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Dynamic NMR Study of 3-Methylene-1-oxaspiro[4.5]decan-2-one and Single-Crystal X-ray Diffraction Analysis of *cis*-8-*tert*-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one

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A dynamic NMR study of 3-methylene-1-oxaspiro[4.5]decan-2-one, a dynamic molecular system, was made to determine the thermodynamic and kinetic properties of the ring reversal process. Low temperature measurements of the integrated areas under the signals corresponding to the individual conformers clearly showed a conformational preference for an axial C–O group rather than an axial methylene group. Measurements of the equilibrium constants at higher temperatures were made using the chemical-shift method. Extrapolation of the chemical-shift data to the lower temperatures yielded a value of $-\Delta G°_{177}$ = 0.058 kcal/mol, in excellent agreement with the values obtained via integrated areas. Complete line-shape analysis permitted the determination of the absolute rate constant for the reversal process. An average value of ΔG^* was 10.9 kcal/mol as determined over a 30° temperature range. A temperature dependence study of the rate constant allowed calculation of values of ΔH^* = 9.60 kcal/mol and ΔS^* = −5.9 eu. A discussion of factors which may influence the thermodynamic and kinetic properties of the ring reversal is also given. In addition, a single-crystal analysis by X-ray diffraction of *cis*-8-*tert*-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one was completed. The compound crystallized in a noncentrosymmetric space group $P2_12_12_1$ via apparent selective crystallization of one of the puckered forms, with unit cell dimensions of a = 11.455 (2), b = 18.356 (2), and c = 6.100 (1) Å. The structure was solved from 1551 diffractometer data. The final R factor is 0.038. The cyclohexyl ring is significantly flattened near the spiro ring.

The isolation of a wide variety of natural products containing an α-methylene-γ-butyrolactone ring which have displayed diverse biological activities[1a,b] has promoted the synthesis of compounds containing this function for use as possible antitumor agents.[2a,b,3] A series of spiro α-methylene-γ-butyrolactones were synthesized in this laboratory in conjunction with a search for such agents.[4] To the best of our knowledge, no study has appeared which has focused on both the thermodynamics and kinetic aspects of a dynamic α-methylene spiro lactone even though such a system has reported activity.[5a]

We have undertaken a dynamic NMR (DNMR) study of 3-methylene-1-oxaspiro[4.5]decan-2-one using three different techniques to obtain values for the various thermodynamic and kinetic parameters associated with the ring reversal process in this particular compound. These data are reported herein, along with a discussion of some of the effects which may influence the preferred conformation of this spiro lactone.

Results and Discussion

The synthesis of the spiro lactones is outlined in Scheme I.[4] In all cases, the Reformatsky reaction was employed under identical conditions for reaction with an appropriate cyclohexanone. Addition of each reaction mixture to H_2SO_4 at 0 °C yielded either an oil or a crystalline product, which was extracted with ether. However, careful recovery of the crude product, followed by purification either by distillation or recrystallization, gave, upon cooling, a crystalline material for each compound listed in Scheme I.[5a,b] All spectral and synthetic data are reported in Table I for the various compounds synthesized.

DNMR Data: Thermodynamic Evaluation of the Ring Reversal Process. Compounds **4a** and **5a** are interconvertable conformers (Scheme I). At temperatures below 198 K (−75 °C) the frequency of interconversion between these two isomers is sufficiently low that signals for each conformer are distinguishable in the low-temperature ^{1}H NMR spectra, i.e.,[6]

$$k_r \ll \pi|\nu_a - \nu_e|/\sqrt{2}$$

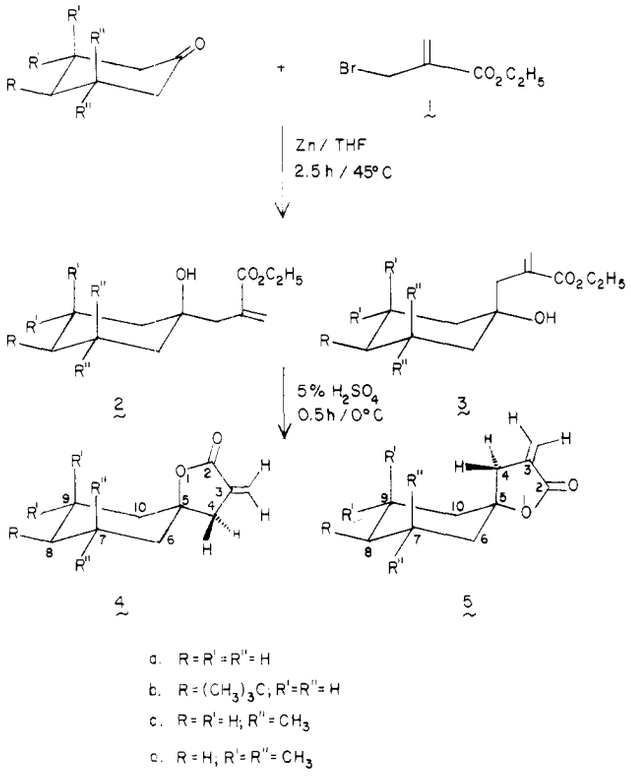
where k_r is the reaction rate constant, ν_a is the chemical shift of H(4) in **4a**, and ν_e is the chemical shift of H(4) in **5a**. Under these conditions, both conformers are easily detected, and the relative peak areas can be measured by integration. In this particular case, **4a** and **5a** give rise to two separate three-line spin patterns (X_2 of an AMX_2 pattern) between 177 and 185 K which are below the compound's coalesence temperature

Table I. Spectral and Synthetic Data for Some Simple Spiro Lactones

compd	R	R′	R″	mp, °C	bp, °C	NMR[d]	IR, cm^{-1}
4a ⇌ 5a	H	H	H	26–27.5	76–77 (0.05 mm)	1.2–1.9 (m, 10 H), 2.78 (2 H),[a] 5.62 (1 H),[b] 6.05 (1 H)[b]	$\nu_{C=O}$ 1761 $\nu_{C=C}$ 1664 (film)
4b	*t*-Bu	H	H	84–85		0.88 (s, 9 H), 1.0–2.0 (m, 9 H), 2.74 (2 H),[a] 5.62 (1 H),[b] 6.05 (1 H)[b]	$\nu_{C=O}$ 1748 $\nu_{C=C}$ 1653 (KBr)
5b	*t*-Bu	H	H	83–84		0.89 (s, 9 H), 1.0–2.0 (m, 9 H), 2.85 (2 H),[a] 5.64 (1 H),[b] 6.05 (1 H)[b]	$\nu_{C=O}$ 1751 $\nu_{C=C}$ 1653 (KBr)
4c ⇌ 5c	H	CH_3	H	38.5–39.5	100–102 (0.25 mm)	0.94 (s, 3 H), 1.04 (s, 3 H), 1.1–1.95 (m, 8 H), 2.78 (2 H),[c] 5.62 (1 H),[b] 6.04 (1 H)[b]	$\nu_{C=O}$ 1757 $\nu_{C=C}$ 1664 (film)
4d ⇌ 5d	H	CH_3	CH_3	102–103		0.95 (s, 6 H), 1.18 (s, 6 H), 1.0–1.9 (m, 6 H), 2.77 (2 H),[a] 5.68 (1 H),[b] 6.08 (1 H)[b]	$\nu_{C=O}$ 1754 $\nu_{C=C}$ 1658 (KBr)

[a] Three-line pattern resulting from X_2 portion of AMX_2, where $J_{AX} \sim J_{MX}$. [b] A or M portion of AMX pattern where $J_{AM} < J_{AX} \sim J_{MX}$. [c] Four-line portion of an AMXY pattern. [d] Ppm from Me_4Si in acetone-d_6.

Scheme I



(T_c) of 209 K (−64 °C). The two concentrations used were 0.024 and 0.036 M solutions in acetone-d_6. A partial spectrum of a solution (0.036 M) of **4a ⇌ 5a** is shown in Figure 1. The equilibrium constant for the ring reversal can be determined from the relative areas and, using these values, calculation of $\Delta G°$ follows:

$$\Delta G° = -RT \ln ([\mathbf{5a}]/[\mathbf{4a}])$$

where [**4a**] and [**5a**] are the measured areas of the separate peaks corresponding to the individual conformers. Values for $\Delta G°$ at various temperatures for the two different concentrations are given in Table II. Qualitative values for $\Delta H°$ are also given. However, the very narrow temperature range accessible because of solubility limitations in the determination of K_{eq}, as well as the very small change in K_{eq} over this temperature range, does not permit extremely accurate $\Delta H°$ values to be obtained. The values of $\Delta H°$ at the different concentrations were calculated to permit relative comparisons between this method of evaluating $\Delta G°$ and the chemical shift method[7] also used in the study.

The values for $\Delta G°$ in Table II clearly show that the conformer corresponding to the upfield signal in the low-temperature NMR spectra of this equilibrating system is favored thermodynamically by a modest amount. Previous work reported in the literature[8] suggested that steric compression due to typical 1,3 interactions with protons on the cyclohexyl ring would cause proton signals for axially situated methylene groups to be shifted to lower field. Based on these observations, we initially concluded that structure **4a** represented the predominant conformer in our system. In order to establish

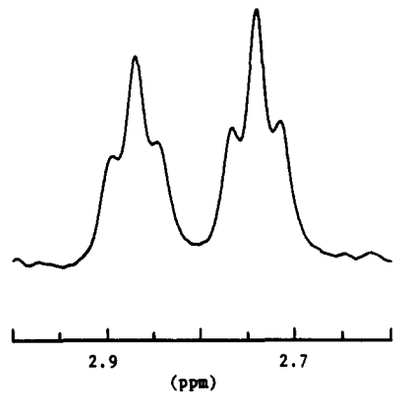
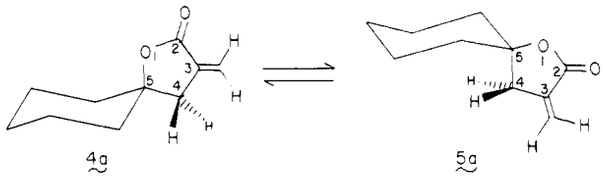


Figure 1. Spectrum of **4a ⇌ 5a:** 177 K; 0.036 M in acetone-d_6; sweep width = 40 Hz; offset = 260 Hz.

Table II. Calculation of Thermodynamic Parameters by Integrated Areas[a]



T, K	K_{eq} ([**5a**]/[**4a**])	$\Delta G°$, kcal/mol	$\Delta H°$, kcal/mol[b]
		0.036 M	
185	0.754 ± 0.009	+0.105 ± 0.005	−0.563 (r^2 = 0.99)
181	0.779 ± 0.023	+0.090 ± 0.011	
177	0.808 ± 0.006	+0.075 ± 0.003	
		0.024 M	
185	0.763 ± 0.005	+0.099 ± 0.002	−0.480 (r^2 = 0.94)
181	0.776 ± 0.020	+0.091 ± 0.009	
177	0.811 ± 0.019	+0.074 ± 0.008	

[a] Samples were prepared in acetone-d_6 with Me_4Si as an internal standard. [b] $\Delta H°$ calculated by least-squares fit of ln K_{eq} vs. $1/T$ using average values of K_{eq}.

Table III. Calculation of Thermodynamic Parameters by Chemical Shifts for 4a ⇌ 5a[a]

T, K	K_{eq}	$\Delta G°$, kcal/mol	$\Delta S°$, eu[b]	$\Delta H°$, kcal/mol[c]
286.5	0.681 ± 0.011	+0.218 ± 0.010		
274.3	0.684 ± 0.022	+0.208 ± 0.009	−1.5	−0.207
251.9	0.720 ± 0.012	+0.164 ± 0.009		(r^2 = 0.96)
232.6	0.736 ± 0.023	+0.142 ± 0.015		
185.0		+0.099 ± 0.002[d] (+0.070)[e]		
181.0		+0.091 ± 0.009[d] (+0.064)[e]		
177.0		+0.074 ± 0.008[d] (+0.058)[e]		

[a] Samples were prepared as 0.24 M solutions in acetone-d_6 with Me_4Si as an internal standard. [b] Calculated from $\Delta S° = (\Delta H° - \Delta G°)/T$. [c] $\Delta H°$ calculated by least-squares fit of ln K_{eq} vs. $1/T$ using average values of K_{eq}. [d] Values calculated from integrated areas (Table II). [e] Values extrapolated from chemical shift data.

unequivocally the conformer in predominance, compounds **4b** and **5b** were synthesized and isolated as shown in Scheme I. Separation of the two isomers was achieved by column chromatography over Florisil. The compound isolated in predominance was submitted for X-ray analysis and was determined to be **4b.** Independent NMR analysis of both isomers in solution showed distinctly that protons of the methylene group at C(4) in **4b** resonate at higher field (δ 2.74) than the analogous protons in **5b** (δ 2.85).

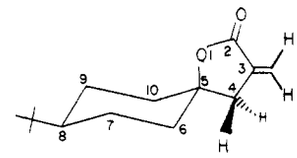
Although the low-temperature method of integrated areas is the most theoretically satisfying technique for determining the equilibrium constant and subsequent calculation of $\Delta G°$, it suffers from several limitations in this case. It was difficult to maintain constant probe temperatures below the coalescence temperature T_c for extended periods of time. The range of temperatures in which determinations could be made was governed by the coalescence process and by the freezing point of the solvent. No other solvents were found to be suitable due to the low solubility of the compound. While the values obtained for $\Delta G°$ for **4a** ⇌ **5a** are of good accuracy, one cannot assume that they represent the equilibrium at higher temperatures, especially in view of the rather high value estimated for $\Delta H°$.

The chemical shift method of determining the equilibrium constant[7] was used to obtain values for $\Delta G°$ at tempertures above T_c, for which $k_r \ll \pi|\nu_a - \nu_e|/\sqrt{2}$. Since a specific signal will result from a time averaging of the independent signals for the individual conformers, weighted by the mean lifetime of the mobile system in each conformational orientation,[9] the equilibrium constant can therefore be calculated by $K_{eq} = (\delta_e - \delta)/(\delta - \delta_a)$. The shifts for δ_a and δ_e were obtained from the spectra of the conformationally locked *tert*-butyl-substituted compounds **4b** and **5b.** The results of this method of determining K_{eq} as well as $\Delta G°$ (and $\Delta H°$) are shown in Table III. Again, the positive values of $\Delta G°$ indicate the conformational preference of **4a** over **5a.** The magnitudes of the values for $\Delta G°$ are greater for this method of calculation than those values obtained by the low-temperature area method by a factor of 3. However, values for $\Delta G°$ at the lower temperatures may be calculated from the higher temperature chemical shift data using $\Delta G° = \Delta H° - T\Delta S°$ and the values calculated for $\Delta H°$ and $\Delta S°$. Comparison of the extrapolated values with actual values calculated at low temperatures by the use of integrated areas (Table III) shows good agreement. A least-squares analysis of the combined chemical shift and integrated area data for the 0.024 M solutions permitted calculation of overall values for $\Delta H°$ and $\Delta S°$ of −0.133 kcal/mol (r^2 = 0.94) and −1.2 eu, respectively, over a temperature range of 109 K.

While this evidence supports the chemical shift method, a special note of caution must be added. Several studies in the past have cast doubt on the validity of this technique in the evaluation of an equilibrium constant.[10,11] It has been pointed out that there are possible effects which the *tert*-butyl group may have on the chemical shifts of protons *bonded directly to the six-membered ring.* It was later argued that the 4-*tert*-butyl group is the best choice for model compounds, and, in cases where the object protons are insulated from the six-membered ring, effects of the 4-*tert*-butyl group would probably be minimal.[12a,b] In our case, not only are the H(4) protons insulated from the ring by a carbon atom, but the X-ray analysis of **4b** shows distortion in the cyclohexyl system due to the spiro ring junction is greater than the distortions due to the *tert*-butyl group. This can best be seen by comparison of the torsion angles listed in Table IV. Angles C(9)–C(10)–C(5)–C(6) and C(10)–C(5)–C(6)–C(7) clearly show a deviation at the spiro end from the normal value of 57° for cyclohexane[13a,b] by 7.6 and 8.2°, respectively. Angles C(6)–C(7)–C(8)–C(9) and C(7)–C(8)–C(9)–C(10) show a deviation at the *tert*-butyl end of 2.4 and 3.4°, respectively. These values of course cannot be extrapolated directly to a solution of **4b.** However, studies of a few simple and substituted cyclohexanes as well as a variety of pentamethylene heterocycles in solution[13a] have shown agreement with X-ray data within ±2°. This suggests that structural changes for such systems upon dissolution are small. Hence, it would be expected that chemical shift differences between biased and unbiased systems in solution due to the *tert*-butyl group would be small relative to the effects at the spiro part of the molecule. The agreement of the extrapolated values in Table III with those values obtained by integrated areas clearly supports this contention.

As stated previously, the thermodynamic parameter $\Delta G°$ calculated displays a small but distinct conformational preference for the conformer **4a** (C–O bond axial). Values in the literature for similar spirodioxolane systems[14] have yielded comparable results for $\Delta G°$ at low temperatures. The $\Delta G°$

Table IV. Torsion Angles from X-ray Analysis of *cis*-8-*tert*-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (4b)



five-membered ring		six-membered ring	
O(1)–C(2)–C(3)–C(4)	6.7°	C(5)–C(6)–C(7)–C(8)	−55.1°
C(2)–C(3)–C(4)–C(5)	−18.6°	C(6)–C(7)–C(8)–C(9)	59.4°
C(3)–C(4)–C(5)–O(1)	23.1°	C(7)–C(8)–C(9)–C(10)	−60.4°
C(4)–C(5)–O(1)–C(2)	−20.5°	C(8)–C(9)–C(10)–C(5)	56.5°
C(5)–O(1)–C(2)–C(3)	8.9°	C(9)–C(10)–C(5)–C(6)	−49.5°
		C(10)–C(5)–C(6)–C(7)	48.8°

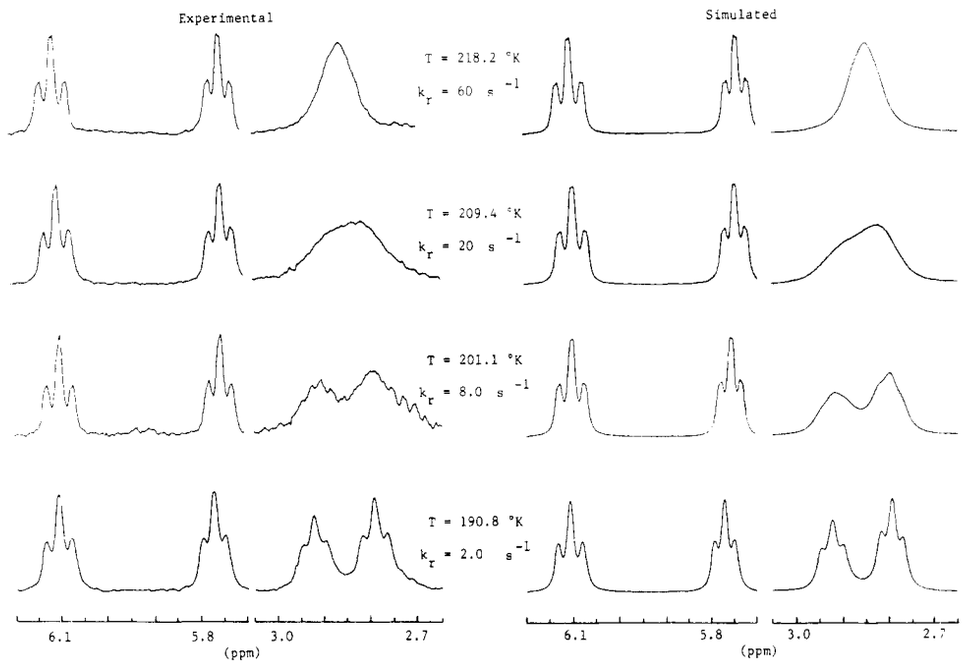


Figure 2. Experimental (left) and simulated (right) $AMX_2 \rightleftarrows AMX'_2$ DNMR spectra of **4a** ⇌ **5a.** Samples were prepared as 0.024 M solutions in acetone-d_6 with Me_4Si as an internal standard.

values obtained at higher temperatures are consistent with those obtained at low temperatures, if one assumes a value of −1.4 eu to be representative for $\Delta S°$. This value is not unreasonable when compared to published values obtained for the entropy change favoring, for example, the less associated OH group in the axial conformer of 3,3,5-trimethylcyclohexanol in strongly associating solvents.[12a] It has also been shown that aprotic, polar solvents can strongly influence the position of an equilibrium when there exists a possible preferential solvation effect for one of the isomers.[12b] Such a preference is likely here and may contribute to the observed thermodynamic values.

In this regard, it should be noted that the ^1H NMR spectrum of the 7,7-dimethyl analogue **4c** ⇌ **5c,** showed an unusual solvent dependence. Chemical shift difference between the spectrum in CCl_4 compared to that in acetone-d_6 for protons on the two C(7) methyl groups was −9 Hz (upfield relative to the shift in CCl_4) for protons on one methyl group and 0.0 Hz for the proton on the other methyl group. Also, H(4) protons appeared as a pseudo triplet in CCl_4, but in acetone-d_6 these signals were shifted +18 Hz *downfield* and were changed to the expected two doublets. It appeared that the more polar acetone solvated **4c** ⇌ **5c** with a preferred solvent orientation around the polar part of the lactone ring. Moreover, the solvation sphere must be of such nature to involve nonsymmetrical shielding of the methyl protons at C(7). In addition, the dissimilar solvent shifts of the H(7) methyl protons, coupled with the appearance of the two doublets for the H(4) protons, strongly suggested that the solvation was dissymmetric with respect to the planes of both the five-membered and the six-membered rings.

Kinetic Evaluation of the Ring Reversal Process. To investigate the kinetics of the ring reversal, a study of the NMR spectra of the mobile system **4a** ⇌ **5a** was undertaken using complete line-shape analysis (LSA).[9] The system was particularly suited to this type of evaluation because of the spiro ring junction which effectively isolates the five-membered ring of the lactone from the six-membered ring. This reduces the spectral pattern of the protons in the lactone ring to a first-order AMX_2 pattern which can be simulated by a DNMR3[15] program. Because of the extensive H–H coupling in the spectrum, as well as the need to evaluate the rate constant over a range of temperatures, the approximate equations[16] which were derived from line-shape theory were not deemed feasible.

Table V. Activation Parameters Calculated from Line Shape Analysis[a]

T, K	k_r (by LSA)	ΔG^*, kcal/mol
218.2	60 ± 5	10.9 ± 0.11
209.4	20 ± 2	10.9 ± 0.11
201.1	8 ± 1	10.9 ± 0.13
190.8	2 ± 0.2	10.7 ± 0.10
	$\Delta H^* = +9.60 \pm 1.3$ kcal/mol[b]	
	$\Delta S^* = -5.9 \pm 6.3$ eu[b]	

[a] Samples were prepared as 0.024 M solutions in acetone-d_6 with Me_4Si as an internal standard. [b] ΔH^* and ΔS^* were calculated from a least-squares fit of ln (k_r/T) vs. $1/T$, $r^2 = 0.998$.

The chemical shifts and coupling constants used in the analysis were determined at low temperatures by direct measurement and were extrapolated to higher temperatures assuming a linear relationship. Values for the transverse relaxation time (T_2) were estimated by measuring the width at half-height of the Me_4Si internal standard. Visual comparison of the simulated spectra with the experimental spectra was used to assess the closeness of the fit. Estimations of the deviations in the rate constant were also done in this fashion. The results of the simulations are shown in Figure 2, and the calculated activation parameters are tabulated in Table V.

Sidebands resulting from a large solvent peak (upfield) are noticeable in the experimental spectrum obtained at 201 K, as shown in Figure 2. Repeated attempts to remove this interference failed at this temperature. However, this problem was minor or did not exist at the other temperatures used in the investigation.

It is interesting that values from the literature[17a,b] for ΔG^* in simple and 1,1-disubstituted cyclohexyl systems are in close agreement with our values for the various temperatures investigated. A comparison of published ΔS^* and ΔH^* for the simple systems with those found for **4a** ⇌ **5a** is difficult, since there appear to be large discrepancies for the magnitudes of

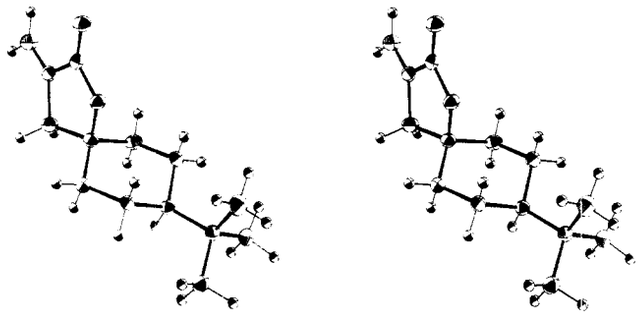


Figure 3. A stereoview of a single molecule of **4b**.[26]

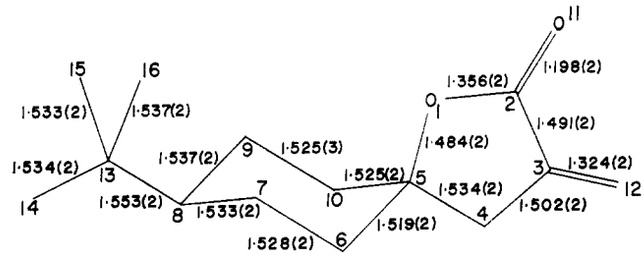


Figure 4. Bond distances and numbering scheme for **4b**. Estimated standard deviations are given in parentheses.

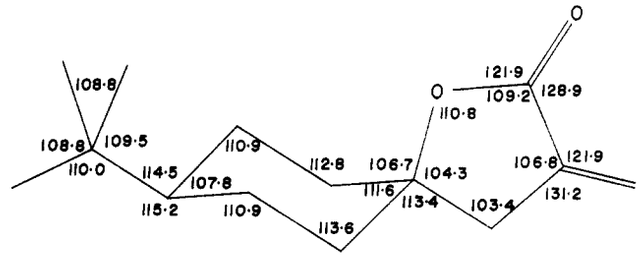


Figure 5. Bond angles for **4b**. The standard deviations are between 0.11 and 0.16°. Additional bond angles are O(1)–C(5)–C(6) = 107.2°, C(4)–C(5)–C(10) = 113.0°, C(8)–C(13)–C(15) = 112.0°, and C(14)–C(13)–C(16) = 107.6°.

these parameters even in simple systems. For example, values for ΔS^* ranging from +4.9 to −5.8 eu have been reported for cyclohexane itself.[17] In this regard, it is known that errors in ΔH^* and ΔS^* are coupled (due to the methods used to calculate them) so that high ΔH^* values correspond to low ΔS^* values and vice versa.[9] While it has been suggested that extension of the temperature range would reduce the error in ΔH^* and ΔS^*, the spectra must remain reasonably sensitive to changes in the rate constant at the extremes of this range.[9] We did not detect any significant change in the spectrum for our system above 235 K (−38 °C).

It will be discussed later that the five-membered lactone ring is puckered in the solid state. Indeed, even though the molecule **4b** does not possess an asymmetric carbon, it crystallizes in the noncentrosymmetric space group $P2_12_12_1$ due to selective crystallization of one of the puckered forms. Although the mirror image of this form would be expected to be of equal energy, the space requirements of a disordered lactone would be too great to allow both conformers of the puckered ring to exist together in a disordered crystal structure.

In solution, the barrier to interconversion of the five-membered ring between two conformers must be very small. One can see from the NMR data in Table I for the 7,7-dimethyl analogue **4c** ⇄ **5c** that this interconversion can be biased indirectly by destroying the symmetry of the system because of increased 1,3 interactions experienced by the five-membered ring, which results in nonequivalence of the H(4) protons. This symmetry of interaction is restored in the 7,7,9,9-tetramethyl-substituted analogue **4d** ⇄ **5d**, resulting in the familiar AMX_2 spin pattern for lactone ring protons. This interconversion (or "breathing motion") of the five-membered ring must occur in solution simultaneously with the six-membered reversal process. Although not strictly analogous, the barrier for interconversion of conformers in cyclopentanone has been determined to be between 2.1 and 3.7 kcal mol^{-1}.[18] This corresponds to a rate of reversal (assuming small ΔS^*) at 190 K of 2.2×10^8 to 1.5×10^{10} s^{-1}. Thus, it would seem to be much too rapid to be detectable via NMR methods. However, if the NMR spectrum is sensitive to changes induced by this process, the possibility of the breathing motion affecting the magnetic field around certain nuclei in the spectrum cannot be eliminated and may be a source of error, especially at the lower temperatures. However, this process would not be expected to interfere with evaluation of the thermodynamic parameters, assuming that this motion in the five-membered ring does not impart any dissymmetric operation preferentially on either of the six-membered conformers.

Single-Crystal Analysis of 4b. A stereoview of a single molecule of **4b** is shown in Figure 3, the numbering scheme and bond distances are shown in Figure 4, and bond angles are shown in Figure 5. The structure consists of a six-membered ring in the chair conformation, a spiro-fused α,β-unsaturated γ-lactone, and an anchoring *tert*-butyl group. The chair conformation of the six-membered ring is significantly flattened near the spiro carbon atom, as can be seen from the torsion angles reported in Table IV. This is most likely due to a 1,3,5 interaction involving the axial O atom attached to the spiro carbon atom, since all other axial positions are occupied by H atoms. The lactone ring is in a flattened twist (C_2) conformation as can be seen from the values of the internal torsion angles in Table IV. The approximate twofold axis passes through atom C(2) and bisects the C(4)–C(5) bond. The α,β-unsaturated γ-lactones in a group of natural products[19–24] show a wide range of conformations for the five-membered ring. Both the envelope (C_s) and twist (C_2) conformations are observed with varying degrees of flatness. The factors affecting the conformation in the present compound may include an attempt to minimize contacts with O(1) and the axial hydrogen atom or atoms C(7) and C(9) and at the same time minimize contacts between the hydrogen atoms on atom C(4) and the axial hydrogen atoms of atoms C(6) and C(10). In addition, crystal packing forces may also affect the conformation. It is interesting to point out that, since many compounds possessing an α,β-unsaturated γ-lactone show biological activity which is attributed to this functional group, a structure–activity relationship might exist which involves the conformation of the lactone ring. At this time, however, sufficient data is not available to test this hypothesis. The *tert*-butyl group which anchors the conformation by occupying the equatorial position on C(8) is staggered with respect to its attachment to the ring. The values of two representative torsion angles are C(7)–C(8)–C(13)–C(16) = 174.8° and C(9)–C(8)–C(13)–C(14) = 182.6°. One of the primary reasons for using X-ray diffraction to determine this structure was to ascertain whether the O atom or $>CH_2$ group occupies the axial position of the spiro C atom. All data including electron densities, bond lengths, least-squares refinement, and location of H atoms show conclusively that the O atom occupies the axial position with no evidence for a disordered structure.

The bond lengths in the lactone compare well with the values reported for several natural products.[19–24] The weighted averages compiled from the literature are O(1)–C(2) = 1.356, C(2)–C(3) = 1.486, C(3)–C(4) = 1.506, C(4)–C(5) = 1.542, C(5)–O(1) = 1.461, C(2)–O(11) = 1.205, and C(3)–C(12)

= 1.324 Å. The largest difference (0.023 Å) is for the C(5)–O(1) distance; all other differences are <0.01 Å. The C(8)–C(13) bond length is slightly lengthened, which is not unexpected for a bond to a bulky substituent. Inspection of bond angles indicates that the surroundings of atoms C(2) and C(3) are planar having the sum of bond angles equal to 360.0 and 359.9°, respectively. The bond angles in the lactone ring show the same trends as those observed for the natural products.

The molecule could contain a mirror plane passing through atoms C(5), C(8), C(13) and the midpoints between C(7)–C(9) and C(6)–C(10). However, if one calculates a least-squares plane through these points one finds that the entire lactone group is significantly out of the plane. The distances from this plane are as follows: O(1), 0.019; C(2), 0.477; C(3), 0.601; C(4), 0.010; C(5), 0.003; O(11), 0.711; and C(12), 1.146 Å. One could also construct a stereoisomer of the molecule in the present structure by taking the mirror image through the least-squares plane, thus flipping the lactone group to the opposite side. This molecule would have exactly the same energy and most likely occurs in both solution and the solid state. Although one enantiomer is selectively crystallized in the present structure, no attempt was made to determine which conformer, although the question could be resolved using the anomalous scattering of the oxygen atoms.[25] It is not possible for both conformers to exist in a disordered crystal structure because the space requirements of a disordered lactone would be too great. Experimentally no evidence for disorder was found, as the refinement of thermal parameters for all C, O, and H atoms of the lactone group was normal and no residual electron density was found in this area of the final difference Fourier map. A calculation of intermolecular distances revealed an unusually short contact between O(11) and H(12A) of 2.41 Å [H(12)] transformed by $(x,y,z-1)$, which is about 0.2 Å shorter than the sum of the van der Waal radii.

Conclusions

The thermodynamic parameters found in this study show a slight predominance of conformer **4a** (C–O bond axial), which suggests that the steric requirements for the methylene group are greater than those for the endocyclic axial C–O bond in 3-methylene-1-oxaspiro[4.5]decan-2-one. It should be noted that, while it is these groups which directly occupy the axial–equatorial positions on the six-membered ring, the substituents on the adjacent carbons may also play an important role in directing the equilibrium, especially in regard to their ability to interact with the solvent. A study involving determination of $\Delta G°$ at one temperature for a series of substituted spirodioxolanes[14] has indicated that these types of interactions can markedly influence the equilibrium process so that predictions of values for the thermodynamic parameters, based on analogous systems in which substituents in the five-membered ring are different, must be done with care.

Interestingly, the ΔG^* values (10.9 kcal/mol) determined for **4a** ⇌ **5a** are similar to those reported for several 1,1-disubstituted cyclohexanes (e.g., 1,1-dimethoxycyclohexane, $\Delta G^* = 10.8$ kcal/mol).[17] Comparison with the values of ΔG^* determined for cyclohexane (10.5 kcal/mol)[17b] suggests that the spiro substitution actually stabilizes the ground-state conformers relative to the transition state by a modest amount. Additional substitution on the six-membered ring, which might increase the energy of the two conformers relative to the transition state via steric 1,3-interactions, might be expected to lower the ring reversal energy barrier. Studies of 1,1,3,3-tetra- and 1,1,3,3,5,5-hexasubstituted cyclohexanes support this conclusion.[17a] Hence it is not surprising that the coalescence phenomenon is not observed for either **4c** ⇌ **5c** or **4d** ⇌ **5d** for temperatures as low as 177 K (−96 °C).

The X-ray analysis conclusively identified *cis*-8-*tert*-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one as structure **4b**. Several novel features of this molecule were notable. The significant flattening of the six-membered ring of the spiro end implied that a distinct interaction exists between the axial oxygen and the axial H atoms on carbons 7 and 9. It was also evident from the X-ray analysis that two forms of the twisted lactone ring could exist, and that these forms probably would rapidly interconvert in solution.

Experimental Section

General. Cyclohexanone and 4-*tert*-butylcyclohexanone were obtained commercially and purified by vacuum distillation. The solvent tetrahydrofuran was dried over NaH and then distilled from $LiAlH_4$. The IR spectra were recorded on a Beckman IR-5A spectrometer. Melting and boiling points were not corrected.

Preparation of Ethyl α-Bromomethylacrylate (1). Ester 1 was synthesized by the procedure of Ferris:[27] bp 56 °C (2.0 mm); reported bp 44–45 °C (1.7 mm).

General Procedure for Synthesis of the α-Methylene Spiro Lactones from the Ketones. A solution of 5.3 g (0.0275 mol) of ester 1 in 15 mL of dry THF was added slowly with stirring to a suspension of 1.7 g (0.027 g-atom) of Zn (20 mesh) in 0.025 mol of the appropriate ketone in 8 mL of dry THF (under N_2). The temperature was allowed to rise during the addition to 45 °C and was maintained at 50 °C for an additional 2 h. After cooling to room temperature, the reaction mixture was poured directly into 200 mL of ice-cold 5% H_2SO_4 with stirring. Stirring was continued for 0.5 h, the product separating either as an oil or as a crystalline solid. This product was taken up with ether and dried ($MgSO_4$). Data for the lactones are in Table I.

Purification of 3-Methylene-1-oxaspiro[4.5]decan-2-one (4a ⇌ 5a).[5a,b] The product resulting from the above reaction using cyclohexanone as the general ketone was isolated from the ether solution as an oil. The oil was dissolved in 50 mL of commercial hexanes (bp 67–71 °C) and filtered. The resulting solution was chilled slowly to −78 °C. A crystalline product formed and was filtered at −78 °C using a jacketed funnel. Vacuum drying of the crystals at room temperature (20 °C) gave 5.2 g of **4a** ⇌ **5a** (86%): mp 26–27.5 °C; bp 76–77 °C (0.05 mm).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.05; H, 8.29.

Isolation and Purification of *cis*- and *trans*-8-*tert*-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (4b, 5b). The product of the reaction as described above using 4-*tert*-butylcyclohexanone was isolated as a crystalline mixture of cis and trans isomers from the ether solution. NMR analysis (in CCl_4) of the product (mp 63–71 °C) revealed a ratio of 4:1 for **4b/5b**. Careful fractional crystallization (CH_3OH) initially afforded colorless crystals, mp 83–84 °C, in which the trans isomer **5b** was no longer detectable via NMR analysis. Subsequent fractions showed evidence of both isomers. These latter fractions of isomers were chromatographed on a column of Florisil (Research Specialties Co.) in a ratio of 30:1 adsorbant/substrate, using 150 mL of hexane, followed by 100 mL of 50:50 benzene/hexane and then 100 mL of benzene. Those fractions containing the trans isomer **5b** identified via NMR analysis were combined and rechromatographed as described above. The trans isomer **5b** (50 mg) was isolated from the benzene fractions, mp 84–85 °C. The total yield was 3.6 g (65%), composed of 2.65 g (48%) of cis isomer **4b** and 50 mg (1.0%) of *trans*-**5b** along with 0.91 g (16.4%) of a mixture of the two. Analysis of the two separate isomers gave the following results.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.73; H, 10.00 (cis); C, 75.48; H, 9.88 (trans).

Synthesis of 7,7-Dimethyl-3-methylene-1-oxaspiro[4.5]-decan-2-one (4c ⇌ 5c). 5,5-Dimethyl-2-cyclohexenone was prepared by the method of Frank and Hall.[28] This ketone (31.7 g) was reduced over a 12-h period by the action of H_2 (1 atm) using Pd–C (10%) with $CH_3CO_2C_2H_5$ as the solvent. Distillation afforded 18.9 g (60%) of 3,3-dimethylcyclohexanone: bp 181 °C (762 mm); reported bp 174–175 °C (757 mm).[29]

This saturated ketone was allowed to react with 1 in the general procedure described previously. The product was isolated as an oil from the ether extract and crystallized upon standing under refrigeration. Recrystallization from commercial hexanes (bp 67–71 °C) afforded 3.64 g of **4c** (or **5c**) (75%): mp 38.5–39.5 °C; bp 100–102 °C (0.25 mm).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.51; H, 9.28.

Purification of 7,7,9,9-Tetramethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (4d ⇌ 5d). The product of 3,3,5,5-tetramethylcyclohexanone participating in a reaction as described above was isolated as a crystalline material from the ether extract. Recrys-

tallization of the solid (hexanes) afforded 4.06 g of **4d** (or **5d**) (73%): mp 101.5–103 °C.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.86; H, 9.98.

DNMR Spectroscopic Studies. The NMR spectra were recorded on a Varian XL-100 (15) NMR spectrometer equipped with a TT-100 PFT accessory, operating at 100.1 MHz with $(CH_3)_4Si$ as an internal reference. All controlled temperature spectra were recorded in acetone-d_6 in the FT mode, with the solvent providing the necessary deuterium lock. A pulse width of 5.7 s was used with a 6-s delay between pulses. Temperature control was provided by a Varian temperature controller. A capillary of CH_3OH with a trace of HCl present was placed in a 5-mm NMR tube containing 0.5 mL of acetone-d_6 and was used to calibrate the temperature according to the method of Van Geet.[30] Calibrations were done before and after each spectrum, and those spectra whose temperature calibrations differed by more than 1 °C were discarded and the shifts were reexamined at that temperature. Integrations were done electronically on the TT-100 computer and cross-checked using hand planimetry on the plotted spectra.

X-ray Analysis and Structure Refinement. Crystals suitable for X-ray intensity measurement were obtained by cooling a solution prepared by dissolving a small amount of **4b** in hot methanol. Initial diffraction experiments showed the crystals to be orthorhombic. The crystal data are: $C_{14}H_{22}O_2$; M_r = 222.32; space group $P2_12_12_1$; a = 11.455 (2), b = 18.356 (2), c = 6.100 (1) Å; V = 1282.6 Å^3 (at −135 °C); Z = 4; $F(000)$ = 488; Ni filtered Cu Kα radiation, λ (Cu Kα_1) = 1.54051 Å for determination of cell constants and λ(Cu K$\bar{\alpha}$) = 1.54178 Å for intensity data. The unit cell parameters were determined by least-squares fit to the $+2\theta$ and -2θ values of 44 reflections distributed throughout all regions of reciprocal space.

A total of 1551 intensities representing all unique reflections with $2\theta \leq 150$ were measured using a Nonius CAD-4 automatic diffractometer and θ–2θ scan techniques. The intensities were corrected for Lorentz and polarization effects and structure factor magnitudes derived. In the data analysis, an experimental weight, based on counting statistics, was assigned to each structure factor.[31] The structure was solved using direct methods and the computer program MULTAN.[32] All structure refinement was performed using the block-diagonal least-square program of Ahmed[33] and all Fourier maps were calculated using Ahmed's Fourier transform program.[34] The refinement of the model using anisotropic thermal parameters for C and O atoms and isotropic thermal parameters for H atoms was terminated when all shifts were small fractions of the corresponding estimated standard deviation. The R value based on the final parameter was 3.8%. While the standard error in the observation of unit weight was 1.18 e, a final difference Fourier map contained no peaks >0.16 e Å^{-3}. Scattering factors for C and O atoms were taken from the "International Tables for X-ray Crystallography"[35] and those for H atoms were from Stewart, Davidson, and Simpson.[36] The final structure factor analysis showed that $\Sigma w \Delta F^2$ did not vary with either $\sin^2\theta$ or $|F_o|$, thus validating the weighting scheme used.[37]

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Registry No.—**1,** 17435-72-2; **4a,** 52978-85-5; **4b,** 67464-47-5; **4c,** 67464-48-6; **4d,** 67464-49-7; **5b,** 67464-50-0; cyclohexanone, 108-94-1; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3-dimethylcyclohexanone, 2979-19-3; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5.

Supplementary Material Available: Listing of positional and anisotropic thermal parameters for C and O atoms (Table VI) and H atoms (Table VII) of **4b** (2 pages). Ordering information can be found on any current masthead page.

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