

Conformational Analysis:
A Force-Field for Ketones and Aldehydes

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A Summary of
CONFORMATIONAL ANALYSIS:
A FORCE-FIELD FOR KETONES AND ALDEHYDES

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September 1978

A force-field currently in use for application to alkanes and alkenes is extended, herein, so as to include a ketone/aldehyde capability. This is done by the inclusion of further constants to take into account terms due to 13 interactions involving the carbonyl group. The force-field is parameterized so as to reproduce as closely as possible the geometries of 27 carbonyl compounds possessing widely differing structural features and also the standard heats of formation of 39 ketones and 10 aldehydes, these being all the carbonyl compounds for which appropriate data are available to date. The actual precise degree of correspondence obtained between the calculated and experimental data is not so high as in the case of the parent hydrocarbon force-field but vies favourably in comparison with the other principal carbonyl force-field in existence.

An analysis follows of the geometrical and thermochemical results of carbonyl compounds for which the appropriate experimental data are as yet unavailable, so precluding comparisons. Miscellaneous applications include analyses of the conformers of ring-ketones and their relative energies and a survey of the compounds of (3.3.1) bicyclic structural types. Calculations find the chair-boat conformer of 1-methyl-7-exo-t-butyl(3.3.1)-bicyclononane-2,9-dione to be more stable than the twin-chair form, in agreement with observation. Similarly, 9-thia(3.3.1)-bicyclononane-2,6-dione is calculated to be slightly skewed, to relieve unfavourable non-bonded interactions, as is found experimentally, and two other sulphur-containing systems, 3-oxa-7,9-dithia- and 9-oxa-3,7-dithia(3.3.1)bicyclononane are conformationally analyzed. For these cases, a further extension of the force-field so as to incorporate sulphide and ether parameters is described.

INTRODUCTION

The method of molecular mechanics, alternatively known as that of the force-field, provides "a reliable way to determine routinely structures and energies for use in other work".¹ Its usage is dictated by expediency, and in those molecular systems within which it has its range of applicability it is of real practical use for obtaining quite good quantitative information.

Traditionally there have been, and will continue to be, alternative ways of obtaining these data. Experimental methods which provide access to determining molecular structure are numerous: the various forms of spectroscopy such as n.m.r., infra-red and Raman, ultra-violet, micro-wave, and optical rotatory dispersion and circular dichroism, as well as diffraction studies using x-rays, electrons and neutrons. All have advantages and limitations in practical use and have restricted applicability, e.g. x-ray diffraction gives an enormous amount of precise structural information about molecules and their mode of packing, but unfortunately its use is limited to crystals.

Some of the spectroscopic methods and also the long-established techniques of calorimetry and electrochemistry are useful for determining thermodynamic quantities such as heats of formation and energy differences between conformations of a given type of molecule. But, again there are drawbacks regarding their usage, and all experimental methods alike are time-consuming and require considerable input of human resource.

The different types of theoretical approach to obtaining geometric and thermochemical data comprise ab initio quantum mechanical calculations and several approximation methods derived from it, and molecular mechanics. The ab initio method is fundamental and in principle will always lead to precise and accurate data. Unfortunately, owing to the complexity of the calculations that need to be performed in order to obtain results the method is practically inapplicable to all but the very simplest systems, the computer time requirement for calculations varying with the fourth power of the number of atomic orbitals involved.

Approximations applied to the ab initio method give rise to several simplified quantum mechanical treatments such as CNDO, MINDO, NDDO, EHT et al., but the time requirements are still large, varying with the square of the number of orbitals, and the results, of course, are now not quite so reliable.

Molecular mechanics, however, is less time-consuming, computing time varying with the square of the number of atoms present, and the calculations are easier to perform. Further, the results can be as good as those obtained by the aforementioned theoretical techniques, and even vie in accuracy with those derived experimentally. Since it is an empirical method it can be applied successfully only in the area of molecular types for which it is fitted, the initial parameterization of a "force-field" being made over a large set of good experimental data. Subsequent information on the other compounds can be then derived, effectively, by interpolation.

Currently the scope of the method permits calculation of organic molecular geometries including conformational parameters, also heats of formation, energies of conformations and barriers separating them, transition state geometries and barrier heights (hence information on reaction kinetics), and it aids in the interpretation of optical and n.m.r. spectra. It is being applied to various types of organic compound, especially to hydrocarbons, keto-compounds and peptides, and there are several types of force-field in existence together with a larger number of minor variants of them. Numerous reviews have surveyed the field, especially relatively recently²⁻⁵ and ever since the time nearly 20 years ago that Hendrickson⁶ pioneered his work on cycloalkanes it has continued to flourish.

The object of his particular work is to describe the extension of a hydrocarbon force-field, currently in use at the University of Glasgow,⁷ in order to include a ketone/aldehyde capability, and several applications of the force-field so derived.

Force-fields

Force-fields are developed so as to fit a mechanical model of a molecule, i.e. a series of masses connected by springs. Deformation of the structure from its reference equilibrium state results in an increase in potential energy which can be calculated from a knowledge of the force-laws and constants involved. These latter comprise the force-field.

That to be described in the present work is an example of a valency force-field. It gives the total potential energy

("steric energy"), E_s , of a molecule as the sum of six independent terms:

$$E_s = E_l + E_\theta + E_\phi + E_r + E_\chi + E_q$$

which are, respectively terms representing bond-length deformations, bond angle deformation, torsional strain, non-bonded interactions, out-of-plane deformations at trigonal atoms, and coulombic energy.⁸

(Since parameterization of the force-field involves use of standard enthalpies of formation, the term "steric enthalpy", H_s would seem more appropriate.)

The force-field assumes natural bond lengths and angles between given atoms in a reference state, and also defines reference states for torsional angles and Van der Waals interactions. In a real molecule deviations from the reference states cause it to possess a steric energy other than zero; subsequently by allowing the molecule to relax a geometry can be obtained for which its steric energy is minimized.

(i) Bond-length Deformation

Using the elastic spring analogy, the potential energy stored in a molecule as the result of stretching and compressing its constituent bonds away from their reference lengths is given by Hooke's Law:

$$E_l = \sum \frac{1}{2} k_l (l - l_0)^2$$

where l_0 and l are the reference and actual bond-lengths respectively and k_l the force-constant. (The term "reference" length is preferred to "unstrained" length since even in any supposedly "strain-free" molecule with all bond-lengths at their reference values, there is still some "strain" present.)

Since bond-lengths are difficult to alter owing to their high force-constants, this energy term is usually low, deformations occurring preferentially in the other geometric parameters having much lower force-constants, when necessary.

(ii) Bond-angle Deformation

Again, a Hooke's law quadratic term is used to represent the energy of bending an angle away from its reference size, but, since the latter is anharmonic, particular at large displacements, a cubic term is added.

$$E = \sum_{\theta} \frac{1}{2} k_{\theta} (\Delta\theta)^2 - k'_{\theta} \Delta\theta^3$$

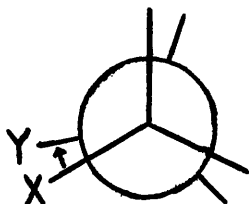
where $\Delta\theta$ is the respective angular displacement and k_{θ} and k'_{θ} are force constants.

(iii) Torsion

Torsional energy is due to the interaction between vicinal groups (or bonds) with respect to rotation about the central bond.

$$E_{\phi} = \sum_{\phi} \frac{1}{2} k_{\phi} (1 + s \cos n\phi)$$

where $s = -1$ or $+1$ for cases where the energy minimum is at eclipsed or staggered conformations respectively, n is the periodicity (i.e. the number of occurrences of the same conformation in one rotation), the dihedral angle, signed conventionally as shown below, and k the barrier to free rotation.



X is rotated clockwise to eclipse Y, so that the torsion angle is defined to be positive.

The reverse situation obtains for negative torsion angles.

The barrier height is relatively insensitive to the nature of the interacting groups, but somewhat more so to their number.

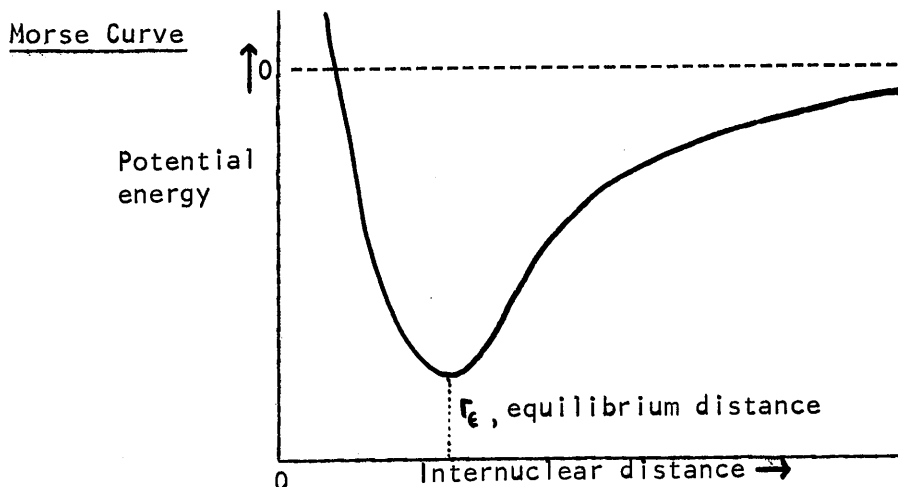
Further discussion about the nature of torsional interactions can be found in the literature.⁹

(iv) Non-bonded Interaction (Van der Waals Energy)

As its name suggests, energy due to non-bonded interactions arises as the result of repulsive and attractive forces between pairs of atoms which are not bonded to each other. The presence of these cohesive forces accounts, for example, for the existence of the condensed phases of noble gases which could not otherwise be formed.

They also exist between atoms that are directly bonded to each other but this aspect is not separately considered, the effect being absorbed by the bond-length deformation factor. Furthermore, they exist between pairs of geminally bound atoms, i.e. atoms connected via a single central atom, but the force-field under discussion does not consider these although they are, however, taken into account in the Urey-Bradley force-field.

The variation of potential energy of a system of two spherical atoms with the distance separating their centres can be expressed by means of a Morse curve, as shown:



The force acting between a pair of atoms is given by the gradient of the curve, and is attractive at large internuclear separations and repulsive for small. Also, for non-spherical atoms, for example the oxygen of a carbonyl group which possesses prominently directed lone electron pairs, the potential energy will vary with orientation¹⁰ and will therefore have a more complicated format. However, for simplicity, the more straightforward treatment is retained here.

In a few cases, namely those of, for example, nitrogen, methane and the noble gases,¹¹ it has been possible to calculate the potential curve from a consideration of their deviations of behaviour from ideality. Normally, however, it is taken from interatomic or intermolecular interaction potentials, a method which usually works well in practice despite its lacking a firm theoretical base.¹²

The two most commonly used forms of Van der Waals potential are the Buckingham potential,

$$E_r = ae^{-br} - cr^{-6}$$

and the Lennard-Jones potential,³

$$E_r = ar^{-n} - br^{-6}; \quad n = 9-12$$

where a , b and c are adjustable parameters, and the terms represent respectively repulsion energy (prominent at small separations) and attractive energy (at all separations). In the absence of other perturbing forces, the equilibrium separation of the atoms corresponds to a state of balance between the attractive and repulsive forces at which point the atoms have their respective Van der Waals radii.

In the force-field under consideration the potential has the form:⁷

$$E_r = \sum_r \epsilon (-2\alpha^{-6} + e^{12(1-\alpha)})$$

where the energy parameter ϵ varies with the size of the atoms and the parameter α is the ratio of the actual Van der Waals distance between two atoms to the sum of the individual Van der Waals radii. ϵ is effectively an independent parameter, but one which was derived initially from the starting point of the geometric mean of a pair of single atom type parameters, in the case of interactions between unlike atoms.

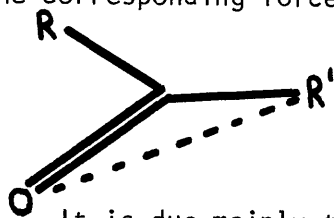
The summation is over all pairs of non-bonded atoms three or more bonds apart, and although such a pairwise additive method sometimes gives incorrect results, by suitably careful parameterization, involving, especially, data at small internuclear separations (where the functions are least reliable) it is possible to obtain satisfactory representation. Successful evaluation of such non-bonded parameters is essential for a good force-field and there has been much discussion in the literature centering on this topic.^{5,14} The evidence available suggests that the parameters for carbon and hydrogen utilized in the present force-field give optimum results in most cases.

(v) Out-of-plane Bending

The potential energy arising from the deformation away from coplanarity of systems consisting of a central trigonal carbon atom attached to three neighbouring atoms is given by:

$$E_x = \sum_x \frac{1}{2} k_x (180 - \theta)^2$$

where χ is the improper torsion angle at the trigonal atom and k_χ the corresponding force-constant.



The improper torsion angle
 $\chi = \text{R-C-O}\cdots\text{R}'$

It is due mainly to π -bond weakening as a result of poorer orbital overlap.

(vi) Coulombic Energy

The Coulombic energy of a molecule results from electrostatic interactions between any polar groups present. It is given by:

$$E_q = \sum_q \frac{q_i q_j}{D r_{ij}}$$

where the q 's are the respective electrostatic charges on the atoms i and j situated a distance r_{ij} apart, and D is the effective dielectric constant.

For alkanes and alkenes and even for monoketones this coulombic energy is minimal and can reasonably be ignored, but this is not the case for oligoketones where interacting polar groups present in the same molecule give rise to a significant coulombic energy contribution.

Parameterization of a Force-field

A force-field, as previously defined "describes the restoring forces which occur in a molecule when the geometry of minimal potential energy is disturbed".³ Hence, optimal values for the

force-field parameters are to be derived so that the geometric and thermochemical (and spectroscopic, where possible) properties of a wide range of molecules of a given class can be accurately derived.

A large set of accurate and diverse experimental data is necessary against which to parameterize the force-field, which itself must have the minimum number of parameters and terms to give precise results yet still permit visualization of the intuitive chemical concepts. (A simple polynomial expression containing terms up to, say, the 30th power could be conceived which reproduces experimental data eminently; it would have little significance in the grasp of a practising chemist, however.)

Starting values for potential functions, reference geometric parameters and force constants are taken from the literature and subsequently modified until parameters calculated from the force-field agree well with observed values. In practice, adjustment of non-bonded parameters tends to be the most difficult of the tasks, and different force-fields in the literature often differ from one another primarily in this area.

Optimum values are found, tediously, by trial-and-error method or, alternatively, by a least-squares process, or a combination of both. All, alike, give good results practically.

Heats of Formation

In force-field calculations the energy of a molecule is minimized with respect to coordinates of the constituent atoms, and the program yields the total steric energy, its components, and

the detailed geometry of the molecule in one or other of its conformational minima (or maxima), which one of the latter depending on the starting geometry.

Since the steric energy relates to an isolated molecule in a hypothetical motionless state at 0 K,¹⁵ the enthalpies of translation, rotation, and vibration and the zero-point energy have to be considered in order that the steric energy calculated can be compared with the experimental standard enthalpy of formation at 298 K. This may be done through statistical mechanics or else empirically by using bond or group increments.

By the former route, a rotational enthalpy contribution ($3RT/2$ per mole), a vibrational contribution, E_{vib} ,

$$E_{\text{vib}} = kT \sum_{i=1}^{3N-6} \ln(1 - e^{-h\nu_i/kT}) \text{ per mole}$$

where h, k are Planck's and Boltzmann's constants respectively, N is the number of atoms per molecule and the ν_i the fundamental vibration frequencies, and the zero-point energy, $E_{\text{vib}}(0 \text{ K})$,

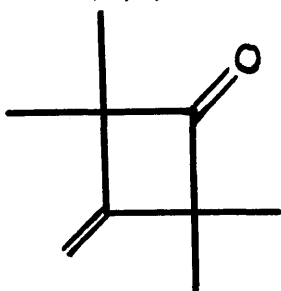
$$E_{\text{vib}}(0 \text{ K}) = \frac{1}{2}h \sum_{i=1}^{3N-6} \nu_i$$

are all added to the calculated steric energy to give the required heat of formation.

This approach is cumbersome and not used in the force-field under discussion. Here the group increment route is followed, (the bond contribution scheme will have done equally as well) which, apart from being easier to use in practice, also partially compensates within itself for small errors which might be found in the force-field. It regards all structural units of a given

type as contributing equally to the overall heat of formation of a molecule, irrespective of its structure. This heat is then simply the sum of all appropriate enthalpy increments added to the steric energy. The increments are themselves obtained by a least-squares process¹⁶ from the experimental enthalpies and steric energies.

e.g. For 2,2,4,4-tetramethyl-3-methylenecyclobutanone,



$$\Delta H_f^\circ (\text{gas}, 298 \text{ K}) = E_s + 4I_{-\text{CH}_3} + 2I_{-\text{C}} + I_{=\text{CH}_2} + 2I_{=\text{C}} + I_{\text{CO}}$$

One feature indicated by the statistical mechanical approach is that since the primary contributions to the enthalpy of a molecule at 298 K, namely the zero-point energy and the vibrational term, are so very similar for different conformations of that molecule, steric energy differences effectively reflect conformational energy differences.

Finally, both methods neglect the fact that in the case, say, of an acyclic molecule which is free to flex, the observed heat of formation is taken over all conformations present in the Boltzmann distribution. This is of no great consequence owing to the internally compensating feature of the enthalpy increment procedure. In the case of such molecules whose conformers are separated by known (calculated or experimental) enthalpy differences, it is then possible, of course, to take into account the small entropy factor, work out the relevant free energy difference and hence do a population analysis of the levels.

Energy Minimization

The geometry of a molecule, whether its coordinates be known precisely as a result of experimental observation or whether they be only approximated to by means of a geometrical consideration of a model, does not (in all probability) represent that of its equilibrium state with respect to the force-field used. Its steric energy has therefore to be minimized with respect to the atomic coordinates, a process which involves progressively and systematically making small adjustments to them until no further lowering in steric energy occurs. Several methods for doing this exist, and all have their respective advantages and limitations.¹⁷ The computer programs for their use normally work with Cartesian rather than internal coordinates because of their ease of manipulation; the latter are output very easily at the end of a calculation.

All methods are founded on the following simple theory:

For an N-atomic molecule whose steric energy E varies with the coordinate vector, x , of its atoms, there is zero net force acting on each of its individual atoms when that molecule is at its energy minimum.

$$-\left(\frac{\partial E_s(x)}{\partial x_i}\right)_j = 0; \quad i = 1, 2, \dots, 3N$$

Expanding the potential (i.e. steric) energy of the molecule in its trial form as truncated Taylor series about the minimum energy point yields:

$$E_s(x + \delta x)_{x=x_0} = E_s(x)_{x=x_0} + \sum_{i=1}^{3N} \left(\frac{\partial E_s(x)}{\partial x_i}\right)_{x=x_0} \delta x_i$$

where x_0 represents the coordinates of the trial geometry (fairly close to the minimum) and δx the differences in respective coordinates of the trial and minimum geometries.

Summing over all the atomic coordinates the condition for an energy minimum is thereby obtained:

$$\sum_{j=1}^{3N} \left(\frac{\partial E_s(x + \delta x)}{\partial x_j} \right)_{x = x_0} = 0 =$$

$$\sum_{j=1}^{3N} \left(\frac{\partial E_s(x)}{\partial x_j} \right)_{x = x_0} + \sum_{j=1}^{3N} \sum_{i=1}^{3N} \left(\frac{\partial^2 E_s(x)}{\partial x_i \partial x_j} \right)_{x = x_0} \delta x_i$$

or, in matrix notation,

$$\nabla E_s(x_0 + \delta x) = 0 = \nabla E_s(x_0) + F_0 \delta x \quad \dots (1)$$

i.e.

$$x = -F_0^{-1} \nabla E_s(x_0) \quad \dots (2)$$

where ∇E_0 is the gradient of E , F_0 is the matrix of second derivative of E , and F_0^{-1} is the inverse of F_0 .

A brief summary of some of the most commonly used energy minimization schemes follows.

(i) Steepest Descent

Historically this was the first general method to be used.¹⁸ It is efficient when the starting geometry is quite distant from the minimum but converges much more slowly as it is neared so that the latter cannot be located with any great precision. In fact, it converges on both minima and maxima of the potential energy hypersurface, but, advantageously is not left hanging in saddlepoints.

In the scheme, the energy variations resulting from successive, independent, small coordinate changes of all that are present in the molecule is monitored. Subsequently, these coordinates are then each moved in the energy-lowering direction by a distance in direct ratio with the partial derivative of the energy with respect to that coordinate, a process which is then repeated until consecutive steric energies are as close to each other as required.

(ii) Pattern Search

This is rather similar to method (i) except insofar as after each perturbation of a coordinate it is not restored to its former value if the energy change is favourable.¹⁹ Thus, convergence is more rapid, particularly so in the case of movement down long valleys of small energy gradient.

It, too, finds both energy minima and maxima, and converges quite slowly near them. Overall, however, its convergence properties are superior to those of the steepest descent method, the ultimate partial derivative obtainable by the latter being merely of the order of 10^{-1} kcal mol⁻¹ Å⁻¹, whereas in the present case it can be 10^{-3} or smaller.

(iii) Parallel Tangents

This again is somewhat similar to method (i), but now two energetically more favoured points are calculated, rather than merely one. The minimum on the curve through these, together with the starting point, then provide a fourth coordinate which is subsequently used for further steps of the same procedure.

(iv) Non-simultaneous Local Energy Minimization

Here the potential energy hypersurface in the vicinity of the minimum is approximated to by the function:

$$E = Ax^2 + By^2 + Cz^2 + Gx + Hy + Iz + J$$

where x,y,z are the Cartesian coordinates of the atom being referred to. The coefficients are found by calculating the energy and its derivatives with respect to each coordinate for two positions of the atom, and then repeating for all atoms. As before, the partial derivative of the energy with respect to each coordinate is zero at the minimum and by repetitions of the procedure the energy can be lowered until the shifts are as small as desired.

(v) Newton-Raphson Method^{20,85}

This is the scheme employed in the present work and is the one of choice since it leads to reliable results and to a very close approximation to the equilibrium geometry; in favourable cases after merely three iterations of the full-matrix program (v. infra) partial derivatives as low as 10^{-11} kcal mol⁻¹ Å⁻¹ can be obtained.

It is a 2-stage process; firstly, approximately 50-100 iterations of the block-diagonal method are applied to bring the initial crude geometry into the neighbourhood of the minimum (after which convergence slows) and subsequently 2 or 3 iterations of the full-matrix method bring it virtually to the absolute minimum point as aforementioned.

The block-diagonal program is so named by reference to the matrix F in equation (1). If $i, j \leq 3$ for each atom, then

$$F \equiv \frac{\partial^2 E_s}{\partial x_i \partial x_j} \quad \text{is a block diagonal matrix.}^{21,22}$$

Its use circumvents the scaling problems met in using the steepest descent method, but it requires a more precisely defined trial structure, even more so than the pure diagonal matrix method.

Derivatives having thereby been reduced to the order of 10^{-1} kcal mol⁻¹ Å⁻¹ the full-matrix method is used so as to greatly improve convergence. Here $i, j = 1, 2, \dots, 3N$. However, equation (2) cannot be solved directly since the matrix

$$F \equiv \frac{\partial^2 E_s}{\partial x_i \partial x_j} \quad \text{is singular.}$$

The reciprocal of F can be determined by the generalized inverse method, which requires the diagonalization of F , or else by the reduced F -matrix technique.⁴ However, since the latter is deficient insofar as it fails to yield a generalized inverse that is unique, it is not used here.

Since the full-matrix method takes into account all inter-atomic interactions (rather than a selection of them) it yields a very good representation of the symmetry of a molecule; because of its excellent convergence properties it also gives better values for the geometrical parameters generally, and torsion angles in particular, the latter being significantly altered when the molecule departs even slightly from its minimum energy state. Energies, however, are relatively little affected. It is preceded by a series of block diagonal iterations, when in use, because of its poor tolerance of geometries that deviate significantly from the equilibrium one.⁸⁶

Finally, involvement of the second derivatives in the calculations permits minima and maxima to be distinguished; the program locates maxima as readily as it does minima, which of the two is present being decided by the nature of the starting geometry.

2. EXTENSION OF THE WHITE-BOVILL FORCE-FIELD (WBFF)⁷ TO KETONES AND ALDEHYDES

2.1 Parameterization

In contrast to the case of alkanes and alkenes for which there are in existence numerous force-fields, as cited in the literature, the area belonging to ketones and aldehydes is very much a neglected one. There are several reasons why this should be so. Firstly, all such extended force-fields necessarily incorporate a hydrocarbon basis; before a carbonyl force-field can be parameterized, a firm such foundation has to be laid. This is why so much effort, relatively, has been put in the direction of hydrocarbon force-fields. Furthermore owing to the many shortcomings of these force-fields in comparison with the WBFF which is unsurpassed in reliability to date,⁸⁷ carbonyl force-fields relying on them would be of dubious merit and utility.⁷ Secondly, there is the practical reason that the quantity of good experimental data - molecular geometries and heats of formation - pertaining to carbonyl compounds is considerably more scarce than is the case for hydrocarbons. Without a broad spectrum of structural types against which the parameterization is to be made, the resulting force-field would be unreliable and also lack generality in its application.

During the last few years a significantly increased amount of the required good experimental data on carbonyl compounds has been forthcoming. Because of this fact and also the recent availability of the new improved hydrocarbon force-field the time was felt ripe to extend the latter so as to incorporate a ketone-aldehyde capability.

The form of the WBFF is retained precisely, along with all its parameters. Additional parameters are then included so as to take into account the presence of one or more carbonyl groups per molecule and the corresponding additional interactions thereby introduced. The parameterization involved the use of data pertaining to the geometries and heats of formation of a variety of ketones and aldehydes of diverse structural types. Although not quite so extensive as the range of hydrocarbons utilized in the formulation of the basis WBFF, on account of relatively less profuse availability, it nevertheless incorporates structural features such as acyclic and cyclic entities with various degrees of strain and steric crowding, and also the novel one of poly-functionality: the occurrence of a mixture of one or more double bonds, keto-groups and strained rings within a single molecule.

The force-field is not parameterized to apply to molecules containing α, β -unsaturated or any other form of conjugated system, and also not to ketenes. Naturally, the exclusions inherent in the WBFF, namely of 3- and 4- membered rings, spiro-, allenic and acetylenic systems, and to conjugated and aromatic hydrocarbons apply here, too.

Starting values for the new parameters are obtained from the literature²³ and by judiciously relating to those in the WBFF. By systematically adjusting them in trial-and-error fashion a close correspondence was eventually attained between experimental and calculated data, namely, molecular geometries, relative conformational energies, torsional energy barriers and heats of formation.

TABLE 1

Force-field Parameters(i) Atom types: 1 = H, 2 = C_{sp2}, 3 = C_{sp3}, 4 = O(ii) Dimensions: Force-constants: kcal mol⁻¹ Å⁻²,
kcal mol⁻¹ deg⁻².
Distances: Å; Angles: deg.
Energies: kcal mol⁻¹

(iii) The Parameters:

(a) Bond stretching

Type 1	Type 2	$\frac{1}{2}k_1$	l_0
2	4	685.0	1.212

(b) Angle bending

Types	1	2	3	$\frac{1}{2}k_\theta$	k'_θ	$\theta_0(1)^*$	$\theta_0(2)$	$\theta_0(3)$
1 2 4	1	2	4	0.0085	0.0	122.0	121.5	
3 2 4	3	2	4	0.0125	0.0096		121.0	119.0

*Superscript refers to degree of substitution of C_{sp2}

(c) Torsion

Types	1	2	3	4	$\frac{1}{2}k_\phi$	s	n
1 3 2 4	1	3	2	4	0.04	-1	3
2 3 2 4	2	3	2	4	0.06	-1	3
3 3 2 4	3	3	2	4	0.06	-1	3

(d) Non-bonded

Types	1	2	r_1	r_2	ϵ
1 4	1	4	2.80	0.0	0.12
2 4	2	4	3.40	0.0	0.12
3 4	3	4	3.40	0.0	0.12
4 4	4	4	3.30	0.0	0.10

(e) Out-of-plane bending

Types	1	2	3	4	$\frac{1}{2}k_x$
1 2 4 3	1	2	4	3	0.0025
3 2 4 3	3	2	4	3	0.0025

(f) Coulombic

Types	1	q
2 (carbonyl)	2	+0.35
4	4	-0.35

The new parameters introduced are shown in Table 1, and for clarity the steric energy expression to which they refer is summarized here:

$$E_s = \sum_l \frac{1}{2} k_l (l - l_0)^2 + \sum_\theta \frac{1}{2} k_\theta (\Delta\theta^2 - k'_\theta \Delta\theta^3) + \sum_\phi \frac{1}{2} k_\phi (1 + s \cos \phi) + \sum_r \epsilon [-2\alpha^{-6} + e^{12(1-\alpha)}] + \sum_x \frac{1}{2} k_x (180 - \chi)^2 + \sum_q \frac{q_i q_j}{D_{r_{ij}}} \dots (3)$$

The significances of all the symbols are related earlier (pp 4-9)

The values of the two group enthalpy increments, derived from the experimental heats of formation and calculated steric energies by a least-squares method, are listed here:

<u>Increment</u>	<u>Enthalpy (kcal mol⁻¹)</u>
>C=O (keto)	+31.07
-CHO (aldehyde)	+28.90

The derivative of the steric energy in all cases calculated is lower than 10^{-7} kcal mol⁻¹ Å⁻¹ (unless stated otherwise, in particular cases). Thus the molecules can be regarded as being in their effectively absolute minimum energy states.

It was felt not to be useful or informative to calculate mean deviations between calculated and experimental geometrical parameters, such as bond lengths, angles and torsion angles in the fashion done for hydrocarbon force-fields. Instead, individual deviations within specific molecules are noted and their particular cases, if significant, commented upon. The reasons for adopting this approach can be enumerated. Firstly the carbonyl compounds involved are generally considerably less symmetric and

also considerably larger than the hydrocarbons. This fact both increases enormously the actual number of geometrical parameters to be evaluated and also makes the true significance of any such final deviations, were they to be evaluated, much less easy to visualize. Some molecules would show large deviations in the region of the carbonyl group whilst others would show it in distant parts: is the carbonyl extension of the force-field lacking, or the original? Some exotic cage-molecules would show unusually large deviations, whereas a series of simpler acyclic molecules would show few: are all the molecules alike to be given equal weighting? Better it is to dispense with the procedure entirely. Secondly, the actual set of molecules whose geometries are compared would differ greatly from the sets of hydrocarbons encountered in the WBFF (and other force-fields). This would therefore not allow a meaningful comparison between the respective efficacies of the force-fields.

The above approach is the one adopted earlier by the other principal worker²³ on carbonyl force-fields, giving some strength to the arguments mentioned. In appropriate instances comparison is made with this work so as to serve as the best indicator of the relative merit of the new force-field.

In contrast, mean deviations for the enthalpies of formation are easily worked out; for the 40 ketones listed in Table 3 the mean deviation is $1.18 \text{ kcal mol}^{-1}$ (or $1.17 \text{ kcal mol}^{-1}$ if the value for tetramethyl-1,3-cyclobutanedione, which contains a 4-membered ring, is omitted). For the 10 aldehydes in Table 2 it is $0.89 \text{ kcal mol}^{-1}$.

Although superficially inferior to the $0.55 \text{ kcal mol}^{-1}$ deviation reported for hydrocarbons in the WBFF the aforementioned mitigating factors have to be borne in mind. Further discussion follows (Section 2.3).

Notes on Specific Force-field Parameters

The reference length for the $\text{C}=\overset{\text{O}}{\text{O}}$ bond of 1.212 \AA is taken as a good average value from many typical experimental values; the stretching force constant is similarly realistic.

Much the same situation exists for angle bending. The $\theta_{\text{O}}^{(1)}$ refers to methanal only, a trivial case which is not incorporated in the parameterization. $\theta_{\text{O}}^{(2)}$ relates to the other aldehydes and $\theta_{\text{O}}^{(3)}$ to ketones.

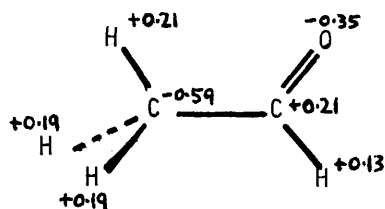
The torsional barrier heights are derived primarily²⁴ by consideration of the effects of rotation in simple molecules (v. infra).

Non-bonded parameters are, as expected, the more difficult of them all to evaluate, and if any future revision of the force-field is contemplated it is likely that it is these that will require the most attention. In the present instance, however, they represent the optimal values obtainable.

The out-of-plane bending force-constant showed little tangible effect on heats or geometries, even when varied quite widely. The value adopted is physically reasonable and also relates satisfactorily to that previously established for the $\text{C}=\text{C}$ group.

Finally, since the coulombic energy for monoketones is calculated to be identically zero, variation of the charges of the $\text{C}=\text{O}$ dipole will have no effect in these cases. For di- and tri-ketones its variation by 0.05 units of electronic charge makes

effectively no difference to geometric bond lengths and angles in these compounds and changes of the order of only 0.1° in torsion angles. Steric energies are somewhat more significantly altered by $0.28 \text{ kcal mol}^{-1}$ and $0.14 \text{ kcal mol}^{-1}$ respectively in the cases of 1,4-cyclohexanedione and 1,6-spiroanedione but, unfortunately, since no experimental thermochemical data is yet available for such compounds, it is not possible to discriminate in favour of the better value on this count. The values of ± 0.35 chosen are realistic and correlate reasonably with the partial charges found by population analysis of compounds such as ethanal:²⁵



The values are in units of electronic charge.

Also, as this example illustrates, the distribution of charge on the carbonyl function is relayed through the remainder of the molecule, and in uneven fashion at that. A more sophisticated force-field could allow for this effect but for the sake of simplicity, in the present case, the straightforward approach is adopted and regarded as good enough on the basis that overall compensation can be obtained and the force-field as a whole. In more accurate work, however, it would have to be allowed for, along with the uneven charge distribution induced in a relevant molecule by the presence merely of an alkene group.

2.2 Discussion of Geometries of Compounds with Known Experimental Values

The experimental geometries of all ketones for which sound data currently exist are compared with the calculated values in Figures 1(a) - 1(l) and in the remainder of this section. Certain

FIGURE 1 (a)

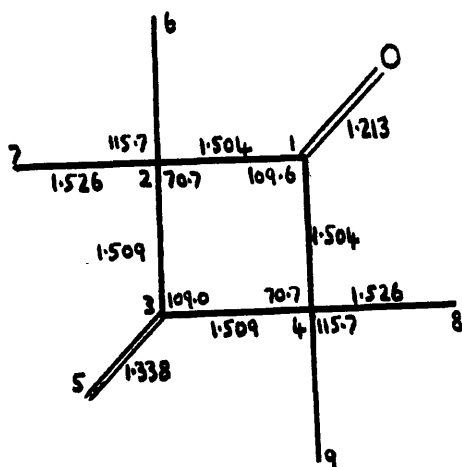
Calculated and experimental geometries (Parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol^{-1})

2,2,4,4-Tetramethyl-3-methylenecyclobutane³⁰ ($\Delta H_f^\circ = -30.39$,

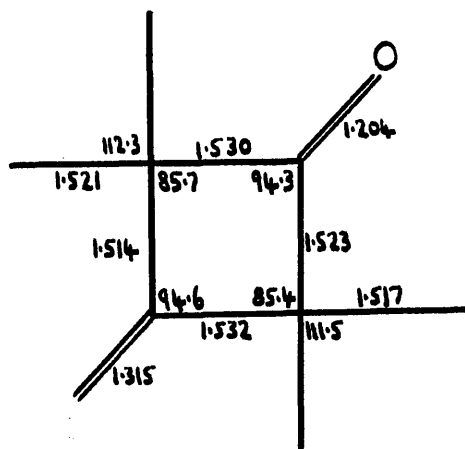
$E_s = 27.89$)

Expt.

Calc.



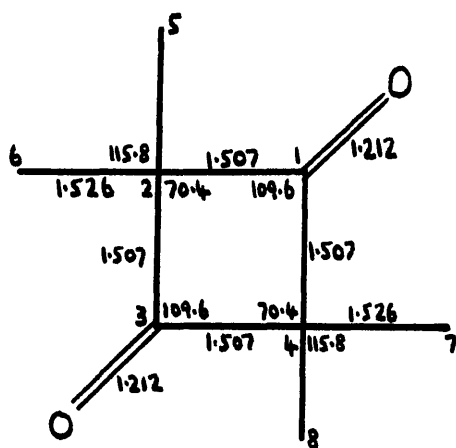
0.0 ϕ 4123
-69.6 ϕ 0148



0.0
-64.8

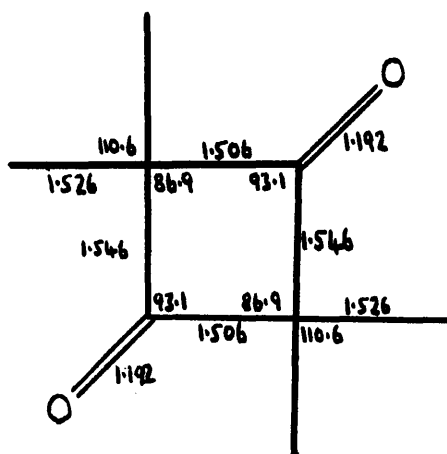
Tetramethyl-1,3-cyclobutanedione³¹

Calc.



0.0 ϕ 4123
-70.1 ϕ 0147

Expt.



0.0
-64.6

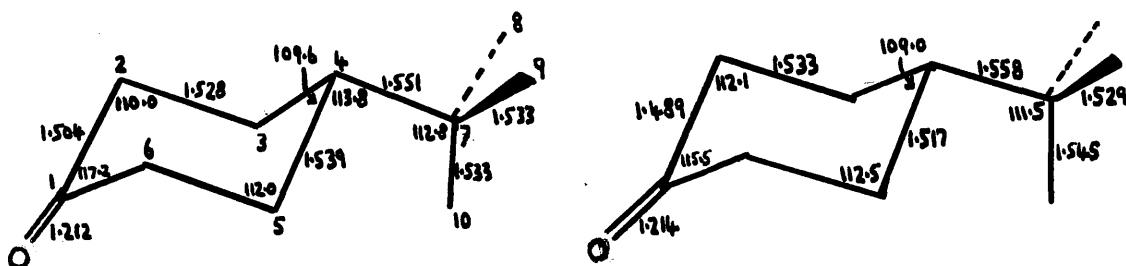
FIGURE 1(b)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

4-1-Butylcyclohexanone³² ($\Delta H_f^\circ = -79.93$, $E_s = 6.58$)

Calc.

Expt.

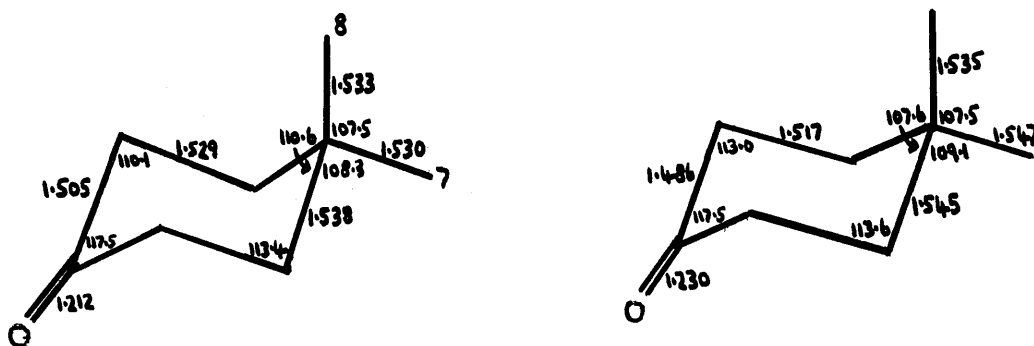


51.0	ϕ 6123	47.4
-52.9	ϕ 1234	-52.1
57.2	ϕ 2345	56.6

4,4-Dimethylcyclohexanone³³ ($\Delta H_f^\circ = -70.03$, $E_s = 3.84$)

Calc.

Expt.

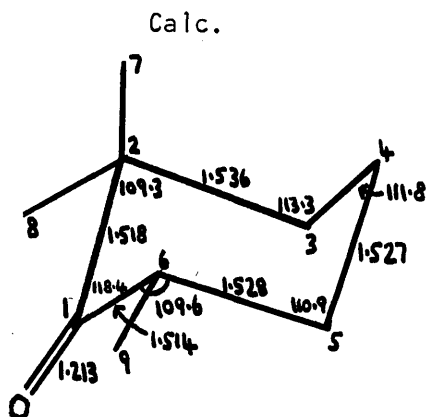


50.7	ϕ 6123	43.0
-50.8	ϕ 1234	-49.8
53.3	ϕ 2345	55.4

FIGURE 1(c)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

2,2,6-Trimethylcyclohexanone³⁴ ($\Delta H_f^\circ = -77.26$, $E_s = 3.96$)

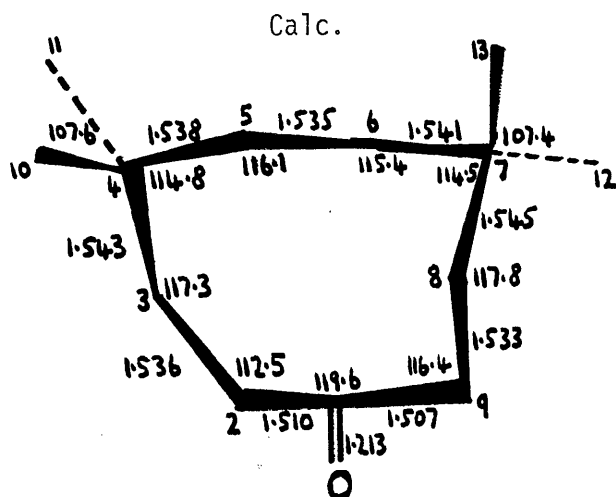


Expt.

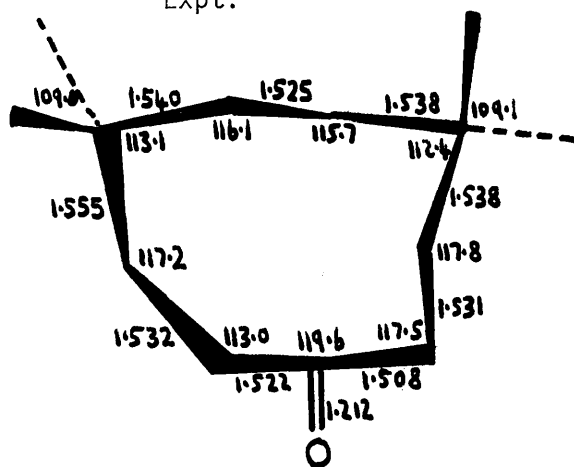
Chair-equatorial conformation. The geometrical parameters cited are inconclusive and not quoted here, other than two torsion angles.

-74.0	Φ 6127	-79.8
-174.8	Φ 2169	-178.2

4,4,7,7-Tetramethylcyclononanone³⁵ ($\Delta H_f^\circ = -92.44$, $E_s = 13.65$)



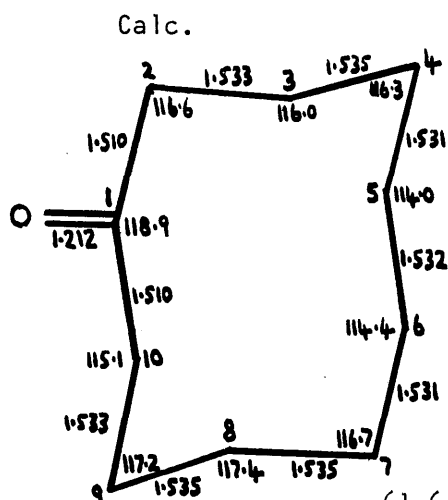
Expt.



133.6	Φ 9123	131.3
-94.3	Φ 1234	-101.2
36.0	Φ 2345	34.6

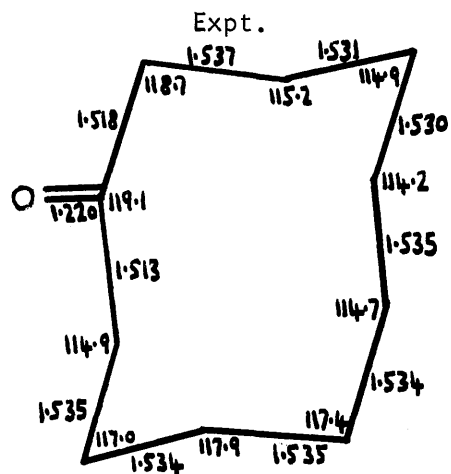
FIGURE 1(d)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

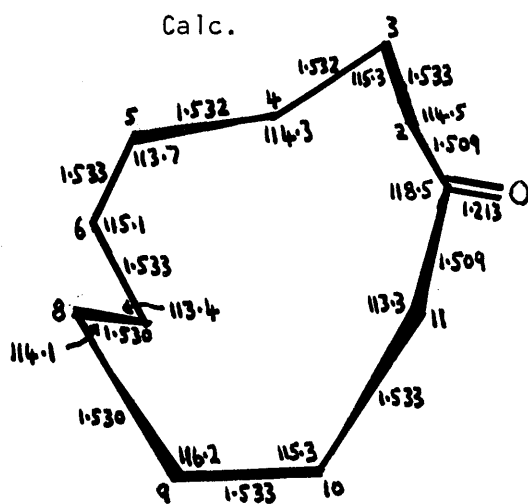
Cyclodecanone³⁶

-61.6
-66.0
61.6
153.5

⊕ 10, 12, 3
⊕ 1234
⊕ 2345
⊕ 9, 10, 12

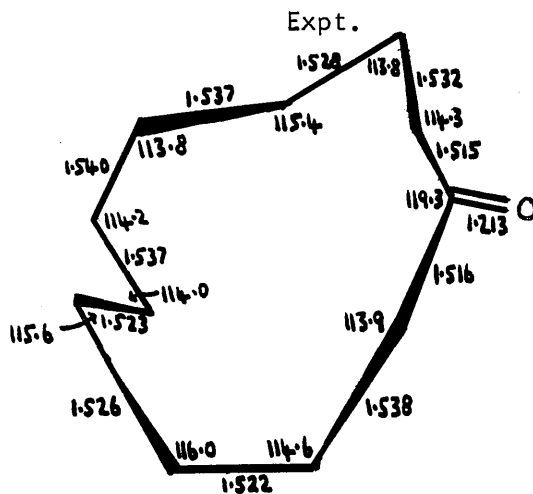


-49.1
-70.2
59.6
152.3

Cycloundecanone³⁷

-161.4
53.6
129.5

⊕ 11, 1, 2, 3
⊕ 1234
⊕ 10, 11, 12



-159.7
59.8
127.2

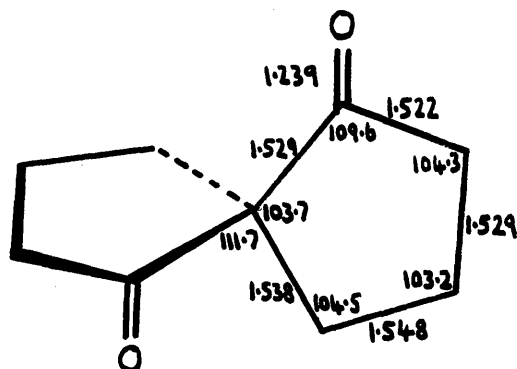
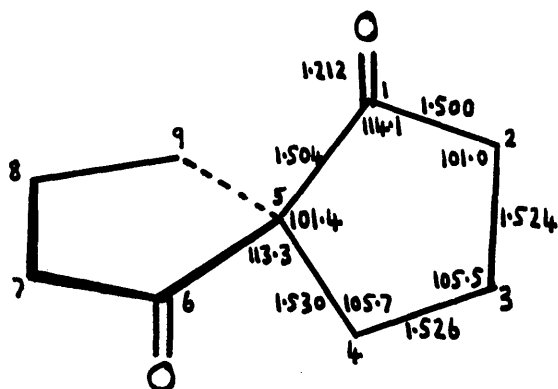
FIGURE 1(e)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

(4.4) Spiro[nonane-1,6]-dione³⁸ ($\Delta H_f^\circ = -82.66$, $E_s = 12.34$)

Calc.

Expt.



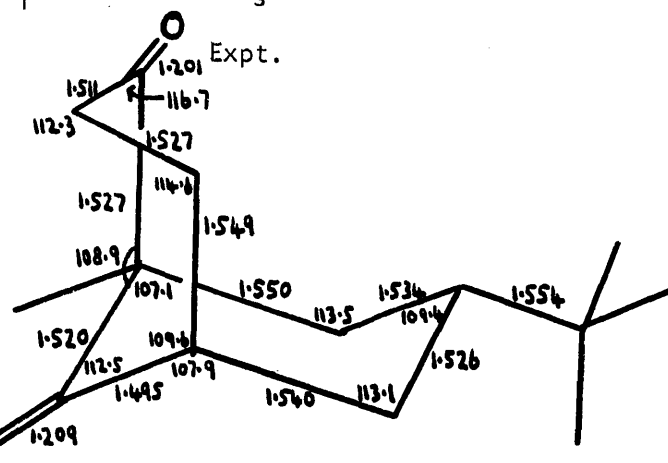
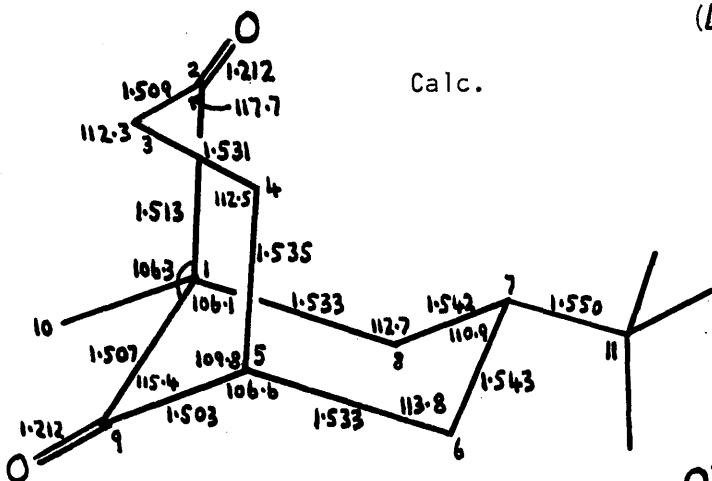
15.2	⊕5123	15
-30.5	⊕1234	-33
36.3	⊕2345	39

1-Methyl-7-exo-t-butyl(3.3.1)bicyclononane-2,9-dione³⁹

($\Delta H_f^\circ = -118.88$, $E_s = 12.46$)

Calc.

Expt.



-61.2	⊕1956	-61.0
-117.1	⊕8123	115.6
50.5	⊕1234	-46.3

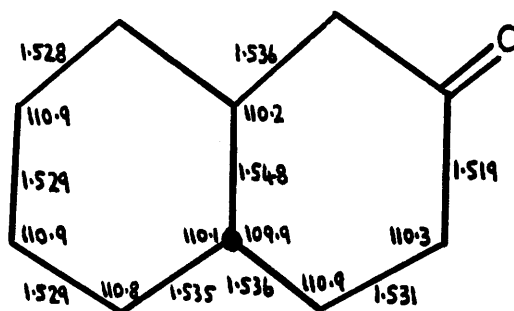
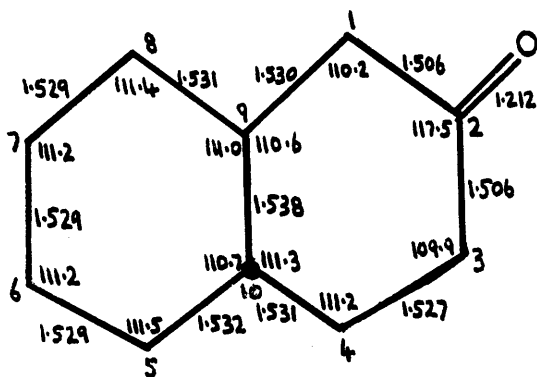
FIGURE 1(f)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

trans-2-Decalone⁴⁰ ($\Delta H_f^\circ = -68.60$, $E_s = 4.26$)

Calc.

Expt.

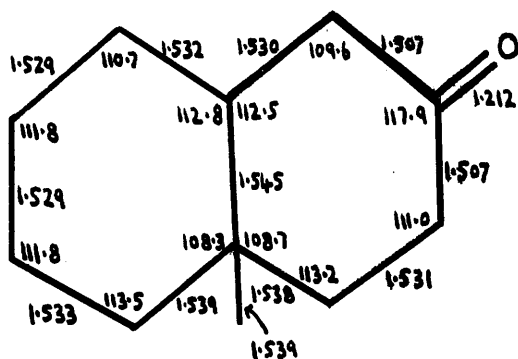


57.7	$\phi_{1,9,10,4}$	59.0
-57.7	$\phi_{9,10,4,3}$	-58.9
52.2	$\phi_{2,3,4,10}$	55.7

10-Methyl-trans-2-decalone⁴¹ ($\Delta H_f^\circ = -73.99$, $E_s = 7.87$)

Calc.

Expt.



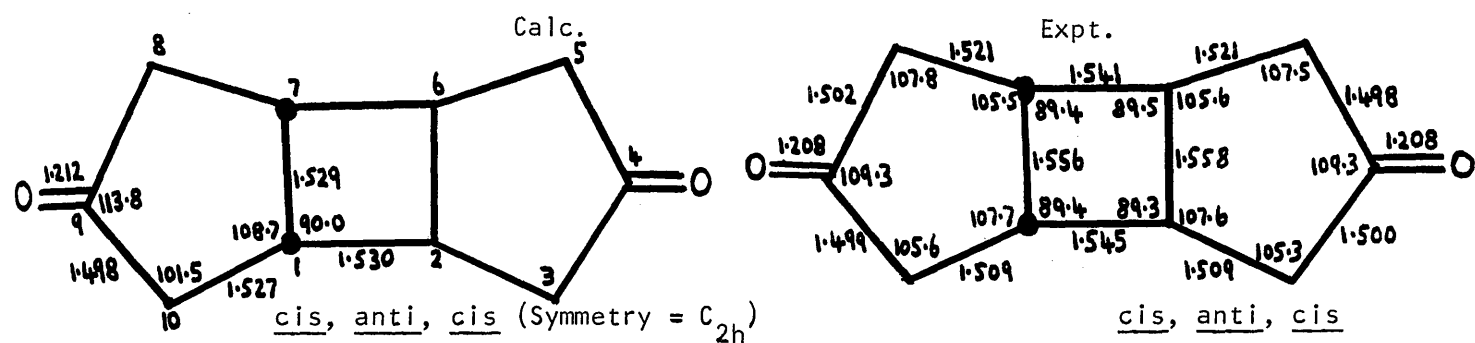
Only torsional parameters are cited in the experimental report.

58.4	$\phi_{1,9,10,4}$	58.3
-55.8	$\phi_{9,10,4,3}$	-60.8
49.6	$\phi_{2,3,4,10}$	52.4

FIGURE 1(g)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

(5.3.0.0^{2,6})Tricyclodecane-4,9-dione⁴² ($\Delta H_f^\circ = -58.27$, $E_s = 34.55$)



-24.2	⊖5432	-21.4
13.7	⊖4326	20.8
0.0	⊖1267	-11.9

6,7-Dimethyl (5.3.0.0^{2,6})tricyclodecane-3,10-dione⁴³

Calc.

Expt.

Structure not calculated.

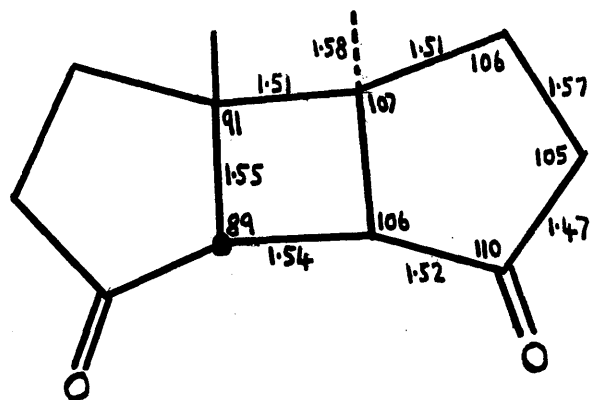
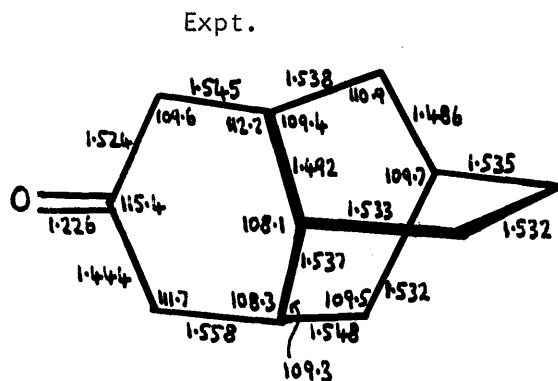
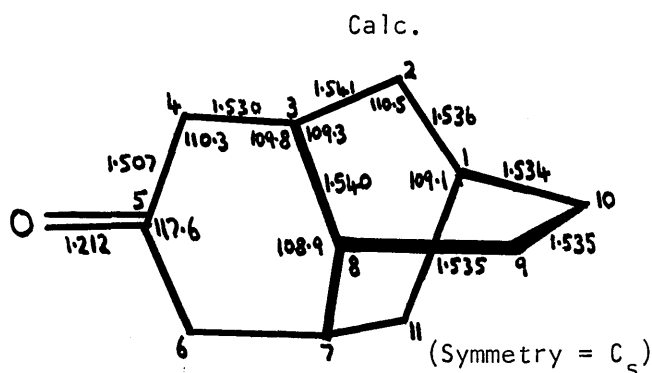


FIGURE 1(h)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

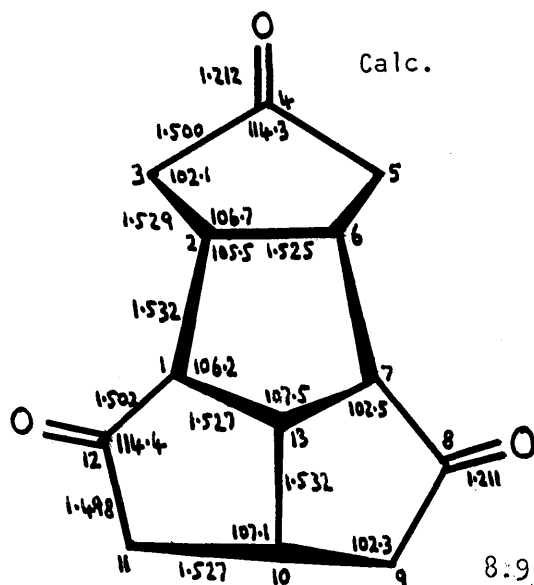
(5.3.1.0^{3,8})Tricycloundecan-5-one⁴⁴ ($\Delta H_f^\circ = -55.72$, $E_s = 16.61$)



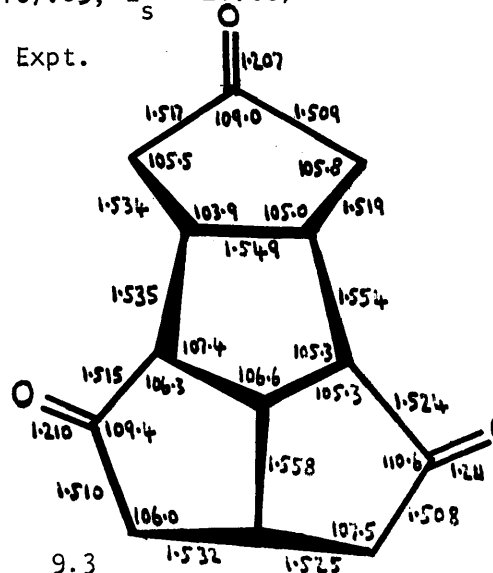
48.7	Φ 6543	49.0
-54.0	Φ 5438	-53.5
62.5	Φ 4387	61.6

endo-(5.5.1.0^{2,6}.0^{10,13})Tetracyclotridecane-4,8,12-trione⁴⁵

($\Delta H_f^\circ = -107.65$, $E_s = 21.00$)



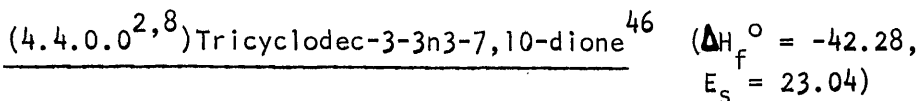
8.9	Φ 3456	
-16.6	Φ 7,8,9,10	
-16.6	Φ 10,11,12,1	



9.3		
-7.0		
-20.2		

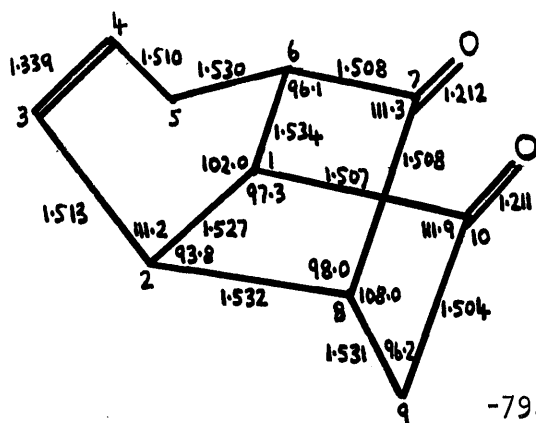
FIGURE 1(i)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)



Calc.

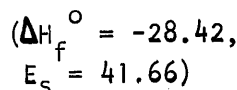
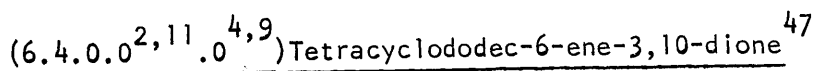
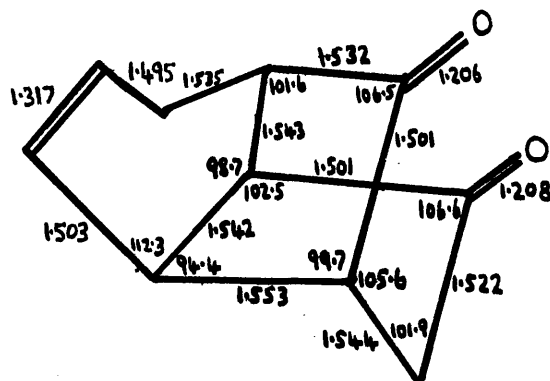
Expt.



-79.6
65.1
2.7

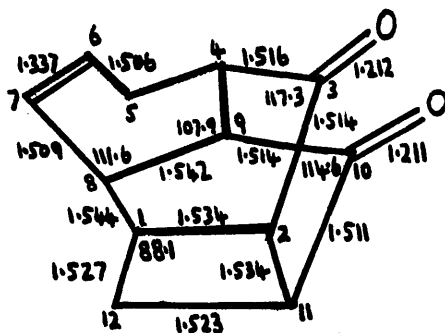
⊕ 6789
⊕ 7,8,9,10
⊕ 8,9,10,1

-74.6
69.0
1.7



Calc.

Expt.



-47.4
34.6
22.8

⊕ 4,3,2,11
⊕ 3,2,11,10
⊕ 2,11,10,9

-46.6
36.9
22.0

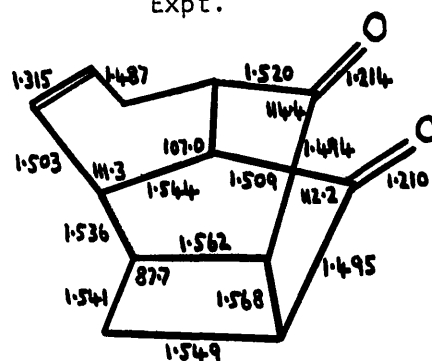


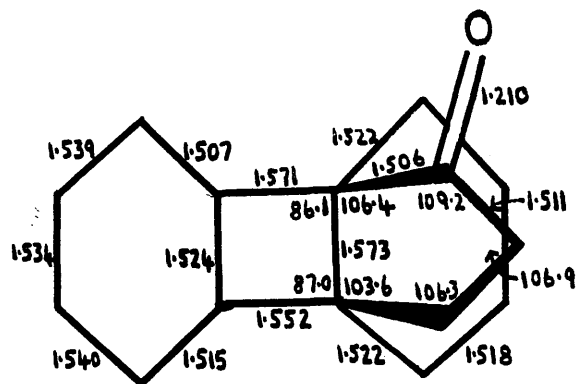
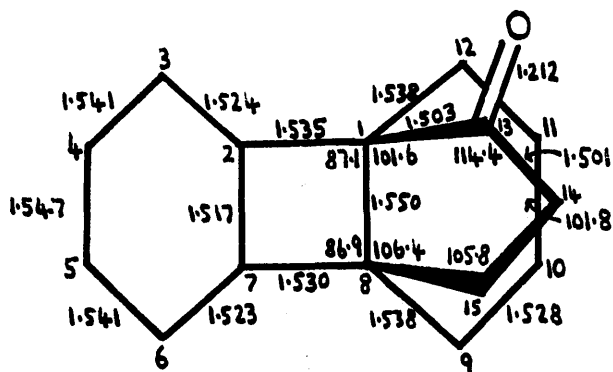
FIGURE 1(j)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol^{-1})

(6.5.3.0.0^{2,7})Tetracyclopentadecan-13-one⁴⁸ ($\Delta H_f^\circ = -40.13$,
 $E_s = 50.84$)

Calc.

Expt.

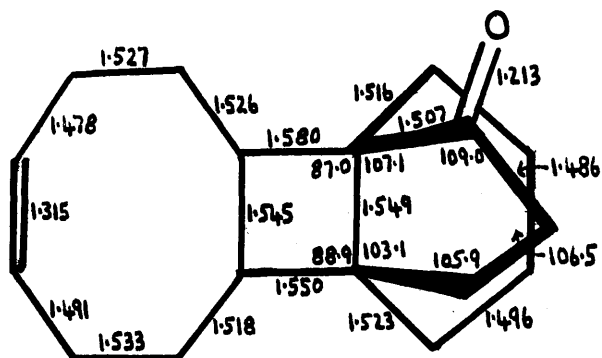
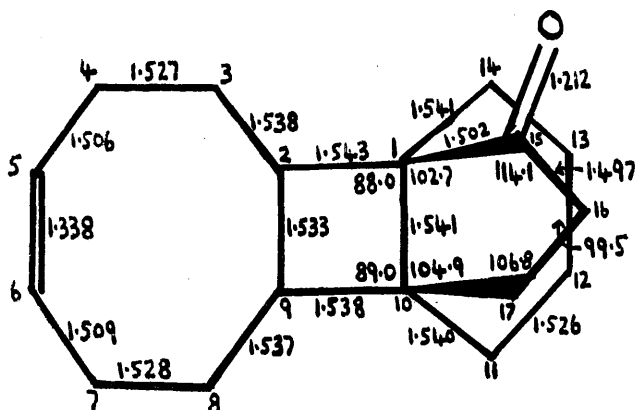


-20.7	$\phi_{13,1,8,15}$	-23.0
-23.0	$\phi_{12,1,8,9}$	-29.0
104.5	$\phi_{13,1,8,9}$	100.8

(8.4.3.0.0^{2,9})Tetracycloheptadec-5-en-15-one⁴⁹ ($\Delta H_f^\circ = -28.73$,
 $E_s = 45.32$)

Calc.

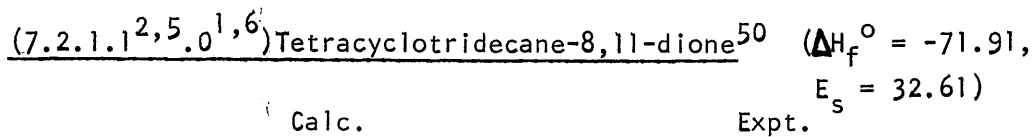
Expt.



-18.0	$\phi_{15,1,10,17}$	-20.1
-21.1	$\phi_{14,1,10,11}$	-25.7
105.5	$\phi_{15,1,10,11}$	103.3

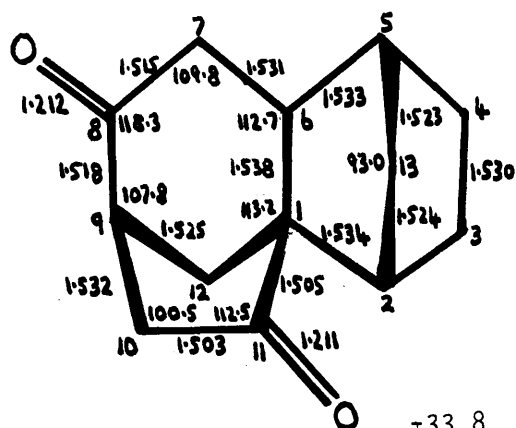
FIGURE 1(k)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol^{-1})



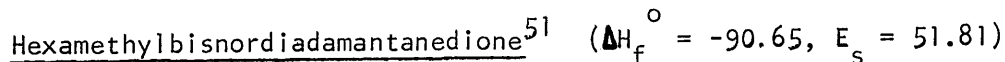
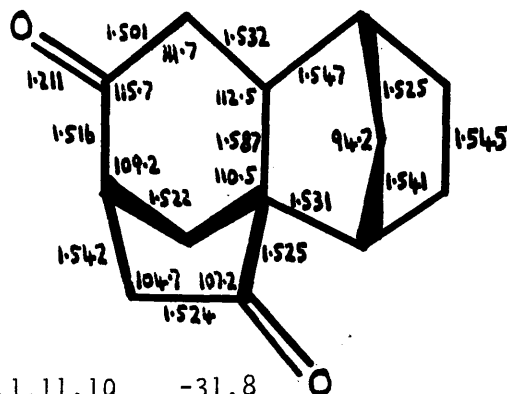
Calc.

Expt.



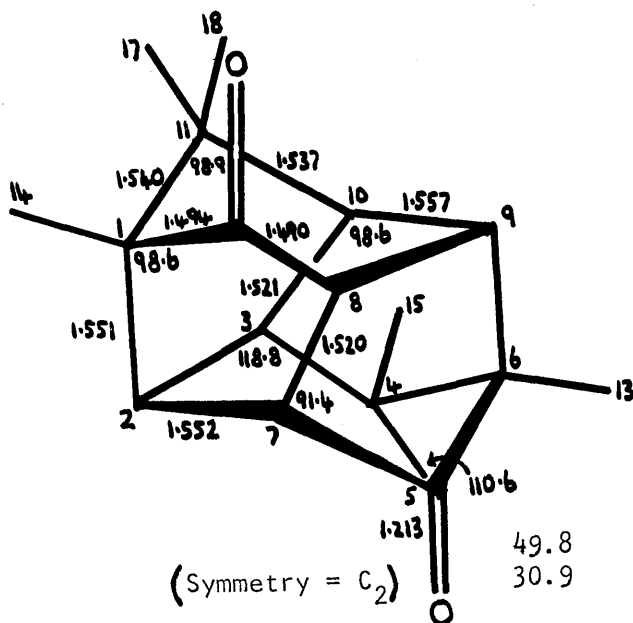
†33.8
-18.5
-88.3

⊙ 12, 1, 11, 10 -31.8
⊙ 7, 8, 9, 12 -21.2
⊙ 8, 9, 10, 11 -91.1



Calc.

Expt.

(Symmetry = C_2)

49.8
30.9

⊙ 6572 50.4
⊙ 7569 30.0

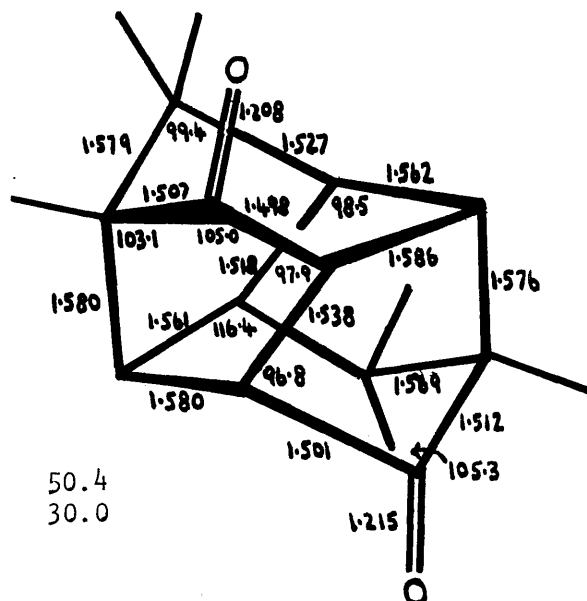
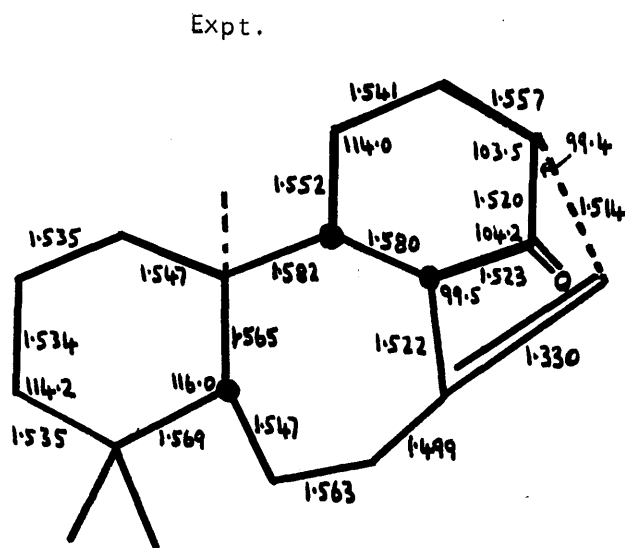
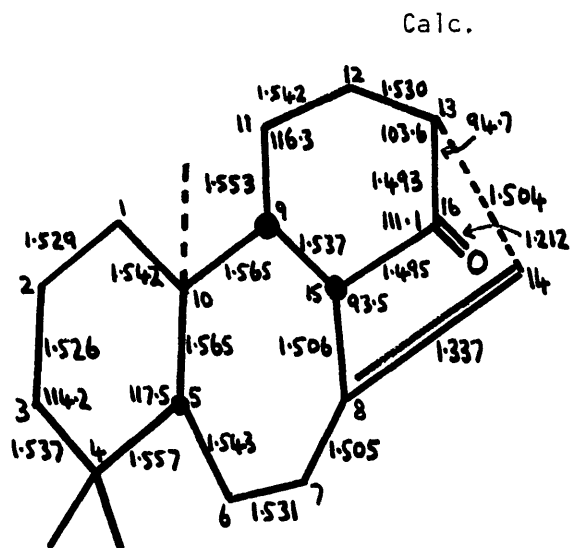


FIGURE 1(1)

Calculated and experimental geometries (parameters in Angstroms and degrees) and calculated heats of formation (gas, 298 K) and steric energies (kcal mol⁻¹)

ent-9(8 → 15 α H)abeo-17-Norkaur-8(14)-en-16-one⁵² ($\Delta H_f^\circ = -53.87$,
 $E_s = 38.52$)

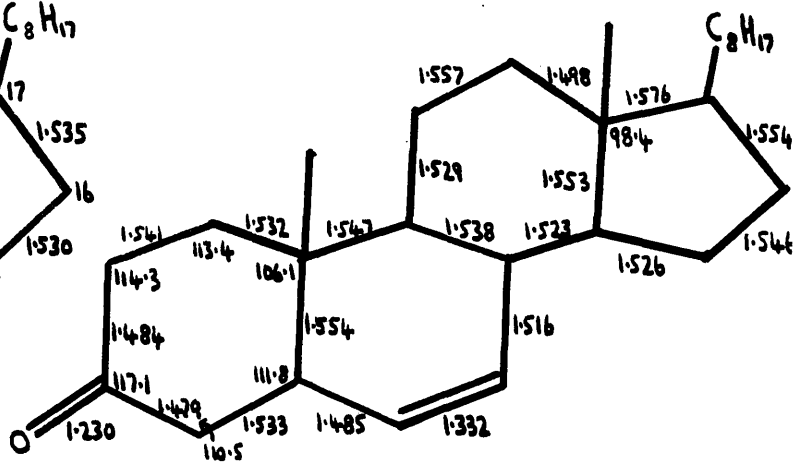
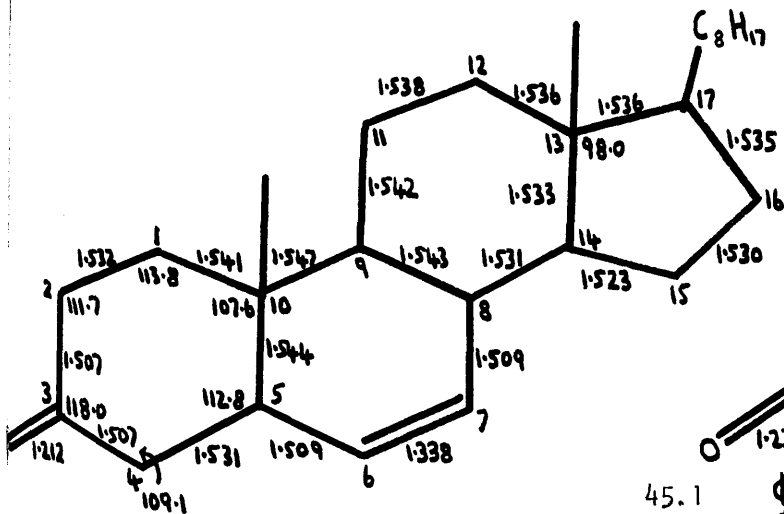


-40.6	ϕ 14, 13, 16, 15	-37.9
-71.8	ϕ 9, 15, 16, 13	-77.1

Δ^6 -Cholesten-3-one⁵³ ($\Delta H_f^\circ = -110.04$, $E_s = 27.21$)

Calc.

Expt.



45.1	ϕ 1234	41.2
-48.5	ϕ 2345	-46.6

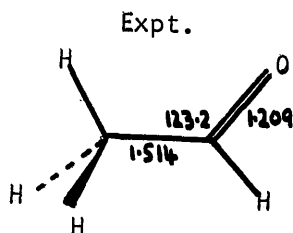
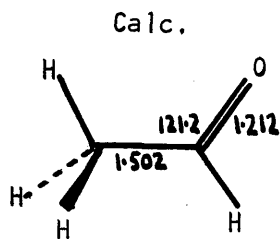
compounds such as butanedione and cyclobutanone^{26,27} with special structural features are arbitrarily excluded as mentioned previously. Also excluded is methanal for which the available data is conflicting slightly^{28,29} and which in any event poses no real test for the force-field on account of its uniquely simple structure.

It would have been a monumental task to quote every single geometric parameter for all the compounds listed, to include for example all carbon-hydrogen distances, all torsion angles, all bond angles, etc. It also seems unnecessary. Instead, for practical reasons, only a selection of parameters are presented, especially those in the vicinity of carbonyl groups but some others too. In particular cases mention is made of those values that illustrate important geometrical features, and unusually large discrepancies (and close correlations) are called attention to.

Not all the compounds listed were utilized in the parameterization. For example several of the polycyclic molecules possess cyclobutane rings, a feature not allowed for in the basic force-field. However, it is felt interesting to include them and see how their calculated structures fare in comparison with the experimental ones. Many of the more elaborate cage-like molecules and polycyclic systems are prepared by photochemical means and consequently in their lack of symmetry and complexity they have no strictly analogous alkane/alkene counterparts to permit comparison. In the parts of such molecules remote from the perturbing effects of the carbonyl group(s) they provide an interesting new test of the parent hydrocarbon force-field.

Some individual cases now follow:

(1) Ethanal²⁹



(Bond lengths in Å; angles in deg.)

The calculated C=O distance is within the quoted experimental error of the observed value, but this is not so for the C-C distance. (The quoted error is a sizeable 0.024 Å.) The experimental C-C-O angle is not quoted but can be deduced from the C ... O non-bonded distance for which the rather large differences are probably an experimental problem, the structure having been determined by electron diffraction as far back as 1969.

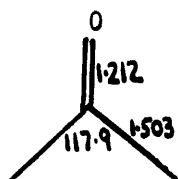
The carbonyl group eclipses a methyl hydrogen, a phenomenon readily represented by using an $s = -1$ torsional parameter in the force-field.

Violent adjustment of the other force-field parameters to unreasonable values for the purpose of arriving at a better fit was considered undesirable, and also tended to upset the consistency of the calculated thermochemical data.

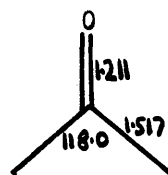
Further experimental data of geometries of aldehydes have to be awaited before work on this aspect can be consolidated.

(ii) Propanone²⁹

Calc.



Expt.



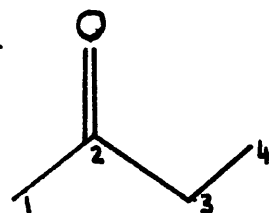
(Bond lengths in Å; angles in deg.)

The C=O bond lengths agree well, as do the angles, but again, as was the case with ethanal and as will be noted in several other examples the $C_{sp^2} - C_{sp^3}$ bond lengths calculated are about 0.01 Å too short. It would appear that the difficulty is due at least partially to the simplified assumption of equating the properties of a C_{sp^2} of an alkene group with that of a carbonyl group. The precise extents of hybridization in the two types can reasonably be expected to differ so that refinement of the force-field will necessitate additional parameters to take account of this, albeit at the expense of an increase in its complexity.

The eclipsing of the carbonyl groups by hydrogens of both methyl groups is again reproduced by calculation.

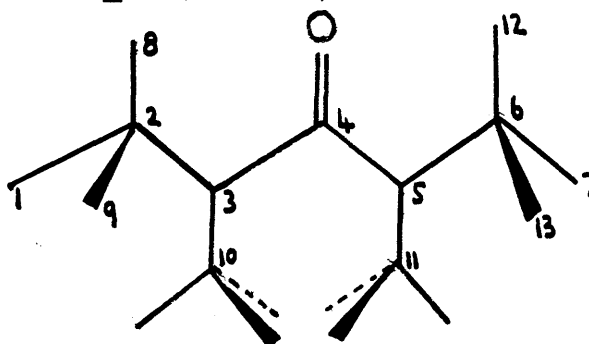
(iii) Butanone⁵⁴

The calculated and experimental C=O bond lengths are 1.213 and 1.218 Å respectively, a satisfactory agreement. Other C-C bond lengths and the $C_2C_3C_4$ and $O C_2C_3$ angles as determined by electron diffraction are not reported unequivocally. Their mean deviations from the calculated values are 0.010 Å and 0.3° respectively, a satisfactory agreement nonetheless.



The eclipsing of the carbonyl group, on the one hand by the hydrogen of the methyl, and on the other by C_4 (rather than hydrogen) are successfully reproduced by calculation.

(iv) 3,5-t-Butyl-2,2,6,6-tetramethylheptanone⁵⁵
 (sym-tetra-t-butylacetone)



The molecule is highly congested sterically and provides a severe test of the force-field.

The experimental C=O bond distance is remarkably short, 1.192 Å, a full 0.021 Å less than the calculated value. When further data on similarly strained ketones becomes available it may well become possible to refine the force-field further to correct an apparent deficiency. At the present time it is not feasible to do this so as to improve the geometry of this large molecule, and no less so than because it consists of as many as 58 atoms. Successive minimizations are extremely consuptive of computer resources and in this instance the root-mean-square magnitude of first derivatives was taken down to only 0.008 kcal mol⁻¹ Å⁻¹, by use of the block-diagonal program alone, and the calculation terminated at that point. Calculated bond lengths can therefore be taken to be very close to their equilibrium values, but this would not really apply to torsion angles.

The C_{sp²} - C_{sp³} distances are experimentally reported to be 2.560 and 1.568 Å, values that are in excess of the reference values by the enormous amounts of 0.059 and 0.067 Å respectively. The calculated values are both 1.535 Å, thus reflecting this high degree of bond lengthening, although to a lesser extent. Adjacent

C-C bonds are similarly elongated, experimentally, which the calculated structure also demonstrates, but again to a lesser degree:

	Calc.	Expt.	
C ₂ -C ₃	1.566	1.589	(Values in Å)
C ₃ -C ₁₀	1.570	1.595	
C ₅ -C ₆	1.570	1.607	In comparison, the C _{sp³} -C _{sp³}
C ₅ -C ₁₁	1.566	1.566	reference length = 1.520.

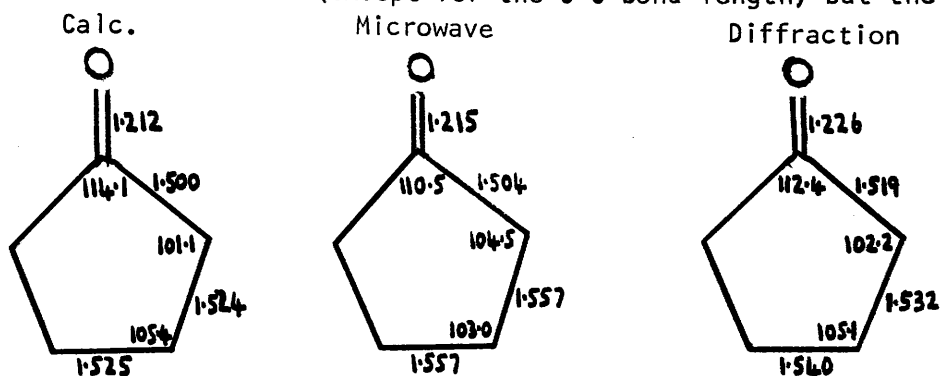
Bond angles compare well, the calculated and experimental values for example for the C-C-C angle at carbonyl being 121.5 and 121.4° respectively. Non-bonded values unfortunately do show some discrepancies, up to 0.24 Å in the worst cases of H···H interactions. The latter are more serious in the case of the calculated structure than in the observed one no doubt reflecting the shorter C-C bond lengths in the former and hence the greater steric crowding.

Finally the calculated structure is significantly more symmetrical than the observed, as suggested by the values of the aforementioned bond lengths, for example. It may well be the case that the molecule truly is unsymmetrical to some extent, but the fact nevertheless suggests at least the possibility of some inaccuracies in the experimental data (an x-ray crystal structure determination).

(v) Cyclopentanone^{56,57}

The structure is calculated to be symmetrical half-chair conformation, in agreement with experimental results based on electron diffraction and microwave determinations. The other unsymmetrical half-chair conformations as trials all relaxed upon minimization to give the symmetrical half-chair.

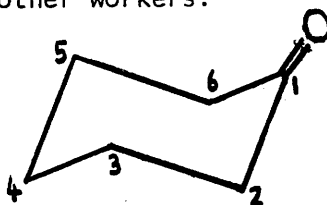
As seen by simple comparison of results the calculated structure is much closer in agreement with the diffraction than with the microwave structure (except for the C=O bond length) but the



figures are still disconcertingly outside the 3 standard deviation limits of the experimental data. As will be noted later, the standard enthalpy of formation is reproduced remarkably well, nevertheless.

(vi) Cyclohexanone

The chair conformation of the molecule is predicted to be the most stable, as found experimentally, and the calculated geometrical parameters are very close both to the experimental ones and those calculated by other workers:



	Expt. (microwave; ref.13)	Calc. (present work)	Calc. (Ref.58)	Calc. (Ref.23)
C ₁ -C ₂ (Å)	1.516	1.507	1.510	1.511
C ₂ -C ₃	1.535	1.528	1.532	1.529
C=O	1.222	1.212	1.225	1.224
C ₆ C ₁ C ₂ (deg)	116.2	117.5	115.9	114.9
C ₁ C ₂ C ₃	110.4	110.0	111.8	110.9

	Expt. (microwave; ref. 13)	Calc. (present work)	Calc. (Ref. 58)	Calc. (Ref. 23)
$C_2C_3C_4$	114.6	111.1	112.2	111.0
$C_3C_4C_5$	110.7	111.9	112.1	110.6

(vii) 1,4-Cyclohexanedione⁵⁹

The twist-boat conformation (D_2) is calculated to reside at an energy minimum, and is the experimentally observed structure. (The pure chair form was not investigated.)



Whereas calculation shows complete D_2 -symmetry, with for example all $C_{sp^2}-C_{sp^3}$ bond-lengths equal, the experimental results do not precisely reflect this and some differences can be noted, such as 0.019 Å between the adjacent bond-lengths just mentioned. This is either an experimental problem (x-ray diffraction) or else is a consequence of crystal-packing forces causing some distortions vis-a-vis the structure of the isolated molecule.

(iii) Substituted Cyclohexanones

A comparison of some available data for three such compounds is shown in figure 1(b,c). It is interesting to note that in the case of the 4-t-butyl- and 4,4-dimethylcyclohexanones the differences between the calculated and experimental $C_{sp^2}-C_{sp^3}$ bond lengths are +0.015 and +0.019 Å respectively, which apart from being opposite in sign to most other similar differences, and in particular that of cyclohexanone itself, are none the less not significantly worse than those appearing in some of the most remote $C_{sp^3}-C_{sp^3}$ bonds in these same molecules.

(ix) Cyclobutanones

These, strictly, are out of the scope of this parameterization, and no calculation was performed on the parent compound. It was considered interesting however to calculate the two other structures for which data exists (figure 1a) so as to see how well, or badly, the force-field would perform under these new conditions, especially as the profusion of substituent groups on the rings can reasonably be expected to "dilute" the influence of the pure, strained 4-membered rings on the overall geometry.

The calculations show, as expected, that the rings in both compounds are planar, in accordance with the experimental data. The ring angles at the C=O groups are however not as small as the observed values, and this discrepancy applied equally well at the exo-methylene substituent in the corresponding molecule. Again, the $C_{sp^2}-C_{sp^3}$ bond distances are too short, although this effect could be as due as much to the usual bond-lengthening in evidence in 4-membered rings as it is to the requirement for a separate such value for carbonyl $C_{sp^2}-C_{sp^3}$ bond distances. Finally, the calculated structures are precisely symmetrical about the axis through the C=O bonds, a state of affairs not quite existing in the observed structures, and one noted previously.

(x) 4,4,7,7-Tetramethylcyclononane (Fig. 1(c))

The calculated structure is very close to the experimental one, respective mean differences for ring bond-lengths and angles being 0.006 \AA and 0.6° . Only in the case of torsion angles at carbonyl are the discrepancies significant.

A conformation of the homologous compound, 4,4,8,8-tetramethyl-cyclodecanone, has been ascertained (boat-chair-chair), but since no extensive parameters are available a calculation cannot be performed in this case.

(xi) Cyclodecanone and Cycloundecanone (Fig. 1(d))

Mean differences for ring bond-lengths and angles of these two strained, medium-ring ketones are, respectively, for cyclodecanone 0.003 \AA and 0.7° , and for cycloundecanone 0.006 \AA and 0.7° , which are (slightly) outside quoted experimental error only in the case of the former compound. Torsion angles at carbonyl again show somewhat larger deviations, but the fit overall is good.

A crystal structure for cyclotetradecanone has been described⁶⁰ but since oxygen atoms were found distributed over 3 positions in the ring and because of the consequent ambiguity arising, no calculation was performed on this molecule.

(xii) (4.4)Spirononane-1,6-dione (Fig. 1(e))

This compound was not utilized in the parameterization other than to the extent of monitoring the effect of variation of coulombic energy in a diketone. Nor was this structural type involved in the basic hydrocarbon force-field. Consequently, it is not very surprising to find quite poor agreement between calculated and experimental structures, mean deviations for ring bond-lengths and angles being 0.016 \AA and 2.7° respectively.

(iii) 1-Methyl-7-exo-t-butyl(3.3.1)bicyclononane-2,9-dione
(Fig. 1(e))

Calculation correctly shows the structure to have a boat-chair conformation. Whereas precise correlations between the

calculated and observed structures show mixed agreement, one noteworthy feature is the compressed C_5-C_9 bond present in the actual molecule and which the calculated structure goes part-way in showing.

Further discussion of this and related molecules appears in section 3.

(xiv) trans-2-Decalone and 10-Methyl-trans-2-decalone (Fig. 1(f))

Only a limited number of geometrical parameters are quoted for these molecules, the structures having been determined by combined vibrational, conformational and electron diffraction studies.

(xv) Various Polycyclic Compounds (Fig. 1(g)-(l))

Perusal of the structures of the variety of polycyclic compounds depicted allows many interesting observations to be made and comparisons drawn.

The calculated tricyclodecanedione structure in Fig. 1(g) deviates significantly in many parameters from the actual one, as a result primarily of the presence of the bis-(cis-substituted) cyclobutane ring; in contrast, its $C_{sp^2}-C_{sp^3}$ bond lengths and the cyclobutane ring internal angles are, fortuitously, virtually ideal.

The tricycloundecanone in Fig. 1(h) is slightly skewed, an effect not shown by calculational results, but far more serious are the considerable differences in bond-lengths that are manifest (bond-angles in this rigid structure are remarkably consistent). This applies even to bonds far removed from the $C=O$ moiety. For example the calculated-experimental bond-length

differences for the C_6-C_7 , C_3-C_8 and C_1-C_2 bonds are 0.028, 0.048 and 0.050 Å respectively, enormous values which are only partially accounted for by the skewing.

The cage diketones in Fig. 1(i) are structurally related and a comparison between the two is instructive. For example, calculations tend to reproduce the diminished C-C-C angles at carbonyl in both cases, an effect caused by the highly strained nature of the ring systems. Yet, not in the least way do they indicate the very short nature (by 0.02 Å) of the remote C=C groups. Similarly, the related compounds in Fig. 1(j) also bear such comparisons: the C-C-C angles at carbonyl are diminished yet again - partially indicated in the calculated structures - and the C=C bond in the cyclooctene unit of the second compound is likewise diminished by about 0.02 Å from its reference value, the effect not indicated in the calculated result. These short bond lengths are not discussed in the original structural papers, it being assumed that they be normal. (It is interesting to note that the C=C bonds in cis,cis-1,5-cyclooctadiene, for comparison, are 1.341 Å, and are calculated to be 1.340 Å.) The explanation possibly lies in the observation that the C-C bonds on the other side of the ring are abnormally long --- not shown in the calculated result --- and this causes the C=C bonds to shorten.

Finally, the polycyclic ketones in Fig. 1(k) serve as the last examples of the ambivalent nature of the calculational results. A parameter, such as the C_1-C_6 bond length in the first structure is calculated to be near normal size (1.538 Å), whereas it is actually distended (1.587 Å). On the other hand the highly

compressed bond angle, $C_3C_{10}C_9$ of the second structure (98.5°) is reproduced almost exactly. Overall, the agreement is less than that truly desired in a precise force-field of generalized applicability, but it is good nevertheless, especially considering the highly ramified nature of these structures, and deserves to promote confidence in further applications.

2.3 Heats of Formation of Compounds with Known Experimental Values

Calculated heats of formation are compared with experimental values for those compounds for which reliable data exist in the literature in Tables 2 and 3.

To summarize, the mean deviations for the ketones and aldehydes are 1.17 and 0.89 kcal mol⁻¹ respectively, taken over 39 and 10 of such compounds. (Exclusive of the cyclobutanedione.) A comparison of the mean deviations of those compounds in these tables for which calculations have been performed by the author of the other well-established ketone/aldehyde force-field is given: (The compounds are marked "†" in the tables.)

	Present Work	Ref.23	Values are
Ketones	1.18	1.30	in -1
Aldehydes	0.85	0.95	kcal mol

Several of the experimental values used in determining the figures in the second column are from recent data and depart slightly from those quoted in the paper; others were not quoted at all owing to unavailability of data at the time. The significant improvement evident in the presently calculated figures is nevertheless noteworthy.

Various individual features merit comment.

In the case of the aldehydes there is a mixed improvement over all the particular compounds. Some, such as ethanal, have a slightly worse difference (0.34 versus 0.28 kcal mol⁻¹) whereas others such as 2-methylpropanal have a better one (1.33 versus 1.77 kcal mol⁻¹). The notable exception to this is the case of 2-ethylhexanal, whose difference is calculated to be 1.07 kcal mol⁻¹ whereas the previously quoted value is as large as 2.59 kcal mol⁻¹. It is not really possible to say with certainty how the overall improvement comes about, and there are in all likelihood a number of contributing reasons.

The agreement found for the cage-like endo-5-methanoyl (2.2.2)bicyclooct-2-ene is no worse than can be expected on account of the highly-strained nature of the aldehyde (high steric energy) and also because the experimental value was estimated following a kinetic study and is of somewhat dubious accuracy.

In the case of the ketones studied there is likewise an assorted improvement in individual molecules. However, for the medium-ring ketones these improvements are particularly outstanding. The values given in the table for cycloheptanone to cyclodecanone of 1.37, 3.59, 1.76 and 2.88 kcal mol⁻¹ respectively compare favourably with the corresponding previously quoted results of 2.51, 5.53, 5.67 and 5.73 kcal mol⁻¹ (these figures based on latest available experimental data and not those used, if any, in the paper itself). Again, it is not easy to determine why there should be such a significant improvement in this region, but it is likely that much of the credit must belong

TABLE 2

Calculated and Experimental Heats of Formation, ΔH_f° (gas 298 K),
and Calculated Steric Energies, E_s (kcal mol⁻¹)

Compound	E_s	ΔH_f° (calc.)	ΔH_f° (expt.)	(c-e)	Ref.
Ethanal †	-0.22	-39.38	-39.73±0.12	0.35	61
Propanal †	0.38	-44.07	-44.46±0.36	0.39	62
2-Methylpropanal†	0.88	-50.92	-52.25±0.37	1.33	61
Butanal †	0.58	-49.16	-48.94±0.34	-0.22	61
2-Ethylhexanal†	2.43	-70.53	-71.60±0.46	1.07	61
Heptanal †	0.93	-64.68	-63.1 ±1.0	-1.58	61
Octanal †	1.04	-69.86	-69.23	-0.63	63
Nonanal †	1.14	-75.05	-74.16	-0.89	63
Decanal †	1.23	-80.25	-79.09	1.16	63
<u>endo</u> -5-Methanoyl (2.2.2)bicyclooct-2-ene	16.80	-18.19	-19.5	1.31	64

TABLE 3

Calculated and Experimental Heats of Formation, ΔH_f° (gas 298 K),
and Calculated Steric Energies, E_s (kcal mol⁻¹)

Compound	E_s	ΔH_f° (calc.)	ΔH_f° (expt.)	(c-e)	Ref.
Propanone †	-0.038	-51.97	-51.90±0.12	-0.07	61
Butanone †	0.11	-56.77	-57.02±0.20	0.25	61
Methylbutanone †	0.79	-63.44	-62.76±0.21	-0.68	65
Dimethylbutanone†	2.35	-70.88	-69.47±0.21	-1.41	65
2-Pentanone †	0.27	-61.90	-61.91±0.26	0.01	65
3-Methyl- pentanone	1.66	-67.86	-67.90±0.32	0.04	66
4-Methyl- pentanone	0.64	-68.88	-69.60±0.34	0.72	66
3,3-Dimethyl- pentanone	4.55	-73.97	-72.60±0.41	-1.37	66
4,4-Dimethyl- † pentanone	1.64	-76.88	-76.60±0.45	-0.28	66
3,3,4-Trimethyl- pentanone	6.10	-79.77	-78.50±0.41	-1.27	66
Tetramethyl-2- pentanone	9.84	-85.03	-83.10±0.42	-1.93	66
3-Pentanone †	0.57	-61.60	-61.65±0.20	0.05	65
Methyl-3- † pentanone	1.18	-68.34	-68.38±0.22	0.04	67
2,2-Dimethyl- † pentanone	2.72	-75.80	-75.00±0.33	-0.80	67
2,4-Dimethyl- † pentanone	1.58	-75.29	-74.40±0.26	-0.89	67
Trimethyl-3- † pentanone	3.02	-82.85	-80.86±0.29	-1.99	67
Tetramethyl-3- † pentanone	9.01	-85.86	-82.65±0.29	-3.21	67
2-Hexanone †	0.39	-67.07	-66.87±0.24	-0.20	65
3-Hexanone †	0.71	-66.75	-66.50±0.21	-0.25	65

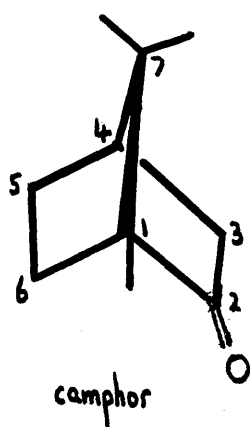
TABLE 3 (continued)

Compound	E_s	ΔH_f° (calc.)	ΔH_f° (expt.)	(c-e)	Ref.
2,2,5,5-Tetra- [†] methylhexanone	4.00	-96.16	-94.14 \pm 0.55	-2.02	67
4-Heptanone [†]	0.85	-71.90	-71.30 \pm 0.31	-0.60	66
2,6-Dimethyl- [†] 4-heptanone	1.48	-85.97	-85.49 \pm 0.29	-0.48	67
2,2,6,6-Tetra- methyl-4-heptanone	3.34	-102.11	-100.67 \pm 0.84	-1.44	66
2-Nonanone	0.70	-82.63	-81.45 \pm 0.42	-1.18	68
5-Nonanone [†]	1.08	-82.25	-82.44 \pm 0.32	0.19	65
6-Undecanone [†]	1.29	-92.62	-92.59 \pm 0.47	-0.03	65
2-Dodecanone	1.18	-98.02	-96.62 \pm 0.59	-1.40	68
Cyclopentanone [†]	6.19	-46.04	-46.03 \pm 0.40	-0.01	61
Cyclohexanone [†]	2.00	-55.52	-54.43 \pm 0.45	-1.09	69
Cycloheptanone [†]	4.88	-57.93	-59.30 \pm 0.31	1.37	69
Cyclooctanone [†]	6.64	-61.46	-65.05 \pm 0.42	3.59	69
Cyclononanone [†]	8.30	-65.09	-66.85 \pm 0.41	1.76	69
Cyclodecanone [†]	8.65	-70.03	-72.91 \pm 0.46	2.88	69
Camphor [†]	22.56	-59.78	-63.9 \pm 0.7	4.12	70
<u>trans</u> -2- [†] Hydrindanone	9.63	-57.94	-59.56 \pm 0.38	1.62	71
<u>cis</u> -2- [†] Hydrindanone	9.39	-58.18	-59.66 \pm 0.31	1.48	71
<u>trans</u> -8-Methyl- [†] 2-hydrindanone	12.83	-63.74	-65.74 \pm 0.55	2.00	23
<u>cis</u> -8-Methyl- [†] 2-hydrindanone	10.00	-66.57	-68.56 \pm 0.81	1.99	23
Tetramethyl-1,3- cyclobutanedione	30.55	-74.87	-73.54 \pm 0.38	-1.33	72
Cycloundecanone	8.08	-75.89	-76.96 \pm 0.52	1.07	69

to the soundness of the underlying hydrocarbon force-field and in particular to its treatment of non-bonded repulsions. The latter have inordinate importance in medium-ring compounds owing to the extensive occurrence of transannular interactions between hydrogen atoms in this class of compound.

Molecules that figure rather prominently in showing relatively large differences between calculated and experimental heats of formation are those containing a certain amount of steric crowding such as the tetramethylpentanones: -1.93 and -3.21 kcal mol⁻¹ respectively. It is doubtful though if all the blame for this resides in the carbonyl interaction parameters insofar as the molecules contain an even greater number of alkane-type ones. However it does illustrate the important point that when a force-field designed for generalized utilization over a broad spectrum of structural types is applied to extreme examples then relatively pronounced discrepancies are almost certain to manifest themselves.

The example of camphor can be cited as another illustration of this point. Its heat of formation is calculated to be 4.12 kcal mol⁻¹ greater than that measured experimentally. Superficially this is a disappointing result, taking into consideration also the fact that the experimental error is quoted to be of the order of 0.7 kcal mol⁻¹. However it is effectively no worse than a previously calculated result,²³ and bearing in mind that with a steric energy calculated at 22.56 kcal mol⁻¹ it is an extreme example of a highly strained molecule, the fact of the occurrence of such a discrepancy can at least be understood.



Tetramethyl-1,3-cyclobutanedione offers an interesting case of how a highly-strained molecule, (on account of the 4-membered ring system) and one outside the formal scope of the force-field, can nevertheless be subject to calculation with an error no greater than that evident in other less extreme examples. A full 25 kcal of the 30.55 kcal mol⁻¹ steric energy is calculated to be due to unfavourable angle bending, but it is perhaps more prudent in this instance not to place undue reliance on the cited apportioning of the internal strain energy between the various coordinates. It may also be recalled that this molecule is one whose geometry was not well reproduced in the calculation.

In contrast, many of the compounds reported in Table 3 have calculated values that lie very close to the experimental ones and well within the quoted experimental errors. This is not entirely unexpected for simple acyclic ketones such as propanone and 2-pentanone but is satisfying to be observed in a molecule such as cyclopentanone where the difference between calculated and observed values is -0.01 kcal mol⁻¹.

Torsional Barrier Heights

Manipulation of torsional parameters yields values that are realistic and closely reproduce the available experimental data.²⁴ The results are summarized in Table 4, the bond about which torsion is measured being drawn in, and it being understood that the carbonyl eclipsed conformation is more stable than the staggered.

TABLE 4

Molecule	Barrier Height (kcal mol ⁻¹)	
	Calc.	Expt.
Ethanal CH ₃ -CHO	1.05	1.16±0.03
Propanal C ₂ H ₅ -CHO	0.90 (gauche-cis)	0.9±0.1
Propane CH ₃ -COCH ₃	0.74	0.78

3. APPLICATIONS OF THE NEW FORCE-FIELD

Results are here discussed for the geometries and heats of formation of compounds for which the appropriate experimental data are not yet available. In the main these consist of compounds mentioned earlier, in section 2, in some other context, but also included are several conformational studies including those of medium ring ketones and some cyclic sulphur derivatives.

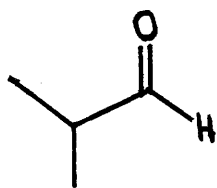
3.1 Geometries

During the normal course of deriving the heats of formation of the compounds for which such thermochemical data exist, the geometries of these compounds are also produced as a result of the energy minimizations. A selection only, can be presented here, in the main related to points of significant interest. At such a time as when experimental data on the compounds become available, the theoretical predictions can be more usefully compared and in a more detailed a fashion.

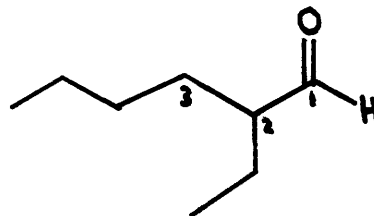
(a) Aldehydes

This set of compounds shows few interesting geometrical features. In all cases the carbonyl group is eclipsed by a β -C-C bond, where it is possible. For methylpropanal and 2-ethylhexanal which are both substituted in the position α to the carbonyl there

are small distortions owing to localized non-bonding interaction effects.



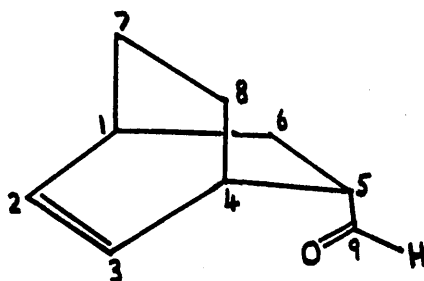
Methylpropanal



2-Ethylhexanal

The respective $OC_1C_2C_3$ torsion angles are 4.8° and 18.5° respectively instead of the unperturbed 0° .

endo-5-methanoyl(2.2.2)bicyclooct-2-ene is predicted to have some moderate geometrical distortions on account of its strained structure. In particular the $C_1C_2C_3$ and $C_2C_3C_4$ angles are compressed at 114.9° and 115.1° respectively, and the $C_1 \cdots C_4$ non-bonded distance is short at 2.16 \AA (reference $C_{sp^3} \cdots C_{sp^3}$ Van der Waals radii sum = 3.85 \AA). However, the presence of the aldehyde group appears to exercise no significant distorting influence on the associated hydrocarbon cage, the $C_1C_6C_5C_4$ torsion angle for example, being only 4.31° , instead of 0° as found in the pure alkene.

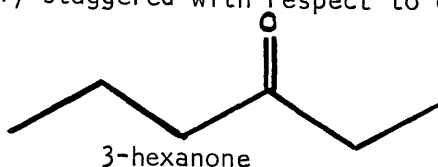


endo-5-methanoyl(2.2.2)bicyclooct-2-ene

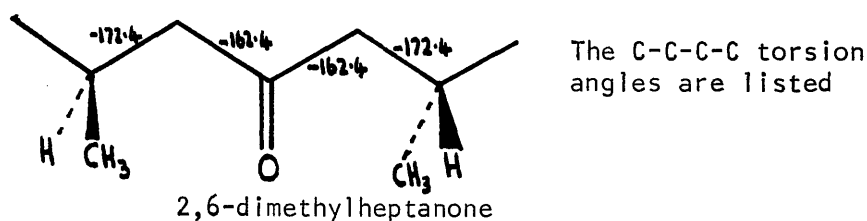
(b) Ketones

(i) The geometries of the acyclic ketones in Table 3 show few unexpected features. The usual pattern of α -C-C bonds' eclipsing carbonyl is adhered to with greater or lesser torsional angle variations according to the extent of local substitution. Thus in

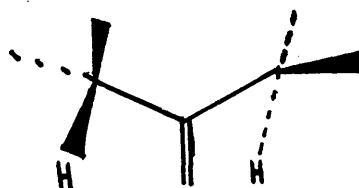
the case of, for example, 3-hexanone, all torsion angles around C-C bonds are perfectly staggered with respect to carbon substituents.



In the case of 2,6-dimethylheptanone, however, the "straightness" of the carbon chain is distorted by the presence of the methyl substituents and it adopts a mild spiral conformation:



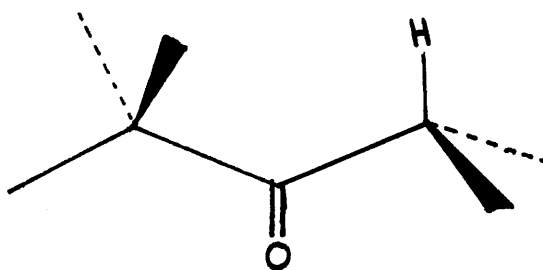
The effect is considerably further enhanced in 2,4-dimethylpentanone where the C-C-C-C torsion angle now deviates by 30° from the 180° value found in pentanone itself.



2,4-dimethylpentanone

Eventually, in the unsymmetrical trimethyl-3-pentanone, the effect dominates and the predicted geometry goes over to that conformation in which the two methyls of the isopropyl group are both gauche to carbonyl. Analysis of the way the steric energy is partitioned amongst individual components seems to suggest that this is due primarily to relief of angle bending strain at the carbonyl and of a number of unfavourable non-bonded interactions.

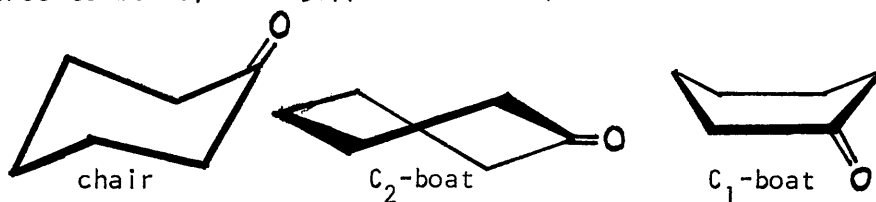
Stable conformation
of
trimethyl-3-pentanone:



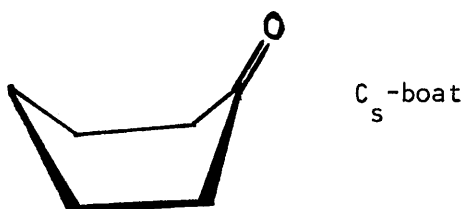
(ii) Monocyclic Ketones

The half-chair conformations of cyclopentanone are discussed on page 42; no calculations were performed on the "envelope" conformations but experiment and other theoretical work indicate they are less stable than the symmetrical half-chair.

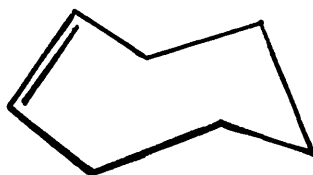
Cyclohexanone is also mentioned previously, on page 43. Its most stable conformation and geometry is that of the chair, but two other conformational minima exist that are higher in energy, the twist-boat (C_2) and the unsymmetrical boat (C_1). These lie respectively 3.89 and 4.19 kcal mol⁻¹ in energy above the chair conformation. (Previous literature calculation estimates these figures to be 2.72 and 3.77 kcal mol⁻¹.)



Present calculations do agree with the previous ones however in finding the symmetric boat (C_s) not to represent an energy minimum.



Cycloheptanone is the smallest of the so-called medium-ring ketones — molecules which are relatively destabilized over their acyclic and normal-ring counterparts (cyclopentanone and cyclohexanone) on account of numerous angle-bending strains and unfavourable torsional and non-bonded interactions present. By analogy with the corresponding cycloalkane, two principal conformational families exist --- the chair- and boat-. The twist-boat-chair form of cycloheptane and the related C_s -chair of cycloheptene having previously been shown to represent respective energy minima, the latter was estimated to serve as a good model for the investigation of cycloheptanone (both molecules contain at least one trigonal C_{sp^2} atom).


 C_s -cycloheptene

Four separate conformational minima are found to exist with the twist-chair conformation, as indicated:

Relative energies (kcal mol^{-1})

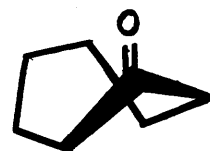
Calculated
(Ref. 23)

1.



0.72
0.25

2.

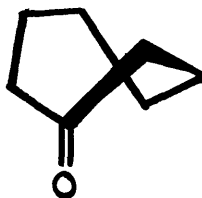


0.00
0.00

Relative energies (kcal mol^{-1})

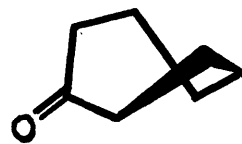
Calculated
(Ref. 23)

3.



0.60
1.80

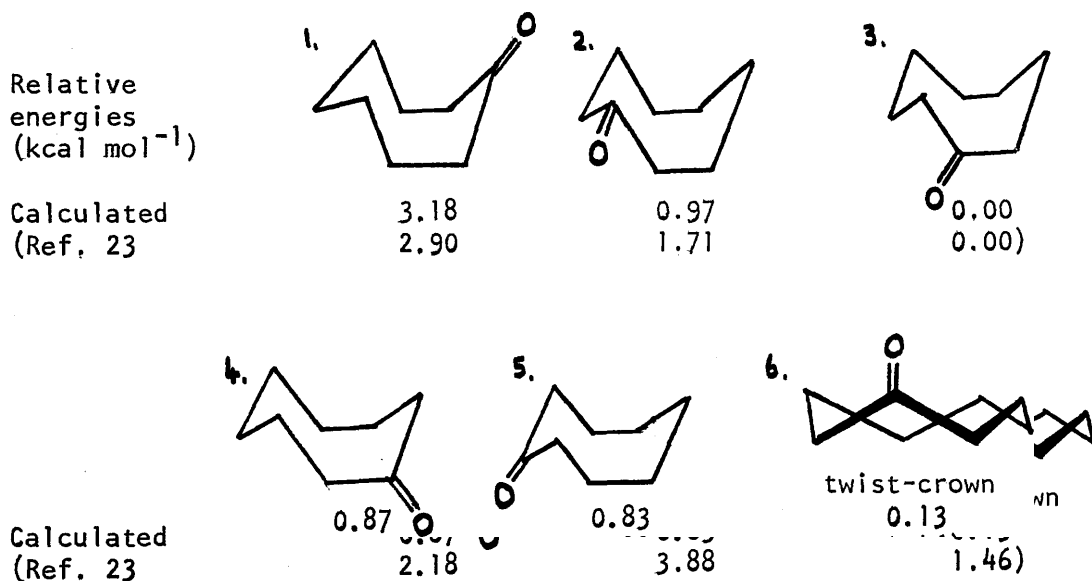
4.



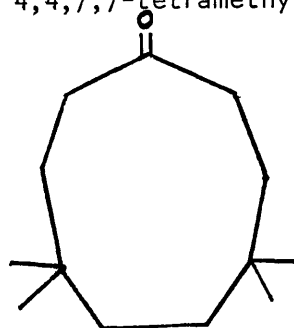
1.59
1.62

The results demonstrate that at 25° C a mixture of conformers 2, and 3, exists, and not of 2, and 1, as suggested by the referred work. However, the lowest energy state appears rather definitely to be 2.

Investigation of the boat-chair conformers and twist-crown of cyclooctanone points to the same conformational minimum as previously found but an altered order energy-wise for several of the other conformers. The twist crown is also noted to be only slightly less stable than the minimum-energy conformer, 3. In any case, the geometry calculated for the latter corroborates the available experimental evidence for its structure.



The starting point for the investigation of the cyclononane conformers was the ground state conformation of cyclononene, chosen as a model on account of its formal similarity by virtue of the trigonal C_{sp^2} atom(s) it contains. Five conformers can thereby be derived, and their geometries and relative energies are listed in Figs. 2(a) - (b). Precise calculated parameters are given to indicate that, in this and similar such cases of a perturbing group's being situated at various positions on a particular ring, its presence exerts a small influence on the precise values of these parameters. The total C_2 -symmetry of 4, for example, is fully evident. Relatively little experimental work has been performed on the conformations of cyclononane but the one assumed here relates closely to the lowest energy conformation of D_3 -symmetry of the parent hydrocarbon as calculated and found experimentally. The actual minimum geometry found, 5, does not agree, however, with that calculated previously, a structure having C_2 -symmetry. Although the other two lowest energy minima described in the literature for cyclononane are less stable than the D_3 -structure it is by no means impossible that replacement of a methylene group in them by a carbonyl at various points in the rings could lead to a yet lower energy conformer for cyclononane itself. Obviously, much more work would need to be done on the matter before a final conclusion could be drawn. Finally the structure calculated for the derivative, 4,4,7,7-tetramethylcyclononane, differs from that of the unsubstituted ketone, and has approximately C_2 -symmetry. (Calculations upon further conformations beyond the

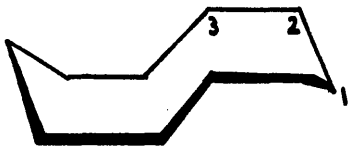
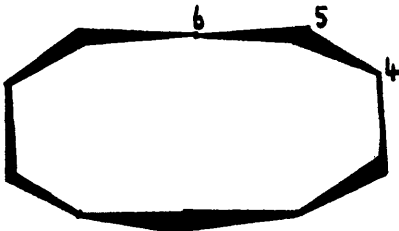
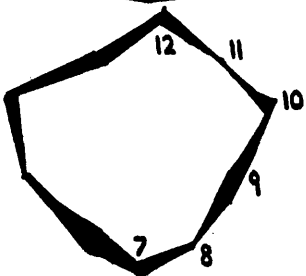


4,4,7,7-tetramethylcyclononane

single one actually performed on this compound would no doubt have yielded a precisely C_2 -symmetric minimum, in line with the experimental evidence.)

Cyclodecane is a flexible molecule with numerous conformations open to it.^{73,74} The lowest is the boat-chair-boat (BCB), and this and the two others next lowest, the twist-boat-chair (TBC) and twist-chair-chair-chair (TCCC), were taken as bases for the conformational analysis of cyclodecanone. Because of symmetry considerations only 3 BCB conformers exist, and, similarly, 6 TBC and 3 TCCC. These are indicated below along with their relative energies. The result for the lowest energy conformer, **BCB 3** is in line with experiment but it is nevertheless seen to be a mere $0.41 \text{ kcal mol}^{-1}$ more stable than the conformer **TBC 9**.

Conformers of cyclodecanone:

		Carbonyl position	Relative energies Calculated (Ref23)	
BCB:		1	1.30	(5.45)
		2	3.81	(2.38)
		3	0.00	(0.00)
TCCC		4	4.10	*
		5	2.65	*
		6	0.44	*
TBC		7	4.92	*
		8	1.24	*
		9	0.41	*
		10	4.24	*
		11	0.87	*
		12	3.99	*

(kcal mol⁻¹)

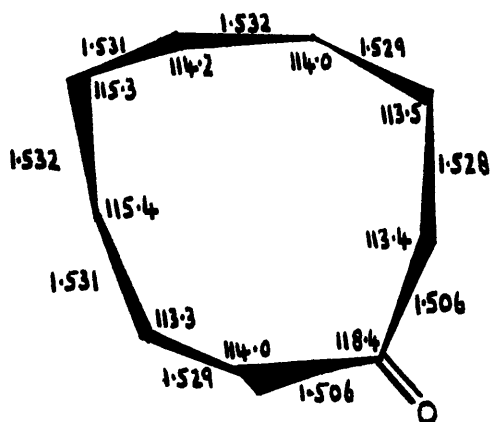
(* = no further data available)

FIGURE 2(a)

Calculated Geometries for Five Conformers of Cyclononane, and their Relative Energies (kcal mol⁻¹)

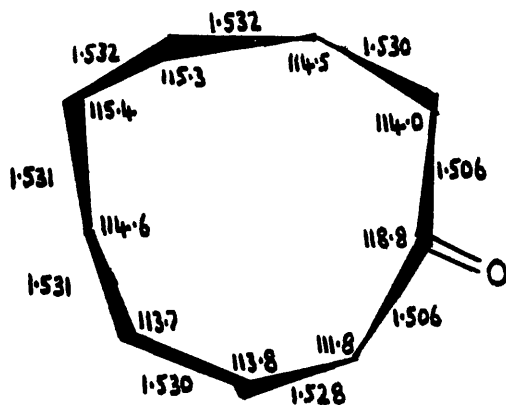
Relative energies
Calculated

1.



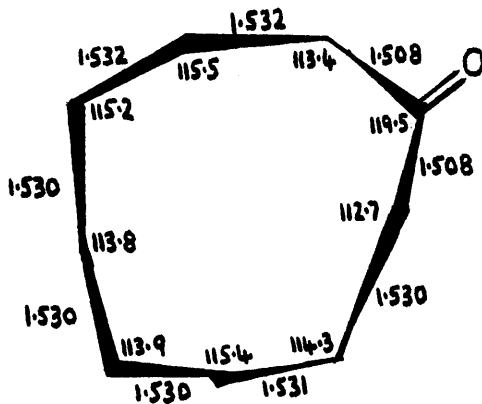
0.27

2.



1.21

3.

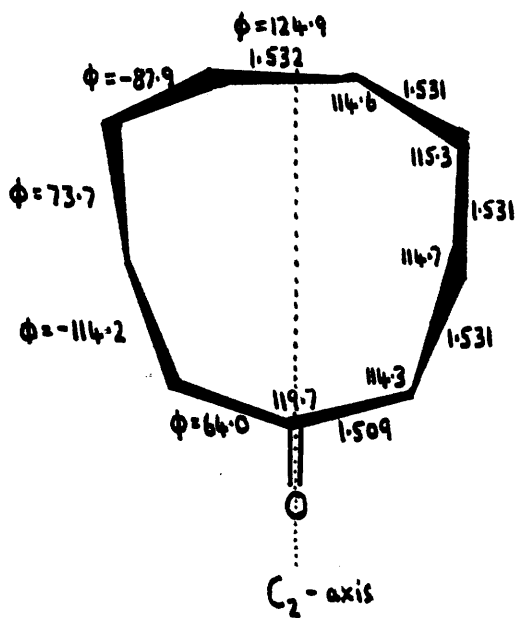


2.85

FIGURE 2(b)

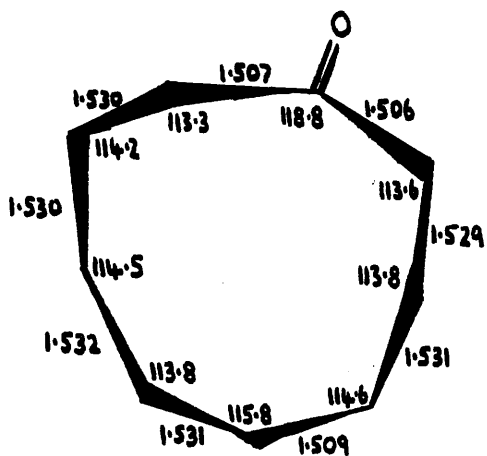
Relative energies
Calculated

4.



3.97

5.

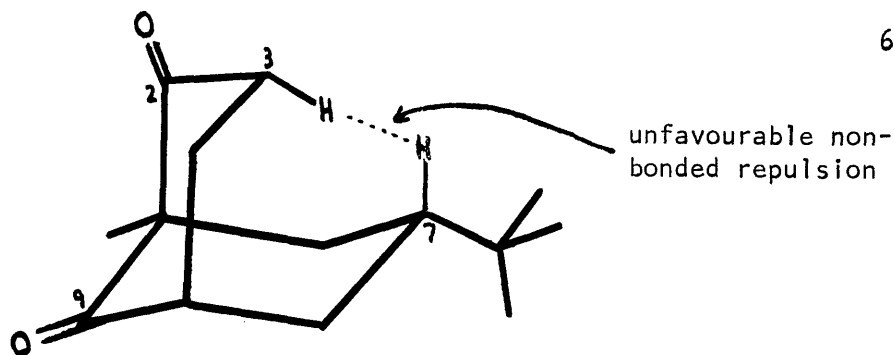


0.00

The more detailed geometries of the most stable conformers of cyclodecanone and cyclundecanone are given in Fig. 1(d). For the latter, higher energy conformers with the carbonyl substituent at the indicated positions 2,3, and 4 are 1.23, 4.25 and 0.59 kcal mol⁻¹ respectively above the minimum one. The molecule was not investigated further.

The molecule of camphor, whose relatively poorly reproduced heat of formation was previously noted (p.54), is calculated to have the highly strained geometric features normally expected for such a (2.2.1)bicyclic system. The highly compressed angles C₁C₇C₄ 91.4°, C₇C₁C₂ 98.0° and C₂C₃C₄ 94.7° are especially noteworthy.

Lastly, the unusual case of the (3.3.1)bicyclononane-2,9-dione system is discussed. Although, as previously noted (p.46) the observed boat-chair conformation of the 1-methyl-7-exo-t-butyl derivative (Fig. 1(e)) is successfully reproduced by calculation, the question arises as to whether the departure of a cyclohexane ring from the normally more stable chair conformation (in favour of a boat) is influenced in any way by the presence of the substituent carbonyl groups which might offer the ring more opportunity to flex, or else by the t-butyl substituent whose presence forces the adjoining axial hydrogen atom into what would be closer contact with an axial hydrogen on carbon-3 of the other six-membered ring were it to be in a chair conformation.



1-methyl-7-exo-t-butyl(3.3.1)bicyclononane-2,9-dione
(unstable chair-chair conformation)

Calculations do indeed show that the presence of the t-butyl group and the keto-groups both favour a boat-chair conformation over a chair-chair. Further, the cyclohexane rings in molecules that lack a buttressing substituent at carbon-3 (or 7) are significantly flattened owing to the $H_3 \cdots H_7$ repulsion.^{75,76} (In the case of endo-1-methyl(3.3.1)bicyclononane-2,9-dione the conformation is calculated to pass over to the boat-chair, as a result of the enhanced flexibility afforded by the diketone ring present.)

3.2 Heats of Formation

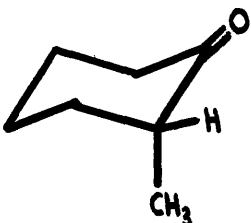
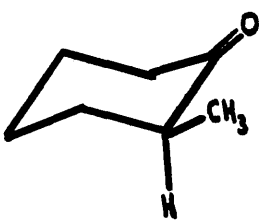
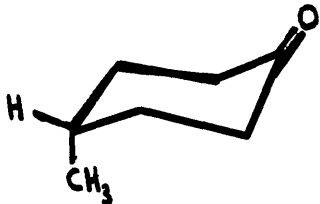
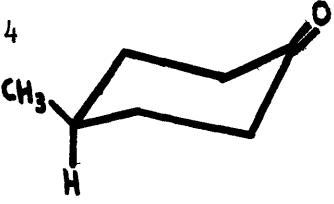
Heats of formation for compounds whose geometries are known, but not so their experimental thermochemical data, are quoted in Fig. 1(a)-(1). Correlations are drawn between some of these data and other that are available, but such tentative inferences would naturally have to await the arrival of suitable experimental data for corroboration. Other miscellaneous calculations performed include those on the heats of formation of the methylcyclohexanones.

Three compounds whose heats of formation are known⁷⁷ but whose values are poorly represented by previous calculations are 2-, 3-, and 4- octanone. Calculations performed using the present force-field reproduce these large discrepancies and affirm the suggestion²³ that the problem is an experimental one.

	ΔH_f° (expt.)	ΔH_f° (calc.)	ΔH_f° (calc., ref. 23)
2-Octanone	-82.47±0.49	-77.44	-77.28
3-Octanone	-80.93±0.80	-77.10	-77.21
4-Octanone	-83.49±0.61	-77.07	-77.17

Calculated enthalpy data for the axially and equatorially substituted conformers of 2- and 4-methylcyclohexanone are presented in Table 5 with calculated data from another source for comparison.

TABLE 5

	E_s	H_f° (calc.)	H_f° (calc., ref. 23)
1 	2.86	-62.01	
2 	2.33	-62.54	-62.26
3 	3.23	-61.64	
4 	2.10	-62.77	-63.56

As expected, the equatorial-Me conformers are more stable than the corresponding axial conformers, owing to reduced adverse non-bonding interactions in the former case. This effect is more marked in the 4-derivative (energy difference $-1.13 \text{ kcal mol}^{-1}$) than in the 2-derivative (energy difference $0.53 \text{ kcal mol}^{-1}$), so illustrating the relative importance of the non-bonded interactions over that of the favourable eclipsing of a carbonyl group by an adjacent methyl (as in 2).

The steric energy of 4,4-dimethylcyclohexanone (Fig. 1(b)) of $3.84 \text{ kcal mol}^{-1}$ is in line with those of the 4-monomethyl conformers (Table 5) whilst that of 4-t-butylcyclohexanone ($6.58 \text{ kcal mol}^{-1}$) is significantly greater on account of the bulky substituent's non-bonded interactions particularly with equatorial ring hydrogens at ring positions 3 and 5. The steric energy of 2,2,6-trimethylcyclohexanone (Fig. 1(c)) of $3.96 \text{ kcal mol}^{-1}$ is similarly in line.

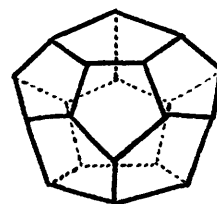
The heat of formation of 4,4,7,7-tetramethylcyclononane (Fig. 1 (c)) reflects its high steric energy of $13.65 \text{ kcal mol}^{-1}$. The latter compares unfavourably with that of the lowest energy conformation of the parent ring ketone, $8.30 \text{ kcal mol}^{-1}$ because of the greater strain involved by the incorporation of the substituent groups. (Its conformation also differs.)

It would be useful to have experimental thermochemical data for the parent and substituted decalones (Fig. 1(f)) not least because of the information that would then be imparted with regard to the effect on the steric energy of a cyclohexanone system caused by the introduction of an axial 4-methyl group. The steric energy of a 10-methyl-trans-2-decalone exceeds that of trans-2-decalone by $3.61 \text{ kcal mol}^{-1}$, as a result of replacing an axial

hydrogen atom by an axial methyl group. The corresponding figure for axial 4-methylcyclohexanone and cyclohexanone is only $1.24 \text{ kcal mol}^{-1}$, thus illustrating the greater degree of adverse interactions between the substituent and the pure hydrocarbon ring of the molecule rather than with the ketone ring.

The highest steric energies (and hence the comparatively low heats of formation) are found particularly amongst the polycyclic ketones, all of which incorporate to a greater or lesser degree considerable amount of geometric strain. The relative amounts of strain can be qualitatively arrived at by examination of the molecular geometries for features such as the presence of small rings, medium rings, unfavourable (boat) conformations of 6-membered rings, unfavourable torsion and non-bonded interactions and so on. Thus, for example, $(5.3.1.0^{3,8})$ tricycloundecan-5-one (Fig. 1(h)) which possesses two rings in the boat-conformation and concomitant unfavourable bond-eclipsing has a relatively high steric energy of $16.61 \text{ kcal mol}^{-1}$. It is still much less, however, than the steric energy ($34.44 \text{ kcal mol}^{-1}$) of $(5.3.0.0^{2,6})$ tricyclodecane-4,9-dione (Fig. 1(g)). In the latter case the number of rings present is the same, three, but two of these are 5-membered rings which are intrinsically more strained than 6-membered rings, whilst the third is a grossly strained cyclobutane ring. Similarly, the superficially rather similar cage-type ketones in Fig. 1(i) present another instructive example of this type, and others can likewise be discerned amongst the structures in Fig. 1(j)-(l).

In all of these highly-strained molecules, as is the case in considering their geometries, the calculated heats of formation data provide a severe test of the quality of the force-field (excluding the exceptional cases of the 4-membered ring systems) and it is hoped that the necessary experimental data for comparison will soon become available. Whereas acyclic molecules yield calculated data that differ from the corresponding experimental data normally by an amount of less than 1 kcal mol^{-1} and even in exceptional cases by no more than about $2\text{-}3 \text{ kcal mol}^{-1}$, the discrepancies possible with polycyclic molecules can be an order of magnitude greater. This is because in such molecules, where the relative contributions of individual strain energy terms are expected to differ from those in the more usual acyclic and monocyclic molecules mainly involved in the parameterization of the force-field, the effect of any rather poorly evaluated parameters will be greatly magnified and not compensated for internally, as would otherwise happen. An extreme example of this phenomenon is that of the as yet unsynthesized polycyclic hydrocarbon, dodecahedrane. It consists entirely of C-H groups. Calculated heats of formation using two different literature force-fields² are the very dissimilar values -0.22 and $+40.88 \text{ kcal mol}^{-1}$ respectively.



dodecahedrane

3.3 Bicyclic Systems Containing Sulphur

As an extension of the investigations described for the molecule 1-methyl-7-exo-t-butyl(3.3.1)bicyclononane-2,9-dione, molecular

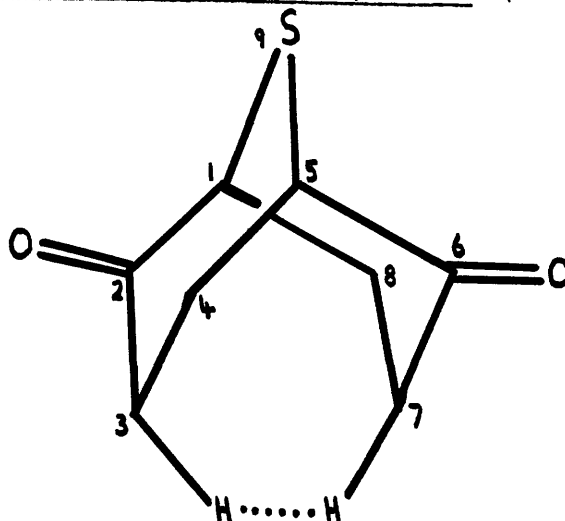
mechanics calculations were performed also on related sulphur-containing derivatives adopting the same (3.3.1)bicyclic structures. These molecules, 9-thia(3.3.1)bicyclononane-2,6-dione⁷⁸ ("sonane") and the pair 3-oxa-7,9-dithia- and 9-oxa-3,7-dithia-(3.3.1)bicyclononane⁷⁹ have the structures illustrated in Figs. 3(i) and 4.

Owing to the presence of the hetero-atoms, additional parameters have to be introduced into the force-field to take account all the further interactions associated with them. The ether-type oxygen is represented for simplicity as the same atom type ("4") as the carbonyl oxygen, although clearly this is a far from precise assumption, whilst the sulphur atoms are designated by a new atom type ("5"). Reasonable values for the various new parameters are taken from the literature^{80,81} and modified systematically so as to give calculated results that agree with the experimental ones for the compounds under consideration. The final parameters are listed in Table 6. The overall force-field cannot claim to be an accurate one with generalized applicability to all organic sulphides and ethers on account of the very limited range of data to which it is fitted but it does qualitatively reproduce the experimental results in the two cases to which it is applied and this fact sufficiently justifies its use in this instance.

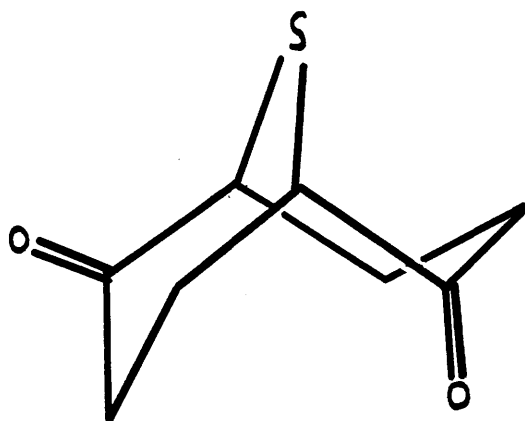
X-ray crystallographic analysis of sonane shows that the ring torsion angles about bonds C_1-C_2 and C_4-C_5 and about bonds C_2-C_3 and C_3-C_4 differ by 15° and 9° respectively. This skewing of the molecule causes the non-bonded $C_3 \cdots C_7$ distance to be increased to 3.18 \AA and also the transannular non-bonded $H_{31} \cdots H_{71}$ distance

FIGURE 3

(i) 9-Thia(3.3.1)bicyclononane-2,6-dione (sonane)



(ii) High Energy Boat-chair Conformation of sonane



(iii) (3.3.1)Bicyclononane-2,6-dione

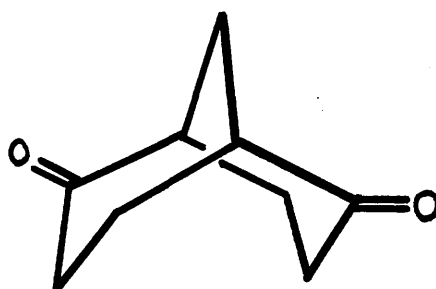
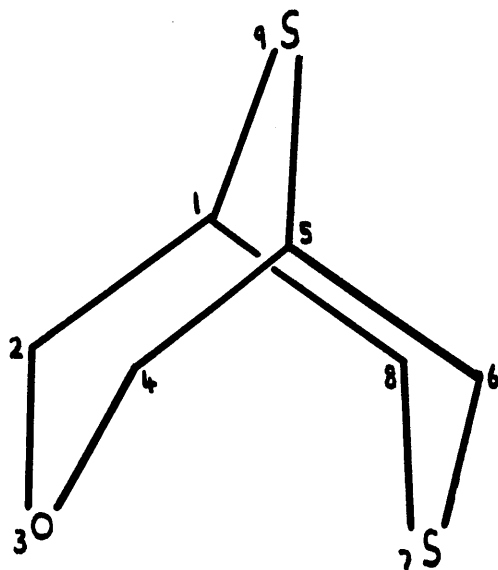


FIGURE 4

3-oxa-7,9-dithia(3.3.1)bicyclononane



9-oxa-3,7-dithia(3.3.1)bicyclononane

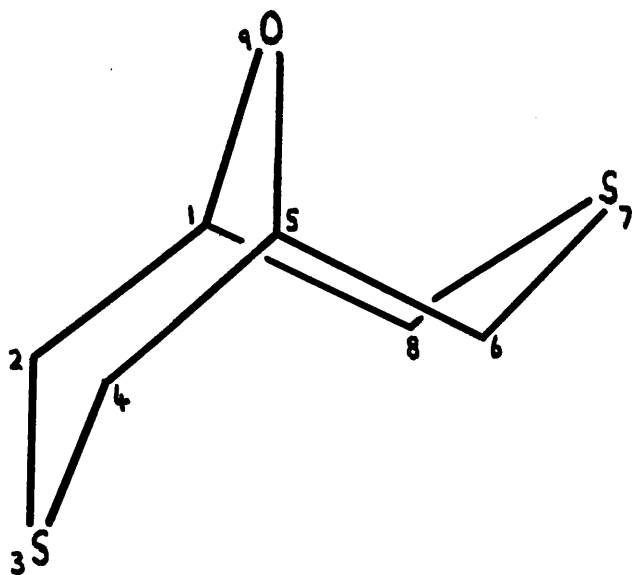


TABLE 6

Additional Force-field Parameters, to Include Sulphur and Ether-Oxygen Interactions.

(i) Atom types: 1-4 (see table 1), 5 = sulphur

(ii) Dimensions: As in table 1.

(iii) The Parameters:

(a) Bond Stretching

<u>Type 1</u>	<u>Type 2</u>	$\frac{1}{2}k_l$	l_o
3	4	340.0	1.416
3	5	462.0	1.820

(b) Angle Bending:

<u>Types</u>	1	2	3	$\frac{1}{2}k_e$	k'_e	$\theta_o(2)^*$	$\theta_o(3)^*$
	1	3	4	0.0090	0.0	109.0	107.2
	3	3	4	0.0120	0.0	109.0	110.0
	3	4	3	0.0200	0.0	110.0	
	1	3	5	0.0130	0.0	109.0	108.2
	2	3	5	0.0140	0.0		107.8
	3	3	5	0.0180	0.0	109.0	107.8
	3	5	3	0.0220	0.0	94.3	

*Superscript refers to degree of substitution of central atom.

(c) Torsion

<u>Types</u>	1	2	3	4	$\frac{1}{2}k_\phi$	s	n
	5	3	3	4	0.10	+1	3
	3	3	3	4	0.10	+1	3
	1	3	3	4	0.08	+1	3
	3	3	4	3	0.10	+1	3
	1	3	4	3	0.08	+1	3
	5	3	3	5	0.15	+1	3
	1	3	3	5	0.08	+1	3
	3	3	3	5	0.08	+1	3
	3	2	3	5	0.12	+1	3
	4	2	3	5	0.12	-1	3
	1	3	5	3	0.24	+1	3
	2	3	5	3	0.24	+1	3
	3	3	5	3	0.24	+1	3

(d) Non-bonded

<u>Types</u>	1	2	r_1	r_2	ϵ
	1	5	4.60	0.0	0.18
	2	5	4.90	0.0	0.20
	3	5	4.80	0.0	0.20
	4	5	4.70	0.0	0.20
	5	5	6.00	0.0	0.22

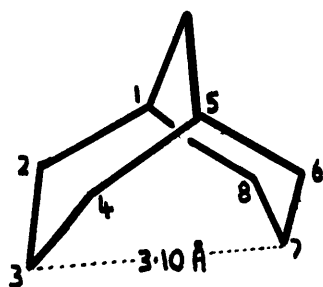
TABLE 6 (continued)(e) Out-of-plane Bending

No additional parameters necessary.

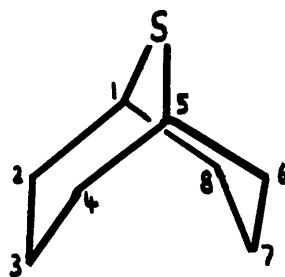
(f) Coulombic

No additional parameters introduced.

to 2.07 \AA , the latter being determined by a neutron diffraction study. However, these transannular $\text{H} \cdots \text{H}$ repulsions in corresponding compounds containing C_{sp^3} atoms in place of the carbonyl C_{sp^2} cause the distortions, instead, to be outwards within the $\text{C}_3\text{C}_9\text{C}_7$ plane, no skewing taking place; the rings are considerably flattened and the transannular $\text{H} \cdots \text{H}$ distance estimated to be less than 2 \AA . The electron diffraction structure⁸² of (3.3.1)-bicyclononane, for example, shows both this ring flattening and a short $\text{C}_3 \cdots \text{C}_7$ distance. No neutron diffraction analysis has been performed on this molecule to enable the corresponding $\text{H}_3 \cdots \text{H}_7$ distance to be determined.



(3.3.1)bicyclononane



9-thia(3.3.1)bicyclononane

The results calculated by means of molecular mechanics broadly agree with the experimental data and show also, that the skewing in sonane is indeed a consequence of the intramolecular interactions present and not of crystal-packing forces, the latter normally being relatively small. (See Table 7)

TABLE 7

Calculated Geometric Parameters

	$H_3 \cdots H_7$ (Å)	Skewing* (deg.)
Sonane (chair-chair)	2.08	6.2
(3.3.1)bicyclononane-2,6-dione	2.09	9.4
9-thia(3.3.1)bicyclononane	2.03	0
(3.3.1)bicyclononane	1.97	0

*"Skewing" is defined as the torsion angle difference $C_8C_1C_2C_3$ minus $C_3C_4C_5C_6$.

The calculated $H_3 \cdots H_7$ separation is a mere 0.01 Å greater than the experimental value and within its limits of error. The experimental skewing value, 12.0°, is somewhat greater than the calculated value, although the respective directions are the same, i.e. both have the torsion angles about the C_1-C_2 and C_5-C_6 bonds increased. It was found impossible to reproduce the experimental skewing unless the Van der Waals radius of sulphur were considered to be unrealistically large. However even this modest reproduction of the data in this respect is satisfying, for notwithstanding the inevitable uncertainty associated with the values assigned to the sulphur force-field parameters, the $H \cdots H$ non-bonded interaction potentials appear to be very well chosen (in the basic hydrocarbon force-field) insofar as the $H_3 \cdots H_7$ distance is concerned. Further, a non-rigid body thermal motion analysis⁸³ of sonane shows that the basic molecular skeleton, excluding hydrogen atoms, is a good rigid body which can be distorted (by skewing, for example) with only great difficulty. The molecule even with its canopy of hydrogen atoms is calculated to be still a fairly good rigid body

barely distortable by thermal effects or effects deriving from the influence of neighbouring molecules (crystal packing forces). This relative rigidity is also shown by following the change in steric energy, as the extent of skewing is varied, by "driving" a torsion angle, such as SC_1C_2O , through a range of values.⁸⁴ The minimization program permits this technique to be used by the inclusion of an offset parameter, which adjusts the value of a stated torsion angle to yield an energy minimum elsewhere than at the normal stipulated value, and also by the use of a multiplying factor which acts on the relevant torsional energy constant, thus allowing "locking" of the molecule into the required conformation. By this means an energy difference for sonane between the observed conformation with skewing 12.0° and that with zero skewing is calculated to be $3.5 \text{ kcal mol}^{-1}$, when the Van der Waals parameters, E , are twice those stated in Table 7; for the actual force-field parameters used, the energy difference is estimated to be rather less than this. Even so, the size of the value renders it highly unlikely that intermolecular interactions can be the cause of the skewing.

Finally a calculation attempted on the boat-chair conformation of sonane, in order to ascertain if the strain associated with the transannular $H \cdots H$ non-bonded interactions can be relieved by a chair-boat transformation of one of the rings (instead of skewing), was unsuccessful. The conformation does not occupy an energy minimum and it reverts to the chair-chair form during the minimization procedure. Evidently, the non-bonded interaction between sulphur and the nearby hydrogen at

atom 7 is too great to allow the maintenance of an equilibrium state under these conditions; however, use of an appreciably smaller sulphur atom does allow the isolation of a (high energy) conformational minimum for the boat-chair form of sonane.

In like manner, molecular mechanics calculations reproduce the experimentally observed chair-chair conformation of 3-oxa-7,9-dithia(3.3.1)bicyclononane, but are unsuccessful when applied to 9-oxa-3,7-dithia(3.3.1)bicyclononane. Calculated structural parameters and steric energies of these molecules along with those of the conformational isomers and the related 3,7-dithia(3.3.1)bicyclononane are given in Table 8. (No comparison with experiment can yet be made for the latter.)

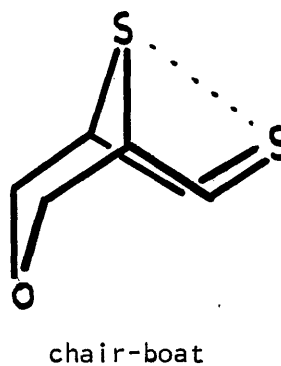
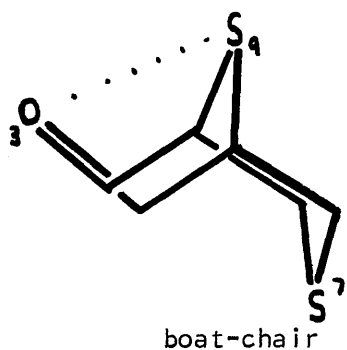
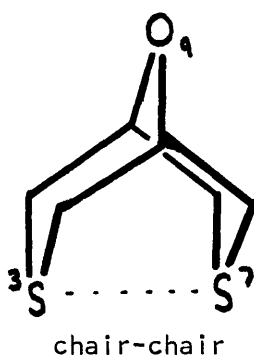
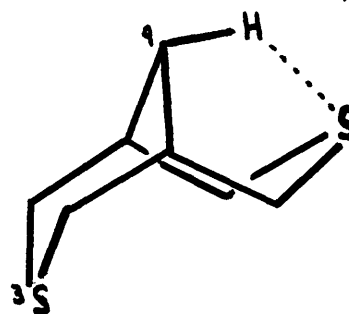
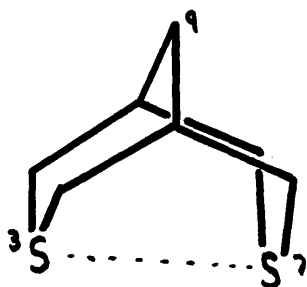
TABLE 8

Derivative of (3.3.1)- bicyclononane	Figure	E_s (kcal mol ⁻¹)	Non-bonded Distance (Å)
chair-chair 9-oxa-3,7-dithia-	5	39.27	(3...7) 4.06
chair-boat " "	4	41.95	(7...9) 3.09
chair-chair 3-oxa-7,9-dithia-	4	64.84	(3...7) 3.48
chair-boat " "	5	*	
boat-chair " "	5	*	
chair-chair 3,7-dithia-	5	43.94	(3...7) 4.00
chair-boat " "	5	*	

*The molecule relaxed upon energy minimization to give the chair-chair conformation.

The chair-chair conformation of 3-oxa-7,9-dithia(3.3.1)-bicyclononane is calculated to be the only stable one, the chair-boat and the boat-chair relaxing upon energy minimization to yield it. The predicted non-bonded distance between the atoms 3 and 7 is 3.48 Å which differs considerably from the observed, 3.12 Å.

FIGURE 5

3-0xa-7,9-dithia(3.3.1)bicyclononane9-0xa-3,7-dithia(3.3.1)bicyclononane3,7-Dithia(3.3.1)bicyclononane

The wrong conformation, however, is predicted to be the most stable in the case of 9-oxa-3,7-dithia(3.3.1)bicyclononane, by the relatively small margin of $2.68 \text{ kcal mol}^{-1}$, and the calculated S...O non-bonded distance in the chair-boat conformation of 3.09 \AA exceeds that observed by 0.25 \AA .

Although it would appear that the Van der Waals radius for sulphur assigned in the parameterization is too large, on the basis of these latter results, a smaller one is found to increase the energy discrepancy between the conformers of 9-oxa-3,7-dithia-(3.3.1)bicyclononane even further, and also has adverse effects in the sonane calculations. Until a more refined force-field for these classes of compound is forthcoming, the problem will have to remain unsettled.

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