Conformational Analysis. LXV. The Calculation by the Westheimer Method of the Structures and Energies of a Variety of Organic Molecules Containing Nitrogen, Oxygen, and Halogen[1,2]

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Abstract: The structures and energies of the conformations of a variety of molecules including ketones, aldehydes, and chlorides and a small number of alcohols, sulfoxides, nitriles, and dichlorides have been calculated by the Westheimer method. The results are generally in good agreement with experiment, indicating the method will be widely useful for functionally substituted organic molecules as well as for hydrocarbons.

In earlier papers in this series,[1,3,4] the original method developed by Westheimer for the calculation of the structures and energies of organic molecules was elaborated and extensively applied to hydrocarbons of various kinds. It was found possible to calculate accurate structures (bond lengths to within 0.01 Å, and bond angles to within 1°) and energies (to within 0.3 kcal/mol) for the majority of a large number of hydrocarbons of different types. The desired accuracy was not achieved in all cases, however. Our present objectives along these lines are twofold, namely: we wish to improve the calculations to the point where they yield acceptable values for substantially all hydrocarbons; and we wish to extend the calculations to organic molecules of other types besides hydrocarbons. The first objective will form the basis of a separate paper. The second objective will be taken up here, that is, the extension of these calculations in a general way to organic molecules containing a small number of heteroatoms.

As a starting point we have chosen the elements nitrogen,[4] oxygen, and halogen as being among the more common ones, which lead to classes of compounds of wide general interest. If one or more of these elements is present in an otherwise hydrocarbon molecule, there are certain additional features that must be taken into account in the calculations.

Each atom is treated as a sphere. Thus any effects due to lone pairs of electrons are not explicitly treated. The data presently at hand do not *require* explicit treatment of lone pairs, so we avoid treating them at this time so as to avoid the introduction of unnecessary parameters into the calculation.

In our earlier papers we discussed at some length the difficulty of ascertaining suitable values for the van der Waals parameters for carbon and hydrogen. Values were finally settled on which were believed to be reasonable. For each additional element one must again choose a van der Waals radius, and a value for the energy parameter (ϵ). Having no really good way to arrive at these values, we have, as a first approximation, decided to use the same values for nitrogen, oxygen, and fluorine as have been experimentally determined for neon, and the values used for chlorine and sulfur are those determined for argon. These values are probably not optimum, but they should be reasonable and at least give us a starting point from which to proceed.

Next, one needs to know the various force constants involved in deforming bonds of which one of these heteroatoms is a component. Most of the force constants needed were taken from the literature. In a few cases it was necessary to estimate them. These values are all summarized in Table I, together with the pertinent references. Each bond length and each bond angle which involves one or more heteroatoms needs to have a natural value (the value which would result in the absence of other forces) assigned to it. These natural values are arbitrarily chosen so as to make the resultant bond lengths and angles calculated in simple molecules equivalent to those which are found experimentally. Thus, for example, the acetone molecule was chosen as a simple carbonyl derivative, which contains, in addition to the hydrocarbon quantities discussed earlier, a carbon–carbon bond length of a new type, a carbon–carbon–carbon bond angle of a new type, a carbon–oxygen bond length of a new type and a carbon–carbon–oxygen bond angle of a new type. In addition, there is a new type of torsional barrier when hydrogen eclipses oxygen or carbon. A natural value for each of these quantities was chosen in such a way as to make the structure finally calculated from these natural values closely similar to that observed experimentally. These natural values were then car-

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[1] Paper LXIV: N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **90**, 5773 (1968).

[2] This research was supported by Public Health Service Research Grant AM-5836 from the National Institute of Arthritis and Metabolic Diseases.

[3] N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Amer. Chem. Soc.*, **90**, 1199 (1968); N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *ibid.*, **89**, 4345 (1967).

[4] Some preliminary results on amines have been reported: N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967).

Table I. Parameters for Calculation of Molecular Geometries

Bond	l_0[a]	k,[b] mdyn/Å^2
C_{sp^3}—C_{sp^2} (carbonyl)	1.501	4.8
H-C_{sp^2} (carbonyl)	1.114	5.3
C_{sp^2}=O	1.221	11.0
C_{sp^3}—C_{sp}	1.509	4.5
C_{sp^3}—Cl	1.788	3.64
C_{sp}≡N	1.157	17.73
C_{sp^3}—S (sulfoxide)	1.788	3.64
S→O	1.48	5.0
C_{sp^3}—O	1.416	5.0
O—H	0.952	7.0

Angle	θ_0[a]	k, mdyn/rad^2
C_{sp^3}—C_{sp^2}—C_{sp^3}	116.9	1.10
C_{sp^3}—C_{sp^2}—H	116.0	0.66
C_{sp^3}—C_{sp^2}=O	121.6	0.65
H—C_{sp^2}=O	118.6	0.50
C_{sp^3}—C_{sp^3}—Cl	107.0	0.82[c]
H—C_{sp^3}Cl	108.0	0.71[c]
C_{sp^3}—C_{sp^3}—C_{sp}	109.8	1.10
C_{sp^3}—C_{sp}≡N	180.0	0.35
C—C—S (sulfoxide)	109.8	1.10
C—S—C (sulfoxide)	95.8	0.9
C—S—O (sulfoxide)	108.6	0.9
C_{sp^3}—C —O	111.0	0.98
C_{sp^3}—O—H	95.2	0.76
H—C_{sp^3}—S (sulfoxide)	108.6	0.64
H—C_{sp^3}—O	107.2	0.5

van der Waals parameters for Hill equation

Atom	r^*	ϵ
C_{sp^2}	1.85	0.020
O, N	1.54	0.070
Cl, S	1.915	0.236
C_{sp}	1.85	0.020

Torsional constants[d]

Angle	Value, kcal/mol
H—C_{sp^3}—C_{sp^2}—H	1.88
C_{sp^3}—C_{sp^3}—C_{sp^2}—H	1.50
C_{sp^3}—C_{sp^3}—C_{sp^2}—C_{sp^3}	1.50
H—C_{sp^3}—C_{sp^2}—C_{sp^3}	1.50
H—C_{sp^3}—C_{sp^2}—O	0.76
C_{sp^3}—C_{sp^3}—C_{sp^2}=O	0.00
H—C_{sp^3}—C_{sp^3}—Cl	1.07
C_{sp^3}—C_{sp^3}—C_{sp^3}—Cl	1.07
C_{sp^3}—C_{sp^3}—C_{sp^3}—C_{sp}	0.49
H—C_{sp^3}—C_{sp^3}—C_{sp}	0.98
C_{sp^3}—C_{sp^3}—S—O (sulfoxide)	1.00
H—C_{sp^3}—S—O (sulfoxide)	0.65
H—C_{sp^3}—C_{sp^3}—S	1.07
C_{sp^3}—C_{sp^3}—C_{sp^3}—S	1.07
H—C_{sp^3}—O—H	0.87
C_{sp^3}—C_{sp^3}—O—H	0.87
C_{sp^3}—C_{sp^3}—C_{sp^3}—O	1.00
H—C_{sp^3}—C_{sp^3}—O	0.65

[a] The values of θ_0 and l_0 were chosen so as to yield calculated values which agreed with experimental values for the simple model compounds: carbonyls, acetaldehyde;[9] acetone;[10] alcohols, P. Venkateswarlu and W. Gordy, *J. Chem. Phys.*, **23**, 1200 (1955); L. Pierce and M. Hayashi, *ibid.*, **35**, 479 (1961); halides, ethyl chloride, R. H. Schwendeman and G. D. Jacobs, *ibid.*, **36**, 1245 (1962); *n*-propyl chloride, Y. Morino and K. Kuchitsu, *ibid.*, **28**, 175 (1958); isopropyl chloride, F. L. Tobiason and R. H. Schwendeman, *ibid.*, **40**, 1014 (1964); *t*-butyl chloride, D. R. Lide, Jr., and M. Jen, *ibid.*, **38**, 1504 (1963); sulfoxides, H. M. M. Shearer, *J. Chem. Soc.*, 1394 (1959). [b] The force constants are taken or estimated from G. Herzberg, "Molecular Spectra and Molecular Structure," D. Van Nostrand Co., Princeton, N. J., 1945, unless otherwise indicated. [c] E. B. Wilson, Jr., J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill Book Co., Inc., New York, N. Y., 1955. [d] These values were chosen to reproduce the rotational barriers: carbonyls, acetaldehyde;[9] acetone;[10] propionaldehyde;[6] halides, ethyl chloride, R. H. Schwendeman and G. D. Jacobs, *J. Chem. Phys.*, **36**, 1245 (1962); D. R. Lide, Jr., *ibid.*, **30**, 37, (1959); alcohols, P. Venkateswarlu and W. Gordy, *ibid.*, **23**, 1200 (1955); L. Pierce and M. Hayashi, *ibid.*, **35**, 479 (1961); sulfoxides, H. M. M. Shearer, *J. Chem. Soc.*, 1394 (1959).

ried over to other types of carbonyl compounds, which are listed in Table I.

The hydrocarbon portion of a molecule is treated as though it were completely nonpolar. With one heteroatom present there will be a dipole in the molecule, but the interaction between the dipole and the rest of the molecule is neglected. However, if there are two or more heteroatoms present in such a way that two or more dipoles are generated within the molecule, then it is necessary to take into account this dipole–dipole interaction in addition to all the other interactions which occur in hydrocarbons. These dipole–dipole interactions are treated in the classical way originally suggested by Jeans,[5] as has subsequently been quite widely used.[6]

Results and Discussion

The torsional barriers constitute a more difficult problem than was realized at the outset. If we consider the aldehydes and ketones first, we may approach the problem in the following way. The barrier in acetaldehyde is known experimentally, and it is a combination of the interaction of a hydrogen on methyl with an oxygen, and another interaction between a hydrogen on methyl and the aldehydic hydrogen. For propionaldehyde, we know that the conformation in which the methyl is eclipsed by oxygen predominates over the conformation in which hydrogen is eclipsed by oxygen by a sizable amount.[7,8] This amount does not come out of the van der Waal's calculation, and hence it is necessary to add it as a torsional term. This means that the torsional barrier for a carbon eclipsing an oxygen is different from that of a hydrogen eclipsing oxygen. This is not surprising, considering that in the hydrocarbon work it was necessary to have different barrier heights for hydrogen eclipsing hydrogen, for hydrogen eclipsing carbon, and for carbon eclipsing carbon. With the carbonyl compounds, however, there are six different torsional interactions that are possible, and these are listed in Table I. Since we do not have enough data to specify them all, we arbitrarily chose one of them to be zero and calculated the others relative to that one. In propionaldehyde, we chose the C_{sp^3}–C_{sp^3}–C_{sp^2}–O to have an energy of zero in the eclipsed form, since that corresponds to the most favorable conformation. The alternative minimum energy conformation for propionaldehyde contains torsion of the type HC_{sp^3}–C_{sp^2}–O, and that quantity is assigned a numerical value of 0.76 kcal/mol in order to give the observed equilibrium constant for propionaldehyde. The latter value also corresponds to the ground-state arrangement of acetaldehyde, and, since the torsional barrier for acetaldehyde is known[9] and the structure corresponding to the energy maximum for acetaldehyde contains an interaction of the type HC_{sp^3}–C_{sp^2}–H, the latter value must be chosen so that in connection with the 0.76 value, the correct barrier for acetaldehyde is

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(5) J. H. Jeans, "Mathematical Theory of Electricity and Magnetism," 5th ed, Cambridge, University Press, Cambridge, England, 1933, p 377.

(6) See the discussion by E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley & Sons, New York, N. Y., 1965, p 460.

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

(8) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965).

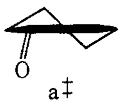
(9) R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *J. Chem. Phys.*, 26, 1695 (1957).

calculated. Finally, the barrier in acetone is known,[10] and this corresponds to the difference between the torsional arrangements HC_{sp^3}–C_{sp^2}–O (0.76 kcal/mol) and HC_{sp^3}–C_{sp^2}–C_{sp^3} which must be chosen to have the value 1.50 kcal/mol in order to fit the barrier data. This leaves us with two types of interaction for which we do not have numerical data. The first of these is C_{sp^3}–C_{sp^3}–C_{sp^2}H, which corresponds to an energy maximum in propionaldehyde, and which we take to be 1.50 kcal/mol, because it is most closely analogous to the HC_{sp^3}–C_{sp^2}–C_{sp^3} interaction of acetone. Finally, in 2-butanone there is an interaction of the type C_{sp^3}–C_{sp^3}–C_{sp^2}–C_{sp^3}, about which no information is available. Again we chose the value 1.50 kcal/mol as being the best estimate available. The latter numbers for which we have guessed values correspond to conformations which in simple molecules will be quite unfavorable, and so the accuracy of the number is not important. In constrained systems, conformations of this type may be important, and this potential source of error must be kept in mind. Using the available data for acetaldehyde, propionaldehyde, and acetone in addition to the hydrocarbon parameters, it was possible to assign all the parameters for ketones.

Karabatsos[8] has recently reported a considerable body of data on the conformations of simple carbonyl molecules. It seemed especially interesting to us that while propionaldehyde has the most stable conformaation with methyl eclipsing oxygen, for *t*-butylacetaldehyde the analogous conformation is less stable than the one which has a hydrogen eclipsing oxygen. Since the latter conformation is a *dl* form, while the *t*-butyl eclipsed conformation is optically inactive, there is an entropy factor of *R* ln 2 favoring the *dl* form. The nature of the experimental determinations reported by Karabatsos was such that the numbers obtained are probably not highly accurate; in particular it is noted that $\Delta H°$ and $\Delta G°$ are both reported to be about 0.8 kcal/mol for the reaction *dl*-propionaldehyde $\rightleftharpoons$ *sym*-propionaldehyde, whereas $\Delta G°$ and $\Delta H°$ should differ by 0.4 kcal/mol, unless this amount is fortuitiously compensated for by a solvation effect (which is possible but seems unlikely). In any case, the experimental value reported for *t*-butylacetaldehyde is +0.25 kcal/mol for $\Delta H°$ for *dl* $\rightleftharpoons$ *sym*. We calculate the value of +0.15 kcal/mol for $\Delta H°$, or +0.55 kcal/mol for $\Delta G°$. The agreement with experiment is therefore quite satisfactory. These values are summarized in Table II.

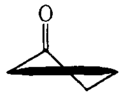
For 2-butanone, we have calculated that the enthalpy difference between the two conformations favors that with methyl eclipsing oxygen by 1.0 kcal/mol. This would give a free energy preference for this conformation of about 0.6 kcal/mol at room temperature. This value does not seem to be known experimentally, but electron diffraction has indicated[11] that this form is the predominant one.

We next examined cyclohexanone. The molecule is believed to exist predominantly in the chair form, but the boat form is of considerably lower energy relative to the chair than is the case with cyclohexane itself.[12] Our calculated enthalpies indicate that the best arrangement of the boat form is 3.2 kcal/mol above that of the chair, which is in good agreement with experiment.[12] The barrier to inversion of the cyclohexanone ring is also of interest. It has been suggested that it is probably substantially lower than that in cyclohexane,[13] and recently a value of 5.0 ± 0.4 kcal/mol has been reported.[14] We have made the simplifying assumption, which we believe to be a good approximation, that the energy maximum which the ring must go through in inverting from a chair form into a boat is one in which four of the ring atoms must lie in the same plane. We have then constrained four of the ring atoms to be coplanar, and allowed the molecule to minimize its energy with respect to all other degress of freedom. The process was repeated for the different possible combinations of the four ring atoms (transition states a‡, b‡, and c‡), and it was found that one transition state (a‡) was considerably lower in energy than the remaining ones. It has a calculated energy 4.8 kcal above that of the chair form.



a‡

b‡



c‡

Cyclohexane-1,4-dione was next studied, as this was one of the unusual molecules which has the ring preferentially a nonchair form.[15] The enthalpies calculated for the chair and for the various kinds of boat forms are summarized in Table II. It is noted that the energy of the most favorable nonchair arrangement, the so-called twist form, is only 1 kcal/mol above that of the chair. Since the chair is rigid and has a much lower entropy than does the boat, the calculations indicate that the two forms ought to be rather similar in free energy. The exact structure which exists in the crystal is not a perfectly symmetrical twist form, but one which is skewed away from that structure by a small amount.[16] It has been variously concluded that the same structure exists in solution,[17] and that the perfectly symmetrical structure exists in solution, with a wide oscillatory motion.[18] The calculations indicate that the symmetrical structure is of lower energy than the skewed one.

We next turned our attention to the methylcyclohexanones. The axial 2-methylcyclohexanone is calculated to have a conformational energy of 1.75 kcal/mol, the axial 3-methylcyclohexanone has a conformational energy calculated to be 1.15 kcal/mol, and, finally, axial 4-methylcyclohexanone has a calculated conformational energy of 1.47 kcal/mol. All of these results on methylated cyclohexanones are consistent with previous experimental work and discussion,[19–22] except the

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(10) R. Nelson and L. Pierce, *J. Mol. Spectrosc.*, **18**, 344 (1965).

(11) C. Romers and J. E. G. Creutzberg, *Rec. Trav. Chim. Pays-Bas*, **75**, 331 (1956).

(12) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

(13) Reference 6, p 186.

(14) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 1066 (1968). We calculated the quoted value from the data given, which contain a typographical error and an ambiguity.

(15) (a) Reference 6, p 474; (b) M. V. Bhatt, G. Srinivasan, and P. Neelakantan, *Tetrahedron*, 21, 291 (1965).

(16) P. Groth and O. Hassel, *Proc. Chem. Soc.*, 218 (1963); A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Lett.*, 1247 (1963).

(17) C. Y. Chen and R. J. W. LeFevre, *Australian J. Chem.*, 16, 917 (1963).

(18) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **83**, 5028 (1961).

(19) B. Rickborn, *ibid.*, **84**, 2414 (1962).

(20) N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961).

(21) N. L. Allinger and L. A. Freiberg, *ibid.*, **84**, 2201 (1962).

Table II. Calculated Conformational Enthalpies

Compound	Energy, kcal/mol Calcd	Exptl
Acetaldehyde (H|O ecl)	0.00	0.00
(H|O stg)	1.16	1.16[a]
Propionaldehyde (Me|O ecl)	0.00	0.00
(H|O ecl)	0.70	0.90,[b] 0.80[c]
(Me|O *anti*)	1.48	
t-Butylacetaldehyde (*t*-Bu|O ecl)	0.15	0.25[c]
(H|O ecl)	0.00	0.00
Acetone (H|O ecl, H|O ecl)	0.00	0.00
(H|O ecl, H|O stg)	0.78	0.78[d]
(H|O stg, H|O stg)	2.18	
2-Butanone (*anti*, C|O ecl)	0.00	
(*gauche*, H|O ecl)	1.04	
Cyclohexanone chair	0.00	0.00[e]
twist (θ = 90°)	3.26	
boat (θ = 60°)	4.34	
boat (θ = 0°)	5.47	
a ‡	4.77	5.0[f]
b ‡	7.04	
c ‡	7.58	
Cyclohexane-1,4-dione chair	0.00	*g*
twist (θ = 90°)	1.05	
boat (θ = 60°)	1.90	
boat (θ = 0°)	5.56	
Cycloheptanone-1	0.78	
Cycloheptanone-2	0.00	
Cycloheptanone-3	1.08	
Cyclooctanone boat–chair *sym*	0.00	
Cyclooctanane boat–chair *unsym*	0.51	
trans-10-Methyl-2-decalone	0.00	*g*
cis-10-Methyl-2-decalone (nonsteroid)	0.20	
cis-10-Methyl-2-decalone (steroid)	0.87	
trans-10-Methyl-1-decalone	0.00	0.00
cis-10-Methyl-1-decalone (steroid)	0.37	0.8[h]
cis-10-Methyl-1-decalone (nonsteroid)	0.70	
Cyclohexen-4-one chair	0.00	
boat	0.36	
2(eq)-Methylcyclohexanone	0.00	0.0
2(ax)-Methylcyclohexanone	1.75	1.6–1.8[i]
3(eq)-Methylcyclohexanone	0.00	0.0
3(ax)-Methylcyclohexanone	1.15	1.3[j]
4(eq)-Methylcyclohexanone	0.00	
4(ax)-Methylcyclohexanone	1.47	
2,6(dieq)-Dimethylcyclohexanone	0.00	0.00
2(eq),6(ax)-Dimethylcyclohexanone	1.91	1.82[k]
2,4(dieq)-Dimethylcyclohexanone	0.00	0.00
2(ax),4(eq)-Dimethylcyclohexanone	1.84	
2(ax)-Methyl-4-*t*-butylcyclohexanone		1.56[j]
3,5(dieq)-Dimethylcyclohexanone	0.00	0.00
3(eq),5(ax)-Dimethylcyclohexanone	1.29	1.3[j]
3,3,5,5-Tetramethylcyclohexanone chair	0.00	*g*
twist	3.78	
Methanol stg	0.00	0.00[t]
ecl	1.07	1.07[t]
ax-Cyclohexanol *sym*	1.19	*g*
ax-Cyclohexanol *unsym*	1.19	
eq-Cyclohexanol *sym*	0.00	
eq-Cyclohexanol *unsym*	0.93	
Ethyl chloride stg	0.00	0.00, 0.00
Ethyl chloride ecl	3.60	3.56,[q] 3.69[r]
n-Propyl chloride *anti*	0.00	0.0–0.6[p]
gauche	0.36	0.0[q]
Isobutyl chloride *sym*	0.20	See text
unsym	0.00	
ax-Chlorocyclohexane	0.56	*s*
eq-Chlorocyclohexane	0.00	
1,2(dieq)-Dichlorocyclohexane[l,m]	0.00	
1,2(diax-Dichlorocyclohexane[n]	0.29	
1(ax),2(eq)-Dichlorocyclohexane[o]	0.49	
1(eq)-Methyl-1(ax)-chlorocyclohexane	0.00	0.00[u]
1(ax)-Methyl-1(eq)-chlorocyclohexane	1.03	1.1
2(ax)-Chlorocyclohexanone	0.00	*w*
2(eq)-Chlorocyclohexanone	0.39	
ax-Thiacyclohexane 1-oxide	0.00	*x*
eq-Thiacyclohexane 1-oxide	0.37	
ax-Cyanocyclohexane	0.36	0.15–0.25[v]
eq-Cyanocyclohexane	0.00	0.00

[a] Reference 9. [b] Reference 7. [c] Reference 8. [d] Reference 10. [e] N. L. Allinger, H. M. Blatter, L A. Freiberg, and F. M. Karkowski-*J. Amer. Chem. Soc.*, **88**, 2999 (1966). [f] F. R. Jensen and B. H. Beck, *ibid.*, **90**, 1066 (1968). [g] See text. [h] N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, **25**, 922 (1960). [i] Reference 6, p 113. [j] N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962). [k] B. Rickborn, *ibid.*, **84**, 2414 (1962). [l] μ_{calcd} 3.39 D; μ_{exptl} 3.5 D (footnote *m*). [m] H. S. Hageman and E. Havinga, *Tetrahedon*, **22**, 2271 (1966). [n] μ_{calcd} 0.60 D; μ_{exptl} 1.1 D (footnote *m*). [o] μ_{calcd} 3.46 D; μ_{exptl} 3.1 D (footnote *m*). [p] Y. Morino and K. Kuchitsu, *J. Chem. Phys.*, **28**, 175 (1958). [q] T. Ukaji and R. A. Bonham, *J. Amer. Chem. Soc.*, **84**, 3631 (1962). [r] R. H. Schwendeman and G. J. Jacobs, *J. Chem. Phys.*, **36**, 1245 (1962). [s] J. A. Hirsch in "Topics in Stereochemistry," N. L. Allinger and E. L. Eliel, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 199. [t] P. Venkateswarlu and W. Gordy, *J. Chem. Phys.*, **23**, 1200 (1955); L. Pierce and M. Hayashi, *ibid.*, **35**, 479 (1961). [u] N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967). [v] N. L. Allinger and W. Szkrybalo, *ibid.*, **27**, 4601 (1962); B. Rickborn and F. R. Jensen, *ibid.*, **27**, 4606 (1962). [w] See ref 6, p 460. [x] C. R. Johnson and D. M. McCants, Jr., *J. Amer. Chem. Soc.*, **86**, 2935 (1964); J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966)

value of the conformational energy of the 4-methyl which is surprisingly small. No experimental value is available here for comparison. We have extended the calculations to more highly substituted cyclohexanones which show the same structural features. Thus, for example, the conformational energy of 2(ax),6(eq)-dimethylcyclohexanone is calculated to be 1.89 kcal/mol (exptl 1.82).[19] The 2(ax),4(eq)-dimethylcyclohexanone is similarly calculated to be 1.84 kcal/mol (exptl 1.56 for *2*(ax)-methyl-4-*t*-butylcyclohexanone). These numbers are slightly greater than for the 2-methylcyclohexanone itself, and this difference is the same type of effect, brought about by deformation upon alkylation at the 3 position, which has been previously discussed for the case of 1,3-dimethylcyclohexane *vs.* the 1,4 isomer.[3]

3(eq),5(ax)-Dimethylcyclohexanone is calculated to have an energy of 1.29 kcal/mol, again, slightly above that of the monosubstituted analog and consistent with experiment.[21]

We have also examined 3,3,5,5-tetramethylcyclohexanone, which necessarily has a severe 1,3-*syn*-axial interaction between methyl groups if the ring maintains a chair form. Because the magnitude of this interaction is known to be some 3.5 kcal/mol,[23] and the energy of the boat form of cyclohexanone above that of the chair is calculated to be only about 3.5 kcal/mol, it was not apparent whether the molecule would prefer a chair or a boat form. The available experimental evidence has been interpreted in terms of a chair form,[24] although the

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apparently structurally analogous molecule 3-phenyl-3,5,5-trimethylcyclohexanone appears to have a boat conformation.[25] In any case, our calculations indicate that the chair form of the tetramethylcyclohexanone is more stable than the boat by 3.8 kcal/mole, so the prediction is clear-cut and unambiguous. We are not prepared to undertake calculations on the phenyl derivative at this time, but hope to do so in the near future.

Next, we examined the series cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, and cyclodecanone. We have calculated the total steric energy of each of these ketones, assuming that they maintain the gross conformation of the parent hydrocarbon, with a keto group at the appropriate point. The difference in energy calculated between the hydrocarbon and ketone for each ring size would enable us to calculate heats of formation for the ketones, but unfortunately these are not known experimentally. Other related properties of the ketones are known, such as the equilibrium constants for the addition of hydrogen cyanide,[26] and the rate of reduction with borohydride anion.[27] The parallel between our calculated energy differences and the rates of borohydride reduction are indicated in the plot in Figure 1, and they show a rather good agreement. The correspondence between the values calculated here and the cyanohydrin data is similar.

Finally, we have looked at some methyldecalones which are related to steroidal systems, and whose conformational behavior is poorly understood. The equilibrium between *cis*- and *trans*-10-methyl-1-decalone has been studied experimentally,[28] and it was found that the free energy favored the *trans* isomer by 0.2 kcal/mol. The analogous 4-keto steroid equilibrium was found to favor the *trans* isomer by more than 2.1 kcal/mol.[29] The reason for this sizable difference has never been clear. However, we have calculated the enthalpies of the *trans* and of the *cis* (steroid conformation), and we find the *trans* more stable by 0.37 kcal/mol. The calculations are in agreement with the experimental data on the bicyclic compounds, but a study of the steroidal system will have to be postponed until we have access to a larger computer.

The 10-methyl-2-decalone system has had an intriguing history. We calculate that the *trans* isomer is the more stable, but only by 0.2 kcal/mol, relative to the favorable conformation for the *cis*. There has been much controversy as to whether the *cis* isomer possesses the steroid or the nonsteroid conformation. Conformational analysis clearly suggested at an early date that the nonsteroid conformation should be preferred.[30] Optical rotatory dispersion measurements, on the other hand, have suggested that the steroid conformation is the favorable one.[31] More recently, nmr measurements have suggested that the nonsteroid conformation is of lower energy.[32] The present calculations indicate that the nonsteroid conformation is more favorable than the steroid conformation by 0.67 kcal/mol. We believe that the calculations are reliable, and that the optical rotatory dispersion curve of the compound was misleading for rather subtle reasons, which we hope to discuss in a future paper.

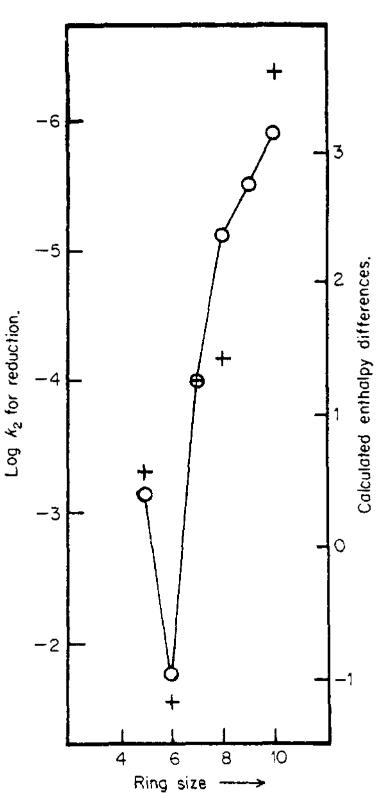

Figure 1. The rates of the $NaBH_4$ reduction of the cyclonones as a function of ring size (circles) and the calculated enthalpy differences between the cyclane and its corresponding ketone (crosses).

The alcohols were examined only briefly. Methanol has been studied by microwave spectroscopy, and both its structure and rotational barrier are known,[33] enabling the required parameters to be estimated. Cyclohexanol was then examined. The axial isomer has two conformations, symmetrical and unsymmetrical, which are calculated to have identical enthalpies (1.19 kcal/mol). The equatorial isomer also has two conformations, the stable symmetrical one ($\Delta H^\circ = 0.00$) and the unsymmetrical one ($\Delta H^\circ = 0.93$). Taking the entropies of mixing into account, the conformational free energy of the axial isomer is calculated to be 0.75 kcal/mol in the gas phase. Experimentally, the values determined range from 0.5 to 0.9 kcal/mol (in inert solvents.[34]

The alkyl chlorides were next considered. The data which are available are somewhat piecemeal in character. The geometries of ethyl, isopropyl, and *t*-butyl chloride are known, but with a relatively low degree of accuracy. The rotational barrier of ethyl chloride is known, and the relative energies of the *gauche* and *anti* forms of *n*-propyl chloride are approximately known. Using the simple molecules, a natural length for the

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(26) V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).
(27) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).
(28) F. Sondheimer and D. Rosenthal, *J. Amer. Chem. Soc.*, **80**, 3995 (1958).
(29) See Table II, footnote *h*.
(30) Reference 6, p 170.
(31) C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.*, **80**, 3986 (1958).
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(33) P. Venkateswarlu and W. Gordy, *J. Chem. Phys.*, **23**, 1200 (1955); L. Pierce and M. Hayashi, *ibid.*, **35**, 479 (1961).
(34) J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., John Wiley & Sons, Inc., New York, N. Y. 1967, p 199.

C–Cl bond was chosen, together with natural values for the various kinds of angles which involve chlorine. The van der Waals parameters used for chloride are those which are known experimentally for the argon atom.

There is not much in the way of structural information which can be used to check out the accuracy of the calculated values. The reason for this situation is that virtually all the compounds about which such data are available have been used fixing the parameters in the calculation. We are able to compare the energies calculated for the different conformations of *n*-propyl chloride and of isobutyl chloride with those observed experimentally, however. It is calculated that *n*-propyl chloride has a somewhat lower enthalpy in the *anti* form, but this is just about cancelled by the entropy difference, so that we calculate a free energy difference between the conformations of approximately zero. The best experimental value appears to be from the electron diffraction work of Morino,[35] from which it is found that the *gauche* form predominates over the *anti* by a factor of 4 to 1. Other experimental data[36] suggest other values (from 0.0 to 0.6 kcal/mol) for the free energy difference between the conformations.

For isobutyl chloride, the experimental data indicate[37] that the unsymmetrical form predominates, again by a factor of about 4 to 1. At first sight this seems peculiar. If the *gauche* arrangement were more favorable than the *anti* arrangement in *n*-propyl chloride, then one might expect that in isobutyl chloride, the symmetrical arrangement, in which there are two *gauche* arrangements, would be better than the unsymmetrical one, in which there is only one *gauche* arrangement. Earlier quantitative calculations have shown that this type of effect is not really additive, however. In addition, entropy favors the *gauche* form of *n*-propyl chloride by $R \ln 2$, whereas in isobutyl chloride it favors the unsymmetrical form by the same amount. We calculate that the symmetrical form of isobutyl chloride has a higher enthalpy than the unsymmetrical form by 0.2 kcal/mol, and when the effect of entropy is added to this, it is predicted that the unsymmetrical form should predominate over the symmetrical form by a factor of about 3 to 1, which is in satisfactory agreement with experiment. Earlier it was suggested that a part of the apparent difference between the *n*-propyl and isobutyl compounds might be associated with different dihedral angles between the methyl and the chlorine. In the *n*-propyl compound this dihedral angle can open out and reduce the repulsion between the chlorine and methyl group—perhaps even separating the two so that the force is an attractive one. A similar deformation in the isobutyl compound would be possible in the unsymmetrical form, but not in the symmetrical form. In the latter, any attempt to improve the situation between the chlorine and one methyl would lead to a poorer situation with respect to the other methyl. The present calculations appear to indicate that *gauche* interactions in the two compounds are not comparable since bond angles are not quite tetrahedral, not all dihedral angles are equal, and some *gauche* interactions are worse than others.

Chlorocyclohexane was next examined. The equatorial conformation is somewhat more stable than the axial,[34] and the calculated value here is in good agreement with experiment. 1-Chloro-1-methylcyclohexane was also studied, as it was suggested earlier from experimental measurements[38] that the effects of the methyl and the chlorine probably were not additive when they were attached to the same carbon atom. The calculations here seem to bear out the conclusion, but the difference between the additive value and the actual calculated value is small. The calculated conformational enthalpy of methyl is 1.77 kcal/mol, while that for chlorine is 0.56 kcal/mol. For 1-chloro-1-methylcyclohexane, then, if additivity is assumed, one calculates that the form with the axial chlorine should predominate over the other form by 1.21 kcal/mol. The value actually calculated is, however, 1.03 kcal/mol. The difference is not attributable to round-off error in the calculations, but is a real calculational difference. It is in excellent agreement with the experimental value,[38] but the experimental measurements were not sufficiently precise to definitely exclude the additivity value. The reason for the lack of additivity may be important, not so much in this particular case as in other possible cases. It seems to come about as follows. If a chlorine is axial on a secondary carbon, it bends out away from the ring some to relieve the *syn*-axial repulsions. If there is an equatorial methyl on the same carbon, the chlorine by so bending would be pushed into the hydrogens of the methyl group, and hence is less free to bend. Moreover, the *syn*-axial repulsions are greater than they would be in the secondary halide. On the other hand, an axial methyl group does not tend to bend out much anyway, so whether the chlorine is present or not makes little difference in that conformation. Hence the energy of the form with chlorine axial is raised relative to that of the other form.

A preliminary examination of the 1,2-dichlorocyclohexanes was next carried out. In this molecule an additional complication of a dipolar repulsion between the two C–Cl bonds occurs. There are two isomers of this compound, *cis* and *trans*, and the *trans* form has two conformations, diequatorial and diaxial. The dipole moments of each isomer are known experimentally from model compounds, and most interesting, the dipole moment of 1,2-(diax)-dibromo-4-(eq)-*t*-butylcyclohexane is known experimentally to have the value 1.1 D.[39] First-order considerations would assign this compound a dipole monent of 0 D. Obviously, first-order considerations are not very adequate in this case.

We have assumed that the dipole interaction energy can be calculated by the classical method of Jeans. In this formulation we treat the interaction energy between the two dipoles, but we do not allow for induction or mutual polarization effects. We have assumed that the dielectric constant of the medium is 2.25 and the interaction energy calculated is included in the energy minimization scheme. The dipole moment of each conformation is determined directly from the geometry. Our calculated dipole moments are in fairly good but not exact, agreement with the ones measured experimentally for the different conformations. We also ob-

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

(39) The moments of the corresponding dichlorides have not been reported, but may be assumed to be similar to those of the dibromides: H. S. Hageman and E. Havinga, *Tetrahedron*, **22**, 2271 (1966).

tain from the calculation the energy of the diaxial conformation relative to that of the diequatorial, from which we can calculate the equilibrium constant. Our calculated value is 0.29 kcal/mol (benzene, $D = 2.25$), favoring the diequatorial isomer. This mixture would give a resultant dipole moment of 2.48 D. The experimental value (for the *trans* isomer) is 2.67, in reasonable agreement with the calculated value.

From this preliminary survey on alkyl chlorides, it is concluded that the van der Waals values used are reasonably good ones, although not necessarily the best ones. The results are, in general, quite reasonable, although they are not as accurate as one would want when there are two halogens close to one another in the molecule. The treatment of dipoles used here, of course, is known to be only a first approximation and can doubtlessly be improved upon.

The thiacyclohexane 1-oxides are an interesting pair of conformations. Since the barrier to inversion at sulfur is very high, an anchoring group placed in the 4 position converts the two conformations into *cis* and *trans* isomers. These are separable, but equilibrium between them can be established.[40] It has been shown that the equilibrium favors the axial oxygen,[40,41] a very unusual circumstance indeed. The only reason apparent for this experimental result seems to be that the carbon–sulfur bonds are very long, and the C–S–C angle is close to 90°. This means that when the oxygen is axial, it is not located in the same way with respect to the ring as would be a similar substituent on the analogous carbocyclic ring. It has been suggested that perhaps the oxygen is sufficiently far from the carbons C-3 and C-5 and their attached axial hydrogens, that there may actually be an attractive van der Waals interaction between the oxygen and those other atoms.[40] The present calculations bear this out. There are no repulsive interactions between the oxygen and carbons 3, 4, or 5 or any of their attached hydrogens, for either conformation of the oxygen. When the oxygen is axial, the individual interactions are each larger than when the oxygen is equatorial, so the net attraction is much larger in the axial form. The calculation indicates that the axial oxygen should be more stable than its equatorial counterpart by 0.37 kcal/mol, while the experimental values span quite a range, depending on the circumstances of measurement.[40,41] Qualitatively the agreement is correct.

A simple nitrile group on a cyclohexane ring was also of interest. Experimentally it is known that the conformational energy of a methyl group is very much larger than that of the nitrile group,[42,43] which indicates that most of the repulsion present when the methyl is axial must be between hydrogens rather than between carbons or between carbon and hydrogen. The calculations here bear this out. The conformational energy of the axial nitrile was calculated to be 0.3 kcal/mol, while the experimental values are 0.15 and 0.25 kcal/mol.[34]

Finally, the 2-chlorocyclohexanone molecule was considered. It was calculated that the equatorial form was the less stable by 0.39 kcal/mol in hexane solvent. The experimental value is 0.6 kcal/mol.[44] The dipole moments were calculated to be 2.93 and 4.22 D for axial and equatorial, while the experimental moments for the 4-*t*-butyl derivatives are 3.17 and 4.29 D, respectively.[44]

Conclusions

The various conformations and energies described herein constitute a survey of the applicability of the Westheimer method to the calculation of such quantities. It can be seen that the method is perfectly general and applicable to ordinary simple organic molecules, and gives very satisfactory results in almost all of the cases discussed. For unstrained, or slightly strained molecules, our survey indicates that for relatively simple organic molecules containing a total of not more than 30 atoms, and containing only one or two heteroatoms, the calculations yield results comparable in accuracy to those obtainable for hydrocarbons (*i.e.*, bond angles to 1°, bond lengths to 0.01 Å, and energies to 0.3 kcal/mol). For more highly strained molecules, the hydrocarbons themselves are not dealt with in a satisfactory manner, and clearly hetero substituted molecules are expected to show the same difficulties. The next important step in extending these calculations in a completely general way to organic molecules of all types is to improve the force field until it is adequate to deal with even rather highly strained molecules. This improvement will form the topic of a subsequent paper.

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Appendix

The calculations were carried out on an IBM 7074 computer using previously described programs. The small molecules required only a few minutes of computer time. Large unsymmetrical molecules such as 2(ax),4(eq)-dimethylcyclohexanone each required 1–3 hr.

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