substituents on the rate of decomposition is small. Electron-repelling substituents seem to cause slightly slower rates of decomposition.

The energy of activation for 4,4′-dichlorobenzalazine was 47 ± 4 kcal. per mole and that of 2,2′-dichlorobenzalazine 54 ± 4 kcal. per mole. The entropies of activation are positive and between 4 and 10 entropy units. The high activation energy is in accord with the difficulty in breaking the —C=N bond. The positive entropy of activation indicates that a cyclic mechanism which can be written for this decomposition probably is not operative.[17]

[17] The original work on this problem was carried out in 1948 and 1949, but since product analyses were not completed the research was not published. Recently an excellent detailed analysis of the products and reaction mechanism has been completed by Zimmerman and Somasekhara, THIS JOURNAL, **82**, 5865 (1960). Our kinetic data are not in conflict with their proposed mechanism.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY, DETROIT 2, MICH.]

Conformational Analysis. XI. The Conformers of 2-Chlorocyclohexanone[1,2]

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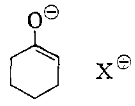
The *cis* and *trans* isomers of 2-chloro-4-*t*-butylcyclohexanone have been prepared and their structures have been assigned from their dipole moments. The infrared and ultraviolet spectra have been determined and differ in a manner analogous to that found earlier for the corresponding bromo compounds. The same properties have been measured for 2-chlorocyclohexanone. Using the data from the conformationally pure substituted compounds, the position of the conformational equilibrium in 2-chlorocyclohexanone has been determined in several independent ways. The isomers of 2-chloro-4-*t*-butylcyclohexanone have been equilibrated by treatment with anhydrous hydrogen chloride, and the position of equilibrium is similar to that found with 2-chlorocyclohexanone. These equilibria shift with changes in concentration, solvent and temperature. A consistent interpretation of the data is given.

Introduction

The original suggestion that the axial or equatorial configuration of a halogen (bromine) adjacent to a ketone could be determined from the frequency of the carbonyl absorption in the infrared was due to Jones and his co-workers.[3] Corey[4] applied this criterion to determine the conformations of various 2-halocyclohexanones, including 2-chlorocyclohexanone itself. Although cyclohexanone is often described as simple when contrasted with the steroids, the reverse is usually true with regards to conformational isomerism. In steroidal systems it is known that the introduction of a chlorine atom next to a carbonyl group causes a shift in the carbonyl absorption of 2–9 cm.$^{-1}$ if the chlorine is axial, but of 18–25 cm.$^{-1}$ if the chlorine is equatorial.[5]

Extensive studies have already been carried out with the related 2-bromocyclohexanone and the conformationally pure *cis*- and *trans*-4-*t*-butylcyclohexanones, and it was shown that when the same conformational arrangements are compared there is a nearly perfect correspondence in spectral properties between the monocyclic and steroidal compounds.[6–11] It therefore seems reasonable that such a correspondence would follow in the chloro series, yet the possibility of a reversal in spectral properties upon going from the monocyclic systems to the steroids has been suggested.[12]

The dipole moments of 2-bromo- and 2-chlorocyclohexanone were measured by Kumler and Huitric in different solvents.[10] It was found, somewhat unexpectedly, that the bromo compound consistently showed the smaller moment. An interpretation which was suggested was that the bromine atom tends to be in the axial position to a greater extent than does the chlorine atom. Since C–Br and C–Cl bonds have the same dipole moments, the steric effect was expected to dictate the relative positions of equilibria, but the results did not appear to correspond to the predictions. Corey and Burke[13] had previously noted cases of 2-halocyclohexanones in which chlorine seemed to show a greater preference for the equatorial position than did bromine, and they suggested that a reason for the apparent anomaly might be found in the valence bond structure I. Since this resonance would be expected to be more important when X was bromine, and could best occur when the halogen was axial, the effect of such resonance would be to shift the equatorial ⇄ axial equilibrium further to the right for the bromo compound.



I

An apparent analogy to the halo ketones exists with the *trans*-1,2-dihalocyclohexanes. The di-

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[1] Paper X, N. L. Allinger and L. A. Freiberg, THIS JOURNAL, **82**, 2393 (1960).

[2] This Research was supported by the Office of Ordnance Research, U. S. Army, under Contracts No. DA-20-018-ORD-14652 and No. DA-20-018-ORD-20046.

[3] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

[4] E. J. Corey, *ibid.*, **75**, 2301 (1953).

[5] E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

[6] J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).

[7] N. L. Allinger, J. Allinger and N. A. LeBel, THIS JOURNAL, **82**, 2926 (1960).

[8] N. L. Allinger and J. Allinger, *ibid.*, **80**, 5476 (1958).

[9] A. Julg, *J. Chim. Phys.*, 453 (1956).

[10] W. D. Kumler and A. C. Huitric, THIS JOURNAL, **78**, 3369 (1956).

[11] R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

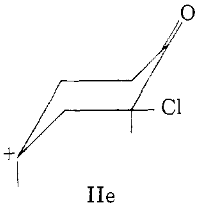
[12] M. L. Josien and C. Castinel, *Bull. soc. chim. France*, 801 (1958).

[13] E. J. Corey and H. J. Burke, THIS JOURNAL, **77**, 5418 (1955).

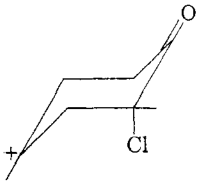
chloride was found to contain more of the diequatorial conformation than the chlorobromide which in turn contained more than did the dibromide.[14] It is difficult to extend the idea of the importance of resonance structures such as I to these cases.

Results

The present work was undertaken to obtain quantitative data on the 2-chlorocyclohexanone system, to test the suggestion of Josien and Castinel,[12] to attempt to find evidence for or against the importance of resonance form I, and to gain a better general understanding of the forces which determine the positions of conformational equilibria. The experimental approach was in general similar to that used with the bromo compounds.[6-8] The *cis* and *trans* isomers of 2-chloro-4-*t*-butylcyclohexanone contain, respectively, equatorial and axial chlorine atoms. Using these compounds as conformationally pure standards, it would be possible to tell from suitable physical measurements where the equilibrium point was for 2-chlorocyclohexanone (IV) itself under various conditions.



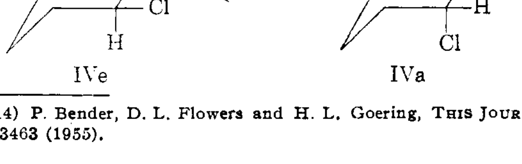
IIe



IIa

The synthesis of the isomers of II was straightforward. Chlorination of 4-*t*-butylcyclohexanone (III) in 90% acetic acid afforded a mixture of the epimeric 2-chloro-4-*t*-butylcyclohexanones (II). After fractional distillation, the *cis* isomer IIe was obtained as a crystalline solid, m.p. 59°, λ_{max} 1748 cm.$^{-1}$ (carbon tetrachloride). The more volatile *trans* compound IIa, estimated to contain 2–8% of IIe by examination of the infrared fingerprint region, was further purified by chromatography on silica gel. Pure *trans*-2-chloro-4-*t*-butylcyclohexanone melted at −15° and had a carbonyl absorption maximum at 1736 cm.$^{-1}$.

Dipole Moment Studies.—While there exist a number of methods by which the configurations of IIe and IIa could have been established, the one which was used in the present work was the completely unambiguous method of dipole moment measurements. The moments of IIe and IIa were found to have the values 4.29 and 3.17 D., respectively, in benzene solution. The observed moment of 2-chlorocyclohexanone was 3.71 D. Kumler and Huitric have reported[10] a value of 3.78 D. for IV in benzene solution. They also reported values of 3.91 D. in dioxane and 3.45 D. in heptane. From the present work the composition of IV in dilute benzene solution was established. Using the data of Kumler and Huitric the compositions in heptane and in dioxane were also calculated. These values are given in Table I. Studies of these compounds were also made by spectroscopic methods.



IVe IVa

TABLE I

PERCENTAGE EQUATORIAL 2-CHLOROCYCLOHEXANONE IN VARIOUS SOLVENTS AT 25°

Solvent	From μ	From infrared (by temp. variation)	From ultraviolet	From equil. of IIa and IIe
Octane[a]	24	27[b,c]	37	..
CCl_4	..	..	..	43[d]
CS_2	..	47[b,c]	..	..
Benzene	44	..	..	63[c,d]
Dioxane	63	75[c,d]	63	72[d]
Me_2SO	..	..	..	..
Neat	..	81	..	..

[a] Isoöctane (spectral grade) was used for the spectral measurements, heptane for the dipole moment studies. [b] Concentration about 3%. [c] The amount of equatorial conformer increased with increasing concentration. [d] Concentration about 10%.

Infrared Studies.—Following earlier arguments,[6,15] it is clear that the concentration of the equatorial conformer will increase at the expense of the axial one as the solvent polarity is increased. By analogy with the bromo compounds it was expected that the carbonyl band would be composed of the separate bands for each conformer, and that its variation with solvent could be analyzed as before. The change in the profile of the carbonyl stretching frequency with solvent was partly analogous to that found with the corresponding bromo compounds, and the curves are shown in Fig. 1. The carbonyl band in each case was a single band with two shoulders. The shoulder on the low frequency side is anomalous, but such bands have been observed and discussed previously.[15] The principal band was at the proper frequency with respect to the parent ketone to have the axial-halo structure assigned to it. The shoulder on the high frequency side was separated from the principal band in each case by 7–12 cm.$^{-1}$ and showed a qualitative variation in intensity with solvent as expected. The resolution was too poor to make any quantitative study possible, however.

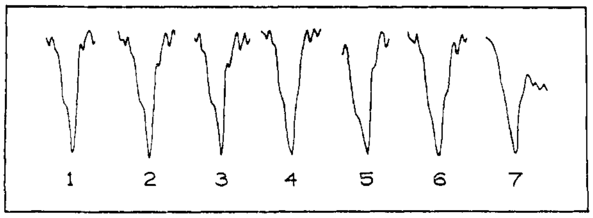


Fig. 1.—Carbonyl absorption curves of 2-chlorocyclohexanone in various solvents: 1, cyclohexane; 2, carbon tetrachloride; 3, carbon disulfide; 4, chloroform; 5, benzene; 6, dioxane; 7, dimethyl sulfoxide. Wave length increases to the right.

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(14) P. Bender, D. L. Flowers and H. L. Goering, THIS JOURNAL, **77**, 3463 (1955).

(15) N. L. Allinger, J. Allinger, L. E. Geller and C. Djerassi, *J. Org. Chem.*, **25**, 6 (1960).

Several bands in the fingerprint region were also recorded in solvents of varying polarity. One set of bands was found to increase at the expense of another set as the polarity was increased, and these sets were assigned respectively to the equatorial and axial conformations. A check of this empirical band assignment was possible, since the bands at about 700 cm.$^{-1}$ and 715 cm.$^{-1}$ can be assigned to the C–Cl stretching modes with a fair degree of certainty, and the higher frequency is expected to correspond to the equatorial halogen,[16] in agreement with the assignment made on the basis of solvent dependence.

The spectra were first obtained in isoöctane at ordinary concentrations (about 15%) at 26° and 83°. The ratio of the concentration of the axial form (C_a) to the concentration of the equatorial form (C_e) is given by the general expression 1, where f is the partition function and ΔE is the difference

$$\frac{C_a}{C_e} = \frac{f_a}{f_e} e^{-\Delta E/RT} \qquad (1)$$

in energy between the axial and equatorial forms ($\Delta E = E_a - E_e$). For a given absorption band, $d = \epsilon C$, where d is the optical density[17] and ϵ is the molar extinction coefficient. Therefore 1 can be rewritten as 2. It is assumed the ratio of the

$$\frac{d_a}{d_e} = \frac{\epsilon_a f_a}{\epsilon_e f_e} e^{-\Delta E/RT} \qquad (2)$$

partition functions is constant over the limited temperature range involved. From measurements at two temperatures, T_1 and T_2, the unknown pre-exponential factor can be eliminated, and 2 can be manipulated into the form 3. Using the solution and temperature described, ΔE was found for the

$$\Delta E = \frac{T_1 T_2 R}{T_1 - T_2} \ln \frac{d_{a_1} d_{e_2}}{d_{e_1} d_{a_2}} \qquad (3)$$

compound from three separate pairs of bands. These pairs were located near the frequencies listed, the band characteristic of the axial form being given first: 700 and 715 cm.$^{-1}$, 822 and 796 cm.$^{-1}$, and finally 918 and 935 cm.$^{-1}$. The values found for ΔE (in isoöctane) were 328, 198, and 271 cal./mole, respectively. Thus under these conditions the equatorial chlorine had a lower energy than did the axial by 0.25 kcal./mole. These measurements were repeated in dioxane solvent, but it was found that the strong absorption of the dioxane prevented determination of the energy in this way.

By analogy with 2-bromocyclohexanone, the axial conformer might have been expected to have the lower energy in octane. The finding of the reverse was a little surprising. Since the spectra were obtained at rather high concentration, it seemed likely that an intermolecular interaction was occurring which tended to stabilize the equatorial conformation. Such a stabilization would be predicted simply from the very large dielectric constant (26.8)[18] of IV. The spectra were therefore obtained at greater dilution (about 3%), and as anticipated, the axial/equatorial ratio had greatly increased. Cryoscopic measurements showed that association was occurring even at these low concentrations.

To determine the actual concentrations a knowledge of the ratio of the partition functions is required. The assumption has been made that this ratio is unity, and this must be a fairly close approximation. (The accuracy of the values in Table I is particularly dependent on this assumption.) Then $\Delta F = \Delta E$, and K can be found at 25° in the octane solution. Knowing K, the ratio C_e/C_a can then be found, and hence the ratio ϵ_e/ϵ_a can be determined for each pair of bands. If it is further assumed f_e/f_a and ϵ_e/ϵ_a are independent of solvent, it is possible to find the ratio of isomers, C_e/C_a, under different circumstances where the ratios of the absorption intensitities can be found. Actually the agreement with the values found by other methods is seen to be quite good. While this work was being carried out there appeared a paper by Kozima and Yamanouchi[18] which also described similar infrared studies on 2-chlorocyclohexanone. Their results and ours are only partly in agreement. The reason for the discrepancy between our work and that of Kozima and Yamanouchi as far as the carbon disulfide solutions are concerned is not clear. We lacked the instrumental facilities for low temperature studies and were not able to duplicate their conditions. We do note a strong dependence of the equilibrium point on the concentration in carbon disulfide solutions, and because of the volatility of the solvent, it may be that the concentrations of the solutions studied by those workers were greater than was thought. For the pure liquids our results and theirs agree within the combined experimental errors.

Ultraviolet Studies.—Examination of the ultraviolet absorption spectra of samples of pure IIa and IIe, synthetic mixtures of IIa and IIe, and IV was carried out in the solvents isoöctane and dioxane. As expected, the ultraviolet properties of the conformationally pure models [and the parent ketones, 4-*t*-butylcyclohexanone (III) and cyclohexanone (V)] did not vary noticeably with changes in the medium. Quite obviously the spectral shifts for the two conformations of an α-chloro ketone are similar in both monocyclic and steroidal systems.[11] The parallelism also obtains when the chloro ketones are compared with the bromo analogs.[6] The axial chloro ketones, however, show smaller (*i.e.*, less positive) shifts in $\lambda_{\max}$ values than do the bromo compounds[6] and the extinction coefficients are lower. Comparisons of the spectra of synthetic mixtures of IIa and IIe with those of the pure isomers show the dominance of the enhanced extinction coefficient of IIa relative to that of IIe. The absorption curves of the mixtures are quite similar to those of the pure *trans* (axial) isomer except

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(16) (a) M. Larnaudie, *J. Phys. Radium*, **15**, 650 (1954); (b) P. Klaeboe, J. J. Lothe and K. Lunde, *Acta Chem. Scand.*, **10**, 1465 (1956).

(17) The band areas are properly used as a measure of the amount of compound present (see R. N. Jones and C. Sandorfy in "Chemical Applications of Spectroscopy," Vol. IX of A. Weissberger's "Technique of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 271.) Because of the rather poor resolution of some of the bands and the shapes of certain others, the optical density (corrected for background) has been used instead of the integrated intensity in the present work.

(18) K. Kozima and Y. Yamanouchi, This Journal, **81**, 4159 (1959).

that they are more skewed and reduced in intensity. A determination of the position of equilibrium of 2-chlorocyclohexanone was made by the methods employed previously, and indicates a composition of 63% axial conformer in isoöctane and 37% axial conformer in dioxane (see Table I). The values are consistent with the interpretation that the equilibrium is shifted toward the equatorial form in the more polar solvent, and are in excellent agreement with those found by other physical measurements, particularly the dipole moments. The data are summarized in Table II.

TABLE II

SPECTRAL SHIFTS OF THE ULTRAVIOLET ABSORPTION MAXIMA OF THE CHLOROKETONES

	Isoöctane		Dioxane	
	$\Delta\lambda_{max}$[a]	$\Delta\epsilon$	$\Delta\lambda_{max}$[a]	$\Delta\epsilon$
IIe	− 6	1	− 5	0
IIa	+14	33	+18	34
IIea[b]	+10	13	+14	16
IV	+11	20	+13	10

[a] Values in mμ relative to the parent ketone.[b] The concentrations are given in Table VI.

Equilibration Studies.—A study of the equilibrium IIe $\rightleftarrows$ IIa was made in several solvents utilizing anhydrous hydrogen chloride as the proton source. The same equilibrium mixture was reached from both sides starting with each of the conformationally pure epimers. Analyses of these mixtures were carried out by a comparison of the infrared spectra in carbon disulfide solution of pure IIa, pure IIe and the equilibrated samples. Table III presents a summary of the results, along with calculated values of the equilibrium constants and free energy changes (25°). As predicted, the equilibrium concentration of the equatorial isomer Ie is increased at the expense of Ia as the polarity of the solvent is increased in the order carbon tetrachloride, benzene and dioxane. The data are in good agreement with the infrared measurements for 2-chlorocyclohexanone (IV), but suggest more IVe isomer than is predicted by the dipole moment studies. That these observations can again be attributed to intermolecular interactions of a polar solute in relatively high concentration (10%) is shown by further studies in benzene solution. As the concentration of chloro ketone (IIa or IIe) in 0.1 M hydrogen chloride–benzene was decreased from 25 to 3%, the equilibrium was shifted slightly in favor of the less polar axial isomer.

TABLE III

RESULTS OF EQUILIBRATION STUDIES AT 25°

Isomer	Solvent[a]	Concn.[b]	Time, hr.	% IIa	% IIe	Normalized % IIa	Normalized % IIe	K	ΔF[c]
IIa	Dioxane	10	61	29	73	28	72	0.38	+0.57
IIe	Dioxane	10	61	26	70	27	73		
IIa	Benzene	25	151	35	69	34	66	.53	+ .38
IIe	Benzene	25	151	36	67	35	65		
IIa	Benzene	10	234	41	68	37	63	.57	+ .33
IIe	Benzene	10	234	38	67	36	64		
IIa	Benzene	3[d]	437	35	57	38	62	.61	+ .29
IIe	Benzene	3[d]	437	34	54	38	62		
IIa	CCl_4	10	90	54	49	53	47	1.08	− .046
IIe	CCl_4	10	113	50	48	51	49		
Synthetic mixt., 52.5% IIa, 47.5% IIe				54	50	52	48		
Synthetic mixt., 74.6% IIa. 25.4% IIe				76	25	75	25		

[a] Approximately 0.1 M in anhydrous hydrogen chloride. [b] % (w./v.); 10% = 100 mg./ml. [c] Kcal./mole. [d] Also studied in approximately 0.2 M anhydrous chloride in benzene. Normalized percentages obtained were: from IIa: 39% IIa, 61% IIe; from IIe; 39% IIa, 61% IIa.

Discussion

It is now quite clear that the chlorine atom has a greater tendency to take up an equatorial position than does the bromine atom. Fluorine appears to show even a greater tendency to do this than does chlorine.[19,20] The explanation offered earlier for these facts[13] can be examined in the light of the dipole moment data which are available. Resonance structure I is important only when the halogen is axial, because of the symmetries of the C–X bond and the carbonyl π-system. Structure I, if purely ionic, would have a dipole moment of about 17.7 D., and hence a sizable contribution from such a form might be expected to increase the dipole moment. The prediction can be made that if resonance form I is important the axial chloro compound IIa may show a smaller moment than the bromo analog, while the equatorial isomers should have more nearly the same moments. A trend in this direction was found (Table IV), but the differences are only of the order of the experimental error. The dipole moment measurements therefore do not offer evidence for an effect of this kind of resonance in determining conformational equilibria. Since the energy involved is so small, however, the actual effect may simply be too small to detect.

Kende suggested[20] that the relative preferences shown by the different halogens for the equatorial position might be explained in terms of interaction with solvent. However, the effect seems to be similar in solvents which differ considerably in polarity and is also observed at infinite dilution. Any explanation for the effect should therefore be based primarily on intramolecular rather than intermolecular or solvent interactions.

TABLE IV

DIPOLE MOMENTS OF 2-HALOCYCLOHEXANONES IN BENZENE AT 25°

Compound	Halogen: Bromine[a]	Halogen: Chlorine
IIe	4.27	4.29
IIa	3.20	3.17
IV	3.49	3.71

[a] The compounds in this column are those in which the chlorine in the structure shown is replaced by bromine.

There are three fundamentally different interactions which might *a priori* cause the observed result, and these are usually referred to as orientation, induction and the van der Waals effects. The orientation effect was dealt with in detail for the bromocyclohexanones.[4,6] A corresponding treatment for the chlorocyclohexanone was made and it was found that the electrostatic interaction of the dipoles tends to put the chlorine axial to a greater extent than it does the bromine. This trend is the reverse of that found experimentally.

The intramolecular inductive effect would operate between the dipoles and the many atoms in the

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(19) H. Blatter, unpublished results.

(20) A. S. Kende, *Tetrahedron Letters*, No. 14, 13 (1959).

molecule in each case, but because the C–Cl and C–Br dipole moments are the same, these separate inductions would be nearly the same in the chloride as in the bromide. The only sizable difference would be the moment induced by the C=O bond in the C—X bond. Since the C–Br bond is more polarizable than the C–Cl, a larger induced moment should occur in the former case. The energy of the induced dipolar interaction is given[21] by 4 where μ is the moment of the C=O bond, α is the polarizability of the C—Br bond, and r is the distance between the dipoles. It is found that the effect is larger for the bromide, and larger when the bromine is in an equatorial position. This effect also tends to put the bromine rather than the chlorine in the equatorial position, but the difference is small.

$$E = \alpha\mu^2/r^6 \qquad (4)$$

The third type of force which needs to be considered is the van der Waals type. Hill has considered the van der Waals interactions of chlorine and bromine with hydrogen, and has outlined a general method for calculation of the energy *vs.* distance function.[22] By extending these calculations to the oxygen–halogen interactions it was possible to calculate the interaction energy for each conformer of both the halogen and the hydrogen attached to the same carbon with each near neighbor.

The sum total of the seven or eight interactions considered turns out to be the same in the two conformers; thus van der Waals interactions appear to play no significant part in determining the position of the equilibrium. While these methods of calculation can only be regarded as approximate, when applied to finding the difference in energy between an axial and equatorial bromine, chlorine or methyl group on a cyclohexane ring, the numerical values obtained[23] agree very well with the experimental ones. They also account[23] for the observed difference between the *trans*-1,2-dichloro- and dibromocyclohexanes, for which the ee form is preferred to a greater extent by the dichloride than by the dibromide.[14] While the dihalide case appears to be superficially analogous to the halocyclohexanone case, the theory does not appear to support such a parallelism. The various energies for the chloro- and bromoketones are summarized in Table V.

TABLE V

COMPONENT ENERGIES OF THE AXIAL AND EQUATORIAL CONFORMERS OF THE 2-HALOCYCLOHEXANONES

Interaction	Axial		Equatorial	
	Br	Cl	Br	Cl
Electrostatic[a]	−2.12	−2.33	+0.22	+0.18
Induced dipole[a]	−0.09	−0.08	− .32	− .27
van der Waals	−0.42	−0.50	− .18	− .28
Totals	−2.63	−2.91	−0.28	−0.37

[a] Assuming $D = 2$.

The electrostatic and induced dipole interactions are functions of dielectric constant. The position of the equilibrium between the conformational isomers IIa and IIe is predicted to lie at nearly 50% in a medium of very high dielectric constant, but IIa will predominate to an increasingly greater extent as the dielectric constant is lowered. If the effective dielectric constant were 2, the axial form would be of lower energy by 2.54 kcal. Actually the effective dielectric constant in the vicinity of the dipoles is not expected to be this low, even in a hydrocarbon solution, and the energy difference is never this great. It is noted that no real difference is predicted between the equilibrium points of the bromo- and chloro-ketones. While it may simply be that the calculations are not sufficiently refined to predict the observed difference (which is really very small in terms of energy), the observed trend seems clear cut, and the contribution of resonance structure I appears to be the most probable explanation for it yet offered.

Experimental

2-Chloro-4-*t*-butylcyclohexanone (II).—A procedure similar to that described for the chlorination of cyclohexanone was employed for the preparation of the chloroketones II,[24] with the modification that 90% acetic acid was the solvent. From 100 g. (0.65 mole) of 4-*t*-butylcyclohexanone (II) there was obtained after distillation of the ether 125 g. of a pale yellow oil. Fractional distillation separated this material into four distinct products. The forerun consisted of 1.0 g. of recovered starting material. Fractions 3–7, collected over the range b.p. 66–67° (0.6 mm.), $n^{25}\text{D}$ 1.4725-49, weighed 38.0 g. (31%). This product was assigned structure IIa on the basis of its dipole moment, and showed an infrared carbonyl absorption maximum at 1736 cm.$^{-1}$ in carbon tetrachloride solution. A higher boiling isomer (56.2 g., 46%), b.p. 84–89° (0.3-0.5 mm.), $n^{25}\text{D}$ 1.4853, was obtained in the next two fractions. These fractions solidified on standing and consisted mainly of the *cis* isomer IIe as was indicated by an infrared carbonyl maximum at 1748 cm.$^{-1}$. Finally, a solid residue remained, which afforded a pure dichloro compound, m.p. 145–146°, after several recrystallizations from *n*-hexane.

***trans*-2-Chloro-4-*t*-butylcyclohexanone** (IIa).—Quantitative comparison of the infrared absorption bands in the 10–14 μ region (carbon disulfide) of the *trans* isomer obtained from the fractional distillation ($n^{25}\text{D}$ 1.4741) with those of pure IIe showed that the axial compound contained 6% of the IIe isomer. Two grams of this slightly impure material was purified by chromatography on 60 g. of silica gel (Fisher, 28–200 mesh). The column was washed with 500 ml. of pure pentane followed by 30% chloroform in pentane, and 200-ml. fractions were taken. After removal of the solvent *in vacuo*, fractions 12–20 were combined and the residue was rapidly distilled at 0.5 mm. to give a colorless liquid, $n^{25}\text{D}$ 1.4737.

Anal. Calcd. for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08; Cl, 18.79. Found: C, 63.88; H, 9.57; Cl, 18.49.

The pure isomer IIa melted at −20 to −15°. Its infrared spectrum at 805 and 962 cm.$^{-1}$ indicated the absence of *cis* compound IIe. *trans*-2-Chloro-4-*t*-butylcyclohexanone (IIa) could be stored indefinitely at Dry Ice temperature. Storage at 0° was accompanied by slight decomposition followed by isomerization to the crystalline IIe.

***cis*-2-Chloro-4-*t*-butylcyclohexanone** (IIe).—The product from the distillation fractions which had solidified was recrystallized several times from pure pentane to give white needles, m.p. 58.5–59.5°.

Anal. Calcd. for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08; Cl, 18.79. Found: C, 63.93; H, 9.04; Cl, 18.63.

2-Chlorocyclohexanone (IV) was prepared according to the described procedure.[25] The crude product was first rapidly distilled and then fractionally distilled through a 2-

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[21] J. A. A. Ketelaar, "Chemical Constitution," Elsevier Publishing Co., New York, N. Y., 1958, p. 357.

[22] T. L. Hill, *J. Chem. Phys.*, **16**, 399 (1948).

[23] Unpublished calculations of the authors.

[24] P. D. Bartlett and R. H. Rosenwald, THIS JOURNAL, **56**, 1992 (1934).

[25] M. S. Newman, M. D. Farbman and H. Hipsher, "Organic Syntheses," Coll. Vol. *III*, J. Wiley and Sons, Inc., New York, N. Y., 1955, p. 188.

foot column of the Podbielniak type. The colorless distillate had b.p. 81° (8 mm.), $n^{25}\mathrm{D}$ 1.4821; reported[25] b.p. 91° (14 mm.). The compound solidified upon standing at 0° and was successfully stored at this temperature protected from light and moisture until used.

Infrared Studies. Carbonyl Absorption Spectra.—The carbonyl absorption spectra were obtained employing a Beckman spectrophotometer, model IR4 and cells of 0.1-mm. path lengths. Just prior to use, the purity of IV was established by refractive index measurements. Commercial cyclohexanone (V) was purified by distillation, $n^{25}\mathrm{D}$ 1.4475 reported[26] $n^{15}\mathrm{D}$ 1.4520. *n*-Heptane and spectral grade cyclohexane were chromatographed on silica gel and the eluates were distilled from phosphorus pentoxide. Dioxane was purified in the usual way.[27] Thiophene-free benzene was refluxed with sodium metal for 12 hours and then distilled. Dimethyl sulfoxide, commercial grade, was purified by simple vacuum distillation just prior to use, b.p. 76° (16 mm.). The solvents carbon disulfide, chloroform and carbon tetrachloride were those designated as "spectral-grade." Solutions of IV and V of known and closely similar concentration, *ca.* 0.1*M*, were prepared in each of the described solvents.

For each solution the carbonyl spectrum was recorded under conditions of optimum resolution at least twice. The chart was run at 5 times the normal chart speed to spread out the spectrum.

A synthetic mixture containing 75% IIe and 25% IIa was prepared, and showed the principal maximum at +15 cm.$^{-1}$ with a shoulder at +2 cm.$^{-1}$ relative to the parent ketone. A second synthetic mixture in which the proportions were reversed showed a single maximum at +6 cm.$^{-1}$ At high resolution these bands could be separated into two distinct peaks. This situation is exactly reversed from that of the corresponding bromoketones,[6,8] with which the synthetic mixtures of pure conformers gave unresolvable shoulders, while 2-bromocyclohexanone itself gave resolvable peaks.

Ultraviolet Studies.—The spectra were obtained employing a Beckman DU spectrophotometer with a Warren Spectracord attachment. The complete data are summarized in Table VI. Analysis of the synthetic mixture for percentage of IIa isomer indicated that Beer's law was obeyed.

TABLE VI

THE ULTRAVIOLET SPECTRA OF 2-CHLOROCYCLOHEXANONE AND RELATED COMPOUNDS

	Isoöctane		Dioxane	
	$\lambda_{\max}$	$\epsilon_{\max}$	$\lambda_{\max}$	$\epsilon_{\max}$
IIe	286	17[d]	283	15[e]
IIa	306	49	306	49
IIea[a,b]	302	29	302	31
III	292	16[c]	288	15[c]
Cyclohexanone (V)	293	17[c]	287	15[c]
IV	304	37	300	25
IVe		11[f]		11[f]
IVa		52[g]		49[g]

[a] Synthetic mixture 3.15 × $10^{-3}M$ IIe, 2.68 × $10^{-3}M$ IIa in isoöctane. [b] Synthetic mixture 2.76 × $10^{-3}M$ IIe, 3.31 × $10^{-3}M$ IIa in dioxane. [c] These values differ from those reported in ref. 8 for the solvents carbon tetrachloride and 95% ethanol, but were reproducible in the course of the present study. [d] ϵ at 304 mμ = 10. [e] ϵ at 300 mμ = 11. [f] Estimated to be equal to $\epsilon_{\mathrm{IIe}}\epsilon_{\mathrm{V}}/\epsilon_{\mathrm{III}}$. [g] Estimated to be equal to $\epsilon_{\mathrm{IIa}}\epsilon_{\mathrm{V}}/\epsilon_{\mathrm{III}}$. (The values used for ϵ_{IIe} are those in footnotes *d* and *e* above for isoöctane and dioxane, respectively.)

The extinction coefficients of pure axial and pure equatorial 2-chlorocyclohexanone were estimated in the manner used for the corresponding bromo ketone[8] employing the measured extinction coefficients for the 2-chloro-4-*t*-butylcyclohexanones and cyclohexanone. Table VI lists these values. From these data it was calculated that the *axial* conformer (IVa) of 2-chlorocyclohexanone was present to the extent of 63% and 37% in isoöctane and dioxane, respectively.

Equilibrium Studies.—Pure *cis*-(IIe) and *trans*-2-chloro-4-*t*-butylcyclohexanone (IIa) (260 mg.) were dissolved at a known concentration in the appropriate solvent which was approximately 0.1 *M* in anhydrous hydrogen chloride. The homogeneous solutions were allowed to stand at room temperature for the required length of time, and then were worked up by the following general procedure. The reaction mixture was poured into 80 ml. of cold water and the equilibrated ketones were extracted with 80 ml. of pentane. The organic phase was washed once with 20 ml. of 5% sodium bicarbonate solution and finally with 20 ml. of water. After being dried over anhydrous sodium sulfate, the solvent was removed by distillation. The residue was rapidly distilled at 0.5 mm. and the distillate, collected in one fraction, was immediately subjected to infrared analysis.

The analyses for the percentage compositions of the mixtures were carried out by comparison of the infrared spectra of 1*M* solutions in carbon disulfide of pure IIa, pure IIe and the equilibrated samples. The spectra of pure IIe and pure IIa were recorded several times throughout the course of these analyses and were found to be quite reproducible. Consequently, average values for the optical densities of these isomers (1*M* in carbon disulfide) were obtained at the four most suitable wave lengths, and these values were used for all the calculations. The wave lengths chosen were 805, 821, 943 and 962 cm.$^{-1}$.

Two sets of simultaneous equations were obtained whose solutions provided estimates of the percentage compositions of the mixtures. As in the case of the bromo compounds, the ratios of IIa to IIe were used (*i.e.*, the actual calculated values were normalized). The analysis of two synthetic mixtures of IIa and IIe provided a check on the accuracy of the analyses. The results of these studies are summarized in Table III. By analogy with the less stable bromo ketones, it was assumed that no detectable isomerization had occurred during the work-up procedure.

TABLE VII

DIPOLE MOMENT DATA, BENZENE SOLUTION, 25°

N_2	d_{12}	ϵ_{12}
2-Chlorocyclohexanone		
0.00450087	0.874087	2.3538
.00384035	.873881	2.3407
.00308605	.873605	2.3268
.00198796	.873179	2.3055
.00090169	.872773	2.2853
.00000000	.872453	2.2681
α = 19.02	β = 0.369	ϵ_1 = 2.2680
d_1 = 0.87245	$P_{2\infty}$ = 314.3	μ = 3.71 D.
cis-2-Chloro-4-*t*-butylcyclohexanone		
0.00329370	0.873712	2.3517
.00251520	.873417	2.3324
.00185616	.873125	2.3151
.00126991	.872925	2.3006
.00074248	.872711	2.2867
.00000000	.872453	2.2681
α = 25.46	β = 0.386	ϵ_1 = 2.2680
d_1 = 0.872435	$P_{2\infty}$ = 427.9	μ = 4.29 D.
trans-2-Chloro-4-*t*-butylcyclohexanone		
0.00396873	0.873825	2.3219
.00286353	.873410	2.3068
.00189344	.873163	2.2927
.00122344	.872874	2.2838
.00057325	.....[a]	2.2748
.00000000	.872453	2.2678
α = 13.76	β = 0.344	ϵ_1 = 2.2672
d_1 = 0.872461	$P_{2\infty}$ = 256.7	μ = 3.17 D.

[a] The value obtained here (0.873196) was so far out of line the computer discarded it, and did the calculation of d_1 and β on the basis of the 5 remaining points.

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(26) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1946, p. 382.

(27) L. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 369.

Molecular Weight Determinations.—The molecular weights of 2-chlorocyclohexanone, 2-chloro-4-*t*-butylcyclohexanone and *n*-heptane (used as a standard to check the experimental procedure) in purified cyclohexane (see above) were determined as described previously.[6] Compound III (52% IIa) gave an experimental molecular weight that was 10% too large, while with IV the experimental value was too large by a factor of 3.3 (all at about 0.1*M* which was the concentration used for the infrared studies). Clearly considerable association occurred with IV.

Dipole Moments.—The dipole moments were obtained using the apparatus described earlier,[28] and the calculations were carried out with an IBM 650 computer.[29] Experimental error was about 0.02 D. The data are summarized in Table VII.

Theoretical Calculations.—The energy of the electrostatic interaction of the dipoles was calculated for the chloroketone by the same method used earlier for the bromoketone,[6,4] using the appropriate constants from Table VIII. The bond dipole moments used for the equatorial isomers were those justified earlier[6,10] for C═O and C—Br. The C—Cl moment was taken as the same as the C—Br. For the axial isomers induction is certainly less important, so it has been ignored and the bond moments for the isolated bonds have been used. Justification for this treatment comes from the fact that the calculated moments of the axial isomers are in better agreement with the experimental ones when this is done. These energies are inversely proportional to the effective dielectric constant of the medium.

The energy lowering due to an induced dipole was calculated from equation 4. The distance between the oxygen and halogen was measured on a model.[30] This energy is also inversely proportional to the effective dielectric constant.

The energy, *E*, of the van der Waals interaction for a pair of atoms is given[22] by

$$E/\epsilon = -2.25/\alpha^6 + 8.28 \times 10^5 e^{-\alpha/0.0736} \qquad (5)$$

where α is the distance between atomic centers (in units of the sum of their van der Waals radii), and ϵ is a constant which is dependent on the pair of atoms involved. For the interactions of interest ϵ has the following values (in cal./mole) where hydrogen is interacting with the second atom: hydrogen, 42.0; chlorine, 115; bromine, 135.8. For the interactions involving oxygen, it was necessary to first calculate ϵ for the interaction of two oxygen atoms. This calculation was carried out using the method outlined by Hill.[22] The value found was 7.77×10^{-15} erg. From this quantity then it was possible to find the ϵ for interaction of oxygen with other atoms as follows (in units of 10^{-15} erg./molecule): hydrogen, 4.77; chlorine, 13.0; bromine, 15.4. To calculate the difference in van der Waals energy between the axial and equatorial halide, the interactions were considered between oxygen-halogen, and oxygen-C_2 hydrogen. The equatorial halogen was considered to interact with the C_3 hydrogens, while the C_2 hydrogen interacted with the axial hydrogens at C_4 and C_6 and the equatorial hydrogen at C_3. When the halogen was axial, the analogous interactions were considered. The distances between atoms were found by direct measurement on models.[30] In a few cases these values were also checked by vector analysis using the cyclohexylidene model of Corey and Sneen[31] with the appropriate modifications.

Table VIII

Numerical Constants Used for Calculations

Bond lengths, Å.	
C═O	1.22
C—Cl	1.76
C—Br	1.94
C—H	1.09

van der Waals radii, Å.	
O	1.40
Cl	1.80
Br	1.95
H	1.20

Dipole moments, D	Eq. halogen	Axial halogen
C═O	2.83	3.00
C—Br	1.91	2.24
C—Cl	1.91	2.24

Oxygen–halogen distances, Å.	Axial	Eq.
Cl	3.56	2.81
Br	3.68	2.91

	Polarizability $\times 10^{+24}$ cm.^{3}
Cl	2.28
Br	3.34
═O	0.84

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(28) M. T. Rogers, This Journal, **77**, 3681 (1955).

(29) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

(30) Dreiding stereomodels were found to be satisfactory for such measurements (see A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959)).

(31) E. J. Corey and R. A. Sneen, This Journal, **77**, 2505 (1955).

[Contribution from the Research Laboratories of Syntex, S. A., Mexico, D. F., Mex.]

Steroids. CL.[1] 10β-Halo Steroids[2]

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Chlorination of steroidal ring A phenols with N-chlorosuccinimide affords the 10β-chloro-$\Delta^{1,4}$-3-ones in about 25% yield together with a smaller proportion of the 10β-(2 or 4)-dichloro-$\Delta^{1,4}$-diene-3-ones. Analogous 10β-fluoro dienones are formed on treatment of ring A phenols with perchloryl fluoride in dimethylformamide solution. Both the 10β-chloro and 10β-fluoro compounds are readily reducible to the original phenols; however, the 10β-fluoro dienones may also be hydrogenated in rather low yields to the saturated 10β-fluoro-5β-3-ketones. Dehydrochlorination of the 10β-chlorodienones affords the $\Delta^{9,11}$-phenols. 10β-Fluoro-Δ^1-dehydro-19-nortestosterone readily undergoes dienone-phenol rearrangement with acetic anhydride-sulfuric acid to yield the *p*-fluorophenol diacetate (XVIa).

The halogenation of steroidal phenols with "positive halogen" reagents such as the N-halo amides and imides has been little investigated. Woodward[3] treated estradiol with N-bromoacetamide in ethanol and obtained 2,4-dibromoestradiol in high yield. We have now examined the reaction of estradiol with N-chlorosuccinimide in a variety of solvents and obtained after chromatography on deactivated alumina two compounds which both showed the characteristic bands at 6.00, 6.15 and 6.25 mμ of the 1,4-diene-3-one system. The first compound eluted and obtained in smaller quantity showed an ultraviolet maximum at 251 mμ, log ε 4.14, and its analysis agreed well with its formulation as 2 (or 4), 10-dichloro-Δ^1-dehydro-19-nortestosterone. The second compound obtained showed an ultraviolet maximum at 243 mμ, log ε 4.13, and its analysis indicated it to be 10-chloro-Δ^1-dehydro-19-nortestosterone (IIa). Recently a publication has appeared by

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(1) Part CXLIX, J. A. Zderic and A. Bowers, *Ciencia*, **20**, 23 (1960).

(2) A preliminary account of part of this work has already appeared; J. S. Mills, This Journal, **81**, 5515 (1959).

(3) R. B. Woodward, *ibid.*, **62**, 1625 (1940).