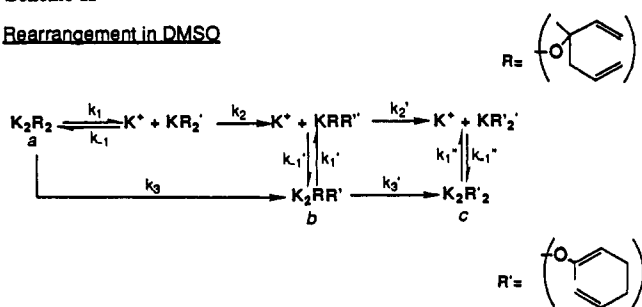


Scheme II

Rearrangement in DMSO



and in the absence of external potassium ion.

However, the rate retardation effect saturates at high concentrations of added potassium salt. This could be due to either accretion of potassium tetrafluoroborate or retardation of the rate via free ions ($k_{-1}[K^+] \gg k_2$) to the extent that a direct pathway within the dimer via k_3 becomes dominant. At higher concentrations of starting material, the rate dependence on initial concentrations in the absence of added salt also appears to be less than a square root dependence. This could also be due to greater incursion of the direct pathway via k_3 .

It is not clear that the dissociation constants for the mixed reactant-product dimer (b), reactant dimer (a), and product dimer (c) are the same so that a constant concentration of potassium ion will be present to ensure first-order kinetics over 2-3 half-lives (Scheme II). Indeed, it is known that K_{as} for KO-*t*-Bu is 270/M

in DMSO for 0.1 M solutions²⁶ and K_{as} for potassium enolates of acetophenone and cyclohexanone is $<20/M$ in DMSO up to concentrations of 0.02 M.²⁷ The dissociation constant ratio would suggest that at the end of the reaction the potassium ion concentration should have increased by a factor of 3, which is well beyond the demands of first-order behavior. However, the reactant-product dimer should have a higher dissociation constant than the starting dimer so its overall rate of reaction may compensate for the increase in potassium ion concentration to allow the kinetics to appear first order with a given concentration of starting material.

The secondary deuterium kinetic isotope effects in the rearrangement of **2** in DMSO suggest that the transition state is highly dissociative. The secondary isotope effect observed for two deuteriums at the bond-breaking site is nearly twice as large as the maximum value, which is 1.35 for two deuteriums at room temperature.¹³ The origin of this anomalously high bond-breaking KIE is under investigation. Again, it is significant that there is but a small inverse kinetic isotope effect at C6, indicating little if any bond making between the terminal carbons in the transition state.

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Lactones. 1. X-ray Crystallographic Studies of Nonanolactone and Tridecanolactone: Nature of CH...O Nonbonded Interactions

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Abstract: The structures of nonanolactone and tridecanolactone have been studied via X-ray crystallography. Nonanolactone adopts an interesting conformation in which a methylene chain and the *Z* ester group are parallel, with nonbonded H...O distances of only 2.76 and 2.34 Å. The conformation is compared with those of cyclodecane, cyclodecanone, and nonanolactam. Tridecanolactone has a regular structure of all trans edges joined by gauche corners. The conformational flexibility of both size rings is discussed. The question of CH...O nonbonded interactions was studied via MP2/6-31G calculations and charge density analysis. The negative charge at oxygen reverses the normal C⁺-H⁻ polarization in alkanes, leading to an attractive interaction. The experimental structural data have been compared with the results of MM3 calculations, and the set of lower energy conformers has been determined. The entropy changes on melting and the changes in ¹³C NMR spectra with temperature are discussed.

Introduction

The lactone group is contained in a large number of important naturally occurring substances.¹ Despite its importance, this group has received relatively little study with regard to energies or conformations.² We have initiated a detailed study of simple

lactones that should provide information useful in modeling compounds having this group using molecular mechanics. This includes studies of enthalpies of hydrolysis of lactones, enthalpies of reduction of lactones to diols, theoretical calculations of conformations and energies, and structural studies. This report will be concerned with the conformation of the 10-membered-ring lactone, nonanolactone, and of the 14-membered-ring tridecanolactone. The 10-membered ring appeared to be interesting for an initial study since cyclodecane,³ cyclodecanone,⁴ and nonanolactam hemihydrochloride⁵ have been studied, allowing a

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Table I. Structural Data for 10-Membered Rings^a

param	nonanolactone (X = O)		cyclodecanone		cyclodecane		nonanolactam (X = N)	
	crystal	MM3	crystal	MM3	crystal	MM3	crystal	MM3
$r(\text{C}=\text{O})$	1.199 (4)	1.209	1.220	1.212			1.275	1.220
$r(\text{C}-\text{X})$	1.339 (4)	1.342					1.305	1.382
$\angle\text{C}-\text{X}-\text{C}$	117.2 (3)	119.6					123.7	122.1
$\angle\text{X}-\text{C}=\text{O}$	123.9 (4)	124.7					120.0	123.7
$\angle\text{C}-\text{C}-\text{X}$	111.4 (3)	111.0					116.8	114.8
$\angle\text{C}-\text{C}=\text{O}$	124.6 (4)	124.3	120.6, 120.2	121.6, 120.9			123.2	121.5
$\angle\text{C}-\text{C}(=\text{O})-\text{C}$			119.1	117.2				
$\angle\text{O}-\text{C}-\text{O}-\text{C}$	10.5 (5)	8.6					10.80	11.12
$\angle\text{C}-\text{C}-\text{O}-\text{C}$	-169.5 (3)	-170.2					-168.27	-167.35
$\angle\text{C}-\text{C}-\text{C}$	156.2 (4)	156.4	158.6	157.5	152.2	152.8	78.5	68.3
$\angle\text{C}-\text{C}(=\text{O})-\text{C}-\text{C}$			-152.3	-154.1				

^aUnits: distances, angstroms; angles, degrees.

comparison among these compounds. The observed structures will be compared with the results of MM3 molecular mechanical calculations.

Structure of Nonanolactone

The structure of nonanolactone was determined by X-ray crystallography at room temperature with a crystal that measured $0.35 \times 0.25 \times 0.20$ mm. Diffraction measurements were made on a Rigaku AFC5S fully automated diffractometer with use of graphite-monochromated Cu K α radiation ($\lambda = 1.54178$ Å). Preliminary indications of the unit cell based on 25 randomly selected reflections revealed orthorhombic symmetry with the following lattice parameters: $a = 16.570$ (3), $b = 120.077$ (2), and $c = 8.800$ (1) Å, with $\alpha = \beta = \gamma = 90.0^\circ$. The space group, based on the observed systematic extinctions, was assigned as *Pbca* (No. 61)⁶ ($Z = 8$) with one molecule of composition C₉H₁₆O₂ forming the asymmetric unit. The volume was 1760.9 (9) Å³, and the calculated density was 1.19 g/cm³. There were 1538 reflections collected with $2\theta \leq 120^\circ$; of those reflections, 915 (59%) with $I \geq 3\sigma(I)$ were judged observed.

The structure was solved with MITHRIL.⁷ The hydrogens were located in the subsequent difference Fourier synthesis. The anisotropic full-matrix refinement of the non-hydrogen atoms and isotropic refinement of the hydrogen positions resulted in the convergence of the crystallographic reliability factors to the following values: unweighted residual (R), 0.063; weighted residual (R_w), 0.083.

The X-ray crystal structure of nonanolactone has a rectangular [2323] diamond-lattice conformation (Figure 1a). The numbers in brackets indicate the number of bonds per edge with use of the nomenclature of Dale.⁸ A side view of the structure shows that the chain skeleton of the longer edges of the rectangle are roughly parallel. The zigzag structure appears to accommodate the Z conformation of the ester group well, only slightly distorting the best possible diamond-lattice skeleton for a 10-membered ring. The O-C-O-C torsional angle of the ester group is 10.5° , nearly the eclipsed Z conformation preferred by simple acyclic esters. The C-C(=O)-O-C torsional angle is -169.5° , and the C-C-C-C torsional angle of the transannular methylene chain is 156.2° . The internal hydrogen of the ϵ -methylene opposite to the carbonyl is 2.76 Å from the carbonyl oxygen. The ethereal oxygen is 2.34 Å from the internal hydrogen of the opposing δ -methylene. Table I contains additional geometric parameters of the crystal structure.

Comparison with Other 10-Membered Rings

Like nonanolactone, the X-ray crystal structures of cyclodecanone and cyclodecane both have a [2323] diamond-lattice conformation with parallel zigzag chains of four carbon atoms linked at each end by a bridge of one carbon atom (Figure 1b,c). The cyclodecane structure has C_{2v} symmetry. The torsional angle of the four-carbon methylene chain in cyclodecane is 152.2° , and that in cyclodecanone is 158.6° . The distance between the car-

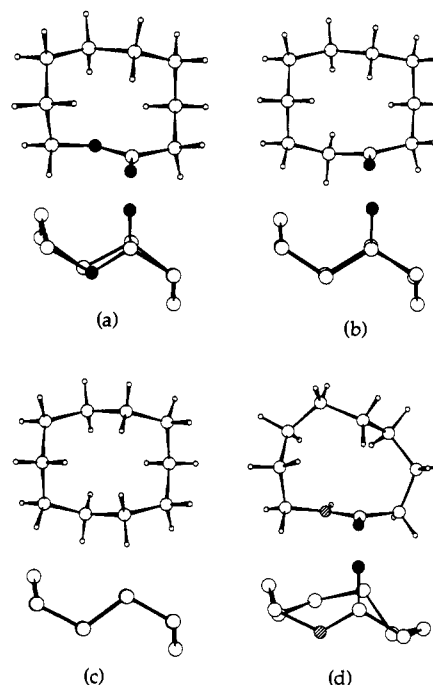


Figure 1. X-ray crystal structures of (a) nonanolactone, (b) cyclodecanone, (c) cyclodecane, and (d) nonanolactam.

Table II. 10-Membered-Ring CH \cdots O Interactions^a

param	cyclodecane	cyclodecanone	nonanolactone
side torsional angle	152.3	158.5, -152.3 (av 155.5)	-169.5, 156.2 (av 162.9)
carbonyl O \cdots H dist		2.80	2.76
etheral O \cdots H dist			2.34
H \cdots H distance	2.048	2.054	
$\angle\text{C}-\text{H}\cdots\text{O}(=\text{C})$		148.1	146.3
$\angle\text{C}=\text{O}\cdots\text{H}(-\text{C})$		63.1	60.4
$\angle\text{C}-\text{H}\cdots\text{O}(\text{ether})$			109.5

^aUnits: distances, angstroms; angles, degrees.

bonyl oxygen and the hydrogen of the opposing methylene group in the parallel chain is 2.80 Å in cyclodecanone.

The structure of nonanolactam (Figure 1d) is greatly distorted from the basic cyclodecane [2323] ring skeleton observed in the other 10-membered rings. The γ -methylene is puckered inward toward the NH of the amide, and the ϵ -methylene group is puckered out away from the internal area of the ring. The carbonyl oxygen is 2.64 Å from the internal δ -methylene hydrogen. The internal hydrogen of the γ -methylene group is 2.77 Å from the amide nitrogen.

Nature of CH \cdots O Nonbonded Interactions

The transannular nonbonded interactions have a significant influence upon the general shape and geometry of the 10-membered rings (Table II). A ring with a pure diamond-lattice

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structure would have two parallel trans methylene chains of four carbons (dihedral angle 180°) linked at each end by a bridge of one perfectly tetrahedral carbon atom. In cyclodecane, however, $H\cdots H$ repulsions ($H\cdots H = 2.048 \text{ \AA}$) serve to push the methylene chains of the sides of the ring outward and a torsional angle of 152.2° is observed for the trans methylene chains in the crystal structure. In cyclodecanone in which a carbonyl group replaces a methylene group, the repulsive interactions in the center of the ring are reduced to allow an observed average torsional angle of the parallel chains of 155.5° (158.6° , -152.3° (ketone-containing chain)). Replacement of another methylene by oxygen in nonolactone affords a further reduction in the transannular repulsions. The rigidity imposed on the ring by the ester group, which prefers a rigid *Z* conformation, brings the average torsional angle of the sides up to 162.9° (156.2° , -169.5° (ester-containing chain)).

With successive narrowing of the transannular gap in cyclodecanone and nonolactone, the methylene chains are brought within close range of highly electronegative oxygen atoms. The nature of the nonbonded interactions that occur between oxygen and alkyl groups not adjacent to activating centers brought close together is not well-known. As seen in Table II, the nonbonded distance between the carbonyl oxygen and the transannular methylene hydrogens in cyclodecanone and nonolactone are 2.80 and 2.76 \AA . The distance between the transannular hydrogen and the ether oxygen in nonolactone is 2.34 \AA . In nonolactone, the $C-H\cdots O$ (carbonyl) angle is 146.3° and the $C-H\cdots O$ (etheral) angle is 109.5° . The $C-H\cdots O$ (carbonyl) angle is 148.1° in cyclodecanone.

There are many examples of nonbonded interactions of oxygen and activated CH groups in the literature.⁹ In nearly all cases, the C-H bond is adjacent to either an electron-withdrawing group or some other activating group (i.e., CN, C=O, S, or halogen), which serves to influence heavily the polarization of the C-H bond. Weak hydrogen bonding or polarization bonding between CH groups and oxygen has been attributed a role in determining molecular packing and conformation in the crystal¹⁰ and has been the subject of some controversy.¹¹ A search of the Cambridge Crystallographic Database has been carried out by Taylor and Kennard.¹² Using recognized values for the van der Waals radii of the CH group and oxygen, they found 59 $CH\cdots O$ contacts of distance at least 0.3 \AA less than the sum of the van der Waals radii and with $C-H\cdots O$ angles greater than 90° , of which 14 involve carbonyl and 19 involve ether, alcohol, or water oxygen atoms. The investigators concluded that the short $CH\cdots O$ contacts, both inter- and intramolecular, occur quite frequently and were likely due to an electrostatic stabilization, resulting in an attractive rather than a repulsive interaction, and can be reasonably described as hydrogen bonds. Recent X-ray crystallographic studies of crown ether complexes with malononitrile (2.23, 2.69 \AA),¹³ dimethyl acetylenedicarboxylate (2.32, 2.45 \AA),¹⁴ dimethyl sulfone (2.50 \AA),¹⁵ dimethyl sulfate (2.50 \AA),¹⁶ and others¹⁷ illustrate the $CH\cdots O$ contact, behaving very much the same way as a hydrogen bond, as integral to the formation of these complexes. The reported $CH\cdots O$ distances are given above in parentheses. Intramolecular $CH\cdots O$ interactions have also been observed and are believed to

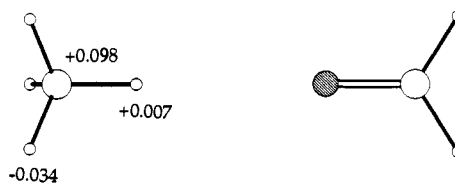


Figure 2. Interaction between methane and the oxygen of formaldehyde calculated at the MP2/6-31G* level. The electron populations are given for each of the atoms of methane.

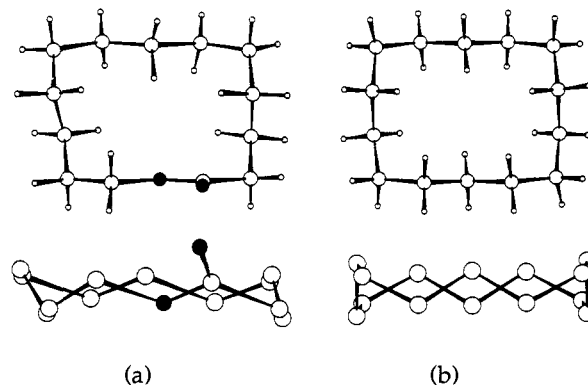


Figure 3. X-ray crystal structures of (a) tridecanolactone and (b) cyclotetradecane.

be important in determining conformational preferences.¹⁸

We have presented evidence that the normal C-H bond dipole has the sense C^+H^- and that it is reversed only when the bond from carbon has high s character, as in acetylene,¹⁹ or when the bond is polarized by substituents. The conclusion is derived from the experimentally determined sign of the dipoles induced by the antisymmetric stretching modes of hydrocarbons along with a charge density analysis of these vibrations. It agrees with the results of calculations of electron populations with Bader's theory of atoms in molecules.²⁰ If the sense is C^+H^- , how many attractive $CH\cdots O$ interactions involving ordinary methylene groups be manifested since the oxygens will have large negative charges? We have examined this question, making use of ab initio molecular orbital calculations. The interaction of a methane hydrogen with the oxygen of formaldehyde was studied at the MP2/6-31G* level of theory²¹ for the orientation shown in Figure 2. A minimum energy was found with the $H\cdots O$ nonbonded distance of 2.58 \AA . A calculation of the electron populations for the atoms via numerical integration of the charge density with the protocol developed by Bader²⁰ led to the atomic charges for the methyl group shown in Figure 2. The negative charge at oxygen has led to a polarization of the C-H bond, which reverses the charge on the hydrogen. This results in a net attractive Coulombic attraction. The orientation of the C-H bond with respect to the oxygen should not be of major importance in this case since the effect of the oxygen on the C-H bond is Coulombic.

Structure of Tridecanolactone

The structure of tridecanolactone was determined with a crystal that measured $0.35 \times 0.35 \times 0.13 \text{ mm}$. Data collection was done at -9°C . Preliminary indications of the unit cell based on 25 randomly selected reflections revealed triclinic symmetry. The data were processed with use of the high-angle cell, which gave the following lattice parameters: $a = 9.156(1)$, $b = 14.136(2)$, and $c = 5.2452(5) \text{ \AA}$ with $\alpha = 98.631(9)^\circ$, $\beta = 104.491(9)^\circ$ and $\gamma = 93.3(1)^\circ$. The space group was assigned as $P\bar{1}$ (No. 2),⁶ $Z = 2$, with one molecule of composition $C_{13}H_{24}O_2$ forming

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Table III. Structural Data for 14-Membered Rings^a

param	tridecanolactone		cyclotetradecane	
	crystal	MM3	crystal	MM3
$r(\text{C}=\text{O})$	1.202 (4)	1.209		
$r(\text{C}-\text{O})$	1.333 (4)	1.343		
$\angle \text{C}-\text{O}-\text{C}$	116.2 (3)	117.4		
$\angle \text{O}=\text{C}-\text{O}$	122.1 (3)	124.9		
$\angle \text{C}-\text{C}-\text{O}$	112.8 (3)	110.4		
$\angle \text{C}-\text{C}=\text{O}$	125.2 (3)	124.8		
$\angle \text{O}=\text{C}-\text{O}-\text{C}$	0.0 (1)	-1.4		
$\angle \text{C}-\text{C}-\text{O}-\text{C}$	-179.8 (5)	180.0		
$\angle \text{C}-\text{C}-\text{C}-\text{C}$	(l) ^b 175.2 (3), -173.2 (3) (s) ^c 176.5	173.5, -174.3 176.5	176.6, -176.0 170.1	175.1, -175.1 171.7

^aUnits: distances, angstroms; angles, degrees. ^bLong side. ^cShort side.

the asymmetric unit. The volume was 646.6 (1) Å³, and the calculated density was 1.09 g/cm³. There were 1921 reflections collected with $2\theta < 120^\circ$, of which 1143 (60%) were judged observed with $I \geq 3\sigma(I)$.

The structure was solved with MITHRIL.⁷ The entire structure was located in the initial electron density map. Anisotropic refinement of the non-hydrogen atoms and calculation of a difference Fourier revealed all of the hydrogen positions. Anisotropic refinement of the non-hydrogen atoms and inclusion of the hydrogen atoms without refinement of their positions resulted in the convergence of the crystallographic reliability factors with the following values: $R = 0.058$, and $R_w = 0.076$. All intramolecular bond distances and bond angles are within normal range.

The crystal structure of tridecanolactone has a rectangular [3434] diamond-lattice conformation of all trans edges (average dihedral angle 176.7°) linked by gauche corners (56.9°, 61.2°) with the Z ester accommodated in the zigzag chain of one of the longer sides (Figure 3). The O=C-O-C torsional angle of the ester group is 0.0°, preserving the preferred Z conformation of the ester moiety. The C-C(=O)-O-C torsional angle is 179.8°.

The crystal structure of cyclotetradecane²² has a very similar [3434] conformation of nearly all trans edges (174.2°) and gauche corners (58.3°, 62.7°). The crystal structure of cyclotetradecanone²³ has been investigated, but the disordered structure of the crystal left the position of the oxygen atom undefined (space group $P\bar{1}$). The ring skeleton, however, has the [3434] rectangular diamond-lattice conformation. The crystal structure of the tridecanolactam has not been investigated.

Comparison with the Results of MM3 Geometry Optimizations

Several geometric parameters of the 10- and 14-membered rings are summarized in Tables I and III. We were interested in seeing how well the MM3 force field²⁴ reproduced the experimental geometries, and therefore MM3 calculations were carried out with use of the observed data as the starting points. In a comparison of the ester group structures of the 10- and 14-membered-ring lactones in the crystal with their MM3-optimized structures, not surprisingly, the ester group of the optimized lactones were found to have adopted the basic features of the MM3-optimized (Z)-methyl acetate structure (Table IV). Interestingly, the ester group geometries in the crystal structures of the lactones more closely resemble the (Z)-methyl acetate X-ray crystal structure²⁵ and its geometry calculated at the MP2/6-31G* level¹⁹ than the MM3-optimized structures (Table IV). Unfortunately, the structure for methyl acetate found via microwave spectroscopy, which should provide a good gas-phase geometry, was not rigorously determined and offers a poor comparison.²⁶ The microwave spectrum of methyl formate is known,²⁷ and the derived

geometry agrees quite well with the geometry calculated by ab initio methods at the MP2/6-31G* level as shown in Table IV. The MM3 geometry of methyl formate, however, differs from both the observed and theoretical geometries.

Dunitz et al. have described the structural characteristics of acyclic esters and lactones.²⁸ Their search of the Cambridge Structural Database for structures containing esters and lactones revealed the general trend that the C-C=O angle is generally larger than the O=C-O angle by 2° in acyclic esters and for δ - and γ -lactones this difference increases to 4.5° and 6.9°. The average values for bond lengths and angles found are included in Table IV. The crystal structures of nonanolactone and tridecanolactone are in very close agreement with the average ester structure, as is that of methyl acetate. MM3 optimization, however, in every case reverses this general trend allowing the O=C-O angle to be approximately the same as or greater than the C-C=O angle by several tenths of a degree. Comparison between crystal-structure bond lengths and those of the MM3 optimizations may not be valid since interatomic distances obtained from mean atomic positions in a crystal at room temperature are generally accepted to be too short by 0.01–0.02 Å. Bond angles, however, are generally believed not to be significantly affected.²⁹ Bürgi has shown previously that MM2 consistently underestimates the C-C=O/O=C-O angle difference in lactones.³⁰ It appears then that the ester group geometries in the present study are still not adequately reproduced by molecular mechanics with the MM3 program. With the exception of the analogous change in geometry of the amide group of nonanolactam hydrochloride, the geometries of the other ring compounds do not change appreciably upon optimization, demonstrating the ability of molecular mechanics to reproduce adequately the overall geometries of the present cycloalkanes and cycloalkanones.

Lowest Energy Conformations of Nonanolactone and Tridecanolactone

M.S. has developed a computer program that is capable of generating conformers of flexible molecules.³¹ It has been demonstrated to work well for finding many previously unexamined conformers of cycloalkanes and bicyclic hydrocarbons. The program creates new conformers by kicking all the atoms of a molecule randomly followed by reoptimization by MM2. The process is then repeated, and any duplicate structures are eliminated. The search is stopped when each of the calculated conformers has been found several times and no new conformers are located.

This procedure has been used to study nonanolactone and tridecanolactone. Over 100 alternate conformers for each lactone were generated. We have examined the five conformers of lowest energy for nonanolactone (Figure 4) and the ten of lowest energy for tridecanolactone (Figure 5). The structures were reoptimized with the MM3 force field. The crystal structures of nonanolactone and tridecanolactone correspond to those of their respective calculated lowest energy conformer. While there may be other higher energy conformers that were not found by the stochastic-search method, the conformers shown in Figures 4 and 5 represent a good set of lower energy conformers. The calculated relative energies of the low-energy conformers have some uncertainty, but they do appear to be in a reasonable order.

These lowest energy structures all maintain the Z conformation of the ester group. In fact, the lowest energy conformer of the 10-membered-ring lactone that has an ester group with an E conformation is 55th from the lowest in energy. An ester with an E conformation is not seen at all in the 100 lowest energy conformers of tridecanolactone.

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Table IV. Simple Ester Geometric Parameters^a

param	methyl acetate (Y = CH ₃)			methyl formate (Y = H)			av crys ^c
	X-ray	ab initio ^b	MM3	microwave ^d	ab initio ^b	MM3	
r(C=O)	1.200	1.219	1.200	1.200	1.214	1.199	1.195 (7)
r(C-O)	1.337	1.353	1.342	1.334	1.345	1.338	1.340 (14)
∠C-O-C	114.9	114.2	116.9	114.5	114.0	116.5	117.4 (16)
∠O-C=O	122.5	123.3	125.2	125.5	125.7	127.7	123.4 (9)
∠Y-C-O	111.8	110.7	109.8	109.2	109.1	109.9	111.2 (10)
∠Y-C=O	125.7	125.9	125.0	125.3	125.1	122.4	125.4 (12)
∠O-C-O-C	-1.2	0.0	0.0				
∠C-C-O-C	179.3	180.0	180.0				

^aUnits: distances, angstroms; angles, degrees. ^bMP2/6-31G*-optimized geometry. ^cReference 28. ^dReference 27.

Table V. Entropies of Melting

compd	ΔH _f ^c	T _f ^d	ΔS _f ^e	ΔH _m ^c	T _m ^f	ΔS _m ^e	ΔH _{tot} ^c	ΔS _{tot} ^e
C ₁₀ H ₂₀ ^a				4912	283	17.32		17.32
C ₁₀ H ₁₈ O ^b				6207	297.4	20.87		20.87
C ₉ H ₁₈ O ₂ ^b				5757	303.6	18.96		18.96
C ₁₄ H ₂₈ ^a	3944	322	12.24	2223	329.3	6.75	6147	18.99
C ₁₄ H ₂₆ O ^b	4547	315.5	14.41	1918	326.6	5.87	6465	20.28
C ₁₃ H ₂₆ O ₂ ^b	3603	289.6	12.45	1724	298	5.78	5327	18.23

^aReference 32. ^bThis study. ^cCalories per mole. ^dSolid-solid transition (K). ^eeu. ^fMelting transition (K).

The five lowest energy conformers of nonanolactone are shown in Figure 4 in the order of the energies calculated by MM3. The lowest four in energy all retain a [2323] form with minor variations, as can be seen by the side views. The lowest energy conformer is stabilized relative to conformations N-II, N-III, and N-IV by ~0.6–1.0 kcal/mol. Conformer N-V is similar in shape to the ring skeleton of the nonanolactam crystal structure and is 1.7 kcal/mol higher in energy than conformation I.

Tridecanolactone has many more conformers available to it in a narrower energy range than does nonanolactone. In Figure 5, conformers T-I, T-II, T-III, and T-VI all have a [3434] skeleton, with the differences visible in the side views. The calculated energies of the lowest three would appear to render them energetically equivalent with structure T-I, narrowly assuming the lowest energy structure by 5 cal! Conformers T-IV, T-V, T-VII, T-IX, and T-X have [4433] shapes, and conformation T-VIII has a [43331] shape. The five lowest energy conformers are all within ~0.5 kcal/mol of the lowest energy structure, all ten within 1.3 kcal/mol of the lowest energy structure as calculated by MM3.

Entropies of Melting, ΔS_m

The entropy of melting of a compound is often discussed in relation to the conformational flexibility of a molecule. Since the melting process is an equilibrium process (ΔG = ΔH - TΔS = 0), the expression for the melting point can be written as T_m = ΔH_m/ΔS_m. Boltzmann's statistical relationship between the entropy of fusion and W_s and W_l, the probabilities available to the solid and the liquid states, respectively, can be expressed as follows:

$$\Delta S_f = R \ln (W_l/W_s) \text{ per mole}$$

We have measured entropies of fusion for the 10- and 14-membered-ring lactones and cycloalkanones. The cycloalkanes have been measured previously.³² All are reported in Table V. A comparison of the melting entropies for the ring compounds reveals striking qualitative and quantitative similarities.

When investigated by DSC calorimetry, the 10-membered rings all exhibit simply the solid-liquid melting transition. No solid-solid transitions are observed for this group. The values for the melting entropies are of similar size and magnitude, leading one to assume that all of the rings in this category undergo very similar processes upon going from the ordered crystalline state to the isotropic melt. Positional, orientational, and conformational order are lost in a single process. This seems to be a particularly noteworthy aspect of the thermal behavior of simple 10-membered-ring compounds. Among cycloalkanes (n < 24), it has been observed that cyclo-

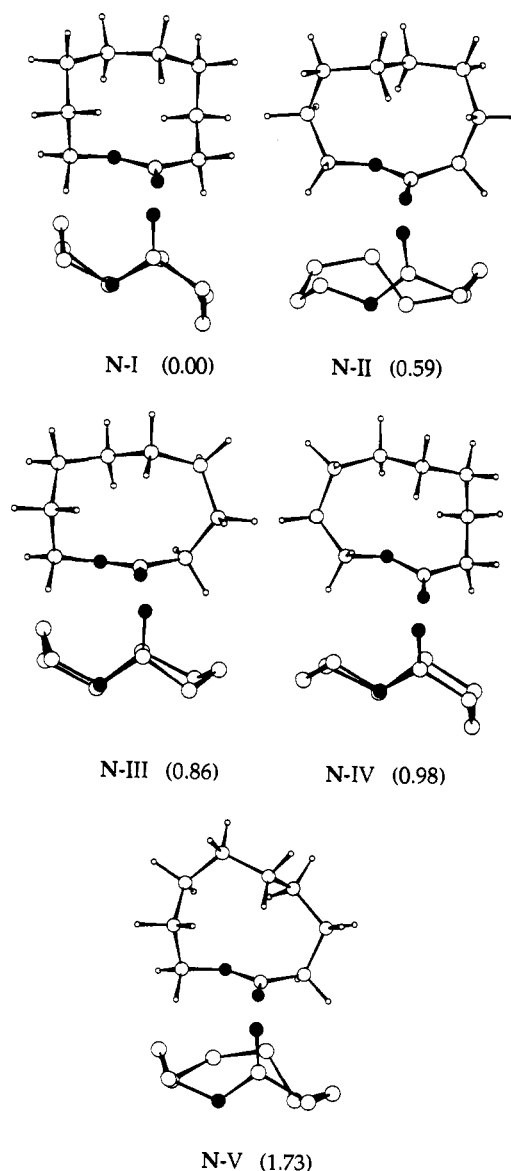


Figure 4. Five lowest energy conformers of nonanolactone. Relative energies are given in kilocalories per mole.

decane is unique in that it does not exhibit one or more solid-solid transitions below its melting point.³²

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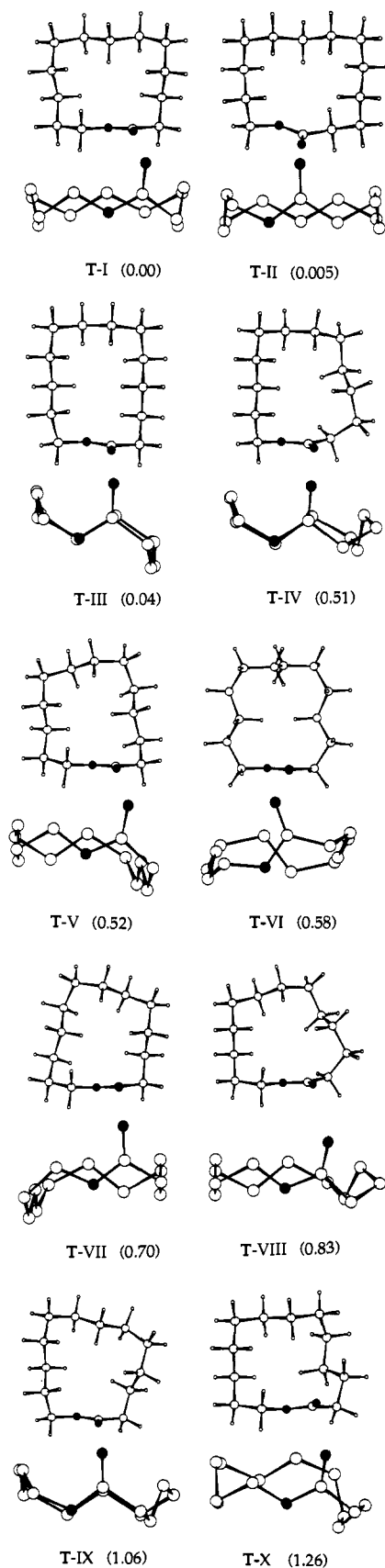


Figure 5. Ten lowest energy conformers of tridecanolactone. Relative energies are given in kilocalories per mole.

The 14-membered rings all exhibit two phase transitions, a solid–solid and a solid–liquid melting transition. The enthalpy change for the solid–solid transition in each case is more than twice as large as the solid–liquid transition. The magnitude of the

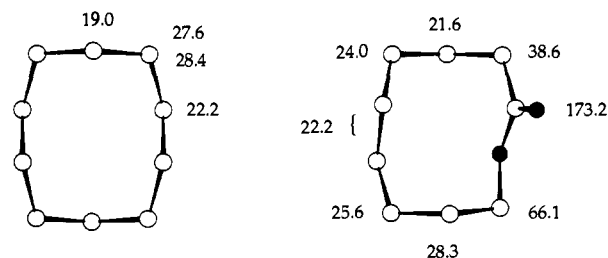


Figure 6. ^{13}C NMR chemical shifts (ppm) of the solid-state CP-MAS spectra of cyclodecane (145 K) and nonanolactone (200 K) as tentatively assigned to the carbon atoms of their X-ray crystal structures.

entropy change for the solid–liquid transition observed in all the 14-membered rings of 5.8–6.8 eu is approximately equal to that estimated for loss of positional order in the crystal ($\Delta S = 1.5\text{--}3.0$ eu, Richard's rule) plus some degree of orientational order as observed for the melting transitions of other organic compounds.³³ The solid–solid transition is attributable chiefly to loss of conformational order and some orientational order.³⁴ A recent study of cyclotetradecane³⁵ has shown that the mesophase, the disordered phase between the solid–solid and melting transitions, is characterized by an increase in lattice symmetry (although still low (monoclinic)), a considerable decrease in density, and a sharp increase in molecular motion. Jumplike dynamic orientational disordering was cited as the chief result of changes in the lattice, allowing greater molecular motion. The disordering of molecules with low symmetry via rotational jumplike motions around one or two axes is a probable origin of considerable loss of orientational order and leads to large transition entropies.

From the data in this study, however, it is not possible to determine the mechanistic details of the processes that are occurring upon melting in the 10- and the 14-membered-ring cycloalkanones and lactones, respectively. Nevertheless, the data suggest that, for each ring size, the processes involve very similar losses of order likely via very similar mechanisms. As the study in the previous section on the availability of conformers to the rings illustrates and the thermal data suggest, the lactone rings studied would appear to have as high a degree of conformational flexibility as their cycloalkane and cycloalkanone counterparts notwithstanding the presence of a rigidity planar ester group. Further study of the mesophases of cyclotetradecane and tridecanolactone via solid-state NMR techniques and optical microscopy would be well merited to determine other similarities in behavior to cyclotetradecane.

^{13}C NMR Spectra

The high-resolution solid-state ^{13}C NMR spectrum of nonanolactone has been measured by magic angle spinning and cross-polarization techniques. In agreement with the fact that nonanolactone exhibits no solid–solid transitions beneath the melting temperature as the DSC measurements demonstrated, the solid-state ^{13}C NMR spectrum undergoes very little change from 283 to 200 K. Assuming that the X-ray crystal structure has the geometry that is likely responsible for the observed spectrum, tentative assignments can be made for the resonance peaks observed (Figure 6). With reference to the solid-state ^{13}C NMR spectrum of cyclodecane³² (19.0 ppm, 1 C gggg; 22.2 ppm, 2 C ggag; and 28 ppm, 2 C ggga), which has a geometry very similar to nonanolactone in the aliphatic portion, the peaks in parts per million are tentatively assigned as follows: 173.2 (C=O); 66.1 (CO); 38.6 (α -C); 28.3 (η -C); 25.6 (ζ -C); 24.0 (γ -C); 22.2 (δ, ϵ -C); and 21.6 (β -C).

The ^{13}C NMR solution spectrum at various temperatures presents some potentially valuable information on the conformational flexibility of nonanolactone in solution. The low-tem-

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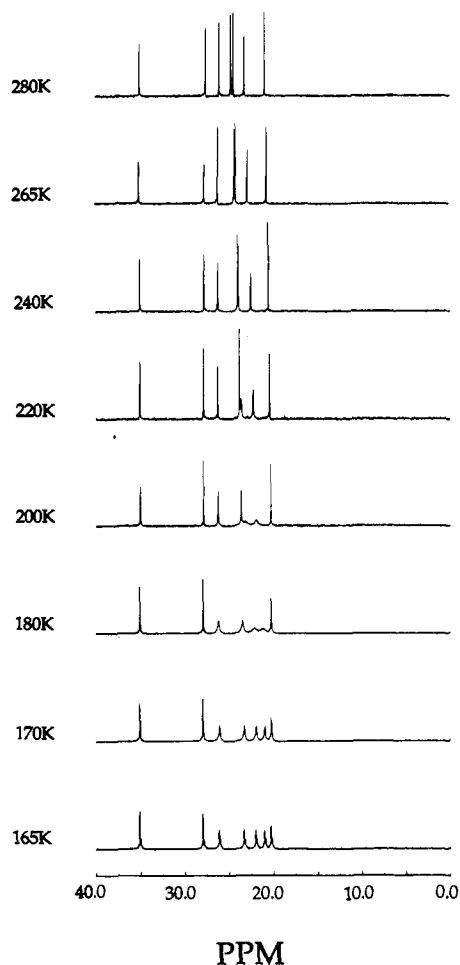


Figure 7. 300 MHz ^{13}C NMR spectra of the aliphatic region of nonanolactone in methylene chloride solution at various temperatures.

perature spectrum appears akin to the solid-state spectrum. In methylene chloride solution at 165 K, carbon resonances are clearly resolved at 174.4, 66.9, 35.1, 28.0, 26.1, 23.3, 22.0, 21.0, and 20.3 ppm. The aliphatic region of the spectrum can be seen in Figure 7. As the temperature is raised, the resonance peaks at 21.0 and 22.0 ppm broaden at 180 K and begin shifting downfield with increasing temperature until, at 280 K, the peaks are clearly resolved at 23.3 and 24.8 ppm. The other resonance peaks at 280 K are found 173.8, 66.2, 35.1, 27.6, 26.0, 24.5, and 20.9 ppm, which are essentially the same as in the lowest temperature spectrum with the exception of the resonance peak at 24.5 ppm, which has shifted downfield approximately 1.2 ppm. Examination of the lowest energy conformations in Figure 4 of nonanolactone suggests that the motion possibly responsible for the broadening and averaging could correspond to the motion of the δ - and ϵ -carbons of the methylene chain transannular to the ester group. Their motion relative to the oxygen atoms opposite them may represent the most significant motion and change of atomic chemical environment among these structures. Although the carbon atoms at the β - and η -positions do undergo significant changes among the lowest energy structures in Figure 4, the relative changes in their chemical environments do not appear to be very great. It is also possible that the chemical shift changes for the two carbon atoms in the NMR spectrum may not correspond to any of the calculated low-energy structures. With the information currently available, this discussion of the conformational flexibility of nonanolactone in solution and assignment of the NMR spectra can only be considered as a conjecture until

further investigation, perhaps via labeling studies, is carried out.

Experimental Section

Nonanolactone and tridecanolactone were synthesized via Baeyer-Villiger oxidations of the corresponding cyclic 9- and 13-membered-ring ketones. The reagent of choice for this reaction is trifluoroacetic acid as used in similar procedures by Emmons and Lucas³⁶ and Huisgen and Ott^{2a} for synthesizing lactones. Moderately good yields and relatively short reaction periods provide a welcome alternative to low-yield, time-intensive ring cyclizations previously used to synthesize these two lactones.

Trifluoroacetic Acid. In a 100-mL round-bottom flask, 3.5 mL (4.66 g, 95.9 mmol) of 70% H_2O_2 (FMC Corp.) was added carefully without stirring to 40 mL of dry methylene chloride at 0 °C via an addition funnel. Over a 30-min period, 24.5 mL of trifluoroacetic anhydride (36.5 g, 173.8 mmol) was added slowly with stirring, while the temperature remained close to 0 °C. The resultant solution of peracid in methylene chloride solution was used immediately in the Baeyer-Villiger oxidation.

Nonanolactone. A solution of 9 g (0.064 mol) of cyclononane in 150 mL of dry methylene chloride was placed along with 42 g of finely powdered Na_2HPO_4 (anhydrous) in a dry nitrogen-purged 500-mL 3-necked flask fitted with an overhead stirrer and addition funnel. The stirred suspension was cooled to 0 °C in an ice bath. The solution of trifluoroacetic acid was added over a period of 30 min. The reaction mixture was maintained at 0 °C for 1 h, then allowed to warm to room temperature, and continuously stirred for another 9 h. After filtration, the methylene chloride solution was washed with concentrated NaHCO_3 solution (100 mL), water, and brine and dried overnight over Na_2SO_4 . Removal of the solvent yielded 8.8 g (88%) of crude lactone. The lactone was purified by distillation (bp 73 °C (3 mmHg)). Simple recrystallization from methanol yielded clear prismatic crystals (mp 34 °C) of >99.95% purity suitable for X-ray crystallography.

Tridecanolactone. In the same manner as described for the nonanolactone synthesis, cyclotridecanone (5 g, 25.5 mmol), Na_2HPO_4 (30 g, finely divided 250 μm), and 200 mL of dry methylene chloride were combined and a solution of trifluoroacetic acid (40 mmol in 30 mL of CH_2Cl_2) was added. The reaction mixture was stirred for a total of 20 h. The crude product was purified via successive recrystallizations from methanol at -50 °C. A white crystalline solid of mp 25 °C and purity >99.5% by GC was obtained after sublimation (yield 3.6 g (66.5%)). A single crystal was obtained via slow evaporation of the solvent from a pentane solution of the lactone over a period of 2 weeks at 0 °C.

DSC measurements were carried out on a Perkin-Elmer Model DSC-4 differential scanning calorimeter. The instrument was calibrated to the equilibrium melting-transition enthalpy and temperature of high-purity indium at a rate of 10 deg/min as recommended by the manufacturer's manual. Measurements reported here were made at that heating rate. Transition enthalpies obtained from the numerical integration of the transition peaks show a variation of less than 3%. Temperature accuracy was better than ± 0.2 K. For cyclotetradecanone and tridecanolactone, the two transition peaks overlapped slightly. Cutouts of the peaks with some minor extrapolation gave satisfactory agreement among several different samples.

High-resolution solid-state and solution ^{13}C NMR spectra were recorded at 75.47 MHz with a Bruker CXP 300 spectrometer. The cross-polarization and magic angle spinning techniques, equipment, and conditions used for the variable-temperature solid-state spectrum of nonanolactone are as reported in a similar study.³⁷

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Supplementary Material Available: Tables of X-ray crystallographic coordinates for nonanolactone and tridecanolactone (4 pages). Ordering information is given on any current masthead page.

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