A DNMR STUDY OF THE RING REVERSAL PROCESS IN 9-METHYLENE-7-OXA-1-THIASPIRO[4.5] DECAN-8-ONE DERIVATIVES

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Synthesis and physical and spectral characteristics of 9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-ones are reported. Investigation of the thermodynamic and kinetic parameters for ring reversal in 9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-one-*3,3,5,5-d*$_4$ by DNMR is described. The barrier height for ring reversal is estimated to be about 7-8.5 kcal/mol.

INTRODUCTION

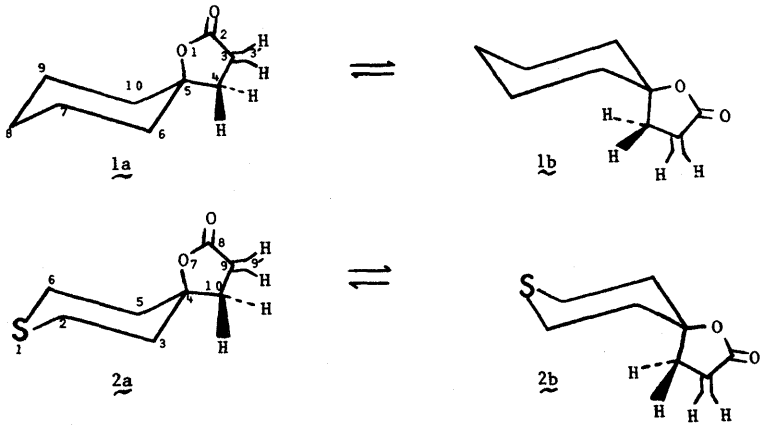
Presented herein are the results of a variable temperature study of 9-methylene-7-oxa-1-thiaspiro[4.5] decan-8-one and derivatives. It is known (1) that many systems containing the α-methylene-γ-butyrolactone unit have potential antitumor activity. This fact and the results of a recent investigation carried out in this laboratory (2) on the dynamic properties of the system $\underset{\sim}{1a} \rightleftharpoons \underset{\sim}{1b}$ prompted us to undertake an investigation of the thermodynamic and kinetic characteristics of the heteraspiro-α-methylene-γ-butyrolactone system $\underset{\sim}{2a} \rightleftharpoons \underset{\sim}{2b}$. Although ring reversal was known to be rapid in many 1-hetera-4-cyclohexanones (3), the original reasoning for the $\underset{\sim}{2a}$ system supposed the spiro system might have a preferred configuration at C-4 because of the long-range polar influence of the hetero atom.

MATERIALS

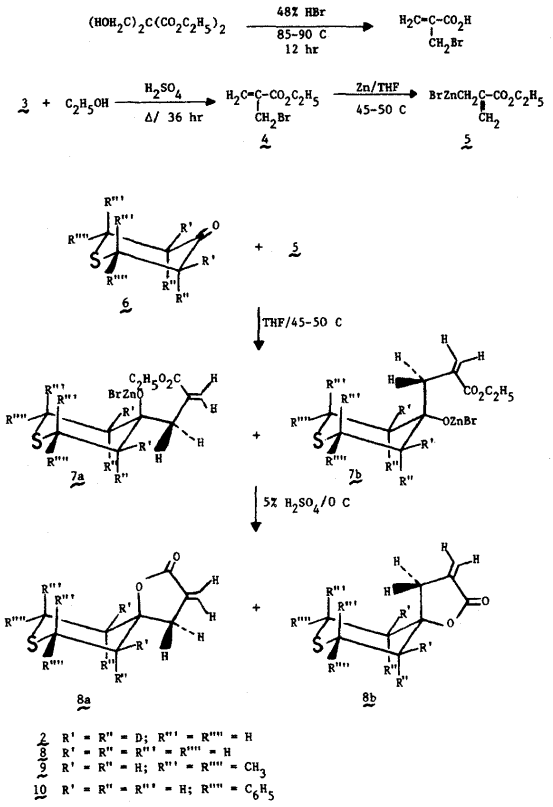
The three spirolactones used in this study were:
9-methylene-7-oxa-1-thiaspiro-[4.5]decan-8-one-*3,3,5,5-d*$_4$ ($\underset{\sim}{2a} \rightleftharpoons \underset{\sim}{2b}$);

2,2,6,6-tetramethyl-9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-one ($\underset{\sim}{9a} \rightleftharpoons \underset{\sim}{9b}$); and

2,6-*cis*-diphenyl-9-methylene-7-oxa-1-thiaspiro–[4.5]decan-8-one ($\underset{\sim}{10a} \rightleftharpoons \underset{\sim}{10b}$). All compounds were synthesized by a Reformatsky type reaction. The appropriate thianone was allowed to react with activated zinc and ethyl α-(bromomethyl)acrylate. Since the usual method of carrying out this reaction, namely, addition of ethyl α-(bromomethyl)acrylate (in THF) to a mixture of zinc and thianone (in THF), resulted in the formation of sulfonium salts, the following modified procedure was adopted. Separate solutions of ethyl α-(bromomethyl)acrylate and the appropriate thianone were first prepared by dissolving 0.01 mole of each reagent in 10 m*l* of dry THF. Ten m*l* each of these two solutions were then placed in two separate pressure-equalizing, addition funnels. Twenty-five drops of the solution of ethyl α-(bromomethyl)acrylate were first added to activated zinc (0.011 g-at) in a 3-necked, 100-m*l* round-bottom flask kept at 45-50 C in an atmosphere of nitrogen. After 3 min, during which time the



Reformatsky reagent formed, twenty-five drops of the thianone solution were added. This was followed by the addition, after 3 min, of twenty-five drops of the solution of ethyl α-(bromomethyl)acrylate. After these alternate additions were completed (ca. 2 hr), the reaction mixture was kept at 45-50 C for a period of 3 hr. The reaction mixture was then added to ice-cold, 5% sulfuric acid (100 m*l*). This usually yielded an oily product. Extraction with ether (75 m*l*), drying the ether extract (anhydrous Na_2SO_4), and evaporation of the ether (on a rotary evaporator), resulted in the formation of crystalline products which were recrystallized from suitable solvents. The physical and spectral characteristics of the compounds are given in Table 1. Although there is a published procedure (4) for preparing ethyl α-(bromomethyl)acrylate, it was possible to improve the yield of the ester while eliminating a step. Instead of isolating β,β'-dibromoisobutyric acid, as reported by the original workers (4), it was possible to obtain, in one step, the unsaturated acid, α-(bromomethyl)-acrylic acid (3). The formation of compounds with phenyl groups in the axial positions is deemed untenable from a steric point of view.



2 R' = R'' = D; R''' = R'''' = H
8 R' = R'' = R''' = R'''' = H
9 R' = R'' = H; R''' = R'''' = CH_3
10 R' = R'' = R''' = H; R'''' = C_6H_5

TABLE 1. *Physical and spectral characteristics*

Cpd[a]	mp°C	^{1}H NMR Data[b]	^{13}C NMR Data[c]	IR(cm^{-1})[d]	Mass Spec *m/e*	%	Analysis Calcd. (%)	Found (%)
	94-96	2.61 [m, CH_2, 2H]	169 [c(8)]	ν_{C-O}1748	188(M)	100		
2a		5.51 [m, -C-H_2, 1H]	134.4 [c(9)]	ν_{C-C}1653	189(M+1)	12.5		
(or 2b)		6.14 [m, -C-H_2, 1H]	122.9 [c(9')]		190(M+2)	6.9		
			40.4 [c(10)]					
	94-95	2.68 [m, CH_2, 2H]	169 [c(8)]	ν_{C-O}1748	184(M)	100	C, 58.65	C, 58.59
8a		5.54 [m, -C-H_2, 1H]	134.4 [c(9)]	ν_{C-C}1653	185(M+1)	10.8	H, 6.58	H, 6.63
(or 8b)		6.16 [m, -C-H_2, 1H]	122.9 [c(9')]		186(M+2)	5.2	S, 17.41	S, 17.45
			40.6 [c(10)]					
	109-111	2.72 [m, CH_2, 2H]	169.1 [c(8)]	ν_{C-O}1754	240(M)	100	C, 64.95	C, 64.88
9a		5.64 [m, -C-H_2, 1H]	134.1 [c(9)]	ν_{C-C}1656	241(M+1)	18.4	H, 8.39	H, 8.41
(or 9b)		6.26 [m, -C-H_2, 1H]	122.2 [c(9')]		242(M+2)	6.6	S, 13.34	S, 13.27
			43.2 [c(10)]					
	148.5-150	2.84 [m, CH_2, 2H]	168.9 [c(8)]	ν_{C-O}1754	336(M)	100	C, 75.00	C, 75.08
10a		5.68 [m, -C-H_2, 1H]	133.9 [c(9)]	ν_{C-C}1664	337(M+1)	20.5	H, 5.95	H. 6.03
(or 10b)		6.30 [m, -C-H_2, 1H]	123.3 [c(9')]		338(M+2)	7.3	S, 9.54	S, 9.72
			41.5 [c(10)]					

[a] Compounds 2 and 8 were recrystallized from CH_3OH, compound 9 from 1:1 CH_3OH and petroleum ether, and compound 10 from 1:1 CH_3OH and petroleum ether containing a little benzene.
[b] Ppm from TMS in $DCCl_3$. Peak positions in the lactone ring alone are given. The center of the multiplet is taken as the peak position.
[c] Ppm from TMS in $DCCl_3$.
[d] Spectra recorded on a KBr pellet.

METHOD

Consider the ring reversal process in the equilibrium, $\underset{\sim}{2a} \rightleftharpoons \underset{\sim}{2b}$. At temperatures sufficiently below the coalescence temperature, the ring reversal process is slow enough to permit NMR examination of the two conformers separately (5, 6). Since the environments of the H-10 protons differ in the two conformers, the chemical shifts are expected to be different. The areas under the respective peaks should be a measure of the relative concentration of $\underset{\sim}{2a}$ and $\underset{\sim}{2b}$ (5). The equilibrium constant can be calculated by:

$$K_{eq} = [\underset{\sim}{2b}]/[\underset{\sim}{2a}]$$

K_{eq} = the equilibrium constant for the reversal process. Measurement of chemical shift differences between protons of methanol and the use of an empirical equation relating chemical shift differences to temperature (7) permitted the accurate determination of various temperatures at which the spectra were recorded. For temperatures sufficiently above the coalescence temperature, the chemical shift method could be applied to calculate K_{eq} (8). Unfortunately, the chemical shifts for the pure axial and equatorial protons were not obtainable at ambient temperatures in system $\underset{\sim}{2a}$; model compounds that were conformationally biased should be used to obtain specific proton chemical shifts (8). In our case, it was reasoned that 2,6-*cis*-diphenyl-9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-ones ($\underset{\sim}{10a} \rightleftharpoons \underset{\sim}{10b}$) could serve as models, by assuming that the phenyl groups were equatorially positioned and would have no appreciable effect on the chemical shift of H-10 protons. However, the Reformatsky reaction of *cis*-2,6-diphenylthian-4-one gave only one isolable isomer of unknown configuration at C-4. Hence use of the chemical shift method could not be justified to study $\underset{\sim}{2}$.

RESULTS

Cooling the solution of 2,2,6,6-tetramethyl-9-methylene-7-oxa-1-thiaspiro[4.5]-decan-8-one ($\underset{\sim}{9a} \rightleftharpoons \underset{\sim}{9b}$) in acetone-$d_6$ to as low as –100 C did *not* result in separation of the signal from H-10 protons. This implied that the ring reversal was still sufficiently rapid to give only one time-averaged signal for these protons. Since the solution freezes below this temperature, no further experiments were attempted. It was considered that the presence of four methyl groups in $\underset{\sim}{9a}$ or $\underset{\sim}{9b}$ would strain the system, and, to relieve the strain, the six-membered ring could flatten. This would have the effect of lowering the energy barrier for ring reversal allowing a fast equilibration even at –100 C. Consequently 9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-one-*3,3,5,5*-d_4 was examined in acetone-d_6 but again no splitting of the H-10 proton signals occurred down to –100 C. Hence, a 1:1 mixture of Freon-21 and acetone-d_6 was tried as the solvent system. Unfortunately no splitting was observed for H-10 protons even down to –110 C.

DISCUSSION

Results of a previous investigation (2) carried out in this laboratory for the system $\underset{\sim}{1}$ gave the following kinetic parameters; $\Delta G^* = 10.9$ kcal/mol and $T_c = -64$ C. Comparison of published ΔG^* and T_c values obtained for cyclohexane (8), piperidine (9,10), oxane (11), thiane (11), selenane (12), and tellurane (12,13) show that as a ring carbon was replaced successively by an element of greater electronegativity from the same period of the periodic table, the barrier height to ring reversal *decreased.* Also replacement of a heteroatom by another heteroatom below it in the same group of the periodic table lowers the barrier height.

TABLE 2. *Calculated ΔG^* values from variations of $\Delta\nu$ and T_c.*

ΔG^* (kcal/mol)	$\Delta\nu$ (Hz)	T_c (°C)
8.6	5	−110
8.3	10	−110
8.2	15	−110
8.0	5	−120
7.7	10	−120
7.7	15	−120
7.5	5	−130
7.3	10	−130
7.2	15	−130

Assuming the separation between the axial and equatorial H-10 proton signals at temperatures well below the coalescence temperature to be between 5 to 15 Hz [which seems reasonable from the results of the system $\underset{\sim}{1}$ (2)] and using the equation $\Delta G^* = 4.58\ T_c\ [9.97 + \log T_c/\Delta\nu]$ cal. mol^{-1} (5), the free energy of activation for $\underset{\sim}{2a} \rightleftharpoons \underset{\sim}{2b}$ can be calculated. Results from three different coalescence temperatures are shown in Table 2. The signal due to H-10 protons *did* begin to broaden

at –110 C but did not split into two separate signals. It is concluded that T_c is probably not much below –110 C. The calculated ΔG^* values in Table 2 show that T_c is the major contributor to barrier height. In contrast, even a threefold increase in $\Delta\nu$ does not change the value of ΔG^* by more than 3% from the average. In summary, we conclude that the ΔG^* value for $\underset{\sim}{2}a \rightleftharpoons \underset{\sim}{2}b$ lies somewhere between 7-8.5 kcal/mol. Apparently ring flattening is extensive and preference for either conformer is small.

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