THE JOURNAL OF Organic Chemistry®

Volume 26, Number 10 October 24, 1961

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Studies of Configuration. XI. A New Method for the Evaluation of Conformational Free Energy Differences[1,2]

DONALD S. NOYCE AND LLOYD J. DOLBY[3]

Received January 30, 1961

The equilibrium between a substituted *cis*-3-hydroxycyclohexanecarboxylic acid and its lactone has been investigated as a method for the direct determination of the conformational free energy preferences (*A* values) for substituted cyclohexanes. *cis*-4-*tert*-Butyl-*cis*-3-hydroxycyclohexanecarboxylic acid exists 96% as the lactone at equilibrium, in contrast to *cis*-3-hydroxycyclohexanecarboxylic acid, which exists as the lactone only to the extent of 12%.

A values have been determined for the methoxyl group (0.74 kcal.) and for the ethoxyl group (0.98 kcal.).

From a study of *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid, *cis*-4-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid, and *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid, it is suggested that *cis*-1,2-interactions are about 0.4 kcal.

The rapid development of conformational concepts[4] has been of great aid in interpreting the reactivity of nonaromatic compounds, in particular of cyclohexane derivatives. These concepts have been placed upon a more quantitative basis by the introduction of the conformational free energy term, designated the *A* value by Winstein and Holness,[5] and ΔF_x by Eliel and Haber.[6] Winstein and Holness[5] have used both first order and second order rate data to assign *A* values to a variety of functional groups. Eliel and Haber[6] and Eliel and Lukach[7] have used second order rate data to evaluate the conformational free energy differences. Equilibrium methods have been investigated; infrared[8] and proton resonance[9] spectroscopy, and complexing methods[10] have been studied for the purpose of assigning *A* value.[11]

In some instances there are considerable differences in the values which have been obtained. Of particular cogency to the present study, the value assigned to the hydroxyl group ranges from 0.4 kcal./mole to 0.96 kcal./mole.[5,7,8,10,12,13]

It is the purpose of the present study to explore the applicability of a further equilibrium method for the determination of *A* values. The system chosen for this study is the equilibrium between a substituted *cis*-hydroxycyclohexanecarboxylic acid and the corresponding lactone. *cis*-3-Hydroxycyclohexanecarboxylic acid (I) is in equilibrium with

(1) Supported in part by grants from the National Science Foundation (NSF-G-2387 and G-5921). Presented in part at the 136th meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

(2) Previous papers, *J. Org. Chem.*, **26**, 1732, 2101 (1961).

(3) Dow Chemical Corp. Fellow, 1958–1959.

(4) For recent reviews see: M. S. Newman, *Steric Effects in Organic Chemistry*, Chap. 1, by W. G. Dauben and K. S. Pitzer, Wiley, New York, 1956; D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956); H. D. Orloff, *Chem. Revs.*, **54**, 347 (1954); E L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

(5) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

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

(7) E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957).

(8) R. A. Pickering and C. A. Price, *J. Am. Chem. Soc.*, **80**, 4931 (1958).

(9) A. J. Berlin and F. R. Jensen, *Chem. & Ind.*, 998 (1960); L. W. Reeves and K. O. Stromme, *Canad. J. Chem.*, **38**, 1241 (1960).

(10) S. J. Angyal and D. J. McHugh, *Chem. & Ind.*, 1147 (1956).

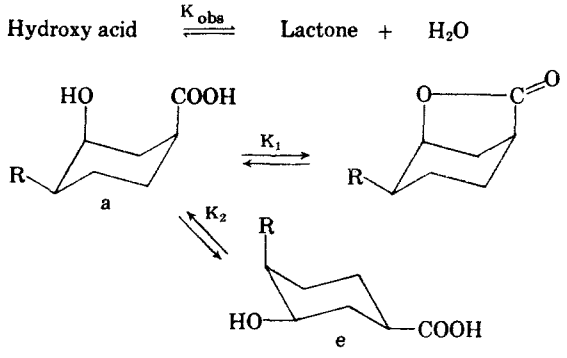
(11) For convenience we shall refer to the conformational *free energy* differences as the *A* values.

(12) M. A. Kabayama and D. Patterson, *Canad. J. Chem.*, **36**, 563 (1958).

(13) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

only 12% of the lactone.[14] This is in sharp contrast to the equilibrium found for most γ-lactones.[15] For example, the lactone of α-methyl-γ-hydroxyvaleric acid (II) is present in the equilibrium mixture to the extent of 98%.[14] As the sum of the A values for the hydroxyl group and the carboxyl group[16] is about 2.5 kcal. per mole, it is not suprising that the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid is unstable with respect to the free acid which can exist in the diequatorial conformation.

When a third substituent is introduced into the cyclohexane ring of a *cis*-3-hydroxycyclohexanecarboxylic acid so that the substituent is equatorial when the lactone ring is closed, the proportion of the lactone at equilibrium is increased. It may be shown that this change in equilibrium is directly related to the A value of the substituent.



Let B equal the total amount of acid at equilibrium and L equal the total amount of lactone at equilibrium. N_a and N_e are the mole fractions of the axial and equatorial conformational isomers of the hydroxy acid. As the concentration of water is essentially unchanged throughout the reaction when the equilibrium is established in dilute aqueous solution, the concentration of water is neglected in the equilibrium expression.

For unsubstituted 3-hydroxycyclohexanecarboxylic acid:

$$K_{obs} = \frac{L}{B} = \frac{L}{N_aB + N_eB} = \frac{L}{N_aB(1 + K_2)} \quad (1)$$

$$K_{obs} = \frac{K_1}{1 + K_2} \quad (2)$$

In a similar fashion the equilibrium expression may be derived from a substituted 3-hydroxycyclohexanecarboxylic acid and a substituted lactone.

$$K'_{obs} = \frac{K_1'}{1 + K_2'} \quad (3)$$

To simplify these relations further, it is necessary to make an approximation, namely that K_2 is large compared to 1, and K_2' is also large compared to unity. Thus

$$K_{obs} \cong \frac{K_1}{K_2};\ K'_{obs} \cong \frac{K_1'}{K_2'} \quad (4)$$

Taking the ratio of these expressions:

$$\frac{K'_{obs}}{K_{obs}} = \frac{K_1'/K_2'}{K_1/K_2} \quad (5)$$

K_1 should be a constant for all compounds of the series (see below), as the conformations of the lactone and the axial form of the hydroxy acid are essentially the same, and the same factors which affect the stability of one will affect the stability of the other equally. Thus

$$\frac{K'_{obs}}{K_{obs}} = \frac{K_2}{K_2'} \quad (6)$$

As K_2 and K_2' are equilibrium constants for the interchange of conformational isomers, they may be evaluated in terms of A values. For the unsubstituted hydroxy acid,

$$\Delta F_2 = -RT \ln K_2 = -RT \ln \frac{N_e}{N_a} = -A_{COOH} - A_{OH} - Z \quad (7)$$

This free energy difference for 3-hydroxycyclohexanecarboxylic acid is equal to the sum of the A values of the hydroxyl and carboxyl groups, plus a term Z which reflects the 1,3-diaxial interaction between these groups.

In a similar manner, the equilibrium expression for a substituted compound may be formulated,

$$\Delta F_2' = -A_{CO_2H} - A_{OH} - Z + A_R \quad (8)$$

where the A value for the substituent is of the opposite sign since the substituent is axial when the carboxyl and hydroxyl groups are equatorial. Putting in the free energy terms associated with the equilibrium constants K_{obs} and K'_{obs}:

$$-\Delta F' - \Delta F = -RT \ln e^{\frac{A_R}{RT}} \quad (9)$$

or

$$\Delta F - \Delta F' = A_R \quad (10)$$

Thus, the A value for the substituent is directly related to the free energy change for the lactone–hydroxy acid equilibrium, upon comparing a substituted hydroxy acid with an unsubstituted hydroxy acid.

The assumption that K_1 remains unchanged throughout the series is a good one. As K_1 is the equilibrium between the diaxial conformer of the

(14) E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1935).

(15) E. J. Boorman and R. P. Linstead, *J. Chem. Soc.*, 580 (1933); A. Kailan, *Z. physik. Chem.*, 101, 63 (1922).

(16) The A value of the carboxyl group has recently been investigated by Stolow and by Tichy, Jonas, and Sicher.[17] Stolow reports a value of 1.6–1.9 kcal./mole, depending upon the assigned A value for the methyl group. Tichy, Jonas, and Sicher report a value of 1.6 ± .3 from pK_a considerations. From the equilibration studies of Zimmerman and Giallombardo[18] on 4-phenylcyclohexanecarboxylic acid a minimum A value of 1.95 for the carboxyl group may be calculated.

(17) R. D. Stolow, *J. Am. Chem. Soc.*, 81, 5806 (1959); M. Tichy, J. Jonas and S. Sicher, *Coll. Czech. Comm.*, 24, 3434 (1959).

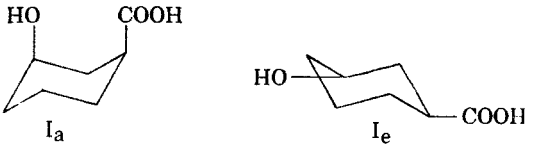
(18) H. E. Zimmerman and H. J. Giallombardo, *J. Am. Chem. Soc.*, 78, 6259 (1956).

hydroxy acid and the corresponding lactone, it represents an intramolecular esterification equilibrium. The aspects of the substituent which might alter K_1 are the ordinary steric and electronic effects of the substituent. In general, the esterification equilibrium is insensitive to polar effects.[19] For example, α,β-unsaturated acids esterify to the same extent as the corresponding saturated acids but at an appreciably slower rate.[20] Esterification equilibria for a group of substituted acetic acids show that the equilibria are only little affected by the introduction of alkyl groups.[20] Furthermore, the equilibrium constants for the esterification of acetic acid and the three chlorinated acetic acids vary only from 4 to 6.[21] Another interesting observation is that the esterification equilibria for the sulfuric acid catalyzed esterification of both benzoic and *o*-nitrobenzoic acid with methanol are virtually identical.[22] In this pair, the two acids differ greatly not only in electronic surroundings but in the amount of steric hindrance near the carboxyl group. This body of evidence furnishes firm support for the view that the esterification equilibrium is not greatly affected by changes in steric and electronic environment.

In the present case, the equilibrium reaction is an intramolecular reaction, and intramolecular reactions are normally very insensitive to steric hindrance effects. This is illustrated by the fact that the lactone–hydroxy acid equilibrium for 3-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid[14] gives a very reasonable A value for the methyl group. In this hydroxy acid the hydroxyl group is tertiary, yet the amount of lactone is even greater than predicted, while ordinary tertiary alcohols give low yields of esters in ordinary esterification reactions. From the evidence presented in the preceding discussion, it seems unlikely that variations in K_1 could cause an appreciable error in the calculation of A values from lactone–hydroxy acid equilibria.

The approximation that $K_2 + 1$ is equal to K_2 is of course only valid as long as K_2 is considerably greater than one. As K_2 is the conformational equilibrium constant for the equilibrium between the two chair forms of the free hydroxy acid which are in equilibrium with the lactone, it cannot readily be measured experimentally.

Three different approaches, however, all suggest similar values for K_2 for *cis*-3-hydroxycyclohexanecarboxylic acid. In the first instance comparison with α-methyl-γ-valerolactone (II) is instructive. The very high percentage of lactone (II) at equilibrium provides a direct estimate of the conformational energy difference as being about 3.8 kcal. Secondly, from the sum of A values for the hydroxyl group and carboxyl group plus the 1–3 interaction term (the Z term) estimated as 1.8–3.6 kcal., a value for the conformational free energy difference $I_a \rightarrow I_e$ of 3.5–5.0 kcal. is obtained.



I_a I_e

Finally, from the lactone-hydroxy acid equilibrium value for 4-*tert*-butyl-3-hydroxycyclohexanecarboxylic acid to be discussed later in this paper, a minimum value of 100 may be calculated for K_2 for I. This leads to a minimum value of 3.7 kcal. for the energy difference $I_a \rightarrow I_e$.[23]

Thus, the assumption that K_2 is much greater than one is good for all substituents, with the exception of very large groups such as *tert*-butyl and possibly isopropyl.

RESULTS

The preparation of the requisite compounds for this study has been reported separately.[2] For examination of the general range of this method, we have studied a group of 4-alkyl-3-hydroxycyclohexanecarboxylic acids. The all *cis* isomer is the one desired for these studies and is accessible by reduction of the corresponding aromatic compound.[2]

Results of equilibration studies for *cis*-4-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (III), *cis*-4-ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid (IV), *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid (V), and *cis*-4-*tert*-butyl-*cis*-3-hydroxycyclohexanecarboxylic acid (VI) are presented in Table I.

Results of the equilibrium studies on the 4-alkyl-3-hydroxycyclohexanecarboxylic acids show a very satisfactory progression. There is general agreement with previously reported[5] A values for the groups methyl, ethyl, isopropyl, and *t*-butyl. Some limitations of the method are revealed by the studies carried out at two different temperatures. Whereas the equilibrium shifts to favor the lactone for the smaller groups, in the case of *cis*-4-isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid (V), the shift is in the other direction. It is to be noted that the

(19) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 213.

(20) N. Menshutkin, *Ann. Chim. et Phys.*, [5] **30**, 81 (1883); for brief reviews see M. S. Newman in M. S. Newman, *Steric Effects in Organic Chemistry*, Wiley, New York, 1956, p. 210; E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Englewood Cliffs, N. J., 1954, p. 601.

(21) D. M. Lichty, *Am. Chem. J.*, **17**, 27 (1895); D. M. Lichty, *Am. Chem. J.*, **18**, 590 (1896).

(22) G. E. K. Branch and D. S. McKittrich, *J. Am. Chem. Soc.*, **45**, 321 (1923).

(23) By making the assumption that *cis*-4-*t*-butyl-*cis*-3-hydroxycyclohexanecarboxylic acid exists completely in the conformation with OH and COOH axial (*i.e.*, $K_2 = 0$) one may then calculate a value for K_1 of 22.8 at 130°. Thus for *cis*-3-hydroxycyclohexanecarboxylic acid (assuming $K_1 = 22.8$) a value of K_2 may be calculated of 102. This leads to the free energy difference between axial and equatorial forms of I of 3.7 kcal. Calculations at 100° using an extrapolated value for VI lead to a value of 4.4 kcal.

TABLE I

MEASURED VALUES FOR THE LACTONE-HYDROXY ACID EQUILIBRIA FOR 4-ALKYL-3-HYDROXYCYCLOHEXANECARBOXYLIC ACIDS

Compound	Temp.	% Acid at Equilibrium	ΔF cal./mole	ΔH cal./mole	ΔS e.u.	*A* Value, 100°	kcal., 140°
I	100	88.5	1510	5390	10.4		
	128	82.3	1220	5100	9.7		
	143	79.1	1100				
	100	88.7[a]					
III	100	36.0	−420	1020	3.8	1.94	
	143	32.8	−590				1.69
IV	100	26.1	−760	1060	4.8	2.27	
	143	23.4	−970				2.09
V	100	6.0	−2040	−7300	−14.1	3.55	
	139	14.0	−1490				2.63
VI	130	4.2	−2480			4.43[c]	3.6[c]
	100	1.6[b]					

[a] Data of Boorman and Linstead.[14] [b] This value is subject to considerable uncertainty, because of the very small amount of acid titrated. At 100° the solution of VI-lactone was not entirely homogeneous. [c] *A* values have been estimated, using the entropy value from V at 100° and 140°.

TABLE II

A VALUES FOR ALKOXYL GROUPS BY THE LACTONE-HYDROXY ACID METHOD

Compound	Temp.	% Acid at Equilibrium	ΔF cal./mole	ΔH cal./mole	ΔS e.u.	*A* Value, 100°	kcal., 140°
cis-4-Methoxy-*cis*-3-hydroxycyclo-	100	73.8	770	4260	9.3	0.74	
hexanecarboxylic acid (VII)	143	61.0	370				0.73
cis-4-Ethoxy-*cis*-3-hydroxycyclohex-	100	67.4	540	3380	7.6	0.98	
anecarboxylic acid (VIII)	143	56.3	210				0.89

calculated entropy difference is also substantially different. This change is undoubtedly the result of a shift in the conformational population for V. The original assumptions were based upon the hydroxy acid being almost exclusively in the conformation with both hydroxyl and carboxyl equatorial. When the substituent is as large as isopropyl, this is apparently no longer true, and substantial populations of both chair conformations appear to be the case.

Nevertheless, the *A* value determined in this fashion is still eminently reasonable, and these considerations point out the utility of the method.

Finally, in the case of 4-*tert*-butyl-3-hydroxycyclohexanecarboxylic acid (VI), the size of the alkyl group dominates the accessible conformations for the hydroxy acid. The *A* value thus calculated is now of significance only as a minimum value.

A values for alkoxyl groups. The determination of *A* values for moderately small groups is thus the most practical by this procedure. We have accordingly determined *A* values for methoxyl and ethoxyl groups (Table II). The values thus obtained (0.74 for methoxyl, 0.98 for ethoxyl) are to be compared with the range of values for hydroxyl, 0.3–0.9.[5,7,8,10,12,13] Furthermore the *A* value increment on changing from methyl to ethyl of about 0.3 kcal. is indicative of an assignment of a value of 0.45 to hydroxyl.

We also attempted to evaluate the *A* value for bromine in a similar fashion, studying the behavior of *cis*-4-bromo-3-hydroxycyclohexanecarboxylic acid lactone. However, another reaction ensues. Upon opening of the lactone solvolytic rearrangement of the bromohydrin immediately takes place. Thus two moles of acid are generated, one mole of bromide ion, and there is formed 3-ketocyclohexanecarboxylic acid in almost quantitative yield.

A value for methyl. The previous discussion has been applied to 4-substituted 3-hydroxycyclohexanecarboxylic acids; but there is no restriction which should limit the method to any particular position in the cyclohexane ring. It is therefore of interest to examine the effect of changing the position of the substituent, and for this purpose a group of x-methyl-3-hydroxycyclohexanecarboxylic acids have been studied. *cis*-2-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (IX) was prepared by the reduction of 2-methyl-3-hydroxybenzoic acid.[2,24] Data for the lactone-hydroxy acid equilibrium of 3-methyl-3-hydrocyclohexanecarboxylic acid are available from the studies of Boorman and Linstead.[14] The preparation of *trans*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (X) has been reported.[2] The configurational assignment was based upon the substantial amount (51%) of lactone in equilibrium with X. In contrast, *cis*-5-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid in equilibrium with only 3% of the corresponding lac-

(24) L. F. Fieser and W. C. Lothrup, *J. Am. Chem. Soc.*, **58**, 749 (1936).

TABLE III

EFFECT OF POSITION OF SUBSTITUENT ON *A* VALUE BY LACTONE-HYDROXY ACID METHOD

Compound	Temp.	% Acid at Equilibrium	ΔF cal./mole	ΔH cal./mole	ΔS e.u.	*A* Value, 100°	kcal. 140°[a]
cis-2-Methyl-*cis*-3-hydroxycyclo-hexanecarboxylic acid (IX)	100	21.61	−950	175	3.0	2.47	
	143	21.51	−1080				2.18
3-Methyl-3-hydroxycyclohexane-carboxylic acid[a]	100	27.9	−700			2.20	
III (4-Methyl)						1.94	1.69
trans-5-Methyl-*cis*-3-hydroxycyclo-hexanecarboxylic acid (X)	100	49.0	−29.7			1.54	

[a] Calculated from data of Boorman and Linstead.[14]

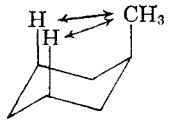
tone (see Table IV). The results of our studies with these compounds are given in Table III.

The *A*- value for the methyl group was assigned as 1.6–1.8 kcal. by Beckett, Pitzer, and Spitzer[25] on the basis of the barriers to internal rotation in acyclic hydrocarbons. Winstein and Holness[5] used 1.8 kcal. as a reference point in calculating many other *A* values. Somewhat more recently other direct investigations have favored the lower range of values for the methyl *A* value. Equilibrations studies on 1,4-dimethylcyclohexane give a value of 1.54 kcal.[17,26] Eliel and Rerick[27] have obtained values of 1.5 ± .1 and 1.8 kcal. from studies of equilibria, for 3- and 4-methylcyclohexanols.

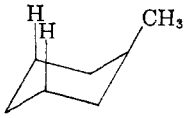
In the present study, the value of 1.54 kcal. (at 100°) is obtained from 5-methyl-3-hydroxycyclohexanecarboxylic acid. Considering temperature and solvent differences, we conclude that 1.8 represents the best value at room temperature.

Nature and magnitude of 1,2-interactions. An additional result of these studies is that some information is forthcoming on the interactions of adjacent groups. In III, there is present a 1,2-interaction between the methyl group and the hydroxyl group, while in IX there are two 1,2-interactions, one between methyl and hydroxyl, the other between methyl and carboxyl. These may be described as *buttressing effects.*

Descriptively this phenomenon is the result of nonideal chair conformations. In methylcyclohexane, the axial conformation is undoubtedly slightly distorted to increase the 1-3 axial distance (XI) by bending the methyl carbon toward the general molecular plane (XII).

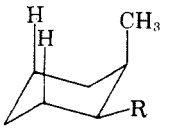


XI

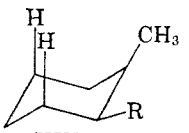


XII

Introduction of an equatorial group on the adjacent carbon (XIII) thus provides an increased repulsion as the methyl moves away from the 3 and 5 axial hydrogens (XIV).



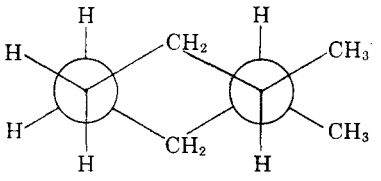
XIII



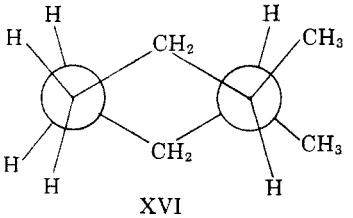
XIV

For interactions between methyl groups and hydroxyl groups, our present data suggest that about 0.4 kcal. should be associated with this *buttressing* phenomenon.

In a similar manner, one might expect *buttressing effects* between 1,2-diequatorial substituents. Thus in *trans*-1,2-dimethylcyclohexane deformation of the ring to provide the greatest separation between substituents would have the effect of flattening the ring and increasing the 1,2-hydrogen repulsions (XV and XVI).[27a]



XV



XVI

In this case the *buttressing effects* should be smaller since only 1,2-interactions are involved.

This analysis provides a rationalization for the observations that in the *cis-trans* equilibria for the methylcyclohexanols[13,28] and the dimethylcyclohexanes the *trans*-1,2-isomers predominate over

(25) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (9147).

(26) A. K. Roebuck and B. L. Evering, *J. Am. Chem. Soc.*, **75**, 1631 (1953).

(27) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

(27a) ADDED IN PROOF: Eliel and Richer (E. L. Eliel and J.-C. Richer, Abstracts of the 139th Meeting of the American Chemical Society, St. Louis, Mo., March, 1961, p. 41-*O*) have recently discussed deformations of the cyclohexane ring, including *cis*-1,2-disubstituted cyclohexanes.

(28) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2527 (1956).

TABLE IV

Compound	Time of Equilibration, Days	Temp.	Acid, %
cis-3-Hydroxycyclohexanecarboxylic acid (I)	2	100	88.58
	2	100	88.47
	2	128	82.28
	3	128	82.23
	3	139	80.80
	3	143	79.12
	2	143	78.99
cis-3-Hydroxycyclohexanecarboxylic acid lactone	3	100	88.27
	7	100	88.43
cis-3-Hydroxycyclohexanecarboxylic acid (I)[a]	1	100	88.00
	3	100	87.30
cis-3-Hydroxycyclohexanecarboxylic acid lactone[a]	1	100	74.70
	2	100	86.8
	4	100	90.1
	6	100	89.5
cis-4-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (III)	3	100	36.16
	3	100	36.26
	2	143	33.20
cis-4-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	5	100	35.85
	5	100	35.84
	2	143	32.40
cis-4-Ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid (IV)	3	100	25.34
	4	100	26.02
	3	100	25.04
	3	100	25.29
	3	143	24.16
cis-4-Ethyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	5	100	27.49
	5	100	27.31
	3	143	22.59
cis-4-Isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid (V)	3	100	5.97
	4	100	5.83
	4	139	14.38
cis-4-Isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	6	100	6.01
	6	100	6.09
	4	139	13.68
cis-4-*tert*-Butyl-*cis*-hydroxycyclohexanecarboxylic acid lactone (VI)[b]	2	128	4.52
	2	130	4.11
	2	130	3.98
cis-4-Methoxy-*cis*-3-hydroxycyclohexanecarboxylic acid (VII)	4	100	73.88
	4	100	74.22
	2	143	61.24
cis-4-Methoxy-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	4	100	73.77
	4	100	73.77
	2	143	60.69
cis-4-Ethoxy-*cis*-3-hydroxycyclohexanecarboxylic acid (VIII)	3	100	67.47
	3	100	67.59
	3	143	55.7
cis-4-Ethoxy-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	7	100	67.12
	3	143	56.87
cis-2-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (IX)	4	100	63.72
	24	100	27.5
	24	100	28.2
	47	100	21.73
	47	100	21.72
	12	143	20.92
cis-2-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	27	100	19.62
	65	100	21.38
	12	143	21.39
trans-5-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid (X)	2	100	48.90
	2	100	48.80
trans-5-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	2	100	49.78
	2	100	48.98
	4	100	49.03
	4	100	48.55
cis-3-Hydroxy-3-methylcyclohexanecarboxylic acid lactone[a]	42 hr.	100	21.6
	48 hr.	100	27.1
	72 hr.	100	28.7
cis-4-Bromo-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	9 hr.	100	200.0[c]
cis-2-Bromo-*cis*-3-hydroxycyclohexanecarboxylic acid lactone[d,e]	2	100	3.0[d] (Br = 1.5%)
	66	100	190.0[e]
trans-4-Isopropyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	7	100	93.92
cis-5-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid	3	100	96.81
cis-5-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone	3	100	92.98

[a] Data of Boorman and Linstead.[14] [b] After titration of the first two samples recorded in the table, the lactone was recovered by extracting it into ether. The ether extracts were washed with sodium carbonate solution, water and dried. The ether was evaporated and the residual lactone was sublimed and recrystallized three times from hexane. The purified lactone of *cis*-4-*tert*-butyl-*cis*-3-hydroxycyclohexanecarboxylic acid obtained in this fashion was used in the last run recorded in the table. [c] After the titration of the sample with standard sodium hydroxide, the solution was acidified with a few drops of concentrated sulfuric acid and treated with a solution of 300 mg. of 2,4-dinitrophenylhydrazine dissolved in aqueous sulfuric acid. The 2,4-dinitrophenylhydrazone of 3-ketocyclohexanecarboxylic acid precipitated immediately. Filtration of the mixture afforded 413 mg. (105%) of the crude 2,4-dinitrophenylhydrazone, m.p. 192–195°. The analytical sample melts at 195.8–196.5° after several crystallizations from aqueous ethanol. *Anal.* Calcd. for $C_{13}H_{14}N_4O_6$: C, 48.44; H, 4.38; N, 17.39. Found: C, 48.40; H, 4.52; N, 17.58. [d] After titration of the sample with standard barium hydroxide solution, it was titrated with silver nitrate using dichlorofluorescein as an indicator. [e] The solution had become cloudy during the long heating period and it was filtered before titration. After titration with standard sodium hydroxide, the solution was acidified with concentrated sulfuric acid and treated with a solution of 300 mg. of 2,4-dinitrophenylhydrazine in aqueous sulfuric acid. There was obtained 239 mg. (60%) of crude 3-ketocyclohexanecarboxylic acid 2,4-dinitrophenylhydrazone. After crystallization from aqueous ethanol the material melts at 194.8–196.5°. No depression in melting point was observed when the material was admixed with varying amounts of the 2,4-dinitrophenylhydrazone obtained above.

the *cis*-1,2-isomers to a greater extent than the *trans*-1,4-isomers predominate over the *cis*-1,4-isomers. From the preceding discussion it is clear that the ground state energy of the *trans*-1,2-isomer should be higher than the ground state energy of the *trans*-1,4-isomer, but most important, there should be a still greater difference between the ground state energies of the *cis*-1,2 and *cis*-1,4 isomers. This is not shown by equilibrium data, but the standard free energies of formation for the iso-

meric 1,2- and 1,4-dimethylcyclohexanes show this order.[29]

EXPERIMENTAL[30]

Methyl 3-hydroxy-4-methoxybenzoate. 3-Hydroxy-4-methoxybenzoic acid was prepared by the silver oxide oxidation of isovanillin as described for the oxidation of vanillin.[31] 3-Hydroxy-4-methoxybenzoic acid was obtained in 55% yield, m.p. 254.8–256.3° (lit.[32] m.p., 255–257°) after crystallization from dilute ethanol. The acid was esterified in the usual manner with methanol-hydrogen chloride to give methyl 3-hydroxy-4-methoxybenzoate, m.p. 66–67° (lit. m.p. 87–88°,[32] 66–67°[33]).

cis-4-Methoxy-cis-3-hydroxycyclohexanecarboxylic acid lactone. Reduction of 42 g. of methyl 3-hydroxy-4-methoxybenzoate, using rhodium on alumina catalyst in acetic acid solution, afforded 31.86 g. of material, b.p. 90–140°/6 mm. The material (18.2 g., 52%) boiling 135–140°/6 mm. solidified upon standing and the infrared spectrum showed a carbonyl band at 1770 cm.$^{-1}$ attributed to the γ-lactone function. The infrared spectra of the lower boiling fractions showed no hydroxyl absorption but ordinary ester absorption at 1740 cm.$^{-1}$ The lower boiling material was not investigated further. The solid lactone was crystallized repeatedly from benzene–petroleum ether (b.p. 00–00°) to yield 8 g. of pure *cis*-4-methoxy-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m. p. 66.5–67.0°, unchanged by further crystallization.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.74; H, 7.74.

cis-4-Methoxy-cis-3-hydroxycyclohexanecarboxylic acid (VII). In a 100-ml. round bottomed flask was placed 5 g. of pure *cis*-4-methoxy-*cis*-3-hydroxycyclohexanecarboxylic acid lactone along with 2.5 g. of sodium hydroxide and 30 ml. of water. The resulting mixture was heated on a steam bath for 7 hr. after which time the homogeneous solution was cooled, acidified to *p*H 1 with hydrochloric acid, and continuously extracted with ether. The ether was evaporated and the solid residue was crystallized several times from methyl acetate to yield 2.76 g. (50%) of pure *cis*-4-methoxy - *cis* - 3 - hydroxycyclohexanecarboxylic acid, m.p. 117.6–118.3°.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10; neut. equiv., 174.19. Found: C, 55.44; H, 8.21; neut. equiv., 176.0.

A sample of the pure acid was converted to the *p*-phenylphenacyl ester in the usual way. It melts at 100–101° after four crystallizations from absolute ethanol.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.89; H, 6.61.

3-Hydroxy-4-ethoxybenzoic acid was prepared by the silver oxide oxidation of 3-hydroxy-4-ethoxybenzaldehyde[34] as described for the oxidation of vanillin.[31] From 85 g. of the aldehyde there was obtained 48.2 g. of 3-hydroxy-4-ethoxybenzoic acid, m.p. 217.5–218.5°, after two crystallizations from 95% ethanol (lit.,[35] m.p. 218–219°). Esterification with methanol-hydrochloric acid afforded methyl 3-hydroxy-4-ethoxybenzoate, m.p. 127–128° (lit.,[35] m.p. 127–128°).

cis-4-Ethoxy-cis-3-hydroxycyclohexanecarboxylic acid (VIII). Reduction of methyl 3-hydroxy-4-ethoxybenzoate (28.7 g.) with 5% rhodium on alumina in acetic acid afforded two main fractions upon distillation. The lower boiling fraction, 6.2 g., b.p. 100–130° (6 mm.), showed no hydroxyl absorption but a strong band at 1740 cm.$^{-1}$ ascribed to a normal ester. This material was not investigated further. The higher boiling fraction, 12.3 g., b.p. 140–160° (6 mm.) showed carbonyl absorption at 1770 cm.$^{-1}$ attributed to the γ-lactone function. There were also weak bands at 1740 and 1700 cm.$^{-1}$ showing that the material was a mixture of free acid, lactone, and normal ester.

The mixture was directly saponified with 7.2 g. of sodium hydroxide and 25 ml. of water. The cooled solution was acidified with concentrated hydrochloric acid whereupon some solid material separated. The solid material was filtered and washed with water. The combined aqueous filtrates were extracted with ethyl acetate. The ethyl acetate extracts were washed with water and flash distilled. The solid material was added to the residue and the combined material was distilled to yield 7 g. of an oil, b.p. 125–160° (6 mm.). The infrared spectrum of this material showed carbonyl absorption at 1770 cm.$^{-1}$ and 1700 cm.$^{-1}$ indicating it was a mixture of the desired lactone and carboxylic acids. The liquid mixture was taken up in ether and washed with sodium carbonate solution, then water. The ether solution was evaporated to yield the crude lactone which was saponified with 5 g. of sodium hydroxide and 25 ml. of water. The saponification mixture was worked up in the usual manner and the crude hydroxy acid was crystallized five times from water to yield 3 g. of pure *cis*-4-ethoxy-*cis*-3-hydroxycyclohexanecarboxylic acid (VIII), m.p. 157.5–158.5°, unchanged by further crystallization.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.42; H, 8.57; neut. equiv., 188.22. Found: C, 57.37; H, 8.36; neut. equiv., 186.0.

cis-4-Ethoxy-cis-3-hydroxycyclohexanecarboxylic acid lactone. A 1-g. (0.053 mole) sample of the pure acid was distilled to furnish 650 mg. (0.038 mole, 72%) of a clear oil, b.p. 142–143°/6 mm., which soon solidified to long needles of *cis*-4-ethoxyl-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m.p. 32–33.2°.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.41; H, 8.28.

cis-2-Bromo-cis-3-hydroxycyclohexanecarboxylic acid lactone. A 5-g. sample of 2,3-dibromocyclohexanecarboxylic acid,[36] m.p. 169–170°, was dissolved in a solution of 3 g. of sodium bicarbonate and 50 ml. of water. The resulting solution was heated on a steam bath for 20 min. during which time an oil separated. The mixture was extracted four times with ethyl acetate and the ethyl acetate extracts were washed with water. The ethyl acetate was evaporated under reduced pressure to leave 4 g. (95%) of crude *cis*-2-bromo-*cis*-3-hydroxycyclohexanecarboxylic acid lactone. The crude lactone was crystallized three times from methyl acetate–ligroin and twice from benzene-ligroin to yield 1 g. (27%) of pure *cis*-2-bromo-*cis*-3-hydroxycyclohexanecarboxylic acid lactone, m.p. 64–65° (lit.[36] m.p. 66.0–66.5°).

cis-4-Bromo-cis-3-hydroxycyclohexanecarboxylic acid lactone was prepared in similar fashion from 3,4-dibromocarboxylic acid, m.p. 86–87° (lit.[37,38] m.p. 86°), by treatment with dilute sodium bicarbonate. Crystallization from benzenepentane afforded the pure lactone, m.p. 100.5–101.1° (lit.[38] m.p. 101°).

Equilibrium studies. The lactone-hydroxy acid equilibria for the substituted *cis*-3-hydroxycyclohexanecarboxylic acids were measured by titrating the equilibrium mixture

(29) F. D. Rossini, Kenneth S. Pitzer, R. L. Arnett, and G. C. Pimentel, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, Pa., 1953, p. 735.

(30) Melting points are corrected; boiling points are uncorrected.

(31) I. A. Pearl, *Org. Syntheses*, **30**, 101 (1950).

(32) E. Fischer, M. Bergmann, and W. Lipschitz, *Ber.*, **51**, 75 (1918).

(33) E. Spath and J. Pikl, *Ber.*, **62**, 2258 (1929).

(34) We are indebted to the Monsanto Chemical Co. for a gift of a generous sample of 3-hydroxy-4-ethoxybenzaldehyde.

(35) H. King, *J. Chem. Soc.*, 1161 (1939).

(36) B. R. Thomas, thesis, University of California, Berkeley, 1957.

(37) W. H. Perkin, *J. Chem. Soc.*, **85**, 433 (1904).

(38) R. Grewe, A. Heinke, and C. Sommer, *Ber.*, **89**, 1976 (1956).

with standardized barium hydroxide solutions. Samples of the acid or lactone under study were weighed into small glass weighing vessels and the weighing vessel containing the sample was transferred directly to a Pyrex test tube (32 × 300 mm.) after which 50 ml. of carbon dioxide-free water was added by means of a pipet. Runs at temperatures above 100° were carried out in heavy - walled test tubes of similar dimensions. Precautions were taken at each step to prevent the sample from picking up carbon dioxide from the atmosphere. The sealed tubes were heated in a constant temperature bath maintained at temperature by means of a boiling solvent for the desired period of time. The cooled sample tube was opened and the contents titrated immediately with standard barium hydroxide of the appropriate concentration. Titrations involving the addition of only small quantities of base were done under nitrogen which had been passed through a tube containing drierite.

The concentration of the samples was normally about 0.02–0.03 molal which required about 200 mg. of the compound per run. It was found that the concentration of the compound under study could be varied considerably without measurably affecting the observed equilibrium.

Perhaps it is worthwhile to point out that the equilibrium was established at *far* different rates for some of the compounds. Substitution in the 2-position slows the rate of establishment of equilibrium markedly. It required at least 30 days at 100° to establish equilibrium in the case of *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid while the 4-substituted compounds attained equilibrium in about 2 days at 100°. The same effect was observed in the solvolytic hydrolyses of *cis*-4-bromo-*cis*-3-hydroxycyclohexanecarboxylic acid lactone and the lactone of *cis*-2-bromo-*cis*-3-hydroxycyclohexanecarboxylic acid. Reaction was complete with the former in a matter of a few hours, while the 2-substituted compound had only reacted to the extent of 1.5% after 2 days. In all but one case, equilibrium was approached from both the hydroxy acid and the corresponding lactone.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Conformational Analysis. XVIII. The Relative Stabilities of the *cis* and *trans* A/B Ring Junctures of Steroidal 4 and 6 Ketones[1,2]

NORMAN L. ALLINGER, MARGARET A. DAROOGE,[3] AND ROBERT B. HERMANN

Received February 6, 1961

From optical rotation measurements in the ultraviolet region it has been found that cholestan-4-one contains 99% of the A/B *trans* and 1% A/B *cis* at equilibrium in methanol at 25°. For cholestan-6-one, the corresponding values are 88% *trans* and 12% *cis*. The conformational analysis of these systems is discussed.

Robins and Walker[4] first considered the conformational effects of converting alkyl substituted cyclohexane rings to cyclohexanones. The relative stabilities of their compounds were attributed to nonbonded interactions which were generalized by Klyne[5] as 2-alkyl and 3-alkyl ketone effects. Accurate experimental data on these effects is very sparse, but recent work on monocyclic cyclohexanones[6] has indicated that the 2-alkyl ketone effect of a methyl group is of negligible importance.

In the present work the 4- and 6-ketocholestanes have been chosen as systems in which to study these effects. These compounds are known in *cis* and *trans* forms, and the rotatory dispersion method[7] offers a convenient way to study quantitatively the epimerization reaction. The compounds were synthesized in general by literature procedures. A marked improvement in the conversion of Δ^5-cholestene to the $5\alpha,6\alpha$-epoxide was developed utilizing monoperphthalic acid in place of perbenzoic acid as the epoxidizing agent.

It was noted that the crude coprostane-6-one obtained in the present work contained an impurity having a very large negative optical rotation at the wave length used for the equilibration studies. Considerable care was therefore taken to obtain samples which were quite pure. For comparison purposes a sample of cholestan-4-one was also synthesized from Δ^4-cholestene by the hydroboration method of H. C. Brown,[8] followed by oxidation of the resulting alcohol.

Conformational analysis of the 6-ketones can be carried out by considering structures It and Ic. These structures should differ energetically from the 9-methyldecalins[9–11] only to the extent that an

(1) Paper XVII, N. L. Allinger, and M. A. Miller, J. Am. Chem. Soc., **83**, 2145 (1961).

(2) This research was supported in part by a grant (E-2267) from the National Institutes of Health, U. S. Public Health Service.

(3) Predoctoral Fellow of the Division of General Medical Sciences, U. S. Public Health Service, 1960–1962.

(4) P. A. Robins and J. Walker, *J. Chem. Soc.*, 3960 (1954); 1789 (1955); *Chem. & Ind.*, 772 (1955).

(5) W. Klyne, *Experientia*, **12**, 119 (1956).

(6) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).

(7) (a) N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960); (b) J. F. Biellmann, D. Francetic, and G. Ourisson, *Tetrahedron Letters*, No. **18**, 4 (1960).

(8) (a) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 5694 (1956); (b) R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959); (c) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).

(9) N. L. Allinger and J. L. Coke, *J. Org. Chem.*, **26**, 2096 (1961).

(10) W. G. Dauben, O. Rohr, A. Labbauf, and F. D. Rossini, *J. Phys. Chem.*, **64**, 283 (1960).

(11) R. B. Turner, *J. Am. Chem. Soc.*, **74**, 2118 (1952).