to that presented for the amino group, then the corresponding eq. 7 contains the difference of frequency terms which, with an approximation analogous to that made above, would be zero for all charged species. However, if both the designations H_A and H_B of Figure 1 are reversed and the chemical shift difference ascribed to the unequal influence of the magnetically anisotropic carboxylate group on the three β-hydrogen positions, then an equation similar to 7 would yield a nonzero result for the chemical shift difference arising from unequal rotamer populations. It can be argued that an ionized carboxylate group is the major factor responsible for an ABX-type spectra for the compounds listed in Table I. The methyl esters of cysteine and histidine do not yield this type of spectra even in basic solutions. According to the kind of analysis presented here, a major role for the carboxylate group in yielding a nonzero result for $\Delta\nu_{AB}$ implies that the population of rotamer g exceeds that of rotamer t.

As pointed out in the spin–spin coupling analysis, reversal of the H_A and H_B designations in Figure 1 yields g > t. All the results in this paper may be rationalized on this basis almost as well or even better than those presented here for t > g. The predominance of rotamer t for malic acid appears established, but the analogous rotamer for cysteine may not be sufficiently similar for the analogy employed in this paper to be valid. It is conceivable that solvation effects could stabilize rotamer g in cysteine, so that the preponderance of rotamer t, though likely on the basis of the assumptions made in this paper, is not definitely established. Studies on the four substituted ethanes, valine, and threonines in this and other laboratories[6,8] reveal coupling constants between the α- and β-hydrogens from 3.6 to 5.1 c.p.s. These low values require that rotamers with the α- and β-hydrogens in *gauche* positions be favored with lesser amounts of the rotamer with the α- and β-hydrogens *trans*.[8] Thus the four substituent groups in these amino acids evidently lie in adjacent *gauche* positions in the favored rotamers.

A Scheme for Strain Energy Minimization. Application to the Cycloalkanes[1]

Kenneth B. Wiberg

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut. Received July 15, 1964

A simple direct method for strain energy minimization which is independent of the specific molecular geometry of a given case has been developed. The required molecular parameters have been estimated from the available thermodynamic, structural, and spectral data. The method has been applied to cyclooctane, cyclodecane, and cyclododecane.

I. Introduction

The increasing interest in compounds which are thermochemically destabilized by bond angle deformation and nonbonded interactions makes it necessary to develop a simple, direct computational scheme for obtaining the minimum energy conformation of a molecule. Simultaneously, it might be possible to estimate the value of the minimum energy. A number of attempts in this direction have been made,[2,3] but in general they have been related to the specific geometry of the compound. Thus, Westheimer and Mayer[4] in their very successful treatment of the rate of racemization of *ortho*-substituted biphenyls based the

calculation on the use of a set of internal coordinates (*i.e.*, bond lengths, bond angles, and torsional angles). In one of the most recent strain energy calculations, Hendrickson[2] also used a set of internal coordinates.

The use of internal coordinates is desirable in those cases in which an analytical solution to the energy minimization problem is possible.[3,4] With more complex cases, these coordinates, although directly related to the structure of the compound, are inconvenient. First, the interrelationships between the internal coordinates are complex, and it is difficult to determine the relationship between a change in one coordinate and the resultant change in all the others. With the relatively flexible cycloalkanes, a change in any one coordinate can be accommodated by any of a large number of alterations in the other internal coordinates, and one does not know which choice to make. Further, the transformation from internal coordinates to Cartesian coordinates is inconvenient. However, the latter (or its equivalent in terms of the internal coordinates) is required if one is to calculate complete sets of nonbonded distances. These considerations have led us to develop an alternate computational scheme.

II. Method of Calculation

We have chosen to work with the Cartesian coordinates of the atoms. The effect of a change in coordinates of any given atom is easily obtained since

(1) This work was supported by the Army Research Office (Durham) and the Petroleum Research Fund.

(2) J. B. Hendrickson, *J. Am. Chem. Soc.*, 83, 4537 (1961); 84, 3355 (1962), and references given therein.

(3) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956.

(4) F. H. Westheimer and J. E. Mayer, *J. Chem. Phys.*, 14, 733 (1946); F. H. Westheimer, *ibid.*, 15, 252 (1947); M. Rieger and F. H. Westheimer, *J. Am. Chem. Soc.*, 72, 19 (1950).

the transformation from Cartesian to internal coordinates is a relatively simple one (*cf.* the Appendix). The energy of any given structure may be obtained by applying the appropriate potential functions to the deviation from the ideal bond lengths and angles, and then including the contributions from the barrier to internal rotation and from nonbonded interactions.

The alteration of the approximate structure so as to minimize the energy may be effected using the method of steepest descent. This requires the evaluation of a $3n$ dimensional vector in which each element corresponds to the partial derivative of the change in energy with respect to one change in coordinate (such as moving atom 10 in the $+y$ direction). The derivatives were estimated by moving each atom in turn by a given amount (usually 0.01 Å.) successively in each of the x, y, and z directions and recalculating the energy for each of these $3n$ modified conformations. The total operation then requires the evaluation of the energies of $3n + 1$ conformations (*i.e.*, the original conformation and each of the $3n$ deformed conformations).

When the set of partial derivatives has been evaluated, each of the original coordinates is changed by an amount equal to a constant times the corresponding partial derivative and a new energy is calculated. The changes in coordinates are continued until the energy no longer decreases. Then a new set of partial derivatives is calculated and the coordinates of the atoms are moved along this new vector. The process is continued until a minimum in energy has been reached.

In practice, a small modification of this procedure proved useful. When the partial derivatives for the carbons are evaluated, the attached hydrogens are moved with them so as to maintain a constant carbon-hydrogen distance. In the initial stages of refining an estimated structure, the hydrogens are not treated independently. However, in the later stages, the independent motion of the hydrogens is included. This procedure considerably reduces the time required for the calculation.

If the structure has some symmetry elements which should be preserved, the symmetrically related atoms are moved simultaneously in calculating the steepest descent coordinate. This also decreases the computation time and prevents distortion of the structure. In a further effort to reduce computing time, only the bond angles and distances which are changed as a result of a given change in coordinates are re-evaluated at each stage of obtaining the partial derivatives.

The determination of the steepest descent coordinate is the most time-consuming part of the entire computation. Without the use of symmetry, a calculation of the set of partial derivatives for the 18 atoms of cyclohexane requires 4 min., and a similar calculation for the 36 atoms of cyclododecane requires 22 min., using an IBM-709 computer. If the hydrogens of cyclododecane are not permitted independent motion, as in the early stages of calculation, the time required for calculating the set of partial derivatives is reduced to 10 min. For cyclohexane, the time required for each step in moving along the steepest descent coordinate was about 0.05 min., and for cyclododecane, the time was 0.1 min.

III. Potential Functions

Once a suitable computer program has been written, the entire computation is simple and requires only a set of approximate atomic coordinates. The major problem is that of setting up suitable potential functions for the evaluation of the energy of a given structure. The terms which must be considered are: (a) bond length distortion, (b) bond angle distortion, (c) 1,3-nonbonded interactions, (d) other nonbonded interactions, (e) barrier to internal rotation, (f) zero-point energies, (g) partition functions, and (h) symmetry.

The bond length variation is minimal in most structures since this involves a rather "stiff" potential. For small displacements, the change in energy may be evaluated from

$$\Delta V = \frac{1}{2} k(r - r_e)^2$$

where r_e is the equilibrium bond length (1.54 Å. for C–C bonds and 1.09 Å. for C–H bonds), and k is the stretching force constant. Both of these bonds have a force constant, evaluated from vibrational spectral data, of 5×10^5 dynes/cm.[2,5]

The bond angle distortion and 1,3-nonbonded interactions must be considered together. As Bartell[6] has pointed out, the bending of bonds, apart from nonbonded repulsions, can be made with a modest cost of energy; thus, the potential function for bond bending should include factors for valence deformation and for repulsion of the two bond orbitals which are involved. In principle, this is done when the Urey–Bradley[7] potential function is used, and it is observed that the parameters determined using this treatment are transferable from one molecule to another.[8] However, the required analysis has not as yet been carried out for the cycloalkanes.

The calculation of thermochemical destabilization resulting from bond angle distortion has commonly been carried out by summing the usual valence deformation expression over all of the bond angles.[2,3]

$$\Delta V = \frac{1}{2} \sum_{6m} k_\theta (\Delta \theta_1)^2$$

Here, k_θ is the bending force constant and $\Delta \theta$ is the angular deformation, and for cycloalkanes, the summation is over the $6m$ angles where m is the number of carbons. For rough calculations, one might assume that the nonbonded potential field for a tetrahedral configuration about an atom would be reasonably approximated by the above expression, provided the angular displacements are small. The bending force constants could then be taken from the results of vibrational analyses for cyclohexane or similar molecules.

However, if one is to do this, the vibrational analysis would have to have been carried out using all of the bond angles as internal coordinates, which would lead to six redundant coordinates (there are $6m - 6$ degrees of freedom left after subtracting translation, rotation, and internal coordinates corresponding to bond stretching, but there are $6m$ bond angles). Vibrational analyses are not normally carried out in this

(5) E. B. Wilson, Jr., J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill Book Co., New York, N. Y., 1955, p. 175.
(6) L. S. Bartell, *J. Chem. Phys.*, **32**, 827 (1950).
(7) H. C. Urey and C. A. Bradley, *Phys. Rev.*, **38**, 1969 (1931).
(8) *Cf.* T. Simanouti, *J. Chem. Phys.*, **17**, 245, 734, 848 (1949); D. F. Heath and J. W. Linnett, *Trans. Faraday Soc.*, **44**, 556, 873, 878, 884 (1948); **45**, 265 (1949); *J. Chem. Phys.*, **19**, 801 (1951); L. S. Bartell and K. Kuchitsu, *ibid.*, **37**, 691 (1962).

fashion. With cyclohexane, for example, the bending internal coordinates were taken as the six C–C–C angles, the six H–C–H angles, and 18 deformations in which the CH_2 group was bent or rotated with respect to the carbon skeleton.[9] It is clear from the above that suitable potential functions and/or parameters for bond bending are not available. This is one of the major stumbling blocks in "strain energy" calculations.

If one wishes to compare the energies of several conformations of a given compound, the exact potential function becomes of less importance, and one may satisfied with one which is reasonable. With this qualification in mind, we have chosen to use the valence deformation expression, summing over all angles. Two sets of force constants were used. In the first, k_θ for all bond angles was taken as equal to the force constant for HCH and CCC bond bending in the above-mentioned analysis for cyclohexane (0.5 × 10^{-11} erg/rad²). In the second, the values suggested by Westheimer[3] and used by Hendrickson[2] (HCH, 0.32 × 10^{-11}; HCC, 0.55 × 10^{-11}; CCC, 0.8 × 10^{-11} erg/rad²) were employed.

If one includes the 1,3-nonbonded interactions with bond angle deformation, the remaining interactions will, for the most part, be attractive. The major repulsive interaction will involve hydrogens at a distance less than about 2.0 Å. Several potential functions have been suggested and many of these have been summarized by Hendrickson.[2] Although the energy may be fairly well estimated for relatively large nonbonded distances,[10] and for short distances,[11] the shape of the potential function in the crucial intermediate range of distances is not known.

An extreme viewpoint, that the repulsive part of the nonbonded potential may be neglected up to quite short distances, has been taken by Pitzer and Catalano.[10] They have been able to account for the difference in energy between branched and straight chain hydrocarbons, and for the difference in energy between cyclohexane and cyclopentane[12] using only the attractive potential. In this connection, it is interesting to note that the preferred conformation for propionaldehyde is one in which the methyl group eclipses the carbonyl oxygen.[13] This conformation is about 1
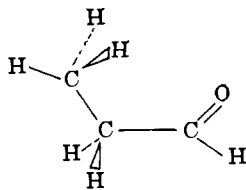
kcal./mole more stable than the one in which the carbonyl group has been rotated through 180° and has a methyl carbon to oxygen distance of about 2.65 Å. An oxygen is of course smaller than a carbon, and the polarizability of the carbonyl group may be of importance. It is certain that at relatively large distances, the carbon–carbon nonbonded interaction will

involve primarily the attractive dispersion force. The data given above suggest that an attractive potential will probably be appropriate to distances as small as 3 Å. (which is 0.35 Å. greater than the C–O nonbonded distance in propionaldehyde).

In the first set of calculations, we have simply used the Pitzer–Catalano function for C–C and C–H nonbonded interactions[10] (in kcal./mole): $V = 325 \Sigma r_{C-C}^{-6}$, $V = 125 \Sigma r_{C-H}^{-6}$. For the H–H interaction, it is necessary to include both the attractive and repulsive parts of the nonbonded interaction. The nonbonded repulsion is the most important part of the potential in considering cycloalkanes from C_8 up since distortion from an ideal diamond-lattice-like structure occurs as a result of repulsion between the hydrogens which are directed inward toward the inside of the ring. In the case of cyclodecane, which is destabilized with respect to cyclohexane by about 13 kcal./mole,[14] two pairs of internal hydrogens are at a distance of 1.9 Å.[15] This must correspond to a repulsive interaction since movement to that distance caused considerable CCC bond angle distortion. We have made a guess that about half of the total destabilization is due to H–H repulsion, giving a potential of about +3 kcal./mole per pair of hydrogens at a distance of 1.9 Å. This value leads to satisfactory results in minimizing the energies of a number of cycloalkane conformations (i.e., the internal H–H distance for the minimum energy conformation is calculated to be 1.9 Å. or greater).

It would be desirable to have the potential energy rise rapidly at shorter distances, regardless of whether such a rise has any physical significance. In the calculation, this would result in a rapid movement of atoms so as to bring the H–H distance to a reasonable value. For this reason, a Morse-type potential function was chosen.

$$ V = 0.35 [(1 - e^{-3.5(r-2.3)})^2 - 1] $$

The values of V for $r = 1.9$, 2.3, and 3.0 Å. are 2.92, −0.35, and −0.06 kcal./mole, respectively. The latter values are close to those calculated using the Pitzer–Catalano function: −0.33 (2.3 Å.) and −0.067 (3.0 Å.).

In the second set of calculations, a more conservative viewpoint was taken, and both the repulsive and attractive parts were included for all nonbonded interactions. The most reasonable set of potential functions appears to be that of Hendrickson.[2] For example, the maximum attractive potential between two carbons is found at 3.2 Å., a distance which is in good accord with intramolecular nonbonded distances.[16] The H–H function gives an energy of 0.55 at 1.9 Å., and thus a somewhat softer repulsive part than that used in the first set of calculations.

The barrier to internal rotation is on the order of 3 kcal./mole and it is usually assumed that a cosine potential function is appropriate, with maximum values at torsional angles of 0, 120, and 240°, and minimum values at 60, 180, and 300°.[17] In examining structural

(9) M. Larnaudie, Compt. rend., 231, 1292 (1950); 232, 318 (1951).

(10) K. S. Pitzer and E. Catalano, J. Am. Chem. Soc., 78, 4844 (1956).

(11) I. Amdur and A. L. Harkness, J. Chem. Phys., 22, 664 (1954); I. Amdur and E. A. Mason, ibid., 23, 415 (195).

(12) K. S. Pitzer and W. E. Donath, J. Am. Chem. Soc., 81, 3213 (1959).

(13) S. S. Butcher and E. B. Wilson, Jr., J. Chem. Phys., 40, 1671 (1964).

(14) J. Coops, H. Van Kamp, W. A. Lambregts, B. J. Visser, and H. Dekker, Rec. trav. chim., 79, 1226 (1960).

(15) J. D. Dunitz and K. Venkatesan, Helv. Chim. Acta, 44, 2033 (1961); J. D. Dunitz and V. Prelog, Angew. Chem., 72, 896 (1960); V. Prelog, W. Küng, and T. Tomljenović, Helv. Chim. Acta, 45, 1352 (1962).

(16) See, for example, the data of S. Silvers and A. Tulinsky, J. Am. Chem. Soc., 86, 927 (1964).

(17) Cf. E. B. Wilson, Jr., Advan. Chem. Phys., 2, 367 (1959); D. J.

data for a variety of compounds, we have been impressed with the importance of avoiding a dihedral angle of 0°—even a relatively small increase in angle appears to be valuable.[18] This might not be expected with a cosine function since it changes very slowly for small angles. A more rapidly changing potential would be $\cos^2$, and there appears to be no theoretical reason for preferring cos over $\cos^2$. Thus, in the first set of calculations, we have used the function

$$V = \Sigma \ 0.33 \ \cos^2 \ (1.5\phi)$$

where ϕ is the torsional (dihedral) angle, and the summation includes all nine angles about a given pair of carbons. The coefficient is one-ninth of 3.0 kcal./mole. This form was used since nothing is known about the effect of departure from tetrahedral angles on the barrier, and thus it appeared reasonable to weight equally each of the nine dihedral angles about a given pair of carbons.

In the second set of calculations, the usual cosine expression was used, and again, the potential was summed over all nine angles about a pair of carbons.

$$V = \Sigma \ 0.165(1 \ + \ \cos \ 3\phi)$$

Here, the coefficient is one-eighteenth of 3.0 kcal./mole.

The zero-point energies are important in calculating the energies of cycloalkanes. As the ring size increases, a larger proportion of the vibrations may have low frequencies because of the flexibility of the rings, leading to a decrease in zero-point energy per CH_2 group. At the same time, the lower frequencies will result in a higher population in the vibrationally excited states for the larger molecules and an increase in the vibrational partition function. In a comparison of several conformations of a single cycloalkane, these factors may be relatively unimportant. In comparisons between cycloalkanes, they should be included.

Similarly, in comparisons between cycloalkanes, the effect of the translational and rotational partition functions should be included, but the effect will be small in comparing different conformations of the same structure. Finally, the effect of symmetry on the number of allowed rotational levels must be considered. This will have no effect on the heat content calculated for a given conformation, but it will effect the free energy and entropy. It must be remembered that the free energy is the proper function to consider in treating conformational equilibria. For a change in symmetry number from 4 to 1, the change in free energy will be favorable by 1 kcal./mole at 25°. Thus, if all other factors are equal, the less symmetrical structure will be favored.

IV. Application to Cyclooctane

Three conformations for cyclooctane have commonly been considered,[19,20] and are shown as I, IV, and VI

Millen, in "Progress in Stereochemistry," P.B.D. de la Mare and W. Klyne, Ed., Butterworth Inc., Washington, D. C., 1962, p. 138.

(18) See, for example, the data on cyclopentane[12] and cyclobutane: A. Almenningen, O. Bastiansen, and P. N. Skancke, *Acta. Chem. Scand.,* **15,** 711 (1961).

(19) *Cf.* N. L. Allinger and S.-E. Hu, *J. Am. Chem. Soc.,* **83,** 1664 (1961); N. L. Allinger, S. P. Jindal, and M. A. Darooge, *J. Org. Chem.,* **27,** 4290 (1962), and references given therein.

(20) The six conformations considered here have also been discussed by J. Hendrickson, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p. 1N.
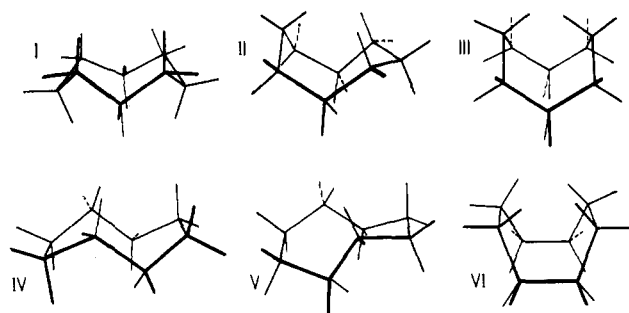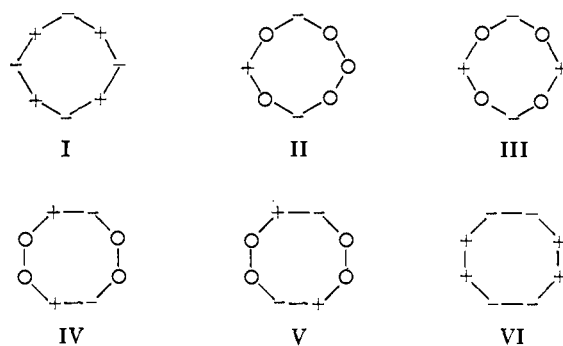

Figure 1. Some cyclooctane conformations with normal bond angles.

below and in Figure 1. Three other conformations, II, III, and V, might also be considered. In each case, ◯ represents a carbon atom in the plane of the paper, + indicates a carbon above the plane, and − indicates one below the plane.

Conformation I has been commonly considered in discussions of cyclooctane,[10] and has been designated the crown conformation. Conformation II is derived from I by moving one atom, and conformation III may then be derived by moving a second atom. In a comparison of these three conformations, it may be seen that I has relatively little H–H nonbonded repulsion, but has poor dihedral angles, and that III has ideal dihedral angles (being based on a diamond lattice)[21] but has strong H–H nonbonded repulsion. Conformation II is a compromise between the other two, but it is difficult to compare it with the others in qualitative terms.

Conformations IV, V, and VI are also related. Conformation VI is commonly known as the tub conformation. Conformation IV is derived from it by moving one pair of carbon atoms, and conformation V is derived from IV by interchanging the z (out-of-plane) coordinates of two carbons. Of the three, VI is probably the least favored because of poor dihedral angles and a considerable degree of H–H nonbonded repulsion. Conformation IV is better with regard to the latter, but still has poor dihedral angles. Conformation V is probably the best of the group since the interchange of two carbon atoms results in no eclipsed conformations about carbons.

The qualitative conclusions are borne out by the detailed calculations. The starting coordinates for conformations I, II, IV, V, and VI were estimated

(21) The possible conformations for a series of cycloalkanes which correspond to having the carbons lie at lattice coordinates for a diamond crystal have been calculated by Professor Martin Saunders. We thank him for supplying his data prior to publication.
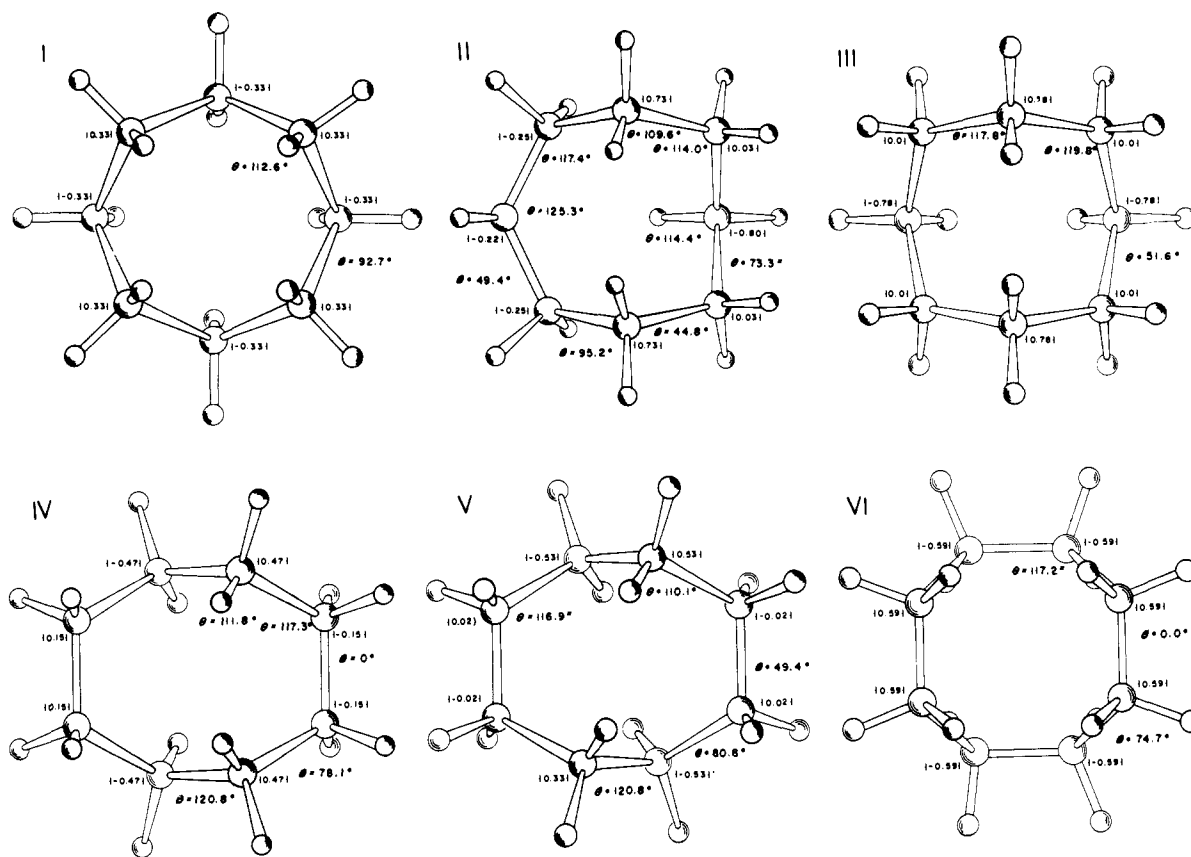
Figure 2. Final minimum energy conformations for the five starting models for cyclooctane. The conformations are drawn to scale. The numbers in parentheses are the z coordinates of the carbons, the values of θ are the CCC bond angles, and the values of ϕ are the dihedral angles.

from Dreiding[22] models, and those for V were based on diamond lattice coordinates.[21] The energy minimization was effected using both of the sets of parameters discussed above. The conformations derived from the first set of parameters are shown in Figure 2 which is drawn to scale. The corresponding energy terms are given in Table I. The energy terms derived from the second set of parameters are given in Table II.[23]

The calculations were first carried out using a procedure which destroyed the symmetry present in the starting conformations. After a given partial derivative of energy with respect to change in coordinate had been evaluated, the atom in question was moved from its original position by the amount of a constant times the partial derivative. When the partial derivatives for the next atom were evaluated, these quantities would be effected by the previous movement of the preceding atom. In this way, each atom could "feel" the effect of the adjustment of coordinates of all previous atoms. This results in marked asymmetry at first, but then there was a slow approach back to a symmetrical form. In each case, the symmetry of the

final conformation was essentially the same as that of the starting conformation.

After a minimum form had been reached for a given conformation, several arbitrary adjustments of coordinates were made and the energy minimization was repeated. This was continued until the coordinates consistently returned to the same values, making it reasonably certain that the true minimum energy form had been reached. The results show that the computational scheme is sound. It is now of interest to see if the parameters used lead to reasonable values of "strain energies."

Let us first consider the results obtained using the first set of parameters. Conformations III, IV, and VI appear to have considerably higher energies than the others, and probably can be dismissed. The remaining three (I, II, and V) have similar energies and considering the uncertainty in the parameters used, any one might be the lowest energy conformation. Conformation I has a higher symmetry than the others, and at room temperature would be disfavored. However, the energy required to effect a small distortion is fairly small and the form with the lowest free energy is probably distorted.

A corresponding calculation for the chair form of cyclohexane gave the results

(22) One of the advantages of the procedure described herein is that the initial coordinates need not be very accurate. They are adjusted appropriately as part of the calculation.

(23) The first set used $k_\theta = 0.5 \times 10^{-11}$ ergs/rad^2 for all bonds, neglected the repulsion term for C–C and C–H nonbonded interactions, and used a cos^2 potential for the barrier to internal rotation. The second set used the parameters employed by Hendrickson.[2] These are (in kcal./mole) $\Delta E_{\text{bend}} = k_\theta(\theta - 109.5)^2$, $\Delta E(\text{H–H}) = 1.00 \times 10^4$ $(e^{-4.6/r}) - 49.2/r^6$, $\Delta E(\text{N–C}) = 1.29 \times 10^4(e^{-4.12/r}) - 125/r^6$, $\Delta E(\text{C–C})$ $= 1.66 \times 10^4 (e^{-3.63/r}) - 325/r^6$, $\Delta E(\text{tors}) = 1.40 (1 + \cos 3\omega)$; k_θ $= 23.0$ (H–C–H), 39.6 (H–C–C), 57.5 (C–C–C).

bond length and angle deformation	0.20
H–H nonbonded interactions	−6.99
other nonbonded interactions	−6.92
	−13.71

Table I. Energy Contributions for Six Cyclooctane Conformations

Conformation	Stretching	Nonbonded		Bond angle bending			Torsional angle	Total
		H–H	Other	HCH	HCC	CCC		
1	0.08	−8.70	−11.70	0.02	0.94	0.91	11.06	−7.38
2	0.30	−8.26	−12.88	0.22	3.09	5.01	4.89	−7.64
3	0.40	−6.17	−10.42	1.29	1.70	7.71	2.29	−3.20
4	0.16	−7.42	−12.23	0.16	0.95	3.02	13.80	−1.55
5	0.22	−7.81	−12.74	0.12	0.70	2.53	9.10	−7.89
6	0.22	−6.72	−12.14	0.67	0.78	5.43	13.08	1.32

Table II. Energy Contributions for Six Cyclooctane Conformations Based on Hendrickson's Parameters[a]

Conformation	Stretching	Nonbonded		Bond angle bending			Torsional angle	Total
		H–H	Other	HCH	HCC	CCC		
1	0.04	−3.56	−6.29	0.02	1.09	1.32	10.99	3.62
2	0.24	−3.16	−6.63	0.15	2.91	5.50	5.00	4.03
3	0.20	−2.11	−6.78	0.77	1.96	9.10	1.91	5.06
4	0.09	−3.09	−6.41	0.11	1.08	3.83	13.78	9.40
5	0.05	−2.97	−6.60	0.05	1.12	1.75	9.25	2.65
6	0.05	−2.67	−6.94	0.38	0.93	7.35	13.06	12.15

[a] The parameters were those used by Hendrickson,[2] plus the C–H and C–C nonbonded interactions for pairs of atoms having other than a 1,3 relationship.

The energy of a hypothetical "unstrained" cyclooctane should be $-13.7 \times 8/6$ or -18.3 kcal./mole. The net destabilization of conformation V is then calculated to be 10.4 kcal./mole. This may be compared with the experimental value of 9.9 ± 0.5 kcal./mole for cyclooctane as a gas.[24] The agreement is quite good.

Let us now consider the results obtained with the second set of parameters. Although the numerical values obtained are quite different, largely owing to the difference in nonbonded interaction parameters, the results are generally in good agreement with those obtained with the first set of parameters.

It may first be noted that for all conformations except III, the difference in calculated energy between Tables I and II is roughly constant at 11 ± 0.5 kcal./mole. The final form for each conformation was roughly the same (cf. Table III) except for conformation III. Here, the bond angles were essentially equal using the second set of parameters, whereas they were significantly different using the first set. This change and the change in the difference in energies calculated from the two sets of parameters arise from the softer H–H nonbonded repulsion curve used by Hendrickson. Conformation III has the largest degree of H–H nonbonded repulsion of all the cyclooctane conformations.

Again conformations I, II, and V are calculated to be the more stable, although the order for I and II is inverted. Conformation V is calculated to have the lowest energy using either set of paramters. The energy of chair cyclohexane is calculated to have the energy

bond length and angle deformation	0.18
H–H nonbonded interactions	−3.08
other nonbonded interactions	−3.41
	−6.31

The energy of "unstrained" cyclooctane should then be $-6.3 \times 8/6$ or -8.4 kcal./mole. The strain energy of

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

Table III. A Comparison of the Two Sets of Final Conformations[a]

Conformation	Bond angles, deg.		Dihedral angles, deg.	
	Set 1	Set 2	Set 1	Set 2
1	112.6	112.6	92.7	92.8
2	125.3	122.4	73.3	72.3
	117.4	116.7	44.8	46.2
	109.6	110.1	95.2	98.7
	114.0	113.1	49.4	51.9
	114.4	113.7		
3	117.8	117.5	51.6	54.
	119.8	117.9		
4	111.8	111.4	0	0
	117.3	116.7	78.1	78.6
			120.8	122.4
5	116.9	114.4	49.4	52.0
	110.1	109.7	80.8	83.4
			120.8	124.7
6	117.2	116.7	0	0
			74.7	75.3

[a] The values for parameter set 1 are given in Figure 2; the values given under parameter set 2 are the corresponding values.

conformation V is calculated to be 11.1 kcal./mole, again in good agreement with the experimental value.

It can be seen that the calculated strain energy is not a very sensitive function of the parameters used. A decision between various possible sets of parameters may possibly be made using good structural information. The nonbonded C–C distances are significantly different between conformations, and it should not be difficult to determine which is the predominant conformation via electron diffraction studies. This does not appear to have been done. If two conformations have similar energies, it might also be possible to determine the proportion of each from the electron diffraction data. These data, coupled with a comparison of calculated and observed C–C nonbonded distances, should give a good basis for selecting between different sets of parameters. Cyclooctane appears to be

Table IV. Energy Contributions for Cyclodecane and Cyclododecane

Compound	Bond stretching	Nonbonded interactions		Bond bending			Torsional angle	Total
		H–H	Other	HCH	HCC	CCC		
Parameter Set 1								
Cyclodecane (exptl. structure)	0.31	−9.51	−16.47	0.56	2.95	5.53	5.91	−10.72
Cyclododecane (exptl. structure)	0.55	−10.85	−21.13	0.13	1.30	1.96	3.84	−24.20
Cyclododecane (diamond lattice model)	3.92	−9.74	−24.92	1.59	7.00	9.80	4.03	−8.32
Parameter Set 2								
Cyclodecane (exptl. structure)	0.14	−2.82	−10.36	0.38	2.75	4.95	4.91	−0.04
Cyclododecane (exptl. structure)	0.27	−5.51	−12.59	0.07	1.39	2.14	3.72	−10.51

an ideal case for such a study since it is complex enough to permit an interplay of the several factors involved, and simple enough that accurate structural parameters might be obtained by electron defraction.

In most chemical problems, the conformation of the basic hydrocarbon is not the datum of major interest; rather the conformation of substituted derivatives is of importance. It is clear from the results that these derivatives may be derived from *any one* of the three low energy conformations, and for cyclooctanone, con-

minimization procedure led to an adjustment of the bond lengths and angles so as to make them more uniform. The energy terms are given in Table IV, and a comparison of observed and calculated bond angles is given in Figures 3a and 3b.

The "strain energies" of cyclodecane and cyclododecane are 13.0 ± 1.0 and 3.4 ± 1.2 kcal./mole, respectively.[14,15,24] Using the first set of parameters, the energies of the hypothetical "unstrained" conformations should be −22.9 and −27.4 kcal./mole, re-
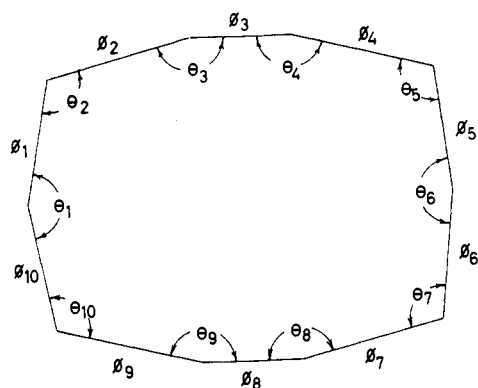

Figure 3a. Cyclodecane. The angles (in degrees) are as follows:

	Exptl.[15]	Set 1	Set 2		Exptl.[15]	Set 1	Set 2
θ_1	120.1	112.4	113.4	ϕ_1	66.2	70.8	71.4
θ_2	118.8	118.9	116.1	ϕ_2	52.6	50.6	52.3
θ_3	112.8	114.8	114.0	ϕ_3	151.9	149.1	153.3
θ_4	116.5	114.8	114.0	ϕ_4	52.5	50.6	52.3
θ_5	115.8	118.9	116.1	ϕ_5	71.9	70.8	71.4
θ_6	116.3	112.4	113.4	ϕ_6	66.7	70.8	71.4
θ_7	117.7	118.9	116.1	ϕ_7	56.8	50.6	52.3
θ_8	114.2	114.8	114.0	ϕ_8	153.4	149.1	153.3
θ_9	112.8	114.8	114.0	ϕ_9	60.0	50.6	52.3
θ_{10}	117.5	118.9	116.1	ϕ_{10}	61.3	70.8	71.4

Figure 3b. Cyclododecane. The angles (in degrees) are as follows:

	Exptl.[25]	Set 1	Set 2		Exptl.[25]	Set 1	Set 2
θ_1	110	112.2	112.3	ϕ_1	161	165.2	166.4
θ_2	117	114.7	113.3	ϕ_2	69	70.1	70.0
θ_3	109	112.2	112.3	ϕ_3	68	66.8	67.2
θ_4	110	112.2	112.3	ϕ_4	155	155.8	157.4
θ_5	116	114.7	113.3	ϕ_5	67	66.8	67.2
θ_6	110	112.2	112.3	ϕ_6	70	70.1	70.0
				ϕ_7	163	165.2	166.4

formation III must also be considered. Calculations in progress are concerned with the conformations of cyclooctanone and of monosubstituted cyclooctanes.

V. Cyclodecane and Cyclododecane

As a further test of the usefulness of the computational scheme, it has been applied to cyclodecane and cyclododecane. Because of the long computation time required with the relatively slow IBM-709 computer, it was not possible to carry out a systematic study of the possible conformations of each. Thus, initially, the conformations deduced by X-ray crystallography were examined.[15,25] With both molecules, the energy

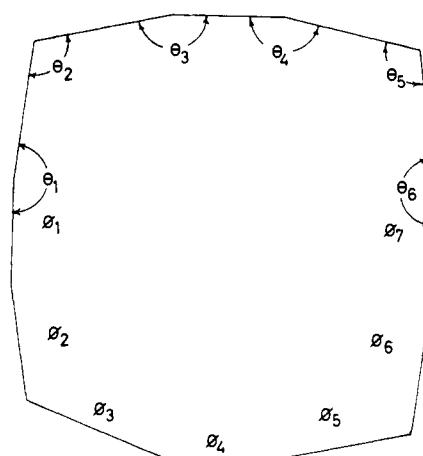(25) J. D. Dunitz and H. M. M. Shearer, *Helv. Chim. Acta*, **43**, 18, (1960).

spectively, based again on cyclohexane. The calculated "strain energies" are then 12.2 and 3.2 kcal./mole, and are again in good agreement with the experimental values. The energies of the "unstrained" conformations based on the second set of parameters should be − 10.5 and − 12.6 kcal./mole, respectively, leading to calculated "strain" energies of 10.1 and 2.1 kcal./mole for the two compounds. Again, these values are reasonable. The experimental results are best fit by the first set of parameters which correctly gives a higher strain energy for cyclodecane than for cyclooctane. However, it is almost certain that another set of parameters could be found which would give as satisfactory results as the first set. The decision as to to the proper set of parameters must be made using other data.
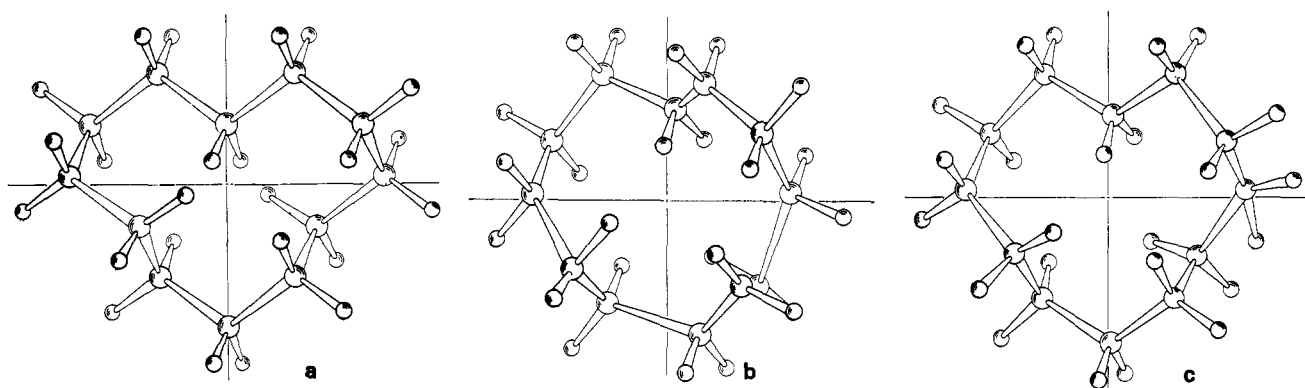
Figure 4. Results of energy minimization for one of the diamond lattice models for cyclododecane. The first (a) is the starting model, the second (b) is the result of moving methylene groups as units, and the third (c) is the final result in which the carbons and hydrogens were moved independently.

It can be seen (Figure 3) that both sets of parameters give bond angles significantly different from the observed values. However, the divergence of values between potentially symmetrical groups of atoms in the experimental structure suggests that distortion due to crystal packing may be involved.

There are four diamond lattice conformations for cyclododecane. Since a diamond lattice conformation is close to the minimum energy conformation of cyclohexane and cyclodecane, it was of interest to test one of these conformations. The coordinates for each have been obtained by Saunders.[21] We have taken the conformation having the least H–H nonbonded interaction and have subjected it to the energy minimization scheme. In Figure 4 there are shown the original conformation (a), the conformation after permitting the CH_2 groups to move as units (b), and the final conformation after permitting the carbons and hydrogens to move independently (c). The energy terms are given in Table IV. Although it is possible to decrease the energy of the starting conformation considerably, using bond angle deformation to permit an increased H–H nonbonded distance, the final energy is still considerably above that of the experimentally determined structure.

The results obtained suggest that none of the diamond lattice models will lead to a conformation having an energy comparable to that of the experimentally determined structure. The H–H nonbonded repulsion in any of the diamond lattice models may be relieved only by a considerable amount of bond angle distortion. The experimentally determined structure combines a low amount of bond angle distortion with a set of fairly good torsional angles leading to a very small strain energy.

It seems clear that given sufficient time, each of the possible starting conformations for any cycloalkane could be examined, and that the minimum energy conformation could thereby be obtained.

VI. Limitations

The application of a mixed potential function such as that used here always has the possibility of causing difficulty. For example, if planar conformations for cyclohexane and cyclopentane are used in the computational scheme, the final calculated structure will still be planar. Suppose we consider the stage in the calculation in which the correction term for moving atom 1 (a carbon) in the z direction (perpendicular to the plane of the ring) is evaluated. The change in z coordinate will cause an increase in bond lengths, a decrease in the CCC bond angle, and changes in the HCC bond angles. Because of the stiffer potential involved in bond stretching than in bond bending, and the temporarily unfavorable changes in HCC bond angles, the net change will be unfavorable, and as a result the z correction term will be set equal to zero. The situation is easily remedied by alternating the direction of displacement in calculating the derivatives of energy with respect to the coordinates (i.e., by using a $+z$ displacement for atom 1, $-z$ for atom 2, etc.), and by using a larger CCC bending force constant and a smaller HCC constant in the early stages of the calculation, returning to a normal value in the later stages. Values of $k_\theta = 2.0 \times 10^{-11}$ (CCC) and 0.2×10^{-11} erg/rad^2 (HCC) appear satisfactory.

In cyclopentane, the bond angles are already smaller than tetrahedral, and so a movement in the z direction will be unfavorable with regard to both bond stretching and bond bending. In this case, the simplest solution is to start with conformations having a relatively large degree of puckering (and more favorable dihedral angles) and then permit the computational scheme to determine what degree of puckering produces a minimum energy.

The potential due to the torsional angles changes only very slowly with a change in coordinates at angles close to 0°. In the early stages of the computation, it is sometimes practical to use an artificial potential which changes more rapidly near 0°.

$$V = 0.33(1 - |\sin 1.5\phi|)$$

The normal potential would then be used in the later stages.

Another problem associated with this method of energy minimization is the possibility of finding false minima. Here, several things may be done. First, the final calculated conformation may be distorted somewhat and the calculation repeated. If the coordinates consistently return to the same values, it is likely that the true minimum has been found. The occurrence of false minima may be reduced if pairwise interactions of atoms are considered. This may be done in part by simultaneously moving symmetrically

related atoms in calculating the derivatives. Since our experience has been that the symmetry of a conformation is generally retained, this will normally not introduce an error.

In any calculation of this type, potential energy barriers will normally not be passed over. Thus, it is necessary to minimize the energy of each possible starting conformation since conversion from one to another will generally involve passing over a potential energy barrier.

VII. Application to Other Compounds and to Reaction Intermediates

The procedure given above is generally applicable, and the main problem is that of obtaining suitable potential functions. If large degrees of bond angle deformation are encountered, as in small ring compounds, several factors must be considered. First, 1,3-nonbonded interactions must properly be taken into account. Second, it must be recognized that the apparent angle is smaller than the angle between the bond orbitals. Third, the bond energies may change when the hybridization changes considerably. Finally, because of the different angles involved, the value of the barrier to internal rotation may be different from that appropriate to the higher cycloalkanes. Our primary interest is with compounds of this type. However, it will be necessary to postpone a detailed discussion of these compounds until the necessary thermodynamic, spectral, and structural data have been obtained and evaluated.

A potentially interesting application is to reaction intermediates, particularly of the homoallylic type. Simonetta and Winstein[26] and Woods, Carboni, and Roberts[27] have discussed this problem. The present procedure provides a way in which to deal with the problem in more detail. The delocalization energy involved in the π-electronic system may be estimated in a straightforward way for any given geometry. The π-electronic energy may be evaluated as an extra term in the strain energy calculation. The energy may then be minimized with respect to both electron delocalization and structural deformation.

Appendix

This appendix describes the transformation of the Cartesian coordinates to internal coordinates. The bond length is of course given by

$$r_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2}$$

where x_i, y_i, and z_i are the coordinates of the first atom, and x_j, y_j, and z_j are the coordinates of the second. The nonbonded distances are calculated in the same way. The bond angle formed by atoms i, j, and

(26) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954).
(27) W. G. Woods, R. A. Carboni, and J. D. Roberts, *ibid.*, **78**, 5653 (1956).

k is obtained using the usual trigonometric formulas

$$a = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2}$$

$$b = \sqrt{(x_j - x_k)^2 + (y_j - y_k)^2 + (z_j - z_k)^2}$$

$$c = \sqrt{(x_i - x_k)^2 + (y_i - y_k)^2 + (z_i - z_k)^2}$$

$$s = (a + b + c)/2$$

$$\theta = 2 \tan^{-1} \left\{ \sqrt{\frac{(s-a)(s-b)(s-c)}{s}} \bigg/ (s - c) \right\}$$

The dihedral angle ϕ is most simply obtained by translating the coordinates of the four atoms involved so as to make those for the second atom 0,0,0. All of the points are then rotated so as to place the third atom on the z axis. The dihedral angle is now seen as a projection on the xy plane and may be obtained using the formulas given above. The required rotation of all points may be effected by calculating the functions

$$\sin \alpha = \frac{y_3}{\sqrt{y_3 + z_3^2}}$$

$$\cos \alpha = \frac{z_3}{\sqrt{y_3^2 + z_3^2}} \times \text{sign of } y_3 \times \text{sign of } z_3$$

$$\sin \beta = \frac{x_3}{\sqrt{x_3^2 + y_3^2 + z_3^2}} \times \text{sign of } x_3 \times \text{sign of } y_3$$

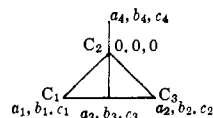$$\cos \beta = \frac{\sqrt{y_3^2 + z_3^2}}{\sqrt{x_3^2 + y_3^2 + z_3^2}}$$

and effecting the following transformation

$$x_i' = x_i \cos \beta + y_i \sin \beta \sin \alpha + z_i \sin \beta \cos \alpha$$

$$y_i' = y_i \cos \alpha - z_i \sin \alpha$$

$$z_i' = -x_i \sin \beta + y_i \cos \beta \sin \alpha + z_i \cos \beta \cos \alpha$$

It is often easier to estimate the locations of carbons using a molecular model than to estimate the location of hydrogens. Once the coordinates of the carbon framework have been obtained, the hydrogens may be placed as follows. C_1, C_2, and C_3 are three carbons

forming a bond angle, and they have the coordinates a_1, b_1, c_1; 0,0,0; and a_2, b_2, c_2 after a translation placing C_2 at the origin. A line drawn from a_3, b_3, c_3 through the origin and extended a distance 1.09 cos (111/2) gives the point a_4, b_4, c_4. The two hydrogens are located on a line through a_4, b_4, c_4 and perpendicular to the plane of the triangle shown. The distance from a_4, b_4, c_4 is ±1.09 sin (111/2).