

Organic and Biological Chemistry

Conformational Analysis. LI. The Conformations of Cyclohexanone Rings in Simple Molecules¹⁻⁸

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Abstract: The values for ΔG°_{525} , ΔH°_{525} , and ΔS°_{525} have been determined for the isomerization of *trans*- to *cis*-3,5-di-*t*-butylcyclohexanone, and are -2.05 ± 0.04 kcal/mole, -3.91 ± 0.10 kcal/mole, and -3.65 ± 0.10 eu, respectively. These quantities are interpreted as characteristic of the boat-to-chair isomerization of a cyclohexanone ring. 1,4-Cyclohexanedione and related compounds have been shown to exist preferentially in a boat form. The thermodynamic quantities for the isomerization of some 2-alkyl-4-*t*-butylcyclohexanones have been measured and interpreted. The conformational energy of the axial alkyl group in these compounds decreases in the order methyl, ethyl, isopropyl. The *t*-butyl compound is exceptional in that the ring is in a boat form.

While the conformations of cyclohexane rings have been well understood for quite some time,⁴ the cyclohexanone ring presents a somewhat more difficult problem. The introduction of the doubly bound oxygen into the otherwise symmetrical ring leads to a number of conformational changes, one of which is that it lowers very much the energy of the boat form of cyclohexanone relative to the chair form, compared to the rather high value that is found for the corresponding difference in cyclohexane itself.^{5,6} That the conformational energy of the boat form would be appreciably lower for cyclohexanone than it is for cyclohexane was recognized some years ago,⁷ but just how much lower it would be long remained uncertain. One reason for this uncertainty stemmed from the lack of knowledge concerning the ground-state conformation of acetone. The problem has been discussed in detail elsewhere,⁸ and we will simply state here that it was not possible to accurately calculate *a priori* the conformational energy of the boat form of cyclohexanone, although an estimate of about 2.8 kcal/mole was made previously.⁷

The conformations of cyclohexanone rings have been studied extensively over the last several years, and we can briefly summarize the available information⁹ by

saying that, generally speaking, in simple molecules where there are no complicating effects, a variety of evidence is consistent with the cyclohexanone ring being primarily, but not necessarily completely, in the chair form. We wish to outline at the outset the evidence for the relative energies of the boat and chair forms in simple cyclohexanone systems, as the amount of boat form present in equilibrium may or may not be significant in any given study, depending on what type of information is being sought and what sort of experimental data are under consideration.

Discussion

The Chair \rightleftharpoons Boat Equilibrium in 3,5-Di-*t*-butylcyclohexanone. The principles and methods which were employed in the present work are quite similar to those used to establish the corresponding conformational energy in the cyclohexane case.⁵ The *cis* isomer of 3,5-di-*t*-butylcyclohexanone may be assumed to exist substantially all in the chair form at room temperature, while the *trans* isomer has a choice of existing either as a chair form with an axial *t*-butyl group, or as a boat form in which it is possible for both of the *t*-butyl groups to simultaneously assume equatorial positions. From the earlier work it might be supposed that the energy of the axial *t*-butyl group would be so high that the *trans* isomer would exist primarily in the boat form, and that this is in fact the case is shown by the present work. The equilibrium between the *cis* and *trans* isomers was measured as a function of temperature, under hydrogenation-dehydrogenation conditions over the range of 483–567°K. From the data it was possible to obtain the free energy, enthalpy, and entropy for the equilibration reaction. Since the *t*-butyl groups occupy unhindered positions in each case, the enthalpy should, to a good approximation, also be applicable to a boat \rightleftharpoons chair interconversion in other simple cyclohexanones, and in the cyclohexanone molecule itself. The entropy change is due in part to the increased flexibility of the ring in the boat form, and in part to the fact that there is an entropy of

(1) Paper L: J. C. Tai and N. L. Allinger, *J. Am. Chem. Soc.*, **88**, 2179 (1966).

(2) This investigation was supported by Public Health Service Research Grant AM-5836 from the National Institute of Arthritis and Metabolic Diseases, and by Grant GP-4290 from the National Science Foundation.

(3) Preliminary communications outlining the present work were published earlier: (a) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); (b) N. L. Allinger and L. A. Freiberg, *ibid.*, **83**, 5028 (1961); (c) N. L. Allinger and F. M. Karkowski, *Tetrahedron Letters*, 2171 (1965).

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 36, 435.

(5) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).

(6) J. L. Margrave, M. A. Frisch, R. G. Bautista, R. L. Clarke, and W. S. Johnson, *ibid.*, **85**, 546 (1963).

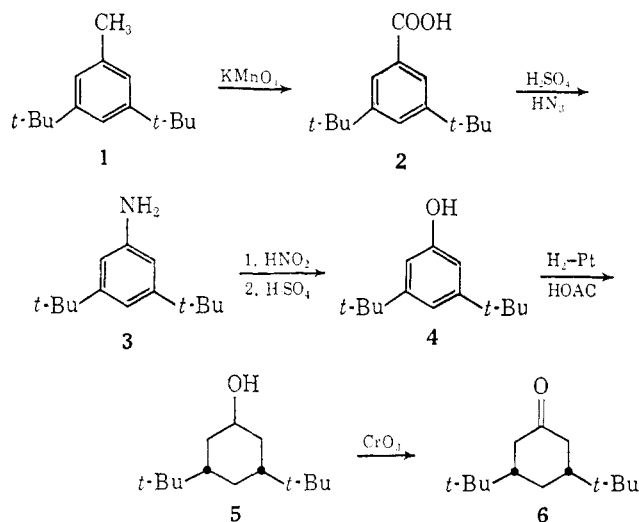
(7) N. L. Allinger, *ibid.*, **81**, 5727 (1959).

(8) N. L. Allinger, J. Allinger, and M. A. DaRooge, *ibid.*, **86**, 4061 (1964).

(9) See ref 4, p 112.

mixing the *dl* forms in the *trans* isomer, which is lacking in the *cis* isomer. Allowing for this substituent effect, the entropy of the boat, relative to the chair, together with the corresponding free energy, was found for the parent cyclohexanone.

The synthesis of *cis*-3,5-di-*t*-butylcyclohexanone (6) was carried out as outlined below. 3,5-di-*t*-Butyltoluene (1) was obtained by the alkylation of toluene with *t*-butyl chloride under equilibration conditions, and it was then oxidized to 3,5-di-*t*-butylbenzoic acid (2). The acid underwent a Schmidt reaction to yield the amine (3), which upon diazotization and hydrolysis yielded 3,5-di-*t*-butylphenol (4). Hydrogenation of the phenol gave 3,5-di-*t*-butylcyclohexanol (5), a mixture of two isomers (differing in the configuration of the hydroxyl, with configurations assigned by means of the C-O stretching frequencies), each of which was oxidized to the pure *cis* ketone (6). The ketone (6) was converted to the



equilibrium mixture of *cis* and *trans* isomers in the liquid phase at different selected temperatures, as indicated in Table I.

Table I. Equilibration Data for the 3,5-Di-*t*-butylcyclohexanones

Temp, °K	483	497	513	537	567
% <i>trans</i>	9.30	10.24	11.48	13.36	16.74

The equilibrium mixtures of the *cis*- and *trans*-3,5-di-*t*-butylcyclohexanones were analyzed by gas phase chromatography on a column composed of a 6-ft length packed with 10% XE-60 on Diatoport X, followed by another 6-ft length packed with 10% TCEP on Chromosorb P. This column cleanly separated both of the isomeric ketones, two of the possible diastereomeric alcohols (which were prepared separately as below), and the starting phenol. One of the possible alcohols was not detected (the one in which the *t*-butyl groups are *trans*). It should have been formed in quite small amounts, and apparently was not separated from one of the other alcohols.

Since the *trans* isomer of 3,5-di-*t*-butylcyclohexanone was not prepared separately, it was important to establish that the peak from the gas chromatogram which was attributed to it did in fact correspond to that compound. It was particularly important to exclude

the possibility that the peak in fact corresponded to the otherwise unidentified diastereomeric alcohol. That the peak corresponds to the *trans* ketone, and not an alcohol, was shown by the fact that a mixture of the *cis* and *trans* ketones, which was separated from other contaminants by gas phase chromatography, underwent a Wolff-Kishner reduction to give the known *cis* and *trans* hydrocarbons (identified by gas chromatography) in the same ratio as the starting ketones. Since an alcohol or other arbitrary contaminant would not behave in this way, the assignment of this peak in the vpc of the equilibration mixture to the *trans* ketone is justified.

Samples of the 3,5-di-*t*-butylcyclohexanone were equilibrated for varying lengths of time, until the proportions of alcohols and ketones became constant. The equilibrium with respect to phenol was established more slowly, but the measured value of the equilibrium constant between the ketones was independent of whether or not equilibrium with respect to phenol had been reached. Hence, the quantities we refer to as equilibrium concentrations are true equilibrium concentrations and not steady-state concentrations. It should be emphasized that mistaking a steady state for an equilibrium in such studies can lead to erroneous conclusions.

In a few of the equilibration runs, two peaks were observed on the gas chromatogram which corresponded to 1,3-di-*t*-butylbenzene and the corresponding cyclohexane, with the latter predominating. These compounds apparently were formed by dehydration of the alcohol and disproportionation of the resulting olefin. The system was not at equilibrium with respect to these components, but their presence did not influence the other equilibria, as the same equilibrium constants were obtained independent of whether or not these hydrocarbons were present. The data are summarized in Table I. From these data the thermodynamic quantities for the isomerization (*trans* \rightleftharpoons *cis*) were calculated. It was found that $\Delta G^\circ_{525} = -2.05 \pm 0.04$ kcal/mole, $\Delta H^\circ_{525} = -3.91 \pm 0.10$ kcal/mole, and $\Delta S^\circ_{525} = -3.56 \pm 0.10$ eu. The entropy change in this case is too great to be accounted for in terms of chair forms, which bears out the original supposition that the *trans* isomer would exist largely as a boat form, and the numerical value is similar to those observed in other boat \rightleftharpoons chair equilibrium reactions. While the value for ΔH° should be generally applicable to simple cyclohexanones, the value of ΔS° will not be. With these particular molecules, since the *cis* is *meso* and the *trans* is *dl*, there is an extraneous entropy of mixing, which when subtracted out gives $\Delta S^\circ = -2.18$ eu for cyclohexanone itself. Actually, this value may be too positive, because some of the pseudo-rotational motion of the ring has been frozen out by the substituents, but we will use it in the absence of other data. These numbers predict a conformational free energy for the boat form of cyclohexanone of 3.3 kcal/mole at 25°, and this value is a good deal smaller than the corresponding value for cyclohexane (4.9 kcal/mole), and is experimental confirmation of the original analysis of the problem.

The lack of knowledge concerning the rotational barrier in acetone delayed for many years the proper calculation of the energy of the boat form of cyclo-

hexanone. With the latter quantity available, it is possible to calculate backwards and determine the magnitude and direction of the rotational barrier about the bond joining the carbonyl group to the α -methylene group which would be required to yield the experimentally observed energy difference. While it is hoped to do this calculation more carefully with the aid of a computer in the future, for the present we will content ourselves with the slide-rule approach, which has been shown to give reasonably good results in the past.^{7,8} The difference in enthalpy between the boat and chair forms of cyclohexanone is 3.9 kcal/mole. Examination of models indicates that the difference between the van der Waals interactions and the angular deformations between the boat and chair forms should be pretty small, and this enthalpy can, to a first approximation, be attributed entirely to torsional energy. Taking the ethane barrier to be 2.9 kcal/mole, the conformational energies of the various arrangements of the flexible form can be calculated as follows (where the meaning of θ is as previously discussed,⁸ and can be seen from the figures pertaining to 1,4-cyclohexanedione below): for $\theta = 0^\circ$, $E = 2.9 + 2.9 = 5.8$ kcal/mole. For $\theta = 60^\circ$, $E = 2.9 + E_T$, where E_T is equal to the energy change involved in proceeding from the torsional arrangement next to the carbonyl which is present in the chair form to that which is present in the boat form, which models show is approximately the energy change involved in going from an eclipsed to a staggered arrangement. For $\theta = 90^\circ$, E has essentially the same value as when $\theta = 60^\circ$, and a smooth potential curve must connect these points with further similar points which make up the full pseudo-rotational cycle. From the experimental value it follows that $E_T = 1.0$ kcal/mole, and it is a positive quantity, indicating that the preferred arrangement has hydrogen eclipsing oxygen. The absolute value of this number is in reasonable agreement with the value found for acetone (0.8 kcal/mole), and this orientation for the minimum energy conformation is in agreement with that found for aldehydes and related compounds, but opposite to that originally predicted by Brown on the basis of thermochemical measurements.⁸

The Conformation of Cyclohexane-1,4-dione. The observation that 1,4-cyclohexanedione possessed a dipole moment of over 1 D. was made many years ago,¹⁰ and an early interpretation was given of this moment in terms of a boat-to-chair equilibrium for the compound. Since the flexibility of the boat form of a cyclohexane ring was not widely appreciated at that time (although it had been noted already in 1890 by Sachse¹¹), the interpretation was not fully correct. The flexibility of the cyclohexane ring was emphasized by Hazebroek and Oosterhoff,¹² and has been subsequently widely exploited. The same sort of considerations obviously would apply to 1,4-cyclohexanedione. One can estimate the torsional energy of the compound in the boat form, relative to the chair, for different values of θ . The values obtained are:¹³ 5.8

kcal/mole at $\theta = 0^\circ$, 1.8 kcal/mole at $\theta = 60^\circ$, and the latter energy value is essentially unchanged between 60 and 120°. Since the enthalpy difference between the boat and chair is this small, and since the boat must have a sizeably larger entropy because of its flexibility, the calculations suggest that the boat form may be as favorable or more favorable than the chair form in solution at room temperature. More precise calculations are probably capable of giving a definitive answer, but we are not able to complete them at this time. It was instead deemed desirable to submit the problem to experimental measurements. There were two experimental determinations that we were able to employ with the facilities available and both were carried out. One determination was to study the dipole moment as a function of temperature, since values can be calculated for the moments of the boat and chair forms individually, and these values can be compared with experiment. Additionally, the moment of the boat form must increase with temperature, as the oscillation which the molecule can undergo will carry it further out of the $\theta = 60$ –120° range as temperature increases, leading to an increasing dipole moment with temperature. An independent available method which might be expected to yield conformational information involved a study of the infrared and Raman spectra of the compound. Because of the symmetry difference between the boat and the chair forms of the dione, an examination of the spectra should enable one to put the molecule in one symmetry class or the other, if it were conformationally pure. The presence or absence of such conformational purity might be established by measuring the spectra of the compound both in the crystal and in solution.

The spectroscopic studies may be considered first. The infrared spectra were determined for both the solid crystalline dione (Nujol mull) and the molten compound, over the 2–15- μ range. There were no bands detectable in the spectrum of the liquid which were not present in the spectrum of the solid, although there was some change in the shapes and relative areas of bands upon melting. The interpretation appeared to be clear-cut, and was that the absence of new bands in the liquid meant that the compound was conformationally pure within the limits of measurement.

The next question was then, what was the conformation, a boat or a chair? The chair form has a center of symmetry (C_{2h}), while the boat form does not (C_{2v} if $\theta = 0^\circ$, D_2 if $\theta = 90^\circ$, otherwise C_2). If the compound has a chair conformation, therefore, coincidences in the Raman and infrared spectra are forbidden, while no such restriction is present if the compound has a boat conformation.

The Raman spectrum of the solid compound was obtained, and it consisted of seven bands between 726 and 1500 cm^{-1} . There were 24 bands in this region in the infrared spectrum, and there was a coincidence for each Raman band (Table VII). Such a high degree of coincidence would appear to definitely exclude the chair conformation of the molecule.

The observed changes in band shapes and areas in the infrared upon going from the crystal to the liquid indicate some vibrational differences in different phases. This is not unexpected since the compound

(1.0 and 0.8 kcal/mole, respectively) since the latter is a poorer analogy, but the barrier is more accurately known than for the former.

(10) (a) C. G. LeFevre and R. J. W. LeFevre, *J. Chem. Soc.*, 1696 (1935); (b) O. Hassel and E. Naeshagen, *Tidsskr. Kjemi, Bergesen Met.*, 10, 81 (1930); (c) M. T. Rogers and J. M. Caneon, *J. Phys. Chem.*, 65, 1417 (1961).

(11) H. Sachse, *Ber.*, 23, 1363 (1890).

(12) P. Hazebroek and L. J. Oosterhoff, *Discussions Faraday Soc.*, 10, 87 (1951).

(13) Using the average of the cyclohexanone and acetone barriers,

Table II. The Calculated Energy Function for Pseudo-Rotation of Cyclohexane-1,4-dione

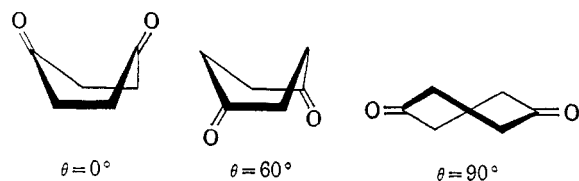
$\chi,^a$ deg	$2E_{T(CH_2CH_2)}^b$	$2E_{T(C^1OC^2H_2)}^c$	$2E_{T(C^1OC^4H_2)}^c$	E_V^d	E_E^e		$E_{\chi'}^f$		θ, deg
					291°K	490°K	291°K	490°K	
76	5800 ^a	0	0	2200	2260	4000	10260	12000	0
78	5250	0	172	1700	2160	3800	9282	10922	
80	4610	0	371	1600	2100	3720	8681	10301	
85	3650	0	557	1250	1980	3500	7437	8957	
91	2900	0	900	960	1840	3260	6600	8020	
98	2150	0	995	800	1740	3080	5645	6985	
111	1070	0	1535	550	1710	3020	4865	6175	
127	99	0 ^g	1800 ^g	300	1540	2730	3739	4929	60
148	0	0 ^g	1800 ^g	50	1480	2620	3330	4470	
180	0	900 ^g	900 ^g	0	1440	2550	3240	4350	90

^a The angle χ is the angle between the dipoles. ^b $E_{T(CH_2CH_2)} = \frac{1}{2}V_0(1 + \cos 3\tau)$ with $V_0 = 2900$ cal/mole. ^c $E_{T(C^1OC^2H_2)} = \frac{1}{2}V_0(1 - \cos 3\tau)$ with $V_0 = 900$ cal/mole. ^d The sum of the interactions of C_1C_2 , C_2C_5 , and C_3C_6 , calculated by the method of Hill using $\epsilon = 107$ cal/mole and $r_0 = 1.70$ Å, for each conformation were plotted and a smooth curve drawn. ^e $E_E = (\mu_1\mu_2/R^3D)(\cos \chi - 3 \cos \alpha_1 \cos \alpha_2)$,⁸ with $D = 1.4$ for the gas phase and 2.48 for benzene solution. ^f $E_{\chi} = 2E_{T(CH_2CH_2)} + 2E_{T(C^1OC^2H_2)} + 2E_{T(C^1OC^4H_2)} + E_r + E_E$. ^g The individual values vary with θ , but the sum of the values ($E_{T(C^1OC^2H_2)} + E_{T(C^1OC^4H_2)}$) is virtually constant at 1800 cal/mole from $\theta = 127^\circ$ to $\theta = 180^\circ$.

would be held rather rigidly by the crystal lattice, with a more nearly fixed value for θ , while in the liquid there should be a considerable oscillation with θ changing very greatly.

The spectroscopic data thus led unequivocally to the conclusion that 1,4-cyclohexanedione exists as a single conformation, both in the liquid and in the solid, and the conformation is not a chair. A thorough analysis of the spectrum should enable the conformation to be specified more exactly, but probably not uniquely, so we have not pursued this aspect of the problem further. These spectra were redetermined recently by Bhatt, Srinivasan, and Neelakantan,¹⁴ and they confirmed the results and conclusions we reported earlier.

Historically the dipole moment of 1,4-cyclohexanedione gave the first indication that the compound had some conformation other than the ordinary chair form,^{10,15} and the spectroscopic data were only in agreement with the molecules possessing a boat conformation of some sort. Since the calculations indicated that the boat form would be undergoing a pseudo-rotation, it was next desired to calculate what the dipole moment of such a pseudo-rotating form would be. Beginning with θ at 0° , the pseudo-rotational motion carries the molecule through the form with $\theta = 60^\circ$, and on to $\theta = 90^\circ$. The rest of the pseudo-rotational cycle gives over again the same conformations and their mirror images.



An energy function can now be constructed from available data to describe the pseudo-rotational motion. The relevant geometries were determined by measurements of Dreiding models for various values of θ . It was assumed that the torsional barriers involved the usual threefold cosine type functions, with $V_0 = 2.9$

kcal/mole between methylene groups, and 0.9 kcal/mole next to a carbonyl group.¹³ Superimposed upon the resultant torsional function were (1) a function giving the van der Waals repulsion between various carbon atoms diagonally across the ring from one another,¹⁶ and (2) a function allowing for the variation in the electrostatic repulsion between the two dipoles.¹⁷ These data are summarized in Table II.

Once the pseudo-rotational energy function is available, the resultant dipole moment is given by the following expression

$$\mu^2 = \int_{180^\circ}^{76^\circ} \mu_{\chi}^2 e^{-\Delta E_{\chi}/RT} d\chi / \int_{180^\circ}^{76^\circ} e^{-\Delta E_{\chi}/RT} d\chi$$

where μ_{χ} is the resultant moment corresponding to an angle between the dipoles of χ , and is given by $\mu_{\chi}^2 = 2\mu_{CO}^2(1 + \cos \chi)$, where μ_{CO} is the moment of a single carbonyl group, here taken to be 3.0 D. The calculation of μ was carried out *via* graphic integration for $T = 291$ and 490°K , and gave values of 1.64 and 1.79 D., respectively. These numbers depend on uncertain quantities such as the exact shape of the torsional barrier, and are subject to error on the order to a few tenths of a Debye. The temperature variation is much less sensitive to such uncertainties, and should be predictable within 0.1 D.

The dipole moment predicted for the chair form is zero, but a small "anomalous atomic polarization" of perhaps 10 cc is expected.¹⁸

The orientation polarization was measured over the range of 291 – 324°K , in benzene solution, and appeared to perhaps decrease slightly, while the dipole moment appeared to increase slightly, but definitely (Table III). Other measurements reported in the literature^{10c} show a continuing drop in the orientation polarization with increasing temperature, while the dipole moment continues to increase. (The literature values cited were determined in the gas phase and the good agreement with the present work may be partly fortuitous.)

The moment definitely appears too large to be attributed to a chair form, while the variation with temperature is too small to allow for appreciable amounts

(14) M. V. Bhatt, G. Srinivasan, and P. Neelakantan, *Tetrahedron*, **21**, 291 (1965).

(15) C. G. LeFevre and R. J. W. LeFevre, *Rev. Pure Appl. Chem.*, **5**, 261 (1955).

(16) N. L. Allinger, M. A. DaRooge, and R. B. Herman, *J. Am. Chem. Soc.*, **83**, 1974 (1961).

(17) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, **30**, 1945 (1965).

(18) E. Charney, *J. Am. Chem. Soc.*, **83**, 578 (1961).

Table III. Variation of Total Polarization ($P_{2\infty}$) and Dipole Moment (μ) of Cyclohexane-1,4-dione with Temperature^a

$T, ^\circ\text{K}$	$P_{2\infty}$	$\mu, \text{D.}$
291.16	60.8	1.26
298.16	61.4	1.28
311.14	61.7	1.32
323.76	59.7	1.31
468.2	52.8	1.39 ^b
490.3	53.6	1.44 ^b

^a The experimental error is about 1 cc in $P_{2\infty}$ or 0.02 D. (benzene solution). Atomic polarization is neglected throughout. ^b These measurements were reported in ref 10c.

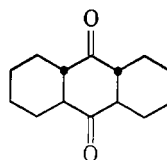
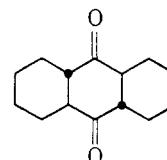
of both the boat and chair forms in equilibrium unless a peculiar fortuitous variation in ΔG° happened to result in a lack of variation of the moment with temperature. The agreement between the dipole moment and its temperature variation calculated for the boat form with that found experimentally is regarded as satisfactory, and the spectroscopic and dipole moment evidence is interpreted as showing unambiguously that 1,4-cyclohexanedione exists preferentially in a boat form, both in the crystal and in solution.

Recently, reports on the X-ray crystallographic structure of cyclohexane-1,4-dione appeared,¹⁹ which also indicate that the molecule has a boat conformation (and a rather unsymmetrical one) in the crystal. (It is reported that the angle between the carbonyl groups is about 150° , which corresponds to about $\theta = 75^\circ$.) One would expect that the molecule would oscillate over a range of θ from about 60 to 120° in solution, since the energy of the molecule is practically constant over this range of θ . Of course some unique value, determined in this case by lattice forces, would be expected to exist in the crystal. Kerr constant measurements have been interpreted as indicating that the conformation is a boat form with $\theta \approx 75^\circ$, in benzene solution.²⁰ These measurements are consistent with $\theta \approx 75^\circ$, but they do not exclude various other possibilities. It seems unlikely on theoretical grounds that the crystallographic conformation is retained unaltered in solution, but this remains to be established experimentally.

The most significant fact connected with the conformation of this molecule, in our view, is that it prefers a boat to a chair conformation, and this was the first molecule to be found in which the ring itself had such a preference.^{3b} All previously known examples of stable boat forms had the system constrained by outside forces (such as the bridge in camphor), or the interaction of bulky groups with the ring (as in *trans*-1,3-di-*t*-butylcyclohexane). One would guess that with 1,4-cyclohexanedione in solution at room temperature, not more than 10% of the chair form could be present and escape detection. Hence free energy of the boat must be lower than that of the chair by at least 1.4 kcal/mole, and yet one calculates the corresponding enthalpy change is unfavorable by 1.8 kcal/mole. The difference might be made up by a favorable entropy, but would require the entropy of the boat to exceed that of the chair by at least 10 eu, or more, and this is an exceedingly large value, very

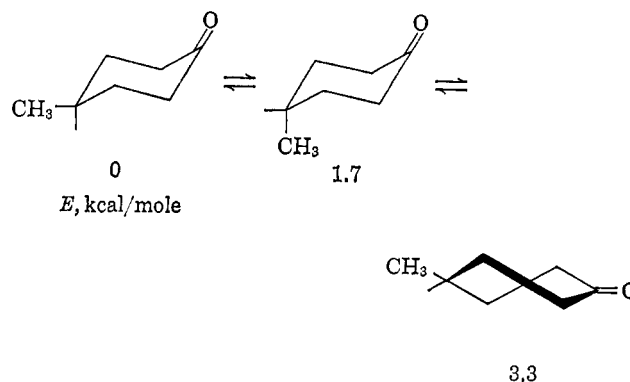
much larger than observed in other boat forms. It seems more likely that the calculated value for the unfavorable enthalpy of the boat form is somewhat too high, perhaps by 1 kcal or so, or else there may be more than 10% of the chair present in solution, which happens to have no strong infrared bands well removed from those of the boat. We are not able to choose between these alternative possibilities at present.

A more complicated 1,4-cyclohexanedione structure was also examined. There are five possible diastereomers of 9,10-perhydroanthraquinone (7), of which three are known.²¹ The three give respectively, *cis*, *trans*, and a mixture of *cis*- and *trans*-hexahydrophthalic acids on oxidation, and they must therefore possess *cis-cis*, *trans-trans*, and *cis-trans* stereochemistries, respectively. There is an ambiguity in the structure of the *trans-trans* isomer, of which *syn* (7_s) and *anti* (7_a) diastereomers are possible. Only one of these com-

7_s, *trans-syn-trans*7_a, *trans-anti-trans*

pounds is known experimentally, which is the thermodynamically stable one, but it is not known whether it is the *syn* or *anti* isomer. Models show that 7_s has the center ring constrained to a chair form, while 7_a has a corresponding boat form. The latter is (from models) somewhat less flexible than cyclohexane-1,4-dione itself, and its dipole moment was predicted to be similar, or a little smaller. The dipole moment of the compound was measured, and it was found to have the value 1.09 D. This is considered consistent with what was expected for the *anti* isomer, which should be the more stable one, and therefore the *trans-anti-trans* (7_a) stereochemistry may be assigned to the compound.

Conformational Energies of Alkylcyclohexanones. Having now established the energy difference between the chair and boat forms of cyclohexanone, the effects of substituents can now be examined and allowances more properly made for the presence of such boat forms as will occur. The conformational energy of a substituent in the 4 position is presumed to be similar to that of a substituent on a cyclohexane ring (to the first approximation): thus for 4-methylcyclohexanone the conformational free energies of the axial methyl and boat forms are 1.7 and 3.3 kcal/mole, respectively, so

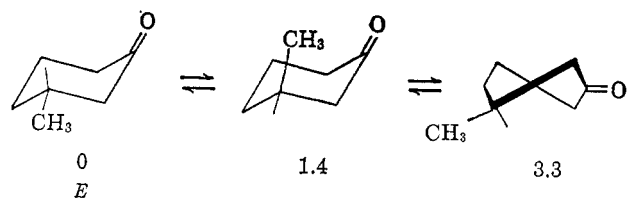


(21) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

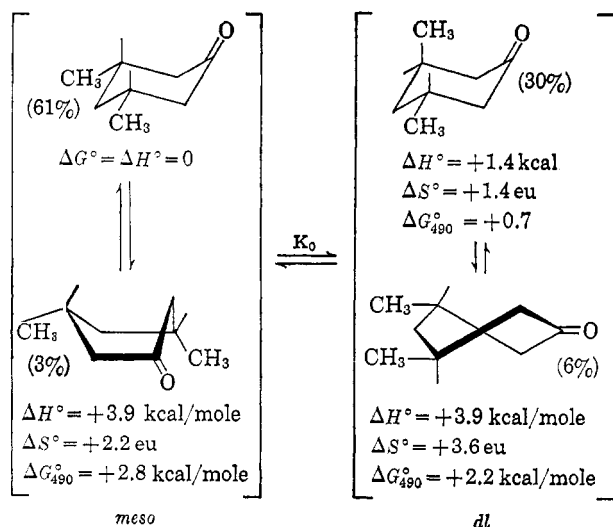
(19) (a) P. Groth and O. Hassel, *Proc. Chem. Soc.*, 218 (1963); (b) A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Letters*, 1247 (1963).

(20) C. Y. Chen and R. J. W. LeFevre, *Australian J. Chem.*, **16**, 917 (1963).

that in the equilibrium mixture at room temperature these different conformers are present to the extent of 94, 5, and 1%, respectively. For a methyl group in the 3 position, the situation is rather similar, but probably not identical. The absence of an axial hydrogen at



C-1 is expected to lead to a reduced interference of the ring with the axial methyl,²² but just how important this reduction is is not completely clear. The first reported measurement of the conformational energy of the 3-axial methyl gave a value of 1.4 kcal/mole,²³ and an independent determination in quite a different way indicated that the energy was lowered not more than a few tenths of 1 kcal from the usual value.²⁴ Later studies confirmed the original value to within experimental error.²⁵ The three conformations in this case are calculated to occur in the amounts of about 90, 9, and 1% at room temperature. Hence, the axial methyl will contribute little, and the boat essentially nothing, to most properties of the molecule (excluding, perhaps, such properties as ORD where a small amount of a powerfully rotating conformation may be important). With a molecule such as *trans*-3,5-dimethylcyclohexanone, however, the boat form is not completely negligible, since it has a free energy just 1.9 kcal/mole above that of the chair (at 25°), and hence is present to the extent of about 4%. (At higher temperatures the amount of boat form present becomes larger; thus as the data in the figure show, the *meso* isomer exists about 5% in the boat form at 490°, and for the *dl* the amount is 20%.) The numbers calculated here predict an equilibrium constant (K_0) of 0.56,



which agrees quite well with the observed equilibrium constant (0.67 ± 0.15), and shows that a neglect of boat forms in cases such as these could lead to serious errors.

If a larger alkyl group is considered in the 3 or 4 position on the cyclohexanone ring, the same considerations apply as above for methyl, and as apply to the larger groups on cyclohexane rings.

The more complicated problem of 2-alkyl substituents on the cyclohexanone ring may now be taken up. Robins and Walker,²² on the basis of some equilibration studies on the perhydro-1,4-dioxophenanthrenes, first suggested that an alkyl group in the equatorial position on a cyclohexanone ring was destabilized relative to the corresponding axial group by an unfavorable interaction between the alkyl and the carbonyl oxygen. Klyne,²² analyzing the then available data (which was not very accurate), suggested that this 2-alkyl ketone effect for a methyl group had a value of about 1 kcal/mole. His assignment of this value was largely influenced by the measurement of Johnston and Read²⁶ on the carvomenthone-isocarvomenthone equilibrium, which is now known to have been rather inaccurate, and by the assumption that an isopropyl group had a very much larger conformational energy than a methyl group. This assumption, while consistent with the data then available,²⁷ has been shown subsequently to be a poor approximation.²⁸ Fieser and Fieser²⁹ pointed out that the distance between the equatorial 2-methyl and the carbonyl oxygen was really too great for any significant van der Waals repulsion to occur, however, and there is no other reason to expect the 2-equatorial methyl to be any less stable than on a cyclohexane ring. One does need to ask if perhaps, instead of the 2-equatorial methyl being destabilized, is the 2-axial methyl stabilized by the presence of the 2-ketone group? An examination of a Dreiding model of cyclohexanone shows that the 2-axial hydrogens bend out away from the ring quite a bit, mainly because of the 120° angle at the carbonyl. Actually, while the exact geometry of cyclohexanone itself is not known experimentally, the best estimate available is based on the data for acetone and cyclohexane,³⁰ and shows that this outward bending is greatly overestimated by Dreiding models. Thus the 2,6-diaxial hydrogens are calculated to be 2.67 Å apart in cyclohexane,³⁰ and 2.81 Å in cyclohexanone,³⁰ while the latter value measured from Dreiding models is about 3.4 Å. One might conclude, therefore, that the 2-axial methyl may be slightly stabilized by the presence of the carbonyl group, and the 2-equatorial methyl will be unaffected. The conformational energy of a methyl group on a cyclohexane ring appears to be 1.7–1.8 kcal/mole (liquid phase),³¹ and a value in this range or somewhat smaller is then predicted for the 2-methyl on a cyclohexanone ring.

The experimental approach was to prepare 2-methyl-4-*t*-butylcyclohexanone, equilibrate the 2 epimers with

(22) W. Klyne, *Experientia*, **12**, 119 (1956); (b) P. A. Robins and J. Walker, *Chem. Ind. (London)*, 772 (1955); *J. Chem. Soc.*, 1789 (1955); (c) A. S. Dreiding, *Chem. Ind. (London)*, 1419 (1954).

(23) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **84**, 2201 (1962).

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

(25) (a) W. D. Cotterill and M. T. T. Robinson, *Tetrahedron*, **20**, 765, 777 (1964); (b) E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, **87**, 5031 (1965).

(26) R. G. Johnston and J. Read, *J. Chem. Soc.*, 1138 (1935).

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

(28) (a) A. H. Lewin and S. Winstein, *ibid.*, **84**, 2464 (1962); (b) N. L. Allinger and S. Hu, *J. Org. Chem.*, **27**, 3417 (1962); (c) N. L. Allinger, L. A. Freiberg, and S. Hu, *J. Am. Chem. Soc.*, **84**, 2836 (1962).

(29) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 213.

(30) Unpublished calculations by J. C. Tai, quoted in ref 4, p 454.

(31) See ref 4, p 439.

base at different temperatures, and determine the equilibrium constant as a function of temperature. From these data the thermodynamic parameters may be extracted. 2-Methyl-4-*t*-butylcyclohexanone was prepared by allowing *t*-butyl chloride to react in a Friedel-Crafts reaction with *o*-cresol in the presence of aluminum chloride. Hydrogenation of the phenol to the cyclohexanol was followed by a Jones oxidation to the cyclohexanone. This procedure might be expected to yield the *cis* isomer predominantly. Vapor phase chromatography showed that the ketone was a mixture of two isomers, with one isomer present to a much greater extent. Treatment with alkali showed that the isomer predominating from the hydrogenation was also the more stable one. Accordingly the predominant isomer was assigned the *cis* configuration and the minor component the *trans*.

Equilibrium between the *cis* and *trans* isomers of 2-methyl-4-*t*-butylcyclohexanone was established by heating the compound in the presence of base in alcohol solution at various known temperatures and for varying lengths of time, quenching the reaction, and analyzing the product by vapor phase chromatography. The other 2-alkyl-4-*t*-butylcyclohexanones were prepared by either the same type of reaction sequence (scheme B), or by starting with 4-*t*-butylcyclohexanone, and allowing it to undergo a Claisen condensation with ethyl oxalate, followed by decarbonylation to give 2-carbethoxy-4-*t*-butylcyclohexanone. This compound was then alkylated with the appropriate halide, and the alkylated keto ester was saponified and decarboxylated (scheme A). Samples of those ketones that were prepared by both methods (X = Me, *i*-Pr) were identical by vapor phase chromatography. The equilibration data for all of the 2-alkyl-4-*t*-butylcyclohexanones are assembled in Table IV.³²

Table IV. Equilibration Data for the Reaction $\text{trans} \rightleftharpoons \text{cis}$ -2-Alkyl-4-*t*-butylcyclohexanone^c

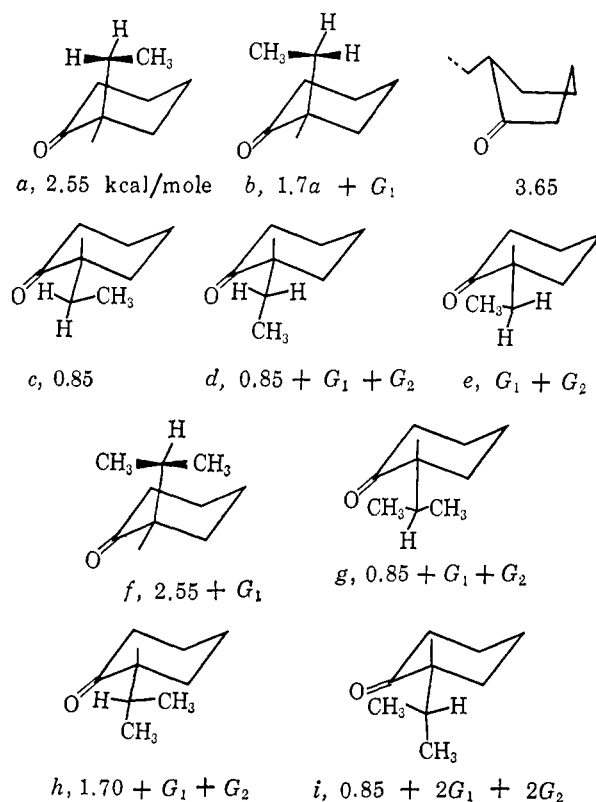
X	Temp, °C	% <i>cis</i>	ΔH° , kcal/mole	ΔS° , eu
Me	64.0	90.84	-1.57 ± 0.21	-0.1 ± 0.6
	25.0	93.08		
Et	64.6	82.17	-1.06^a	0 ^b
	25.0	86.37		
<i>i</i> -Pr	64.0	71.25	-0.44 ± 0.12	$+0.5 \pm 0.3$
	25.0	72.96		
<i>t</i> -Bu	80.3 ^d	89.45	-2.39 ± 0.38	-2.5 ± 1.0
	25.0	94.13		

^a Calculated assuming $\Delta S^\circ = 0$ (see b). ^b The vapor phase chromatographic curves were not completely separated, and there was some arbitrariness in the way the band resolution was carried out. The resolution was done in such a way as to make ΔS° come out equal to zero (the expected value). ^c That little (X = Et) or no isomerization occurs on the vapor phase chromatographic column is shown by the clean separability of the isomers. ^d This number was given incorrectly in the earlier paper (ref 3a).

Restricting ourselves for the moment to the 2-methyl compound, it is noted that the measured value for the entropy of isomerization is zero (within experimental error), as one would predict. The value for ΔH° is therefore the same as the value for ΔG° , which is 1.6

kcal/mole. (When the boat forms present are allowed for by the methods outlined earlier, the conformational energy of a 2-axial methyl group is still found to be 1.6 kcal/mole.) With this information in hand, the data for the other alkyl groups may now be examined. It is convenient to consider the ethyl group and isopropyl group together, and to postpone discussion of the *t*-butyl group for the moment. The analysis which follows is similar to that given for the ethyl and isopropyl cyclohexanones earlier.^{28b,33} In the earlier work it was noted that the free energies of the conformational changes could be predicted accurately, while neither the entropy nor the enthalpy could be predicted as well as one would like. The difficulty appears to be multifold, but is due in part to the fact that because of the presence of boat forms the assumption of a constant ΔH° and ΔS° over temperature ranges of the order of 500° is not a very good approximation. For the present, we will restrict ourselves to a consideration of free energy only.

The conformations we need to consider are shown below. Under each conformation is listed the appropriate interactions which must be considered to determine its energy. Since if all of the interactions which are different are considered, there are more of them than there are data to determine their values, a certain simplification is necessary. Thus interactions which are almost but not quite identical are assigned the same energies. This can best be seen by example. If we examine the conformations *d* and *e*, the interactions between the methyl group and the oxygen appear to be very similar in the two cases, as the orientation and distances involved appear very similar (but not quite identical). Since this interaction energy does not appear to be very large, the approximation of taking these two interactions as identical would not be ex-



(32) The same types of measurements were made with 2,6-dialkylcyclohexanones in a study carried out simultaneously by Rickborn²⁴ and his results are in good agreement with those reported herein.

(33) N. L. Allinger and S. Hu, *J. Am. Chem. Soc.*, **84**, 370 (1962).

pected to lead to a serious error. The energy of this type of interaction will be called G_2 , and it is one of the quantities which will be determined. Similarly, the interaction between the methyl group and the carbonyl carbon is taken to be the same in d and e , and an estimate of the magnitude of this interaction (which will be referred to as G_1) can be made from other data.³⁴ The energy G_1 corresponds to the van der Waals interaction between the carbonyl carbon and the methyl group in d or e . The interaction energy of a *gauche* butane is 0.8 kcal/mole, and some of this repulsion may be presumed to come from repulsions between the carbon atoms, some from repulsions between the hydrogens, and some from repulsions between carbons and hydrogens. Since the hydrogens are missing from one end of the system in this case, it would seem safe to set 0.8 kcal/mole as an upper limit for this particular type of *gauche* interaction. The conformational energy of the axial methyl of 3-methylcyclohexanone (1.4 kcal/mole) is composed of one ordinary *gauche* interaction, plus G_1 . Evaluated in this way, G_1 is 0.55 kcal/mole.

If one considers the equilibration of the *cis* and *trans* isomers of the 2-alkyl-4-*t*-butylcyclohexanones, one might be led to suspect that as the size of the R group is increased from methyl to ethyl to isopropyl, the conformational energy would increase, since this is what happens when these groups are attached to a cyclohexane ring. The first suggestion that this might not be the case came from the determination of the optical rotatory dispersion curve of 2-isopropyl-5-methylcyclohexanone.³⁵ The equilibration of the 2-alkyl-4-*t*-butylcyclohexanones was carried out in the present study, and the results are summarized in Table IV. It is seen that the conformational free energy decreases with increasing group size. An examination of the conformations shown in the figure indicates that this result is reasonable if a methyl group in a conformation such as b shows a smaller interaction with the carbonyl group than with the corresponding saturated group, without a corresponding reduction in energy for the important equatorial conformations. Quantitatively, sufficient data are available to permit us to write down and solve equations containing G_1 and G_2 , together with the conformational energies determined by equilibration and the known value for a simple *gauche* interaction.

Beginning with the isopropyl group, the axial conformation is unambiguously f . Inspection of the energies of the equatorial conformations shows that g has the lowest energy, irrespective of the values of G_1 and G_2 . The isomerization of *trans*-2-isopropyl-4-*t*-butylcyclohexanone to the *cis* isomer involves a free-energy change of -0.6 kcal/mole, and is approximated by $f \rightarrow g$. Hence we can write

$$-0.6 = (0.85 + G_1 + G_2) - (2.55 + G_1) \quad (1)$$

which can be solved for G_2 , which is found to have the value 1.1 kcal/mole.

Now turning to the ethyl group, and knowing the value of G_2 to be 1.1 kcal/mole, the equatorial con-

formation of minimum energy must be c , which has an energy of 0.85 kcal/mole. The axial conformation of minimum energy will be b , unless G_1 is greater than 0.85 kcal/mole, which as we have indicated previously is not possible. The free-energy change for the isomerization of *trans*-2-ethyl-4-*t*-butylcyclohexanone to the *cis* isomer then can be approximated by $b \rightarrow c$ which gives

$$-1.0 = (0.85) - (1.70 + G_1) \quad (2)$$

which when solved gives $G_1 = 0.15$ kcal/mole.

It is noted that G_1 has a different value here (0.15) than in the 3-methylcyclohexanone (+0.55), although these numbers do not differ by significantly more than experimental error. Probably the former number is actually smaller, as the open chain has more freedom of torsional motion in seeking a minimum of energy, and we will regard these values as different and use them as appropriate.

With these approximate values for G_1 and G_2 available, and knowing the energy of a boat form, we could now redo the calculations more properly allowing for entropy and the presence of boat forms in the equilibrium mixture. It is rather doubtful if the refined values so obtained would be significantly better than the above, however, in view of the theoretical approximations and experimental limitations involved. Since such treatment is a perfectly straightforward exercise,^{28,33} it will not be presented here.

Cotterill and Robinson²⁵ recently described studies on the 2-alkyl ketone effect which in general used the same methods and obtained the same results as we described earlier³⁴ and have discussed above. They offered one interpretation which was novel, in that they wished to explain the observed conformational energy of the 2-methyl as the sum of a very small repulsion energy for the axial methyl and a large hyperconjugative energy of an axial hydrogen, relative to methyl. While this possibility is intriguing, the only evidence for it appears to be the erroneous geometry of cyclohexanone suggested by a Dreiding model, together with unpublished heat of combustion work, and interpretations of data obtained in open-chain systems (which may not be applicable here³⁶).

The analysis given here is completely consistent with all of the data discussed so far; however, the equilibration data for the 2,4-di-*t*-butylcyclohexanone ($\Delta G^\circ_{298} = -1.7$ kcal/mole) are not satisfactorily explained on that basis. If it is assumed that the interaction referred to as G_2 is the same in d as in e , then the two interactions which correspond to those in the case of the 2-equatorial *t*-butyl must also have the same numerical value. These two interactions give the 2-*t*-butyl group an interaction energy with the carbonyl of 2.5 kcal/mole, which is comparable with that of a boat form. If 2-*t*-butylcyclohexanone adopts a boat form, the *t*-butyl group can locate itself so as to completely relieve one of the ($G_1 + G_2$) interactions, and greatly reduce or relieve the other one also. The amount of compound in the boat form in 2-*t*-butylcyclohexanone is therefore going to be appreciable, and this situation will be reflected among the physical properties such as optical rotatory dispersion.³⁷ In the chair form of *cis*-2,4-di-*t*-butyl-

(34) In order to extend this type of calculation properly and apply the full-scale Westheimer method, it is necessary to use interaction between atom pairs as a basis. An alternative way of dissecting the interactions has been proposed,²⁸ but cannot be conveniently extended.

(35) See C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 106.

(36) Compare, for example, the conformational energy of a methylene *gauche* to a chlorine in *n*-propyl chloride with that in cyclohexyl chloride (ref 4, p 457).

cyclohexanone, the same situation applies, and the 4-*t*-butyl group can locate itself comfortably in an equatorial position in the favorable arrangement of the boat form. For the *trans* isomer, however, the situation is much less clear. The chair form is unfavorable, as it requires an axial *t*-butyl group, and the entropy of isomerization (Table IV) is consistent with the *trans* isomer having a boat form. This boat form cannot, however, simultaneously locate both of the *t*-butyl groups in completely unhindered positions. It is difficult to see from an examination of models how one can relieve both of the G_2 interactions, without introducing other serious repulsions into the system, unless there is some sizeable bond angle deformation. This possibility seems to us rather unlikely, although it cannot be satisfactorily explored by hand calculation and we will have to postpone consideration of it until machine computation can be undertaken. Another possible explanation for the relatively high stability of the *trans* isomer must also be considered. We have taken both values of G_2 (as in *d* and *e*) to have the same energy, and yet, in the undistorted molecule, the distances between the two methyl groups and the oxygen are not identical. They in fact correspond to hydrogen-oxygen distances of 2.12 and 1.88 Å. There is a comfortable arrangement of the boat form of the *trans* isomer in which the ketone oxygen lies equidistant from these two methyls (at about 2.00 Å). Clearly the repulsion in the first case will be worse than in the second case, because of the exponential form of the van der Waals curve. The differences in distance are not very great, however, and the real question is whether the corresponding differences in energy would be sufficient to explain the observed result. By the Hill method,³⁰ the repulsion energies between the methyl groups and the oxygen at distances of 2.12, 2.00, and 1.88 Å were calculated and found to have the values 2.0, 0.7, and 0.3 kcal/mole. The equatorial *t*-butyl on the ring in the chair form would therefore suffer a repulsion of 2.3 kcal/mole, compared to a value of 1.4 kcal/mole for the properly located group in the boat form. This amount of energy is just sufficient to explain the observed value of ΔH° for the isomerization, but again this type of calculation must really be done taking into account all the other possible deformations in this system, and we can only conclude that the calculated energy differences may be sufficient to explain the observed result. If this is correct, G_2 has very different values for groups located in slightly different places, and the models are misleading indeed.

Experimental Section

3,5-Di-*t*-butylaniline (3). Fifty-two grams of 3,5-di-*t*-butylbenzoic acid (2) having mp 171.5–173° (from acetic acid)³⁸ was dissolved in 600 ml of chloroform and the solution was added to a 3-l. three-necked flask fitted with a condenser and stirrer. Two hundred and fifty milliliters of concentrated sulfuric acid was added to the stirred solution; then 15.9 g of sodium azide was added in small portions over a period of 6 hr. The reaction was stirred for 60 hr at 23.5°, 24 hr at 30°, and 4 hr at 38°, and then was cooled to 15° and 200 ml of cold water was added slowly. The chloroform was distilled, the reaction was cooled, and the pH was carefully adjusted to 5 with cold 50% sodium hydroxide solution.

Three hundred milliliters of ether was then added, and the pH was raised slowly to 11 by adding more base. The mixture was extracted with ether, the ether extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered, and the ether was evaporated to yield an orange semi-solid. On sublimation at 50° (0.1 mm) there was obtained 37.8 g (83%) of white needles, mp 53–53.5°. The infrared spectrum showed a moderately weak doublet at 3600 cm⁻¹.

Anal. Calcd for C₁₄H₂₃N: C, 81.89; H, 11.29; N, 6.82. Found: C, 82.02; H, 11.30; N, 6.68.

3,5-Di-*t*-butylphenol (4). In a 1-l. erlenmeyer flask was placed 20.5 g of very finely powdered 3,5-di-*t*-butylaniline (3). A solution of 32 ml of concentrated sulfuric acid in 168 ml of water was added with stirring, the mixture was warmed on a steam bath, and 1 ml of amyl alcohol was added. The mixture was cooled with stirring to 5°, and to the cold mixture was added in portions a cold solution of 7.6 g of sodium nitrite in 20 ml of water. The reaction was monitored by means of starch-iodide paper. After the last of the sodium nitrite had been added, the reaction was stirred for 5 min and 3 g of urea was added to react with excess nitrite. The reaction was stirred and kept at 5° during the subsequent steps.

In a flask fitted with a downward condenser and dropping funnel were placed in order, 115 ml of water, 100 ml of concentrated sulfuric acid, 150 g of sodium sulfate, and several boiling chips. A steam inlet tube was fitted and the mixture was brought to boiling. The cold, well-stirred diazotization solution was introduced at such a rate as to keep the reaction boiling, and steam was introduced at intervals to assist the distillation. After all the diazo compound had been added, 250 ml of water was dropped in at the same rate and the additional distillate was collected. The total volume collected over 4 hr amounted to 1500 ml. Upon cooling, an orange organic layer separated from the distillate and was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The solid gave a positive ferric chloride test and showed an intense band in the infrared at 2.78 μ . The crude product was sublimed at 70° (0.1 mm) to yield 11.2 g (59%) of white, hard needles, mp 89.5–90°. Chromatography over acid-washed alumina with benzene and 10% chloroform yielded white needles, which when resublimed had mp 92.5–93°. The infrared showed an intense band at 3300 cm⁻¹, and the nmr showed a singlet at τ 8.81, singlet at 4.13, doublet at 3.49, and a triplet at 3.19.

Anal. Calcd for C₁₄H₂₂O: C, 81.49; H, 10.75. Found: C, 81.62; H, 10.63.

3,5-Di-*t*-butylcyclohexanol (5). Two grams of platinum oxide and 50 ml of glacial acetic acid were placed in a hydrogenation bottle and a solution of 20.6 g of 3,5-di-*t*-butylphenol (4) in 100 ml of glacial acetic acid containing 2 drops of perchloric acid was added. The mixture was hydrogenated at 60 psi and 70°. After 3 equiv of hydrogen had been absorbed, the uptake stopped. The cooled reaction mixture was filtered and extracted with ether. The ether solution was washed thoroughly with water and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated to yield a light yellow oil which had a distinct fruity odor. The oil exhibited no hydroxyl hydrogen peak in the infrared but gave distinct bands at 1845 and 1235 cm⁻¹. The compound gave negative tests with ferric chloride and dinitrophenylhydrazine. It was dissolved in 50 ml of ether and the solution was added dropwise to a stirred mixture of 4 g of lithium aluminum hydride in 500 ml of ether and the resulting mixture was stirred for 24 hr. The excess lithium aluminum hydride was decomposed carefully with water, and dilute hydrochloric acid was added until the aqueous and ether layers were clear. The ether layer was separated and washed with 200-ml portions of water and saturated bicarbonate solution. The ether solution was dried over anhydrous magnesium sulfate and filtered, and the ether was evaporated to yield a semisolid material which was dissolved in hexane and recrystallized, mp 104–107°. Further recrystallizations from hexane and from benzene yielded 15.3 g (72%) of square, colorless plates, mp 108–110°. The infrared spectrum showed intense bands at 3450 and 1040 (equatorial hydroxyl) and a weak band at 990 cm⁻¹ (axial hydroxyl).

Anal. Calcd for C₁₄H₂₈O: C, 79.18; H, 13.29. Found: C, 79.00; H, 13.29.

The reaction was repeated with 9.5 g of phenol. When the crude alcohol was chromatographed on acid-washed alumina, 1.6 g of white solid was eluted with 90% hexane–10% ether, which exhibited mp 99–100° and showed infrared bands at 3450 and 990 cm⁻¹ (axial hydroxyl). With 80% hexane–20% ether, 6.2 g of white solid was eluted, mp 108–110°, mmp 93–97°. The low-melting

(37) C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Am. Chem. Soc.*, **86**, 78 (1964).

(38) W. van Hartingswelt, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **75**, 349 (1956).

alcohol was very soluble in hexane and recrystallized as prisms. The latter proved to be soluble with difficulty in hexane and more soluble in benzene. Vapor phase analysis showed one peak for the low-melting alcohol with a retention time of 18.25 min on a 10% XE-60-10% TCEP column at 170°.

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.19; H, 13.42.

The second alcohol melting at 108–110° showed two peaks in a 1:10 ratio with retention times 18.25 and 22.8 min under the above conditions, even after repeated recrystallization and sublimation. It is assigned the *cis,cis* structure from the infrared spectrum, but contains a little of the other epimer. The total yield of both alcohols was 82% of theory based on the phenol. The composition was about 79% of the high-melting alcohol and 21% of the low-melting alcohol. Both were oxidized to the same ketone. After this paper was written our attention was called to a study by Hanack and Heinz in which these compounds were obtained pure and described.³⁹ Their axial isomer has mp 101.7°, and their equatorial one has 116.5°.

3,5-Di-*t*-butylcyclohexanone (6). To a stirred solution of 10 g of alcohol **5** in acetone at room temperature in a water bath was slowly added a 12 *N* solution of chromic acid until a distinct brown color remained for 5 min. The solution was back titrated with isopropyl alcohol until the green color appeared. The mixture was filtered through Celite and the solvent was cautiously evaporated to yield a white, solid, mp 37–40°. After sublimation at 35° (0.2 mm) there was obtained 9.37 g (95%) of white, hard needles, mp 43–44.5° (sealed capillary). Infrared showed the absence of hydroxyl hydrogen absorption and the presence of a strong band at 1740 cm^{-1} .

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.94; H, 12.41.

Equilibration of 3,5-Di-*t*-butylcyclohexanone. The equilibration samples were prepared in soft glass tubing, 4-mm i.d., 6-mm o.d. The tubes were charged with 18–21 mg of 10% palladium on carbon and 200–210 mg of 3,5-di-*t*-butylcyclohexanone (**6**). The tubes were warmed in a water bath to melt the ketone in order to obtain the smallest volume possible, and the inside surface was swabbed with clean cotton. The sample was cooled in a Dry Ice bath, wiped dry, and immediately sealed with a length not exceeding 4.5 cm. By this procedure less than half the volume of the tube was air space. The samples were equilibrated in an oven for various lengths of time at various temperatures. The temperatures were recorded by means of a potentiometer and were accurate to $\pm 1^\circ$. When the samples were removed from the oven they were immediately plunged into an ice bath, which cooled them below room temperature within 1 min. The sample tubes were broken open and washed with pentane, and the solution was filtered and evaporated to dryness.

Preliminary Study of the Vapor Phase Chromatographic Analysis of Ketone 6. The equilibrated samples were analyzed by vapor phase chromatography utilizing an F and M scientific gas chromatograph with Dynamaster recorder. A 10% TCEP on Chromosorb P column at 140° yielded retention times of known samples as follows: 19.2 min for the 3,5-di-*t*-butylcyclohexanone (**6**), 19.5 min for equatorial 3,5-di-*t*-butylcyclohexanol (**5e**), 14.0 min for the axial isomer (**5a**), and 37 min for 3,5-di-*t*-butylphenol (**4**). A typical equilibrated sample showed four peaks at 14.0, 19.5, a new peak at 23.2, and a peak at 37 min. When treated with sulfuric acid the peak at 14 min disappeared, the one at 19.5 min appeared diminished, and the other peaks appeared unchanged. This was interpreted to mean that the new peak at 23.2 was the *trans* form of ketone **6**. The equatorial cyclohexanol unfortunately had a retention time coincident with the starting ketone. Under the same conditions a 10% XE-60 on Diatoport S column gave retention times for compounds **5a**, **5e**, **6**, and **4** of 18.2, 22.0, 25.8, and 42.0 min, respectively. Sulfuric acid wash caused the peaks at 18.25 and 22 min to disappear. The conclusion was that the TCEP column could separate the axial alcohol and the boat form of the ketone from the mixture, but could not separate the equatorial alcohol from the chair form of the ketone. The XE-60 column could accomplish the separation of the ketones from the two alcohols but not the ketones from each other. The dual column described below was therefore constructed.

Construction of a Dual XE-60-TCEP Column. A 12-ft length of 6-mm o.d. copper tubing was temporarily plugged with glass wool at one end and suspended. The packing was prepared by dissolving the cyanoethylation product of glycerol in methylene

chloride. This was added to a sufficient amount of Chromosorb P solid support to make a 10% by weight composition of TCEP. The slurry was agitated in a large open dish while gently warming, to dispel the methylene chloride. The solvent-free support was poured into the copper tube with constant mechanical agitation, which was continued until the column was filled to capacity. The packing was then removed and weighed. Half the amount of packing was replaced, and the copper tube was agitated for 5 hr. A 10% composition by weight of XE-60 on Diatoport S was prepared similarly, introduced into the top half of the copper tube, and the agitation was continued for 6 hr. The tube was then plugged with glass wool and coiled.

Vapor Phase Chromatographic Analysis of Equilibrated Samples of Ketone 6. An equilibrated mixture of ketones **6**, with the aid of the dual column exhibited five peaks at 170°. The retention times for the five peaks were (a) 15.3 min, (b) 19.8 min, (c) 23.5 min, (d) 26 min, and (e) 68 min, and these peaks (except d) were shown to correspond, respectively, to compounds **5a**, **5e**, *cis*-**6** (*trans*-**6**), and **4**. The material emerging from the detector under peak d was collected, and furnished a low-melting, colorless, easily sublimable substance. This product was washed onto a salt plate with two drops of methylene chloride. The solvent was allowed to partially evaporate, leaving a slight film of compound in solvent which showed a strong band at 1720 cm^{-1} in the infrared. The vapor phase chromatography results are summarized in Table V.

Table V. Summary of Equilibration Data on Ketone 6

Temp, °C	Time, hr	% <i>trans</i>	% <i>cis</i>	Av <i>K</i> <i>trans/cis</i>
210	22.5	91.55	8.45 ^a	9.7526
	34	90.66	9.35	
	34	90.69	9.31	
	39	90.72	9.28	
	68	90.74	9.25	
224	3	89.98	10.05 ^a	8.7656
	9	89.71	10.29	
	12	89.86	10.14	
	12	89.72	10.28	
240	6	88.54	11.47	7.7108
	6	88.44	11.58	
	9	88.55	11.45	
	9	88.56	11.44	
264	5	86.71	13.39	6.4850
	7.5	86.53	13.47	
	7.5	86.67	13.33	
294	3	84.46	15.54	5.3532
	6	84.25	15.76	
	6	84.26	15.74	
	9	84.30	15.60	

^a This sample does not appear to be at equilibrium, hence the value was not used to determine *K*.

Reduction of *cis*-3,5-Di-*t*-butylcyclohexanone (6). To a stirred solution of 0.93 g of potassium hydroxide and 0.71 g of 85% hydrazine hydrate in 25 ml of diethylene glycol at 40° was added 0.50 g of **6**, and the temperature was slowly raised to reflux. Reflux was maintained (140°) for 90 min, and the excess hydrazine hydrate and water were distilled until the internal liquid temperature reached 175–180°. The condenser was replaced and the internal temperature was raised and maintained at 190–210° until nitrogen evolution ceased (6 to 10 hr). The reaction mixture was cooled and poured into water. The solution was extracted with pentane, and the hydrocarbon layer was dried over anhydrous sodium sulfate and filtered, and the solvent was slowly distilled until the temperature reached 60°. The crude product was then analyzed by vpc. A single peak resulted with a retention time identical with that of an authentic sample⁶ of *cis*-1,3-di-*t*-butylcyclohexane, both alone and mixed together.

Isolation and Reduction of Equilibrated Ketone 6 Mixture. Equilibrated samples remaining after analytical vpc work had been completed were collected and analyzed by vpc on the dual column under the same conditions as for the analytical procedure. The chromatogram showed the peak areas of the *cis* and *trans* ketones corresponded to 90.33 and 9.67% of the mixture. About 650 mg

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Table VI. Properties of 2-Alkyl-4-*t*-butylcyclohexanones

R	Prepn method	n_D^{25}	Bp, °C (mm)	Formula	Anal				Mp, °C	DNP			
					Calcd C	Calcd H	Found C	Found H		Calcd C	Calcd H	Found C	Found H
Methyl	A	1.4586	75 (3.2)	C ₁₁ H ₂₀ O	78.51	11.98	78.79	12.11
	B	1.4582	77 (3.1)		78.51	11.98	78.79	11.96	164.5	58.60	6.94	58.58	7.01
Ethyl	A	1.4592	88 (2.7)	C ₁₂ H ₂₂ O	79.05	12.16	79.22	12.02	140	59.65	7.23	59.88	7.48
	B	1.4591	89 (2.7)	C ₁₂ H ₂₂ O	79.53	12.32	79.50	12.31	144.5	60.62	7.50	60.52	7.54
Isopropyl	A	1.4591	89 (2.7)	C ₁₃ H ₂₄ O	79.53	12.32	79.75	12.37
	B	1.4590	86 (2.6)		79.53	12.32	79.75	12.37
<i>t</i> -Butyl	A	1.4599	89 (2.3)	C ₁₄ H ₂₆ O	79.93	12.46	79.55	12.53	179	61.52	7.74	61.35	7.88
	B	1.4599	89 (2.3)		79.93	12.46	79.55	12.53	179	61.52	7.74	61.35	7.88

of the mixture was treated with 20 ml of cold, concentrated sulfuric acid for 40 sec with vigorous agitation. The sulfuric acid solution was quickly poured into 50 ml of cold water and extracted with 200 ml of ether. The ether extract was dried over anhydrous sodium sulfate and decanted, and the ether was evaporated to yield a dark, viscous residue. This residue was analyzed by vpc with the dual column under the analytical conditions. The chromatogram exhibited various new peaks all with retention times less than 8 min, and two peaks corresponding to the *cis* and *trans* ketones with an area ratio of 90.29 to 9.71. This mixture was quickly passed through a chromatograph column containing 25 g of neutral alumina and the column was eluted with pentane until evaporation of the fractions yielded no detectable ketone. The first three fractions were discarded and all remaining fractions were combined and analyzed by vpc under the usual conditions. The chromatogram exhibited only two peaks, which corresponded to the *cis* and *trans* ketones with areas of 89.82 and 10.18%, respectively.

The Wolff-Kishner reduction of 0.12 g of the ketone mixture was carried out as described for the reduction of *cis*-6. The pentane was evaporated from the resulting solution to yield 80 mg (71%) of slightly colored oil. The oil was subjected to vpc analysis on a 6-ft 10% silicone gum rubber column. The column was programmed at 100° for 10 min and a temperature increment of 1°/min. Retention times were 29.5 min for *cis*-1,3-di-*t*-butylcyclohexane and 32 min for the *trans* isomer.⁵ The ratios of the areas corresponding to *cis*- and *trans*-1,3-di-*t*-butylcyclohexane exhibited a vapor phase chromatogram of two peaks with retention times identical for both the product and authentic samples.

Phenol to Alcohol and Ketone (6) Ratio Analysis. The ratio of phenol to the total amount of alcohols and ketones was investigated at both ends of the temperature scale on a 10% XE-60 Diatoport S column. The chromatography was programmed from 80° with the temperature increasing 4°/min until four incompletely resolved peaks appeared with retention times of 31.5–36 min. At 230° a peak was observed which corresponded to the known phenol. Because of the inaccuracy of measuring the ratios of the areas of the four partially resolved peaks to that of the phenol, the method employed was to trace the total area, cut it out, and weigh it. That the ketone-ketone, ketone-alcohol, and alcohol-alcohol ratios did not change was known since the equilibrated samples used were the same as those employed in the analytical procedure. At the low end of the temperature range (210°) the phenol to (ketone + alcohol) ratio after 39 hr was 1.99; after 68 hr the ratio was 1.89. At the high end of the temperature scale (294°) the phenol to ketone ratio was 0.896 after 6 hr, and 0.893 after 9 hr.

2-Alkyl-4-*t*-butylcyclohexanones. Representative illustrations of different syntheses are given below. The properties of the products are summarized in Table VI.

Scheme B. 2-Isopropyl-4-*t*-butylphenol (9). A mixture of 50.0 g of colorless, redistilled 2-isopropylphenol, bp 111–112.5° (21 mm), n_D^{25} 1.5253 (lit.⁴⁰ bp 106° (20 mm)), 60.0 g of *t*-butyl chloride and 5.0 g of anhydrous aluminum chloride was stirred at room temperature for 2.5 hr. An additional 20.0 g of *t*-butyl chloride was then added and the orange solution was heated with stirring over a period of 1 hr at a temperature of 55°. It was maintained at 55° for 2.5 hr and then an additional 12.0 g of *t*-butyl chloride was added. Heating and stirring were continued for another 3.5 hr. After cooling the mixture to room temperature, 250 ml of water was added and the resulting mixture was extracted with ether. The ether extract was washed with water, then with a 4% aqueous sodium hydroxide solution, followed by a saturated solution of sodium chloride, and finally it was dried over anhydrous sodium sulfate. The filtered solution was concentrated and the residue was distilled through a

Table VII. Vibrational Spectra (cm⁻¹) of Cyclohexane-1,4-dione^a

Infrared ^b	Raman ^c	Infrared	Raman
...	73 (w)	1312 (s)	1318 (m)
...	413 (w)	1328 (s)	...
...	515 (w)	1342 (s)	...
...	586 (w)	1370 (m)	1362 (s)
726 (w)	726 (w)	1408 (s)	1410 (m)
741 (w)	...	1429 (s)	1432 (w)
778 (w)	...	1443 (s)	...
806 (w)	...	1705 (s)	1702 (w)
844 (w)	2912 (s)
873 (m)	2969 (s)
941 (m)	3036 (s)
968 (s)	3094 (s)
1010 (s)	1013 (m)
1029 (w)
1062 (m)
1085 (m)	1088 (w)
1146 (s)
1164 (s)
1179 (m)
1209 (m)
1230 (w)	1230 (m)
1266 (m)
1294 (w)

^a The probable error in the frequencies is about ± 3 cm⁻¹. ^b The infrared spectrum was obtained both as a solid film and as a Nujol mull. ^c The Raman spectrum was obtained from a compressed disk.

24-in. Podbielniak column to give 39.2 g (55.5%) of product as a colorless viscous liquid, bp 139.5° (28 mm), n_D^{25} 1.5073.

Anal. Calcd for C₁₃H₂₀O: C, 81.19; H, 10.48. Found: C, 81.09; H, 10.70.

2-Isopropyl-4-*t*-butylcyclohexanol (10). A solution of 19.6 g of 9 in 150 ml of glacial acetic acid was hydrogenated at room temperature and 46 psi of initial pressure, using 1.0 g of platinum oxide. The theoretical volume of hydrogen (3 molar equiv) was absorbed in 9 hr, and a 4% excess of hydrogen was absorbed during the following 50 hr. After filtration from the catalyst and evaporation of the solution to dryness under vacuum, the pale yellow liquid residue was diluted with ether. The ether solution was washed with a saturated aqueous sodium bicarbonate solution, then dried over anhydrous sodium sulfate. The filtered solution was concentrated and the residue was distilled through a Podbielniak column to give 14.3 g (71%) of product as a colorless, viscous liquid, bp 87° (1.8 mm), n_D^{25} 1.4671. A center fraction was redistilled once for analysis, n_D^{25} 1.4666.

Anal. Calcd for C₁₃H₂₀O: C, 78.72; H, 13.21. Found: C, 78.78; H, 12.85.

2-Isopropyl-4-*t*-butylcyclohexanone (11). To 9.43 g of 10 in 75 ml of acetone (purified by treatment with potassium permanganate) was added dropwise with swirling a total of 13.00 ml of 8 *N* chromic acid reagent⁴¹ (equivalent to an excess of 9%). Intermittent ice bath cooling was used to keep the solution at or just below room temperature at all times. The brown-orange mixture was allowed to stand at room temperature for 0.5 hr and was then diluted with water and extracted twice with ether. The combined ether extracts were washed twice with water and then dried over anhydrous sodium sulfate. The filtered solution was evaporated to dryness under reduced pressure and the pale yellow liquid residue

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(41) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

Table VIII. Dipole Moment Data

Compound	Temp, °C	α	ϵ_1	β	d_1	$P_{2\infty}$	μ
Perhydroanthraquinone	25.0	1.725	2.2732	0.516	0.87315	84.76	1.09 \pm 0.03
Cyclohexane-1,4-dione	18.0	2.240	2.2868	0.326	0.88088	60.77	1.26 \pm 0.02
	25.0	2.261	2.2741	0.331	0.87330	61.39	1.29 \pm 0.02
	38.0	2.237	2.2501	0.349	0.86000	61.68	1.35 \pm 0.03
	50.6	2.133	2.2226	0.349	0.84581	60.45	1.32 \pm 0.02

was distilled through a Podbielniak column to yield 7.5 g (80%) of product as a colorless liquid. (See Table VI.)

Vapor phase chromatography (see below) clearly indicated the presence of an impurity as a separate small peak in addition to two slightly skewed, well-defined separate peaks corresponding to the *cis* and *trans* isomers of 2-isopropyl-4-*t*-butylcyclohexanone. A mixed chromatographic study using approximately equal amounts of material from methods A and B proved the identity of the two.

The Synthesis of 2-Ethyl-4-*t*-butylcyclohexanone (Scheme A). 2-Carbethoxy-4-*t*-butylcyclohexanone (12). The procedure used was similar to that described for the preparation of ethyl 2-ketohexahydrobenzoate.⁴² Sodium (29.8 g) was dissolved in 400 ml of dry ethanol in a 2-l. three-neck flask equipped with a stirrer, a dropping funnel, and a condenser carrying a drying tube. The flask was immersed in an ice-salt bath and the stirrer was started. When the temperature of the solution had reached 10°, an ice-cold solution of 200 g of 4-*t*-butylcyclohexanone and 190 g of ethyl oxalate in 200 ml of dry ethanol was added during 30 min. The ice bath was retained for 1 additional hr, and then the red solution was stirred at room temperature for 6 hr. The dark red mixture was decomposed by the careful addition of ice-cold dilute sulfuric acid prepared by the addition of 36 ml of concentrated acid to 320 g of ice. During this neutralization the temperature of the mixture was maintained at 5–10° by means of an ice-salt bath. The mixture was then diluted with cold water to a volume of about 3 l., and the heavy oil that separated was removed by means of a separatory funnel. The aqueous phase was extracted with benzene. The heavy oil was combined with the extracts, the resulting solution was washed with water, and the benzene was removed under reduced pressure. To the pale red liquid residue in a 500-ml boiling flask equipped with a condenser was added 1 g of powdered soft glass and a trace of iron powder. The flask was heated at 160–170° in an oil bath for 8 hr, after which time gas evolution essentially ceased, and then the residue was fractionally distilled through a 2-ft Vigreux column. A total of 40.8 g (20%) of 4-*t*-butylcyclohexanone was recovered, bp 71° (2.7 mm). The product (12) distilled as a very pale yellow liquid, bp 128.5–129° (6.0 mm), n_D^{25} 1.4768. The yield was 146.0 g (62.5% based on unrecovered 4-*t*-butylcyclohexanone). An analytical sample was obtained from a center fraction, n_D^{25} 1.4780.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.95; H, 9.91.

2-Carbethoxy-2-methyl-4-*t*-butylcyclohexanone (13). The procedure used was similar to that described for the preparation of 2-carbethoxy-2-methylcyclohexanone.⁴³ The yield was 77% of a colorless liquid, bp 105.5° (1.3 mm) n_D^{25} 1.4610.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.13; H, 10.08.

2-Ethyl-4-*t*-butylcyclohexanone (14). (Scheme A). Potassium (4.41 g) was dissolved in 110 ml of dry *t*-butyl alcohol (distilled from sodium) and to this solution at room temperature was added 24.0 g of 12 over a 15-min period with stirring. The warm red solution that resulted was heated to reflux and then 17.5 g (0.112 ml) of ethyl iodide was added dropwise during 5 min with stirring. The mixture was heated under reflux with stirring for 6 hr and was then allowed to stand at room temperature for an additional 4.5 hr. About 80 ml of *t*-butyl alcohol was removed by distillation, and the cooled mixture was diluted with water and extracted with *n*-pentane. The pentane extracts were washed with water and with a saturated aqueous solution of sodium chloride. The solvent was then evaporated to give a yellow liquid residue which was dissolved in 200 ml of methanol. To this solution was added a solution of 11.1 g (0.278

mole) of sodium hydroxide in 200 ml of water, and the mixture was heated under reflux for 57 hr. Virtually all of the methanol was removed by distillation, and, after cooling to room temperature, a solution of 34 ml of concentrated hydrochloric acid in 25 ml of water was carefully added (frothing). The mixture was refluxed for 4 hr, then was cooled and diluted with water. It was extracted twice with pentane and the combined extracts were washed with a saturated aqueous solution of sodium bicarbonate and water and then dried over anhydrous sodium sulfate. The filtered solution was concentrated to dryness and the pale orange liquid residue was distilled through a 19-in spinning-band column to yield 10.7 g (55%) of 14 as a colorless liquid, bp 96.5° (3.6 mm). For analysis the center fractions were combined and redistilled through the same column (see Table VI). Vapor phase chromatography (see below) showed the redistilled center fractions to be pure 14 without any trace of 4-*t*-butylcyclohexanone.

The 2,4-dinitrophenylhydrazone of 14 was prepared and after chromatographing on alumina it was twice crystallized from methanol (Table VI).

Equilibration Studies. All temperatures reported in the equilibration studies have been corrected. Absolute methanol (Baker Analyzed Reagent) and absolute ethanol (Commercial Solvents Corp.) were used without further purification.

Equilibration of 2-Isopropyl-4-*t*-butylcyclohexanone (11). 2-Isopropyl-4-*t*-butylcyclohexanone from method B was used for all equilibration studies.

A. The equilibration of 0.3237 g of 11 was carried out by heating under reflux in a solution of 30 ml of methanol containing 0.25 g of sodium for 15 hr (solution temperature 63.8°). The hot solution was poured onto cracked ice and the product was extracted with ether. The ether extracts were washed and dried and the solvent was evaporated. A slightly cloudy, slightly viscous yellow liquid, 0.2696 g (83% recovery), was obtained.

B. To 0.79 g of freshly cut sodium dissolved in 80 ml of absolute methanol was added 1.0074 g of 11 in 10 ml of absolute methanol. The stoppered colorless solution was placed in a constant temperature bath at 25°. After 259 hr, a colorless 25-ml portion was removed and worked up in a manner similar to that described in equilibration procedure A except the reaction was diluted with water at 25° instead of pouring on ice, yielding 0.2182 g (78% recovery based on 25/90 of starting 11) of a slightly cloudy, slightly viscous, yellow liquid.

C. Another colorless, 25-ml portion was withdrawn from equilibration procedure B after a total of 297 hr. It was worked up exactly as described under B above, and yielded 0.2270 g (81% recovery based on 25/90 of starting 11) of a slightly cloudy slightly viscous yellow liquid.

Description of Vapor Phase Chromatography. The column used was 181.5 cm in length and was constructed of 7-mm glass tubing bent into a U shape. It was contained in a vertical heating jacket. The column was packed with glyceryl β -tricyanoethyl ether (25% by weight) absorbed on 60–80 mesh base-washed firebrick. During the period of analysis (which lasted for several weeks) the column temperature was maintained at 138–140°. The ratio of isomers in each sample was calculated from the relative areas under each peak as determined by a Leeds and Northrup disk chart integrator. Sample sizes ranged from 0.003 to 0.006 ml for those containing no solvent and from 0.0065 to 0.013 ml for those diluted with dry redistilled *n*-pentane. Representative times of *cis*- and *trans*-11 at a column temperature of 139° were 31.4 and 43.0 min, respectively.

Dipole Moments. The experimental dipole moments were determined at 25° in benzene solution using previously described apparatus⁴⁴ and methods.⁴⁵ Molar refractivities were calculated

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Boron Fluoride Catalyzed Alkylation. II.¹ Tertiary Butylation at Low Temperatures

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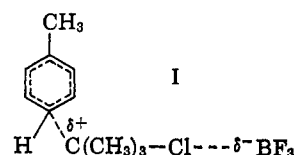
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Abstract: It is found that Friedel-Crafts *t*-butylation caused by decomposition of the alkylbenzene-*t*-butyl chloride-boron fluoride 1:1:1 oriented π complexes at low temperatures shows high substrate selectivity. The isomer distribution of *t*-butyltoluene formed is 100% *para* isomer. Hence the electrophile in this aromatic substitution is not a *t*-butyl cation or an incipient *t*-butyl cation but a polar donor-acceptor complex $\delta^+\text{C}(\text{CH}_3)_3$, the electrophilic character of which is very weak.

Olah, *et al.*,² found that Friedel-Crafts *t*-butylation of toluene and benzene with *t*-butyl bromide and isobutylene under nonisomerizing conditions at room temperature shows intermediate substrate selectivity ($k_{\text{toluene}}/k_{\text{benzene}} = 13\text{--}16$) and that the isomer distribution of *t*-butyltoluene formed is 5.7–7% *meta* and 94.3–93% *para* isomers.

Allen, *et al.*,³ suggested that all *t*-butylations of toluene can be obtained by alkylations producing isomeric mixtures containing 7% *m*- and 93% *p*-*t*-butyltoluene, 67% *m*- and 33% *p*-*t*-butyltoluene, or an intermediate distribution; the first isomer distribution is the substitution distribution and the second the thermodynamically controlled subsequent or concurrent isomer distribution caused by predominant intermolecular migration of the *t*-butyl group.

In a recent publication¹ we reported that when a small amount of toluene was dissolved in polarized *t*-butyl chloride-boron fluoride complex and the absorption spectrum of the solution was measured at -95° , strong absorption characteristic of a toluene-*t*-butyl chloride-boron fluoride 1:1:1 complex was observed around 260 and 361 m μ . When the solution was diluted with liquid isopropyl chloride at low temperatures, the strong absorption disappeared and the fine structure of the benzenoid band of toluene was observed. The 1:1:1 complex is a dissociable π complex, but its absorption band closely resembles those of benzenium ions.⁴ The thermodynamic isotope effect showed that the complex system contains $-\text{Cl}\cdots\delta^+\text{BF}_3$ but not BF_3Cl^- . Hence the complex seems to be an oriented π complex such as structure I but not an unlocalized π complex. When a small portion of the boron fluoride was withdrawn from the solu-



tion that dissolved the oriented π complex, the peaks became faint and the fine structure of the benzenoid band of *t*-butyltoluene appeared, overlapped with the above peaks. When boron fluoride was withdrawn completely, the peaks disappeared and only the fine structure of the benzenoid band of *t*-butyltoluene remained. Hence *t*-butylation can proceed at low temperatures by decomposition of the oriented π complex. In the present work the relative reactivity and isomer distribution in this Friedel-Crafts *t*-butylation are investigated.

Results

The dissociation pressure of the toluene-*t*-butyl chloride-boron fluoride 1:1:1 oriented π complex, which melts at -122° , is approximately 760 mm at -95° . The vapor is composed mostly of boron fluoride. The vapor was withdrawn through a leak into an evacuated reservoir, while the liquid complex was kept in a constant temperature bath at -95° (melting point of toluene) until the amount of boron fluoride introduced in the reservoir became nearly equal to that of the boron fluoride contained in the complex. Ammonia was added to the liquid in order to quench the trace of boron fluoride. This caused the white solid boron fluoride-ammonia complex to deposit. After the liquid was allowed to warm to room temperature, the separated liquid was analyzed by gas-liquid partition chromatography and found to be composed of *t*-butyl chloride, toluene, and *t*-butyltoluene in an amount which was only about 3% of that of toluene, as shown in Table I. By complete withdrawal of boron fluoride, the oriented π complex dissociated mostly into toluene, yielding only a small amount of *t*-butyltoluene.

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