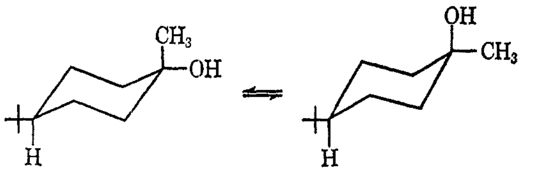
As a result, the chemical shift of the hydroxyl proton of *trans* **3** (4.0 Hz) should be nearly identical with that of *trans* 2 (4.8 Hz) while that of *cis* 2 (25.2 Hz) should be close to *cis* 2 (27.9). This is indeed the case.

The experimental free energy of −0.35 kcal/mol for equilibrium 1 in DMSO is considerably smaller than the value of −1.1 kcal/mol, which would be expected assuming additivity of $\Delta G°(x)$ values for the methyl (1.7 kcal/mol)[14] and hydroxyl (0.6 kcal/mol)[14,15] groups. This lack of additivity applies not only to equilibrium 1 but also to the analogous equilibrium between the isomers of 1-methyl-4-*t*-butylcyclohexanol—*cis* 2 and *trans* 2. Each isomer was separately equilibrated in aqueous acetic acid containing sulfuric acid at 25°. Analysis of the equilibrated alcohols by gas chromatography on a Carbowax 20M column showed the presence of about 58.5% *trans* 2 and 41.5% *cis* 2. This corresponds to a value of $-\Delta G° = 0.2$ kcal/mol for equilibrium 4. This value is in good agreement with that obtained by nmr spectroscopy in DMSO, but is in poor agreement with the calculated value, $-\Delta G° = 0.8$ kcal/mol ($-1.7 + 0.9 = -0.8$ kcal/mol). It should be noted that the calculated values for $-\Delta G°$ are different for the two experiments because of the solvent change from DMSO to aqueous acid. Available data suggest that $\Delta G°(OH)$ is greater in H-bond-donating solvents (*ca.* 0.9 kcal/mol), than in either H-bond-accepting solvents or nonbonding solvents (*ca.* 0.6 kcal/mol).[15]



(4)

cis 2 *trans* 2

The leveling effect which geminal substitution has had on the conformational preference of the CH_3 and OH groups stands in contrast to most of the available data (Table I) on 1,1-disubstituted cyclohexanes. The reasons for the lack of additivity remain obscure[16] and probably can best be uncovered through a detailed analysis of the Westheimer type.[6,17]

Experimental Section[18]

Materials.—All nmr spectra were obtained on a Varian A-60 nmr spectrometer equipped with a variable-temperature probe. The reported spectral data are the result of several independent measurements, using different batches of solvent and sample. The water concentration in the DMSO varied from about 1% to less than 0.3%. The probe temperature was 35°.

DMSO was dried by heating over calcium hydride and distilling from calcium hydride under reduced pressure (bp *ca.* 80°) as previously described.[10c]

The three 1-methylcyclohexanols (**1**, **2**, and **3**) were all obtained by addition of an ether solution of the appropriate ketone to an ether solution of methylmagnesium iodide. The procedures for preparation and separation of isomers were modeled after those described by DePuy and King.[19] Cyclohexanone gave 1-methylcyclohexanol, bp 62–64° (15 mm) [lit.[20] bp 68 (24 mm) and 56.5 (10 mm)]. 4-Methylcyclohexanone gave a mixture of *cis*- and *trans*-1,4-dimethylcyclohexanol. Chromatography on activated alumina using hexane–benzene mixtures (0–100%) for development gave first samples of the *trans* isomer, mp 70–72° (lit.[21] mp 72.5), followed by the *cis* isomer as an oil (lit.[21] mp 24°). In a similar fashion from 4-*t*-butylcyclohexanone, *cis*-4-*t*-butyl-1-methylcyclohexanol, mp 88–91 (lit.[19] mp 97.5–98°), and *trans*-4-*t*-butyl-1-methylcyclohexanol, mp 72–74° (lit.[19] mp 70.5–71°), were obtained.

Equilibration Studies.—Separate samples of *cis*- and *trans*-4-*t*-butyl-1-methylcyclohexanol (10–30 mg) were dissolved in 2–4 ml of a solution containing concentrated sulfuric acid (20 ml), glacial acetic acid (20 ml), and water (10 ml). After 4 days at 25°, the equilibrated mixtures were diluted with an equal volume of 15% sodium hydroxide solution and extracted three times with 5–10 ml of ether. The ether solutions were washed with a few milliliters of 15% sodium hydroxide solution and concentrated at atmospheric pressure. The concentrated solutions were then analyzed by vpc on a 5% Carbowax 20M column at 130–140°. The response ratio (*trans*/*cis*) for the isomers was found to be 1.02 ± 0.02 with the *cis* isomer being eluted last. Starting with the *cis* isomer, K_{eq} was found to be 1.37 and from the *trans* isomer K_{eq} was 1.43. Therefore, K_{eq} was taken to be about 1.40 and $-\Delta G°$ (25°) = 0.20 kcal/mol. Control experiments demonstrated that this procedure did not fractionate known synthetic mixtures of the alcohols.

Registry No.—**1**, 590-67-0; *cis* **2**, 16980-56-6; *trans* **2**, 16980-55-5; *cis* **3**, 16980-60-2; *trans* **3**, 16980-61-3.

Acknowledgment.—We wish to thank Mr. Warren Cole for his assistance in the preparation of materials used in this work and to the National Science Foundation for a grant to purchase an nmr spectrometer.

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[14] J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967, pp 199 ff.

[15] E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

[16] It should be pointed out that changes in the rotamer populations of substituents will occur in going from a mono- to a 1,1-disubstituted cyclohexane. The attending free-energy changes, while often small, are nevertheless not taken into account by a simple addition of free energies.

[17] J. B. Hendrickson, *ibid.*, **83**, 4537 (1961); J. B. Hendrickson, *ibid.*, **84**, 3355 (1962); J. B. Hendrickson, *ibid.*, **86**, 4854 (1964); K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

[18] All melting points and boiling points are uncorrected.

[19] C. H. DePuy and R. W. King, *ibid.*, **83**, 2743 (1961).

[20] T. D. Nevitt and G. S. Hammond, *ibid.*, **76**, 4124 (1954); K. V. Anwers, R. Hintersuber, and W. Trippmann, *Ann.*, **410**, 257 (1915).

[21] G. Chiurdoglu, *Bull. Soc. Chim. Belges*, **47**, 241 (1938).

Conformational Analysis. LXIII. The 1-Methylcyclohexanol System[1,2]

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The conformational energies of simple groups on cyclohexane rings are now rather well known.[3,4] One of the questions which we are now in a position to consider concerns the degree of additivity which will result when two or more substituents are simultaneously present on the ring. If two substituents have a 1,2 relationship, their interaction is sizable.[5] If the relationship is 1,4, the interaction has long been assumed to be negligible,[6]

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[1] Paper LXII: N. L. Allinger and W. Szkrybalo, *Tetrahedron*, in press.

[2] This research was supported by Grant GP 4290 from the National Science Foundation.

[3] J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967, p 199.

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965, p 436.

[5] Reference 4, p 50.

[6] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

TABLE I

EQUILIBRATION OF 1-METHYL-4-*t*-BUTYLCYCLOHEXANOL

Temp, °K	Time, hr	K_2^{-1}		K_{av}
331	168	1.46	1.44	
		1.44	1.40	1.43 ± 0.03
		1.43	1.40	
348	24	1.43	1.44	
		1.44	1.40	1.43 ± 0.03
		1.42		
366	2	1.43	1.39	
		1.38	1.37	1.40 ± 0.03
		1.43		

TABLE II

EQUILIBRATION DATA FOR THE REACTION *trans*-4-*t*-BUTYL-1-METHYLCYCLOHEXANOL ⇌ 4-*t*-BUTYL-1-METHYLCYCLOHEXENE

Temp, °K	Olefin/alcohol
331	1.03
348	1.70
366	3.02

TABLE III

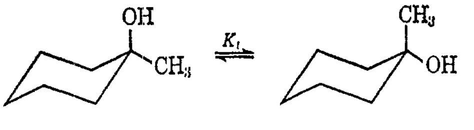
Equilibrium No.	Reactants	$\Delta G°_{345}$, kcal/mol	$\Delta H°$, kcal/mol	$\Delta S°$, eu
2	*trans* alcohol $\overset{K_2}{\rightleftharpoons}$ *cis* alcohol	+0.24 + 0.01	+0.14 ± 0.06	−0.30 + 0.18
3	*trans* alcohol $\overset{K_3}{\rightleftharpoons}$ olefin + H_2O	−2.40 ± 0.05	+8.6 ± 0.8	+32 ± 3

and this assumption has been borne out by recent detailed theoretical calculations.[7] A 1,3 arrangement of substituents has been found to yield a small but definite lack of additivity,[8] and calculations[7] show that this results from the small geometrical changes which accompany substitution.

Few studies of 1,1 disubstitution have been reported. It has been calculated[9] that the 1-chloro-1-methylcyclohexane system will favor the equatorial chlorine to a slightly greater extent than additivity (based on cyclohexyl chloride and methylcyclohexane) would predict. The experimental measurements[10] are in good agreement with the calculations, but also within experimental error of the values required for additivity.

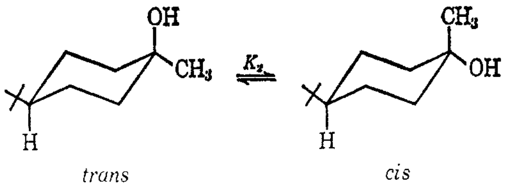
The conformational energies of methyl and hydroxyl are known[11] to have values of 1.7 ± 0.2 and 0.9 ± 0.3 kcal/mol. This paper is concerned with a measurement of the difference between these values when the two groups have a 1,1 relationship.

The equilibrium of interest is given in eq 1. The most straightforward way of finding the equilibrium constant K_1 appeared to be to measure K_2, and assume $K_1 = K_2$. The usual assumption is made, *i.e.*, that the effect of the 4-*t*-butyl group is negligible.[6]



(1)

The required compounds are known (see Experimental Section) and their structures have been established. It was necessary only to equilibrate them, and this was done as a function of temperature so that the enthalpy and entropy of the equilibrium could be determined.[12] It was decided that, since the hydration of an olefin to a tertiary alcohol is a reversible reaction which takes place readily in the presence of acid, the equilibrium (eq 2) should be easily established with perchloric acid in aqueous dioxane at elevated temperatures, and such was found to be the case. Equilibrium (eq 2) was approached from both starting alcohols and the product was analyzed by vpc. Some 1-methyl-4-*t*-butylcyclohexene was also formed in the equilibration, and the amount of this olefin was also measured. The thermodynamic parameters for the reaction *trans*-4-*t*-butyl-1-methylcyclohexanol ⇌ 4-*t*-butyl-1-methylcyclohexene (equilibrium 3) were also determined. The equilibration data are given in Tables I and II.



(2)

The thermodynamic quantities for the reactions were found to have the numerical values given in Table III.

The value of $\Delta G°$ for eq 2 shows that qualitatively the methyl group prefers to be equatorial and the hydroxyl is axial, as the $\Delta G°$ values of the groups indicate they should. The observed value for $\Delta G°_{343}$ is only 0.24 ± 0.01 kcal/mol, whereas the value calculated[11] from the group conformational energies[11] is larger, 0.8 ± 0.3 kcal/mol. Quantitatively, the experimental difference is significantly smaller than the strict additivity of the group energies would predict. It should be noted that the $\Delta H°$ is only 0.14 kcal/mol, but there is a small entropy term working in the same direction. Since these numbers are quite small, we do not wish to speculate as to the reasons for the observed values. We hope that detailed structural calculations will eventually provide an answer, but we are not able to carry out the calculations at this time. Meanwhile, it seems worthwhile to point out that a quantitative lack of additivity of conformational energies has now been observed in the 1,1-disubstituted case, and this observation may serve as a warning that even a qualitative lack of additivity may be possible in other cases, and examples of such a situation will probably be uncovered in due course. It would therefore seem prudent to avoid assumptions of group additivity in previously unstudied systems.

For equilibrium 3, the large entropy change characteristic of a reaction involving one molecule going to two is observed, the numerical value being

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(7) N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, **89**, 4345 (1967).

(8) E. L. Eliel and T. J. Brett, *ibid.*, **87**, 5039 (1965).

(9) M. A. Miller and J. A. Hirsch, unpublished results.

(10) N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967).

(11) Reference 3, pp 204, 208. The value for the latter is for hydroxylic solvents.

(12) Reference 4, p 141.

roughly the translational entropy of water. The enthalpy change is also large, but favors the reverse reaction, and hence the balance gives a relatively small free-energy change.

Experimental Section

***cis*- and *trans*-4-*t*-Butyl-1-methylcyclohexanol.**—A mixture of the alcohols was prepared by the addition of methyl Grignard to 4-*t*-butylcyclohexanone.[13] A 3.0-g sample of the mixture was dissolved in hexane and chromatographed on 150 g of Merck chromatographic grade alumina. The column was developed with a hexane–benzene mixture (100 to 100%) and each fraction collected was 150 ml. Totally, 80 fractions were collected and the elution was effected with benzene. The first eluate (fractions 30 to 51) contained the *trans*-1-methyl-4-*t*-butylcyclohexanol: yield 1.2 g (40%); mp 69–70° from hexane (lit.[13] mp 71°). The second eluate (fractions 64 to 76) contained *cis*-1-methyl-4-*t*-butylcyclohexanol: yield 1.0 g (33%); mp 91–92° from petroleum ether (bp 30–60°) (lit.[13] mp 97.9°).

Equilibration of the *cis* and *trans* Isomers of 1-Methyl-4-*t*-butylcyclohexanol.—A 0.5-g sample of *trans*-enriched (1.8:1) 1-methyl-4-*t*-butylcyclohexanol was dissolved in 6 ml of dioxane containing 4 ml of 1.75 M aqueous perchloric acid.[14] The equilibration was carried out at 75°. Aliquots of reaction mixture were removed after 18 and 36 hr and were worked up and analyzed immediately by vpc using a column of Dow polyglycol E-20,000 on base-washed firebrick at 130° and 11 psi of helium pressure. The equilibration reaction was quenched with a large amount of ice and water and the mixture was extracted with ether. The ether layer was thoroughly washed with water and then dried over magnesium sulfate. After removal of the solvent, the liquid remaining was analyzed. The retention times of *trans*- and *cis*-1-methyl-4-*t*-butylcyclohexanol were 17 min and 24 min, respectively. The retention time of 1-methyl-4-*t*-butylcyclohexane was 3 min. The ratio of the isomeric alcohols was taken as equal to the ratio of the peak areas, as determined by the product of the band height and the half-band width. Each sample was analyzed at least four times. The equilibrium mixture contained 59% *trans* and 41% *cis* alcohol at 75°.

The equilibration data at 58 and 93° were also obtained in a similar manner and the values of $\Delta H°$ and $\Delta S°$ for the reaction *cis*-4-*t*-butyl-1-methylcyclohexanol $\rightleftharpoons$ *trans*-4-*t*-butyl-1-methylcyclohexanol were determined from the slope and intercept of a line drawn by the method of least squares through points obtained from a plot of ln K against $1/T$. The values along with the probable errors (estimated by statistical methods) are $\Delta H° = -0.14 \pm 0.06$ kcal/mol and $\Delta S° = 0.3 \pm 0.18$ cal/deg mol.

The equilibrations were carried out in homogeneous solution, but in a few cases an oil suspension (olefin) appeared on the surface. In such a case, care was taken in the process of quenching so as not to get oil into the aliquot being removed.

The gas phase analysis indicated that during the prolonged heating of the reaction mixture, some undesired products were beginning to form which made the analysis inaccurate. The amount of decomposition product became significant if the period of heating was longer than twice that which was needed for equilibration. If the heating was continued beyond this time, the total percentge of alcohol decreased with respect to the increased amount of the side products, and, in addition, the ratio of the alcohols changed. The retention times for these side products were 20 and 29 min. No attempt was made to identify them, but they are believed to be ethers of *cis*- and *trans*-4-*t*-butyl-1-methylcyclohexanol with glycols which arose from decomposition of the dioxane. The results are summarized in Table I.

The temperature variation of the equilibrium between olefin (from dehydration) and *trans*-4-*t*-butyl-1-methylcyclohexanol was also measured. The vpc peak corresponding to 4-*t*-butyl-1-methylcyclohexene was collected, and the structure of the compound was assigned from the nmr (chloroform solvent) spectrum which showed a multiplet at τ 4.5 (1 H), a singlet at 8.35 (3 H) and 9.2 (9 H), and multiplets at 8.15 (4 H) and 9.0 (3 H).

In Tables I and II, the data for the calculation of entropy and enthalpy of isomerization of 4-*t*-butyl-1-methylcyclohexanol and the interconversion of *trans*-4-*t*-butyl-1-methylcyclohexanol $\rightleftharpoons$ 4-*t*-butyl-1-methylcyclohexene are tabulated.

Registry No.—1-Methylcyclohexanol, 590-67-0; *trans*-4-*t*-butyl-1-methylcyclohexanol, 16980-55-5; *cis*-4-*t*-butyl-1-methylcyclohexanol, 16980-56-6; 4-*t*-butyl-1-methylcyclohexene, 3419-74-7.

Synthesis of (*R*)-3-Methylpentanoic Acid

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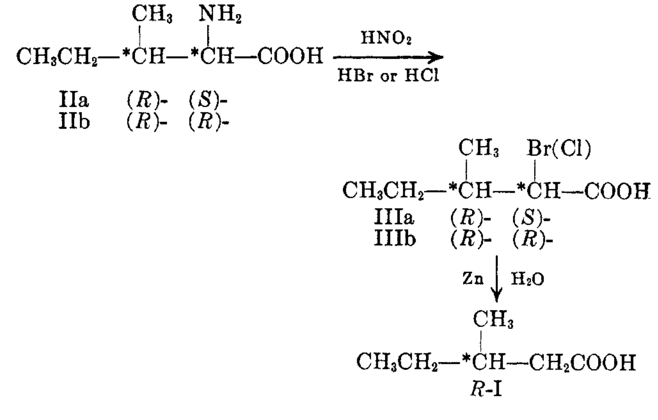
In the course of our study of optically active imidazole-containing polymers,[1] we found it necessary to obtain (*R*)-3-methylpentanoic acid (*R*-I) and (*S*)-3-methylpentanoic acid (*S*-I) in high optical purity in order to prepare the corresponding enantiomeric pair of substrate esters. While *S*-I could be readily prepared from the commercially available (*S*)-2-methylbutyl alcohol,[2] *R*-I was difficult to obtain because *R* isomers are not usually naturally occurring. All attempts to resolve racemic 3-methylpentanoic acid utilizing alkaloids failed. Moreover, there have been no reports in the literature describing the preparation of *R*-I or of (*R*)-2-methylbutyl alcohol in high optical purity or in workable quantity. (*R*)-2-Methylbutyric acid, prepared by Markwald[3] in 1896, can be reduced[4] to (*R*)-2-methylbutyl alcohol which can then be converted into *R*-I. However, the low optical purity (61%) of the acid ruled out the possibility of utilizing it in our work.

In the present investigation, however, we found that *R*-I could be obtained in good optical purity (92%) and in reasonable quantity from optically active isoleucines (IIa or IIb) *via* diazotization[5] in concentrated acids (HCl or HBr) at ~5° and subsequent reductive dehalogenation of the resulting α-halo acids (IIIa or IIIb) by zinc in neutral water (Scheme I).

SCHEME I



$$CH_3CH_2\text{—}{}^*\overset{\overset{\large CH_3}{|}}{C}H\text{—}{}^*\overset{\overset{\large NH_2}{|}}{C}H\text{—}COOH \xrightarrow[\text{HBr or HCl}]{\text{HNO}_2}$$

IIa (*R*)- (*S*)-
IIb (*R*)- (*R*)-

$$CH_3CH_2\text{—}{}^*\overset{\overset{\large CH_3}{|}}{C}H\text{—}{}^*\overset{\overset{\large Br(Cl)}{|}}{C}H\text{—}COOH$$

IIIa (*R*)- (*S*)-
IIIb (*R*)- (*R*)-

$$\Big\downarrow \text{Zn, H}_2\text{O}$$

$$CH_3CH_2\text{—}{}^*\overset{\overset{\large CH_3}{|}}{C}H\text{—}CH_2COOH$$

R-I

This synthesis would give the desired acid *R*-I from both D-isoleucine (IIb) and L-alloisoleucine (IIa),

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[14] C. A. Bunton, K. Khaleeluddin, and D. W. Whittaker, *Tetrahedron Lett.*, 1825 (1963).

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(2) K. B. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, **78**, 1640 (1956).

(3) O. Schütz and W. Markwald, *Ber.*, **29**, 52 (1896).

(4) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

(5) For a review of the diazotization of amino acids, see A. Neuberger, *Advan. Protein Chem.*, **4**, 333 (1948).