Conformational Analysis. XXIX. The Isopropyl Group[1,2]

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The thermodynamic quantities for the isomerization of an isopropyl group from an axial to an equatorial position on a cyclohexane ring have been calculated to be: $\Delta H_{298}°$ -1.63 kcal./mole, $\Delta S_{298}°$ -1.59 e.u., and $\Delta F_{298}°$ -2.10 kcal./mole. Equilibrations of the *cis* and *trans* isomers of 1,3-diisopropylcyclohexane with palladium at elevated temperatures have been carried out and indicate that while there is considerable deviation between the calculated and experimental values of $\Delta H°$ and $\Delta S°$, these differences are compensating, and the correctness of the calculated value for $\Delta F°$ was experimentally confirmed. Similar equilibration studies were carried out with 1,3- and 1,4-dimethylcyclohexanes, and the thermodynamic quantities found for these compounds are in agreement with thermochemical values.

The changes in energy involved in moving alkyl groups from equatorial to axial positions are of fundamental importance for quantitative conformational studies. The free energy change involved for a methyl group has been assigned the value 1.8 kcal./mole,[3] while that for an ethyl group is 1.86 kcal./mole.[4,5] The present work described studies aimed at specifying this quantity for the isopropyl group.

The free energy of an axial isopropyl (relative to the equatorial) has been reported as 3.3 kcal./mole.[5] Simple considerations would seem to indicate that this value might be too large. If an ethyl substituent is considered, the conformation in which the methyl of the ethyl is over the ring (Fig. 1) is of high energy as compared to the form in which it is away from the ring, and this form therefore contributes little to the thermodynamic properties of the substance. The principal result of changing an axial methyl to an axial ethyl is to reduce by one the number of conformations. With an axial isopropyl, two potential conformations are of very high energy, and essentially only one remains. To a first approximation then, the entropy of an axial isopropyl relative to an equatorial would be decreased (compared to an ethyl), but its enthalpy should be changed little. The expected free energy of an axial isopropyl might thus be expected to have a value only slightly more positive than that of a methyl or ethyl, and yet the only reported numerical value for the free energy of an axial isopropyl is quite large. Other measurements seem reasonably consistent with the reported value.[6]

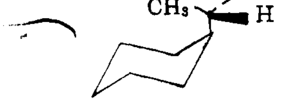

Figure 1

Earlier work[7] has shown that a convenient method for determining the thermodynamic quantities involved in the epimerization of hydrocarbons is equilibration with a palladium catalyst at elevated temperatures and determination of the equilibrium composition by gas phase chromatographic analysis. As a check on the experimental method, and to confirm the earlier values obtained by thermochemical measurements, it was considered desirable to determine the energy of an axial methyl, relative to an equatorial. The equilibrations of the isomers of the 1,3- and the 1,4-dimethylcyclohexanes were studied,[8] and the thermodynamic constants for an axial methyl relative to an equatorial were found. In these cases the statistics are particularly simple and have been discussed previously.[3] The compounds were equilibrated at four different temperatures in the 530–600°K. range. Each sample was analyzed twice by vapor phase chromatography. The stable isomer was in each case present to the extent of 70–75%, and this value was reproducible to about ±0.1%. The data are given in Tables V and VI. A plot of log K_{eq} against $1/T$ (by the method of least squares) gave the $\Delta H°$ and $\Delta S°$ of the equilibration. These quantities are summarized in Table I, and excellent agreement with the thermochemical values is noted.

Since the enthalpy of an axial methyl found in the present work (1.97 kcal./mole) is in such good agreement with that found from thermochemical studies (1.92 kcal./mole[3]), these values suggest that the 1.6–1.8 kcal./mole generally used for an axial methyl is somewhat low, and a value of 1.9 kcal./mole is probably more nearly correct in general. The value of 0.8 kcal./mole for a gauche interaction was derived from open-chain hydrocarbons. In such compounds it is reasonable that a gauche in-

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[1] Paper XXVIII, N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **84**, 2201 (1962).

[2] This research was supported by a grant from the National Science Foundation.

[3] (a) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (1947); (b) K. S. Pitzer and C. W. Beckett, *ibid.*, **69**, 977 (1947).

[4] N. L. Allinger and S. Hu, *ibid.*, **84**, 370 (1962).

[5] S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955).

[6] (a) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956); (b) W. Tagaki and T. Mitsui, *J. Org. Chem.*, **25**, 1476 (1960).

[7] N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, **81**, 4080 (1959); **82**, 2553 (1960).

[8] The equilibrations of the dimethylcyclohexanes have been studied earlier by (a) N. D. Zelinsky and E. I. Margolis, *Ber.*, **65**, 1613 (1932); (b) A. K. Roebuck and B. L. Evering, *J. Am. Chem. Soc.*, **75**, 1631 (1953); at the time of these studies, the available methods for the analysis of hydrocarbon mixtures were rather limited, and the equilibrium constants were determined by less satisfactory methods. They are consequently of low accuracy by present standards.

TABLE I

THERMODYNAMIC DATA FOR THE REACTION AXIAL-EQUATORIAL ⇄ DIEQUATORIAL-DIMETHYLCYCLOHEXANE[a]

	Theory		Thermochemical		Present work	
Isomer	ΔH°	ΔS°	ΔH°	ΔS°	ΔH°	ΔS°
1,3	−1.90	−1.40	−1.94	−1.10	−1.97 ± 0.3	−1.58 ± 0.4
1,4	−1.90	−1.40	−1.91	−1.58	−1.97 ± 0.3	−1.57 + 0.4

[a] The enthalpy values are in kcal./mole, the entropy values in e.u.

teraction have a smaller energy value, since by a slight rotation the van der Waals repulsion can be decreased with little increase in torsional energy. In a cyclic system such a motion is not possible. The best values for a gauche interaction therefore appear now to be 0.8 kcal./mole for an aliphatic system, and 0.95 kcal./mole for a cyclic system,[9] and the latter value has been used in this work.

Returning now to the case of an isopropyl group, the approach used was to prepare 1,3- and 1,4-diisopropylcyclohexane, equilibrate the *cis* and *trans* isomers of each, and treat the data as was done for the methyl compounds. The synthetic method in each case involved as a final step the hydrogenation of the corresponding diisopropylbenzene with platinum in acetic acid at 25°, and consequently a mixture of isomers, predominantly *cis*, was expected.

It was found that the 1,3-diisopropylcyclohexanes could be separated very well, though not perfectly, by vapor phase chromatography on a column of γ-nitropimelonitrile on firebrick. With isomeric saturated hydrocarbons, retention time increases with increasing boiling point. The structures of the isomers can be safely assigned from the conformational rule[10]; the low-boiling one is *cis*. This isomer predominates in the synthetic mixture and is also the thermodynamically stable, and the structural assignment is unambiguous. It turned out that none of the available columns gave any separation with the 1,4-isomers, so the equilibration studies were consequently limited to the 1,3-isomer.

Since there was no convenient available way to obtain the individual isomers free from one another, the equilibrations were carried out with mixtures. It was of course, considered desirable to approach equilibrium from both sides. The synthetic material was found to contain 78% of the *cis* isomer. Preliminary equilibration experiments showed that the equilibrium point was at about 85% *cis*, and this value increased slightly with decreasing temperature. A large sample of material was therefore equilibrated at 536°K., the lowest temperature at which the equilibration proceeded at a reasonable rate. This mixture was 86.6% *cis* and was used to approach equilibrium from the *cis* side at higher temperatures.

The equilibrations were carried out at four temperatures over the range 536–570°K., equilibrium was approached from both sides at each temperature, and each equilibrated sample was analyzed at least twice. The data are given in Table IV and the results are summarized in Table II.

TABLE II

THERMODYNAMIC QUANTITIES FOR THE REACTION *trans*- ⇄ *cis*-1,3-DIISOPROPYLCYCLOHEXANE

	Calcd.	Found
ΔH° kcal./mole	−1.47	−3.57 ± 0.3
ΔS° e.u.	+0.66	−2.97 ± 0.5
$\Delta F_{560}{}^\circ$	−1.84	−1.91 ± 0.01

These thermodynamic quantities may in principle be calculated by a simple statistical treatment if a few assumptions are made. The assumptions have been made before and gave good results with various methyl and ethyl cyclohexanes.

An axial isopropyl has one conformation as shown (Fig. 2) which contains four gauche interactions. An equatorial isopropyl has three possible conformations, a *meso* one with two gauche interactions and a *dl* pair with three gauche interactions.

In the 1,3-diisopropylcyclohexane molecule various conformational combinations of the groups are possible. In the *cis* diequatorial arrangement there are nine possible arrangements with various enthalpies as given in Table III. The *cis* diaxial conformations are of such high energy that they are also neglected. For the *trans* isomer there are six conformers, and their energies are also given in Table III. The relative entropy of each isomer was taken as just the entropy of mixing the conformations; $S_{\text{mix}} = R\Sigma_{\text{i}}\, N_{\text{i}} \ln N_{\text{i}}$.

TABLE III

THE CONFORMATIONS OF THE ISOMERS OF 1,3-DIISOPROPYLCYCLOHEXANE

	trans		*cis*		
H^a kcal./mole	5.7	6.65	3.8	4.75	5.7
No. of forms	2	4	1	4	4
Mole fract.[b] of each	0.2703	0.1148	0.2921	0.1241	0.0528

[a] The relative heat contents were determined using 0.95 kcal./mole for each gauche interaction, and were calculated relative to a hypothetical form containing zero gauche interactions. [b] Calculated for 560°K.

The conformations of the isomers of 1,3-diisopropylcyclohexane and their energies are summarized in Table II. From this information the calculated thermodynamic quantities are $H_{cis}{}^\circ$ = 4.67 kcal./mole, $S_{cis}{}^\circ$ = 4.01 e.u., $H_{trans}{}^\circ$ 6.14 kcal./mole, $S_{trans}{}^\circ$ = 3.38 e.u. Thus for the reaction *trans* ⇄ *cis*-1,3-diisopropylcyclohexane, ΔH° and ΔS° are −1.47 kcal./mole and + 0.63 e.u., respectively. As is shown in Table II, the agree-

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(9) K. S. Pitzer, *Chem. Rev.*, **27**, 39 (1940).

(10) N. L. Allinger, *J. Am. Chem. Soc.*, **79**, 3443 (1957).

ment between these statistical values and the experimental ones is quite poor. The entropy of the *trans* isomer, relative to the *cis*, is 3.6 e.u. higher than calculated. The enthalpy of the *trans* isomer is 2.1 kcal./mole higher than calculated. However, these factors compensate one another so that the free energy of the *trans* isomer which was found experimentally was within 0.1 kcal./mole of the calculated value.

Of more general interest are the thermodynamic quantities corresponding to the movement of an isopropyl group in an arbitrary organic molecule from the axial to the equatorial position. As before the values calculated for H_{ax}°, S_{ax}°, H_{eq}°, and S_{eq}° are 3.80 kcal./mole, 0.00 e.u., 2.17 kcal./mole, and 1.59 e.u. For the isomerization ($\sigma = 1$) axial-isopropyl $\rightleftarrows$ equatorial-isopropyl, the calculated values are: ΔH_{298}° -1.63 kcal./mole, ΔS_{298}° $+1.59$ e.u., and ΔF_{298}° -2.10 kcal./mole. Thus the calculated values for the free energies of methyl and isopropyl groups are in fact quite similar at room temperature, 1.9 and 2.1 kcal./mole, respectively.

Returning to the difference between the calculated and found values for ΔH° and ΔS° for the isomerization of 1,3-diisopropylcyclohexane, it may be noted that the differences between theory and experiment which are found here are in the same direction as, but much larger than those found for both the 1,3- and 1,4-diethylcyclohexanes. One of the assumptions made in the calculation seems a poorer approximation here than in previous cases. The assumption was that boat forms and other high energy forms are present in negligible quantity. The reason for the questionability of the approximation here stems from the fact that there are in the most stable form a larger number of gauche interactions involving the isopropyl than there are with the smaller alkyls, and at the high temperatures used, this may lead to the presence of a significant amount of higher energy forms. Since so little is known about the properties of boat forms, no quantitative calculations are possible. However, if this idea is correct, then a determination of ΔH° and ΔS° at lower temperatures would lead to experimental values more nearly in agreement with the theoretical ones, and such appears to be the case.[11]

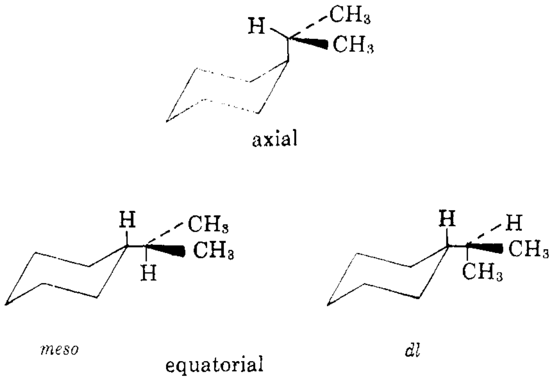

Figure 2

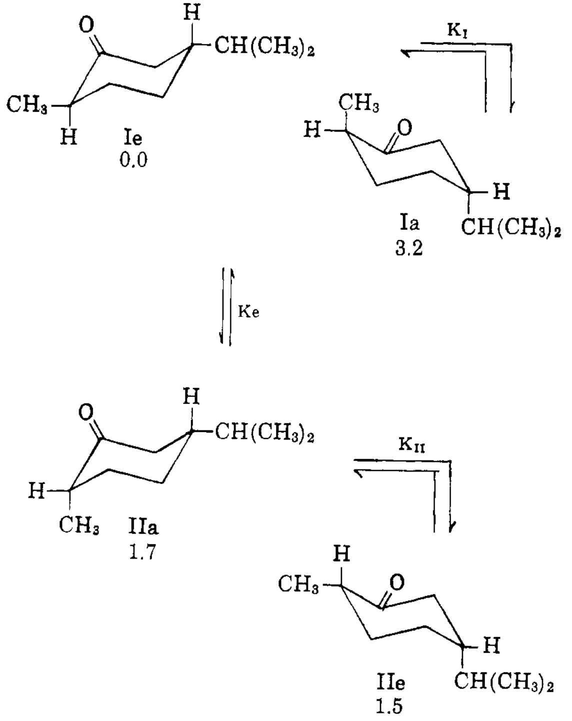

Figure 3

While the data here presented cannot be taken to support the calculated values for ΔH° and ΔS°, the calculated ΔF° is in agreement with experiment and it is concluded that the axial isopropyl group is energetically only slightly less favorable than the axial methyl. This means that in the conformational analysis of compounds like isocarvomenthone (II) it is no longer sufficient to consider the isopropyl group as exclusively equatorial (IIa) as has commonly been done in the past,[12] but rather the presence of IIe must also be taken into account (Fig. 3). Using the best values now available for the energies of the various groups involved in the carvomenthone $\rightleftarrows$ isocarvomenthone equilibrium, the constant K_e can be calculated. The necessary values are the energy of the axial methyl adjacent to the carbonyl (1.7 kcal./mole[13,14]), and the energy of an axial isopropyl β to the carbonyl (2.1 kcal./mole -0.6 kcal./mole for the 3-alkyl ketone effect,[1] or 1.5 kcal./mole). The energy of each structure is given under it in kcal./mole. At 25°, the calculated values for K_{I}, K_{II}, and K_e are, respectively, 0.005, 1.40, and 0.137. The predicted amount of II at equilibrium is thus 12.0%, and an experimental value of 9% has been reported. These values are certainly within the combined limits of error of the determinations.

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(11) Unpublished work of Dr. L. A. Freiberg.

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

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

(14) B. Rickborn, *ibid.*, **84**, 2414 (1962).

Experimental

1,3-Dimethylcyclohexane.—Ten grams of *m*-xylene (Matheson Coleman and Bell Division, Matheson Co.) was dissolved in 50 ml. of glacial acetic acid and reduced in a Paar hydrogenator in the presence of 1 g. of platinum oxide as catalyst. After the calculated amount of hydrogen was taken up, the catalyst was removed by filtration, and the solution was diluted with 100 ml. of water. The separated 1,3-dimethylcyclohexane was then washed with water, 10% sodium bicarbonate solution, and water. Nine grams of product was obtained after distillation. Gas phase chromatography showed that it was a mixture of 78% *cis*- and 22% *trans*-1,3-dimethylcyclohexane, n^{25}_{D} 1.4248 (reported[15] *cis* n^{25}_{D} 1.4206, *trans* 1.4283).

1,4-Dimethylcyclohexane.—Ten grams of *p*-xylene (Matheson Coleman and Bell Division, Matheson Co.) was hydrogenated as above. Nine grams of product was obtained which was shown by vapor phase chromatography to be 80% *cis*- and 20% *trans*-1,4-dimethylcyclohexane, n^{25}_{D} 1.4268 (reported[15] *cis* 1.4273, *trans* 1.4885).

1,3-Diisopropylbenzene.—Anhydrous aluminum chloride, 337 g., and thiophene-free benzene, 235 g., were cooled in an ice bath while 120 ml. of isopropyl acetate was added dropwise. The mixture was stirred for 30 hr., then decomposed by the careful addition of ice and water. The organic material was taken up in ether, the ether solution was washed with 5% sodium hydroxide then water. The solution was dried over magnesium sulfate, the ether was evaporated, and the product was distilled, b.p. 184–210°, wt. 46.8 g. The crude material was sulfonated with 129 g. of concentrated sulfuric acid at room temperature. After 7 hr. the sulfonated hydrocarbon was separated, dissolved in 30 ml. of water, and hot saturated barium hydroxide solution was added until a pH of 7 was reached. The solution was acidified with dilute sulfuric acid, neutralized with barium carbonate, 250 ml. of water was added, and the solution was boiled for 10 min. The barium sulfate was collected, suspended in 150 ml. of water, and the mixture was boiled and filtered. The combined filtrates were cooled overnight. The crystals of the barium sulfonate were collected and recrystallized five times from water. The barium salt was decomposed with 90 ml. of 16 *N* sulfuric acid. The barium sulfate was removed by filtration, and the filtrate was subjected to steam distillation. The hydrocarbon was taken up in pentane, dried with anhydrous magnesium sulfate and the pentane was evaporated. The residue was distilled and gave 9 g. of pure *m*-diisopropylbenzene, b.p. 202°, n^{25}_{D} 1.4868 (lit.,[16] b.p. 203.18°, n^{20}_{D} 1.4883).

1,3-Diisopropylcyclohexane.—Eight grams of pure *m*-diisopropylbenzene was hydrogenated by the procedure described for the hydrogenation of *m*-xylene to 1,3-dimethylcyclohexane. The distilled product, 7.4 g., had b.p. 206°, n^{25}_{D} 1.4481.

TABLE IV

DATA FOR THE REACTION *trans*- ⇄ *cis*-1,3-DIISOPROPYLCYCLOHEXANE

T,°K.	% *cis* Start 78% *cis*	% *cis* Start 86.6% *cis*	Average % *cis*	Eq. time (hr.)
536	86.8, 86.7	86.5, 86.7, 86.5	86.64	120
547	85.4, 85.5	85.4, 85.7, 85.4	85.48	72
560	84.8, 84.7, 84.7	85.0, 85.0	84.84	24
570	84.0, 84.0, 84.1	84.0, 84.3	84.08	22

TABLE V

EQUILIBRATION DATA FOR THE REACTION *trans*- ⇄ *cis*-1,3-DIMETHYLCYCLOHEXANE

T, °K.	% *cis*	Time (hr.)
530	74.6	192
553	73.6	96
587	71.0	20
600	70.4	8

TABLE VI

EQUILIBRATION DATA FOR THE REACTION *cis*- ⇄ *trans*-1,4-DIMETHYLCYCLOHEXANE

T, °K.	% *cis*	Time (hr.)
553	73.1	96
570	72.3	48
587	71.3	20
600	70.3	8

Anal. Calcd. for $C_{12}H_{24}$: C, 85.88; H, 14.22. Found: C, 85.92; H, 14.32.

Gas phase chromatography of the compound on a 10-ft. column of γ-nitropimelonitrile on firebrick at 102° showed two peaks with areas in the ratio of 78:22 and retention times of 8 and 9 min., which were assigned to the *cis* and *trans* isomers, respectively.

Equilibrations.—The sample of 1,3-diisopropylcyclohexane described above was used to approach equilibrium from the *trans* side. A sample of the above material was heated with palladium on carbon at 263° for 120 hr., which changed the composition of the mixture to 86.6% *cis*. This mixture was used to approach equilibrium from the *cis* side.

Equilibrium was established at different temperatures as given in Table IV. The equilibration samples (*ca.* 100 mg.) were sealed in small glass tubes and heated with a palladium-on-carbon catalyst in a furnace maintained at the desired temperature ±1° for a length of time found suitable by preliminary experiments. The equilibrations were quenched, the tubes were opened, the catalyst was settled by centrifuging, and the mixture was analyzed by gas phase chromatography. The analytical results are given in Table IV. The equilibrations with the dimethylcyclohexanes were carried out in a similar manner. The data on these compounds is summarized in Tables V and VI.

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(15) A. F. Forziati, A. R. Glasgow, Jr., C. B. Willingham, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **36**, 129 (1946).

(16) F. W. Melpolder, J. E. Woodbridge, and C. E. Headington, *J. Am. Chem. Soc.*, **70**, 935 (1948).