CONFORMATIONAL ANALYSIS OF MEDIUM-RING KETONES*

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Abstract—The conformations of cyclooctanone, cyclooctane-1,5-dione, cyclononanone, cyclodecanone, cyclodecane-1,6-dione, and cycloundecanone are discussed.

INTRODUCTION

Medium rings have attracted much attention in organic chemistry because of their unusual properties.[1] For example, the medium-ring cycloalkanes, $(CH_2)_n$, n = 8 to 11, are strained and have a higher heat content per methylene group than do either the common-ring (n = 5 to 7) or the large-ring (n ⩾ 12) cycloalkanes. Transannular reactions often occur in the medium rings and many functional groups incorporated into such rings display unusual reactivities. Thus, the cycloalkanones in the medium rings have very low reactivities to addition of hydrogen cyanide[2] and to reduction by sodium borohydride.[3]

The conformational properties of medium rings have been gradually elucidated during the last 15 years, with most of the information coming from three sources, namely (i) X-ray diffraction studies of crystalline compounds,[4] (ii) strain–energy calculations,[5] and (iii) NMR measurements.[6] Additional useful data have also been obtained from determinations of IR spectra and dipole moments.[7]

Remarkably little direct structural information exists on the medium-ring cycloalkanes and cycloalkanones themselves.[4] Because these compounds exist as liquids at room temperature, or as disordered crystals, all the X-ray structural determinations refer to derivatives which lack these undesirable properties. No simple derivative of any medium-ring cycloalkanone has, as yet, had its structure established by X-ray methods, with the exception of cyclodeca-1,6-dione,[4] which must be considered as a diketone rather than a derivative of a monoketone. The situation is better as far as derivatives of the cycloalkanes are concerned, especially for 8- and 10-membered rings.[4]

Semi-empirical strain-energy calculations have been applied to the medium-ring cycloalkanes with considerable success.[5] The approximate nature of these calculations makes it difficult to establish the reliability of the conclusions reached, especially when energy differences of 1 to 2 kcal/mol are involved. In the case of ketones,[5] the calculations require many more parameters, some of which can only be guessed, and at present the conclusions reached can only be regarded as tentative.

NMR is a very valuable tool for conformational studies, but it also has limitations and often requires the synthesis and examination of partially deuterated derivatives because of the spectral complexities which otherwise prevent any useful analysis.[6] Amongst the advantages of NMR is that the solution rather than the solid (crystalline) state is investigated, and thus lattice forces can be excluded. Also, conformational barriers can be determined, provided that the values are above about 4 kcal/mol. Unfortunately, if the barrier is less than 4 kcal/mol, the chemical shifts and coupling constants which are obtained refer to averages for different conformational situations and thus there can be ambiguity about the true symmetry of the conformation, or indeed, whether more than one conformation is present or not. It is clear that NMR provides the most information under conditions such that as many conformational processes as possible are slow on the NMR time scale. For barriers of 8 and 4 kcal/mol, this requires temperatures in the range of − 120° and − 185°C respectively. It is very advantageous to make NMR measurements at the highest possible magnetic fields, and to examine the proton resonances in a CHD rather than in a CH_2 group. Slow molecular tumbling at very low temperatures results in relaxation effects which lead to much larger line widths (theoretically by a factor of 14) for the protons in a CH_2 group as compared to that in an otherwise similar CHD group.[9] Another and better known advantage of deuteration is the removal of strong coupling effects, thereby making spectral analysis possible, and in most cases, trivial.

IR measurements have proved very useful for testing whether the conformation in the crystalline state of a compound is also the predominant con-

formation in solution.[7] The spectra of medium rings are invariably too complex for any meaningful analysis, and early attempts to use IR spectra to obtain direct conformational information have generally led to ambiguous or incorrect results.

The application of dipole moments in conformational analysis is largely limited to compounds which have at least two polar groups. Diketones, in particular, have dipole moments which are strongly dependent on ring size and thus on conformational effects.[10]

In this article we will discuss the conformational properties of saturated medium-ring mono- and diketones, and the relationships of the conformations of the ketones to those of the corresponding hydrocarbons.

DISCUSSION

General considerations. In view of the lack of structural data for medium-ring ketones and the present uncertainty of strain–energy calculations for systems other than hydrocarbons, we feel that the best qualitative *a priori* approach to the conformation of cyclic ketones is one which is based on the known conformational properties of the cycloalkanes. The replacement of a methylene by a CO group can then be regarded as a perturbation with more or less predictable consequences. Three such consequences can be enumerated, and in fact form the basis of more "quantitative" strain–energy calculations. The first of these effects is the difference in the "natural" or unstrained internal angle at an sp^3 *versus* an sp^2 C atom. Good models are butane and acetone where the C–C–C bond angles are 112° and 117° respectively.[11,12] There will also be differences in the force constants for distortion of these natural angles, and in ketones it is necessary to consider both in-plane and out-of-plane distortions separately.[8] Since the variations in the internal bond angles found for different conformations of a given cycloalkane are relatively small (± 1 to $\pm 2°$),[4,5] the difference between the internal angle at a methylene and a carbonyl group is not expected to lead to significant conformational changes in most cases.

A second difference between a ketone and a hydrocarbon occurs in the parameters for torsional strain about single bonds. The barrier to rotation about the sp^3–sp^3 single bond in ethane has the well-known value of 2·9 kcal/mol,[13] even though the precise origin of the barrier has been hotly debated.[14,15] The barrier in propane has the somewhat higher value of 3·4 kcal/mol.[16] By contrast, the barrier to methyl rotation in acetone is only 0·78 kcal/mol.[12,17]

The potential energy minimum in acetone is the so-called "eclipsed" conformation (1).[18] Although a C–H bond is eclipsed with the C–O bond in 1, it should be noted that the same C–H bond is *staggered* with respect to the C(O)–CH₃ bond and that

the description of 1 as an "eclipsed" form rather than a "staggered" form is purely arbitrary. The prevailing usage is in fact unfortunate because if the CO group is considered in the bent-bond formalism, conformation 1 is unambiguously staggered. At the very least, the bent-bond formalism provides a very satisfactory mnemonic for remembering the energy minima about both sp^3–sp^3 and sp^3–sp^2 bonds. The naming of 1 as an eclipsed conformation is also very confusing when it is of interest (as it is in the present paper) to estimate the effect of replacing a methylene group in a given conformation by a CO group.

The conformations of 2-butanone (2) and 3-pentanone (3) present interesting additional features, for in these compounds an sp^2–sp^3 bond prefers an arrangement where the methyl moiety of the ethyl group is eclipsed with the CO group. Conformation 2, which belongs to our generalized (bent-bond) "staggered" kind, is apparently substantially lower in energy than the other possible "staggered" conformations (2a). Various estimates of the energy difference between 2 and 2a lie in the range of 1 to 1·5 kcal/mol.[8] The reason for the preference of 2 over 2a is a good deal more obscure than the precise nature of the barrier in ethane. It is interesting that *ab initio* calculations show that the barrier in ethane is repulsive-dominant, whereas the barrier in acetaldehyde (and presumably in acetone) is attractive-dominant.[14] It is thus possible that the increased stability of 2 over 2a is due to an attraction between the O atom and the Me portion of the Et group. In any case, the reactivity of cyclohexanone, as compared to diethyl ketone, can be attributed to the fact that cyclohexanone cannot take up a conformation analogous to that of 3.[8,19] In the chair form of cyclohexanone both sp^2–sp^3 single bonds are in arrangements which are undoubtedly local energy minima as far as torsional strains are concerned, and it is therefore not correct to ascribe the reactivity of cyclohexanone to eclipsing effects of the equatorial α C–H bonds with the carbonyl group as in Brown's explanation.[20] It may be noted that the bond arrangement of 3 cannot occur in medium rings, because a 14 or larger-membered ring is required to accommodate such a structure. Arrangement 3a, which is intermediate between 3 and 3b, can, however, be included in a 10-membered ring with only a slight distortion.

The barrier to rotation about the sp^2–sp^3 bond in 2-butanone or 3-pentanone is not known, but is undoubtedly considerably smaller than the internal rotational barrier in propane or butane. Therefore, if there is a choice between a methylene group in an eclipsed environment and one in a staggered arrangement for (formal) replacement by a CO group, the lower energy conformation of the ketone will result from the eclipsed hydrocarbon conformation. Such considerations are important in the transition state for ring inversion in cyclohex-

anone,[8] and for the ground state of 8-membered ring ketones.[6b,21]

The third and final conformational difference between a C=O and CH_2 group concerns the non-bonded interaction parameters for these groups. It seems clear that a CO group is less demanding in space than a methylene group, at least when the interaction is with other methylene groups and refers to the face of the CO group. For example, the A-value of cyclohexyl methyl ketone (1·2 kcal/mol) is appreciably lower than that of methylcyclohexane (1·7 kcal/mol).[22] The replacement of methylene groups in medium rings by CO groups is therefore expected to lead to a relief of transannular non-bonded repulsions. In fact, the lack of reactivity found in the medium-ring ketones has been ascribed to this effect.[1]


1   2   2a

3   3a   3b
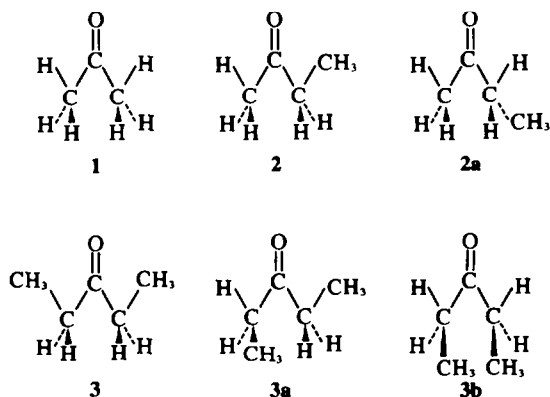
Eight-membered ring ketones

Before discussing the conformations of ketones in this series, we will very briefly outline the conformations found in 8-membered rings. Cyclooctane and its "simple" derivatives have been shown to exist predominantly in boat-chair (BC) conformations.[6c] Cyclooctane itself has been shown recently to exist to a minor extent (ca 5% at room temp) in a conformation of the crown family.[23] Heavily substituted cyclooctanes, as well as heterocyclic 8-membered rings possessing several hetero atoms, are also known to exist to a greater or lesser extent in crown family forms.[6c] The boat-chair conformation (BC) has C_1 symmetry and has two torsional angles which are not far from eclipsed ($\approx 100°$ ring dihedral angle or nearly anticlinal). Transannular repulsions in BC occur between "axial" protons at positions 3 and 7 as well as between 1, 4 and 6.

Until a few years ago only symmetrical conformations had been seriously considered for cyclooctanone.[1] It was then shown by low temperature NMR studies that cyclooctanone exists predominantly in an unsymmetrical boat-chair conformation, or more strictly, as a 1:1 mixture of the two mirror-image chiral forms BC-3 and BC-7.[6a,21,24,25]

We will now discuss in some details the basis for this conclusion.

BC

TBC

BC-7

BC-3

CC-3
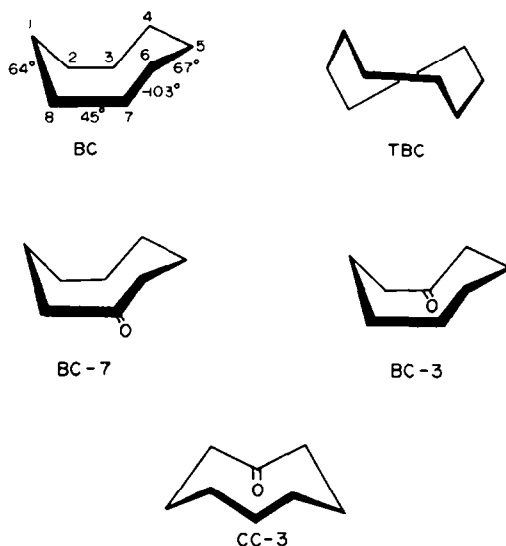
The NMR measurements were made on isotopic isomers of cyclooctane-d_{13} in which the lone proton is at either the α, β, γ, or δ position. At temperatures below about $-160°C$, four resonances in the ratio of 1:1:1:1 are observed for each of the α, β, and γ isomers. The δ isomer, however, gives only two resonances, in the ratio of 1:1. These results virtually demand the existence of a single kind of conformation, which must be unsymmetrical. Furthermore, one of the δ resonances has a chemical shift of only 0·67 ppm downfield from TMS. Such an abnormally high field shift for an isolated methylene proton can only be explained if the proton lies directly above the face of the CO group. In the boat-chair conformation only the BC-3, and its mirror-image, BC-7, have the required geometric relationship of a δ proton and the CO group. The only conformation in the crown family which has the required geometry of a δ proton and the CO group is the CC-3 form. However, this can be *rigorously* excluded as the predominant conformation of cyclooctane, since it is too symmetrical, and can only give two resonances for either the α, β or γ proton. A boat–boat conformation (BB-1) can also be excluded for the same reasons that the CC-3 form is not allowed. A twist–boat–boat form is formally allowed, but would be expected to undergo reversible interconversion with its mirror-image *via* the BB-1 form with such a low barrier that it also could not exhibit four distinct resonances for the α, β or γ protons at temperatures of $-160°$. Quantitative strain–energy calculations show that the barrier to conformational racemization of the twist–boat–boat in cyclooctane itself is less than 1 kcal/mol.[26,27] Thus, the experimental NMR data

are in agreement only with the BC-3 and BC-7 conformations.

The four lines observed for the α, β or γ isomers broaden above $-160°C$ and give rise to two lines at about $-135°C$. The free energy barrier for this process is calculated by a line-shape analysis to be 6·3 kcal/mol at $-145°C$. The two lines observed at about $-135°C$ broaden and finally coalesce to a single shape line above $-100°C$, in a process with a $\Delta G\ddagger$ of 7·5 kcal/mol. The low-energy conformational process in cyclooctanone is best explained as a pseudorotation of the BC-3 form to its mirror-image, BC-7. The pseudorotation of the boat-chair proceeds *via* the twist–boat–chair (TBC, C_2 symmetry) as an intermediate (not transition state). Actually, several stages of BC$\rightleftarrows$TBC$\rightleftarrows$BC are required to transform the BC-3 into the BC-7 form, namely BC-3 $\rightarrow$ BC-6 $\rightarrow$ BC-5 $\rightarrow$ BC-4 $\rightarrow$ BC-7, or proceeding in the alternate way around the ring, BC-3 $\rightarrow$ BC-8 $\rightarrow$ BC-1 $\rightarrow$ BC-2 $\rightarrow$ BC-7. The forms other than BC-3 and BC-7 are not appreciably populated and are thus not observable. A possible way of determining which is the lower of the two overall pseudorotation paths can be made by studying substituent effects, as will be discussed below.

The overall pseudorotation process, as it affects the γ proton of cyclooctanone-d_{13}, is shown in Scheme 1. It should be noted that the deuterium labelled molecule is chemically chiral, and that Scheme 1 shows the required conformations for only one enantiomer. The other enantiomer can be obtained by exchanging the H and D of the CHD groups in the depicted conformations. Thus, pseudorotation leads to a conformational racemization in cyclooctanone itself, but only to a conformational diastereomerization in the γ isomer of cyclooctanone-d_{13}. It can be shown that the δ proton is unaffected by the pseudorotation process, and the only process which can be observed experimentally in this isomer indeed corresponds to the

CC-3,7

BC-3,7

4

5

6
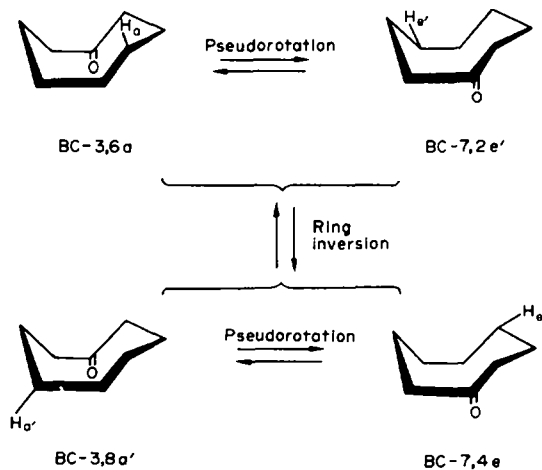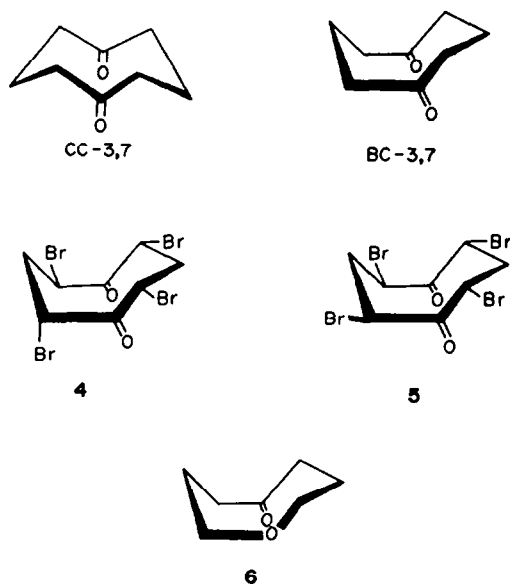
higher barrier in the γ isomer. Thus, the low-energy process cannot be one which exchanges the two δ geminal protons. A complete discussion of the dynamics of this system will not be presented here, but suffice it to say that the high-energy process in cyclooctanone probably involves interconversion to the chair or twist–chair form, or possibly to rapidly pseudorotating boat–boat forms and can be called a ring inversion.[6c]

It is satisfying that the conformation of cyclooctanone deduced by NMR measurements has the carbonyl group in a position which partly relieves both the non-bonded and eclipsing strains which are present in the parent cyclooctane boat–chair conformation. Very recent quantitative strain–energy calculations also demonstrate that the BC-3 (or BC-7) form is of substantially lower energy than any other boat–chair form, the next best conformation (BC-4 and its mirror-image BC-6) being 1·7 kcal/mol higher in energy.[8] The best crown conformation, actually a twist–chair–chair, is calculated to be 1·5 kcal/mol higher than the BC-3 form.[8]

The NMR spectrum of 5-t-butylcyclooctanone shows evidence at low temperatures for restricted rotation about the t-Bu ring bond and for a conformational process with a $\Delta G^{\neq}$ of 8·0 kcal/mol.[6b,24,28] If the conformation is a boat–chair with the CO group at the 3 position and the t-Bu group at the 7 equatorial position (the axial position at 7 is extremely hindered), the process seen in the low-temperature NMR work cannot be ring inversion, as this leads to equatorial–axial interconversion of the large t-Bu group. Pseudorotation, however, is possible and if the path BC-3 $\rightarrow$ BC-6 $\rightarrow$ BC-5 $\rightarrow$ BC-4 $\rightarrow$ BC-7 is chosen, the t-Bu group finally

BC-3,6a

BC-7,2e'

Pseudorotation

Ring inversion

BC-3,8a'

BC-7,4e

Pseudorotation

SCHEME I

resides in an equatorial position, and as well remains unhindered at all stages of the process. The alternate path, described earlier, requires that the t-Bu group be placed in a highly hindered position during the change from the BC-3 to the BC-7 form. Since the pseudorotation barrier is appreciably higher in 5-t-butylcyclooctanone than it is in cyclooctanone itself, it appears that cyclooctanone pseudorotates most easily *via* the BC-1 form. This process is forbidden in the t-Bu derivative, however, and as a result pseudorotation is forced to occur by the less favorable pathway, i.e. *via* the BC-5 form. A possible objection to these conclusions is that the t-Bu group, even if it remains in equatorial positions, may have an appreciable effect on the pseudorotation barrier. A determination of the conformational barrier in 5-methylcyclooctanone should help to resolve this question.

The dipole moment of 5(p-chlorophenyl)cyclooctanone has been determined to be 3·39D, compared to a dipole moment of 2·93D for cyclooctanone itself.[29] Although this observation was originally rationalized on the basis of a mixture of conformations and then on the basis of a chair–chair conformation,[30] the data actually fit quite well with the BC-3 conformation.

The low stretching frequencies of CO groups in medium-ring ketones are best ascribed to bond angle expansion effects,[29] and not to hydrogen-bonding to "O-inside" conformations.[31] Definite evidence on this point exists for 5,5-dideuteriocyclooctanone, which has been shown to have normal C-D stretching frequencies.[32]

Cyclooctane-1,5-dione has been found to have the same IR spectrum in solution as in the solid state.[10] This fact, together with the sharpness of the spectral bands, strongly indicates a single kind of conformation in both phases. The high dipole moment (4·8D) is consistent with a parallel arrangement of the CO groups. The above evidence, together with considerations of the low eclipsing strain of the bonds next to a CO group, led Alvik, Borgen and Dale to suggest the symmetrical chair–chair conformation (CC-3,7) for cyclooctane-1,5-dione.[10] However, recent NMR work has shown that the conformation is of lower symmetry than CC-3,7, and that all the facts can be explained on the basis of the BC-3,7 conformation.[33] The proton spectrum of the 2,2,4,4,6,6,8,8-octadeuterio derivative of the 1,5-diketone consists of two AB quartets at − 150°. Line-shape changes at higher temperatures indicate the presence of two conformational processes with $\Delta G^{\neq}$'s of 6·1 and about 7 kcal/mol, presumably corresponding to ring pseudorotation and inversion respectively.

^{13}C NMR spectra of the cyclooctane-1,5-dione show 1:1 doublets for the α and β carbons at low temperatures, and single sharp resonances at temperatures higher than − 100°C.[33] These spectral changes are consistent, of course, with the BC-3,7 conformation for the 1,5-diketone.

The conformations of two isomers of 2,4,6,8-tetrabromocyclooctane-1,5-dione have been examined by Heller and Dreiding,[34] who conclude that both compounds have BC-3,7 conformations. The bromine atoms are all equatorial in one isomer (4); in the other isomer (5) three bromines are equatorial and one is in an unhindered quasiaxial position.

Low-temperature ^{1}H and ^{13}C NMR measurements on 5-oxocanone (5-oxocyclooctanone) show that the conformation of this compound lacks symmetry.[35] The NMR evidence is best accommodated by a boat-chair conformation (6) analogous to that of cyclooctanone. The barriers to ring pseudorotation and inversion in 5-oxocanone are 7·8 and 9·0 ± 0·2 kcal/mol respectively, and are therefore somewhat higher than the corresponding barriers in cyclooctanone itself.[35] The increase in barrier height is most likely due to a transannular interaction of the oxygen ether atom with the CO group.

In summary, saturated mono- and diketones in 8-membered rings have so far been found only in boat–chair conformations and the carbonyl groups are always at positions 3 or 7. However, it is to be expected that appropriately substituted derivatives of cyclooctanone will possess conformations other than boat–chairs. These conformations will most likely be chair–chairs or twist–chair–chairs.

Nine-membered ring ketones

Comparatively little is known about 9-membered rings in general. Strain–energy calculations favor a conformation of D_3 symmetry (the so-called twist–boat–chair or [333] conformation[36]) for cyclononane itself,[5,36] but the conformation found in cyclonononylamine hydrobromide has a different sequence of torsional angle signs and has approximately C_2 symmetry.[4] The C_2 form (or [12222] conformation[36]) is calculated to be 2 to 4 kcal/mol higher in energy than the D_3 form.[5,36] Two other conformations, one of approximately C_2 symmetry[5a] and the other asymmetric,[36] are also of low energy. Trimeric acetone peroxide, it should be noted, does have a [333] (D_3) conformation in the crystalline state.[37] On the other hand, the mercuric chloride complex of cyclononanone has been found to have a structure closely related to the [12222] conformation, but there are comparatively large uncertainties in bond lengths and bond angles in this structure determination.[38]
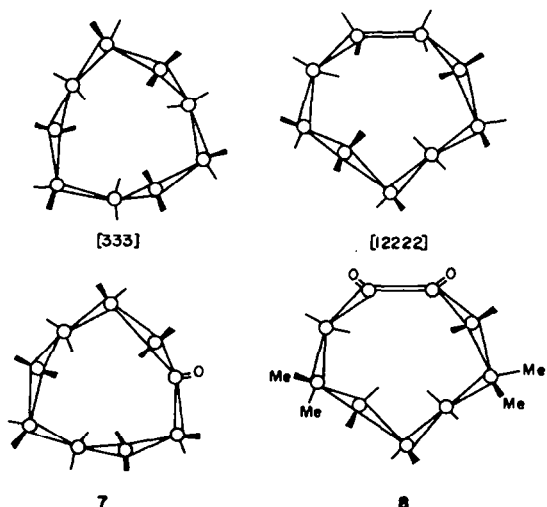
^{13}C NMR studies of cyclononane at low temperatures support the D_3 conformation for this hydrocarbon.[39] For cyclononanone, CMR spectra at low temperatures show the presence of a single CO resonance but two distinct resonances for the α carbons.[40] The proton NMR spectrum of cyclononanone shows evidence for two conformational changes, with free energies of activation of

5·0 and 6·5 kcal/mol.[40] The simplest interpretation of the NMR data is that cyclononanone exists as a single unsymmetrical conformation. The structure found in the mercuric chloride complex of the ketone fits this requirement, but an unsymmetrical conformation (7) based on the D_3 skeleton favored for cyclononane also looks attractive. Recent strain-energy calculations on several cyclononanone conformations seem to show that the lowest energy form has an approximate C_2 axis passing through the CO group, [8a] in disagreement with the NMR results. A more detailed strain-energy study of cyclononanone conformations would seem desirable.

Dale and Borgen[41] have found that 4,4,7,7-tetramethylcyclononanone gives a temperature-dependent proton NMR spectrum and have suggested a [333] conformation with a C_2 axis passing through the CO group. This places the *gem* dimethyl groups on unhindered corner carbons. Strain-energy calculations,[8a] however, show that another conformation, which is unsymmetrical, may have a slightly lower energy than the C_2 form described above.

The presence of *gem* dimethyl groups strongly hinders ring pseudorotation and the tetramethyl derivative has a ΔG^* of about 14 kcal/mol, which is very much greater than the conformational barriers in the parent ketone (ΔG^*'s of 5 and 6·5 kcal/mol).

Another compound with a pair of *gem* dimethyl groups is 4,4,8,8-tetramethyl-1,2-cyclo-non-anedione,[42] which has a conformational barrier of about 21 kcal/mol. A [12222] conformation (8) is possible for this compound, as the Me groups can be in unhindered positions, with the CO groups in positions which relieve eclipsing strains.

reasonably clear. Both crystal structure[4] and strain-energy evidence[5,36] point to the "diamond-lattice" boat–chair–boat (BCB or [2323]) conformation as being of lowest energy. The presence of *gem* dimethyl groups in a 1,5 relationship forces the molecule to adopt the [2233] or the [1333] conformation.[4,36]

There are three different kinds of carbons in the [3232] form and thus the introduction of a CO group can lead to three kinds of conformations, which can be conveniently named as BCB-1, BCB-2 and BCB-3. The BCB-1 form has a plane of symmetry so that the two α carbons must have the same chemical shifts. The other two conformations are chiral and each should show two different α carbon chemical shifts under conditions where conformational changes are slow on the NMR time scale. Since the ^{13}C NMR spectrum of cyclodecanone at $-160°$C shows two clear chemical shifts for the α carbons and only one shift for the carbonyl group[40] (Fig 1), a

[333]　　　　　　　　　[12222]

7　　　　　　　　　　8

Ten-membered ring ketones

The conformational picture in 10-membered rings having a limited number of substituents is
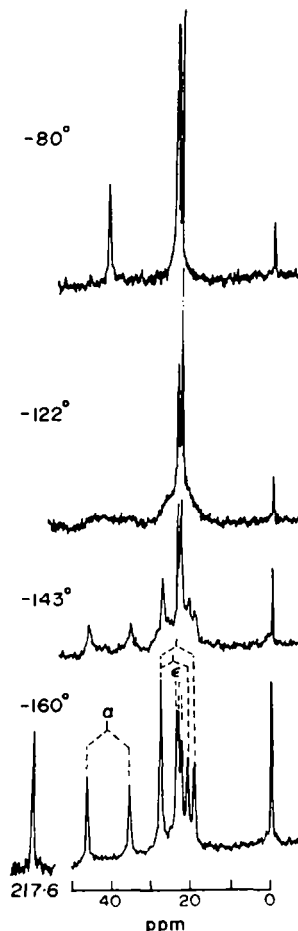

Fig 1. ^{13}C NMR spectrum (63·1 MHz) of cyclodecanone at various temperatures. Protons are noised decoupled and the reference (0 ppm) is tetramethylsilane[40] (reproduced by permission of the American Chemical Society).

symmetrical conformation such as BCB-1 can be excluded. Of the unsymmetrical BCB conformations, BCB-2 is much less likely than the BCB-3 since it does not relieve transannular strain, nor does it have a favorable disposition of bonds about the CO group. Quantitative strain–energy calculations indeed show that the BCB-3 conformation is of lowest energy.[8b] The ^{1}H NMR spectrum of cyclodecanone also supports the BCB-3 form. At low temperatures the α protons exhibit four chemical shifts and the coalescence of these peaks at higher temperatures takes place in a step-wise fashion, producing first two peaks and then one peak. The two conformational processes which are involved in these changes have $\Delta G^{\ne}$'s of 6·5 and 7·3 kcal/mol respectively, and most probably involve several pseudorotations of the type described by Dunitz[43] and Dale[44] for cyclodecane.

The lowest energy pseudorotation in cyclodecanone most likely involves the following sequence: BCB-3 → BCB-6 → BCB-9, where BCB-9 is the mirror image of BCB-3, and BCB-6 is not appreciably populated. During this pseudorotation itinerary the CO group remains in a position which relieves transannular strain. The exchange which results from this process causes (i) the two α carbons to become equivalent and (ii) the stereochemically *cis* protons on the α and α' carbons to become equivalent, but the protons which are *trans* to one another on these carbons are still different. Since the molecules all pass through the BCB-6 form in this process, the minimum observable time averaged symmetry must correspond to that conformation. The BCB-6 (≡ BCB-1) has a plane of symmetry passing through the CO group and bisecting the C–C(O)–C angle. The alternative pseudorotation has the following itinerary: BCB-3 → BCB-10 → BCB-7 → BCB-4. This requires a higher energy than the path considered previously, since the CO group is forced to remain in the unfavorable corner position during the BCB-10 to BCB-7 step.

Although both cyclooctanone and cyclodecanone show two distinct conformational processes, the dynamics in the two systems are not really similar. In cyclodecanone, the two processes are closely related, and the basic pseudorotation steps are of the same kind. In cyclooctanone, by contrast, the two processes are of entirely different kinds. The source of these differences is that two processes, namely a pseudorotation and a ring inversion occur in the cyclooctane boat–chair, and both processes must occur rapidly for all the protons in cyclooctane to become isochronous. In the cyclodecane boat–chair–boat, only a single pseudorotation process needs to be fast for all the protons to be isochronous.

The crystal structure of cyclodecane-1,6-dione has been established and the conformation is the BCB-3,8.[4] This conformation is obviously closely related to the BCB-3 conformation deduced for

cyclodecanone by NMR methods. However, the situation in solution turns out to be more complex than indicated by the evidence just presented. It has been shown that the IR spectra of cyclodecane-1,6-dione in the crystal phase and in solution are quite different.[10] In fact, the solid state spectrum lines can be recognized as a *minor* component of the spectrum in the liquid state. Additionally, the observed dipole moment in solution is very low, and the enthalpy and entropy of melting are both abnormally large.[10] These facts suggest that the major conformer in solution is centrosymmetric (as is the BCB-3,8 conformation in the crystal) and that the CO groups are in close intramolecular association.[10] Thus, conformations such as the BCB-2,7 and the BCB-1,6, which are the only other possibilities based on a BCB skeleton, must be considered as unlikely. Alvik *et al.* suggest a distorted "decalin-like" conformation (9).[10] This conformation belongs to the crown family and, in Hendrickson's terminology (although Hendrickson has not specifically considered this conformation) is a twise–chair–chair–chair (TCCC). In Dale's nomenclature, it is a [1414] conformation, and in the case of cyclodecane itself, the [1414] is calculated to be only 0·8 kcal/mol higher than the [2323] or BCB conformation.[36]

9

[2323] ≡ BCB

BCB-1   BCB-3   BCB-2
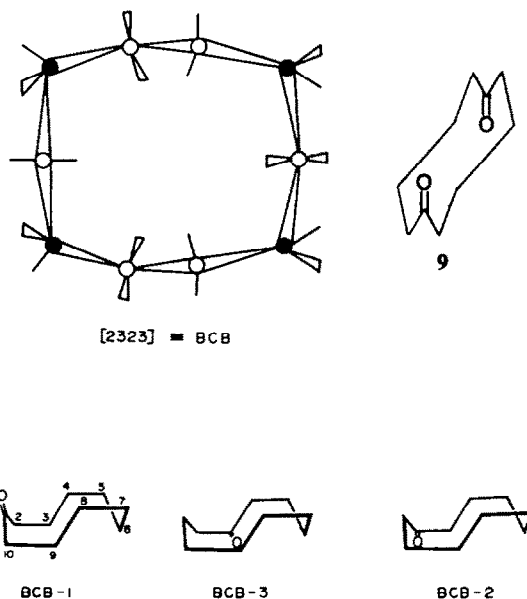
Recent ^{13}C and ^{1}H NMR studies [45] have confirmed the view of Alvik *et al.* regarding the solution conformation of cyclodecane-1,6-dione. At low temperatures the main conformation has a single resonance for either the α or β or CO carbons. The protons on the α carbons give rise to only two chemical shifts, as also do those on the β carbons. These data nicely fit the highly symmetric (C_{2h}) con-

formation **9**. Furthermore, a second minor conformation of lower symmetry, presumably the BCB-3,8 form can also be detected. The conformational energy barrier separating **9** from the BC-3,8 form is fairly high ($\Delta G^{\neq} \simeq 10$ kcal/mol). Dale has shown that there is no easy path between these two conformations, at least for cyclodecane itself. This high barrier is, we believe, closely related to the relatively high barrier separating the boat–chair form of cyclooctane from the twist–chair–chair form, which belongs to the crown family.[23,27]

Eleven-membered ring ketones

11-Membered rings are rather rare, and it is thus not surprising that structural data on cycloundecane or its simple derivatives are non-existent. Strain–energy calculations show that several conformations are of similar energies. NMR spectra on cycloundecane at low temperatures do not lead to clear conclusions. However, the NMR spectra of cycloundecanone are fairly informative.[40] The CMR spectrum at low temperatures shows the presence of a single CO resonance, and two α carbons resonances. The proton spectrum is complex, but shows clear evidence for two conformational processes, with $\Delta G^{\neq}$'s of 6·0 and 6·9 kcal/mol. The main conclusion which can be drawn from the above data is that cycloundecanone exists predominantly in a single, unsymmetrical conformation. Further work is needed to determine the precise structure of cycloundecanone.

CONCLUSIONS

It is interesting from a historical point of view that crown-family conformations were favored in both the 8- and 10-membered rings until about 15 years ago, when evidence of the type mentioned in the Introduction indicated that boat–chair and boat–chair–boat conformations were preferred. However, it is now clear that the best crown-family conformations are only slightly higher in energy than the boat–chair or boat–chair–boat forms, and that appropriate substituents can easily lead to a reversal of these energy relationships. In view of the small number of ketones in the medium rings which have been examined in detail by NMR or by X-ray methods and the approximation involved in strain–energy calculations, it is perhaps surprising that our present understanding of the conformations of these compounds is as good as it is. Future work will undoubtedly greatly expand our knowledge in this area.

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