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CONFORMATIONAL ANALYSIS—CXXIII

CARBOXYLIC ACIDS AND ESTERS IN FORCE FIELD CALCULATIONS[1]

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Abstract—Force field calculations have been extended to include carboxylic acids and esters. Necessary parameters were chosen mainly by fitting to available experimental data on small molecules. A few key facts are not known experimentally, and these were found by carrying out *ab initio* (STO-3G) calculations. Other molecules were then studied and structural predictions were made. It is predicted that in isobutyric acid a methyl group is twisted 15° from eclipsing the carbonyl oxygen in the ground state. The relative energies and torsional functions for cyclohexanecarboxylic acid are reported. Except for rather simple compounds, such as normal chains, the carboxyl is usually twisted with respect to the attached chain. Some conformations of lactones were also examined. For δ-valerolactone it is predicted that the boat conformation is more stable than the chair. Heats of formation of the compounds can be calculated with fair accuracy.

INTRODUCTION

Force field or molecular mechanics calculations have now been developed sufficiently so that the structures and energies and sometimes other properties of hydrocarbons can now be calculated quickly and with high accuracy.[2] To make such calculations really useful to organic chemists, it was next necessary that they be extended to include functional groups of all kinds, and in all combinations. This extension is still in progress and has not proceeded very far to date. For several of the common functional groups the results obtainable are now nearly as good as those obtainable for hydrocarbons, where the accuracy of the available experimental data is really the limiting factor. These groups include[2,3] aldehydes, ketones, ethers, alcohols, thiols, thioethers, disulfides, and halides. Many other miscellaneous structural types have been subjected to a cursory examination.

Common functional groups present in organic compounds include the carboxyl group and its derivatives such as esters, amides, etc. While some studies of amides have been carried out in connection with protein calculations, because of the size of the proteins, that work has utilized many approximations. It has generally been quite inferior to what one would hope to accomplish with small molecules, and it will not be further discussed here.[4]

RESULTS AND DISCUSSION

Carboxylic acids

The carboxyl group combines two features we have previously examined, namely the carbonyl group and the hydroxyl group. Because of their proximity, however, the carboxyl group is quite a different structural entity than a simple summation of the two fragments. In this paper, we will show a set of parameters developed to deal with the carboxyl group, and also with the ester group, which are compatable with our previously published 1973 force field.[2,3]

Force constants for carboxylic acids have been reported by Brooks and Haas,[4] and they seem comparable with the other force constants used in the 1973 force field. They were averaged to make them "transferable" and these values were used here (Table 1).

With the force constants for bending and stretching settled, and the electrostatics carried over from the treatment of carbonyl and hydroxyl groups, the next step was to choose the natural bond lengths and angles so as to fit the ground state structures for simple compounds. The calculated structural data, and the experimental data that were fit to are summarized in Table 2.

Next we considered the question of the torsional barriers about the bonds attached to the carbonyl group. Because of delocalization of the π electrons on the hydroxyl group into the carbonyl, there is a strong tendency for the hydroxyl to remain in the plane of the carbonyl. Mainly because of the alignment of dipoles, the hydroxyl hydrogen is preferentially cis to the carbonyl oxygen. The available experimental and theoretical data concerning torsional potential functions for acids and acid derivatives is sketchy. For consistency, we have carried out a series of *ab initio* calculations at the STO-3G level of the various kinds of potential functions of interest, some of which were previously known.

Beginning with formic acid, the present STO-3G calculations show that the *cis* conformation is more stable than the trans by 4.73 kcal/mole. One experimental result[6] gives this value as greater than 4 kcal/mole, although the value 2 kcal/mole was reported from IR work.[7] The torsional constants about the C–O bond were chosen so that the calculated rotational barrier for formic acid (9.99 kcal/mole) is in good agreement with experimental and other theoretical estimates[7-9] (8.1, 10.9 and 13.4 kcal/mole). These data are summarized in Table 3.

From the force constants given in Table 1, and the structure of formic acid discussed previously, together with the data on rotational barriers (Table 3), the torsional parameters necessary to reproduce the data on formic acid were evaluated, and these are also listed in Table 1. These give the *cis-trans* energy difference as 4.70 kcal/mole, and the rotational barrier as 9.95 kcal/mole. With those quantities fixed, two more torsional parameters, which correspond to torsion of the types C–C–O–H and H–C–C–O, had to be chosen to fit the data on acetic acid. These parameters are also given in Table 1. They yielded a *cis-trans* energy difference for acetic acid of 5.97 kcal/mole and a rotational barrier of 10.33 kcal/mole. The methyl rotational barrier calculated

Table 1. Force constants used[a,b]

Stretching	l_o	k_s	Bond moment
C_{sp^3}–C_{sp^2}	1.504	4.4	0.3
C=O	1.207	10.8	2.60
C_{sp^3}–O	1.384	5.36	0.73
C_{sp^2}–O	1.328	5.05	0.10
O–H	0.972	7.2	−1.25
Bending	θ_o	k_θ	
C_{sp^3}–C_{sp^2}=O	122.8	0.57	
H–C=O	120.6	0.25	
C_{sp^3}–C_{sp^2}–O	108.0	0.702	
H–C_{sp^2}–O	107.0	0.702	
O=C–O	124.0	1.128	
C_{sp^2}–O–H	106.5	0.736	
C_{sp^2}–O–C	110.0	0.65	
Torsion	V_1	V_2	V_3
C_{sp^3}–C_{sp^2}–O–H	0.56	0.0	3.15
C_{sp^3}–C_{sp^3}–C_{sp^2}=O	0.0	0.0	−1.75
C_{sp^3}–C_{sp^3}–C_{sp^2}–O	0.0	−0.9	−0.2
H–C_{sp^2}–O–H	0.3	0.0	3.0
H–C_{sp^3}–C_{sp^2}=O	0.0	0.0	−0.75
H–C_{sp^3}–C_{sp^2}–O	0.0	0.0	−0.29
H–O–C_{sp^2}=O	0.0	0.0	3.1
H–C–O–C_{sp^2}	0.0	0.0	−1.08
C–O–C_{sp^2}=O	−0.65	9.2	0.0
C–O–C_{sp^2}–H	0.0	0.0	0.0
C–O–C–C	0.65	3.15	0.0
C–C–O–C_{sp^2}	3.5	−1.65	0.0
Van der Waals			
H (of the O–H of a carboxyl group)			
r* 0.90 Å, ϵ (0.015)			

[a]Units are mdyne/Å^2 for stretching, mdyne/rad^2 for bending and torsion, and Debye units for moments.

[b]For references detailing the pertinent force constants (except for alcohols and ethers) (see Ref. 2a). For alcohols and ethers (see Ref. 3b).

Table 3. Torsional data on carboxylic acids and esters

Compound	Rotation about C–O bond (*cis–trans*)	Barrier 90°	Ref.
Formic acid	4.77	12.34	14
	4.72	9.98	This work (STO-3G)
	4.70	9.95	This work (MM)
	6.3		15
Acetic acid	7.25	13.18	14
	5.97	10.37	This work (STO-3G)
	5.97	10.33	This work (MM)
	7.7		15
Propionic acid	5.80	10.32	This work (STO-3G)
	6.04	10.36	This work (MM)
Methyl formate	3.68	11.36	14
	3.73	11.24	This work (MM)
	5.56		15
Methyl acetate	7.80		This work (MM)

The interesting case of the rotational barrier about the C_{sp^2}–C_{sp^3} bond in propionic acid has not been previously reported. It was studied in the present work by carrying out a rigid rotation† about the bond, and repeating the STO-3G calculations at 60° intervals. The methyl group eclipses the carbonyl in the ground state, which is also found to be true with aldehydes and ketones. Conformations which have a hydrogen eclipsing the carbonyl also correspond to energy minima, and they are slightly less stable than the ground state (0.25 kcal/mole by molecular mechanics and 0.26 kcal/mole by STO-3G). The conformations which differ by about 60° in torsional angle from the minima correspond to energy maxima. They are rather low (methyl-hydroxyl eclipsed: 1.75 kcal/mole by molecular mechanics, 1.57 kcal/mole by STO-3G; hydrogen-hydroxyl eclipsed, 0.65 kcal/mole and 0.68 kcal/mole, respectively), similar to the values found for barriers for other carbonyl compounds, and as opposed to barriers about saturated bonds which are usually significantly higher (about 3 kcal/mole).

Table 2. Ground state geometries of carboxylic acids

Compound	Bond lengths[b] exp (calcd)[a] C=O	C–O	C_{sp^2}–H	C_{sp^2}–C_{sp^3}	Bond angles exp (calcd)[a] HOC	OC=O	O=C–R	CCC
Formic acid[10]	1.213(−7)	1.361(0)	1.106(+12)	—	107.5(−2)	123.6(0)	126.1(−13)	—
Acetic acid[11]	1.214(−8)	1.364(−9)	—	1.520(−11)		122.8(+6)	126.6(−10)	—
Propionic acid[12]	1.211(−5)	1.367(−12)	—	1.518(−6)		122.1(+12)	126.7(−11)	112.8(+3)
Propionic acid[13]	1.210(−4)	1.352(+3)	—	1.509(+3)	105.8(+15)	122.4(+9)	125.8(−2)	112.7(+4)

[a]The calcd. value given is the amount (last figure) to be added to the experimental value to obtain the corresponding calculated value.

[b]O–H calcd. in each case 0.972 Å (0.970 Å experimentally[13]).

was 0.53 kcal/mole. The force field calculations are summarized in Table 3.

For acetic and propionic acids, the difference between the energies of the *cis* and *trans* forms is larger than in formic acid. The calculated value for the barrier to methyl rotation in acetic acid (0.53 kcal/mole) is in good agreement with the experimental results[16,17] (0.48 kcal/mole from microwave studies).

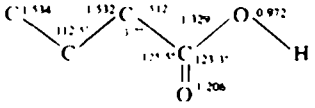
One additional set of torsional parameters had to be chosen for propionic acid (C–C–C_{sp^2}–O) before this compound could be studied and the values chosen are given in Table 1. It was then calculated that the *cis* form was more stable than the *trans* by 6.04 kcal/mole and the rotational barrier was 10.36 kcal/mole. The calculated energies for the conformations of propionic acid are given in Table 3, both from the *ab initio* and the molecular mechanics calculations, and the agreement is reasonable.

Finally, one must know something of the van der Waals characteristics of the hydrogen attached to the

†A rigid rotation was used here, because according to the molecular mechanics calculations, very little relaxation occurs upon rotation.

oxygen of the carboxyl group. Experimentally it is known that the electron density around this hydrogen is very small. Such hydrogens cannot ordinarily be located by X-ray crystallography, and they are strongly deshielded in the proton NMR spectrum. This low electron density is, of course, correlated with the high acidity of the proton. What this means is that the van der Waals characteristics of such a hydrogen are different from those of a hydrogen attached to an oxygen in an alcohol (which in turn differs from a hydrogen in a hydrocarbon). We have fixed these van der Waals characteristics for the acidic hydrogen by a consideration of the dimer of formic acid. With the values finally settled on (r^* 0.90 Å, ϵ 0.015), the calculated O···O distance bridged by the acidic hydrogen is 2.80 Å, in agreement with the experimental value[18] (2.73 ± 0.05 Å). There is some arbitrariness here, because the two van der Waals parameters are strongly correlated, but these values seem reasonable. The bond energy of the dimer (two hydrogen bonds) was calculated to be 7.2 kcal/mole (experimental value, 7.2 kcal/mole[19]).

The parameters for carboxylic acids had all been fit at this point, and it was now possible to investigate the structures of some additional simple and more complicated compounds of this class. Butyric acid was next examined. Only conformations in which the carbonyl is eclipsed by a carbon–carbon bond were studied in each case. The conformation *anti* about the α–β bond was found to be the most stable, as one would expect. The corresponding *gauche* conformation was calculated to be 0.50 kcal/mole higher in energy. The calculated geometry of the *anti* conformation is shown. The conformation *gauche* about the 3,4 bond was a dihedral angle of 68.5°, but the bond lengths and angles are the same as in the *anti* form. The structure of the compound has not been reported experimentally:



Pentanoic and hexanoic acids were also examined in their stable conformations, and they are unexceptional.

Turning to isobutyric acid, there are no parameters to fit here, the calculation was simply carried out. Interestingly, it was found that the most stable conformation for the carboxyl group was not the carbonylmethyl eclipsed one which might have been anticipated, but rather a conformation in which the dihedral angle between a methyl and the acid hydroxyl group was 44.5°. A second conformation, only 0.21 kcal/mole less stable than the other, was found in which this dihedral angle was 180°. The calculated ground state structure is shown, and the calculated torsional energy function is summarized in Table 4. No experimental structure has been reported.

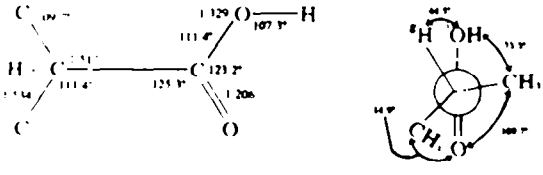


Table 4. Relative energies for isobutyric acid as a function of the torsional angle about C_1–C_2

kcal/mole	ω(H*CCO')
0.31	0.0
0.00	45.0
1.06	90.0
1.24	135.0
0.21	180.0

Actually, the irregular conformation of the ground state for this molecule, and of other related carboxylic acids, should not be particularly surprising. Certainly, alkanes have very symmetrical, regular structures, unless they become highly congested or contain rings. This is because the torsional barriers are relatively large, the hydrogens which tend to interfere with one another are relatively small, and the chains are effectively trapped in torsional potential wells. It can be anticipated that as the substituents become larger, or the torsional barriers become smaller, the simple regularity of the conformations will be lost, and this has been previously found in rather congested molecules such as tri-*t*-butylmethane.[20] In the case of carboxylic acids the torsional barrier about the C–C bond attached to the carboxyl group is quite low, about 0.5 kcal/mole in acetic acid, for example. Hence, we can anticipate that relatively small groups may in many cases be sufficient to lead to a distorted ground state structure. Isobutyric acid is found to be such a case. There seems to be no experimental information on this point for simple carboxylic acids.

The structures of cyclobutane- and cyclopentanecarboxylic acids were also calculated and, not surprisingly, also proved to be irregular. For cyclohexanecarboxylic acid, two groups of conformations were investigated, one with the carboxyl group axial, and the other with the group equatorial. The equatorial was found to be the more stable by 1.01 kcal/mole (experimental best value, 1.35 kcal/mole in solution[21]).

For the equatorial conformation, the most stable torsional arrangement is unsymmetrical. The carbonyl oxygen is twisted about 15° away from being eclipsed by the C–C bond. There are two mirror-image arrangements of this sort. A third energy minimum, which is only 0.2 kcal/mole above the other two, has the hydroxyl of the carboxyl on the symmetry plane, and the carbonyl oxygen is eclipsing a hydrogen. A sketch of the energy as a function of torsional angle is shown in Fig. 1.

The energy maximum at a torsional angle of 0° is only about 0.3 kcal/mole, much less than RT. Only the barriers at torsional angles of ± 120° significantly impede the torsional motion, and there the barrier height is 1.7 kcal/mole.

With the axial conformation the carbonyl oxygen does eclipse the C–C bond in the lowest energy conformation. The barrier is at a torsional angle of 0°, where the hydroxyl eclipses hydrogen, and it is higher than in the equatorial isomer (0.7 kcal/mole). The other barrier is also a little higher, 1.9 kcal/mole. The conformation in which the carbonyl oxygen eclipses hydrogen, which is quite stable in the equatorial isomer, is here rather unstable, due largely to the unfavorable interaction between the hydroxyl and the *syn*-axial hydrogens. This conformation has an energy of 1.28 kcal/mole. Thus one

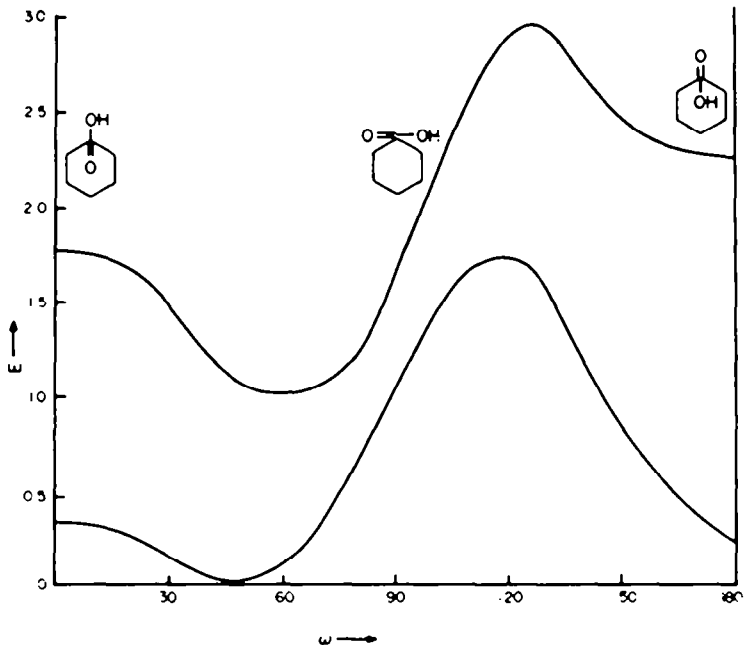


Fig. 1. The energies of the axial (upper curve) and equatorial conformations of cyclohexanecarboxylic acid as a function of the dihedral angle at the carboxyl group.

can conclude that equatorial carboxyl groups should be found in crystals with a wide variation in torsional angle, only angles near 120° being unfavorable. On the other hand, the axial conformation shows a definite preference for a torsional angle near 60°.

The structures and energies of the conformers of 1-methylcyclohexanecarboxylic acid were also examined. The stable conformer has the methyl group equatorial, and it is more stable than the axial isomer by 0.7 kcal/mole. This is essentially an additive value for the two groups, indicating that they have no significant differential steric interaction in the two different conformations.

3-Methylcyclohexanecarboxylic acid was also examined. Relative to the diequatorial chair conformation of the *cis* isomer, the conformation of the *trans* isomer with an axial carboxyl has an energy of 1.00 kcal/mole, while that with an axial methyl has an energy of 1.55 kcal/mole. Putting both groups axial simultaneously leads to an energy of 2.94 kcal/mole. The first two values are in good agreement with the expected energies for those groups. To move the equatorial carboxyl to the axial position when a methyl is already axial at C-3 requires a calculated energy of 1.39 kcal/mole, while the experimental value is 2.98 ± 0.30 kcal/mole.[22] The experimental system was a more complicated molecule, and a close agreement is not expected, but it does seem that the calculated value is definitely too low, and we attribute this to our carboxyl group being too "thin". There seems to be no simple way to improve the situation now, however, so it must simply be kept in mind that this defect in the force-field exists.

Succinic acid was briefly examined. Apart from the carboxyl groups, the carbon skeleton may have either an *anti* or a *gauche* geometry. It was concluded from the Raman spectrum[23] that the *gauche* form is more stable in aqueous solution. However, from the NMR spectrum it was concluded that the *anti* form is more stable than the *gauche* in dioxane by 0.22 kcal/mole.[24]

We calculated that for the anti conformation the entire carbon–oxygen skeleton is planar. The *gauche* form was found to be 0.13 kcal/mole higher in energy than the *anti* form when the dielectric constant was 1. It has a slightly more favorable dipole interaction energy than the *anti* (by 0.15 kcal/mole), and hence its energy would be raised slightly relative to the *anti* by an increase in dielectric constant. Thus as the dielectric constant approaches infinity, the enthalpy of the *gauche* form will exceed that of the *trans* by 0.28 kcal/mole. In terms of free energy, the *gauche* form, being a *dl* pair, would be favored slightly over the *anti* form.

Esters

We next turned our attention to the structures of esters. Both methyl formate and methyl acetate have been studied by means of microwave spectroscopy, and their structures have been reported in the literature.[25,26] The necessary parameters deduced to fit the ground state structure are given in Table 1. There were no bond length parameters to be evaluated (as they had all been previously evaluated to deal with the structures of carboxylic acids or ethers). There was only one bond angle that had to be fit, which was the C_{sp^2}–O–C_{sp^3} angle. There were a number of torsional constants which had to be fit.

The experimental data for the ground states are given in Table 5, together with the differences between the calculated and experimental structures. The fit is generally good.

Ethyl (and higher) esters require the evaluation of a few more torsional parameters. The structure of ethyl formate has been studied,[27] and it is known that the *gauche* conformation is higher in energy than the *trans* by 0.19 ± 0.06 kcal/mole. The barrier separating them has a height of 1.10 ± 0.25 kcal/mole. The compound has the

Table 5. Ground state geometries of carboxylic esters

Compound	Bond lengths exp[a] (calcd)[a]					Bond angles exp (calcd)				
	C=O	C_{sp^2}–O	C_{sp^2}–C_{sp^3}	O–C_{sp^3}	C_{sp^3}–C_{sp^3}	R–C_{sp^2}–O	R–C=O	O–C=O	C_{sp^2}–O–C	O–C_{sp^3}–C_{sp^3}
Methyl formate[25]	1.200(+8)	1.354(+20)	—	1.437(−24)		109.3(+23)	125.5(−28)	125.2(+5)	115.0(−1)	—
Methyl acetate[26]	1.200(+9)	1.334(+12)	1.520(−8)	1.437(−24)		109.0(+14)	125.1(−8)	125.9(−6)	114.8(+4)	—
Ethyl formate[27]					1.528(+3)					113(+19)

[a]The calcd value given is the amount (last figure) to be added to the experimental value to obtain the corresponding calculated value.
[b]O–H calcd in each case 0.972 Å (0.970 Å experimentally[31]).

expected *anti* configuration about the C–O bond. The conformation *syn* about this bond was estimated to have a higher energy by 5.1 kcal/mole. The torsional potential constants given in Table 1 were chosen to reproduce these data.

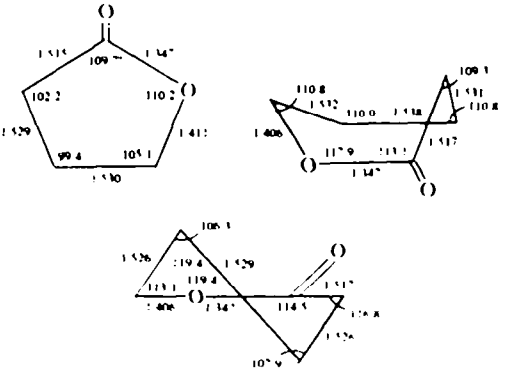
Thus these few experimental data lead us to the conclusion that the esters, like the acids, do not have strong conformational preferences for the internal rotation about either of the bonds by which the alkyl groups are attached to the ester group. With both the esters and the acids, there is a very strong preference for planarity of the carboxyl, or carboalkoxy group, with rotation about the C–O being hindered by a barrier by the order of 10 kcal/mole, and with the *trans* conformation being several kcal/mole more stable than the *cis*. It has long been known from studies on macrocyclic lactones that if the geometric constraints of the system permit, the *trans* conformation is preferred in such molecules. If geometric constraints do not so permit, rather than twisting substantially about the C–O bond, the molecule tends to go over to a *cis* conformation.[28]

Lactones

Calculations indicate that γ-butyrolactone has the β-carbon out of the plane of the remaining four ring atoms. This permits the four ring atoms for which a planar arrangement is optimum to achieve that geometry, while the remaining atom prefers to and does achieve a staggered arrangement. The bond angles are smaller than their preferred values, however, so the ring is substantially strained. The calculated structural parameters are shown.

The δ-valerolactone molecule is especially interesting. It has been discussed at length in the literature,[29-31] but no experimental determination of the conformation of the parent molecule has been reported. Extensive structural studies have been carried out on molecules which contain this ring as a part of a more complex structure. It is found frequently in the form of a flattened chair, and frequently in a boat form (more nearly a classical boat than a twist boat). The chair form is rather unstable because of the strong tendency for the four-atom segment of the carboalkoxy group to be planar. A 6-membered ring (cyclohexane) tends to have dihedral angles of near 60°. These two requirements are contradictory, and the ring is calculated to reach a compromise with a dihedral angle of 36.9° about the C–O bond.

The boat form of δ-valerolactone is as shown.



The four atoms on the near side of the ring are nearly co-planar ($\omega_{C-O} \simeq 11.8°$). The bow and stern hydrogens inside the ring are closer than they prefer to be, and the

molecule is twisted slightly to relieve this repulsion. There is also an eclipsed butane unit on the back side of the molecule. Thus we find that both conformations of this molecule are quite strained. Interestingly, it is calculated that the boat is more stable than the chair.†

In a recent review on 6-membered rings, only one case was listed where a simple molecule existed preferentially in a boat form, (excluding cases where bulky substituents or ring fusions constrain the molecule.) This was the 1,4-cyclohexanedione molecule (and its oxime). In that case, the twist boat form was found.[31] There do not appear to be any experimentally established examples of an unconstrained 6-membered ring existing preferentially in a classical boat form. According to the calculations, δ-valerolactone has such a classical boat conformation. We accordingly sought experimental confirmation for these calculated results, but were not able to obtain definitive evidence either way. The carbonyl stretching frequency in the IR has been interpreted as indicating a chair form.[29-31] This frequency is really a measure only of the bond angle at the carbonyl group,[34] and does not give evidence directly as to the conformation. Note that the calculated internal carbonyl angle is larger in the chair form than in the boat, consistent with earlier IR conclusions. This angle is, of course, also expected to be influenced by substituents. The NMR spectrum was too complex and poorly resolved (at 100 mHz) for us to unambiguously extract the coupling constants of the protons β and γ, so it was not possible to find the dihedral angles. When the α and δ protons were replaced by deuterium exchange, the β and γ protons combined showed a sharp singlet, which was uninformative, and which did not split apart upon changing the solvent from chloroform to benzene.

Dipole moments

While the molecular mechanics method does not in its simplest form give very accurate values for dipole moments, they are at least given approximately with the 1973 force field directly from the moments of bonds and lone pairs. It is thought that when inductive effects are included, this approach can probably be made quite precise. However, at the present stage of development we will settle for approximate calculated moments. These are summarized in Table 6 for some typical small acids and esters. The bond moments from ethers, alcohols, and carbonyl compounds were carried over here unchanged, as was the lone pair moment of ether oxygen. Only one parameter needs to be assigned, the bond moment of the C_{sp^2}–O bond (Table 1).

Heats of formation

The calculation of the heats of formation of hydrocarbons and other compounds by the force field method has been previously described in detail.[20] In order to extend these calculations to carboxylic acids and esters, it is necessary to evaluate a minimum of just one parameter, namely the bond energy of the bond connecting the alkyl oxygen to the carbonyl carbon. Our formal sequence counts the carbonyl bond and the alkyl-carbonyl carbon bond in the acid as though they were in a ketone. Alternatively, we might use 2 parameters, and

†While we have not yet studied the corresponding lactam, it would appear that the same arguments would also apply in that case, and δ-valerolactam is also predicted to be most stable in the boat conformation.

Table 6. Dipole moments of some acids and esters (Debye units)

Compound	Calcd	Exper.[35]
Formic acid	1.58	1.5 ± 0.2
Acetic acid	1.63	1.75
Methyl formate	1.86	1.77
Methyl acetate	1.96	1.71
Ethyl formate	1.87	1.94
Ethyl acetate	1.96	1.85 ± 0.1
β-Propiolactone	3.63	4.0 ± 0.2
γ-Butyrolactone	3.74	4.0 ± 0.2

treat acids and esters separately. Both approaches were tried. However, using the minimum of one parameter and picking the optimum value for it so as to reproduce as well as possible the heat of formation data for the smaller molecules for which data have been reported in gas phase at 25°C (as listed in Table 7), the results were not particularly impressive; the average deviation between the experimental and calculated results was 1.47 kcal/mole, which may be compared with the average experimental error claimed by the experimental investigators for the same set of compounds (0.65 kcal/mole). However, perusal of the published data leads one to question whether it is really that good. Multiple determinations from different laboratories often do not agree to within the combined limits of experimental error, and heats of vaporization are often estimated.

The alternative treatment is to treat acids and esters separately. The rather unique character of the acidic hydrogen in the acids suggests that as a practical matter we can assign a bond energy to the C_{sp^2}–O bond (for both acids and esters), and a separate bond energy to the O–H bond of the acids. With these two parameters, better agreement could be obtained, the esters now differing from experiment by an average of ± 1.50 kcal/mole, compared with a claimed experimental error of ±0.81 kcal/mole, while for the acids the respective values are 0.68 and 0.39 kcal/mole.

Further examination of the experimental data shows that with either of the above schemes, there are three esters for which large probable errors in the experimen-

Table 7. Calculated heats of formation (kcal/mole)

Compound	Experimental[36]	Calcd	Difference
Formic acid	−90.57 ± 0.14	−91.73	1.18
Acetic acid	−103.26 ± 0.12	101.93	+1.34
Propionic acid	−108.40 ± 0.5	−107.77	+0.63
Butyric acid	−122.40 ± 0.6	112.73	−0.33
Valeric acid	−117.15 ± 0.45	−117.67	−0.52
Capric acid	−122.70 ± 0.5	−122.62	+0.08
Ethyl acetate	−106.34 ± 0.16	−105.30	+0.79
Isopropyl acetate	−115.12 ± 0.19	−114.80	+0.05
Methyl pentanoate	−112.70 ± 0.4	−114.99	−1.09
Methyl α-methyl-butanoate	−117.70 ± 1.8	115.57	—
n-Butyl acetate	−116.10 ± 0.20	−115.27	+0.57
Methyl isovalerate	−119.0 ± 1.8	−114.73	—
Methyl pivalate	−122.8 ± 1.8	−118.46	—
Methyl hexanoate	−118.0 ± 0.4	118.83	−1.08
Ethyl 4-pentenoate	−92.1 ± 0.6	−91.42	+0.71
Ethyl 3-*trans*-pentenoate	−93.2 ± 0.7	−93.05	+0.06

Table 8.

Structure	Strain energy (Calcd, kcal/mole)
γ-Butyrolactone	10.0
δ-Valerolactone	
Boat	10.6
Chair	11.9

tal values are reported (± 1.8 kcal/mole), and which show even larger deviations between calculation and experiment. These three experimental values are from the same paper. A fourth value from that paper was discarded by Cox and Pilcher,[36] and it shows the same kind of deviation from an independently determined value. We therefore feel that these values contain a large systematic error. This is unfortunate, because they are the only available examples of such diverse structural types. However, the best approach seems to be to not use these values, and this was done. When this abbreviated set of data (13 compounds) was used, and two parameters were fit (C_{sp^2}–O = −39.460; O–H = −23.734 kcal/mole), the results were as in Table 6. The final results show average deviations and experimental error respectively for acids as 0.61 and 0.39, and for esters 0.62 and 0.38 kcal/mole. With hydrocarbons, where there are more data, and more reliable data, the average deviation between the experimental and calculated results over a large sample of compounds was about 0.5 kcal/mole,[24] which is comparable with the average experimental error and is a limitation of the calculational method in its present form. The calculations here are less reliable, but they will probably be good on the average to about 1.0 kcal/mole. We feel that the method is better than this, but is for now limited for acids and esters by the paucity and inaccuracy of the available data.

As discussed previously, while heats of formation are useful for many purposes, if molecules other than isomers are being compared, strain energies are more advantageous.[2a,37] The calculated strain energies for some lactones are summarized in Table 8.

Note that in δ-valerolactone the strain is worse in the chair than in the boat, but it is sizable in the latter too. It is less in the 5-membered ring, although still sizable because of bond angle deformations. H. C. Brown postulated many years ago[38] that a double bond was preferentially *exo* to a 5-membered and *endo* to a 6-membered ring. These lactones were cited as examples in support of this thesis. Actually, while there is more strain in the 6-membered lactone than in the 5-membered one, according to the present calculations, this is the result of a variety of interactions, none of which has any direct apparent connection with the *exo*/*endo* relationship of double bonds.

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REFERENCES

[1]J. Kao and N. L. Allinger, *J. Am. Chem. Soc.* **99**, 975 (1977).
[2]For reviews, see [a]N. L. Allinger, *Advan. in Phys. Org. Chem.* **13**, 1 (1976); [b]C. Altona and D. H. Faber, *Topics in Current Chem.* **45**, 1 (1974); [c]J. E. Williams, P. J. Stang and P. von R. Schleyer, *Ann. Rev. Phys. Chem.* **19**, 531 (1968).
[3a]N. L. Allinger, M. J. Hickey and J. Kao, *J. Am. Chem. Soc.* **98**, 2741 (1976); [b]N. L. Allinger and D. Y. Chung, *J. Am. Chem. Soc.* **98**, 6798 (1976).
[4]For reviews, see G. Ramachandran and V. Sasisekharan, *Adv. Protein Chem.* **23**, 283 (1968).
[5]W. V. F. Brooks and C. M. Haas, *J. Phys. Chem.* **71**, 650 (1967).
[6]D. R. Lide, Jr., *Trans. Am. Crystallogr. Assoc.* **2**, 106 (1966).
[7]T. Miyazawa and K. S. Pitzer, *J. Chem. Phys.* **30**, 1076 (1959).
[8]P. Ras, *J. Chem. Phys.* **49**, 4902 (1968); M. Schwartz, E. F. Hayes and S. Rothberg, *J. Chem. Phys* **52**, 2011 (1970).
[9]D. L. Bernitt, K. O. Hartman and I. C. Hisatune, *J. Chem. Phys.* **42**, 3553 (1965).
[10]A. Almenningen, O. Bastiansen and T. Motzfeld, *Acta Chem. Scand.* **23**, 2848 (1969).
[11]J. L. Drissen, *J. Mol. Struct.* **7**, 67 (1971).
[12]J. L. Drissen, *J. Mol. Struct.* **7**, 81 (1971).
[13]O. J. Stiefvater, *J. Chem. Phys.* **62**, 233 (1975).
[14]M. Perricaudet and A. Pullman, *Int. J. Peptide Protein Res.* **5**, 99 (1973).
[15]L. Radom, W. A. Latham, W. J. Hehre and J. A. Pople, *Aust. J. Chem.* **25**, 1601 (1972).
[16]W. J. Tabor, *J. Chem. Phys.* **27**, 974 (1957).
[17]L. C. Krisher and E. Sagebarth, *J. Chem. Phys.* **54**, 4553 (1971).
[18]J. Karle and I. O. Brockway, *J. Am. Chem. Soc.* **66**, 574 (1944).
[19]G. C. Pimentel and A. L. McClellan, *The Hydrogen Bond*, p. 350. Freeman, San Francisco (1960).
[20]L. S. Bartell and H. B. Burgi, *J. Am. Chem. Soc.* **94**, 5239 (1972).
[21]J. A. Hirsch, *Topics in Stereochemistry* (Edited by N. L. Allinger and E. Eliel) **1**, 199 (1967).
[22]N. L. Allinger, J. C. Graham and B. B. Dewhurst, *J. Org. Chem.* **39**, 2615 (1974).
[23]L. Bardet, J. Maillais and H. Maillais, *C.R. Acad. Sa. Paris* Ser. **B270**, 158 (1970).
[24]L. Zelta and G. Gatti, *Tetrahedron* **28**, 3773 (1972).
[25]R. F. Curl, Jr., *J. Chem. Phys.* **30**, 1529 (1959).
[26]G. Williams, N. L. Owen and J. Sheridan, *Trans. Faraday Soc.* **67**, 922 (1971).
[27]J. M. Riveros and E. B. Wilson, Jr., *J. Chem. Phys.* **46**, 4605 (1967).
[28]R. Huisgen, I. Ugi, E. Ravenbusch, V. Vossius and H. Oertel, *Ber.*, **90**, 1946 (1957).
[29]A. M. Mathieson, *Tetrahedron Letters* 81 (1963).
[30]K. K. Cheung, K. H. Overton and G. A. Sim, *J.C.S. Chem. Comm.* 634 (1965).
[31a]R. N. Johnson and N. V. Riggs, *Tetrahedron Letters* 5119 (1967); [b]F. I. Carroll, G. N. Mitchell, J. T. Blackwell, A. Sobti and R. Merr, *J. Org. Chem.* **39**, 3890 (1974); [c]M. J. Gasic, Z. Djarmati and S. W. Pelletier, *J. Org. Chem.* **41**, 1219 (1976).
[32]G. M. Kellie and F. G. Riddell, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger), Vol. 8, p. 225. Wiley-Interscience, New York (1974).
[33]For a recent review, see N. L. Allinger and D. H. Wertz, *Rev. Latinoamericana de Quimica* **4**, 127 (1973).
[34]See for example E. L. Eliel, N. L. Allinger, G. A. Morrison and S. J. Angyal, *Conformational Analysis*, p. 197. Wiley-Interscience, New York (1965).
[35]A. L. McClellan, *Tables of Experimental Dipole Moments*. Freeman, San Francisco (1963).
[36]J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organometallic Compounds*. Academic Press, New York (1970).
[37a]P. v. R. Schleyer, J. E. Williams and K. R. Blanchard, *J. Am. Chem. Soc.* **92**, 2377 (1970); [b]D. F. DeTar and C. J. Tenpas, *J. Am. Chem. Soc.* **98**, 4567 (1976).
[38]H. C. Brown, J. H. Brewster and H. Shechter, *J. Am. Chem. Soc.* **76**, 467 (1954).