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ON THE CONFORMATIONS OF LACTONE RINGS

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Abstract- The structures and relative energies of the various conformations have been determined for the simple lactones containing 4-8 ring members by molecular mechanics (MM2) calculations. The 4-, 5-, 6-, 7-, and 8-membered rings are found as conformational mixtures of 1, 1, 2, 1 and 4 conformations, respectively, neglecting conformations with energies more that 2 kcal/mol above the most stable conformation. There is good agreement with the (fragmentary) experimental information available.

The lactones constitute a common class of compounds which are widely found in nature. Of special interest are the large-ring compounds, the macrolides. These are for the most part complicated polyfunctional molecules. Specific conformations are known for several of the macrolides and a few other lactones from crystallography and otherwise (Ref. 1), and the conformations of the 14-membered macrolide have been considered in some detail (Ref. 2). The general principles of the conformations of lactones are not well worked out, and indeed, the conformations of the smaller members of the series (containing 4-8 ring members) were very poorly understood at the outset of this work.

How might we determine the conformation, or more generally, the three-dimensional structures of the lactones? The one or two smallest members of the series might be studied by electron diffraction. Alternatively, with sufficient isotopic species, the same compounds might be studied by microwave spectroscopy, but neither of these kinds of studies has been carried out in any detail. Specifically, only the microwave spectrum of a single isotopic species was reported for each of the two lower members of the series prior to this work (Ref. 3, 4) From these spectra, the moments of inertia (or the rotational constants) were available, but these do not provide enough evidence to permit us to say very much about the structures. Recently the microwave spectra of the 6- and 7- membered ring lactones have been determined, again only for one isotopic species in each case.

In principle, the structures of these simple lactones could be determined by X-ray crystallography, although in practice, many of them are liquids at room temperature, so this may not be very convenient. In any case, such studies have not been reported. Other methods available for the determination of complete and detailed molecular structures are computational in nature. Ab initio calculations in principle could be applied here, but because of the relatively large size and low symmetries of these molecules, plus the fact that there are several possible conformations for each, such calculations would be extremely time consuming and expensive, if possible at all. Semi-empirical methods might be used, but generally speaking, these tend to be significantly less accurate than experimental methods. On the other hand, molecular mechanics is capable of providing structural information which is competitive in accuracy with that obtainable by experimental or ab initio methods, if the necessary force constants are available for the class of compounds in question (Ref. 5). The force constants and other quantities needed to study the lactones were largely available in the literature (Ref. 6) or were determined from preliminary studies in the present work, which involved an examination of small open-chain esters by various experimental and theoretical techniques, and this information was then combined with that in the previously available MM2 hydrocarbon force field (Ref. 7) to yield what we believe is an excellent force field for the calculation of the structures and energies of esters, including lactones. These calculations were then applied to the compounds in question, and from a preliminary examination of models, all feasible conformations were located, and their energies were minimized. For each molecule there was obtained a set of conformations which correspond to energy minima, and which is believed in each case to be the complete set for that molecule. The 4- and 5-membered lactones are simple in that they have a single conformation (where a pair of enantiomers is considered a single conformation). The 6-, 7-, and 8-membered lactones have respectively 2, 4, and 4 different conformations which have energies within a few kcal of the ground state.

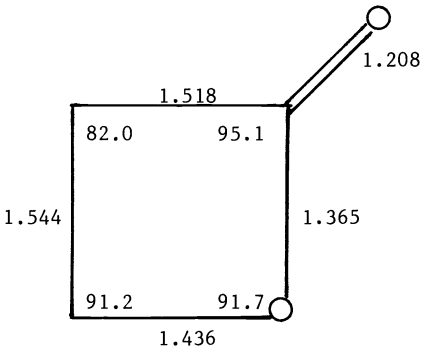
Simple Esters

We reported earlier a study of simple esters, carboxylic acids, and lactones, based on the older MM1 force field (Ref. 6). The advantages of the MM2 force field over MM1 have been documented for hydrocarbons (Ref. 7). With respect to the esters, the following was also considered. In the MM2 force field in general, the bending force constants required to give good structures and energies have previously been found to be about 0.6 times the size of the corresponding force constants obtained from spectroscopic valence force fields. This is in part because of the neglect of van der Waals interactions in the latter. But in any case, the multiplicity factor .6 has been found to be approximately correct for several different functionally substituted systems. In the MM1 force field, the corresponding factor was 0.5. But our earlier (MM1) force field for esters (Ref. 6) was devised before we were aware of this factor of .5, and the full values were used from spectroscopic force constants. They are, therefore, too large relative to the other force constants in the MM1 force field. The ester part of the molecule tended not to distort enough, and the remainder of the molecule distorted excessively when steric forces deformed the system. The results with the MM1 force field are thus considered to be only preliminary.

The force constants determined for the MM2 force field were placed in the program, and are already available in the QCPE version of MM2 (Ref. 8). No parameters remained to be fixed, and the calculations were carried out in a straight-forward manner.

Results

β-Propiolactone. -The structure obtained for the 4-membered ring compound is shown. The molecule was found to be planar, and the calculated heat of formation was -67.30 kcal/mol. Experimentally, the microwave spectrum has been determined (Ref.3), and from this the rotational constants and the moments of inertia. From the relationships between the latter, it was concluded that the skeleton was planar (Ref. 3). From the heat of combustion, the heat of formation in the gas phase at 25° was found to have the value -67.60 kcal/mol (Ref. 9). The calculated and experimental values for the moments of inertia are also shown.



β-Propiolactone - Moments of Inertia and Dipole Moments[a]

	I_x	I_y	I_z
Calcd.	6.79	15.94	21.54
Exper[3]	6.77	16.00	21.69

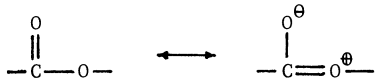
	μ_x	μ_y	μ_z	μ_{tot}
Calcd.	3.42	1.07	0.0	3.59
Exper.[3]	3.67	1.99	0.0	4.17
	μ			

(a) In $gm \cdot cm^2 \cdot 10^{-39}$ and Debyes, respectively.

Since molecules undergo vibrational motion, the microwave spectrum gives a structure which is averaged over this motion in a particular way. The same structure obtained for the molecule by electron diffraction would be somewhat different, if the usual methods were employed, because the method of averaging is somewhat different. From previous work we have found that an error of 1% or less in the moments of inertia usually corresponds to agreement that is good, and essentially down to the limit where the differences in definition may outweigh the differences in the actual quantities being calculated and measured, and so discrepancies of this order of magnitude or smaller are regarded in the present context as insignificant. It will be seen that the experimental and calculated moments of inertia for the molecule agree within this limit, and hence we feel that the calculated structure proposed here has the same order of accuracy and reliability as other structures commonly determined by electron diffraction methods, or by good quality molecular mechanics

calculations on similiarly well-understood molecules.

Only a few points concerning this structure seem worthy of comment. First, it is not necessarily obvious that the molecule will be planar. Cyclobutane has a puckered conformation, and so do many cyclobutane derivatives. These rings pucker in an effort to relieve the torsional strain which is imposed upon a planar ring system. In this molecule there is an eclipsed ethane-type linkage, which would prefer to twist to avoid this eclipsing. However, to do so, it would be necessary also to twist the bond between the carbonyl carbon and the oxygen (the ester bond). The barrier to torsion about the ester bond is quite high, of the order of 10 kcal/mol, due to the ester type resonance:

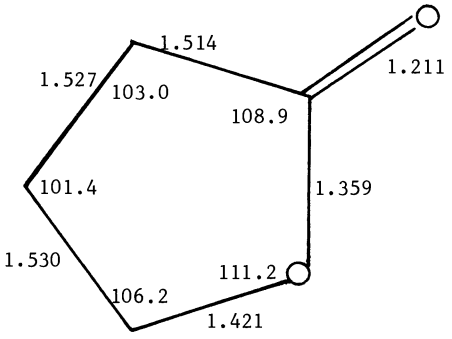


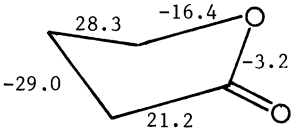
The result is that the height of the barrier about this bond dominates the situation, and twisting about the other bonds, though desirable, does not occur.

It is also perhaps of note that the bond angle at the carbonyl group is 95.1°. The bond angle at the other oxygen is 91.7°. Since the former atom has sp^2 hybridization, while the latter has a tetrahedral hybridization, this is what is expected. However, this is not what is found in most molecules (vide infra).

The MM2 program calculates molecular dipole moments, based on a bond moment scheme. This scheme gives semi-quantitative values for these quantities. It is known how to allow for induced dipole moments, and thus to calculate much better values for the molecular moments (Ref. 10), but these methods have not yet been made a part of the MM2 program. But using the simple bond moment scheme, the components of the dipole along the principal axes of inertia were calculated, and these values are shown. Note that while the total moment calculated is somewhat too small (3.59 D vs. 4.17 D experimental), the components are divided up reasonably well. The zero value for the C component shows that the heavy atoms are coplanar.

γ-Butyrolactone.-Calculations show that the 5-membered ring lactone has a single conformation (or more precisely, two conformations which are enantiomers), with 4 ring atoms plus the carbonyl oxygen in a plane, and the remaining carbon out of the plane. This is an almost ideal situation with respect to torsion, because that part of the molecule which prefers to be planar is planar, while that part which prefers to be non-planar is non-planar. The out-of-plane carbon is not as far out-of-plane as the torsional situation would prefer, however, in an effort to reach a compromise with the bending forces. Some of the bond angles are seen to be quite distorted. The calculated structure is shown. The calculated and experimental (Ref. 4) moments of inertia are also given, and the agreement is again excellent.





	I_x	I_y	I_z
Calcd.	11.54	23.44	32.71
Exper.[4]	11.53	23.41	32.75

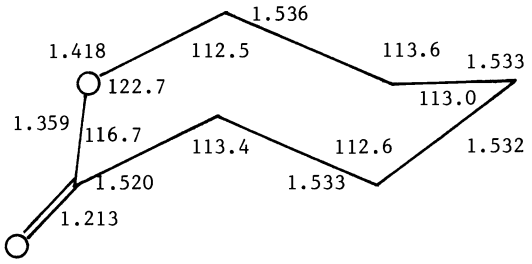
	μ_x	μ_y	μ_z	μ_{tot}
Calcd.	3.65	0.81	0.35	3.75

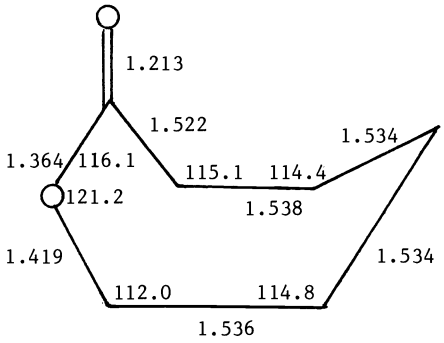
Note that the angles are smaller at the carbonyl than at the alkyl oxygen. This is contrary to expectations, but seems quite general except for 4-membered rings. The calculated components of the dipole moment are also of interest, and show that the molecule is non-planar, but the deviation from planarity is not very great. Thus the components of the moment are similar to those found for the 4-membered ring. In both cases the principal contributor to the dipole moment is the C=O bond, second most important being the lone pairs on the alkyl oxygen. The A axis of interia lies close to the C=O bond, tilted toward the

other oxygen a bit. The C axis is perpendicular to the plane of the 4-membered ring, and the dipole component is thus zero. The out-of-plane methylene in the five-membered ring tilts the principal axes so that, with reference to the figure, the dipole moment is in the plane of the ester group, but the A axis of inertia is tilted upward toward the methylene. This leaves a non-zero projection of the dipole moment on the C axis.

δ-Valerolactone .-Models suggest that this molecule has two conformations, a boat and a chair, and much literature is available concerning derivatives (Ref. 1). Briefly, there are many examples available of compounds which seem to have the ring in the chair comformation, and many which appear to have the boat comformation (Ref. 1). The calculations showed that for the parent compound, the chair conformation is more stable than the boat by 0.5 kcal/mol. Accordingly, the microwave spectrum of the compound was examined, and indeed, both comformations were found (Ref. 11), with the chair being the predominant conformation. Since the full details of this work were published earlier, they will not be repeated here.

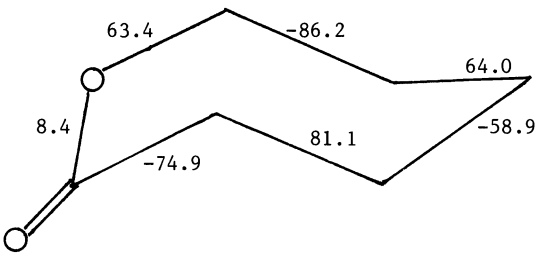
ε-Caprolactone .-The situation here is a good deal more complicated than with the smaller rings, a total of 4 conformations having been found. All four are stable in the sense that they correspond to energy minima, and are predicted to be present in a conformational equilibrium in the gas phase. The energies of three of these conformations are so high relative to the fourth however, that only the latter is expected to be detectable by most available experimental techniques (at room temperature). (The relative energies are 2.72, 4.24 and 5.32 kcal/mol for the boat, half-chair and trans conformations, relative to the stable chair conformation). The microwave studies of this compound have been carried out recently, and only one conformation was detected (Ref. 12). The moments of inertia calculated here are in somewhat poorer agreement with experiment than are those for the smaller rings (errors here up to 1.9%), but there is such a wide disparity between the moments of inertia calculated for the different conformations that the conformational assignments are unambigous.

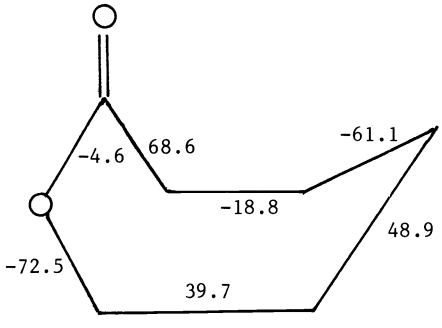




	I_x	I_y	I_z
Calcd.	26.71	43.24	61.61
Exper.	26.22	43.70	62.22
	μ_x	μ_y	μ_z
Calcd.	3.52	0.04	1.44
Exper.			"substantial"

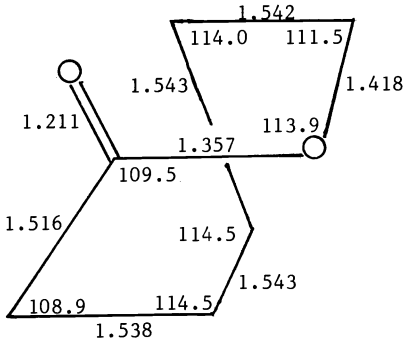
	I_x	I_y	I_z
Calcd.	28.03	41.66	56.50
Exper.			
	μ_x	μ_y	μ_z
Calcd.	3.28	0.33	1.90





It may be noted that three of the conformations of ε-caprolactone have the ester linkage in the cis conformation, and hence have a large dipole moment. There is a single trans conformation with a small dipole moment (and a high energy, 5.32 kcal/mol). If the compound were placed in a polar solvent, the conformations with the larger dipole moment would be solvated more strongly (in the MM2 approximation, at least), so the effect would be only to

raise the energy of the trans conformation even higher, relative to the other conformations. The experimental dipole moment (Ref. 13) shows that the compound exists exclusively in cisoid conformations.

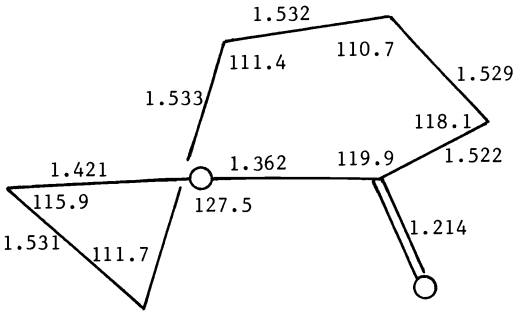


Dihedral Angles

1	2	3	4	50.2
2	3	4	5	-64.1
3	4	5	6	84.3
4	5	6	7	-41.2
5	6	7	1	-43.1
6	7	1	2	107.3
7	1	2	3	-82.8

	I_x	I_y	I_z
Calc	31.99	34.77	51.53

	μ_x	μ_y	μ_z	μ_{tot}
Calc	2.06	0.04	1.46	2.52



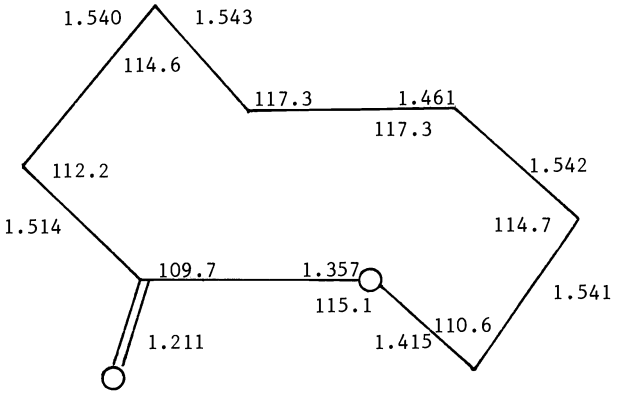
Dihedral Angles

1	2	3	4	-83.7
2	3	4	5	42.3
3	4	5	6	44.8
4	5	6	7	-85.3
5	6	7	1	25.3
6	7	1	2	15.6
7	1	2	3	26.5

	I_x	I_y	I_z
Calc	25.25	45.12	61.81

	μ_x	μ_y	μ_z	μ_{tot}
Calc	3.81	0.15	0.11	3.82

7-Hydroxyheptanoic acid lactone (ζ-Enantholactone). - This compound is calculated to have at least four stable conformations, but in contrast to the smaller homolog, here all four are similar in energy. Three of the conformations are trans lactones (A, B, and C) and one is cis (D). The relative energies of these four are respectively 0.0, 1.06, 1.02, and 1.31 kcal/mol in the gas phase. Since the cis will be more strongly solvated than the others, as discussed for the lower homolog, the energy of D will go down relative to the others when they are dissolved in a polar solvent, and as the dielectric constant of the solvent goes to infinity, D becomes more stable than A by 0.34 kcal/mol. The calculations are consistent with the experimental dipole moment (Ref. 13), which shows that the compound is a mixture of cisoid and transoid conformations in benzene solution.



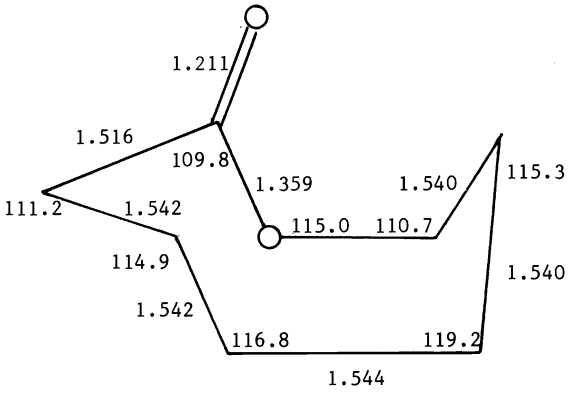
Dihedral Angles

1	2	3	4	47.5
2	3	4	5	-89.5
3	4	5	6	83.4
4	5	6	7	-87.2
5	6	7	8	48.5
6	7	8	1	55.0
7	8	1	2	-136.0
8	1	2	3	49.5

A E = 0.0

Calc	Ix	Iy	Iz
	43.28	44.02	67.89

Calc	μ_x	μ_y	μ_z	μ_{tot}
	1.54	0.04	1.52	2.16



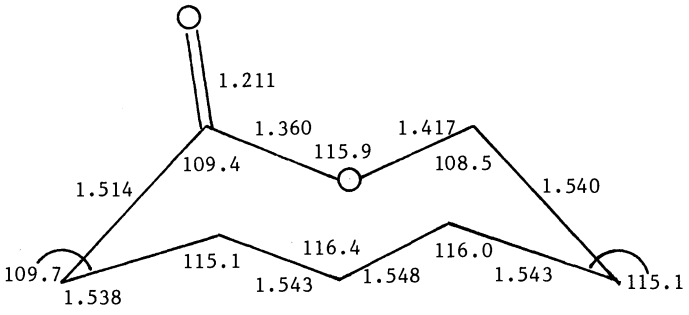
Dihedral Angles

1	2	3	4	62.3
2	3	4	5	-95.4
3	4	5	6	48.4
4	5	6	7	56.3
5	6	7	8	-60.0
6	7	8	1	-52.5
7	8	1	2	127.3
8	1	2	3	-75.5

B E = 1.02 Kcal/mol

Calc	Ix	Iy	Iz
	40.51	46.43	69.19

Calc	μ_x	μ_y	μ_z	μ_{tot}
	1.84	0.38	1.26	2.26



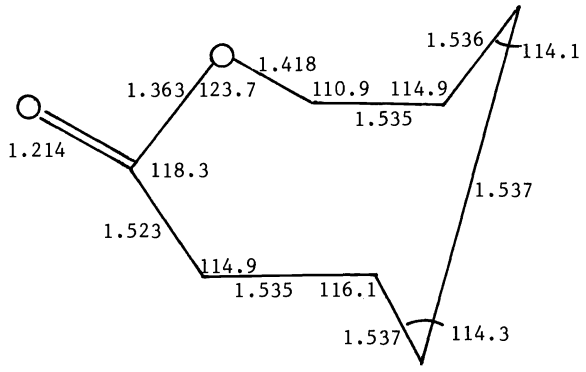
Dihedral Angles

1	2	3	4	-55.9
2	3	4	5	78.6
3	4	5	6	-110.0
4	5	6	7	79.8
5	6	7	8	-51.9
6	7	8	1	92.1
7	8	1	2	-137.3
8	1	2	3	88.0

C E = 1.06 Kcal/mol

	Ix	Iy	Iz
Calc	41.84	45.81	70.30

	μ_x	μ_y	μ_z	μ_{tot}
Calc	0.65	1.29	1.58	2.15



Dihedral Angles

1	2	3	4	74.2
2	3	4	5	-67.8
3	4	5	6	100.3
4	5	6	7	-54.1
5	6	7	8	-55.7
6	7	8	1	90.1
7	8	1	2	9.4
8	1	2	3	-89.6

D E = 1.31 Kcal/mol (vac.)

	Ix	Iy	Iz
Calc	39.42	52.41	75.04

	μ_x	μ_y	μ_z	μ_{tot}
Calc	3.03	0.39	2.28	3.81

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