of the cathodic wave remained constant, with increasing amounts of nickel. The half-wave potential of the anodic wave of β-mercaptopropionic acid decreased by 17 millivolts for each micromole of Ni(II) or Zn(II) added. Similar results were obtained when zinc and nickel were added to solutions of thioglycolic acid. The half-wave of the anodic wave of thioglycolic acid decreased by 20 millivolts for each micromole of Ni(II) or Zn(II) added.

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

An Estimate of the Conformational Equilibrium in Cyclohexanol from Infrared Spectra[1]

BY ROGER A. PICKERING AND CHARLES C. PRICE

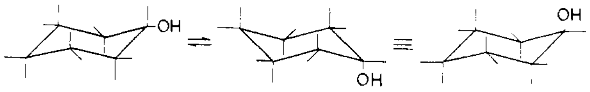
RECEIVED APRIL 2, 1958

The C–OH stretching frequency for *cis*- and *trans*-4-*t*-butylcyclohexanol is empirically assigned to the strong absorption occurring at 955 and at 1062 cm.$^{-1}$, respectively. By comparing the intensity of absorption of cyclohexanol at 1069 cm.$^{-1}$ with that of the *trans* isomer at 1062 cm.$^{-1}$, it may be estimated that cyclohexanol exists 62.6–66.2% in the equatorial conformation. This estimate, based on the assumption of equal absorbance for the equatorial hydroxyl group in cyclohexanol and its *trans*-4-*t*-butyl homolog, gives a value for the free energy difference between the equatorial and axial conformations for the hydroxyl group in cyclohexane (0.3–0.4 kcal./mole) which is lower than other estimates.

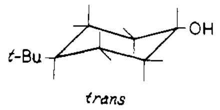
Introduction

In recent years the concept of conformational analysis has been established as an approach of great value in the solution of a wide variety of problems in structural organic chemistry.[2] Specifically, it has been shown that a substituent on a cyclohexyl ring can be bonded in two ways—axially or equatorially—in the favored chair conformation and that the reactivity of the substituent will be affected accordingly. The principles of conformational analysis having been established chiefly through studies of fused ring systems of rigid conformation such as terpenes and steroids, it has been a problem of some interest to extend the approach to those simpler cyclohexane derivatives which are conformationally mobile.

Winstein and Holness[3] and Eliel and co-workers[4] have approached the problem from the standpoint of the effects of conformation on rates of reactions. Their work introduced the use of 4-*t*-butylcyclohexyl derivatives in which the steric bulk of the *t*-butyl group is a remote control effectively fixing the conformation of the cyclohexyl ring. The paper of Winstein and Holness showing that *cis*- and *trans*-4-*t*-butylcyclohexanol constitute a chromatographically resolvable pair of epimers having pure axial and pure equatorial C–OH, respectively, suggested the idea that an alternative method for the quantitative study of conformational equilibria might be feasible using infrared spectral techniques, inasmuch as it was well known that axial and equatorial bonds differ in their infrared stretching frequencies.[5] This involves the assumption that the corresponding C–OH stretching absorptivities in cyclohexanol (I) and the 4-*t*-butylcyclohexanols (II and III) are the same. It was hoped that the validity of this assumption could be determined by measuring the concentration of axial C–OH in cyclohexanol using the *cis* epimer concurrently with a determination of the concentration of equatorial C–OH using the *trans* epimer and checking whether or not the results were self-consistent.

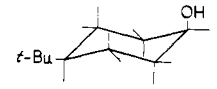


I



trans

II



cis

III

Results and Discussion

A preliminary survey of the spectra of cyclohexanol and the pair of 4-*t*-butyl derivatives was promising, and a quantitative infrared analysis was accordingly undertaken. On dilution and more careful analysis, it readily was apparent, however, that the absorption in cyclohexanol corresponding to the strongest absorption in *cis*-4-*t*-butylcyclohexanol at 955 cm.$^{-1}$ is complex, undoubtedly due to coupling between the C–OH frequency and one of the numerous skeletal frequencies in this spectral region. A comparison of the absorption in cyclohexanol corresponding to that in the *trans* epimer alone accordingly was carried out, although the self-consistency of the system could not be demon-

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(1) Presented at the Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, February 5, 1958.

(2) For general reviews: W. G. Dauben and K. S. Pitzer, in "Steric Effects in Organic Chemistry," M. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Ch. 1; D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956); W. Klyne, "Progress in Stereochemistry," Vol. I, Buttersworth Scientific Publications, London, 1954, Ch. 2; H. D. Orloff, *Chem. Revs.*, **54**, 347 (1954).

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

(4) (a) E. L. Eliel and R. S. Ro, *Chemistry & Industry*, 251 (1956); THIS JOURNAL, **79**, 5995 (1957); (b) E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957).

(5) *Cf.* R. N. Jones and C. Sandorfy, in "Chemical Applications of Spectroscopy," W. West, ed., Vol. IX, "Technique of Organic Chemistry," A. Weissberger, ed., Interscience Publishers, Inc., New York, N. Y., 1956, Ch. 4; E. A. Braude and E. S. Waight, in "Progress in Stereochemistry," Vol. I, W. Klyne, ed., Academic Press, New York, N. Y., 1954, Ch. 4.

strated. By adjusting concentration so as to obtain a precise matching of intensities a rather good comparison was possible with the results shown in Table I.

TABLE I

QUANTITATIVE INFRARED ANALYSIS OF THE C–OH STRETCHING ABSORPTION IN CYCLOHEXANOL AND *trans*-4-*t*-BUTYLCYCLOHEXANOL

Compound	Wt., mg. per g. CS_2	Absorbance[a] Trace 1	Trace 2	Avg.
Cyclohexanol, run 1	30.05	0.477	0.476	0.476
Cyclohexanol, run 2	30.06	.475	.474	.474
trans-4-TBCH, run 1	31.04	.476	.476	.476
trans-4-TBCH, run 2	31.04	.475	.476	.476

[a] Absorbance read at the maxima: 1069 cm.$^{-1}$ for cyclohexanol and 1062 cm.$^{-1}$ for *trans*-4-*t*-butylcyclohexanol.

The 31.04 mg. concentration of the *trans* epimer (mol. wt. 156.26) in Table I corresponds to an equivalent weight of 19.90 mg. of cyclohexanol (mol. wt. 100.16), so that on this basis cyclohexanol in 0.3 molal carbon disulfide solution at 20° exists 66.2% in the equatorial conformation.

The fact that *cis-4-t*-butylcyclohexanol does not absorb near 1070 cm.$^{-1}$ establishes that the absorption in cyclohexanol at 1069 cm.$^{-1}$ must be due entirely to equatorial C–OH and also shows that the equatorial *t*-butyl group should not introduce extraneous absorption at this point in the *trans* epimer. There is an anomaly, however, in that there is a very weak absorption in our purest *trans* material at 958 cm.$^{-1}$ in the region corresponding to the absorption at 955 cm.$^{-1}$ in the *cis* compound. Since this absorption is a peak which slowly diminishes in successive elution fractions on chromatography over alumina until it stabilizes at the value shown, it is uncertain whether it is an intrinsic absorption or is due to a residual trace of *cis* epimer.[6] If one assumes this to be due to 1.69 mg. of residual *cis* material in the 31.04-mg. sample (base line method: absorbance = 0.014; *cf.* 2.45 mg. *cis* = 0.022 and 1.13 mg. = 0.007), a correction may be calculated giving an alternative value of 62.6% equatorial conformation (a spread of 3.6% in uncertainty).

The largest uncertainty in our results lies, however, in the basic assumption of identical absorptivity for the C–OH in the two different molecules. There is still a great deal of controversy among spectroscopists concerning the C–O stretching absorption, particularly in the matter of possible coupling with C–C stretching and O–H and C–H bending vibrational modes. Nevertheless the assumption of identical absorptivity seems plausible in this case where the immediate molecular environment of the C–OH group is identical. In discussing the frequency shift between equatorial and axial bond absorption in steroids, Jones[5] has suggested the participation of ring contraction and expansion. It might be hypothesized that the major skeletal interaction with the C–O stretching is this ring vibration. Since the 4-*t*-butyl group, in addition to being remote, is symmetrically substituted on the ring with respect to the C–OH groups, it does not seem unreasonable to assume that its effect on the C–O absorption can be neglected. Further work to check this assumption of equal absorptivity is planned.

From the concentration of equatorial conformation one may calculate the conformational equilibrium constant, K, and from this the free energy

$$K = c_e/c_a = 0.662/0.338 = 2.0$$
$$(\text{or, } K = 0.628/0.372 = 1.7)$$

difference, ΔF^0, between the conformations may be calculated

$$\Delta F^0 = -RT \ln K = -2.303RT \log(2.0) = -0.4 \text{ kcal./mole}$$
$$(\text{or, } \Delta F^0 = -2.303RT \log(1.7) = -0.3 \text{ kcal./mole})$$

The most pertinent published values for ΔF^0 between the equatorial and axial C–OH conformations have been gathered for comparison with our results in Table II.

TABLE II

COMPARISON OF ΔF^0 VALUES FOR EQUATORIAL *vs.* AXIAL HYDROXYLS ON THE CYCLOHEXANE RING[7]

Method	ΔF^0	*t*, °C.	Solvent	Reference
1, Infrared analysis	−0.4 (− .3)	20	CS_2	This work
2, Acetylation rate	− .52	25	Pyridine	4*b*
Acetylation of 4,4-diMe	− .55		Pyridine	4*b*
3, Chromic acid oxidation	− .8	40	75% HAc	3
4, Calculation of interaction	− .9	. .	Water	8
5, Epimerization of 4-TBCH	− .96	89	*i*-PrOH	9

It is beyond the scope of this paper to discuss the data in Table II in detail, but it seems pertinent to point out that measurements based on rates of reaction (using the relation $K = (k_a - k)/(k - k_e)$ or analogous equations), such as 2 and 3 in Table II, are based on certain assumptions which may require further examination. Winstein and Holness assume equilibration of conformations in the starting material which is rapid compared to the conversion to products through the two distinct transition states. They further assume that the rate constants for the equatorial and axial isomers can be reliably determined from rates of reaction of molecules of fixed conformation. With isomers of flexible conformation, it does not seem possible to rule out a competing conversion of the axial starting material to a transition state of intermediate conformation. The more bulky transition complex would be more favored in the equatorial form, which would favor this "by pass" route for flexible molecules. Should this occur, k_a' for a flexible molecule would become greater than k_a for a fixed molecule. This would in turn lead to an overestimate of the

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(6) In a private communication, E. L. Eliel has informed us that samples of *trans*-4-*t*-butylcyclohexanol which are homogeneous to gas chromatography exhibit this weak absorption. This is strong evidence that the bond is an intrinsic absorption.

(7) M. A. Kabayama and D. Patterson, *Can. J. Chem.*, **36**, 563 (1958), have proposed $\Delta F = -0.33$ kcal./mole from the heat of mutarotation for a number of sugars, in water at 25°. R. U. Lemieux and P. Chu, 133rd Meeting A.C.S., San Francisco, Calif., April, 1958, also suggest a value of −0.35 kcal./mole for this figure on the pyranose ring.

(8) S. J. Angyal and D. J. McHugh, *Chemistry & Industry*, 1147 (1956).

(9) E. L. Eliel and R. S. Ro, THIS JOURNAL, **79**, 5992 (1957).

concentration of equatorial isomer and of the energy difference between the two conformations.

Infrared analysis, on the other hand, may be taken as a direct measure of the equilibrium in the ground state, providing, however, that our assumption of equal absorptivities in fixed and flexible molecules is valid. There may also be solvent effects which need to be considered. In connection with this latter question, a check was made by running an analysis of cyclohexanol in cyclohexane. When a cyclohexane solution was compared with a carbon disulfide solution on a mole fraction basis, no appreciable change in the intensity of the C–OH absorption was apparent.

Experimental

Materials.—Following the procedure of Winstein and Holness,[3] the pure *cis*- and *trans*-4-*t*-butylcyclohexanols were isolated by chromatography of crude 4-*t*-butylcyclohexanol (supplied by the Dow Chemical Co.; now commercially available from Matheson, Coleman and Bell) using neutral alumina as absorbent and either pentane-ether or petroleum ether (low boiling)-ether to elute. The purity of the eluted fractions was followed by infrared analysis. The pure epimers thus obtained were identical in infrared spectra and melting points to authentic samples (furnished by E. L. Eliel). The cyclohexanol (Matheson, Coleman and Bell) was distilled twice through a small Vigreux column, b.p. 161°.

Analysis.—The infrared analyses were made on a Perkin-Elmer model 21 spectrophotometer, using sodium chloride optics. Analytical conditions for the runs using 0.1-mm. fixed thickness cells: slits at 225 μ, gain 3.5, suppression 0, response 1:1, scattered light filter in. Direct absorbance measurement was used, the base lines being reasonably identical. A large number of solutions were made up and interpolations made to the desired concentrations. To eliminate all possible variables and reduce sources of error, final analyses were made at concentrations precisely duplicating the intensities of the analytical bands. By using great care in reproducible technique the experimental precision in measuring concentrations of equal absorption was brought to ±0.5% in the final determinations. Care also was taken to minimize the time of exposure to the radiant beam energy, several tests being made to ascertain that the intensity did not change within experimental limits. Integrated absorbance was not used since the instrument was linear in wave length and any additional precision likely to result from a calculated integrated intensity was offset by the uncertainty in the purity of the *trans* compound and in the basic assumption, as discussed. The three spectra in the 9–11 μ region are illustrated in Fig. 1.

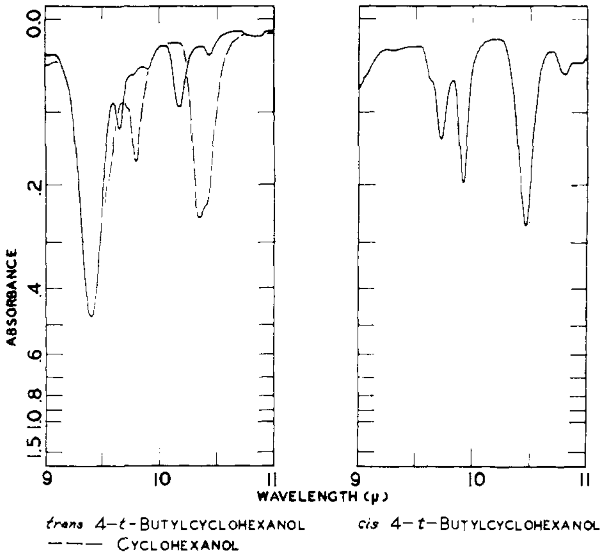

Fig. 1.—Infrared spectra in carbon disulfide solution: left, *trans*-4-*t*-butylcyclohexanol (31.04 mg./g.), ———, and cyclohexanol (30.05 mg./g.), ---------; right, *cis*-4-*t*-butylcyclohexanol (29.25 mg./g.). The cyclohexanol curve has been shifted 0.05 μ to superimpose the major C–OH absorption.

Acknowledgment.—Acknowledgment is gratefully made to the National Science Foundation for financial support, to E. L. Eliel for specimen samples and helpful suggestions and to E. C. Britton and the Dow Chemical Co. for a generous quantity of starting material.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF BRANDEIS UNIVERSITY]

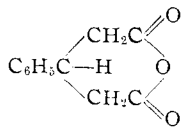
Preparation and Reactions of Acylals[1] of Disubstituted Malonic Acids

BY PAUL J. SCHEUER[2a] AND SAUL G. COHEN[2b]

RECEIVED FEBRUARY 17, 1958

Cyclic acylals (4,6-dioxo-1,3-dioxanes) have been prepared from acetone and phenylmalonic acid (V), acetone and ethylphenylmalonic acid (VI), acetone and methylphenylmalonic (VII), and cyclopentanone and methylphenylmalonic acid. Acylals VI and VII react rapidly and practically quantitatively with sodium methoxide to form the methyl half-esters. Reactions of VI and VII with alkali metal salts of 2-propanol and other secondary alcohols did not proceed well, leading largely to the disubstituted malonic acids. Acylal VII reacted with benzylamine, forming the N-benzyl half-amide, but reaction of VI and VII with α-phenylethylamine failed to form the half-amides. Methyl ethylphenylmalonanilide and methyl N-benzylmethylphenylmalonamide are also described. The infrared absorption spectra are discussed.

In our study of asymmetry in the reactions of molecules of type C, a,b,d,d, with optically active reagents at the two sites d we have reported[3] results of the reaction of β-phenylglutaric an-



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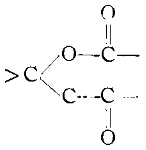
[1] The term *acylal* was proposed by C. D. Hurd and S. M. Cantor, THIS JOURNAL, **60**, 2678 (1938), for compounds containing the grouping



[2] (a) On sabbatical leave from University of Hawaii. (b) To whom inquiries should be addressed.

[3] R. Altshul, P. Bernstein and S. G. Cohen, THIS JOURNAL, **78**, 5091 (1956).