Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.91. Found: C, 73.78; H, 8.81; N, 3.91.

3β-Acetoxy-5-androstene-17-one (VI).—Either IV or V (0.2 g.) was heated at reflux for an hour with 3 ml. of 80% aqueous pyridine. The reaction mixture was diluted with a large excess of water and the crystalline product filtered which yielded, after drying, 0.16 g. of product, m.p. 167–170°. The mixed melting point with an authentic sample remained unaltered.

17-Iso-5-pregnene-3β,17β-diol-20-one (IX).—A solution of 4.5 g. of 3β-acetoxy-17α-cyano-17β-(2′-tetrahydropyranyloxy)-5-androstene (II) in 75 ml. of anisole was treated with 130 ml. of an ethereal solution of methylmagnesium bromide (obtained from 9 g. of magnesium). The ether was removed and the reaction mixture held at 95° for 18 hours. After decomposition with 180 ml. of acetic and 140 ml. of water, the mixture was heated at reflux for 15 minutes and the solvent was removed by steam distillation. The aqueous suspension was filtered and the product recrystallized from methanol to yield 2.65 g. of material, m.p. 175–177°, $(\alpha)_D -58°$.[7]

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.81; H, 9.68.

17aβ-Methyl-D-homo-5-androstene-3β,17aα-diol-17-one (**X**) was obtained from the preceding substance IX by treatment with KOH; m.p. 275°, $(\alpha)_D -108°$ (diox.).[8,9]

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H. 9.70. Found: C, 75.78; H, 9.73.

5-Pregnene-3β,17α-diol-20-one (XI).—To a solution of 4.5 g. of the oily 3β-acetoxy-17β-cyano-17α-(2′-tetrahydropyranyloxy)-5-androstene (III) in 75 ml. of anisole was added 130 ml. of an ethereal solution of methylmagnesium bromide (from 9 g. of magnesium). The ether was removed and the reaction mixture held at 95° for 18 hours. After decomposition with 180 ml. of acetic acid and 140 ml. of water, the mixture was refluxed for 15 minutes and then the solvent removed by steam distillation. The residual aqueous suspension was filtered and the product, crystallized from acetone, yielded 2.5 g. of 5-pregnene-3α,17α-diol-20-one (XI) with m.p. 265–267°, $(\alpha)_D -36°$ (diox.)[10]; the melting point remained unchanged when mixed with an authentic sample.

3β-Acetoxy-5α,6α-epoxy-17-cyanoandrostane-17-ol (XIII).—In 40 ml. of freshly prepared acetone cyanohydrin[17] was dissolved 10.0 g. of 3β-acetoxy-5α,6α-epoxy-androstane-17-one (XII)[12] while stirring and heating lightly. After allowing the reaction to stand for 2 hours, the product, partially crystallized, was completely precipitated by dilution with water, filtered and dried in vacuum. In this manner was obtained 10.58 g. of compound, m.p. 178–180° dec., $(\alpha)_D -61°$.

Anal. Calcd. for $C_{22}H_{31}O_4N$: C, 70.75; H, 8.36; N, 3.75. Found: C, 70.82; H, 8.35; N, 3.78.

3β-Acetoxy-5α,6α-epoxy-17-cyano-17-(2′-tetrahydropyranyloxyandrostane) (XIV).—Ten grams of 3β-acetoxy-5α,6α-epoxy-17-cyano-androstane-17-ol (XIII) was treated with 40 ml. of 2,3-dihydropyran and 200 mg. of *p*-toluenesulfonic acid for 2.5 hours at the boiling point. The solution was diluted with ether, washed with aqueous solution of sodium carbonate, water, and the solvent removed by vacuum distillation. The residue, crystallized with ether, gave 8.9 g. of material, m.p. 183–186°, $(\alpha)_D -48°$.[14]

Anal. Calcd. for $C_{27}H_{39}O_5N$: C, 70.86; H, 8.59; N, 3.06. Found: C, 71.01; H, 8.55; N, 3.11.

6β-Methylpregnane-3β,5α,17α-triol-20-one (XVI).—A solution of 3 g. of 3β-acetoxy-5α,6α-epoxy-17-cyano-17-(2′-tetrahydropyranyloxy)-androstane (XIV) (mixture of α- and β-epimers) in 70 ml. of anisole was treated with 150 ml. of an ethereal solution of methylmagnesium bromide (from 10 g. of magnesium) for 2 days at room temperature. After the ether was evaporated, the mixture was heated at 95° for 18 hours. The reaction mixture was decomposed with 200 ml. of acetic acid and 160 ml. of water and refluxed for 15 minutes, after which the solvent was removed by steam distillation. The aqueous suspension was filtered and the product crystallized several times from acetone yielding 0.97 g. of material, m.p. 247–249°, $(\alpha)_D -34°$.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.48; H, 9.95. Found: C, 72.51; H, 9.98.

6β-Methylpregnane-5α,17α-diol-3,20-dione (XVII).—A solution of 0.5 g. of 6β-methylpregnane-3β,5α,17α-triol-20-one (XVI) in 5 ml. of pyridine was added at room temperature to the pyridine–chromic acid complex obtained from 0.5 g. of chromic acid in 5 ml. of pyridine[15] and left at the same temperature overnight. After dilution with water and filtration, the product was crystallized from methylene chloride–acetone and 0.39 g. was obtained with m.p. 270–273°, $(\alpha)_D -6°$[11]; the melting point remained unaltered in mixture with an authentic sample obtained by other means.

6α-Methyl-17α-hydroxyprogesterone (XVIIIa).—A suspension of 0.3 g. of 6β-methylpregnane-5α,17α-diol-3,20-dione in 24 ml. of ethanol was brought to the boiling point and 0.3 ml. of concd. HCl added, with continued boiling. After about 20 minutes, the insoluble product went into solution and the heating was prolonged for one hour in total. The reaction mixture was then concentrated under vacuum to one-third its volume and subsequently diluted with water. The crystalline product was filtered and dried to yield 0.23 g. of 6α-methyl-17α-hydroxyprogesterone (XVIIIa), m.p. 218–222°, $(\alpha)_D -73°$, λ_{max}^{EtOH} 241 mμ (16,000).[11]

MILAN, ITALY

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(17) *Org. Syntheses*, **20**, 43 (1940).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Conformational Analysis. III. Applications to Some Medium Ring Compounds[1,2]

BY NORMAN L. ALLINGER

RECEIVED MARCH 26, 1959

A simple potential function derived from the rotational barrier of ethane has been assumed to hold in cyclic compounds. Using this function, together with values for the dihedral angles as obtained from direct measurements on scale models, the enthalpies of various conformations have been calculated for the flexible ("boat") form of cyclohexane, for cycloheptane, cycloöctane, the corresponding ketones and a few selected related compounds. The preferred conformation in each case is predicted, and the agreement with the experimental heats of combustion and other data is in all cases reasonable.

Introduction

Although the conformational analysis of cyclohexane rings has been quite extensively pursued,[3] no similar detailed studies have been made in rings of other sizes. The chair form of cyclohexane is unique in that the dihedral angles of the substituents are an optimum 60°. There is also good reason to believe that the six-membered chair also differs from most other simple rings in being rigid,

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(1) This work was supported by a research grant from the National Science Foundation.

(2) Paper II, N. L. Allinger and J. Allinger, THIS JOURNAL, **80**, 5476 (1958).

(3) For recent reviews see the following: (a) W. G. Dauben and K. S. Pitzer in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 1; (b) W. Klyne, in "Progress in Stereochemistry," Vol. 1, Academic Press, Inc., New York, N. Y., 1954, p. 36; (c) D. H. R. Barton and R. C. Cookson, *Quart. Revs.*, **10**, 44 (1956).

that is, it lies in a deep potential well and cannot flex in any way except by bending bond angles. It has been calculated that to convert to the flexible form or to the inverted chair the cyclohexane ring must surmount a 7–10 kcal. energy barrier.[4] This high barrier formally puts the molecule in quite a separate class from all other simple ring compounds larger than cyclopropane.

The six-membered "flexible form" and the simple cycloalkane rings containing seven or more carbons do not show this rigidity. They may undergo violent conformational changes by changing the dihedral angles while keeping the bond angles constant, and the energy differences between conformational isomers are usually only a fraction of a kilocalorie.

There are several difficulties which stand in the way of precise calculations of the conformations of the larger rings. The principal difficulty can be visualized in this way. If one of the larger rings is considered as a collection of points (carbon atoms) with 109° bond angles and 1.54 Å. bond lengths, and if all potentials between non-bonded atoms are neglected, then there are an infinite number of conformations the ring may assume. When the potentials between all atoms are taken into account and only conformations which lie at potential minima are considered, it may be presumed that only a relatively small number of such conformations will exist. Even this "relatively small number" increases rapidly with ring size and has necessitated limiting the detailed aspects of the present work to rings which contain no more than eight atoms, although a cursory examination of the ten- and twelve-membered rings was also made.

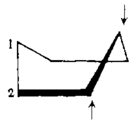
To decide where the potential minima for the molecule are, it is necessary to know the interaction potential of every atom in the molecule with every other atom in the molecule in every possible conformation. Further, the interaction potentials between bound hydrogen atoms, which are overwhelmingly important here, are very imperfectly known.[5,6]

While rigorous theoretical solutions to the conformational problems presented by the medium rings are desirable, they do not now seem feasible. The development of a simplified theory by making use of a few rather severe assumptions would therefore appear timely, and such a theory is outlined in this paper. Experimental tests of certain of the predictions made by the theory have been devised and carried out, and the results will be discussed in subsequent papers.

Discussion

The flexible form of the six-membered ring was quite well described by the elegant work of Hazebroek and Oosterhoff.[7] Their approach, with suitable modification, appears to be applicable to the two forms of the seven-membered ring in which each form is also limited to a one-dimensional pseudo rotation, but it would loose its attractiveness with the more flexible larger rings.

The approach taken in this paper was to utilize actual models[8] and to measure dihedral angles (ϕ) directly by projection on a protractor. The procedure is equally applicable to the flexible form of the six-membered ring, and to the seven- and eight-membered rings. The method employed herein is straightforward, and is illustrated for the six-membered flexible form. A model of I was made and the dihedral angles were measured. The energy of the whole molecule was then found by summing the energies for each angle as calculated from the potential function. The model was next deformed a little way toward II and the measurements and calculations were repeated. The model was then deformed further in the same direction, and the measurements and calculations were again repeated and so on. Finally a plot was made of the energy of the molecule as a function of conformation I to II.



I

II


III

The hydrogen–hydrogen repulsions for each conformation were divided into three groups: (1) those between hydrogens on carbons which were bound together: (2) those between hydrogens on non-adjacent carbons which were small enough to be neglected: (3) those between hydrogens on non-adjacent carbons which were assumed infinite. All of the hydrogens on non-adjacent atoms are as a first approximation assumed either to fall into group 2 and are neglected or to fall into group 3 in which case the entire conformation may be neglected. The division of hydrogens between groups 2 and 3 was accomplished with the aid of Catalin scale models and questionable cases are discussed individually.

For a given conformation, the repulsions of group 1 may be calculated only if we know the potential function for the rotation about the central bond of a tetramethylene chain and can allow for the "end" effects in this rotation. The necessary potential function for the rotation about the central

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[4] (a) W. D. Kumler, This Journal, **67**, 1901 (1945); (b) C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946); C. W. Shoppee, *Ann. Rept.*, **43**, 200 (1946).

[5] (a) I. Dostrovsky, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 173 (1946); (b) F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.*, **14**, 733 (1946); (c) D. H. R. Barton, *J. Chem. Soc.*, 340 (1948); (d) K. E. Howlett, *ibid.*, 4353 (1957).

[6] E. A. Mason and M. M. Kreevoy, This Journal, **77**, 5808 (1955).

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

[8] The models used for accurate measurements were designed and constructed by Mr. Robert Hermann in this Laboratory. They consisted of metal tubes about 3" long, into the ends of which heavy wire bent to appropriate angles was inserted. The wire turned smoothly inside the tube. A drop of candle wax was placed on each angle to hold the model rigid. After completing the measurements on one conformation the angles were warmed and the model was twisted into a new conformation and allowed to set. The dihedral angles could be measured by projection to an accuracy of about 2°. In conjunction with these models, a set of Catalin Scale models were also used so that transannular hydrogen–hydrogen repulsions could be taken into account. Dihedral angles could be measured with these models by means of a paper protractor inserted between the atoms. The accuracy in this case was perhaps 3–4°. The accuracy to which the enthalpies could be estimated are in part limited by the accuracy of the models, and the error thus introduced is estimated to be 0.4 kcal. or less with the six-membered ring but increasing with ring size to perhaps 2 kcal for the 10- and 12-membered rings.

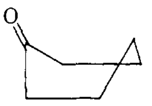
bond of a tetramethylene chain is not unambiguously known. The potential function for the rotation of *n*-butane about its central bond is also only partly known,[3a] and is probably somewhat different. Various functions have been used to describe the rotation of a tetramethylene chain, and for the present work the function (1) with $V_0 = 2.8$ kcal. was chosen as most realistic.[9]

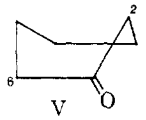
$$E = \frac{V_0}{2}(1 + \cos 3\phi) \qquad (1)$$

Function (1) adequately describes the internal rotation of ethane. A similar value for V_0 (2.8 kcal.) was considered earlier by Spitzer and Huffman[9] as yielding a predicted heat of combustion much higher than that found experimentally. They concluded that either a lower barrier (1.9 kcal.) should be used, or else the shape of the barrier should be changed by adding another term to the series expansion. The shape of the potential curve has been often discussed,[6,10] and there would seem to be available at present no compelling evidence for other than the simple cosine curve. The most recent ideas on the nature of the barrier[11] would suggest 2.8 kcal. is more appropriate here than 1.9 kcal. The present work leads to more reasonable conclusions when a barrier height of 2.8 kcal. is used, and the cycloöctane case of Spitzer and Huffman can be reconciled with this value.

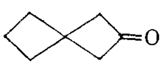
The Six-membered Ring.—The flexible form of the cyclohexane ring will be examined first, as it is the most simple and the results may be compared with those of Hazebroek and Oosterhoff.[7] If we begin with the regular boat I and imagine that we push on the indicated atoms, we obtain another boat, II. Because of symmetry, the only conformations we need to consider are those which form the family intermediate between I and II.

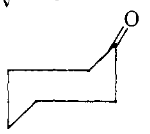
The energy of the "flexible" form at the potential minimum (skewed form III) as found in this way was 5.1 kcal., which is somewhat less than the amount usually quoted as the energy of the "boat" form (5.6 kcal.).[3] The actual regular boat structure (I) was found to lie at a potential maximum with an energy of 5.6 kcal. In fact, the energy in the regular boat form may be somewhat higher than the calculated value because of the 1,4-hydrogen–hydrogen repulsions, but such interactions are probably unimportant in the skew form. Hazebroek and Oosterhoff used a value for V_0 of 2.75 kcal., and obtained energies of 4.75 and 5.25 kcal., respectively, for the skew and boat forms, so the agreement between the two sets of calculations is good.


IV



V


VI


VII

When cyclohexanone, as opposed to cyclohexane, is considered, the results are somewhat different. There are three conformations for the flexible form of cyclohexanone which need to be examined (IV, V and VI) relative to the single chair conformation (VII). The keto-oxygen in VII very nearly eclipses the equatorial hydrogens on the adjacent carbons. If the energy of such an interaction is taken to be 0.8 kcal. per hydrogen eclipsed,[12] structures IV and VII each have their steric energies increased (relative to cyclohexane) by 1.6 kcal. Structure V has increased the energy by 0.8 kcal. from eclipsing the hydrogen at carbon 2, but the relief of the eclipsing at carbon 6 has lowered the energy by 1.6 kcal. Hence V should be of lower steric energy relative to the chair by 0.8 kcal. than the regular boat in the hydrocarbon system. The difference in energy between VII and V should therefore be $5.1 - 1.6 - 0.8 = 2.7$ kcal. If V is now skewed toward VI to eliminate the transannular interaction the best arrangement of the flexible form is obtained, and its energy relative to the chair is probably close to this value.

This predicted energy difference between the boat and chair forms of cyclohexanone would lead at room temperature to a mixture which would contain at most a few per cent. of the boat form. This conclusion is of interest in connection with various studies that have been reported on the conformation of 2-bromocyclohexanone.[14] Kumler and Huitric suggested that 2-bromocyclohexanone might exist largely in the flexible form, but proof of such a situation was not obtained. The experimental findings were later shown to be interpretable in terms of only chair forms.[2,13] The single case in which an α-halo ketone has been shown to prefer to be in the flexible form[15] is one in which a chair form would require a bromine and two methyls to all be in axial positions on the same side of the ring. In a solvent such as carbon tetrachloride, the energy of a bromine axial at carbon 2 in structure VII was less than that of the equatorial conformer by 0.6 kcal.[13] Thus 2.0 kcal. in enthalpy separates the chair form with an equatorial bromine and the skewed boat form with an axial bromine. Models suggest that VIII and X are

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[9] R. Spitzer and H. M. Huffman, THIS JOURNAL, **69**, 211 (1947).

[10] (a) K. S. Pitzer and J. L. Hollenberg, *ibid.*, **75**, 2219 (1953); (b) K. S. Pitzer, *Discussions Faraday Soc.*, **10**, 66 (1951).

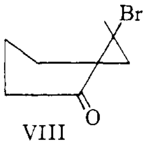
[11] (a) E. B. Wilson, Jr., *Proc. Natl. Acad. Sci.*, **43**, 816 (1957); (b) L. Pauling, *ibid.*, **44**, 211 (1958).

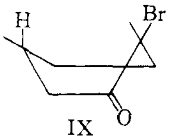
[12] This value is arrived at by assuming that the steric effect of the oxygen should be similar to that of a hydrogen, and the eclipsing is not quite exact (ref. 13). Some justification for this value is obtained from a comparison of the difference in the heats of combustion of acetone and propane with the corresponding difference between cyclohexanone and cyclohexane. The heats of hydrogenation of acetone and cyclohexanone lead to the same qualitative conclusion (for a summary and discussion of this data, see H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954)). These methods suggest, respectively, that the eclipsing energy per equatorial hydrogen adjacent to the carbonyl should be 0.4 and 1.0 kcal. On the other hand, the height of the potential barrier to rotation in acetaldehyde as determined by microwave spectra (R. W. Kilb, C. C. Lin and E. B Wilson, Jr., *J. Chem. Phys.*, **26**, 1695 (1957)) suggests this energy amounts to −0.2 kcal. The value used in the present work can be reconciled with the thermal data, which seems like the better analogy.

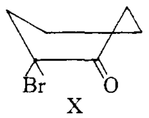
[13] J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).

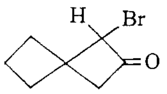
[14] (a) E. J. Corey, THIS JOURNAL, **75**, 2301 (1953); (b) W. D. Kumler and A. C. Huitric, *ibid.*, **78**, 3369 (1956).

[15] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem Soc.*, 2907 (1957).


VIII

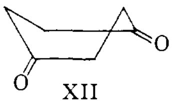

IX

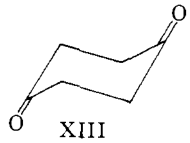

X

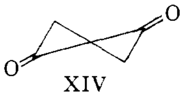

XI

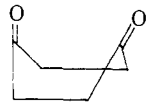
electrostatically unfavorable as the bromine is (approximately) equatorial. In IX the transannular bromine–hydrogen interaction is probably sizeable as the Catalin model cannot be made without considerable angular distortion. A structure such as XI in a somewhat skewed modification with the C—Br dipole twisted further away from the C=O dipole would appear to be the best arrangement of the flexible form. The angle between dipoles is roughly the same as for the axial chair structure. It would therefore seem that the amount of material in the flexible form in 2-bromocyclohexanone is small. If, as an approximation, the probable small difference in entropy between the different forms is neglected, 2-bromocyclohexanone in carbon tetrachloride can be calculated to be 72% chair with the bromine axial, 27% chair with the bromine equatorial and 1% flexible, mainly XI.

We may also consider 1,4-cyclohexanedione in the light of the foregoing discussion. Structure XII would have an energy with respect to XIII (proceeding as for cyclohexanone) of $5.0 + (-1.6 - 0.8)(2) = 0.2$ kcal. Actually XII is one extreme of the flexible form, XIV and XV are other extremes. Boat form XV, with two pairs of eclipsed atoms, is quite unfavorable and the flexible form is probably most stable as XIV. Structure XII is probably at a small energy maximum and the flexible form oscillates between XII and XIV by pseudo rotation. The LeFevre's have interpreted[16] the Kerr constant of 1,4-cyclohexanedione as indicating that the compound existed as a mixture of XII and XIII containing 80% of the latter, and the dipole moment measurements appeared consistent with this interpretation. Forms XIII and XIV may well show apparent moments of the order of several tenths of a Debye from the "atomic orientation polarization" which may be expected[17] for these structures. Consequently, the observed apparent moment can be accounted for by having present only a few % of XII, or, more likely, a correspondingly larger amount of structures intermediate between XII and XIV. The Kerr constants to be expected for these intermediate forms have not been calculated but it seems likely that the flexible and chair forms are both present in substantial amounts in this compound.

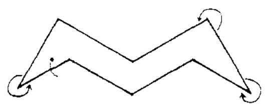

XII

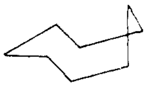

XIII


XIV


XV

Eight-membered Ring.—Numerous conceivable structures for the cycloöctane ring were examined and found to be exceedingly unfavorable with respect to transannular hydrogen repulsions, dihedral angles or both. Only two general families of structures appeared to require consideration, the crown (XVI) and the boat (XVII).


XVI


XVII

For the centrosymmetric crown the dihedral angles are all the same (96°),[18] and the energy of the structure calculated from the potential function is 14.4 kcal./mole. The regular crown may be deformed in various ways. The distortion shown in XVI appears to lead to the structure of lowest energy. It is not completely clear to what extent this distortion should be carried, since the sum of the 1,2 interactions is still lessening after certain of the transannular distances have come well within the van der Waal's radii. If the deformation is continued until one pair of angles has expanded to 130° and one pair has diminished to 60° (the other pairs measured on models are 92° and 90°), the closest pair of hydrogens is just touching in the Catalin models. The calculated energy for this conformation is 11.1 kcal./mole.

Catalin models show that the only other form of cycloöctane which might have an energy in this general range is XVII. If the hydrogens on the underside of the ring just miss touching, those on top interefere badly. Ignoring the latter interaction the calculated energy is 7.9 kcal. It appears that the transannular interaction would in this case increase the energy of XVII well beyond the experimental value, and there is probably little of this form present in cycloöctane.[19]

The calculated energy of each of these structures is still further reduced, the transannular van der Waal's repulsion is lessened, and the dihedral angles are improved by expanding the carbon-carbon bond angles. In the regular crown, expanding each bond angle by 4° raises the energy of the ring by 0.28 kcal./carbon atom, but the improved dihedral angle lowers the energy by 0.43 kcal.[20]/carbon atom. Consequently the ring as a whole is stabilized by 1.2 kcal. With the stable skewed form only half of the angles can be improved by this expansion, so the total energy

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[16] C. G. LeFevre and R. J. W. LeFevre, *Rev. Pure Applied Chem.*, **5**, 261 (1955).

[17] L. Paoloni, THIS JOURNAL, **80**, 3879 (1958).

[18] L. Pauling, *Proc. Natl. Acad. of Sci.*, **35**, 495 (1949).

[19] The dipole moments of *cis*- and *trans*-3,7-diethyl-3,7-dinitro-1,5-diazacycloöctane has been interpreted as indicating that in these compounds the eight-membered ring is in the crown form: R. Koliński, H. Piotrowska and T. Urbański, *J. Chem. Soc.*, 2319 (1958).

[20] For details of these calculations and experimental evidence for the bond angle expansion see N. L. Allinger and S. Greenberg, THIS JOURNAL, **81**, 5733 (1959).

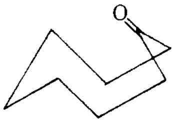
lowering is taken to be 0.6 kcal./mole.[21] The predicted heat content for cycloöctane in the skewed crown form is thus finally calculated to be 10.5 kcal., compared with the experimental value of 9.9 kcal.

The introduction of a keto group into the eight-membered ring to give cycloöctanone will have an effect which can be predicted in the following way. Maintaining the thesis that the size of the rotational barrier can be taken as relatively independent of the size of the rotating group[11] (within reasonable limits), changing the $>C<\begin{smallmatrix}H\\H\end{smallmatrix}$ group to a $>C{=}O$ group will eliminate two pairs of interactions between the original adjacent groups and the two hydrogens, and introduce two new repulsions, between the oxygen and the attached groups. If the barriers are taken to be the same for rotation of a hydrogen past either another hydrogen or an oxygen and ϕ is zero when the hydrogen eclipses the groups on the adjacent atom, the energy change upon insertion of the keto group relative to the same change in the chair form of cyclohexane is given by (2).

$$\Delta E = 0.467\,[\cos 3(\phi + 60°) - 2\cos 3\phi] - 0.42 \quad (2)$$

The ΔE's are then summed for the two interactions on both sides of the ketone. The fact that the bond angle at the carbonyl carbon has changed from 109 to 120° has been neglected.

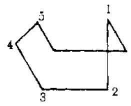
With cycloöctanone, introduction of the keto group into the distorted crown at the position leading to the greatest stability would lower the repulsion energy by 2.2 kcal. giving a calculated steric energy of 8.3 kcal.



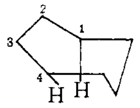
XVIII

Introduction of the ketone group into the boat form as in XVIII would eliminate the very unfavorable transannular interaction, but would raise the eclipsing energy by about 1.1 kcal. Again, these structures would be expected to lower their energies by 0.9 kcal. by bond angle expansion (since six-dihedral angles can be thus improved[22]), giving finally a calculated energy of 8.1 kcal. for XVIII. Cycloöctanone then can be predicted to be a mixture of XVIII and the skewed crown form.

The Seven-membered Ring.—With the cycloheptane ring there are two families of conformations to be considered and which may by analogy be called boats and chairs (XIX and XX, respectively). As in the case of the six-membered ring, to interconvert a boat and chair requires a sizable angular distortion, and there must therefore be a substantial energy barrier to interconversion.



XIX



XX

XXII

Each form can undergo a pseudorotation analogous to that of the flexible form of cyclohexane, and the energies of the various conformations can be calculated as was done for the six and eight-membered rings. In this case, neglecting all interactions between methylene groups other than adjacent, the boat form appears to be of lower enthalpy. The regular chair is calculated to have an energy of 8.6 kcal., whereas for the skewed form the value is 6.7 kcal. For the boat, the values are 5.8 and 5.3 kcal., respectively. There are, however, clearly some 1,4-hydrogen interactions on the underside (in XIX and XX) in both the chair and boat forms, the sum of which appears to be less in the skew form. There would appear to be also a severe interaction on top of the boat of a hydrogen atom on carbon 1 with hydrogens on carbons 4 and 5. These interactions cannot now be calculated quantitatively, but would be expected to raise the heat of combustion appreciably above the value calculated.

The skewed chair form (XX) may be considered first. If the bond angles are expanded by a small amount (on the order of 4°) it will be possible to obtain more favorable dihedral angles and decrease the transannular repulsion thus decreasing the energy of the whole molecule by an amount which is estimated at 0.6 kcal./mole, analogous to the cycloöctane case. Taking this energy into account the calculated heat of combustion of the chair form of cycloheptane is 6.1 kcal., as compared to the experimental value of 6.4 kcal. The chair form of the hydrocarbon is then consistent with the heat of combustion.

With the boat form of cycloheptane, bond angle expansion will lower the energy of the minimum to about 4.7 kcal. plus the transannular interaction energy. The latter cannot be negligible, since the heat of combustion is 6.4 kcal. If the transannular interaction energy is small, perhaps one kilocalorie, the agreement with the experiment would be reasonable and cycloheptane would be a mixture of boat and chair forms in which the former predominated. This energy may on the other hand be very large, in which case the hydrocarbon will exist exclusively as the chair form, or an intermediate situation may exist. These various possibilities cannot now be further differentiated.

The introduction of a ketone group into the cycloheptane ring can now be considered. If the keto group is placed as in XXII, the calculated steric energy is raised above that of the hydrocarbon, so XXII is definitely unfavorable. The introduction of the keto group into the skewed form of the chair in the position shown in XXIII would lower the calculated energy to 5.0 kcal. Similarly introduction of the ketone into the positions shown in XXI, XXIV, XXV, lead to the energies 5.5, 3.4, and 3.5 kcal., respectively, always assuming the structure is skewed to the point of minimum

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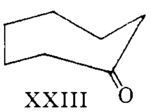
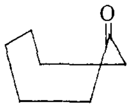
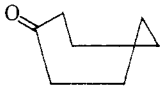
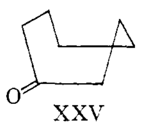
[21] There also may be a contraction of bond angles where the dihedral angles are greater than 120°, but in the absence of numerical data this possibility will be ignored.

[22] The dihedral angles measured in XVII, beginning with either carbon–carbon bond joining the carbon which becomes the carbonyl carbon in XVIII and going away from the plane of symmetry are 75, 109, 44 and 77°.


XXIII


XXI


XXIV


XXV

energy, and neglecting transannular interactions. Judging from the fact that these interactions appear to be large enough so that the boat does not appear to predominate in the hydrocarbon, XXIV and XXV likewise will probably not predominate here. It would appear that XXIII is the most favorable structure, but cycloheptanone can also be expected to contain a substantial amount of XXI. It is predicted that its steric energy is 1.1 kcal. lower than that of cycloheptane. Again, the adjustment of bond angles is expected to stabilize the ketones as was discussed for the hydrocarbons.

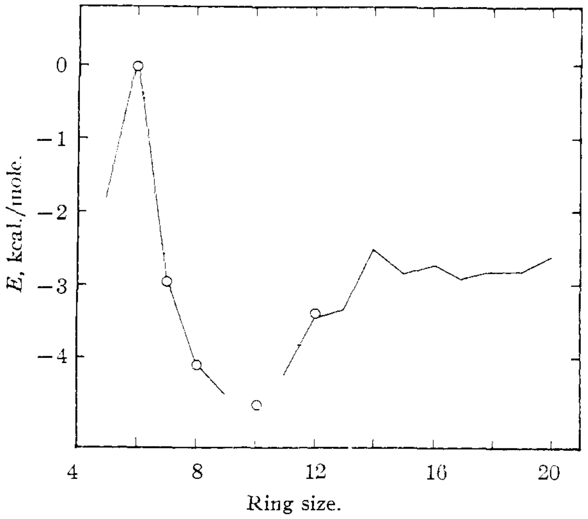


Fig. 1.—The relative free energies of dissociation of the cycloalkanone cyanohydrins as a function of ring size. The line records the experimental values of Prelog and Kobelt (ref. 25). The points are the values calculated in the present work.

Larger Rings.—Because of the rapid increase in the complexity of the conformational problem with increasing ring size the larger rings were examined only briefly. For cyclodecane the regular crown would have all the dihedral angles equal to 115°, and thus an energy of 27.5 kcal./mole. Cyclododecane in the regular crown form would similarly have dihedral angles of 126°, and an energy of 32.8 kcal./mole. For the ten-membered ring in the crown form, if the *cis*-hydrogens on one side of the ring on carbons 1, 5 and 7 are all twisted in toward the center of the ring, and the *cis*-hydrogens on the other side of the ring on carbons 2, 6 and 10 are simultaneously twisted in toward the center on the other side, the 109° bond angles can be maintained while the dihedral angles become more favorable. With the twelve-membered ring a similar deformation can be made, bending inward the hydrogens on carbons 1,5 and 9 on one side of the ring, and those on 2, 6 and 10 on the other side. For the 10-membered ring, the lowest energy seems to be obtained when this distortion has gone as far as it can without bending bond angles. At this point the dihedral angles and the number of each is: 150° (4), 106° (4) and 102° (2). The calculated energy is 19.80 kcal./mole. Again, bond angle expansion may be expected to reduce this value to perhaps 18.9 kcal./mole. With the twelve-membered ring an energy minimum appears to be reached when the angles are: 97° (3), 147° (6) and 60° (3). This structure is predicted to have an energy of 15.50 or 15.0 kcal./mole after bond angle expansion. The calculated and experimental energies of the cyclanes are summarized in Table I.

TABLE I

HEATS OF COMBUSTION FOR THE CYCLANES

Ring	Structure	ΔHc Calcd.	Hydrocarbons Found[a]	$\Delta H/CH_2$ Calcd.	$\Delta H/CH_2$ Found
6	Chair	0	0	0	0
6	Flexible	5.1	..	..	..
7	Skewed chair	6.1	6.4	0.87	0.91
8	Distorted crown	10.4	9.9	1.30	1.24
9	....	..	12.9	..	1.43
10	Distorted crown	18.9	..	1.89	..
12	Distorted crown	15.0	..	1.25	..

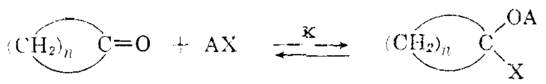
[a] S. Kaarsemaker and J. Coops, *Rec. trav. chim.*, **71**, 261 (1952).

Unfortunately, modern accurate heat of combustion data for some of these compounds are not available. Since one or more of the many conceivable irregular forms of the 10- and 12-membered rings may be of still lower energy, the heats of combustion calculated for these two rings are really upper limits and may be too large.

The relative steric energies of cyclodecanone and cyclododecanone were found by placing the ketone group in the most favorable place using equation 2 as was described for cycloöctanone. In these cases the ketones are of lower steric energy than the hydrocarbons by 2.8 and 1.7 kcal., respectively.

I-**Strain Calculations.**—The qualitative idea that the high energies of the medium rings result from the unfavorable dihedral angles[23] is generally accepted, and this energy has been designated as *I*-strain.[24] From the exact conformations of the medium rings it was possible to undertake a semiquantitative calculation of the change in enthalpy that is to be expected when the cyclane is converted to the cyclanone.

Neither heat of combustion data nor heat of hydrogenation data are available for comparison, but there does exist experimental data which can be compared. If an equilibrium of the type shown is examined, and if A and X are effectively small



$$(CH_2)_n\,C{=}O + AX \underset{}{\overset{K}{\rightleftharpoons}} (CH_2)_n\,C\genfrac{}{}{0pt}{}{OA}{X}$$

groups, it might be hoped that a variation in n will not lead to any significant entropy change

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(23) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(24) H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951).

throughout the series, and therefore the relative free energies calculated from the equilibrium constants should compare with the quantities given as ΔH in Table I.

The free energies for the addition of hydrogen cyanide to the cyclanones have been reported,[25] and seem well suited for the comparison at hand. These free energies, relative to cyclohexanone, are shown by the line in Fig. 1. The enthalpies as calculated in the present work for the introduction of the keto group into the cyclanes are indicated by circles on the same figure, and the agreement is fortuitously good.

Many other properties of medium rings which involve conversions of a trigonal ring atom to a tetrahedral atom also vary throughout the series in a manner qualitatively similar to that of the hydrogen cyanide addition,[23,26] but these other properties are all sterically more complicated which might induce other interactions, or else they involve charged species which would render questionable the assumption of the lack of dependence of entropy on ring size.

Prelog has proposed[23] that the "O-inside" conformations of the medium rings are stabilized by transannular hydrogen bonding and this effect increases in importance with increasing nucleophilicity of the atom forming the hydrogen bond. Spectroscopic evidence for transannular hydrogen bonding in cycloöctanone has also been reported.[27] The present work indicates that there is no need to invoke these effects to explain the available energy data, and while it seems likely that these effects are in fact real, they probably lead to only small energy changes.

The ultimate justification for the many severe approximations and assumptions made in the present work comes from the fact that the agreement between the simple calculations and the available experimental data is as good as it is.

[25] V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).

[26] O. H. Wheeler, THIS JOURNAL, **79**, 4191 (1957).

[27] G. B. B. M. Sutherland, quoted in ref. 23.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Conformational Analysis. IV. The Conformations of the Cycloöctanone Ring[1,2]

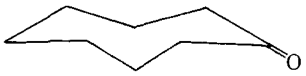
BY NORMAN L. ALLINGER AND SEYMOUR GREENBERG

RECEIVED MARCH 26, 1959

5-(4-Chlorophenyl)-cycloöctanone was prepared by an unambiguous method. Its dipole moment in benzene solution was found to be 3.39 D. This value is taken as evidence that the cycloöctanone ring exists in two principal conformations, "O-inside" and "O-outside," and that these are of similar free energy. It is concluded that in general compounds containing simple cycloöctanone rings will exist as mixtures containing comparable amounts of these two conformations.

Introduction

Theoretical considerations have indicated that cycloöctanone may exist in either a crown (I) or in a chair (II) form,[3] and quantitative calculations using a reasonable potential function for rotation about a C–C bond,[1] have suggested that they are of similar energies. No experimental differentiation between these possibilities was made. The principal evidence available earlier which can be interpreted as supporting structure II comes mainly from the infrared spectrum. Cycloöctanone has its carbonyl stretching frequency at 1701 cm.$^{-1}$, considerably less than that of cyclohexanone (1714 cm.$^{-1}$) in carbon tetrachloride.[4] Since in II there exists the possibility of transannular hydrogen bonding, the lowering of the carbonyl frequency here and in the other medium rings has been taken as indicative of the existence of conformation II ("O-inside" conformation).[5]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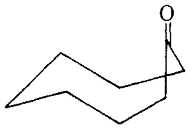
II

An alternative interpretation of the infrared data is possible, however. The carbonyl stretching frequencies of the simple cyclanones can be divided into three groups. One group contains fewer than six-ring members, and the frequencies are quite high. The second group consists of six-membered rings together with rings containing eleven or more carbons. These compounds all absorb at 1709–1714 cm.$^{-1}$ (in carbon tetrachloride) as do typical open-chain compounds. The 7–10-membered rings, on the other hand, absorb uniformly at 1701–1702 cm.$^{-1}$. The work of Halford[6] suggests that, since there is no reason to suspect that the force constants or attached masses of the carbonyls should be grouped together in such a way, the C–C–C bond angle at the carbonyl group is expanded above its normal value in the medium rings. Presumably all of the C–C–C bond angles are so expanded in an effort to relieve both transannular strain and unfavorable dihedral angles. An expansion of each angle by 4° would be sufficient to account for the carbonyl frequency. It would raise the enthalpy of the regular crown by 0.28 kcal. per carbon atom from the bond bending but the more favorable dihedral angles (90° instead of 96°) would lower the en-

[1] Paper III, N. L. Allinger, THIS JOURNAL, **81**, 5727 (1959).

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

[3] See ref. 1 for a summary and references.

[4] N. J. Leonard and F. H. Owens, THIS JOURNAL, **80**, 6039 (1958). We wish to thank Dr. Leonard for sending us a copy of this manuscript prior to publication.

[5] V. Prelog, *J. Chem. Soc.*, 420 (1950).

[6] J. O. Halford, *J. Chem. Phys.*, **24**, 830 (1956).