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PART I

CONFORMATIONAL ANALYSIS OF 1,4-DISUBSTITUTED CYCLOHEXANES.

PART II

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF TWO BICYCLIC ANALOGUES OF CYCLOHEXANE-1,4-DIONE .

BY

EDMUND P. WOO

A Dissertation

Submitted to the Faculty of Graduate Studies through the
Department of Chemistry in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy at the
University of Windsor

Windsor, Ontario

1968

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ABSTRACT

PART I

The conformational equilibria of *cis*-1,4-bromochlorocyclohexane, *trans*-1,4-dibromo-, *trans*-1,4-dichloro-, and *trans*-1,4-bromochlorocyclohexane were measured by integration of the separate axial and equatorial proton signals at low temperature.

The two possible chair forms of the *cis* compound were shown to exist in equal amounts, contrary to the result of Atkinson and Lunde.

The free energy difference between the diaxial form and the diequatorial form of each of the *trans* compounds was shown to be roughly one-fifth of what one would expect if additivity of conformational energies was assumed. This was attributed to the greater electrostatic attraction in the diaxial form. Related cases from the literature were also discussed.

PART II

The two bicyclic analogues of cyclohexane-1,4-dione studied were bicyclo[3.2.2]nonan-6,8-dione (**11**) and bicyclo[3.3.1]nonan-3,9-dione (**28**). The first diketone was prepared by the thermal decarboxylation of 1,5-dicarboxybicyclo[3.2.2]nonan-6,8-dione. A discussion of this decarboxylation in relation to Bredt's Rule was presented. The principal mass spectral feature of two derivatives of **11** was presented.

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The diketone **11** has two possible conformations each of which has a cyclohexane-1,4-dione ring locked in a flexible form by a trimethylene bridge. The conformational composition of **11** was determined by dipole moment measurement.

The conformations of the diketone **28** and its 9-ethylene ketal were determined by infrared and nmr spectroscopy, and dipole moment measurements. The ethylene ketal was tentatively assigned a non-flattened twin-chair conformation, while **28** was shown to be an equilibrium mixture of 90% of twin-chair and 10% of chair-boat, with the cyclohexane-1,4-dione moiety in the boat form.

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ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to Dr. G.W. Wood for his patient guidance and inspiring direction during the course of this work.

To the members of my committee and the staff of the Department of Chemistry who have helped me in so many ways I offer my heartfelt thanks.

Also, I would like to thank my colleague Mr. M. Miskow for proof-reading this dissertation, and my wife for her forbearance.

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TABLE OF CONTENTS

PART I

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PART II

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LIST OF TABLES

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

LIST OF FIGURES

Figure Page

PART I

PART II

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PART I

CONFORMATIONAL ANALYSIS OF 1,4-DISUBSTITUTED CYCLOHEXANES

CHAPTER I

INTRODUCTION

The origin of present-day stereochemistry can be traced to the proposal of tetrahedral carbon by van't Hoff and LeBel in 1874. Consequently the cyclohexane molecule could no longer be envisioned as a flat ring. Sachse[1] first recognized in 1890 the existence of the two puckered forms of cyclohexane free of angle strain, the chair and the flexible forms. The existence of the chair form was later confirmed by electron diffraction.[2] Two types of protons can be distinguished in the chair form of cyclohexane: six are perpendicular to the plane of the ring (axial), and the remaining six are roughly parallel to the plane of the ring (equatorial).

The term "conformation" is used to denote any one of the infinite number of arrangements of the atoms in space that result from rotation about single bonds. It was believed at one time that rotation about C-C bond was entirely free. That this is not a justified assumption was shown by Pitzer[3] and co-workers whose calculation of the enthalpy and entropy

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(1) E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill Book Co., Inc., New York, N.Y., 1962, p. 24.

(2) O. Hassel, Quart. Rev., 7, 221 (1953).

(3) J.D. Kemp and K.S. Pitzer, J. Chem. Phys., 4, 749 (1936).

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of ethane by means of statistical mechanics gave poor agreement with the experimental values unless it was assumed that there is a barrier of about 3 kcal/mole to free rotation. Just as ethane can exist in three equal but distinct staggered conformations which are interconvertible by internal rotation, cyclohexane can exist in two distinct chair conformations. These two forms can interconvert, but a relatively high energy ($\Delta H^{\ddagger}$ = 10.8 kcal/mole[4]) is required to overcome the non-bonded repulsion and also to change the bond angles during the intermediate states. During interconversion (Fig. I-1) cyclohexane passes through an energy minimum (5.5 kcal/

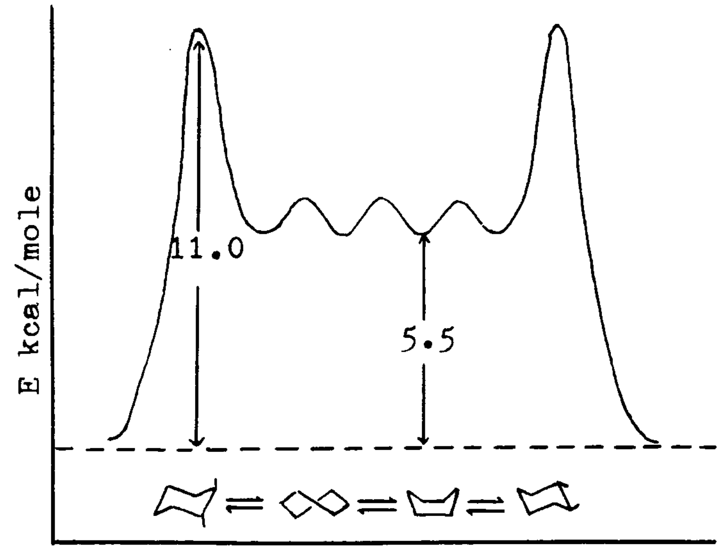

Fig. I-1

Chair-chair interconversion of cyclohexane.

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[4] F.A.L. Anet and A.J.R. Bourn, <u>J. Am. Chem. Soc.</u>, <u>89</u>, 760 (1967).

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mole[5]) known as the flexible or twist form and a smaller energy maximum (6.4 kcal/mole[6]) corresponding to the boat form. The energy levels were obtained by nmr[4], heat of combustion[5], computer calculation[6], or equilibration studies[7].

As a result of the 5.5 kcal/mole difference in enthalpy between the chair and the flexible forms of cyclohexane, the former predominates almost exclusively provided the entropy difference between the chair and the twist is reasonably small (experimental evidence thus far indicates $\Delta S < 4$e.u.). The interconversion process may thus be considered as a rapid equilibrium of the two chairs. At room temperature, the nmr spectrum consists of a single line which implies rapid equilibration of the two chairs, since, in principle, axial and equatorial protons in cyclohexane resonate at different fields[8] and one might expect two lines to appear in the spectrum. Upon cooling, the rate of interconversion is reduced so that at low temperature ($< -62^\circ$), one does see two separate families of lines.[9] The rates[4] of interconversion at

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(5) W.S. Johnson, V.J. Bauer, J.L. Margrave, M.A. Frisch, L.H. Dreger, and L.A. Freiberg, J. Am. Chem. Soc., 83, 606 (1961).

(6) (a) N.L. Allinger, M.A. Miller, F.A. Van Catledge, and J.A. Hirsch, ibid., 89, 4345 (1967); (b) J.B. Hendrickson, ibid., 7036 (1967).

(7) N.L. Allinger and L.A. Freiberg, ibid., 82, 2393 (1960).

(8) R.L. Lemieux, R.K. Kulling, H.J. Bernstein, and W.G. Schneider, ibid., 80, 6098 (1958).

(9) F.R. Jensen, D.S. Noyce, C.H. Sederholm, and A.J. Berlin, ibid., 84, 386 (1962).

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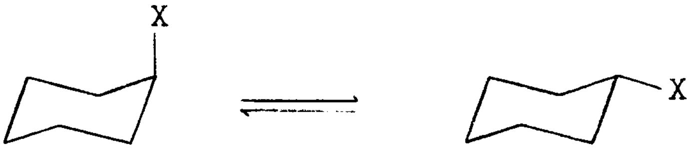
various temperatures have been measured, for example, at -81.8°, k = 4.0 sec^{-1}, and at -24.0°, k = 2490 sec^{-1}.

Monosubstituted Cyclohexanes

As pointed out before, there are two types of hydrogens in the cyclohexane ring, namely, the equatorial and axial. On interconversion, these hydrogens exchange places (Fig. I-1). A monosubstituted cyclohexane may exist in either the conformation with the substituent at the axial position (**1a**) or the equatorial position (**1b**). The barrier to interconversion of these two forms is roughly the same as that in cyclohexane. The two conformers are thus in rapid equilibrium and the only report[10] in the literature on separation of the conformers is the isolation of pure equatorial chlorocyclohexane by crystallization at -151°.



1a **1b**

The conformational equilibria for a large number of monosubstituted cyclohexanes have been studied and in practically all cases[11] the equatorial isomers are preferred. The free

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(10) F.R. Jensen and C.H. Bushweller, J. Am. Chem. Soc., **88**, 4279 (1966).

(11) With the possible exception of X = HgBr; the conformational equilibrium constant in this case was deduced to be unity. F.R. Jensen and L.H. Gale, ibid., **82**, 145 (1960).

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energy difference between the two conformers can be calculated from the equilibrium constant (equation I-1).

$$-\Delta G_x^o = RT\ln K \qquad (I-1)$$

The term "conformational energy" ($-\Delta G_x^o$) has been introduced to denote the free energy of a conformation above that of the one of minimum energy, for example, the $-\Delta G_x^o$ for the process $\underset{\sim}{1a} \rightleftharpoons \underset{\sim}{1b}$ is the conformational energy of $\underset{\sim}{1b}$. Conformational energies of a large variety of substituents have been compiled in a standard text[12]. There have been at least twenty-two independent determinations by a number of methods of the conformational energies of bromine and chlorine. By integration of the nmr peak areas of the separate axial and equatorial methine protons of cyclohexyl halides at low temperature, $-\Delta G^o$ values (kcal/mole) of 0.41 and 0.51 were found for chlorine, and 0.51 and 0.48 for bromine[13]. The values of 0.4 for chlorine and 0.5 for bromine have been widely accepted[12]. At first sight the fact that $-\Delta G_{Br}^o = 0.5$ kcal/mole and $-\Delta G_{Me}^o = 1.7$ kcal/mole may be surprising since methyl and bromine have approximately the same van der Waals radii. Jensen and Berlin[13] had pointed out that the halogen atoms are highly polarizable compared to the methyl group; hence the attractive

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(12) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, Conformational Analysis, Interscience Publishers, New York, N.Y., 1965, Chapter 7.

(13) (a) A.J. Berlin and F.R. Jensen, Chem. Ind. (London), 998 (1960); (b) L.W. Reeves and K.O. Strømme, Can. J. Chem., 38, 1241 (1960).

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London forces become more important for such atoms. London forces are particularly important just within (and just outside) the van der Waals radial distance. This would lead to a deeper and broader well in the van der Waals potential function. Furthermore the C-methyl bond (1.54Å) is much shorter than the C-Br bond (1.94Å), therefore a small bending of the axial C-Br bond away from the central axis of the ring would yield greater relief of unfavourable interaction with the *syn*-3,5-axial hydrogens.

Disubstituted Cyclohexanes

Disubstituted cyclohexanes may exist in two different chair conformations. Four types of disubstituted isomers are possible, namely, the 1,1-, 1,2-, 1,3-, and 1,4-disubstituted.

In a 1,1-disubstituted cyclohexane, chair-chair interconversion interchanges the axial and equatorial substituents, the stable conformer being the one with the "large" substituent in the equatorial position.

A 1,2-disubstituted cyclohexane exhibits *cis*-*trans*-isomerism. The *cis* isomer will have an axial and an equatorial substituent and interconversion will produce its mirror image. The *trans* isomer, however, exists as an equilibrium mixture of diaxial and diequatorial forms. Any prediction on the most stable form is complicated by ring deformation and dipole-dipole interaction when one or both substituents have an appreciable dipole moment. Thus, the 1,2-diaxial form of *trans*-1,2-dichlorocyclohexane is favoured over the diequator-

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ial one[14], and the *trans*-1-iodo-2-(perfluoroalkyl) cyclohexanes (except where alkyl is methyl) prefer the flexible form[15].

In 1,3-disubstituted cyclohexanes, *cis* and *trans* isomers are possible. In the *cis* epimer the diequatorial form is usually more stable than the sum of the $-\Delta G^{o}$ values of the substituents would indicate due to the very strong *syn*-1,3-interaction in the diaxial form.

A 1,4-disubstituted cyclohexane also exhibits *cis*-*trans*-isomerism. The *cis* epimer has substituents in the axial and equatorial position while the *trans* epimer can be diaxially or diequatorially substituted. The conformational equilibria of *cis* isomers where the two substituents are different, are, in principle, similar to the 1,1-disubstituted compounds; the conformation with the large substituent in the equatorial position is the more stable. As for *trans* isomers, the diequatorial forms are preferred in all known cases with the possible exception of *trans*-1,4-dichlorocyclohexane (*vide infra*).

Methods for Determination of Conformational Energies.[16-19]

Since the equilibrium **1a**$\rightleftharpoons$**1b** is established in a very short time at room temperature, direct measurement of the

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[14] L.W. Reeves and K.O. Strømme, *Trans. Faraday Soc.*, *57*, 391 (1961).

[15] N.O. Brace, *J. Am. Chem. Soc.*, *86*, 665 (1964).

[16] Ref. 12, Chapters 2 and 3.

[17] E.L. Eliel, *Angew. Chem. Intern. Ed. Engl.*, *4*, 761 (1965).

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position of equilibrium is possible only by physical methods. However various chemical methods have been devised to determine the equilibrium position indirectly.

The thermochemical method usually involves accurate measurements of heat of combustion. In the two epimers of 1,4-dimethylcyclohexane the cis has only one methyl group in the equatorial position while the trans has both in that position. Therefore the difference in the heats of combustion equals the enthalpy difference of the epimers, which could be related to $-\Delta G^{o}_{Me}$. In order to achieve 10% accuracy in $-\Delta G^{o}$ values an accuracy of roughly 1 part in 10,000 is required in the heat of combustion data. The difficulty associated with such accurate measurement has prevented this method from wider application.

An alternate and experimentally easier method is to equilibrate a pair of cis-trans epimers by chemical means, and measure the composition of the mixture by gas chromatography. With properly chosen compounds this method yields very reliable data.

The kinetic method is based on the idea that the reactivity of a functional group is governed by its conformational disposition in the ground state. This assumes that the ground state energy difference between two conformers is re-

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(18) N.R. Franklin and H. Feltkamp, Angew. Chem. Intern. Ed. Engl., 4, 774 (1965).

(19) M. Hanack, Conformational Theory, Academic Press, New York, N.Y., 1965, Chapter 3.

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tained in the transition state. Since this assumption has been seriously questioned and proved invalid in certain cases, further discussion is not offered.[20-24]

Electron diffraction and X-ray diffraction, in principle, are methods for total structural determinations. Electron diffraction is best suited to the study of gases or substances that are thermally stable and sufficiently volatile to give a vapour pressure of a few millimeters of mercury at elevated temperatures. One obtains a radial distribution curve which is essentially the probability of finding a pair of atoms at a given distance. Then a theoretical curve is calculated based on a model which is adjusted until the theoretical and experimental curves are in good agreement. This method is useful mainly for simple molecules because with a complex molecule there are too many pairs of atoms of roughly the same interatomic distance making accurate analysis impossible. Results obtained from X-ray studies are often biased by deformations in the crystalline state, and therefore are not representative of the true conformations of the

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(20) Ref. 19, p. 117.

(21) J.L. Mateos, C. Perez, and H. Kwart, Chem. Commun., 125, (1967).

(22) H. Kwart and T. Takeshita, J. Am. Chem. Soc., 86, 1161 (1964).

(23) F. Shak-Malak and J.H.P. Utley, Chem. Commun., 68, (1967).

(24) (a) W.H. Saunders, Jr., and K.T. Finley, J. Am. Chem. Soc., 87, 1384 (1965); (b) V.J. Shiner, Jr., and J.G. Jewett, ibid., 1382, 1383 (1965).

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molecules.

Dipole moment measurements are well suited for conformational analysis if the two conformers in question have very different dipole moments. For instance, calculation from models indicate that the diequatorial form of trans-1,2-dichlorocyclohexane would have a dipole moment of 3.13 D and the diaxial form a moment of ca. 0 D. The experimental value as determined in benzene was found to be 2.63 D which corresponds to 71% of the diequatorial form.[25]

Infrared and Raman spectroscopy have been used rather extensively for determination of equilibrium position. For quantitative work, the molar extinction coefficients of the characteristic bands assigned to each conformer are needed. These values are unfortunately not readily available and some authors have assumed that they are equal[26] or have used some arbitrary ratio.[27] Furthermore, assignments of bands are not always unequivocal.[28] It has been suggested[29] that the molar extinction coefficients may be obtained from conformationally homogeneous systems (vide infra) such as 4-t-butylcyclohexyl

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(25) W. Kwestroo, F.A. Meijer, and E. Havinga, Rec. Trav. Chim. Pays-Bas., 73, 717 (1954).

(26) See, for example, C.G. LeFévre, R.J.W. LeFévre, R. Roper, and R.K. Pierens, Proc. Chem. Soc., 117 (1960).

(27) K. Kozima and T. Yoshino, J. Am. Chem. Soc., 75, 166 (1953).

(28) N.L. Allinger and C.D. Liang, Tetrahedron, 21, 603, (1965).

(29) R.A. Pickering and C.C. Price, J. Am. Chem. Soc., 80, 4931 (1958).

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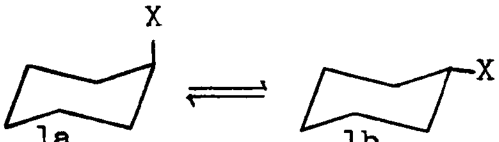
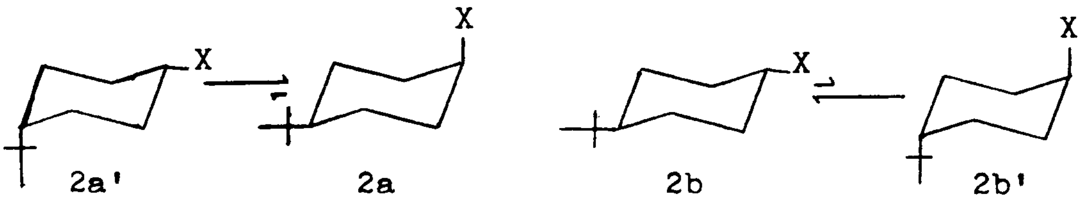
compounds. These values are then applied to the monosubstituted cyclohexanes. There is no evidence to show that the presence of a 4-t-butyl group does not affect the extinction coefficient; in fact, Hall and Wilson[30] have cautioned against such practice.

Nuclear magnetic resonance spectroscopy is probably the most useful tool for conformational analysis. Franklin and Feltkamp[18] have reviewed its applications. The chemical-shift method and the peak-area-integration method will be discussed briefly since they are most often used. The chemical-shift method requires the knowledge of the chemical shifts of the equatorial (CHX) proton in **1a** and that of the axial proton in **1b**. These values may be obtained from the model compounds *cis* and *trans*-1-X-4-t-butylcyclohexanes (**2a** and **2b**). The



1a **1b**



2a' **2a** **2b** **2b'**

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[30] J.R. Hall and N.K. Wilson, *Spectrochim. Acta.*, **22**, 1739 (1966).

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conformational energy of the *t*-butyl group is so large (> 5.5 kcal/mole) that the presence of the axial-4-*t*-butyl isomers **2a'** and **2b'** (< 0.001%) may be ignored. Thus **2a** may be considered a "fixed" axially substituted cyclohexane and the chemical shift of its methine (CHX) proton may be assumed to be that of **1a**. Similarly the chemical shift of the methine proton of 2b may be taken as that of **1b**. At room temperature the equilibrium **1a** ⇌ **1b** is very fast compared to the rate of nuclear transition being examined, therefore one does not observe two methine proton peaks due to two conformers but only one peak, the location of which is assumed to be related to the proportions of the conformers in equilibrium. Substituting into equation I-2, the chemical shifts of the methine

$$K = \frac{\nu_a - \nu}{\nu - \nu_e} \qquad \text{(I-2)}$$

protons of **1** (ν), **2b**, (ν_a), and **2a** (ν_e), the equilibrium constant, K, can be obtained. Alternatively, the ν_a and ν_e values can be determined by observing the low temperature spectrum of **1**. As pointed out previously, monosubstituted cyclohexanes have roughly the same energy barrier as cyclohexane. Therefore on cooling two distinct peaks should be observed from which the chemical shifts ν_a and ν_e could be measured. Values obtained this way should be more reliable since it is no longer necessary to assume that ν_a and ν_e are not influenced by the 4-*t*-butyl group.(31)

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(31) S. Wolfe and J.R. Campbell, (Chem. Commun., 872 (1967)) have shown that in certain cases this assumption is invalid due to ring deformation caused by the 4-*t*-butyl group.

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Another nmr method involves integration of the axial and equatorial peak areas. Since at low temperatures, the spectrum of **1** usually shows two separate methine signals, the relative peak areas should then be a direct measurement of the proportions of the conformers. This method is only applicable, of course, to cases where the axial and equatorial signals do not overlap. It is not always possible to find a solvent in which the compound in question is sufficiently soluble at low temperatures (-50 to -100°). Nonetheless, if one does not extend the data obtained at low temperatures to situations at room temperature without taking into consideration the entropy changes, then one would not be making any basic assumption. In this work, the conformational energies used for comparison were obtained at similar temperatures, and hence the results should be internally consistent.

Additivity of Conformational Energies

It has been a rather popular assumption that conformational energies are additive provided that the presence of the second substituent does not introduce significant entropy change and/or serious ring deformation. The following two cases serve as examples. By dilution studies the chemical shifts of the monomeric hydroxyl protons of 1-ethynylcyclohexanol (**3**), 1-ethynyl-*trans*-4-*t*-butyl-cyclohexanol (**4**), and 1-ethynyl-*cis*-4-*t*-butylcyclohexanol (**5**) were determined.[32] The equilibrium constant can be obtained by substituting the

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(32) R.J. Ouellette, *J. Am. Chem. Soc.*, *86*, 3089, (1964).

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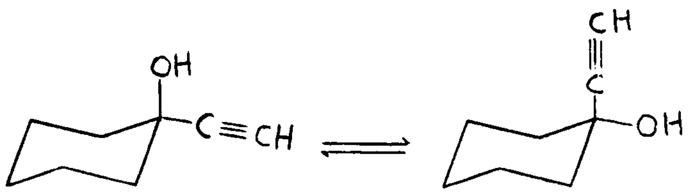
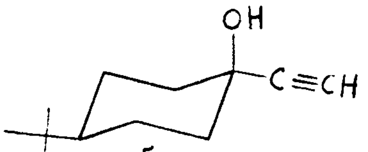
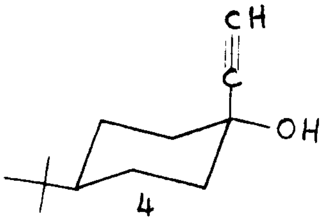


3a (87.4 c.p.s.) 3b



5

(70.1 c.p.s.)



4

(94.0 c.p.s.)

chemical shifts of the hydroxyl proton of 4 (ν_a), 5 (ν_e), and 3 (ν), into equation I-2. From equation I-1, the conformational preference of the ethynyl group in 3 is smaller than that of the hydroxy by 0.6 kcal/mole. The assumption is now made that the conformational energy of the hydroxy group in cyclohexanol (0.78 kcal/mole) is the same as in 3; therefore, by subtraction, the conformational energy of the ethynyl group is 0.18 kcal/mole.

The above assumption has not been proved, but for the only investigation reported concerning additivity in a 1,1-disubstituted compound it appears to be valid.[33]

Della[34] determined the $-\Delta G^{o}$ for the process $6a \rightleftharpoons 6b$ by nmr techniques, and equated it to the difference of $-\Delta G^{o}_{CF_3}$ and $-\Delta G^{o}_{Me}$. The $-\Delta G^{o}_{CF_3}$ was thus calculated to be 2.5 kcal/mole. Again in the absence of bulky substituents, the addivity rule

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

(34) E.W. Della, J. Am. Chem. Soc., 89, 5221 (1967).

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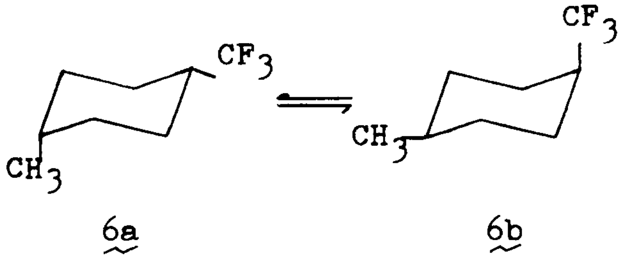
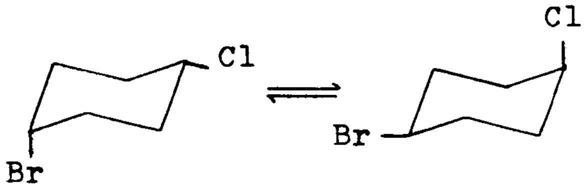
seems to hold as Eliel[35] has shown that the conformational



equilibrium of cis-4-methylcyclohexyl bromide could be predicted by the difference of $-\Delta G^o_{Me}$ and $-\Delta G^o_{Br}$. (See also Chapter II).

Statement of Problem

In view of the above discussion it was surprising to note that cis-1,4-bromochlorocyclohexane (7) had been reported[36] to prefer the axial-bromine equatorial-chlorine conformation (7a) to the extent of at least 98%, corresponding to a free energy difference of at least 2.3 kcal/mole. Since the conformational energies of bromine and chlorine are 0.5 and 0.4 kcal/mole respectively[12] one would expect 7a and 7b to exist in roughly



7a 7b

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(35) E.L. Eliel, Chem. Ind. (London)., 568 (1959).

(36) V.A. Atkinson and K. Lunde, Acta Chem. Scand., 14, 2139 (1960).

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equal amounts. The almost exclusive predominance of **7a** was deduced from electron diffraction and infrared studies. A theoretical radial distribution curve was calculated to fit the experimental one by varying the proportions of **7a** and **7b**. Statistical analysis showed that compound **7** must be all or nearly all in the conformation **7a** in order to obtain a good fit. In addition its ir spectrum remained unchanged even down to -170°; hence it was concluded that only one conformation was present. van Dort and Sekur[37] later showed, however, that the nmr spectrum of **7** at 35° was essentially different from that at -55°, a result which is difficult to reconcile with the previous analysis.

It is possible that electron diffraction is not really suited for such a purpose as evidenced by the study of _cis_-1,4-dibromocyclohexane.[38] This compound should consist of two energetically identical conformations in equal amounts[39] but even for a model with increased C_2-C_3-C_4 and C_4-C_5-C_6 angles, there was still considerable disagreement between the calculated and experimental curve.

The _trans_-1,4-dihalocyclohexanes have received even less attention. There have been two attempts to study their conformational equilibria as far as the author could ascertain.

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(37) H.M. van Dort and Th. J. Sekur, _Tetrahedron Lett._, 1301 (1963).

(38) S. Furberg and O. Hassel, _Acta Chem. Scand._, _6_, 1300 (1952).

(39) A certain amount of flexible form has been suggested to be present in _cis_-1,4-dibromo-and dichlorocyclohexane. M. Larnaudie, _Compt. Rend._, _236_, 909 (1953).

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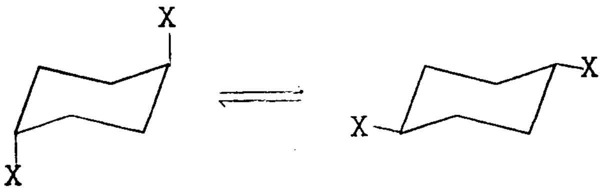
Thus by electron diffraction, Atkinson and Hassel[40] found that in trans-1,4-dichlorocyclohexane (8) and trans-1,4-dibromocyclohexane (9) the diaxial and diequatorial forms were present in nearly equal amounts. Kozima and Yoshino[41] concluded from Raman spectroscopy studies that 8 favoured the diaxial forms in each of the six solvents investigated. Although the ratio of the two conformers varied from solvent to solvent, no correlation of solvent effect was apparently possible. Since it appears that for 1,1-disubstituted and 1,4-disubstituted systems the additivity rule seems to hold the literature data discussed above were thought to deserve further investigation.



8, X = Cl

9, X = Br

Accordingly we set out to prepare cis-1,4-bromochlorocyclohexane (7), trans-1,4-dichloro- (8), trans-1,4-dibromo- (9), and trans-1,4-bromochlorocyclohexane (10), and to determine their conformational equilibria in solution (equations I-3 to I-6).

If a significant amount of conformation 7b is present in

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(40) V.A. Atkinson and O. Hassel, Acta Chem. Scand., 13, 1737 (1959).

(41) K. Kozima and T. Yoshino, J. Am. Chem. Soc., 75, 166 (1953). Solvents: heptane, cyclohexane, benzene, carbon tetrachloride, ether, and ethanol.

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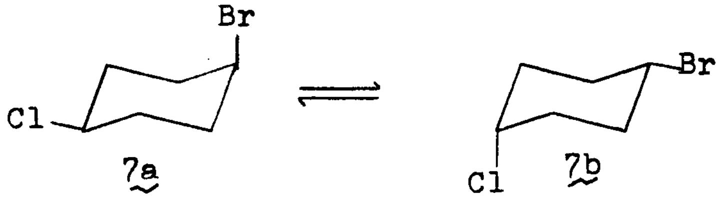
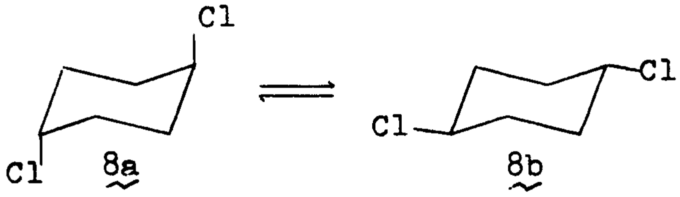
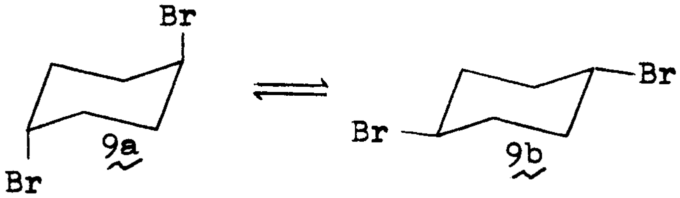
the cis compound (equation I-3) then one should observe in the nmr spectrum of 7 two equatorial proton signals (CH-Cl and CH-Br) at sufficiently low temperature. Assignment of these signals can be based on the chemical shifts of the methine protons



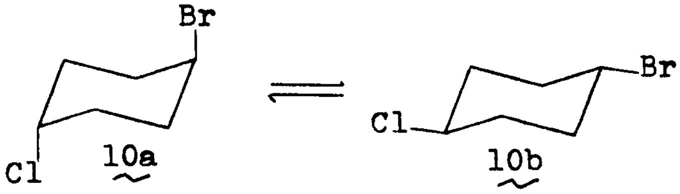
(I-3)



(I-4)



(I-5)



(I-6)

of cis-1,4-dibromo- and dichlorocyclohexane observed at low temperature. Similarly each of the trans isomers should give two separate methine signals representing the diaxial and

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diequatorial conformers. The equilibrium mixture may be determined by integrating the areas of the peaks.

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CHAPTER II

RESULTS AND DISCUSSION

cis-1,4-Bromochlorocyclohexane

The nmr spectrum of cis-1,4-bromochlorocyclohexane (7) was recorded at several temperatures between room temperature and -79°. The methine proton signal, a broad single peak at room temperature, slowly broadens as the temperature is lowered (Fig. II-1) until the coalescence temperature (ca.-40°) is reached. Below this temperature two peaks can be discerned which are increasingly separated upon further cooling. When the temperature approaches -60°, the low field signal now consists of two overlapping signals which, on further cooling, are centered at τ 5.25 and τ 5.40. These are assigned to the bromo- and chloro-substituent respectively. It is well known that an equatorial proton in cyclohexyl halides resonates at lower field than an axial one.[1] Furthermore the chemical shifts of the equatorial protons in cis-1,4-dichlorocyclohexane (11) and cis-1,4-dibromocyclohexane (12) are τ 5.45 and τ 5.21 respectively (Table II-1), which agree well with the assignments made in 7.

The nmr spectra of compounds 11 and 12 show almost identical changes to that of 7, except, of course, only one equatorial methine signal was observed in each case. The coalescence temperature of 11 and 12 is also roughly -40° which corresponds

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(1) E. L. Eliel, Chem. Ind. (London), 568 (1959).

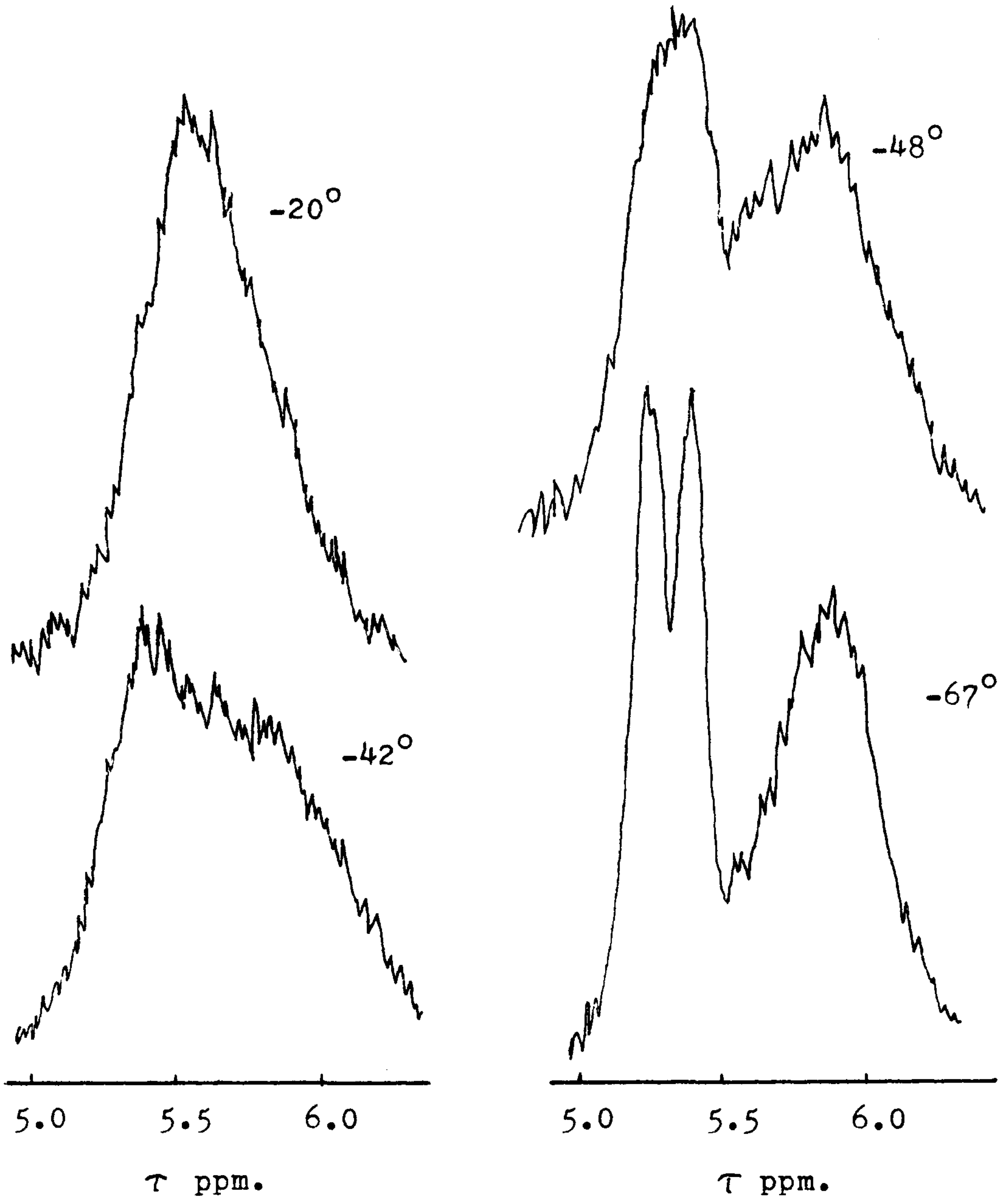

Fig. II-1

Nmr spectra of cis-1,4-bromochlorocyclohexane.

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TABLE II-1

Chemical Shifts (τ) of the Methine Protons of *cis*-1,4-Dihalocyclohexanes

Compound	Chemical Shifts at Room Temperature (τ)	Chemical Shifts at Limiting Separation (τ)
Dichloro	5.80	5.45, 5.98
Dibromo	5.55	5.21, 5.78
Bromochloro	5.70	5.25, 5.40, 5.86

to a first order rate constant of *ca*. 70 $\sec^{-1}$ at this temperature (equation II-1)[2]. The $\Delta G^{\ddagger}$ of interconversion[3] is calculated to be *ca*. 12 kcal/mole (equation II-2), which is

$$k_{rate} = \frac{2\pi(\nu_e - \nu_a)}{\sqrt{2}} \qquad \text{(II-1)}$$

$$k_{rate} = \left(\frac{kT}{h}\right)\exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right) \qquad \text{(II-2)}$$

approximately the same as that of cyclohexane. Thus it is reasonable to assume that we are dealing with a chair-chair interconversion process since the barrier for interconversion

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(2) F.R. Jensen, D.S. Noyce, C.H. Sederholm, and A.J. Berlin, *J. Am. Chem. Soc.*, *84*, 386 (1962).

(3) A.A. Frost and R.G. Pearson, *Kinetics and Mechanism*, John Wiley and Sons, Inc., New York, N.Y., 1961, p. 99.

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of flexible forms is expected to be much lower. Although Larnaudie[4] has suggested the presence of a certain amount of flexible forms, there is no evidence in our nmr data to support their existence. In fact, our results indicate an equilibrium of two chair forms within the temperature range studied. In the spectrum of **7**, the signals at τ 5.25 and τ 5.40 are of approximately equal width and height (Fig. II-1), as would be expected from equal amounts of the two conformations.

Our infrared studies of **7** support this conclusion. The spectrum at 23° is essentially the same as that at -70° in carbon disulphide and acetone. This is consistent with an unchanging proportion of the two conformers.

A possible explanation of the result of Atkinson and Lunde is as follows: the difference in bond length of C-Br and C-Cl bonds is less than 0.15Å, therefore the interatomic distances between halogen and carbon atoms cannot be expected to differ by more than this amount in the two conformations. From examination of a Dreiding model, the various C-halogen distances in **7a** can be seen to be very close to those in **7b**.

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(4) M. Larnaudie, Compt. Rend., 236, 909 (1953).

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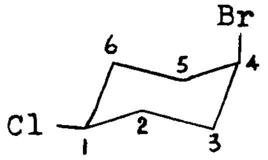
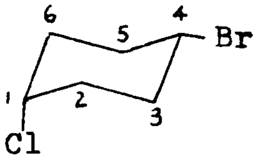


7a



7b

$Cl-C_3$	4.20Å	$Br-C_2$	4.30Å
$Cl-C_4$	4.70Å	$Br-C_1$	4.80Å
$Br-C_2$	3.20Å	$Cl-C_3$	3.15Å
$Br-C_1$	3.85Å	$Cl-C_4$	3.80Å

Thus it would be difficult to differentiate a mixture of equal proportions of 7a and 7b from 7a alone.

trans-1,4-Dihalocyclohexanes

The conformational equilibria of *trans*-1,4-dibromo-(9), *trans*-1,4-dichloro-(8) and *trans*-1,4-bromochlorocyclohexane (10) were determined by integration of their low-temperature nmr spectra.

At room temperature the peak widths at half-height of the methine protons are 15-18 c.p.s., in agreement with the reported values.[5] Changes of the nmr spectra with cooling

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[5] H.M. van Dort and Th. J. Sekur, *Tetrahedron Lett.*, 1301 (1963).

follow the same pattern as the *cis* epimers. At sufficiently low temperature two separate signals were observed. The broader peak at high field corresponds to the axial hydrogens, and that at low field to the equatorial hydrogens. Compound **10** shows two partially resolved equatorial protons at τ 6.10 and 6.25 which are assigned to the proton *alpha* to bromine and chlorine respectively. The use of toluene as solvent offers the advantage of preferentially shifting the axial proton signal upfield. It can be seen from Table II-2 that the equatorial proton of **8** is shifted upfield by 0.7 ppm and the axial proton is shifted by 0.95 ppm (relative to CD_2Cl_2-$CDCl_3$). Separation of the axial and equatorial signals thus occurs at higher temperature in this solvent. *trans*-1,4-Dichlorocyclohexane is sufficiently soluble in CD_2Cl_2-$CDCl_3$ (60:40 v/v) at low temperatures so that it can be used to determine the influence of aromatic solvent on the conformational equilibrium.

TABLE II-2

Chemical Shifts of the Methine Protons of *trans*-1,4-Dihalocyclohexanes

	Dibromo	Dichloro	Dichloro	Bromochloro
Solvent	Toluene-d_8	Toluene-d_8	CD_2Cl_2-$CDCl_3$	Toluene-d_8
(ppm) (^{o}K)	6.35 (293)	6.55 (293)	5.92 (293)	6.50 (293)
	6.10, 6.95 (230)	6.18, 7.10 (226)	5.48, 6.15 (223)	6.10, 6.25, 7.13 (205)

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The data in Table II-3 show no appreciable solvent effect.

TABLE II-3

Integration Data on trans-1,4-Dihalocyclohexanes

	Dibromo	Dichloro	Dichloro	Bromochloro
Solvent	Toluene-$\underline{d}_8$	Toluene-$\underline{d}_8$	CD_2Cl_2-$CDCl_3$	Toluene-$\underline{d}_8$
Temperature (^oK)	230	218	206	205
$K = N_{ee}/N_{aa}$	1.59	1.45	1.46	1.52
No. Integrations	8	14	10	11
$-\Delta G^o_{aa\rightarrow ee}$ (cal/mole)	213	162	156	171
95% confidence limit (cal/mole)	±35	±16	±11	±15
$-\Delta G^o_{aa\rightarrow ee}$ (cal/mole)*	1000	800		900

* Expected values assuming additivity.

Since the high field signals represent the diequatorially substituted conformers and the low field ones the diaxially substituted conformers (Fig. II-2), the ratio of the peak areas is a direct measure of the equilibrium constant of the process **8a** → **8b**. Eight to fourteen integrations were carried out for each compound, from which the equilibrium constants and the free energy differences ($-\Delta G^o_{aa\rightarrow ee}$) were derived. The values of K and $-\Delta G^o_{aa\rightarrow ee}$ are "best" values calculated by the method of least squares (Chapter III).

If addivity of $-\Delta G^o$ values is assumed, then one would

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expect $-\Delta G^{o}_{aa\rightarrow ee}$ to be 1.0 kcal/mole for 9, 0.8 kcal mole for

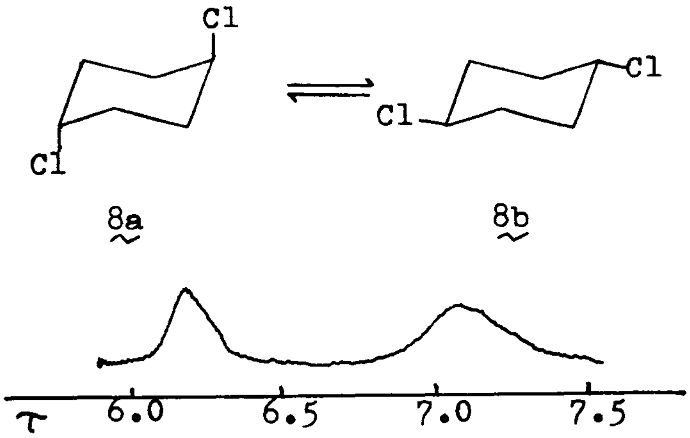

Fig. II-2
Nmr spectrum of trans-1,4-dichlorocyclohexane at -53°.

8 and 0.9 kcal/mole for 10, taking $-\Delta G^{o}_{Cl} = 0.4$ kcal/mole and $-\Delta G^{o}_{Br} = 0.5$ kcal/mole.[6] It is clear from Table II-3 that the expected values are roughly five times larger than the experimental ones. In spite of this discrepancy the experimental values are internally consistent for the compounds studied, and in no case is the diaxial conformation preferred.

It is not possible to explain the results in terms of ring deformation as Atkinson[7] and Hassel[8] had shown that the axial C-Cl bonds in cyclohexyl chloride and trans-1,4-dichlorocyclohexane are tilted away from the central axis of the ring by

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(6) El. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, Conformational Analysis, Interscience Publishers, New York, N.Y., 1965, p.44.

(7) V.A. Atkinson, Acta Chem. Scand., 15, 599 (1961).

(8) V.A. Atkinson and O. Hassel, ibid., 13, 1737 (1959).

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6.3° (Fig. II-3). Hence whatever effect is produced by ring deformation should be present in both cases. Perhaps it is appropriate to note here that steric compression between the axial-halogen and the _syn_-3,5-diaxial-hydrogens do not cause the instability of the axial conformer. These interactions are actually attractive. It is the difference in the total attractive interactions that stabilizes the equatorial conformer.[9] Comparison of the diaxial forms of the dihalides with the axial-halocyclohexanes, and the diequatorial forms with the corresponding equatorial-halocyclohexanes, will show that it is difficult to rationalize the results in terms of van der Waals interaction.

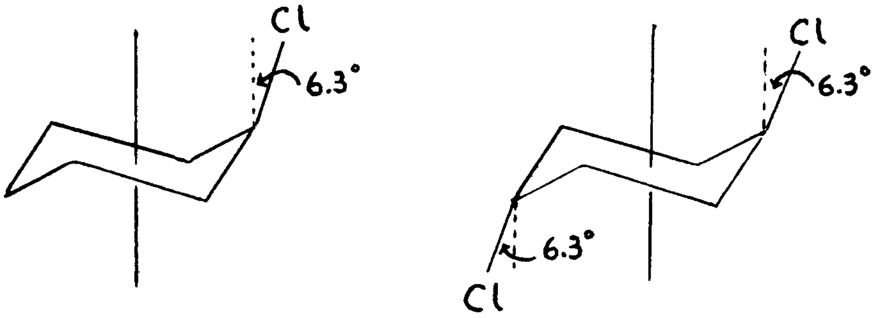

Fig. II-3. Ring deformation as shown by electron diffraction.

One plausible explanation involves electrostatic interaction (field effect). If we consider the electrostatic interaction in the diaxial form, the distance between the poles

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(9) Ref. 6, Chapter 7.

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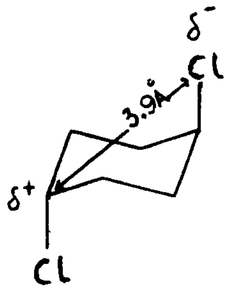
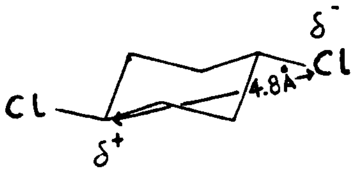
of opposite charge is 3.90Å as compared to 4.80Å in the diequatorial form (C-Cl = 1.81Å [7,8]). Since the potential





energy of such an interaction varies inversely with the square of the distance ($E \propto \frac{1}{r^2}$),[10] the diaxial form is thus stabilized (this factor is obviously very small in cyclohexyl halides). The actual difference in electrostatic interactions between the two forms may be even greater than indicated due to variations in the effective dielectric constant, ϵ. From consideration of models, it is difficult to envisage the intervention of a solvent molecule in the space between the chlorine atom and the carbon atom in the diaxial form; therefore, ϵ should be close to unity. However, in the diequatorial form, the force operates very nearly in the plane of the ring and thus a higher value of ϵ (<u>ca</u>. 2 for carbon chains) would be appropriate.

There are a few cases in the literature where interaction of this type may be invoked to account for experimental observations. Most notable is the work of Trager[11] <u>et</u>. <u>al</u>. They

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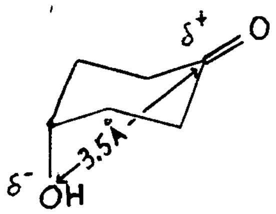
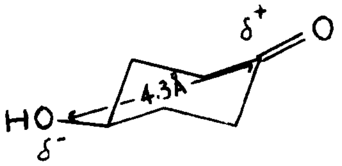
(10) K.B. Wiberg, Physical Organic Chemistry, John Wiley and Son, Inc., New York, N.Y., 1964, p.282.

(11) W.F. Trager, B.J. Nist, and A.C. Huitric, J. Pharm. Sci., 56, 698 (1967).

have found from nmr measurements that in 4-hydroxycyclohexanone, the equatorial hydroxyl conformation was present to the





extent of only 47±4% (in pyridine), 46±4% (in $CDCl_3$), and 61% in D_2O. The corresponding conformational energies of the hydroxy group (at 37°) are approximately zero in the first two solvents and 0.27 kcal/mole in D_2O. This reduction of $-\Delta G^{\circ}$ value is parallel to our results. Although the authors did not offer any explanation, it seems likely that electrostatic interaction is responsible.

The decrease in $-\Delta G^{\circ}_{OH}$ from 0.7 kcal/mole in cyclohexanol (in aprotic solvent) to zero in 4-hydroxycyclohexanone may be attributed to two factors. Substitution of a methylene by a carbonyl will tend to decrease the energy required for small angular deformation, whereby the van der Waals repulsion between the axial hydroxyl and the syn-3,5-diaxial hydrogens may be relieved, at least partially, by tilting these hydrogens away from the hydroxyl. Secondly, the C=O bond is more polarized than a C-Br bond (dipole moments of 3.0 and 1.9D respectively), and oxygen is more electronegative than bromine or chlorine, hence an electrostatic interaction between a C-O and C=O would be stronger than that in trans-1,4 dihalocyclohexanes.

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The small preference of the hydroxyl group (in 4-hydroxycyclohexanone) for the equatorial position in D_2O may be due to two factors. The first one is the increase in the effective size of the hydroxyl group through hydrogen bonding with water[12]; and the second, the increase in the dielectric constant (D_2O, 78) as compared to pyridine(12) and $CDCl_3$(4.8). Although the effective dielectric constant is the required parameter, the bulk dielectric constant is the only value available. Therefore the high dielectric of D_2O will diminish the electrostatic interaction. The relative importance of these two factors is not known; however, it seems likely from the work of Eliel[12] that the first one is of greater importance.

Another case reported[13] in the literature is the equilibration of 4-chlorocyclohexanol where 54.5% of the equilibrium mixture was the *cis* isomer. Similarly, hydride reduction of 4-chlorocyclohexanone[14] led to a predominance of the *cis* alcohol (59-69%). This result could be accommodated by an intramolecular electrostatic interaction between the $Cl-C_4$ and C_1-O groups. Such interactions are more favourable in structures related to the *cis*-chloro alcohol than in those related to the *trans*-chloro alcohol.

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(12) Eliel showed that $- G^{o}_{OH}$ varied from 0.70 in benzene to 0.94 kcal/mole in isopropyl alcohol. E.L. Eliel and S.H. Schoeter, *J. Am. Chem. Soc.*, *87*, 5031 (1965).

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

(14) M.G. Combe and H.B. Henbest, *Tetrahedron Lett.*, 404, (1961).

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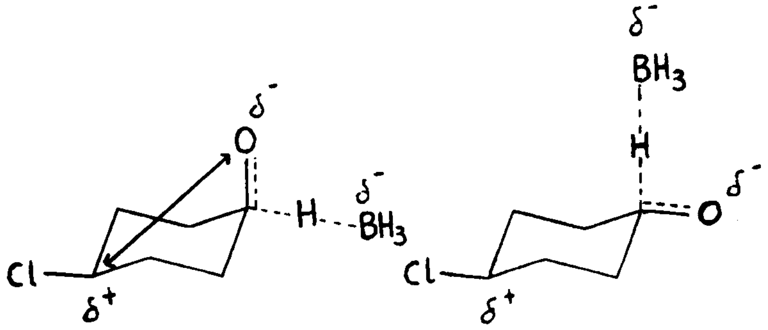

A related case is the solvolysis of 4-X-cyclohexyl tosylates (X = t-butyl, Br, Cl, and CN). In 4-t-butyl compounds[15] the $k_{trans} : k_{cis}$ ratio is ca. 0.5 but with the polar substituents $k_{trans} : k_{cis}$ ratios vary from 1.13 to 2.36. This reversal[16] was attributed to the influence of the geometrical position of the dipole in relation to the developing charge in the transition state, a direct field effect.

The conformational energy of a nitro group has been found to be 0.8 - 1.0 kcal/mole[17,18] and yet protonation of cyclohexane-1,4-bisnitronate ion gave 55% of the cis isomer.[19] It was originally suggested[19] that the product distribution was due to the hindrance to axial protonation of the intermediate

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(15) J.L. Mateo, C. Perez, and H. Kwart, Chem. Commun., 125 (1967).

(16) D.S. Noyce, B.N. Bastian, and R.S. Monson, Tetrahedron Lett., 863 (1962).

(17) W.F. Trager and A.C. Huitric, J. Org. Chem., 30, 3257 (1965).

(18) N.C. Franklin and H. Feltkamp, Ann. Chem., 683, 55 (1965).

(19) A.T. Nielsen, J. Org. Chem., 27, 2001 (1962).

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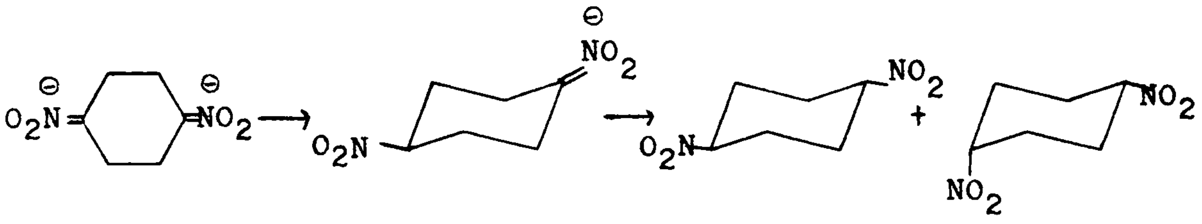
(**13**). However, recent work has shown that steric hindrance



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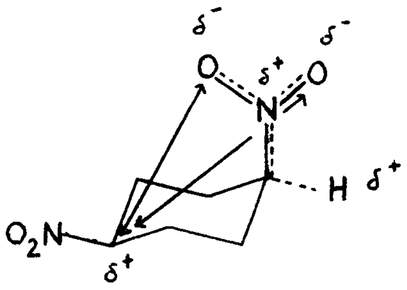
to axial protonation is not significant.[20] We propose that the same intramolecular interaction is operative in the protonation of cyclohexane-1,4-bisnitronate ion, where the structure related to the *cis* isomer is stabilized at the transition state.



In medium-ring chemistry, transannular interactions are very common.[21] Even in the ground state, 1-methy-1-

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(20) F.G. Bordwell and M.M. Vestling, *J. Am. Chem. Soc.*, **89**, 3906 (1967).

(21) A.C. Cope, M.M. Martin, and M.A. McKervey, *Quart. Rev.*, **20**, 119 (1966).

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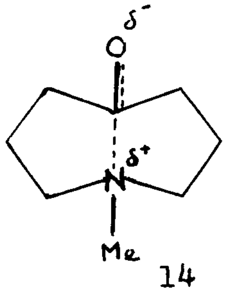
azacyclooctan-5-one (14) and 1-thiacyclooctane-5-one (15) exhibit such interactions as demonstrated by infrared spectro-



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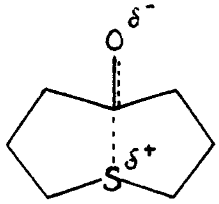

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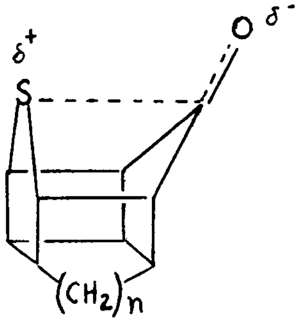
scopy. Ultraviolet studies also demonstrated that certain caged thiaketones (16) and (17) behaved similarly.[22]



16, n = 1

17, n = 2

Conclusion and Suggestion for Future Work

Our results indicate that intramolecular interaction causes a significant enhancement of the stability of a conformation when the disposition of polar groups favours such interaction. It should be pointed out here that we have yet no proof for the existence of such interaction even though it can account for our observations and some data in the chemical literature as well.

At this time, we are unable to rule out the possibility

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(22) L.A. Paquette and L.D. Wise, J. Am. Chem. Soc., **89**, 6659 (1967).

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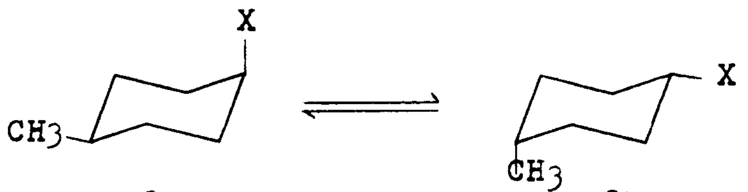
that in 1,4-disubstituted cyclohexanes, the $-\Delta G^{\circ}$ values are simply not additive due to some as yet unknown interactions of non-electrostatic nature. One system that will help to define the importance of this electrostatic interaction is *cis*-1-X-4-methylcyclohexanes (18) with polar substituents, X. The reasons for choosing the 4-methyl group, besides it being non-polar, are threefold: firstly, the conformational energy of the methyl group is known very accurately. Secondly, the



18a 18b

$-\Delta G^{\circ}_{Me}$ value (1.7 kcal/mole) is small enough so that the relative proportions of 18a and 18b would be roughly 85 : 15 for most polar groups (i.e.,$\Delta G_{18b} - \Delta G_{18a}$ = *ca.* 1 kcal/mole). Finally, the methyl group, being symmetric, does not introduce any appreciable entropy change going from the equatorial position to the axial one. If in this system the $-\Delta G^{\circ}$ values are additive then one can be reasonably sure that the electrostatic interaction is the cause of non-additivity.

It was mentioned in Chapter I that Eliel had shown that the conformational equilibrium of *cis*-4-methylcyclohexyl bromide could be predicted by the difference of $-\Delta G^{\circ}_{Me}$ and $-\Delta G^{\circ}_{Br}$. However, the method employed was the chemical-shift method with 4-*t*-butylcyclohexyl bromides as references. Since the validity of this method has been questioned we feel the prob-

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lem should be reinvestigated. Furthermore, additional compounds, such as _trans_-1,4-diX-cyclohexanes (X = polar groups), _cis_-1-X-4-methylcyclohexanes, and 4-halocyclohexanones should be studied with the goal of obtaining a correlation of substituent polarity and non-additivity.

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CHAPTER III

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded with a JEOL JNM 60 Mc. instrument in 15-20% acetone-$\underline{d}_6$ solutions for the *cis* compounds, and in 10% solutions for the *trans* compounds. Room temperature spectra were recorded at an average probe temperature of near 20°. The temperature readings appeared to be roughly 4° too low as indicated by the determination of the coalescence temperature of cyclohexane. Our instrument showed a range of -65 to -66° as compared with the reported temperature of -61.4°.[1,2] Limiting separation was assumed when further cooling for 10° or more produced no detectable change. The peak positions are the average values of five determinations, and are estimates of the mid-points of the multiplets. For the broad (axial) peaks, the standard deviation of the recorded values is ±0.015 ppm.

The low-temperature infrared spectra (15-20% solutions) were recorded with a Beckmann IR-10 instrument and a variable temperature cell purchased from Research and Industrial

---

(1) F.A.L. Anet and A.J.R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967).

(2) The coalescence temperature of cyclohexane was quoted by Eliel *et. al.* (E.L. Eliel, N.L. Allinger, S.J. Argyal, and G.A. Morrison, *Conformational Analysis*, Interscience Publishers, New York, N.Y., 1965, p. 41) as -66.7°. We have quoted this temperature in our paper (G. Wood and E.P. Woo, *Can. J. Chem.*, **45**, 2477 (1967)) but examination of the source of Eliel's reference showed that this temperature was misquoted.

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Instruments Co., London.

Gas chromatography was carried out with an F and M 720 instrument. The preparative column, 8 ft x 0.5 in. was packed with 10% diethyleneglycol succinate on Diatoport W, 60-80 mesh, and the analytical column, 10 ft x 0.25 in., was packed with the same material.

Melting points, determined with a Fisher-Johns or Thomas-Hoover Apparatus, and boiling points were uncorrected. Petroleum ether refers to the fraction boiling at 35-60°. Anhydrous magnesium sulphate was used throughout as drying agent.

Comments on Synthetic Routes

It is known that reaction of cyclohexane-1,4-diol with phosphorus tribromide or hydrobromic acid gives *cis*- and *trans*-1,3- and 1,4-dibromocyclohexanes. Separation of these isomers involves a complex procedure.[3] Similarly, treatment of *cis*-1,4-epoxycyclohexane with hydrobromic or hydrochloric acid led to the corresponding undesirable mixtures.[4] Therefore, attempts were made to prepare the desired 1,4-dihalocyclohexanes from the diol without structural isomerization. An early report by Horner *et*. *al*.[5] and recent work by Wiley[6,7] showed

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(3) B. Franzus and B.E. Hudson, Jr., *J. Org. Chem.*, *28*, 2238 (1963).

(4) E.L. Bennett and C. Niemann, *J. Am. Chem. Soc.*, *74*, 5076 (1952).

(5) L. Horner, H. Oediger, and H. Hoffmann, *Ann. Chem.*, *626*, 26 (1959).

(6) G.A. Wiley, R.L. Hershkowitz, B.M. Rein, and B.C. Chung, *J. Am. Chem. Soc.*, *86*, 964 (1964).

(7) G.A. Wiley, B.M. Rein, and R.L. Hershkowitz, *Tetrahedron Lett.*, 2509 (1964).

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that alcohols could be converted in good yields to the halides by triphenylphosphine dihalides. Unfortunately, reaction of triphenylphosphine dibromide with cyclohexane-1,4-diol gave a poor yield of 1,4-dibromocyclohexanes together with some 1,3-dibromo isomers. Thionyl chloride is another reagent which appeared to be promising because of the nature of its reaction mechanism with alcohols[8] and also the reported stereospecific conversion of <u>trans</u>-4-chlorocyclohexanol to <u>cis</u>-1,4-dichlorocyclohexane.[9] However, with cyclohexane-diol, the yield of the desired dichloro compounds was very low under a variety of conditions. The method of Jenkins and Kellet[10] which involves displacement of tosylate by bromide was also investigated. But treatment of the ditosylate with calcium bromide resulted in good yield of bromocyclohexene and 5-10% yield of 1,4-dibromocyclohexanes.

It was then decided that it would be less time consuming and more economical to follow known procedures. However, it seems in retrospect that the Hunsdiecker reaction of cyclohexane-1,4-dicarboxylic acid and the procedure developed by Wolfe[11] deserve investigation.

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(8) J. Hine, <u>Physical Organic Chemistry</u>, McGraw-Hill Inc., New York, N.Y., 1962, p. 140.

(9) T.W. Lunney, A.M. Waley, and H.W. Davies, <u>J. Am. Chem. Soc.</u>, <u>74</u>, 3428 (1952).

(10) G.C. Jenkins and J.C. Kellet, Jr., <u>J. Org. Chem.</u>, <u>27</u>, 624 (1962).

(11) J.R. Campbell, J.K.N. Jones and S. Wolfe, <u>Can. J. Chem.</u>, <u>44</u>, 2339 (1966).

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1,4-Dibromocyclohexanes[3]

Cyclohexane-1,4-diol (21 g, 0.183 mole) was slurried with 200 ml of cyclohexane in a 3-necked flask fitted with a mechanical stirrer, condenser, and dropping funnel. Phosphorus tribromide (50 g, 0.185 mole) was added dropwise over a period of one-half hour. After addition was complete, the mixture was refluxed for 18 hr. The organic layer was separated, washed with water and saturated sodium carbonate solution. The oil (24 g) obtained after removal of solvent was distilled at reduced pressure (11 mm., 102-107°) to give a mixture of _cis_- and _trans_-1,3- and 1,4-dibromocyclohexane. Storage at -20° overnight and filtration of resultant solid afforded 7.5 g of crude _trans_-1,4-dibromocyclohexane which was recrystallized from ethanol four times to give 1.5 g of pure _trans_ isomer, m.p. 111-112° (lit.[3] m.p. 111.5 - 112°).

The isomeric mixture above after removal of crude _trans_ compound was fractionated three times with a spinning band column (25 plates) and the fraction boiling at 50°/0.5 mm was collected. Recrystallization from ethanol gave the pure _cis_ compound, m.p. 49-50° (lit.[3] m.p. 48°). It was found later that repeated distillation was not necessary. The isomeric mixture could be purified by reverse crystallization with ethanol in the following manner: a saturated solution of the oil (at room temperature) in ethanol was cooled at 0° and the crystalline material was filtered. The filtrate was evaporated to dryness and the residue recrystallized from petroleum ether four times, m.p. 49-50°.

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1,4-Dichlorocyclohexanes[12]

Cyclohexane-1,4-diol (40 g, 0.345 mole) was heated with conc. hydrochloric acid (400 ml) at 100° with stirring for 28 hr. The solution was extracted with two 250-ml portions of petroleum ether. The organic phase was washed with saturated sodium carbonate solution and dried. Removal of solvent afforded 32 g of oil. After storage at -20° for 30 hr, the solid material was filtered and then recrystallized twice from ethanol to give 3 g of pure trans compound, m.p. 101.8-102.2° (lit[12] m.p. 101-102°).

The filtrate was distilled through a spinning band column at 17 mm. The low boiling fractions (35-86°) gave 2.5 g of trans isomer. The higher boiling fraction (86-89°) was redistilled to give 5.8 g of cis isomer, b.p. 88-89°/17mm. Gas chromatography with the analytical column at 135° showed 98% purity. A sample was further purified by preparative glc at 130° before use.

An interesting conversion of cis-1,4-dichlorocyclohexane to phenylcyclohexane was observed. A purified sample was stored in a vial covered by a piece of aluminum foil and a screw-cap. A few months later, the sample was found to contain about 50% of phenylcyclohexane. Subsequent investigation of the reaction of aluminum chloride with dichlorocyclohexane and cyclohexa-1,3-diene showed that small amounts (2-10%) of phenylcyclohexane were produced. We have been unable to ar-

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(12) W. Kwestroo, F.A. Meijer, and E. Havinga, Rec. Trav. Chim. Pays-Bas, 73, 717 (1954).

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rive at the proper conditions and/or the right starting materials to reproduce the 50% conversion to phenylcyclohexane.

1,4-Bromochlorocyclohexane[13]

Cyclohexane-1,4-diol (50 g, 0.43 mole) and 50 ml of conc. hydrochloric acid were heated slowly to 100° for 3.8 hr. The acid solution was poured onto 100 g of ice and neutralized with solid sodium bicarbonate. The mixture was saturated with sodium chloride and extracted with three 100-ml portions of ether. After drying and removal of solvent, an oil was obtained which was distilled at 11 mm. The fraction (20.5 g) boiling at 100-102° was collected. This liquid was placed in a 3-necked flask fitted with a thermometer, dropping funnel, condenser, and stirrer. Phosphorus tribromide (56 g) was added dropwise with cooling (ice-bath). Towards the end of addition, the ice-bath was removed and the solution was slowly heated to 70° for one hour. Water (200 ml) was then added and the mixture was extracted with two 100 ml portions of ether. After washing with saturated sodium bicarbonate and dried, the solvent was evaporated. The resultant oil (19.1 g) was stored at -20° overnight and filtered. The solid material was recrystallized four times from ethanol and twice from heptane to give 1.2 g of trans compound, m.p. 99.6-100.1° (lit[13] m.p. 102°).

The filtrate was distilled through a spinning band column at 11 mm. The fraction boiling at 91° was redistilled (95% purity by glc). A sample was further purified by preparative glc before use.

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(13) O. Hassel and K. Lunde, Acta Chem. Scand., 6, 1126 (1952).

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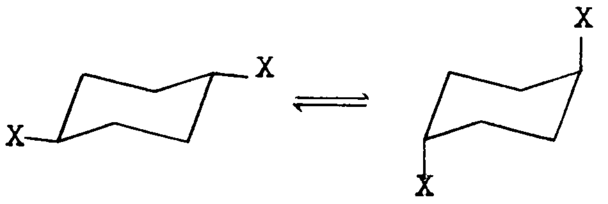
Peak Area Integration of trans-1,4-Dichlorocyclohexanes, Treatment of Data

The ratio of the integrated peak areas of the diequatorial form (e_x) to that of the diaxial form (a_x) corresponds to the equilibrium process represented by equation III-1. A least square analysis of a series of equilibrium constants for each compound was performed (equation III-2) to obtain a "best"



(III-1)

$$\underline{K} = \frac{\sum (a_x)_i \ (e_x)_i}{\sum (a_x)_i^2} \qquad \text{(III-2)}$$

value, $\underline{K}$, which was then used to calculate the "best" value of the conformational energy[14] ($-\Delta G^{o}_{aa \to ee}$) according to equation III-3.

$$-\Delta G^{o}_{aa \to ee} = RT \ln \underline{K} \qquad \text{(III-3)}$$

The 95% confidence limits[15] were calculated according to equation III-4.

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(14) Although the conformational energies presented in Chapter II were calculated with the temperature recorded by our instrument[2], a discrepancy of 4° does not amount to more than 2% error which is well within the experimental limits.

(15) The author is grateful for the assistance of Dr. E.W. Channen with the statistical analysis.

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$$95\% \text{ confidence limit} = \pm 2 \, \frac{\left\{ \frac{\sum(-G_i^o)^2}{n} - (\overline{-\,G_i^o})^2 \right\}^{\frac{1}{2}}}{n^{\frac{1}{2}}} \qquad \text{(III-4)}$$

$\overline{-\,G_i^o}$ = conformational energy calculated from $\overline{K}$ (the average value of the equilibrium constants).

n = total number of integrations.

A sample of data and calculation is presented in Table III-1.

TABLE III-1

Low Temperature Peak Area Integrations of

<u>trans</u>-1,4-Dichlorocyclohexane in Toluene-$\underline{d}_8$ (218°K)

No	$(a_x)_i$	$(e_x)_i$	$K_i = \frac{(e_x)_i}{(a_x)_i}$	log K_i	$-\Delta G_i^o$ (cal/mole)
1	11.7	15.5	1.30	0.1139	114.2
2	11.2	17.3	1.55	0.1903	190.8
3	11.2	18.6	1.66	0.2201	220.7
4	11.2	18.0	1.61	0.2068	207.4
5	11.0	19.0	1.70	0.2304	231.1
6	12.4	16.7	1.35	0.1303	130.7
7	11.7	17.6	1.50	0.1761	176.6
8	13.0	15.9	1.22	0.0864	86.6
9	14.8	21.3	1.44	0.1584	158.8
10	12.8	18.1	1.44	0.1584	158.8
11	12.2	18.4	1.51	0.1790	179.5
12	13.9	18.8	1.35	0.1303	130.7
13	13.2	19.2	1.45	0.1614	161.9
14	14.5	19.4	1.34	0.1271	127.5

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$\sum (a_x)_i^2 = 2193.0$ $\sum K_i = 20.4$

$\sum (e_x)_i (a_x)_i = 3177.7$ $\bar{K} = 1.46$ $\sum (- G_i^o)^2 = 392513.7$

$\underline{K} = 1.45$ $-\overline{\Delta G_i^o} = 164.9$ cal/mole

$-\Delta G^o_{aa \longrightarrow ee} = 161.9$ cal/mole 95% confidence limit = ± 16 cal/mole

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PART II

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF TWO BICYCLIC ANALOGUES OF CYCLOHEXANE-1,4-DIONE

CHAPTER I

INTRODUCTION

Non-chair Forms of Cyclohexanone and Cyclohexane-1,4-dione

The two forms of cyclohexane suggested by Sachse in 1890 were the chair and the boat. A third conformation was later proposed which has been variously known as the flexible, stretched, skewed, or twist form. This form is obtained during the conversion of one boat into another by twisting the C-C bonds. The energy barrier between these forms is so low (see Part I, Fig. I-1) that facile interconversion between them is possible. Hence the term "flexible form" has been suggested as a general name for all puckered non-chair conformations, while the term "boat form" refers to the specific conformation which resembles the shape of a boat.

It is well known that cyclohexane and its derivatives exist predominantly in the chair form which is thermodynamically more stable. In the chair form all the adjacent C-H and C-C bonds are staggered. However, there exists in the boat form torsional strain (of the type encountered in the eclipsed form of ethane) involving the four pairs of hydrogens at the side of the boat. There is also strain due to the interference of the pair of hydrogens at the prow and stern of the boat (Fig. I-1). The difference in energy

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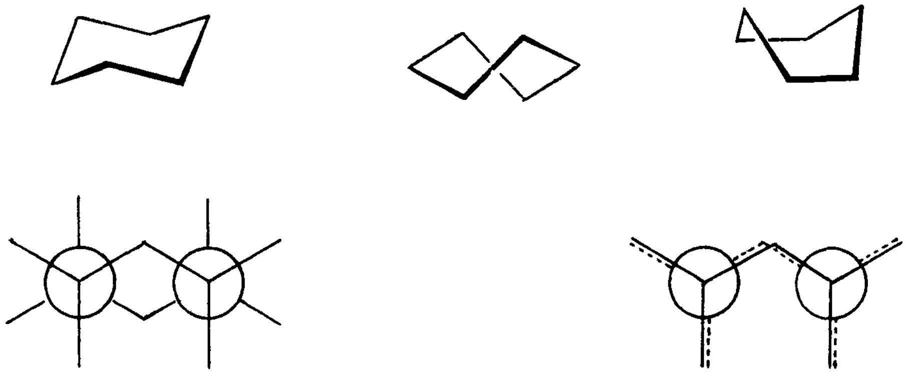
between the chair and the flexible forms may be approximated as twice the rotational barrier of ethane (2 x 2.9 kcal/mole).



chair twist boat

Fig. I-1. The chair and flexible forms of cyclohexane.

In cyclohexanone, one of the methylene groups of cyclohexane is replaced by a carbonyl group. Therefore, certain flexible forms are possible, each of which has only one eclipsed ethane unit.[1,2] The net effect of the carbonyl, then, is to reduce the energy difference between the flexible and the chair forms. Cyclohexane-1,4-dione, with two carbonyl groups, would be expected to have certain flexible forms of even lower energy. The energies (relative to the chair forms) of the flexible forms of cyclohexanone and cyclohexane-1,4-dione have been calculated by Allinger *et. al.*[2] (Table I-1). The values

---

(1) N.L. Allinger, J. Allinger, and M.A. DaRooge, *J. Am. Chem. Soc.*, *86*, 4061 (1964).

(2) N.L. Allinger, H.M. Blatter, L.A. Freiberg, and F.M. Karkowski, *ibid.*, *88*, 2999 (1966).

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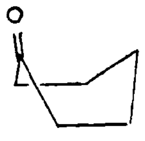
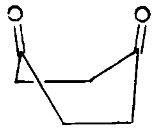
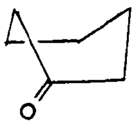
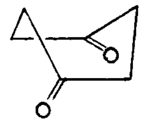
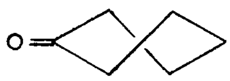
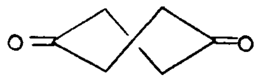
calculated for cyclohexanone agree well with experimental data.[2-4]

TABLE I-1

The Energies of the Flexible Forms of Cyclohexanone and Cyclohexane-1,4-dione

	E (kcal/mole)		E (kcal/mole)
	5.8		5.8
	3.9		1.8
	3.9		1.8

Cyclohexane-1,4-dione[2] and cyclohexane-1,4-dimethylenes[5] have captured the interest of many chemists because they prefer the flexible conformation without steric interaction or outside constraint. Historically the dipole moment (1.3D) of cyclohexane-1,4-dione was assumed to be the result of an

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

(4) N.L. Allinger and F.M. Karkowski, Tetrahedron Lett., 2171 (1965).

(5) F. Lautenschaeger and G.F. Wright, Can. J. Chem., **41**, 1972 (1963).

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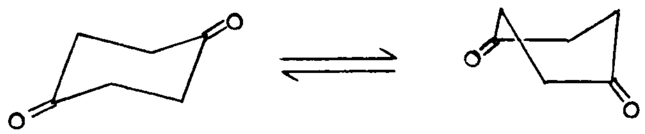
equilibrium mixture of 20% of the boat form and 80% of the chair form.[6] However, evidence from X-ray crystallography[7],



80%   20%

Kerr constant measurement[8], and infrared and Raman spectroscopy[9] all support the exclusive preference for the flexible form. The reason for this is not clear. Allinger and coworkers[2] closed a detailed discussion by stating:

> One would guess that in solution, not more than 10% of the chair form could be present and escape detection. Hence the free energy of the boat must be lower than that of the chair by 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 e.u., 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...... is somewhat too high......, or else there may be more than 10% of the chair in solution. We are not able to choose between these alternative possibilities at present.

Therefore it seems that more experimental work is called for.

---

(6) D.L. Robinson and D.W. Theobald, Quart. Rev., 21, 314, (1967).

(7) A. Mossel, C. Romers, and E. Havinga, Tetrahedron Lett., 1247 (1963).

(8) C.-Y. Chen and R.J.W. LeFevre, Aust. J. Chem., 16, 917 (1963).

(9) N.L. Allinger and L.A. Freiberg, J. Am. Chem. Soc., 83, 5028 (1961).

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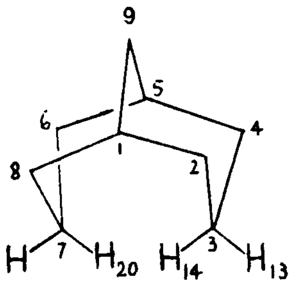
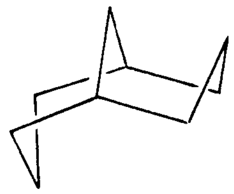
Bicyclo[3.3.1]nonane

Bicyclo[3.3.1]nonane (1) was believed[10] at one time to exist in the chair-boat conformation (1b) due to the severe



1a



1b

steric compression between the C_3 and C_7 atoms in 1a. These two atoms are only 2.56Å apart, much less than the sum of the van der Waal's radii of two carbon atoms (2 x 1.7Å). In addition, the axial hydrogens at C_3 and C_7 are separated by only *ca*. 1.0Å, causing an intolerable transannular interaction; it was suggested that the molecule might seek relief of strain by reverting to the chair-boat form. This was later proved to be incorrect by the X-ray crystallographic work of Brown *et. al.*[11,12] They showed that the conformation of 1-*p*-bromobenzenesulphonyloxy-5-methylbicyclo[3.3.1]nonan-9-ol is a flattened twin-chair in which the C_3 and C_7 atoms are 3.06Å apart, and that the average bond angles assume a value

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(10) E.L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill Book Co., Inc., New York, N.Y., 1962, p. 296.

(11) W.A.C. Brown, G. Eglinton, J. Martin, W. Parker, and G.A. Sim, *Proc. Chem. Soc.*, 57 (1964).

(12) W.A.C. Brown, J. Martin and G.A. Sim, *J. Chem. Soc.*, 1844, (1965).

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of 114°. Allinger and co-workers[13] recently arrived at a slightly different structure for the parent hydrocarbon by computer calculations: C_3-C_7 distance = 3.18Å, H_{14}-H_{20} distance = 2.25Å, and $H_{13}C_3H_{14}$ angle = 95.2°. They also calculated that the chair-boat form (**1b**) is 2.73 kcal/mole less stable than the distorted twin-chair form.

Infrared studies[11,14] of a series of bicyclo[3.3.1]nonane derivatives revealed that the transannular compression in the twin-chair form leads to two characteristic methylene absorptions at 2990 and 1490-1480 cm^{-1}. These bands are observed in the solid phase as well as in the liquid phase, thus providing evidence for the preference of the twin-chair form in the liquid phase. It was also noted that these bands disappear upon the replacement of the sp^3 carbon by a sp^2 carbon at the C_3 and/or C_7 positions, for example, bicyclo[3.3.1]non-2-ene and bicyclo[3.3.1]nonan-3,7-dione. The disappearance of the band was attributed to the reduction of transannular compression by the removal of one of the interfering hydrogen atoms, and the increased separation of the C_3 and C_7 atoms.

The conformations of some bicyclo[3.3.1]nonane derivatives and their heterocyclic analogues have been investigated. *exo*-Bicyclo[3.3.1]nonan-3-ol (**2**) was shown to prefer a

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(13) N.L. Allinger, J.A. Hirsch, M.A. Miller, I.J. Tyminski, and F.A. Van Catledge, *J. Am. Chem. Soc*., **90**, 1199 (1968).

(14) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc*., 1243 (1965).

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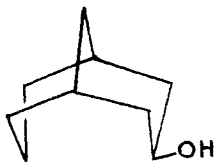
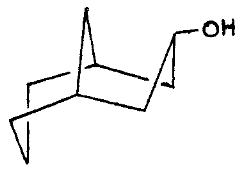
flattened twin-chair conformation.[15] The chair-boat form was suggested for the _endo_ epimer (**3**), presumably due to the larger bulk of the oxygen atom.[15] A number of heterocyclic analogues (**4**, **5** and **6**) also have been shown to exist in the flattened twin-chair form.[16,17,18] Chen and LeFévre[19] assigned the same conformation to _exo_-9-methyl-9-azabicyclo[3.3.1]-



2



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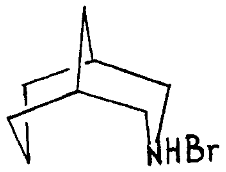

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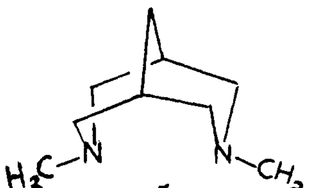

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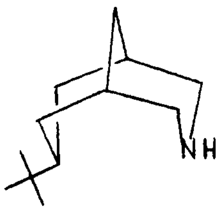

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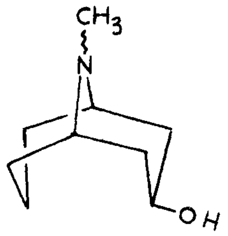
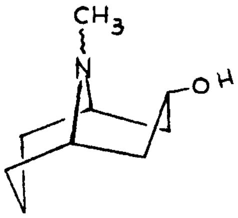
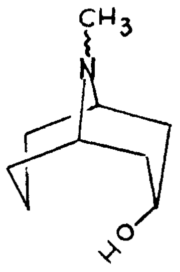


7



8a



8b

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(15) W.D.K. Macrosson, J. Martin and W. Parker, _Tetrahedron Lett._, 2589 (1965).

(16) M. Dobler and J.D. Dunitz, _Helv. Chem. Acta._, **47**, 695 (1964).

(17) J.E. Douglass and T.B. Ratliff, _J. Org. Chem._, **33**, 355 (1968).

(18) N.W.J. Humphrey and M.T.J. Robinson, _Chem. Ind. (London)_, 1903 (1963).

(19) C.-Y. Chen and R.J.W. LeFévre, _J. Chem. Soc., B_, 539, (1966).

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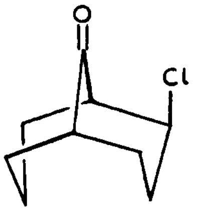
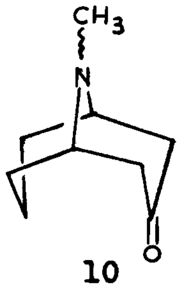
nonan-3-ol (7), and a chair-boat form to the *endo* epimer (8a) based on nmr data. However infrared studies[20] disagreed with the latter assignment, and the distorted twin-chair form (8b) was proposed. A recent X-ray crystallographic work[21] showed that 9 has the twin-chair conformation. LeFévre and co-workers[22] assigned an undistorted twin-chair to 10 based on dipole moment measurement but later concluded[19] that the twin-chair is flattened, from an analysis of the nmr spectrum of 10.



9



10

It appears, in general, that a twin-chair form (distorted or undistorted) is preferred by all bicyclo[3.3.1]nonane derivatives, except those with *endo* substituents at C_3 in which cases the chair-boat form is preferred.

Bicyclo[3.2.2]nonane

Although Alder *et. al.*[23] had studied the synthesis and

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(20) H.S. Aaron, C.P. Ferguson, and C.P. Rader, *J. Am. Chem. Soc.*, 89, 1431 (1967).

(21) N.C. Webb and M.R. Becker, *J. Chem. Soc., B*, 1317 (1968).

(22) J.M. Eckert and R.J.W. LeFévre, *ibid.*, 358 (1964).

(23) K. Alder and H.H. Molls, *Chem. Ber.*, 89, 1960, 1972, (1956).

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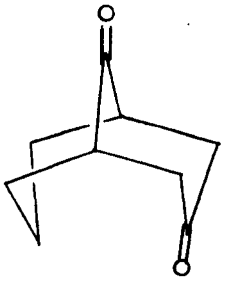
chemistry of bicyclo[3.2.2]nonane quite thoroughly, 6,8-disubstituted derivatives are uncommon. The report by Guha[24] seems to be the only attempt in the synthesis of these compounds.

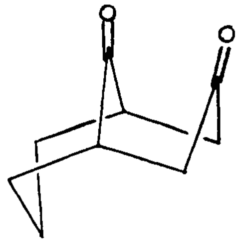
The bicyclo[3.2.2]nonane skeleton has two possible conformations; the cyclohexane moiety of both is locked in the flexible form by a trimethylene bridge. Therefore it should be possible to determine the conformational equilibrium provided a suitable derivative is available.

Statement of Problem

Bicyclo[3.2.2]nonan-6,8-dione lends itself to the determination of conformational equilibrium by dipole moment measurements because the calculated dipole moments of the two possible conformations are very different. It may also be used as a precursor in the preparation of other disubstituted cyclohexanes locked in a twist form.

An interesting feature of bicyclo[3.3.1]nonan-3,9-dione is that it has a cyclohexane-1,4-dione ring which cannot exist in the twist form due to the trimethylene bridge. However, the cyclohexane-1,4-dione ring may interconvert from a





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(24) P.C. Guha, *Chem. Ber.*, **72**, 1359 (1939).

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chair form to a boat form. Accordingly we set out to synthesize bicyclo[3.2.2]nonan-6,8-dione and bicyclo[3.3.1]nonan-3,9-dione and to determine their conformational equilibria by dipole moment measurements and spectroscopic methods.

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CHAPTER II

RESULTS AND DISCUSSION

The Synthesis of Bicyclo[3.2.2]nonan-6,8-dione

Scheme I shows the synthetic pathway for bicyclo[3.2.2]-nonan-6,8-dione. We chose alkylation of diethyl succinylsuccinate with 1,3-dibromopropane as entry to the bicyclo[3.2.2]nonane system. This method has been used previously in preparing bicyclo[3.2.2]nonanes[1], bicyclo[2.2.2]octanes[1-3] and bicyclo[2.2.1]heptanes.[1] The established procedure[4] for the synthesis of diethyl succinylsuccinate by condensation of two moles of diethyl succinate requires three to four days of reflux. We found that with sodium hydride in monoglyme, the reaction time was shortened to 12 hr with improved yield (75%). Heating the disodium salt of diethyl succinylsuccinate with 1,3-dibromopropane gave 50-55% yield of 1,5-dicarbethoxybicyclo[3.2.2]nonan-6,8-dione (**12**), a substantial increase from the 30% yield reported by Guha.[1] Acid hydrolysis of **12** afforded the corresponding diacid (**13**).

When the diacid (**13**) was heated to a temperature slightly above its melting point (*ca*. 245°) for a few minutes, a

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(1) P.C. Guha, *Chem. Ber.*, *72*, 1359 (1939).

(2) L.M. Humber, G. Myers, L. Hawkins, C. Schmidt, and M. Boulerice, *Can. J. Chem.*, *42*, 2852 (1964).

(3) (a) H.D. Holtz and L.M. Stock, *J. Am. Chem. Soc.*, *86*, 5183 (1964); (b) J.D. Roberts, W.T. Moreland, and W. Frager, *ibid.*, *75*, 637 (1953).

(4) C.R. Hauser and B.E. Hudson, Jr., *Org. Reactions*, *1*, 283 (1942).

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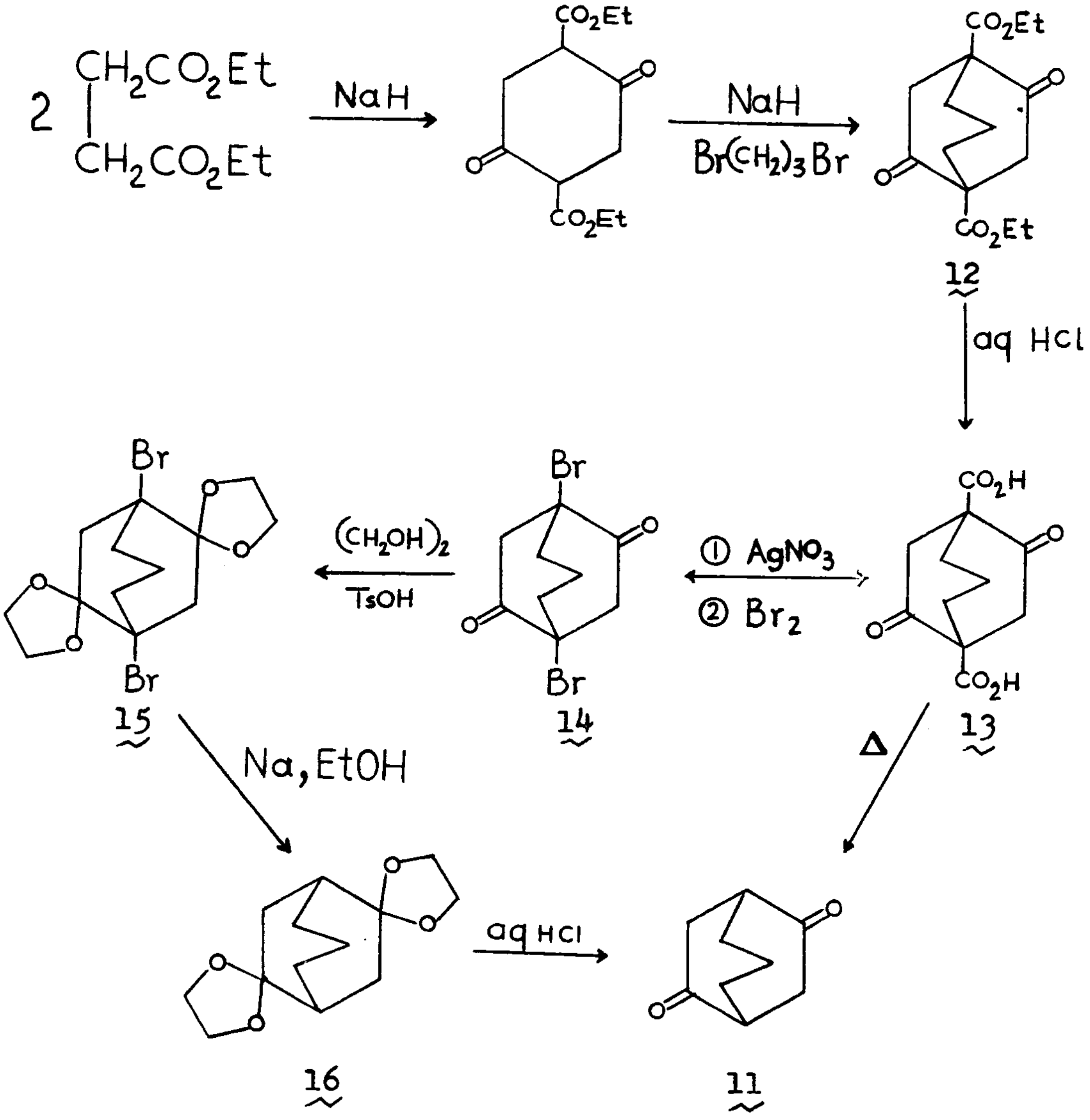
Scheme I



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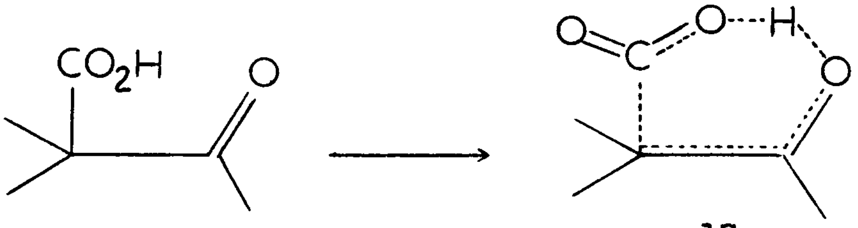
ketone was obtained. The same compound could be obtained in 60-65% yield by refluxing 13 in triglyme for 3-5 hr. It was identified as 11 by the following data. It gives a disemicarbazone and has ir absorption at 1725 cm^{-1} (C=O). Its nmr spectrum shows multiplets at τ 7.20 (2 H), 7.37 (4 H), and 8.20 (6 H) which are assigned to the bridgehead protons, methylene protons *alpha* to carbonyl groups, and the six protons of the trimethylene bridge, respectively. Further proof of structure was accomplished by the synthesis of 11 through another pathway (Scheme I). The diacid (13) was decarboxylated by the Hunsdiecker reaction to 14. Conversion of 14 to the diketal (15) and subsequent hydrogenation afforded 16. Acid hydrolysis of 16 gave a diketone identical to that obtained from thermal decarboxylation.

Decarboxylation of 13 and Bredt's Rule

Thermal decarboxylation of β-keto acids in general is believed to proceed by a non-ionic mechanism with an enolic intermediate.[5] At the transition state (17) the carbon bearing



17

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(5) (a) H.H. Wasserman in *Steric Effects in Organic Chemistry*, M.S. Newman, Ed., John Wiley and Sons, Inc., New York, N.Y., 1956, pp. 351-354; (b) E.L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill Book Co., Inc., New York, N.Y., 1962, pp. 298-302.

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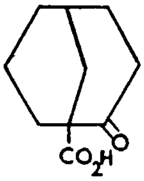
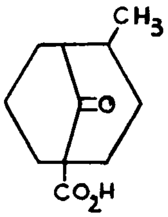
the carboxyl group is sp^2 hybridized. Overlap of the p orbital of the sp^2 carbon bearing the carboxyl group and the p orbitals of the carbonyl group stabilizes the transition state. However, if this carbon atom is at a bridgehead position, attainment of sp^2 hybridization is possible only in relatively large-ring compounds. Fawcett[6] has attempted to define the limits of Bredt's Rule by introducing the *S* number.[7] Thus those compounds with bridgehead double bonds should be isolable[8] if $S > 9$, and species with a bridghead double bond should have a transient existence as reaction intermediates if $9 \geq S \geq 7$. However, bicyclo[3.3.1]nonane derivative 18 decarboxylates with ease while 19 does not, and yet



18



19

both compounds have $S = 7$. From a study of a series of bicyclic compounds, (Table II-1, first four entries), Ferris and

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(6) F.S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

(7) *S* number refers to the total number of atoms between the two bridgehead atoms, *e.g.* $S = 7$ in bicyclo[3.2.2]nonane and bicyclo[3.3.1] nonane.

(8) The recent successful preparation of bicyclo[3.3.1]-non-1-ene suggests that the concept of *S* number needs modification. (a) J.A. Marshall and H. Fauble, *J. Am. Chem. Soc.*, **89**, 5965 (1967); (b) J.R. Wiseman, *ibid.*, **89**, 5966 (1967).

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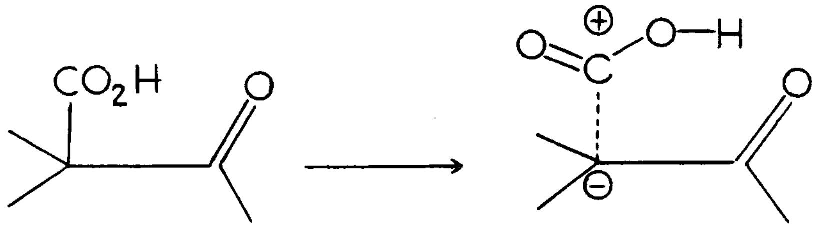
Miller[9] proposed an ionic mechanism in which the carbon atom bearing the carboxyl group has considerable ionic character.



The ease of decarboxylation depends on the extent of overlap of the sp^3 orbitals of the developing carbanion with the p orbitals of the carbonyl group. A portion of the results of Ferris and Miller is presented in Table II-1. The first five entries showed that the overlapping orbital angles are related to the temperature of decarboxylation. In fact, a straight line was obtained by plotting the cosine of the angles versus the temperatures. Examination of Dreiding models, however, showed that 13 has two conformations (vide infra) and the angles of the interacting orbitals are ca. 90 and 78° (three separate models were constructed and the average of 20 measurements is reported). Therefore a temperature exceeding 400° would be required according to the linear plot. From a recent report[8b], it appears that an alternative to the S number concept is possible while retaining the non-ionic mechanism. Assuming that decarboxylation proceeds through a bridgehead enol, such a bicyclic system (20) may be considered as

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(9) (a) J.P. Ferris and N.C. Miller, *J. Am. Chem. Soc.*, 85, 1325 (1963); (b) J.P. Ferris and N.C. Miller, *ibid.*, 88, 3522 (1966).

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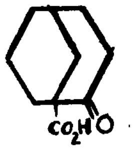
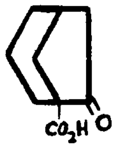
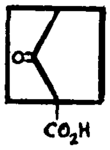
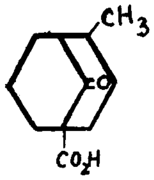
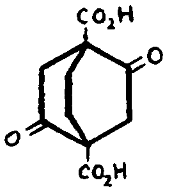
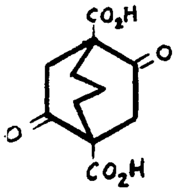
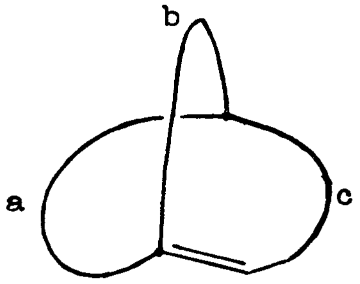
Table II-1

Thermal Decarboxylation of Bicyclic Keto Acids

Compound	Oribital Angles (degree)	Temp. (°C)	Ring-Size of *trans*-olefin
	30	145[a]	8
	50	260[a]	7
	60	320[a]	7
	90	No Reaction[a]	5
	90	No Reaction[b]	6
	90	No Reaction[c]	6
 13	78	240[c]	7

[a] Ref. 9, [b] Ref. 5, [c] See text.

composed of two cycloalkenes: a trans-cycloalkene (ring a c) and a cis-cycloalkene (ring b c). The ease of decarboxyla-



20

tion would be a function of the relative stability of the trans-cycloalkenes of various ring-sizes. trans-Cyclooctene has been known for some time[10], and trans-cycloheptene[11] has been demonstrated, by chemical evidence, to exist as a very reactive intermediate. Even trans-cyclohexene has been proposed as an intermediate in the photoisomerization of endocyclic olefins to exocyclic olefins.[12] A qualitative relationship is seen between the temperatures of decarboxylation and the ring-sizes of the trans-cycloalkenes (Table II-1, third and fourth columns). With ring-size of 6 or less, decarboxylation cannot be effected. With ring-sizes of 7 and 8, reaction proceeds with increasing ease. It can be seen that the diketo diacid **13** (last entry in Table II-1) is comparable in reactivity to other compounds of the same ring-

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(10) K. Ziegler and H. Wilms, *Ann Chem.*, **567**, 1 (1950).

(11) E.J. Corey, F.A. Carey, and R.A.E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965).

(12) P.J. Kropp, *ibid.*, **88**, 4091 (1966).

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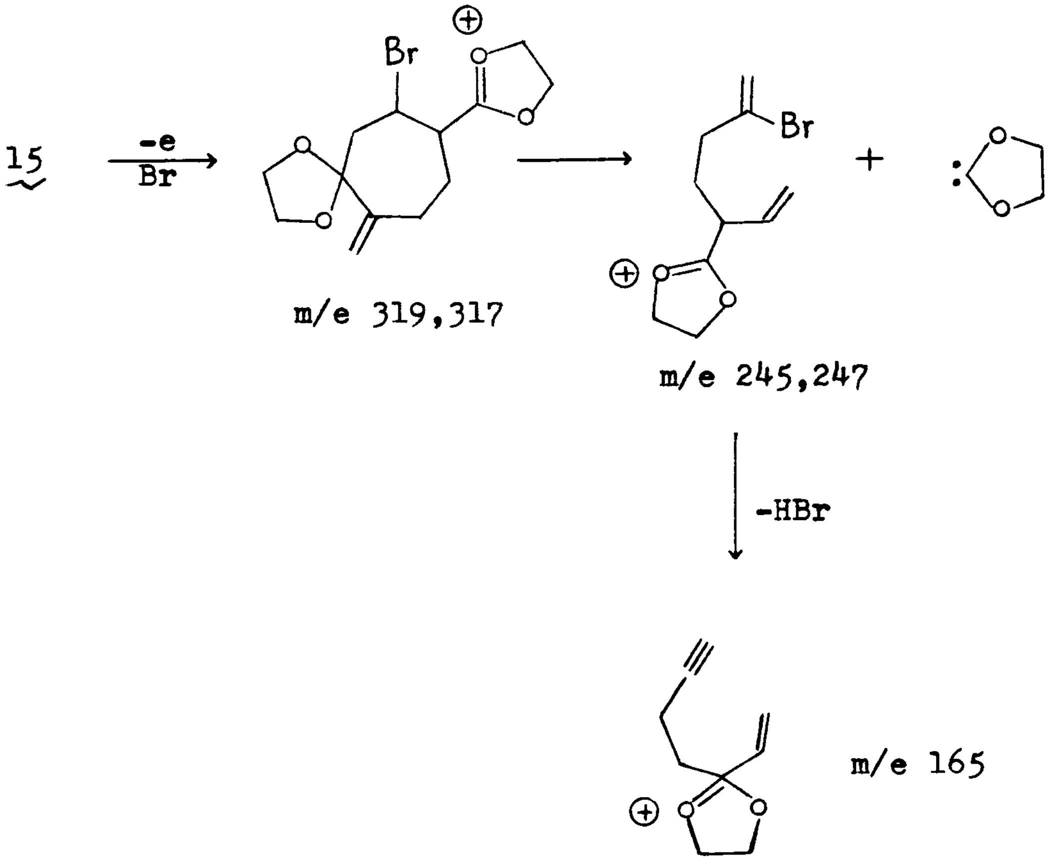
size (second and third entries). Guha[1] reported that 1,4-dicarboxybicyclo[2.2.2]octan-2,5-dione (sixth entry in Table II-1) could be monodecarboxylated but not didecarboxylated. However, we have repeatedly failed to reproduce this result.

Mass Spectral Data of Diketals 15 and 16

The mass spectra of 11, 14, 15 and 16 were recorded. They are generally too complex for extraction of meaningful interpretation without selective deuteration. It is worth noting, however, that the diketals 15 and 16 (Tables II-2 and II-3) eliminate a neutral fragment ($C_3H_4O_2$) which may be assigned a carbenoid structure derived from 1,3-dioxacyclopentane. The fragmentation pathway of 15 may be rationalized as



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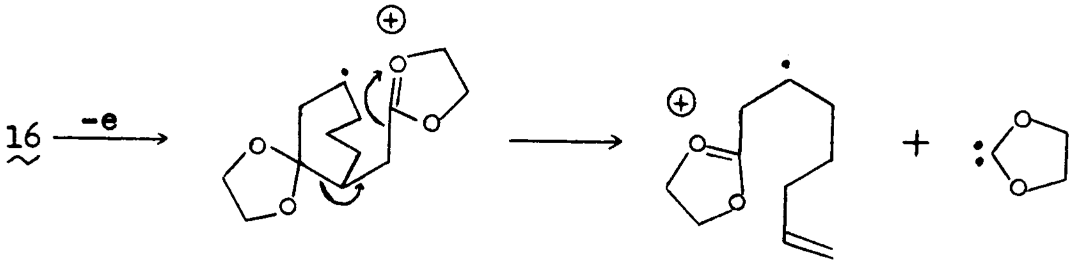
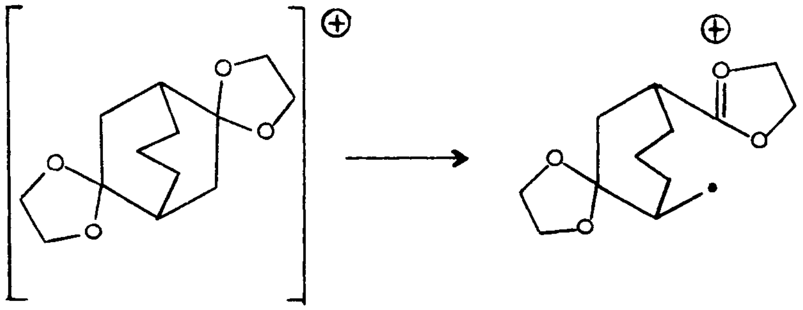
A metastable ion[13] at m/e 190.5 corresponding to m_2/e 317, 319 and m_1/e 245, 247 supports the depicted pattern. The high relative abundance of ions at m/e 245, 247 (base peak) and m/e 165 (51.2%) demonstrate the importance of this pathway. Similarly 16 gives an ion at m/e 168, and may be rationalized as



m/e 240 m/e 168

Again this pathway is supported by a metastable ion at m/e 118 corresponding to m_2/e 240 and m_1/e 168. The ion at m/e 168 is of lower intensity (13.4%) than the corresponding one derived from 15. This is probably due to the availability of another route for ring opening upon electron impact, for example,



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[13] (a) I. Fleming and D.H. Williams, Spectroscopic Methods in Organic Chemistry, McGraw-Hill Publishing Co., Ltd., London, 1966, p. 142; (b) F.W. McLafferty, Interpretation of Mass Spectra, W.A. Benjamin, Inc., New York, N.Y., 1966, p. 64.

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TABLE II-2

Mass Spectrum* of the Diketal of 1,5-Dibromobicyclo-[3.2.2]nonan-6,8-dione (**15**)

m/e	Relative Abundance	m/e	Relative Abundance	m/e	Relative Abundance
26	5.0	77	31.9	121	21.1
27	53.1	78	9.6	125	17.3
28	30.4	79	34.6	137	6.5
29	10.4	80	5.8	138	6.5
32	5.8	81	9.6	149	7.7
39	26.9	83	7.3	151	4.6
40	15.8	86	13.5	152	5.0
41	22.7	87	11.9	165	51.2
42	16.5	89	7.7	166	11.9
43	19.2	91	26.2	167	7.7
45	18.5	92	7.7	169	6.2
46	4.6	93	35.8	237	6.5
51	9.6	94	8.5	245	100 (Base)
52	7.3	95	7.0	246	13.4
53	30.5	99	11.8	247	98.0
54	9.6	105	7.0	248	12.7
55	13.4	107	23.0	263	7.0
65	13.5	109	20.8	265	6.2
66	8.1	111	23.0	273	5.4
67	12.3	112	8.0	275	5.0
68	9.5	113	61.5	317	88.5
69	12.3	114	5.8	318	14.6
73	15.0	119	7.7	319	86.0
				320	14.2

*Only ions of relative abundance of 5% or greater are tabulated.

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TABLE II-3

Mass Spectrum* of the Diketal of Bicyclo[3.2.2]nonan-6,8-dione (16)

m/e	Relative Abundance	m/e	Relative Abundance
27	9.8	81	5.7
28	8.3	86	33.1
29	6.9	87	7.0
39	8.3	99	100 (Base)
41	19.9	100	11.0
42	9.4	112	8.3
43	9.3	113	12.4
45	5.5	125	35.9
53	6.2	127	6.5
55	29.4	155	6.9
67	5.7	168	13.4
69	5.2	197	6.6
79	5.5	240	13.4
		241	2.4

---

* Only ions of relative abundance of 5% or greater are tabulated.

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To the best of our knowledge, the elimination of such a carbenoid fragment in mass spectrometry has not been documented; however, thermal decomposition of norbornadienone ketals has been shown to give similar fragments.[14]

The Synthesis of Bicyclo[3.3.1]nonan-3,9-dione

The Stork reaction[15] of acrolein and 1-N-pyrrolidylcyclohexene was chosen as the entry to the bicyclo[3.3.1]nonane system (Scheme I). The keto amine was converted to the ketal and oxidized to the amine oxide. Pyrolysis of the amine oxide produced the ketal olefin (23). Hydroboration of 23 yielded essentially two alcohols (24a and 25a) which were separated by column chromatography. The acetate 24b exhibits nmr peaks at τ 8.2 (broad, unresolved, 12 H), 8.0 (s, 3 H), 6.03 (m, 4 H), and 4.95 (single peak, $W_{\frac{1}{2}}$ = 7.5 c.p.s., 1 H). The signal at τ 4.95 is assigned to the equatorial proton at C_2 based on the peak width at half-height. Its ir spectrum has absorption at 1480 cm^{-1} confirming the twin-chair conformation[16] of the bicyclic skeleton. The parent alcohol 24a has the same ir band at 1480 cm^{-1}, and also a rather sharp O-H stretching at 3540 cm^{-1} which does not change upon dilution to 0.0025 molar (in carbon tetrachloride). From models it can be seen that the bicyclo[3.3.1]nonane derivative that

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(14) D.M. Lemal, E.P. Gosselink, and S.D. McGregor, J. Am. Chem. Soc., 88, 582 (1966).

(15) G. Stork and H.H. Landesman, ibid., 78, 5126 (1956).

(16) W.A.C. Brown, J. Martin, and G.A. Sim, J. Chem. Soc., 1844 (1965).

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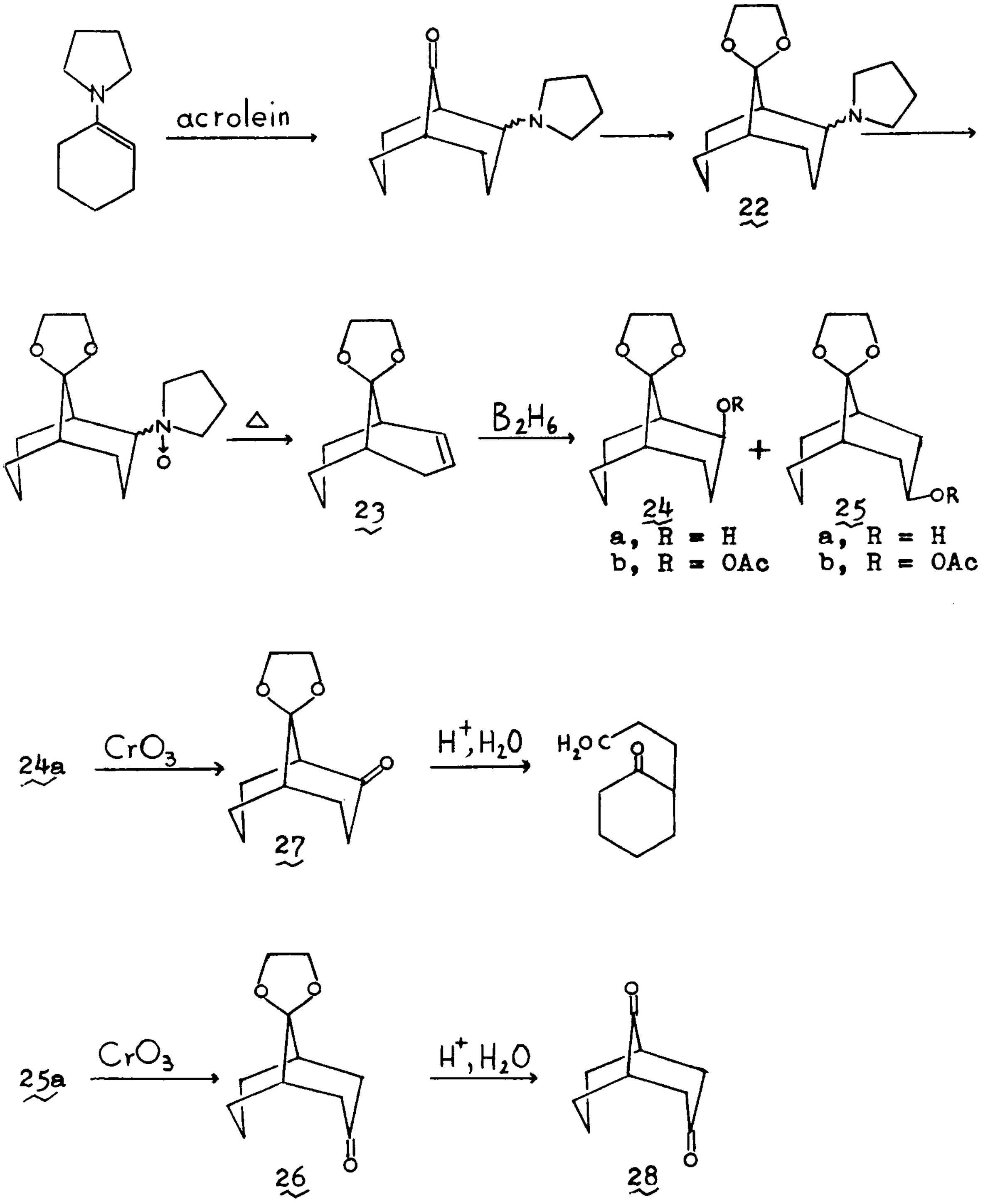
Scheme II



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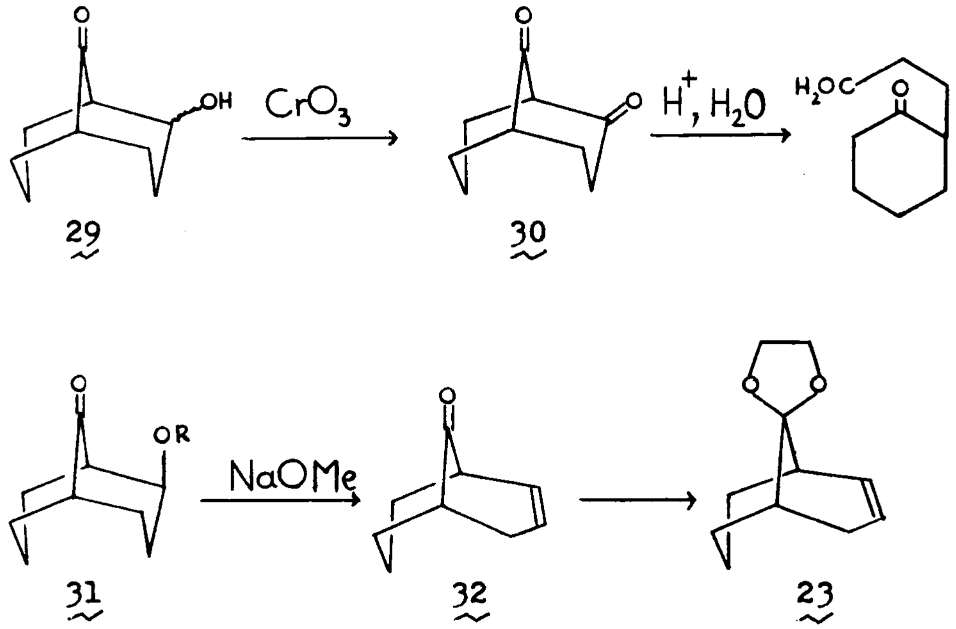
Scheme II



a, R = H
b, R = Ts

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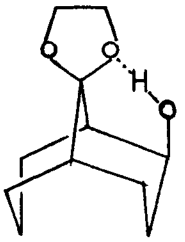
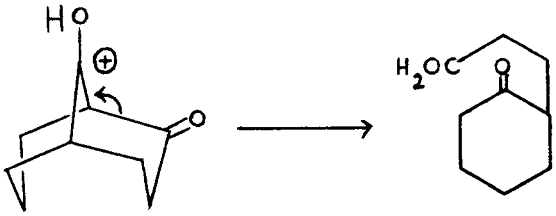
has the correct geometry for strong intramolecular hydrogen bonding[17] and an equatorial methine proton must be 24a. Oxidation of 24a gave the ketal ketone 27 which upon treatment with dilute acid cleaved to 2-(β-propionic acid)cyclohexanone, probably through the 9-protonated bicyclo[3.3.1]nonan-2,9-dione. Treatment of the diketone 30 gave the same product.



24a



The structural assignment of the ketal alcohol 25a was based on the stereochemical course of the hydroboration reaction and spectroscopic data. It is known that in the hydroboration of bicyclo[3.3.1]non-2-ene, the diborane adds preferentially to the *exo* side of the twin-chair form[18] leading

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[17] (17) It has been shown that axial-2-hydroxybicyclo[3.3.1]-nonan-9-one (31a) exhibits the same strong intramolecular hydrogen bonding. A.C. Cope, D.L. Nealy, P. Scheiner, and G. Wood, *J. Am. Chem. Soc.*, 87, 3130 (1965).

[18] (18) (a) J.P. Schaeffer, J.C. Lark, C.A. Flegal, and L.M. Honig, *J. Org. Chem.*, 32, 1372 (1967); (b) M. Hanack, W. Kraus, W. Rothenwöhrer, W. Kaisen, and G. Wentrup, *Ann. Chem.*, 703, 44 (1967).

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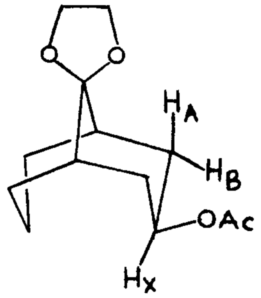
to exo-bicyclo[3.3.1]nonan-2-ol and 3-ol. The ketal olefin 23 is not expected to behave differently. The acetate 25b shows a triplet nmr signal at $\tau 4.50$ for the C_3 methine proton, line separation of 10 c.p.s. This is consistent with a 9-line A_2B_2X spectrum with J_{AX} = 10 c.p.s. and J_{BX} = 5 c.p.s. The fact that the expected 9-line signal was not observed was probably due to the low concentration of 25b at which the spectrum was recorded (the two outermost lines should be one-fifth the intensity of the centre line). The ir spectrum of the parent alcohol shows the 1480 cm^{-1} band but no intramolecular hydrogen bonding. Oxidation of 25a led to a ketal ketone (26) which has a very different ir spectrum from that of 27. Acid hydrolysis gave the desired bicyclo[3.3.1]nonan-3,9-dione (28).



25b

In order to obtain further structural proof, 2-hydroxybicyclo[3.3.1]nonan-9-one[17] (29) was oxidized to bicyclo[3.3.1]nonan-2,9-dione which has very different ir and nmr spectra from those of 28. The tosylate 31b was converted by treatment with base to the keto olefin 32 which was in turn converted to the ketal olefin 23, thus completing proof of structures.

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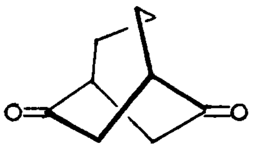
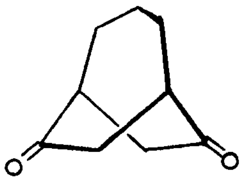
The Conformational Equilibrium of Bicyclo[3.2.2]nonan-6,8-dione (11)

The dipole moment of 11 in benzene solution at 20° was determined to be 1.39D. To check on the method used, the dipole moment of cyclohexane-1,4-dione was also determined. It was found to be 1.25D which agrees well[19] with 1.26D at 18°.

The diketone (11) can exist in two conformations (33 and 34). That these two forms are in equilibrium in solution may be deduced from the ir spectra of 11 in the solid phase and in solution. The ir spectra are identical in band locations but the band intensities in the region of 1400-1100 cm^{-1} are quite different. The variations in band intensities imply that only one conformation is present in the solid phase (probably due to crystal forces) and two conformations exist in solution. In the structure 33, the two carbonyl dipoles are oriented at an angle of 175°, and in the other conformation, they are perpendicular (angles are averages of ten measurements using two separate models). Taking the moment of a carbonyl group to be 3.00D[19], the expected dipole moments are


33


34

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[19] N.L. Allinger, H.M. Blatter, L.A. Freiberg, and F.M. Karkowski, J. Am. Chem. Soc., 88, 2999 (1966).

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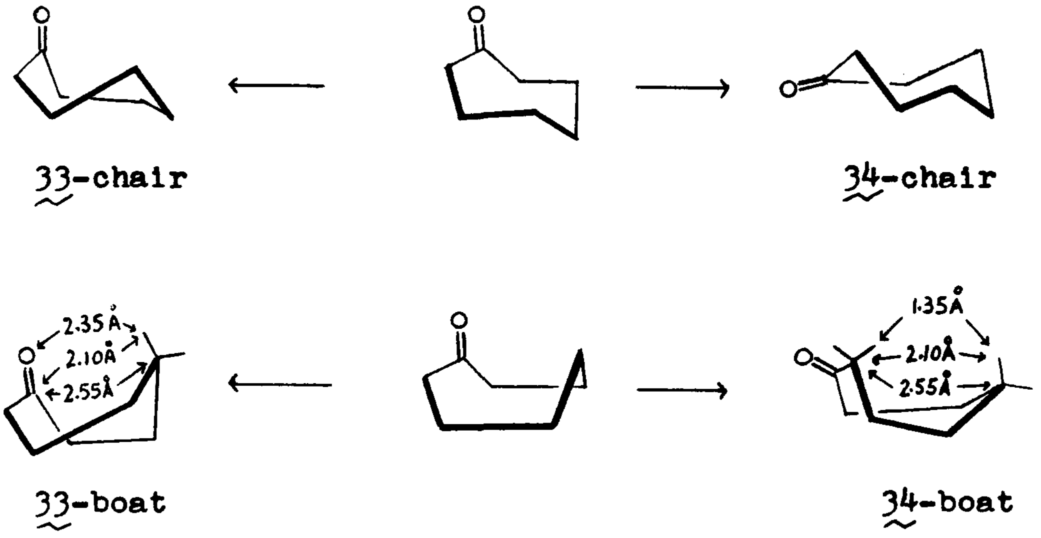
calculated to be ca. 0 D and 4.23D. The experimental dipole moment of 1.39D therefore indicates an equilibrium mixture of 89% of 33 and 11% of 34, corresponding to a free energy difference of 1.2 kcal/mole. The difference in free energies may be attributed to the methylene-methylene interaction in 34. Each of these structures may be regarded as a composite of a slightly twisted chair and a slightly twisted boat of cycloheptanone. Inspection of models shows that the chair rings of 33 and 34 do not differ appreciably in steric interaction, but prow-stern interaction is expected in the boat rings (Fig. II-1). The net difference between these two boat rings may be equated to one H-H interaction and one C-H interaction, disfavouring the conformation with methylene groups at the prow and stern positions. The value of 1.2 kcal/mole is prob-


33-chair

34-chair

33-boat

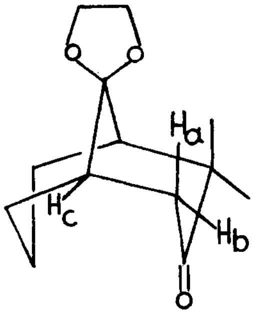
34-boat

Fig. II-1. The chair and boat rings of the cycloheptanone moieties of 33 and 34.

ably a minimum one for these interactions because in the boat ring of 34 some relief of strain can be achieved by a small flattening of the trimethylene bridge.

The Conformation of Spiro[1,3-dioxolane-2,9'-bicyclo[3.3.1]nonan-3'-one] (26)

The nmr spectrum (Fig. II-2) of 26 in benzene may be interpreted in two ways. The first interpretation is similar to the one for 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (10)[20] which is believed to have a twin-chair conformation. The doublet centered at τ 7.78 and the quartet at τ 7.17 are assigned to the C_2 equatorial and axial protons respectively. The equatorial proton (H_b) is coupled to the geminal axial proton (H_a), J_{gem} = 17 c.p.s. The proton H_a, in addition to the geminal coupling, is also coupled to the bridgehead proton (H_c), J_{vic} = 5.5 c.p.s. The fact that $J_{H_bH_c}$ is not detected implies[21] that the dihedral angle θ_1 is smaller than θ_2 as illustrated



26a

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(20) C.-Y. Chen and R.J.W. LeFèvre, J. Chem. Soc., B, 539 (1966).

(21) N.S. Bhacca and D.H. Williams, Applications of Nmr Spectroscopy in Organic Chemistry, Holden-Day Inc., San Francisco, 1964, pp. 50-52, and 156.

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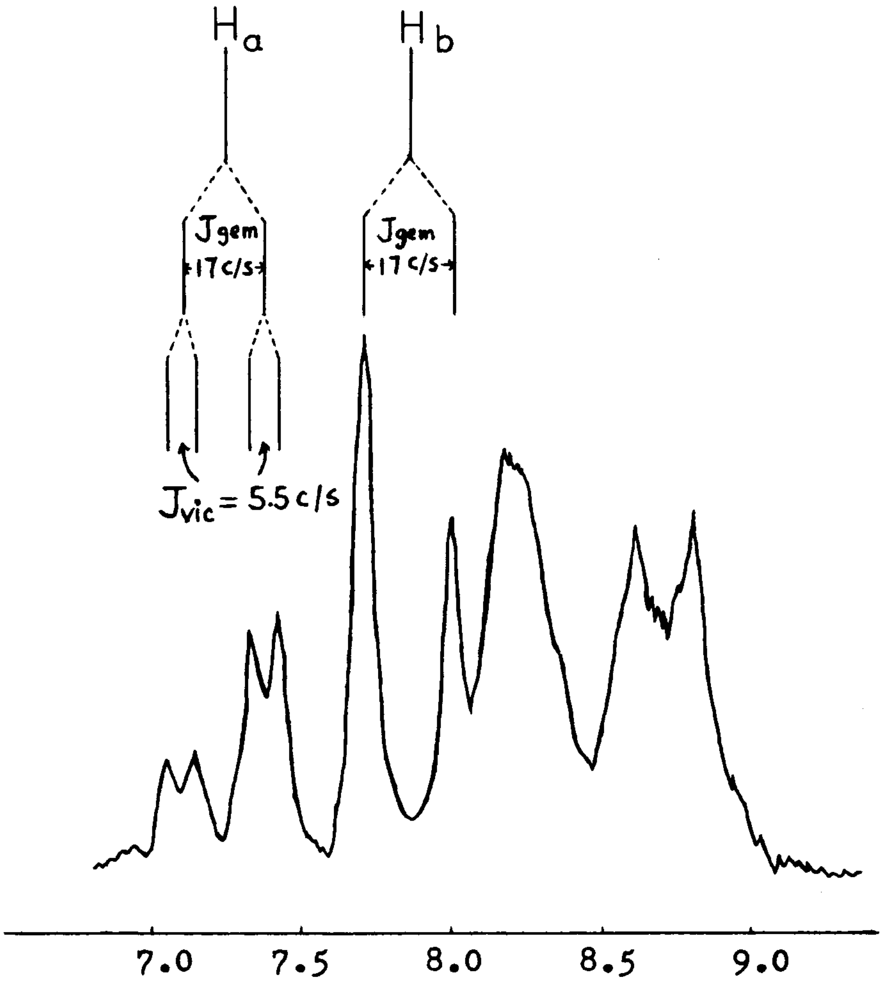

Chemical Shift (τ) ppm

Fig. II-2

Nmr spectrum of spiro[1,3-dioxolane-2,9'-bicyclo[3.3.1]nonan-3'-one]

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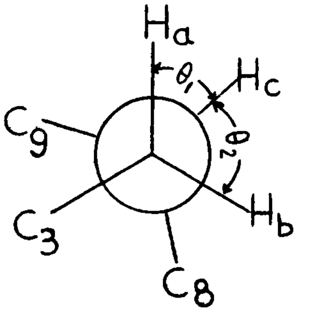
in 35, and is consistent with predictions based on a Dreiding model. The signal at τ7.65 has a width at half-height of 4.5 c.p.s. It could well consist of a doublet with separation of ca. 1 c.p.s., and is split further by coupling to the equatorial proton at C_4 through the carbonyl group (ref. 21, p. 121). The net result of these assumed couplings is a relatively broad peak. Bhacca and Williams[21] have cautioned against over-reliance on the vicinal coupling constants for determination of dihedral angles. Such practice is probably even more hazardous when one is dealing with protons alpha to a carbonyl group. Therefore, we did not attempt to evaluate the dihedral angles θ_1 and θ_2 from the coupling constants.



35

Normally the equatorial proton adjacent to a carbonyl resonates at a lower field than the axial one[22], but the assignment above is of the reverse order. A possible explanation is that the oxygen atom of the ketal group which bears a 1,3-diaxial relationship to H_a has a deshielding effect on

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(22) (a) N.S. Bhacca, J.E. Gurst, and D.H. Williams, J. Am. Chem. Soc., 87, 302 (1965); (b) A. Nickon, M.A. Castle, R. Harada, C.E. Berkoff, and R.O. Williams, ibid., 85, 2185 (1963).

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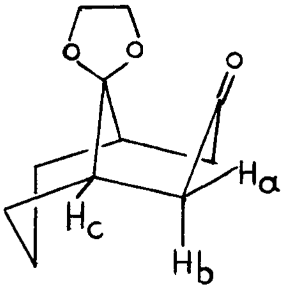
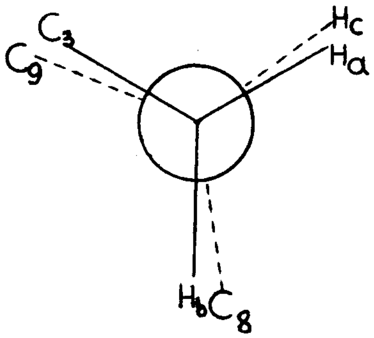
it. This effect has been observed with an axial hydroxyl group.[23]

Another interpretation assumes a chair-boat conformation (26b). The equatorial proton (H_a) is now assigned to the low-



26b

field quartet, and the axial proton (H_b) assigned to the up-field doublet. A Newman projection along the C_1-C_2 bond is shown as 36. Again, the coupling constants are in accord with



36

the magnitude of the dihedral angles.

The coupling constants are real and are not due to fortuitous benzene-induced chemical shift variations. This can be shown by the spectrum of 26 in deuterochloroform, which is

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(23) W.F. Trager, B.J. Nist, and A.C. Huitric, J. Pharm. Sci., 56, 698 (1967).

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almost identical to the one in benzene, except small changes in peak locations, and the coupling constants extracted are the same.

Although the nmr spectrum does not enable one to choose between the two possible structures, the twin-chair form is more likely. As we have seen, substitution of a methylene by a carbonyl group leads to a reduction in the transannular interaction of at least 1.2 kcal/mole (*vide supra*). It has also been noted that in some bicyclo[3.3.1]nonane derivatives the absence of an absorption band at 1490-1480 cm^{-1} has been attributed to the same cause.[24] The ir spectrum of **26** does not show any absorption in that region, in agreement with the above idea.

Further, the chair-boat (**26**b) has two eclipsed ethane-like units and possibly a quite severe dipole-dipole repulsion between the carbonyl oxygen and the ketal oxygen atom. Therefore, the transannular repulsion would have to be much greater than the sum of these two interactions to effect a predominance of **26b**. This is very unlikely and can be deduced from bicyclo[3.3.1]nonane (**1a**). It prefers the twin-chair form even though it suffers a greater transannular repulsion and has no dipole-dipole repulsion in the chair-boat form. The distortion is distributed throughout the molecule to minimize angular deformation. The total energy involved in deformation must then be smaller than that of the chair-boat form (**1b**).

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(24) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

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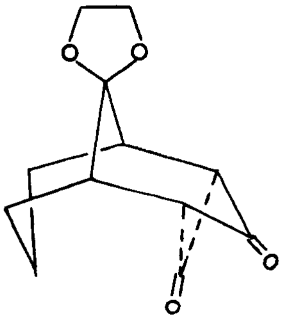
Indeed, Allinger and co-workers^{25} have calculated that **1b** is less stable than the flattened **1a** by 2.73 kcal/mole.

In **26a**, the flattening (dotted line to solid line) is probably not very severe, *i.e.* the angular deviation of the C_3 atom from the $C_1C_2C_4C_5$ plane is not less than 40° (in cyclohexanone^{26,27} the deviation is 50°). Allinger and Da Rooge^{28} have shown that a flattening of the cyclohexanone ring in 3-ketosteroids is accompanied by a decrease in the carbonyl stretching frequency. Based on their results and with the aid of models, we found that ring flattening, *i.e.* a decrease in the angular deviation of the carbonyl carbon from 50° to 39.5 $\pm 1^\circ$, is accompanied by a decrease of the carbonyl stretching frequency^{28} from 1706 to 1699 cm^{-1}. If one may use cyclohex-



26a

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(25) N.L. Allinger, J.A. Hirsch, M.A. Miller, I.J. Tyminski, and F.A. Van Catledge, *J. Am. Chem. Soc.*, **90**, 1199 (1968).

(26) C. Romers, *Rec. Trav. Chim. Pays-Bas*, **75**, 956 (1956).

(27) N.C. Webb and M.R. Becker, *J. Chem. Soc., B.*, 1317 (1968).

(28) N.L. Allinger and M.A. DaRooge, *J. Am. Chem. Soc.*, **84**, 4561 (1962).

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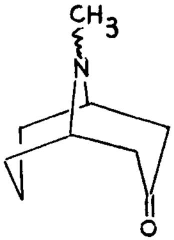
anone[29] (C = O stretching, 1716 cm^{-1}) as the reference, then the ketal ketone 26a (C = O stretching, 1718 cm^{-1}) is not appreciably deformed, if at all. Similar conclusions were reached in the cases of 10 and 37 from the fact that the ex-



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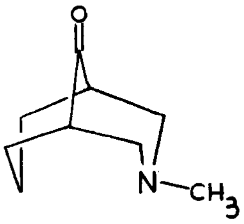

37

perimental dipole moments of these compounds agree very well with the calculated ones based on undistorted models.[30,31]

Application of the ir criterion to bicyclo[3.2.1]octan-3-one (38) predicts that the cyclohexanone ring is flattened (C = O stretching,[32] 1711 cm^{-1}). This prediction[31,33] is supported by a consideration of models and by experimental data.

---

(29) The influence of the ethylene ketal group on the carbonyl frequency is probably small since the 4-ethyleneketal of cyclohexane-1,4-dione shows carbonyl absorption at 1712 cm^{-1} (P. Yates and C.D. Anderson, *Can. J. Chem.*, *41*, 1033 (1963)). The reason that this compound is not used as the reference is that its conformation is unknown.

(30) J.M. Eckert and R.J.W. LeFevre, *J. Chem. Soc.*, 358 (1964).

(31) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, *Conformational Analysis*, Interscience Publishers, New York, N.Y., 1965, p. 247.

(32) B. Waegell and C.W. Jefford, *Bull. Soc. Chim. Fr.*, 844 (1964).

(33) C.W. Jefford and B. Waegell, *Tetrahedron Lett.*, 1981 (1963).

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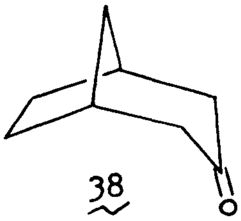
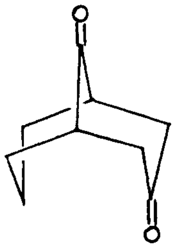


38

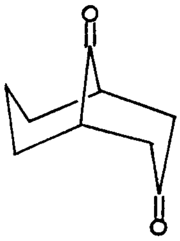
The Conformational Analysis of Bicyclo[3.3.1]nonan-3,9-dione

There are four possible conformations for bicyclo[3.3.1]-nonan-3,9-dione, shown below together with the calculated dipole moments.



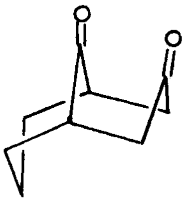
28a

ca. 0D



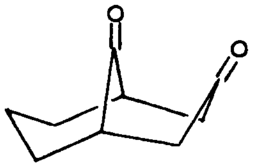
28b

ca. 0D



28c

4.72D



28d

4.72D

The experimental dipole moment of 28 is 1.62D in benzene and carbon tetrachloride solutions at 20°. Although this value does not leave one with a clear-cut choice, 28d may be eliminated from consideration on the basis that it has four eclipsed ethane-like units more than the twin-chair (28a) and two more than the chair-boat forms (28b and 28c).

Serious deformation of the cyclohexane-1,4-dione chair in 28b is not expected since whatever transannular interaction in the twin-chair is gone. Therefore, 28b alone cannot account

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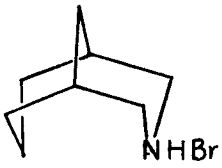
for the measured dipole moment. The experimental value, then, represents either a severely distorted 28a or an equilibrium mixture of 28a, 28b and 28c.

One of the arguments for the twin-chair form is, of course, that it has all the adjacent C-H and C-C bonds in a staggered arrangement (the eclipsing of the bridgehead hydrogens and the equatorial C_2 and C_4 hydrogens by the carbonyl groups is believed to be favourable^{19}). Also, the fact that a number of related compounds (3, 4, 5, 9, 10, and 37) as well as 26 from the discussion above, all prefer the twin-chair form, suggests the same conformation for 28 by analogy.



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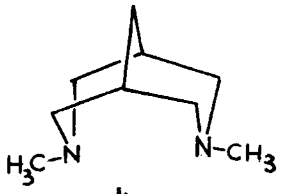

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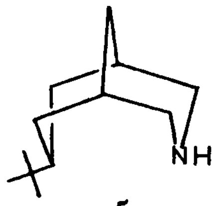

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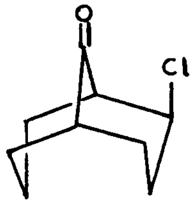

9

Now let us consider the arguments for an equilibrium mixture. Firstly, the ir spectra of 28 recorded with a KBr pellet and in carbon tetrachloride solution show almost identical absorption frequencies, but the band intensities in the 1300-1000 cm^{-1} region are significantly different. This may be interpreted as the result of the presence of more than one conformation in solution but only one conformation in the solid phase. The same phenomenon is observed in bicyclo[3.2.2]-nonan-6,8-dione which has two distinctly different conformations in equilibrium. Secondly the nmr spectrum of 28 shows

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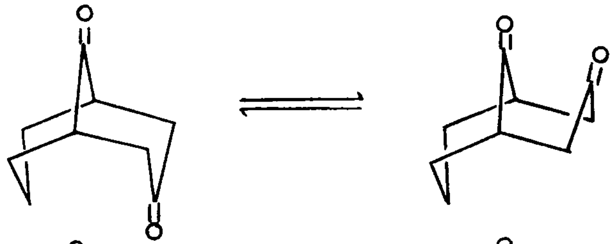
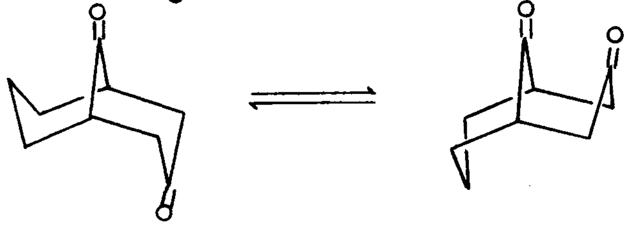
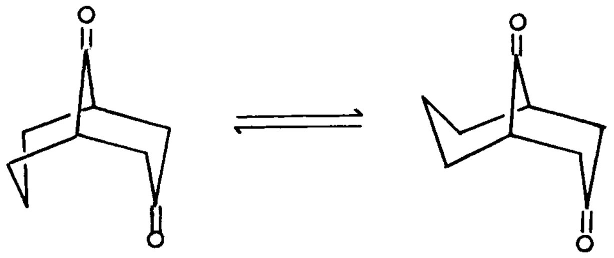
significant temperature dependence. The spectrum remains essentially unchanged from room temperature to -47°, but at -90°, the small peaks at τ6.90, 7.55 and 8.30 have become doublets (Fig. II-3). Although we are not able to make assignments to these peaks, it is clear that the temperature dependency implies the presence of a ring inversion process which becomes slower as the temperature is lowered (see also Part I). The ring inversion processes, as illustrated by equations II-1, II-2, and II-3, will explain this observation.


(II-1)


(II-2)


(II-3)

The first and second equilibrium processes will, of course, account for the experimental dipole moment, but with the third process (equation II-3), the twin-chair form will have to be very severely flattened (39). If one assumes the presence of 10% of 28b (to account for the temperature dependence), then the dipole moment of the distorted twin-chair

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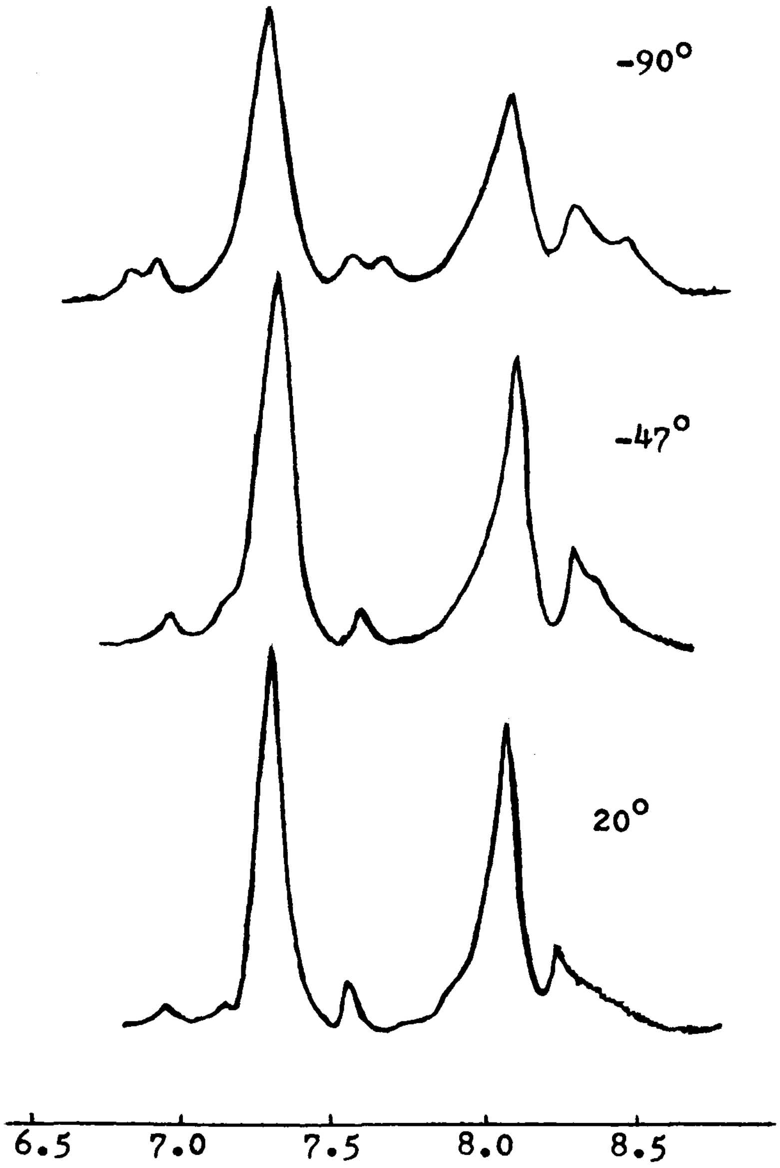

Fig. II-3

Nmr spectra of bicyclo[3.3.1]nonan-3,9-dione.
Temperature dependence.

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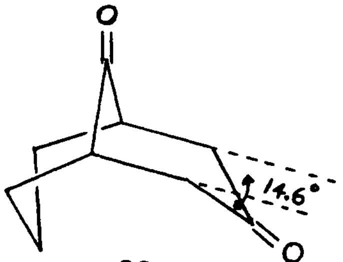
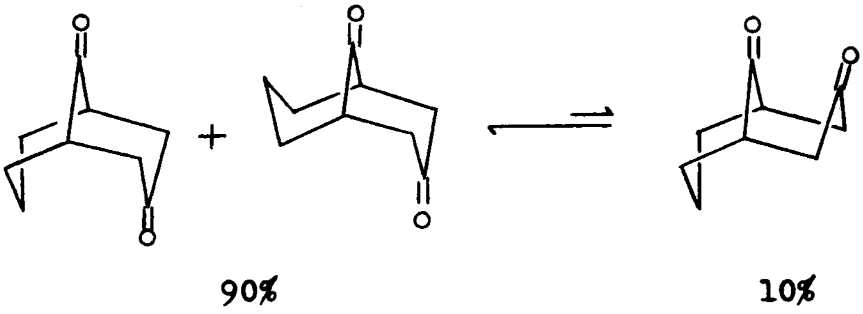
would have to be 1.78D. The C_3 atom now would be displaced from the $C_1C_2C_4C_5$ plane by 14.6° (39), an arrangement of high



39

energy. Even ignoring 28b, the angular deviation (18.6°) would be still too small. In the discussion on the conformation of 26, it was tentatively concluded that the bicyclo-[3.3.1]nonane skeleton is not appreciably deformed. One would expect the same here, and therefore a process involving 39 is unlikely.

After an examination of all possibilities we find that an equilibrium mixture of 28a, 28b and 28c (equation II-4) is most reasonable. We are unable to determine the percentage of



28b since it has the same calculated dipole moment as 28a.

It must be pointed out, in conclusion, that the postulation of 10% of 28c is contrary to conformational theory and is not based on unequivocal evidence. The only justification

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is that it is the most reasonable rationalization of our experimental data. We hope to obtain more definitive evidence for, or against, the postulated equilibrium process in the future.

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CHAPTER III

EXPERIMENTAL

Mass spectral analyses were performed by Morgan and Schaffer Corporation, Montreal. Dipole moments were calculated according to the method of Moll and Lippert[1] from the dielectric constants determined with a Wissenschaftlich-Technische Werkstätten (Germany) Dipolemeter DM01. Atom polarization was neglected throughout. Preparative glc columns were all of the same dimensions (8 ft x 0.5 in) and packed with 10% silicone gum rubber SE-30 or LAC-728, on Diatoport W, 80-100 mesh. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

The structures of all compounds reported are in accord with their ir and nmr spectra.

Diethyl Succinylsuccinate

Sodium hydride (0.2 mole, 9.6 g of 50% dispersion in mineral oil) was stirred in 80 ml of monoglyme (dried over sodium wire). *t*-Butyl alcohol (0.5 g) was added and the solution was heated at 60° until gas evolution ceased. Ethyl succinate (0.2 mole, 34.9 g) was added dropwise over a period of 0.5 hr. After addition was complete, the viscous slurry was stirred and heated at 60-65° for 12 hr. Sufficient cold 6*N* sulphuric acid was added to acidify the solution. The solid material was filtered and washed with petroleum ether and

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(1) F. Moll and E. Lippert, *Z. Elektrochem.*, *58*, 853 (1954).

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water. Upon recrystallization from ethanol, 37 g (75% yield) of light-yellow solid was obtained, m.p. 125.5-126.5° (lit.[2] m.p. 126-127°).

1,5-Dicarbethoxybicyclo[3.2.2]nonan-6,8-dione (12)

Sodium hydride (0.555 mole, 25 g of 53.5% dispersion) and diethyl succinylsuccinate (0.25 mole, 64 g) were added alternately in small portions to 500 ml of dry monoglyme. After all the reagents had been added, the slurry was heated at 100-110° for 3 hr. Monoglyme was removed *in vacuo* and 710 ml of 1,3-dibromopropane (freshly distilled) and 90 ml of monoglyme were added. Heating was continued for 22 hr. The mixture was filtered and the filtrate was steam distilled. The residue was allowed to cool with occasional shaking and crystallized from ethanol. The product was washed with 1% sodium hydroxide solution until the washing was no longer yellow. Subsequent washing with water, cold ethanol and petroleum ether, and recrystallization from ethanol gave 38.5 g (52%) of 12, m.p. 130-132.5° (lit.[3] m.p. 132°).

1,5-Dicarboxybicyclo[3.2.2]nonan-6,8-dione (13)

The diester 12 was hydrolyzed by refluxing with 6*N* hydrochloric acid for 8 hr. Two recrystallizations from water gave an analytical sample, m.p. (dec.) 245-247° (lit.[3] m.p. 238).

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(2) C.R. Hauser and B.E. Hudson, Jr., *Org. Reactions*, *1*, 283, (1942).

(3) P.C. Guha, *Chem. Ber.*, *72*, 1359 (1939).

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Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04.
Found : C, 54.88; H, 5.08.

1,5-Dibromobicyclo[3.2.2]nonan-6,8-dione (14)

A solution of the diacid 13 (5 mmoles, 1.2 g) in 20 ml of warm water was titrated to the end-point of phenolphthalein with 0.5N sodium hydroxide, and treated with 20% silver nitrate solution. The precipitate was filtered and repeatedly washed with water, methanol and ether. After drying in a vacuum desiccator for 24 hr, the disilver salt was mixed with 35 ml of carbon tetrachloride (dried over P_2O_5). Bromine (0.011 mole, 1.76 g, distilled from P_2O_5) was added dropwise with vigorous stirring. The solution was slowly heated to boiling and refluxed for 8 hr in the dark. The mixture was filtered and the filtrate distilled to give a residue which upon crystallization from a methanol-chloroform mixture gave 270 mg of 14, m.p. 181-184°, 19% yield. An analytical sample was obtained by recrystallization from a chloroform-carbon tetrachloride mixture, m.p. 184.5-185.5°.

Anal. Calcd for $C_9H_{10}O_2Br_2$: C, 34.88; H, 3.25; Br, 51.59.
Found : C, 34.88; H, 3.45; Br, 51.61.

Diketal of 1,5-Dibromobicyclo[3.2.2]nonan-6,8-dione (15)

The diketal 15 was prepared by refluxing 14 (3.6 g, 11.6 mmoles) with 0.5 g of p-toluenesulphonic acid and 5 ml of ethylene glycol in 20 ml of benzene for four days. The benzene solution was washed with 5% sodium hydroxide and water. After removal of the solvent, the residue was crystallized from a hexane-ethanol mixture to give 3.47 g (75%) of 15, m.p. 127-

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130°. Two more recrystallizations gave an analytical sample, m.p. 128.5-130°.

Anal. Calcd for $C_{13}H_{18}O_4Br_2$: C, 39.22; H, 4.56; Br, 40.15.
Found : C, 39.43; H, 4.54; Br, 39.96.

Diketal of Bicyclo[3.2.2]nonan-6,8-dione (16)

Sodium (6.8 g) was added in small pieces over a period of 2 hr to a well-stirred solution of 15 (3.27 g, 8.2 mmoles) in 110 ml of absolute ethanol. Precipitation of sodium bromide was observed when about one-quarter of the sodium had been added. The solution was cooled and poured into 600 ml of water and was extracted with five 100-ml portions of 1:1 mixture of petroleum ether and ether. The solvents were removed after drying to give a yellow oil which solidified on standing. Preparative glc (silicone gum rubber) gave 16 in 53% yield, m.p. 63-64.2°.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39.
Found : C, 65.17; H, 8.31.

Hydrolysis of 16

The diketal 16 (430 mg, 1.8 mmoles) and 6 ml of 1.2N hydrochloric acid was refluxed for 7 hr. The solution was poured onto 15 g of ice and extracted with methylene chloride. After washing with a 10% sodium bicarbonate solution and drying, the solvent was evaporated to give 290 mg (79%) of bicyclo[3.2.2]nonan-6,8-dione (11). The crude product was purified by sublimation (85°/5 mm) to give 215 mg of pure material, m.p. (sealed tube) 218-223°. This sample was shown to be pure by glc and tlc (silica gel). Multiple recrystal-

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lizations from various solvents and sublimations did not narrow its broad melting range.[4]

Anal. Calcd for $C_9H_{12}O_2$: C, 71.10 ; H, 7.95.
Found : C, 70.85; H, 7.86.

The disemicarbazone of **11** melts at 277.5-279°.

Anal. Calcd for $C_{11}H_{18}O_2N_6$: C, 49.61; H, 6.81; N, 31.56.
Found : C, 49.66; H, 7.00, N, 31.86.

Decarboxylation of 1,5-Dicarboxybicyclo[3.2.2]nonan-6,8-dione

(a) The diacid **13** (0.5 g) was placed in a sublimator which was quickly heated to 240-245° in an oil bath. The solid melted with evolution of gas and a light-yellow solid began to collect on the coldfinger. Reaction was complete after 15 min. Recrystallization from ether afforded 61 mg of impure **11**, m.p. (sealed tube) 194-212°. Purification was achieved by conversion of **11** to its diketal (**16**). A sample obtained this way is identical in every respect (ir, nmr, glc, m.p.) to that obtained previously.

(b) A solution of **13** (24 g, 0.1 mole) and 300 ml of triglyme was refluxed for 5 hr (temperature of the solution was 210-218°). Evolution of carbon dioxide was followed by the weight increase of an ascarite tube. The reaction became very slow after 3 hr of heating. At the end of 5 hr, the weight of carbon dioxide generated indicated a conversion of 80% of diacid to **11**, while glc showed 81.5% yield. The triglyme solu-

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(4) Similar melting behaviour was observed in tricyclo[4.4.0.$0^{4,9}$]decan-3-one. J. Gauthier and P. Deslongchamps, Can. J. Chem., **45**, 297 (1967).

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tion was poured into 2.5 litres of benzene and extracted with five 1-litre portions of water. Benzene was removed after drying to give a heavy oil which upon treatment with pentane gave a crystalline solid and a gummy material. The solid was dissolved in methanol and filtered to remove the gummy material. Evaporation of methanol and recrystallization from a hexane-benzene mixture afforded 16.1 g of **11**. One sublimation gave 13.9 g (62%) of pure material.

1-N-Pyrrolidylcyclohexene

The pyrrolidine enamine of cyclohexanone was prepared by the method of Stork[5], b.p. 93-95°/5 mm (lit.[5] b.p. 105-107°/ 13 mm).

Bicyclo[3.3.1]nonan-2,9-dione (**30**)

2-Hydroxybicyclo[3.3.1]nonan-9-one[6] (3.2 g) in 20 ml of acetone was stirred and cooled in an ice-bath. Jones reagent (5 ml) was added dropwise and the solution stirred for 0.5 hr. The solution was diluted with water and extracted with four 50-ml portions of ether. Evaporation of ether and purification by sublimation gave 1.1 g of broad melting waxy solid.[7]

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(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, J. Am. Chem. Soc., **85**, 207 (1963).

(6) The author is grateful for a generous gift of this compound from Mr. C. Barker who prepared it by the method of Cope et. al. (A.C. Cope, D.L. Nealy, P. Scheiner, and G. Wood, ibid., **87**, 3130 (1965).

(7) This compound has been reported variously as a heavy oil, waxy solid, and crystalline solid which melts at 110°. See ref. 8, and W. Hickmott and J.R. Hargraves, Tetrahedron, **23**, 3151 (1967).

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Axial-2-tosylbicyclo[3.3.1]nonan-9-one (31b)

The keto alcohol 29 which was a mixture of axial and equatorial isomers was sublimed at 90-100°/0.2 mm. The white solid (m.p. 166-169°, lit.[8] m.p. 169-171°) was shown by tlc (silica gel, 2% methanol in carbon tetrachloride as developing solvent) to be almost pure 31a. The tosylate was prepared in the usual manner and was recrystallized twice from methanol, m.p. 121-122.5° (lit.[8] m.p. 122-123°).

Δ^2-Bicyclo[3.3.1]nonen-9-one (32)

The tosylate 31b (0.5 g) was refluxed with 10 ml of monoglyme and 0.1 g of sodium methoxide for 24 hr. The solution was diluted with water and extracted with ether. The solvent was evaporated after drying to give 45 mg of crystalline solid (32) which was purified by sublimation, m.p. (sealed tube) 97-98° (lit.[9] m.p. 98-99°).

The ether-insoluble material was taken up in methylene chloride. After drying and removal of the solvent, 350 mg of starting material was recovered.

2-(N-Pyrrolidyl)bicyclo[3.3.1]nonan-9-one (21)

The procedure of Hanack *et. al.*[10] was followed, b.p. 101.5-103/0.03 mm (lit. b.p. 155-158°/15 mm).

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(8) J. Martin, W. Parker, B. Shroot, and T. Stewart, *J. Chem. Soc., C*, 101 (1967).

(9) C.S. Foote and R.B. Woodward, *Tetrahedron*, *20*, 687 (1964).

(10) M. Hanack, W. Kraus, W. Rothenwohrer, W. Kaisen, and G. Wentrup, *Ann. Chem.*, *703*, 44 (1967).

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Ethyleneketal of 2-(N-Pyrrolidyl)bicyclo[3.3.1]nonan-9-one (**22**)

The amino ketone **21** (0.174 mole, 36 g), ethylene glycol (108 g), and *p*-toluenesulphonic acid (0.192 mole, 36.5 g) were heated in an oil bath at 85-90° for 3 hr. After cooling to room temperature, the solution was poured into 650 ml of cold water containing 30 g (0.53 mole) of potassium hydroxide. The yellow oil was separated and the aqueous solution extracted with ether. The combined organic phase was dried and the solvent was evaporated. The residue was distilled to give 35.6 g (82%) of **22**, b.p. 100-108°/0.03 mm, $n_D^{22.2}$ 1.5180.

Ethylene ketal of Δ^2-bicyclo[3.3.1]nonen-9-one (**23**)

The amino ketal **22** (35.6 g, 0.14 mole) in 50 ml of methanol was treated with 125 g (0.52 mole) of 30% hydrogen peroxide. After stirring for 2 hr, the solution was no longer basic to phenolphthalein. Platinum black (20 mg) was added to decompose excess peroxide. Stirring was continued for two days and the platinum black was removed by filtration. Most of the methanol and water were removed by a rotary evaporator (40-45°), and finally with an oil pump at 3.5 mm, giving an amber solid. The temperature of the oil bath was raised to 115-120°, during which time the solid slowly melted and eventually thickened to a very viscous paste. The temperature of the oil bath was quickly raised to 160° and held at this temperature for 3 hr. The pyrolysate was collected in an acetone-dry ice trap. Water (200 ml) was then added and the content of the pyrolysis flask steam distilled. The pyrolysate and distillate were combined and extracted with 150 ml

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of ether. After washing with 1*N* hydrochloric acid and drying, the ether was evaporated. Distillation of the residue afforded 13 g (50%) of 23, b.p. 103-110°/8 mm (lit.[9] b.p. 98-109°/12 mm).

Hydroboration of 23

(a) With Sodium Borohydride and Methyl Iodide

The olefin 23 (5 g) and 2 g of sodium borohydride in 50 ml of diglyme were treated with a solution of methyl iodide (2.5 ml) and 20 ml of ether over a period of 1.25 hr. After stirring for 3 hr, 10 ml of water were added cautiously followed by 10 ml of 3*N* sodium hydroxide and 20 ml of 30% hydrogen peroxide. The solution was diluted with 300 ml of water and extracted with six 50-ml portions of ether. The ether layers were combined and washed with four 200-ml portions of water and dried. Removal of ether gave 2.2 g of oil. Glc analysis (6 ft x 0.25 in, 10% carbowax 20 M) showed that the product consisted of 60% of 24a and 30% of 25a.

(b) With Diborane

The olefin 23 (12.6 g, 70 mmoles) was added dropwise to 150 ml of anhydrous tetrahydrofuran (cooled in an ice-bath) containing 40 mmoles of diborane (generated from sodium borohydride and boron trifluoride etherate). The reaction was followed by glc. After 2 hr of stirring, 10 ml of water was added followed by 15 ml of 3*N* sodium hydroxide and 15 ml of 30% hydrogen peroxide. The solution was saturated with potassium carbonate and the organic layer was separated. The aqueous layer was extracted with two 100-ml portions of

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tetrahydrofuran. The combined organic layer was dried and the solvent was evaporated. The oil (11.8 g, 84%) thus obtained consisted of 44% of **24a** and 52% of **25a**.

Alumina Column Chromatography of Hydroboration Product

A column (2.5 x 23 cm) was prepared with 90 g of alumina (neutral, Brockman activity I) in hexane. The hydroboration product (6.2 g) was introduced as a hexane solution. Elution with hexane and 10% benzene in hexane gave **24a** contaminated with a small amount of **25a**. Further elution with benzen-hexane mixtures, benzene, and benzene-ether mixtures afforded almost pure **25a** (3.3 g). Recrystallization from petroleum ether-benzene and petroleum ether-carbon tetrachloride mixtures gave pure **25a**, m.p. 66.1-66.7°.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.68; H, 9.08.
Found : C, 66.47; H, 9.09.

The impure **24a** was re-chromatographed in the same manner to give a colourless oil. A sample was further purified by preparative glc (LAC-728).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.68; H, 9.08.
Found : C, 66.52; H, 9.04.

The hydroboration product was converted to two isomeric acetates by stirring it with pyridine and acetic anhydride at room temperature. The acetates were separated by preparative glc (LAC-728). The component of shorter retention time was shown to be **24b** by lithium aluminum hydride reduction. The second component was similarly reduced to **25a**.

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Oxidation of 25a

The alcohol **25a** (240 mg) in 5 ml of acetone (cooled in an ice-bath) was treated with 0.5 ml of Jones reagent. After work-up as in the preparation of **30**, 180 mg of **26** was obtained. Recrystallization from hexane afforded a pure sample, m.p. 50-50.5°.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.37; H, 8.16.
Found : C, 67.63; H, 7.94.

Oxidation of 24a

In a similar manner 1.177 g of **24a** was oxidized to give 840 mg of light-yellow oil (**27**). A sample was purified by preparative glc (LAC-728) but did not give a satisfactory analysis.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.36; H, 8.16.
Found : C, 66.39; H, 7.95.

This sample was probably contaminated by water.

Acid Hydrolysis of 27

The ketone **27** (600 mg) was refluxed with 1*N* hydrochloric acid for 3 hr. Extraction with methylene chloride afforded a white solid. Recrystallization from a hexane-carbon tetrachloride solvent pair gave 400 mg of 2-(β-propionic acid)cyclohexanone, m.p. 63-64° (lit.[8] m.p. 60-62°). Bicyclo[3.3.1]-nonan-2,9-dione when treated in the same way gave the same product.

Bicyclo[3.3.1]nonan-3,9-dione (28)

The ketone **26** (2.79 g) was refluxed with 50 ml of 1*N*

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hydrochloric acid for 4 hr. The solution was extracted with four 10-ml portions of methylene chloride. After washing with 10% sodium bicarbonate solution, the solvent was evaporated to give 1.8 g of crude **28**. Two sublimations (80-90°/2.5 mm) followed by two recrystallizations from hexane-benzene mixture gave pure **28**, m.p. (sealed tube) 202-205.2°.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95.
Found : C, 71.25; H, 8.02.

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Conformational analysis of *trans*-1,4-dihalocyclohexanes, G.W. Wood and E.P. Woo, *Can. J. Chem.*, **45**, 2477 (1967).

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