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Conformational Study of Oxacyclooctan-2-one by Dynamic NMR Spectroscopy and Computational Methods

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The slow-exchange ^{13}C NMR spectrum of the eight-membered lactone, oxacyclooctan-2-one (**1**), at −154.2 °C shows the presence of two conformations with populations of 25.6 and 74.4%. Free-energy barriers of 6.98 and 7.23 kcal/mol were determined at the coalescence temperature for the carbonyl carbon peak (−128.6 °C). The ^{1}H NMR spectrum of the CH_2O protons splits into two multiplets of equal intensity by −100 °C, and the corresponding free-energy barrier of 9.16 kcal/mol at −85.2 °C was suggested to be associated with exchange of the geminal protons. Relative free energies and populations at +25 and −160 °C were estimated by using Allinger's MM3 program, and free energies and dipole moments were obtained for three conformations using ab initio calculations at the HF/6-311G* and MP2/6-311G* levels. The spectra were interpreted in terms of two conformations having the *E* configuration of the lactone group and resembling the boat-chair conformation of cyclooctane.

Introduction

Acyclic esters generally have a strong preference for the *Z* configuration,[1] but lactones of sufficiently small ring size adopt the *E* configuration. The dipole moment of oxacycloheptan-2-one in benzene (4.45 D)[2] showed the compound to have the *E* configuration, and the low-temperature ^{19}F NMR spectra of a difluoro derivative of this lactone were interpreted[3] in terms of a chair conformation, with a free-energy barrier of 10.0 kcal/mol for ring inversion. Dipole moments for oxacyclooctan-2-one (**1**) (3.70 D)[2] and oxacyclononan-2-one (2.25 D)[2] in benzene were interpreted in terms of a predominant *E* configuration for **1**, with possibly a small amount of the *Z* configuration, and the reverse for the nine-membered lactone. The electronic absorption spectra of a series of esters and lactones in isooctane were also interpreted[4] in terms of a change in configuration from *E* to *Z* on going from the eight-membered to nine-membered lactone. Conformational assignments have been made in the present work using low-temperature NMR spectroscopy and molecular mechanics calculations for estimation of free energies at the temperatures of interest, with the dipole-moment study of Huisgen and Ott[2] also taken into consideration. MM3 strain energies and free energies for **1** at other temperatures have previously been reported by Saunders.[5] A number of naturally occurring eight-membered ring lactones have been discovered,[6] and the ring conformations of the parent compound may be found in some of these natural products.

Experimental and Methods

Baeyer−Villager oxidation[7,8] of cycloheptanone with a mixture of pertrifluoroacetic acid and Na_2HPO_4 was used to prepare oxacyclooctan-2-one. Cycloheptanone was purchased from Aldrich Chemical Co., and 70% H_2O_2 for preparation of pertrifluoroacetic acid was purchased from FMC Corporation.

The lactone was purified by distillation under reduced pressure, followed by preparative gas chromatography at 108 °C using a $^{1}/_{4}$ in. × 4 ft column containing 20% DC 200 on 80/100 chromosorb P. The structure and purity of the lactone were established by the room-temperature ^{13}C and ^{1}H NMR spectra.

A 5% solution of the lactone in a 3:1 mixture of $CHClF_2$ and $CHCl_2F$ was prepared in a 5 mm thin-walled NMR tube, and the sample temperature was maintained below 0 °C most of the time. *Caution*: pressure. A small amount of TMS was added to provide an internal reference for the spectra, which were recorded on a General Electric Model GN-300 wide-bore NMR spectrometer, operating at a frequency of 75.57 MHz for carbons and 300.52 MHz for protons. Spectra were taken with a 5 mm dual probe, and spinning was discontinued below about −120 °C. Sweep widths were ±12500 and ±3200 Hz for carbon and proton spectra, respectively, and the block size and the tip angle were 64 K and 45°. For the carbon spectra, the delay times between pulses were 12.0 s at + 17.6 °C, 8.0 s at −154.2 °C, and 1 s at intermediate temperatures. A delay time of 1 s was used for the ^{1}H spectra. The signal-to-noise ratios of the ^{13}C spectra were enhanced by exponential multiplication of the FID, resulting in an increase of 3 Hz in the line width. The ^{13}C NMR spectrum of **1** was also taken at −154.5 °C for a 2% solution of the lactone in 1:1 acetone-d_6/acetaldehyde; a delay time of 10 s and tip angle of 90° were used.

Because of the difficulty in ejecting the sample at lower temperatures, the temperature calibration was performed separately, using a copper−constantan thermocouple immersed in the same solvents contained in a nonspinning dummy sample tube and under conditions as nearly identical as possible. The emf's were measured using a Leeds-Northrup

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10.1021/jo981117x CCC: $18.00

Model 8690-2 millivolt potentiometer. The uncertainty in the temperatures was estimated to be ±2 °C.

The rate constants from the carbon spectra were obtained by line shape matching using an Apple computer and a two-site exchange program written by R. A. Newmark.[9] An approximate equation, $k_C = (\pi/\sqrt{2}) \times \Delta\nu$, was used to obtain the rate constant from the spectrum of the CH_2O hydrogens at −85.2 °C.

Initial structures for conformations of oxacyclooctan-2-one were generated with Spartan 3.0[10] using Cartesian coordinates provided by Saunders and Jimenez-Vazques.[11] Energy minimizations followed by thermochemistry calculations were performed, using an external MM3 program.[12] The strain energies obtained in these calculations were in close agreement to the reported values. The geometries obtained from MM3 for three conformations of **1** and the conformations of lowest strain energy for oxacycloheptan-2-one and oxacyclononan-2-one were used as starting points for the ab initio calculations. The Gaussian 94 series of programs[13] was used for full geometry optimization, followed by calculations of vibrational frequencies and thermodynamic properties. For the frequency calculations, the default scaling factor of 0.89 was used.

Results and Discussion

The ^{13}C NMR spectrum of a 5% solution of **1** in 3:1 $CHClF_2/CHCl_2F$ at +17.6 °C showed the expected seven peaks at δ 178.68 (C=O), 69.01 (CH_2O), 32.38, 31.65, 29.35, 26.79, and 24.94 (Figure 1). By −154.2 °C, signals for two conformations, with populations of 74.4 and 25.6% corresponding to a free-energy difference of 0.25 kcal/mol have appeared. Populations of 70.6% and 29.4% were estimated at −128.6 °C, the coalescence temperature for the carbonyl carbon peak, with the assumption that the free-energy difference does not change with temperature. Free-energy barriers of 6.98 and 7.23 kcal/mol were calculated at this temperature.

The ^{1}H NMR spectrum of the CH_2O protons decoalesces into two multiplets of equal intensity by −100 °C (Figure 2). A free-energy barrier of 9.16 kcal/mol was calculated for the exchange of the geminal hydrogen positions at −85.2 °C. Small changes were found for the two multiplets on going to −156.0 °C, but separate bands for the two conformations were not observed in this region. However, the multiplet centered at δ 2.47 at 0 °C does split into four bands for the two conformations by −156.0 °C.

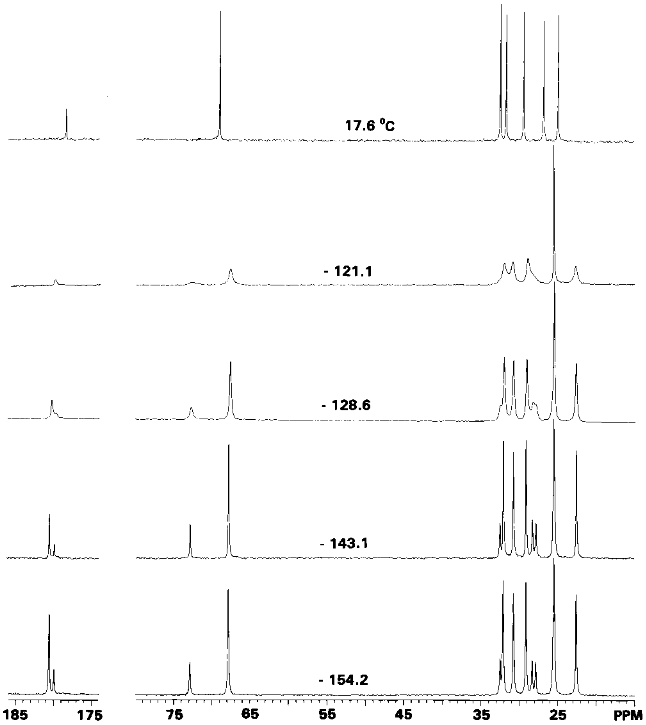

Figure 1. Low-temperature ^{13}C NMR spectra of 5% oxacyclooctan-2-one in 3:1 $CHClF_2/CHCl_2F$.

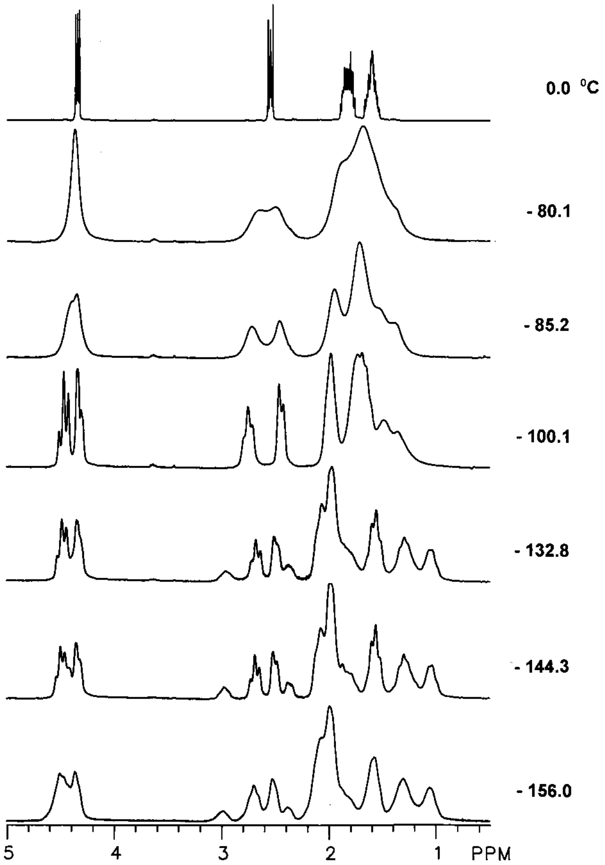

Figure 2. ^{1}H NMR spectra of oxacyclooctan-2-one in 3:1 $CHClF_2/CHCl_2F$.

The first six conformations of **1** are shown in order of increasing strain energy in Figure 3. The relative strain energies and free energies calculated for +25 °C and −160 °C are listed in Table 1. The dipole moment of **1** in benzene solution at +25 °C showed that the compound has mostly the *E* configuration, and the higher dielectric constant of the solvent system used in the present study should reinforce this preference. Conformations **1a**−**d** of Figure 3 have the *Z* configuration, and the spectra are best interpreted in terms of a mixture of **1e** and **1f**, which are the first two calculated *E* isomers. These conforma-

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[10] Spartan Version 3.0 from Wavefunction, Inc., Irvine, CA.

[11] We thank Professor Saunders and Mr. Jimenez-Vazques for sending a complete set of calculations for **1**.

[12] Version MM3 (94) was used. The latest version of the MM3 program, which is referred to as MM3 (96), is available to academic users from the Quantum Chemistry Program Exchange and to commercial users from Tripos Associates, 1699 South Hanley St., St. Louis, MO 63144.

[13] Gaussian 94: Rev. E. 2, Frisch M. J.; Trucks, G. W.; Gill, P. M. W.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Cheeseman, J. R.; Gomperts, R.; Keith, T.; Petersson, G. A.; Montgomary, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, J. V. O.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Fox, D. J.; Head-Gordon, M.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Defrees, D. J.; Baker, J.; Stewart, J. J.; Pople, J. A.; Gaussian, Inc., Pittsburgh, PA, 1995.

Table 1. Configurations, Relative Strain Energies,[a] Relative Free Energies, and Populations of Different Conformations of Oxacyclooctan-2-one, Calculated Using Allinger's MM3 Program[b]

		25 °C		−160 °C	
conformations (configurations)	relative strain energies (kcal/mol)	relative free energies (kcal/mol)	populations	relative free energies (kcal/mol)	populations
1a (*Z*)	0.000	0.000	0.822	0.000	0.993
1b (*Z*)	1.239	1.047	0.141	1.106	0.007
1c (*Z*)	1.637	2.040	0.026	1.943	0.000
1d (*Z*)	2.270	2.559	0.011	2.518	0.000
1e (*E*)	3.989	4.332	0.000	4.379	0.000
1f (*E*)	4.084	4.477	0.000	4.505	0.000
1g (*Z*)	6.129	5.894	0.000	6.003	0.000
1h (*Z*)	6.651	6.178	0.000	6.386	0.000
1i (*E*)	7.565	8.009	0.000	8.038	0.000

[a] Previously calculated in ref 5. [b] Conformations are numbered according to increasing relative strain energy.

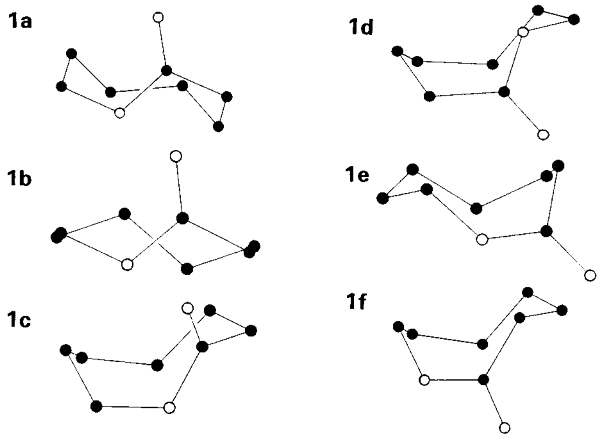

Figure 3. Conformations of oxacyclooctan-2-one.

tions are separated by a calculated free-energy difference of only 0.13 kcal/mol at −160 °C, which is close to the experimental free-energy difference of 0.25 kcal/mol at −154.2 °C. The next *E* isomer (**1i**) is calculated to be 3.53 kcal/mol higher in free energy than **1f** and is not likely to be measurably populated. The calculations are for the gas phase, and this could partially account for the lower calculated energies for the first four *Z* structures.

The effects of solvent polarity and temperature on the *E*−*Z* equillibria of *tert*-butyl formate were determined in a detailed NMR study,[14] and ab initio calculations[15] predicted that the *E*−*Z* free-energy difference of methyl formate decreases from 5.16 kcal/mol in the gas phase to 1.66 kcal/mol for a dielectric constant of 35.9 (acetonitrile). The difference for methyl acetate was reduced from 8.51 to 5.24 kcal/mol.

Smaller free-energy differences between conformations **1a** and **1e** or **1f** were obtained by ab initio calculations at the HF/6-311G* and MP2/6-311G* levels (Table 2), and these calculations provide some support for the assignment of *E* conformations to **1** in solution. The ^{13}C spectrum for a 2% solution of **1** dissolved in 1:1 acetone-d_6/acetaldehyde showed two peaks at −154.5 °C for the carbonyl carbon at δ 177.72 and 177.08, corresponding to populations of 75.0 and 25.0%, respectively. The good agreement of these percentages with the results obtained for the less-polar solvent mixture (3:1 $CHClF_2/CHCl_2F$) provides evidence that the conformations have the same configuration (*E* or *Z*); the dipole moment for **1** in the nonpolar solvent benzene indicates[2] that the major conformation is *E* under these conditions, and both conformations are likely to be *E* in the polar acetone-d_6/acetaldehyde solvent mixture.

Dipole moments calculated for three conformations of **1** are shown in Table 2, and the dipole moments for the seven-membered and nine-membered lactone conformations calculated[5] to have lowest strain energy were also estimated. The results for oxacycloheptan-2-one overestimate the dipole moment of the lactone in benzene, although the possible effect of different media (gas phase or solution) is not known, and other *E* conformations could contribute to the dipole moment under the experimental conditions. The larger-than-experimental dipole moments calculated for **1e** and **1f** could be due to one or more of several factors, including the following: error in the calculated values, the effect of different media, or a significant population of a *Z* conformation such as **1a** at room temperature in the nonpolar solvent benzene.

Conformations **1e** and **1f** both resemble the preferred boat-chair conformation of cyclooctane (**2**, Figure 4), with the positions of the carbonyl group and "ether" oxygen interchanged on going from one conformation to the other. Cyclooctane has, in addition, a minor crown family conformation (twist-chair-chair, chair-chair, or crown) that amounts to about 6% at room temperature and 0.3% at −123 °C.[16] A boat-chair conformation has also been assigned to *cis*-cyclooctene (**3**),[17] as shown in Figure 4, and two conformations have been found[18] for the eight-membered lactam.

In an early study of oxocane (oxacyclooctane) (**4**), the plane-symmetrical conformation **4a** of Figure 4 was proposed[19−21] to account for the lack of change in the ^{13}C spectra for temperatures to −170 °C, although the position of oxygen was later described as not well defined.[22] Later molecular mechanics calculations predicted[23−25] that conformation **4b** is lower in energy than

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Table 2. Dipole Moments and Free Energies of Several Lactones at the HF/6-311G* and MP2/6-311G* Levels

		HF/6-311G*			MP2/6-311G*			
		relative free energies (kcal/mol)			relative free energies (kcal/mol)			
lactone	conformer	25 °C	−155 °C	dipole moments (D)	25 °C	−155 °C	dipole moments (D)	expt.[a] (D)
oxacycloheptan-2-one[b]		–	–	5.09	–	–	5.28	4.45
oxacyclooctan-2-one	**1a**	0.000	0.000	2.64	0.000	0.000	2.44	3.70
	1e	3.028	3.080	4.95	2.767	2.909	5.10	
	1f	3.823	2.869	4.89	2.511	2.605	5.00	
oxacyclononan-2-one[c]		–	–	2.29	–	–	2.15	2.25

[a] Experimental results are for a solution in benzene (ref 2) and are weighted averages over all conformations present. [b] Calculations are for the chair conformation, which is predicted to have the lowest strain energy by MM3 (ref 5). [c] Calculations are for the conformation found to have the lowest strain energy by MM3 (ref 5).

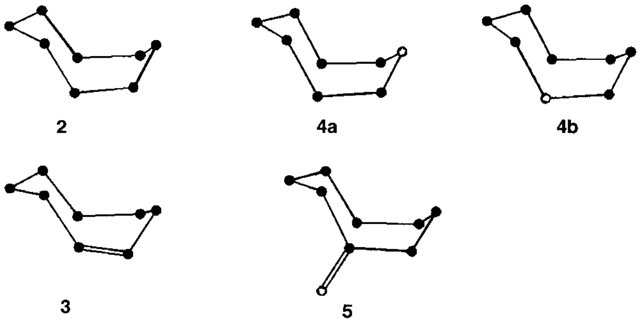

Figure 4. Conformations of cyclooctane (**2**), *cis*-cyclooctene (**3**), oxocane (**4**), and cyclooctanone (**5**).

4a, and lanthanide shift NMR experiments[25] have also been interpreted in terms of **4b**. A crown-family conformation of **4** with a free energy about 1 kcal/mol higher than the boat-chair conformation has also been found by low-temperature NMR spectroscopy.[25−27] ^{13}C spectra of **4** at 126 MHz did not show decoalescence for slow pseudorotation of the boat-chair by −135 °C.[25] Cyclooctanone (**5**) has also been shown[17] to adopt a boat-chair conformation by low-temperature NMR, as shown in Figure 4.

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