[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Quantitative Relationship between Dissociation Constants and Conformational Equilibria. Cyclohexanecarboxylic Acids[1]

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The preparations of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid are described. Their apparent dissociation constants are reported and compared to that of cyclohexanecarboxylic acid. A quantitative relationship between dissociation constants and conformational equilibria has been derived and applied to the prediction of the dissociation constants of some 3- and 4-alkylcyclohexanecarboxylic acids. Published dissociation constants were employed to calculate the conformational equilibrium constants ($\mathbf{K} = (a)/(e)$, where in chair conformation *a*, the carboxyl group is axial; and in *e*, equatorial) of *cis*- and *trans*-4-methylcyclohexanecarboxylic acid and cyclohexanecarboxylic acid. The average calculated values of **K** at 25° for these acids are 1, 0.003 and 0.06, respectively.

Different conformations of a single mobile molecule are distinct chemical species, each having different chemical and physical properties.[3] The properties of the mobile molecule are an average of the individual properties of its several conformations, weighted according to the population of each conformation.[3] The purpose of this paper is to demonstrate the application of these principles to equilibria such as those involved in the ionization of carboxylic acids.

A discussion of the connection between the rate of a reaction and the distribution of the reacting species among various conformations has been presented by Winstein and Holness.[3,4] Exclusive attention was directed toward the two chair conformations of simple cyclohexane derivatives. A method of quantitative conformational analysis based on rate measurements was derived with the aid of transition state theory and the assumption that conformational equilibration is rapid relative to the rate of reaction. A similar derivation has been reported independently by Eliel and Lukach.[5]

Analogous equations based on equilibrium constants rather than rate constants are derived in this paper.[6]

Derivation.—The equations derived below are applicable to all suitable reversible dissociation reactions. However, since the examples to be discussed involve proton transfer to solvent (S), the derivation has been expressed in terms of the dissociation of a proton. The derived equations are generally applicable to dissociation reactions, at equilibrium, of molecules which can be assumed to exist in two conformations which are in equilibrium with one another. Similar equations may be derived involving equilibrium among more than two conformations (such as equation 12, below). At first, only the two chair conformations of cyclohexane derivatives are to be considered.[7] The equilibria involved are illustrated in Fig. 1, where A is an acid, B is its conjugate base, "a" designates the chair conformation in which the functional group is *axial*, "e" designates the chair conformation in which the functional group is *equatorial*, K_a and K_e are the specific dissociation constants for the pure "a" and "e" conformations, respectively, and **K** is the conformational equilibrium constant. The equilibria involved are defined by equations 1–4. The experimental thermodynamic dissociation constant is expressed by equation 5.[8] Substitution of relations from equations 3 and 4 into equation 5 gives equation 6. Substitution of the relation $(A_a) = \mathbf{K}_A \cdot (A_e)$ from equation 1, and solution for the conformational equilibrium constant of the acid, converts equation 6 to 7. A similar derivation which combines equations 2–5 leads to equation 8, the relationship between the conformational equilibria of the acid and its conjugate base.[9] Equations 7 and 8 together express the simple quantitative relationship between dissociation constants and conformational equilibria.

$$\begin{tikzcd}
A_e + S \arrow[r, shift left, "\mathbf{K}_A"] \arrow[d, shift right, swap, "K_e"] & A_a + S \arrow[l, shift left] \arrow[d, shift right] \\
B_e + SH^+ \arrow[u, shift right] \arrow[r, shift left, "\mathbf{K}_B"] & B_a + SH^+ \arrow[l, shift left] \arrow[u, shift right, swap, "K_a"]
\end{tikzcd}$$

Fig. 1.

$$\mathbf{K}_A = (A_a)/(A_e) \qquad (1)[8]$$

$$\mathbf{K}_B = (B_a)/(B_e) \qquad (2)$$

$$K_e = (B_e)(SH^+)/(A_e)(S) \qquad (3)$$

$$K_a = (B_a)(SH^+)/(A_a)(S) \qquad (4)$$

$$K = [(B_a) + (B_e)](SH^+)/[(A_a) + (A_e)](S) \qquad (5)$$

$$K = [K_a(A_a) + K_e(A_e)]/[(A_a) + (A_e)] \qquad (6)$$

$$\mathbf{K}_A = (K - K_e)/(K_a - K) \qquad (7)$$

$$\mathbf{K}_B = (K_a/K_e)\mathbf{K}_A \qquad (8)$$

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(1) Taken in part from the author's Ph.D. Thesis, University of Illinois, 1956; *Dissertation Abstr.*, **17**, 751 (1957). Presented in part at the 135th Meeting of the American Chemical Society, Boston, Mass. April 6, 1959.

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(3) S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5562 (1955).

(4) A concise discussion of the conformational concept as applied to reactivity has been presented by W. G. Dauben and K. S. Pitzer, in M. S. Newman, ed., "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 44–47; see also W. Hückel and M. Hanack, *Ann.*, **616**, 18 (1958); R. C. Cookson, *Ann. Reports* (*London*), **54**, 172 (1957).

(5) E. L. Eliel and C. A. Lukach, THIS JOURNAL, **79**, 5986 (1957).

(6) Background references concerning cyclohexane stereochemistry and conformational analysis are cited in refs. 3–5. For an excellent review of the relationship between dissociation constants and the structure of organic compounds, see H. C. Brown, D. H. McDaniel and O. Häfliger, in E. A. Braude and F. C. Nachod, eds., "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, pp. 567–655.

(7) The relative importance of other conformations will be discussed in connection with equation 12, below.

(8) The symbols in parentheses represent activities.

(9) Replacing the terms (A_e) and (A_a) of equation 5 by $(SH^+) \cdot (B_e)/K_e(S)$ and $(SH^+)(B_a)/K_a(S)$ from equations 3 and 4, dividing numerator and denominator by B_e, replacing $(B_a)/(B_e)$ by $\mathbf{K}_B$ (equation 2), solving for $\mathbf{K}_B$, and replacing the term $(K - K_e)/(K_a - K)$ by $\mathbf{K}_A$ (equation 7) gives equation 8.

Substitution of the mole fractions of each conformation, defined by equations 9 and 10, converts equation 6 to 11. The general equation 12, for the case where *n* different conformations are considered to exist in equilibrium, may be derived analogously.

$$N_{A_a} = (A_a)/[(A_a) + (A_e)] \tag{9}$$

$$N_{A_e} = (A_e)/[(A_a) + (A_e)] \tag{10}$$

$$K = K_a N_{A_a} + K_e N_{A_e} \tag{11}$$

$$K = K_a N_{A_a} + K_b N_{A_b} + \ldots + K_n N_{A_n} \tag{12}$$

Discussion and Results

Equations 11 and 12 state that the experimental dissociation constant, K, is a weighted average of the specific dissociation constants. The weighting factor is the mole fraction (or relative population) of each conformation.[10]

Consideration of conformations other than the two chair conformations of cyclohexane derivatives is necessary at this point.[11] The *skewed* (or *stretched*) conformation (s) is of greatest interest, because it is predicted to be the most stable flexible conformation of cyclohexane.[12,13]

(s)

By a method of computation "based upon a crude approximation," Howlett has calculated that whereas the boat conformation (b) is 8 kcal./mole less stable than the chair conformation (c), the skewed[12] or "half-rotated"[13] conformation (s) is only 4 kcal./mole less stable than the chair.[13,14] Assuming the value *ca.* 4 kcal./mole, the corresponding population ratio, (s)/(c), is 0.001 at 25° for cyclohexane. Although negligible for cyclohexane, the population of a flexible conformation might be much larger, for example, for certain *cis*-1,4-disubstituted cyclohexanes. For *cis*-4-alkylcyclohexanecarboxylic acids (Fig. 2), the corresponding population ratio of the most stable flexible (n) and chair (generally a) conformations is estimated to be (n)/(a) = *ca.* 0.02, at 25°, and "n" could contribute 2–10% to the value of K.[15]

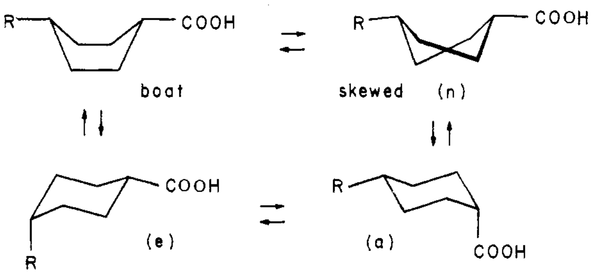

Fig. 2.

Although the possibility is recognized that flexible conformations might contribute up to 10% to the value of K for *cis*-4-alkylcyclohexanecarboxylic acids (if $F_c - F_s > 4.0$ kcal./mole), refinement of the calculations to include small contributions from flexible conformations would seem unwarranted until they are shown by experiment to be non-negligible. Therefore, in the calculations to follow, the contributions of flexible conformations are assumed to be negligible (as would be expected if $F_c - F_s > 5.8$ kcal./mole).

The quantities needed for the calculation of the conformational equilibrium constants ($\mathbf{K}_A$ and $\mathbf{K}_B$) by the use of equations 7 and 8 are the particular values of K, K_e and K_a for the compound in question; K can be measured experimentally; K_e and K_a can be evaluated by introducing the assumption that they are constant for a suitable series of compounds. An example of such a series would be the 4-alkylcyclohexanecarboxylic acids.[16] This assumption opens the way toward two approaches for the evaluation of K_e and K_a: (1) the solution of simultaneous equations, and (2) the use of "pure" axial and equatorial conformations.[19] The use of simultaneous equations in the evaluation of K_e and K_a is illustrated by the 4-alkylcyclohexanecarboxylic acids. For this series of compounds, the necessary data for the calculation of K_e and K_a at 25° have been taken from the literature. Three equations (7a, 7b and 7c) can be written in the form of equation 7, one for each of the compounds: *trans*-4-

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[10] The *form* of the relationship between dissociation constants and conformational equilibria is identical to that reported between rate constants and conformational equilibria in refs. 3–5. However, with dissociation constants rather than rate constants, one has the advantage that no assumptions are necessary concerning the path of the reaction, the transition state or the rate of equilibration of the conformations involved.

[11] It follows from equation 12 that the contribution of a given conformation, n, to the experimental dissociation constant, K, will be negligible if $K_n N_{A_n} \ll K$. In general, this condition can be considered satisfied when $N_{A_n} < 0.001$ and $K_n < K$, but not when $K_n > K$, nor when $N_{A_n} > 0.001$. With this criterion, the importance of other conformations may be estimated.

[12] P. Hazebroek and L. J. Oosterhoff, *Disc. Faraday Soc.*, **10**, 87 (1951); R. E. Reeves, *Ann. Rev. Biochem.*, **27**, 15 (1958).

[13] K. E. Howlett, *J. Chem. Soc.*, 4353 (1957).

[14] See Dauben and Pitzer, ref. 4, pp. 14–15, for a review of other calculations of the energy difference between the boat and chair conformations of cyclohexane, which give values ranging from 1–11 kcal./mole.

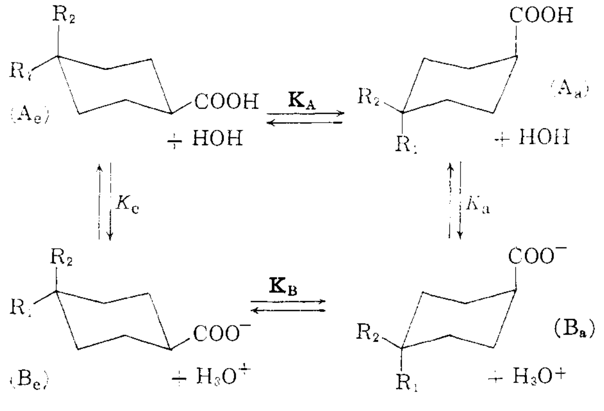
[15] For the *cis* isomer, the chair conformations (a and e) must have one group axial, while for the flexible conformations, (b and n), both substituents may have a nearly equatorial environment. The resulting free energy difference between the most stable chair and flexible conformations would be about 2.3 kcal./mole, equivalent to (n)/(a) = *ca.* 0.02 at 25°. (The energy difference between axial (a) and equatorial (e) cyclohexanecarboxylic acid $(F_a - F_e)_{C_6H_{11}COOH}$ was calculated to be *ca.* 1.7 kcal./mole (*vide infra*). Assuming (1) the environments of the substituents of "n" are equivalent to equatorial environments, (2) the additivity of free energies and (3) $(F_n - F_e)_{C_6H_{11}COOH} = 4$, then $F_n - F_a = (4 - 1.7) = 2.3$ kcal./mole for a *cis*-4-alkylcyclohexanecarboxylic acid.) Since K_n is likely to be 2 to 5 times K_a (as is K_e, *vide infra*), the percentage contribution of "n" to K may be correspondingly greater than its percentage population.

[16] The relatively non-polar 4-alkyl group, being far from the site of reaction, exerts a strong influence upon the conformational equilibrium without significant independent influences upon the dissociation equilibrium (such as electrical effects or steric inhibition of solvation of the functional group). Evidence in support of this assumption is the fact that the 3- and 4-methylcyclohexanecarboxylic acids of corresponding conformational orientation have about the same thermodynamic dissociation constants: 10^5K for *cis*-3(e,e) 1.31, *trans*-4-(e,e) 1.30; and for *trans*-3(e,a) 0.9, *cis*-4-(e,a) 0.92, ref. 17. However, with such substituents as hydroxyl or carboxyl, where polar effects are expected, there are significant differences between the dissociation constants of the corresponding acids (see ref. 18). Further evidence for the absence of polar effects and direct steric effects of 4-alkyl substituents is presented by Eliel.[5]

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

[18] M. Kilpatrick and J. G. Morse, THIS JOURNAL, **75**, 1846 (1953).

[19] The second approach has been described for the case of rate constants.[3,5] Both approaches are applicable to rate data as well as equilibrium data.



Structure of the cyclohexanecarboxylic acid	R_1	R_2	Thermodynamic dissociation constant[17]
1. *trans*-4-Me	CH_3	H	$10^5K_1 = 1.30 \pm 0.005$
2. *cis*-4-Me	H	CH_3	$10^5K_2 = 0.922 \pm 0.005$
3.	H	H	$10^5K_3 = 1.26 \pm 0.005$

Fig. 3.

methylcyclohexanecarboxylic acid (A_1), *cis*-4-methylcyclohexanecarboxylic acid (A_2) and cyclohexanecarboxylic acid (A_3). The equilibria involved are illustrated in Fig. 3. The three equations in five unknowns cannot be solved without further information. By the aid of an additional assumption, the additivity of free energies, two more equations may be obtained.

The free energy difference between the two chair conformations of a 1,4-disubstituted cyclohexane is assumed to equal the sum of the free energy differences between the two chair conformations of each of the corresponding monosubstituted cyclohexanes.

The free energy difference between the two chair conformations of methylcyclohexane is defined by equation 13, where F_a is the free energy of the chair conformation in which the methyl group is axial; and F_e, equatorial. Similarly, ΔF for cyclohexanecarboxylic acid is defined by equation 14, and ΔF for cyclohexanecarboxylate anion, by equation 15. The assumption of additivity of free energies permits equations 16 and 17 to be formulated for the acids A_1 and A_2. Substitution of equation 14 into 16 and 17, gives equations 18 and 19.

$$\Delta F_{CH_3} = F_a - F_e = x \qquad (13)$$

$$\Delta F_{COOH} = y = -RT \ln \mathbf{K}_{A_3} \qquad (14)$$

$$\Delta F_{COO^-} = z = -RT \ln \mathbf{K}_{B_3} \qquad (15)$$

$$\Delta F_{A_1} = y + x = -RT \ln \mathbf{K}_{A_1} \qquad (16)$$

$$\Delta F_{A_2} = y - x = -RT \ln \mathbf{K}_{A_2} \qquad (17)$$

$$x = RT \ln (\mathbf{K}_{A_3}/\mathbf{K}_{A_1}) \qquad (18)$$

$$x = RT \ln (\mathbf{K}_{A_2}/\mathbf{K}_{A_3}) \qquad (19)$$

Given the value of x, equations 7a, 7b, 7c, 18, and 19 can be solved simultaneously. Solution, first assuming x = 1800 cal./mole,[20] and then assuming x = 1540 cal./mole,[22] gave two sets of values, reproduced in Table I.

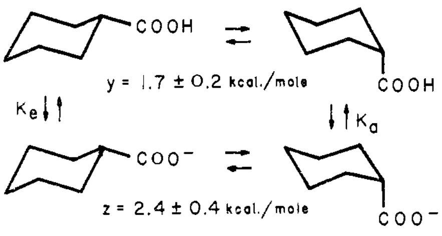
TABLE 1

CALCULATED CONFORMATIONAL EQUILIBRIA AND RELATED DATA FOR 4-ALKYLCYCLOHEXANECARBOXYLIC ACIDS[a]

x, kcal./mole[b]	1.80	1.54
y, kcal./mole	1.58	1.86
z, kcal./mole	2.0	2.8
$K_e \times 10^5$	1.30	1.30
$K_a \times 10^5$	0.66	0.27
K_e/K_a	2.0	4.8
$\mathbf{K}_{A_1}$	0.0033	0.0032
$\mathbf{K}_{A_2}$	1.5	.59
$\mathbf{K}_{A_3}$	0.070	.044
$\mathbf{K}_{B_1}$	.0017	.00067
$\mathbf{K}_{B_2}$	.74	.12
$\mathbf{K}_{B_3}$	.035	.0090

[a] Equations 13–15 define x, y and z. The equilibrium constants are illustrated in Fig. 3. The subscripts 1, 2 and 3 denote *trans*-4-methyl-, *cis*-4-methyl- and unsubstituted cyclohexanecarboxylic acid (A) or cyclohexanecarboxylate anion (B), respectively; **K** is the conformational equilibrium constant at 25°. [b] Given this value for x, the other values in the column were calculated.[20-22]

The calculated value of K_e is essentially independent of the value of x, and is as certain as the experimental value, K_1, used in the calculation. The value calculated for K_a is strongly affected by the value of x, and is uncertain. The calculated values of y indicate that the free energy difference between axial and equatorial carboxyl is about the same as that between axial and equatorial methyl (x), *i.e.*, 1.7 ± 0.2 kcal./mole. The free energy difference for the carboxylate anion (z), 2.4 ± 0.4 kcal./mole, is greater than for the carboxyl group (y) (*cf.* Fig. 4). The factors which make the preference for the equatorial conformation stronger for the carboxylate anion than for the carboxyl group ($\mathbf{K}_A > \mathbf{K}_B$ for cyclohexanecarboxylic acid) are the same factors which are responsible for the greater acidity of the equatorial carboxyl group relative to the axial carboxyl group ($K_e > K_a$). Equation 8 states this concisely. The major factor involved is probably the greater steric hindrance to solvation of the functional group when it is in the more crowded axial conformation. This is a far more important destabilizing factor for the carboxylate anion than for the uncharged carboxyl group.[23]



$10^5K_e = 1.30 \pm 0.01$; $10^5K_a = 0.46 \pm 0.2$

Fig. 4.—Cyclohexanecarboxylic acid in water.

The calculated value of K_e leads to the prediction that all *trans*-4-alkylcyclohexanecarboxylic acids have the experimental thermodynamic dissociation constant $K = 1.30 \times 10^{-5}$. The small population of the axial conformation ($\mathbf{K} < 0.004$)

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[20] A calculated value[21] of 1800 cal./mole was also assumed by Winstein and Holness.[9]

[21] C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

[22] An experimental value of 1540 cal./mole was calculated from the equilibration data for 1,4-dimethylcyclohexane given by A. K. Roebuck and B. L. Evering, *ibid.*, **75**, 1631 (1953).

[23] The acid-weakening steric effect found with few exceptions when bulky alkyl groups are accumulated about a carboxyl function has been attributed mainly to steric hindrance to solvation of the carboxylate anion; G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955).

should make a negligible contribution to the dissociation constant in each case. Based on the calculated value of K_a, *cis*-4-alkylcyclohexanecarboxylic acids are predicted to have dissociation constants in the range $K = 0.26 \times 10^{-5}$ to 0.93×10^{-5}. The experimental thermodynamic dissociation constant of the *cis*-4-*t*-butyl acid is predicted to be *ca.* $0.46 \pm 0.2 \times 10^{-5}$. In order to test these predictions, and at the same time to determine K_e and K_a by the use of "pure" conformations, the syntheses of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acids were undertaken (*vide infra*).

The assumptions made (concerning the absence of polar substituent effects for alkyl groups) lead to the prediction that all *cis*-3-alkylcyclohexanecarboxylic acids, as well as the *trans*-4-acids, should have essentially the same experimental K, *ca.* 1.30×10^{-5}. The value reported for *cis*-3-methylcyclohexanecarboxylic acid ($K = 1.31 \times 10^{-5}$) is in agreement.[17] Also, each *trans*-3-alkyl acid should have essentially the same K as the corresponding *cis*-4-alkyl acid. For *trans*-3- and *cis*-4-methylcyclohexanecarboxylic acids, the values reported for $10^6 K$ are 9 and 9.2, respectively.[17] The success of the predictions for the case of the methyl group leads one to suggest that one could determine the *cis* or *trans* configuration of any 3- or 4-alkylcyclohexanecarboxylic acid simply by measuring its dissociation constant, even when the epimer is not available for comparison.

In the case of the 2-alkylcyclohexane derivatives, the conformational equilibria will be altered by steric interactions between the substituent and the dissociating group. This direct interaction plus steric inhibition of solvation would alter the dissociation equilibria which would depend on the size and shape of each alkyl group. Because of these and other factors, the dissociation constants would not be expected to be simple functions of the conformational equilibria. The reported[17] values for *cis*- and *trans*-2-methylcyclohexanecarboxylic acid ($K = 1.84 \times 10^{-5}$ and 0.92×10^{-5}, respectively) augur no simple correlation.

The second approach for the evaluation of K_a and K_e requires "pure" conformations.[19,24] In this case, determination of the experimental dissociation constants of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid would give K_a and K_e, respectively. Then the conformational equilibria of other 4-alkylcyclohexanecarboxylic acids (such as 4-Me, Et, *i*-Pr, etc.) and cyclohexanecarboxylic acid would be calculable from their measured values of K by the use of equation 7.

Dissociation Constants.—The apparent dissociation constants of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid and cyclohexanecarboxylic acid in 66% dimethylformamide are recorded in Table II. The "pure" equatorial carboxyl group of the *trans* acid is more strongly acidic than the "pure" axial carboxyl group of the *cis* acid. The apparent dissociation constants are consistent with the interpretation that the unsubstituted cyclohexanecarboxylic acid exists as a mixture of the "a" and "e" conformations, in which the population of the "e" conformation is greater by roughly a factor of 10. Therefore, the apparent dissociation constants for the *cis*- and *trans*-4-*t*-butyl acids are in agreement with the thermodynamic dissociation constants predicted by the solution of simultaneous equations.[25]

Table II

Dissociation Constants of Cyclohexanecarboxylic Acids in 66% Dimethylformamide–34% Water[a]

Acid	pK[b]
cis-4-*t*-Butylcyclohexanecarboxylic[c]	8.23 ± 0.01
Cyclohexanecarboxylic[d]	7.82 ± .01
trans-4-*t*-Butylcyclohexanecarboxylic[c]	7.79 ± .01

[a] The author is indebted to Dr. H. Boaz of Eli Lilly and Co., Indianapolis, Ind., for the determinations of the dissociation constants reported here. [b] The pK is the negative logarithm of the measured dissociation constant of the acid. The values reported are "apparent" pK values, not the thermodynamic pK values; the reported relative error is recorded. [c] Portions of the analytical sample described in this paper. [d] A sample submitted by Prof. E. L. Eliel of the Univ. of Notre Dame.

Calculation of the apparent conformational equilibrium constant for cyclohexanecarboxylic acid by substituting the values (from Table II) of the apparent dissociation constants of *cis*-4-*t*-butyl (K_a), *trans*-4-*t*-butyl (K_e) and cyclohexanecarboxylic acid (K) into equation 7, gives the value $\mathbf{K}_A = 0.12 \pm 0.08$. Thus, the carboxyl group of cyclohexanecarboxylic acid prefers the equatorial orientation over the axial orientation in a chair conformation by 1.0–2.0 kcal./mole. The data in Table II do not permit a more accurate calculation of this free energy difference (y) because the dissociation constants of the *trans*-4-*t*-butyl and the unsubstituted cyclohexanecarboxylic acids differ by so small an amount. However, the free energy value calculated by the use of "pure" conformations (1.0–2.0 kcal./mole) brackets the value calculated by the solution of simultaneous equations (1.7 ± 0.2 kcal./mole).

The results confirm the hypothesis that polar effects are negligible as compared to the conformational effect in controlling the relative acidities of these compounds. If polar effects were significant, one would expect that the electron-releasing prop-

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(24) For a cyclohexane derivative which may be considered to exist entirely as the "a" conformation, the experimental dissociation constant (K) is equal to K_a for that compound. Similarly, for a "pure" equatorial cyclohexane derivative, $K = K_e$. If both of these cyclohexane derivatives belong to a series of similar compounds for which K_e and K_a are assumed to be constant, then the conformational equilibrium constant of any other compound in the series can be calculated from its measured value of K plus the measured K values of the two conformationally "pure" compounds. In the series of 4-alkylcyclohexyl derivatives, it is assumed that for the *trans*-4-*t*-butylcyclohexyl derivative, $K = K_e$, and for the *cis*-4-*t*-butylcyclohexyl derivative, $K = K_a$. These assumptions must be applied with caution, since they are not valid when any other conformation makes a significant contribution to K. For example, when the functional group is bulky, the equilibrium concentration of the "e" conformation of the *cis*-4-*t*-butyl isomer can no longer be considered neglible, and its $K \neq K_a$. Even when the equilibrium concentration of a minor conformation, n, is very small, it could be significant if $K_n >> K$.

(25) There is good reason to expect that the change of solvent from water to 66% dimethylformamide–34% water would not alter the relative acidities of these acids because for each the substituent is far from the site of dissociation, and the substituent has no free electron pairs, no hydrogens which are likely to enter into hydrogen bonding and no other features which would result in important specific differences in solvation of the substituent.[26]

(26) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 727.

erties of the *t*-butyl group would make the *trans*-4-*t*-butyl acid weaker than the unsubstituted acid. Such is not the case. The importance of the conformational effect upon the dissociation constants is demonstrated by the difference between the dissociation constants of the *cis*- and *trans*-4-*t*-butyl acids, the inductive effects of which would be expected to be identical.

Preparation and Configuration.—*cis*-4-*t*-Butylcyclohexanecarboxylic acid was prepared by the catalytic hydrogenation of *p*-*t*-butylbenzoic acid. Hydrogenation with platinum oxide in acetic acid proceeded readily at room temperature and 2 to 4 atmospheres pressure to produce a mixture which contained about 70% of the *cis*- and 30% of the *trans* acid. The *cis* acid was isolated easily from dilute hexane solutions of the mixture by slow crystallization (Experimental procedure B). Several recrystallizations from hexane yielded *cis*-4-*t*-butylcyclohexanecarboxylic acid, m.p. 117.5–118.5°.

Hydrogenation of sodium *p*-*t*-butylbenzoate in 10% aqueous sodium hydroxide (with Raney nickel catalyst at 200° and 3000 lb./sq. in.) was employed in the preparation of the *trans*-acid.[27] Although adequate for this work, the procedure was repeatedly unsatisfactory because of incomplete hydrogenation and experimental difficulties.[28] The resulting mixture of reduced acids and *p*-*t*-butylbenzoic acid was dissolved in dilute ammonium hydroxide and the solution was boiled to expel excess ammonia. The *trans* isomer crystallized from the solution. Recrystallization from hexane gave *trans*-4-*t*-butylcyclohexanecarboxylic acid, m.p. 176–177°.

The assignment of steric configuration to the isomers of 4-*t*-butylcyclohexanecarboxylic acid is consistent with the data available at present and with accepted generalizations based on analogy. Although no rigorous proof of configuration has been carried out, the evidence supports the assignment beyond any reasonable doubt.

According to conformational considerations, the *trans* isomer should be thermodynamically more stable than the *cis* isomer. Equilibration has been employed to demonstrate the greater thermodynamic stability of the higher melting isomer of 4-*t*-butylcyclohexanecarboxylic acid.[27] Therefore, the higher melting isomer should possess the *trans* configuration.

The energy difference between *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylate anions can be approximated by the difference in energy (z) between the axial and equatorial chair conformations of cyclohexanecarboxylate anion, calculated above to be *ca.* > 2.0 kcal./mole (corresponding to a mixture containing >90% *trans* and <10% *cis* anion at equilibrium at <200°). The reported isolation of 90% of the higher melting isomer from the hydrogenation of sodium *p*-*t*-butylbenzoate at 200° under conditions which favor equilibration provides further evidence in support of the assignment of the *trans* configuration to the higher melting of the two stereoisomers of 4-*t*-butylcyclohexanecarboxylic acid.[27]

The lower melting isomer was formed in about 70% yield by rapid hydrogenation of *p*-*t*-butylbenzoic acid with platinum oxide in acetic acid. In general, this procedure for saturation of naphthoic and substituted benzoic acids is reported to give more of the *cis* isomer than of the *trans* isomer.[29–31]

Further evidence supporting the assigned *cis* configuration of the lower melting acid was provided by its conversion, by use of the stereospecific Schmidt reaction, into the isomer of 4-*t*-butylcyclohexylamine which has been assigned the *cis* configuration.[1,32]

Finally, the results of the determination of the apparent dissociation constants are in agreement with the assigned configurations. The order of decreasing acidity predicted from the solution of simultaneous equations (*vide supra*) is *trans*-4-*t*-butylcyclohexanecarboxylic acid > cyclohexanecarboxylic acid >> *cis*-4-*t*-butylcyclohexanecarboxylic acid. The results give the predicted sequence.

Experimental[33]

***trans*-4-*t*-Butylcyclohexanecarboxylic Acid (I).**—A solution of 20.1 g. (0.113 mole) of *p*-*t*-butylbenzoic acid[34] (recrystallized from ethanol–water, m.p. 167–168°) in 65 ml. of 10% aqueous sodium hydroxide was hydrogenated[27,30,31] at 200° and 3000 lb./sq. in. hydrogen pressure in the presence of 5 g. of Raney nickel. The catalyst was removed and the clear, colorless filtrate was acidified with concentrated hydrochloric acid. The infrared spectrum of the white solid obtained (m.p. 113–140°) showed the presence of starting material as well as *trans*-4-*t*-butylcyclohexanecarboxylic acid which exhibits characteristic absorption at 1045 and 1187 cm.$^{-1}$. Part of the product, 4.79 g., was dissolved in 80 ml. of water plus 6 ml. of concentrated aqueous ammonia. The solution was heated for 3 hr. on a steam-bath and then was allowed to cool at room temperature for 2.5 hr. The white crystals which formed were filtered, washed with water, and dried. The yield of I was 1.03 g. (21%), m.p. 172–174.5°. Two recrystallizations from hexane gave colorless crystals, 0.31 g., m.p. 176–177°, reported[27] m.p. 174.5–175°.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.82; H, 11.26.

***cis*-4-*t*-Butylcyclohexanecarboxylic Acid (II). (A) High Pressure Hydrogenation of *p*-*t*-Butylbenzoic Acid.**—A solution of 19.5 g. (0.110 mole) of *p*-*t*-butylbenzoic acid (m.p. 167–168°) in 90 ml. of acetic acid was hydrogenated at 60° and 3000 lb./sq. in. hydrogen pressure in the presence of platinum oxide catalyst (2.16 g., augmented by 1.37 g. when absorption of hydrogen ceased before the calculated amount had reacted). The infrared spectrum of the white solid product indicates the presence of starting material as well as *cis*-4-*t*-butylcyclohexanecarboxylic acid which exhibits characteristic absorption at 1035 and 1155 cm.$^{-1}$. Recrystallization from ethanol–water gave 13.2 g. of white crystals, m.p. 88–134°. A solution of 10.6 g. of the crys-

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[27] N. V. de Bataafsche Petroleum Maatschappij, British Patent 703,516 (1954); *C.A.*, **49**, 5522*i* (1955).

[28] A glass liner should not be used under these conditions unless special precautions are taken to avoid the firm cementation of the glass joint by the action of the alkaline mixture.

[29] W. G. Dauben, R. C. Tweit and C. Mannerskantz, THIS JOURNAL, **76**, 4420 (1954); W. G. Dauben and E. Hoerger, *ibid.*, **73**, 1504 (1951); R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. Whetstone, *ibid.*, **64**, 1985 (1942), and subsequent papers; M. Delépine and M. Badoche, *Ann. chim.*, [11], **17**, 179 (1924).

[30] R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, 1245 (1939).

[31] A. K. Macbeth, J. A. Mills and D. H. Simmonds, *ibid.*, 1011 (1949).

[32] D. Y. Curtin, R. D. Stolow and W. Maya, THIS JOURNAL, **81**, 3330 (1959).

[33] Melting points are corrected. The microanalyses were performed by Mr. J. Nemeth and his co-workers at the University of Illinois Microanalytical Laboratory. Infrared spectra were recorded by Mr. James Brader and Mrs. Louise Griffing, by the use of a Perkin-Elmer model 21 infrared spectrophotometer and sodium chloride cells.

[34] A generous sample of *p*-*t*-butylbenzoic acid was supplied by the Shell Chemical Co.

tals in 300 ml. of water plus 38 ml. of concentrated aqueous ammonia was boiled 1 hr., heated on a steam-bath 1 hr., and then was allowed to cool to room temperature. The fine, needle-like, white crystals which separated from the solution were filtered, washed with water, and dried. The solid, 1.88 g., m.p. 117–117.5°, did not dissolve completely in 30 ml. of hot hexane. The mixture was filtered and the collected solid was washed with warm hexane. The dried hexane-insoluble solid, 1.30 g., m.p. 117–117.5°, partly insoluble in water, but completely soluble in sodium carbonate solution, was probably a mixture of *cis*-4-*t*-butylcyclohexanecarboxylic acid and its unstable ammonium salt as indicated by the following observations. The melting point of a mixture of the hexane-insoluble solid with a sample of hexane-soluble *cis* acid (m.p. 118–119°, crystallized from hexane) was 117–118.5°. A strip of moist red litmus paper, when held over a boiling chloroform suspension of the hexane-insoluble solid, instantly became blue. The recovered hexane-insoluble solid amounted to 0.68 g. The combined hexane filtrates yielded 0.45 g. of crystals in the form of colorless plates, m.p. 117–118°. Recrystallization from hexane gave 0.30 g. of similar crystals, m.p. 117–118°.[35]

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.63; H, 11.12.

(B) **Low Pressure Rapid Hydrogenation of *p*-*t*-Butylbenzoic Acid.**—Four batches of *p*-*t*-butylbenzoic acid (m.p. 166–167°), each dissolved in 160 ml. of glacial acetic acid, were hydrogenated consecutively at room temperature in the presence of platinum oxide catalyst by the use of a Parr hydrogenation apparatus[37] (initial pressures 33–38 lb./sq. in.). The data are summarized in Table III.

In each run, the acetic acid solution was filtered from the catalyst immediately after the uptake of hydrogen ceased. The bottle and filter were rinsed with 70-100 ml. of glacial acetic acid (in 3-4 portions). Part of the resulting solution (0.6-0.7 ml.) was diluted with 5 ml. of water. The resulting solid was filtered, washed with water, and dried. The infrared spectrum of a 10.0% solution of the solid in carbon tetrachloride was recorded. No absorbance attributable to *p*-*t*-butylbenzoic acid was detected. The spectra are consistent with a mixture of 70% *cis*- and 30% *trans*-4-*t*-butylcyclohexanecarboxylic acid.

TABLE III

HYDROGENATION OF *p*-*t*-BUTYLBENZOIC ACID

Run	*p*-*t*-Butylbenzoic acid G.	*p*-*t*-Butylbenzoic acid Mole	Platinum oxide, g. added[a]	Time, min.	H_2, % used	II, % in product[b]
2	12.13	0.0681	1.12	120	97	64
3	14.57	.0818	0.68	80	99	74
4	14.55	.0817	.34	90	100	71
5	14.56	.0818	.66	90	99	73

[a] Most of the platinum from run 2 was reused in run 3 with the addition of the amount of platinum oxide indicated. Subsequent runs were similarly conducted. Except for moderate losses during filtration, the amount of catalyst present was cumulative. [b] The tabulated percentages of *cis*-4-*t*-butylcyclohexanecarboxylic acid (II) were calculated by infrared spectroscopic analysis from the absorbancies at 1156 cm.$^{-1}$. The spectrum of run 5 and the spectra of the pure *cis* acid, the pure *trans* acid and *p*-*t*-butylbenzoic acid which were used in the calculatons have been reproduced in ref. 1. The spectra show that the amount of *p*-*t*-butylbenzoic acid remaining in the product is negligible, as one would expect from the percentage hydrogen used.

The acetic acid solutions were evaporated to dryness (at about 20 mm.) and the residues were recrystallized once from ethanol–water. The resulting mixture of *cis* and *trans* acids was fractionally recrystallized from hexane. Very slow crystallization from dilute hexane solutions at room temperature produced large colorless crystals of fairly pure *cis* acid. Further recrystallizations from hexane yielded 10.0 g. (17%) of *cis*-4-*t*-butylcyclohexanecarboxylic acid, m.p. 117.5–118.5°, and fractions of lesser purity from which further pure *cis* acid could be obtained by fractional recrystallization.

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(35) Other melting points recorded for "4-*t*-butylcyclohexanecarboxylic acid" are: m.p. 89.5-90.5°, ref. 27; and m.p. 111°, ref. 36. The compositions of these samples are not reported.

(36) K. Adler, K. Heimbach and E. Kühle, *Chem. Ber.*, **86**, 1364 (1953).

(37) R. Adams and V. Voorhees, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 66, Fig. 6.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Allylic Rearrangements. XLVI. The Thermal Decomposition of the Butenyl Chloroformates[1]

BY K. L. OLIVIER[2] AND W. G. YOUNG

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Kinetics and products of the thermal decomposition of α-methylallyl and crotyl chloroformate in a series of solvents have been scrutinized. The experimental findings are discussed in terms of alkyl–oxygen heterolysis and ion pairs. An interpretation of the decomposition of other chloroformates in the light of the present findings is presented.

Introduction

Considerable attention has been given to the reaction of various allylic alcohols with thionyl chloride.[3] However, these investigations have been almost exclusively confined to a study of product composition as a function of such variables as solvent, order of addition of reagents and presence or absence of tertiary amines and their hydrochlorides. Detailed kinetic study of the reaction is virtually precluded by the extreme lability of the intermediate chlorosulfinate ester. Indeed, only one allylic chlorosulfinate, the parent allyl chlorosulfinate, has been reported,[3a] and this substance was found to be highly sensitive to traces of moisture.[3b] Recently the α- and γ-trifluoromethylallyl chlorosulfinates have been isolated in this Laboratory by James Pegolotti, but no kinetic studies have yet been published.

Formally analogous to the decomposition of chlorosulfinate esters is the decomposition of chloroformate esters. It was anticipated that allylic chloroformates would be capable of being isolated, purified and separately decomposed under

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[2] National Science Foundation Predoctoral Fellow, 1956–1957.

[3] (a) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956); (b) S. H. Sharman, F. F. Caserio, R. F. Nystrom, J. C. Leak and W. G. Young, THIS JOURNAL, **80**, 5965 (1958).