 0.08 g. (*ca.* 50% yield) of white crystals, m.p. 30–32°, was obtained. Recrystallization at low temperature from *n*-hexane gave crystals, m.p. 32–33°. The highest literature value for the melting point of *cis*-4-methylcyclohexanecarboxylic acid is 28–29.5°.[10]

Epimerization Studies.—Ethyl *trans*-4-*t*-butylcyclohexanecarboxylate (2.12 g., 0.01 mole) was refluxed with sodium ethoxide prepared from 0.0238 g. (0.001 mole) of sodium in 40 ml. of anhydrous ethanol for 70 hours at 80°. The solution was cooled, diluted with water and extracted with ether. The extract was washed and dried over anhydrous magnesium sulfate. The ether was distilled and the concentrated residue (2.6 g.) was analyzed directly by gas chromatography on a Tide column at 196° and a helium flow rate of 60 ml./min. A similar procedure was followed with the *cis*-ester. Analysis was carried out by peak-height, half-width measurements with the following results: from *trans*-ester, *trans*, 85.3%, *cis*, 14.7%; from *cis*-ester, *trans*, 84.1%, *cis*, 15.9%. A synthetic mixture consisting of 81.1% *trans* and 18.9% *cis*, gave an analysis of 81.0% *trans* and 19.0% cis. Acidification of the water washings of the esters gave only a trace of solid.

Preparative Saponification of Ethyl *cis*-4-*t*-Butylcyclohexanecarboxylate.—Aqueous sodium hydroxide, 30 ml. of 0.0968 *N* solution (2.90 mole), was diluted to 100 ml. with absolute ethanol and mixed with a solution of 0.6156 g. (290 mmoles) of ethyl *cis*-4-*t*-butylcyclohexanecarboxylate in 70% ethanol (total volume 100 ml.). After 7 days at 25°, back-titration of an aliquot of the solution indicated that saponification had proceeded to the extent of about 50%. The reaction mixture was acidified with hydrochloric acid and extracted with petroleum ether. The petroleum ether layer was washed with water and then extracted twice with 50-ml. portions of 0.1 *N* sodium hydroxide. After washing further with water, the petroleum ether layer was dried and concentrated. The infrared spectrum of the residual ester was identical with that of the *cis* starting material, indicating that no epimerization had occurred.

TABLE I

SAPONIFICATION RATE OF ETHYL CYCLOHEXANECARBOXYLATE IN 70% ETHANOL AT 25.2°

Base, 30 ml. of 0.2206 *N* NaOH; ester equivalent, 1.0341 g. quench acid, 10 ml. of 0.05043 *N* HCl, indicator, phenolphthalein; back titration alkali, 0.05651 *N* NaOH; a = 0.03308 mole/l.

Time, sec.	Titer, ml. of NaOH 0.05651 *N*	x, mole/l.	$a - x$, mole/l.	Reaction, %	$k \times 10^4$, l./mole/sec.
Zero	3.07	0	0.03308	0	..
10175	4.21	0.00644	.02664	19.5	7.19
13892	4.56	.00842	.02466	25.5	7.39
17474	4.79	.00970	.02336	29.3	7.21
20673	5.03	.01107	.02201	33.5	7.34
22701	5.14	.01170	.02138	35.4	7.26
25624	5.27	.01243	.02065	37.6	7.13
27779	5.44	.01339	.01969	40.5	7.42
85455	7.01	.02226	.01082	67.3	7.24
98900	7.22	.02345	.00963	70.9	7.41
				Mean k =	7.29

TABLE II

SUMMARY OF SAPONIFICATION RUNS

Ethyl ester of acid	a, mole/l.	$k \times 10^4$, l. mole^{-1} sec.$^{-1}$	Reacn., %
Cyclohexanecarboxylic	0.03414	7.31 ± 0.14[b]	68
	.03408	7.16 ± .07	67
	.03395	7.17 ± .11	67
	.03308	7.29 ± .09	71
	.02746[a]	7.31[a] ± .13	63[a]
cis-4-*t*-Butylcyclohexanecarboxylic	.03410	0.428 ± .016	28
	.03308	0.427 ± .012	26
trans-4-*t*-Butylcyclohexanecarboxylic	.03414	8.52 ± .13	51
	.03442	8.48 ± .12	47
	.03297	8.49 ± .18	45
cis-4-Methylcyclohexanecarboxylic	.02788[a]	2.82[a] ± .19	42[a]
	.02758[a]	2.47[a] ± .03	53[a]

[a] These runs were carried out using 15 ml. of 0.2 *N* NaOH and an equivalent amount of ester, each diluted to 50 ml. of 70% ethanolic solution. [b] This figure and all corresponding ones indicate mean deviations.

The basic aqueous layer was acidified with concentrated hydrochloric acid and the acid liberated was extracted with petroleum ether. The crude acid recovered from the petroleum ether layer in the usual manner melted at 107–112°, raised to 115–117° by one recrystallization from petroleum ether (b.p. 30–60°). Its infrared spectrum was identical with that of the pure *cis*-acid (lit.[6] m.p. 117–118°), indicating that little if any epimerization had occurred in the saponification.

Kinetic Saponification Runs.—The alkali solution for the kinetic runs was prepared by diluting exactly 30 ml. of standardized 0.2 *N* carbonate-free aqueous sodium hydroxide to 100 ml. by means of absolute ethanol in a volumetric flask. An amount of ester exactly equivalent to 30 ml. of the alkali was weighed out in a small weighing bottle, transferred to a 100-ml. volumetric flask and made up to the mark with absolute ethanol after prior addition of exactly 30 ml. of boiled distilled water. Both solutions then were placed in a thermostat at 25.2° for at least 60 minutes and then mixed by pouring them through a wide-necked funnel into a 250-ml. glass-stoppered round-bottom flask in the thermostat. A 10-ml. aliquot was withdrawn immediately and the clock started. This sample and all aliquots subsequently withdrawn were quenched in a mixture of 10 ml. of standardized hydrochloric acid and 25 ml. of absolute ethanol (in some cases 15 ml. of absolute ethanol) and back-titrated with 0.05 *N* sodium hydroxide using phenolphthalein as an indicator. A blank was run at the start of each saponification run.

Specific rates were calculated from the equation $k = x/a \times t(a-x)$ where t is the time in seconds, a is the initial concentration of ester or base in moles/l. and x is the amount of ester or base, expressed in moles/l. consumed in time t.

A typical saponification run is detailed in Table I. Table II summarizes the specific rates determined in this investigation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES 24, CALIF.]

Electrophilic Substitution at Saturated Carbon. XI. Steric Course of the Base-catalyzed Decarboxylation Reaction[1]

BY DONALD J. CRAM AND PAUL HABERFIELD

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The steric course of the base-catalyzed decarboxylation of optically pure 2-cyano-2-phenylbutanoic acid to 1-cyano-1-phenylpropane has been studied. The reaction was found to occur with from 16% net retention to 11% net inversion. The steric course was controlled by the dissociating power and acidity of the solvent and, in some media, by the character of the cation. In *t*-butyl alcohol, the ammonium salt gave 10% retention, whereas metal salts provided almost completely racemic product. In ethylene glycol, the extreme inversion solvent, the stereospecificity of the reaction was independent of the concentration and nature of the cation for five different cations. In phenol, ammonium and potassium salts gave 16% and 8% net retention, respectively, whereas lithium and tetramethylammonium salts gave 5% and 6% net inversion, respectively. The results are interpreted in terms of a mechanistic scheme in which intimate ion pairs cleave to give retention, and solvent-separated or dissociated anions to give inversion of configuration. Both processes involve carbanion intermediates, which collapse to optically active product because of the asymmetric character of their environment. The more acidic the proton donor, the shorter the life of the carbanion, and the more stereospecific the reaction.

The decarboxylation of carboxylic acids has long been considered one of the most ubiquitous examples of an electrophilic substitution reaction. Suggestions have been made[2] that this reaction

(1) This work was supported by a grant from the Petroleum Research Fund Administered by the American Chemical Society. Grateful acknowledgment is hereby made to donors of this fund.

(2) (a) H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 514 (1948); (b) B. R. Brown, D. L. Hammick and A. J. B. Scholefield, *J. Chem. Soc.*, 778 (1950).