Conformational Analysis of 1,3-Dioxacyclohept-5-enes. Proton and Carbon-13 Magnetic Resonance. Evidence for a Twist–Boat Conformation

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Twist-boat conformations have been assigned to cis- and trans-4,7-dimethyl-1,3-dioxacyclohept-5-ene and to r-2-tert-butyl-cis-4,trans-7-dimethyl-1,3-dioxacyclohept-5-ene on the basis of carbon-13 substituent effects. These assignments are consistent with pmr spectra. The data also suggest that 2,2-dimethyl-1,3-dioxacyclohept-5-ene is in a twist-boat conformation but r-2-tert-butyl-cis-4,cis-7-dimethyl-1,3-dioxacyclohept-5-ene is in a chair conformation.

Conformational analysis of the 1,3-dioxacycloalkanes has received considerable recent attention.¹⁻⁴ The 1,3-dioxacyclopentanes² and 1,3-dioxacycloheptanes have numerous low-energy conformations available to each of an equilibrating pair of diastereoisomers. In contrast 1,3-dioxacyclohexane has only one favorable low-energy chair conformation for each isomer of a cis-trans pair.¹

An analogous situation is found for simple cycloalkanes. Five- 5 and seven-membered⁶ cycloalkanes pseudorotate among several low-energy conformations whereas cyclohexane has only one low energy conformation.

Nmr studies indicate that 1,2-benzocycloheptene, 5,5dimethyl-1,2-benzocycloheptene, cycloheptene, and 5,5difluorocycloheptene exist in chair conformations. Lowtemperature nmr studies on 1,3-dioxacyclohept-5-ene, 2,2dimethyl-1,3-dioxacyclohept-5-ene, and 1,3-dioxa-5,6-benzocycloheptene failed to define a specific conformation for these compounds but did reveal that 2,2-dimethyl-1,3dioxa-5,6-benzocycloheptene exists in a twist-boat conformation.^{7c} It has been shown that 3,5-dioxabicyclo[5.1.0]octane exists in a twist-boat conformation.9a In contrast cycloheptene oxide exists in an equilibrium of two chair conformations.^{9b} Encouraged by the discovery of these twist-boat conformations and by data on the carbon-13 hydrogen coupling constants of C2 in some 1,3-dioxacycloalkanes^{7d} a search was initiated for twist-boat conformations among the 1,3-dioxacyclohept-5-enes. We now report the results of that search and also a correlation of carbon-13 substituent effects.

Configurational Assignments. The cis and trans isomers of 4,7-dimethyl-1,3-dioxacyclohept-5-ene were separated by gas chromatography. Configurational assignments were made on the basis of proton magnetic resonance spectral data. Examination of models indicates that the C2 protons for the cis isomer are diastereotopic in all conformations. The cis configuration was therefore assigned to that isomer whose C2 protons gave an AB nmr spectrum with chemical shifts of 302 and 283 Hz. These values compare favorably with those reported for the C2 protons of *cis*-4,7-dimethyl-1,3-dioxacycloheptane, 290 and 272 Hz.³

The trans configuration was assigned to the remaining isomer which had a single C2 proton signal at 287 Hz. This value compares favorably with a reported value of 282 Hz for the C2 protons in *trans*-4,7-dimethyl-1,3-dioxacycloheptane.^{3,10}

Configurational assignments for r-2-tert-butyl-cis-4,cis-7-dimethyl-1,3-dioxacyclohept-5-ene and r-2-tert-butylcis-4,trans-7-dimethyl-1,3-dioxacyclohept-5-ene were made on the basis of the meso-d,l isomer ratio found for the 3-hexene-2,5-diol¹⁰ starting material. The 4,7-dimethyl-1,3-dioxacyclohept-5-enes prepared from the 3hexene-2,5-diol gave products with a cis-trans ratio of 4:1 as indicated by the areas for the C2 protons in the nmr spectrum. It follows that the meso-d, l ratio is 4:1. The cis,cis-cis,trans isomer ratio for the r-2-tert-butyl-4,7-dimethyl-1,3-dioxacyclohept-5-enes prepared from the same 3-hexene-2,5-diol paralleled the 4:1 distribution.

The pmr spectra are consistent with these assignments. The C2 proton for the r-2-tert-butyl-cis-4,cis-7-dimethyl isomer absorbs at higher field, 248 Hz, than the C2 proton for the cis-4,trans-7 isomer, 261 Hz. This parallels the data for cis- and trans-2-tert-butyl-4-methyl-1,3-dioxacycloheptane which gave signals for the C2 protons at 246 and 250 Hz, respectively. It is also accordant with C2 proton signals for cis,cis and cis,trans isomers of r-2-tert-butyl-4,7-dimethyl-1,3-dioxacycloheptane.⁴

Carbon-13 Chemical Shifts. All the carbon-13 spectra were recorded at ambient temperatures at which the rates of interconversions of the conformations were fast. Therefore the chemical shifts are average values to which each of the conformations contributes according to its population.

The carbon-13 chemical shifts for a series of 1,3-dioxacyclohept-5-enes are summarized in Table I. The assignments of the carbon resonances were made on the basis of relative intensities and comparison with chemical shifts for 1,3-dioxacycloheptanes.

Assignments were made in a straightforward way. The *tert*-butyl methyl signals were readily distinguished from the methyl groups substituted directly on the ring by signal intensity. That for the quaternary carbon of the *tert*-butyl group was distinguished by reduced intensity and the chemical shifts for C5 and C6 were readily assigned because of the magnitude of the downfield shift expected for vinyl carbons. The signals assigned to C2, C4, and C7 correspond to chemical shifts for C2, C4, and C6 in 1,3-dioxacyclohexanes.

Some important observations can be made from the data in Table I. The difference in geometry between the 1,3dioxacycloheptanes and the 1,3-dioxacyclohept-5-enes has little effect on the saturated carbon-13 chemical shifts. The signals for C2 are within 4 ppm of the corresponding signals for the dioxacyclohexanes and dioxacycloheptanes. The C4 and C7 methyl signals fall within a very narrow range and suggest that these methyl groups experience very similar surroundings. It was this observation which first indicated that *cis*- and *trans*-4,7-dimethyl-1,3-dioxacyclohept-5-ene exist in twist-boat conformations.

The signals for the methyl carbons of the *tert*-butyl groups fall within a narrow range and are not affected by

Entry	Compd	Registry no.	C2	C4,7	C5,6	Me	t-BuMe	Cq ^b
		Carbo	on-13 Chemi	cal Shifts				
1	1,3-Dioxacyclohept- 5-ene	5417-3 2- 3	96.38	66.95	130.58			
2	2-tert-Butyl-	53586-63-3	110,81	68.10	128.99		24.96	36.21
3	2,2-Dimethyl	1003-83-4	101.73	61.23	129.74	24.02		
4	cis-4,7-Dimethyl-	53643-36-0	93.26	74.16	134.39	21.29		
5	trans-4,7-Dimethyl-	53586-64-4	93.77	71.23	134.71	21.58		
6	r-2-tert-Butyl-cis- 4,cis-7-dimethyl-	53586-65-5	109.88	74.60	134.06	22.21	24.92	36.44
7	<i>r-2-tert-</i> Butyl- <i>cis-</i> 4, <i>trans-</i> 7-dimethyl-	53626-27-0	109.88	74.60	134.06	22,15	25.02	36.96
		Prot	on Chemical	\mathbf{Shifts}^{c}				
1			286	251	340			
2			2 48	261,254	340		53	
3				248	336	80		
4			302,283	268	331	77		
5			287	267	328	74		
6			248	257	329	75	54	
7			261	257	323	68	54	

 Table I

 Chemical Shifts for Some 1,3-Dioxacyclohept-5-enes^a

^a All chemical shifts are in ppm downfield from internal TMS. ^b The quaternary carbon of the *tert*-butyl group. ^c All chemical shifts are in Hz downfield from internal TMS.

 Table II

 Carbon-13 Chemical Shift Substituent Effects for Some 1,3-Dioxacyclohept-5-enes^{a,b}

Entry	Compd	C2	C4,7	C5,6
1	2-tert-Butyl-	-14.43 (-15.27)	-1.15 (-1.46)	+1.59(+0.34)
2	2.2-Dimethyl-	-5.35	+5.72	+0.84
3	cis-4.7-Dimethyl-	+3.12(0.60)	-7.21 (-8.65)	-3.81 (-3.71)
4	trans-4,7-Dimethyl-	+2.61 ($+2.72$)	-4.28 (-5.15)	-4.13 (-6.46)
5	r-2-tert-Butyl-cis-	-13.50 (-14.21)	-7.65 (-7.88)	-3.48(-3.74)
	4. cis-7-dimethyl ^c	[0.93]	[-6.50]	[-5.07]
6	r-2-tert-Butyl-cis-	-13.50 (-10.93)	-7.65 (-3.30 , -10.66)	-3.48(-6.59)
	4, trans-7-dimethyl-°	[0.93]	[-6.50]	[-5.07]

^a All values are in ppm calculated from 1,3-dioxacyclohept-5-ene. A negative value indicates a signal downfield from the reference compound. ^b Values in parentheses are for corresponding 1,3-dioxacycloheptanes taken from ref 4. ^c Values in brackets are referenced to 2-*tert*butyl-1,3-dioxacyclohept-5-ene.

 Table III

 Carbon-13 Chemical Shift Substituent Effects Produced by Substitution on 1,3-Dioxacyclohept-5-ene and 2-tert-Butyl-1,3-dioxacyclohept-5-ene^a

Entry	Compd	α	в	γ	δ
1	2-tert-Butyl	-14.43 (-15.27)		-1.15 (-1.46)	+1.59(+0.34)
2	2,2-Dimethyl-	-5.35		+5.72	+0.84
3	cis-4,7-Dimethyl-	-7.21 (-8.65)	-3.81 (-4.47)	+3.12(+3.17, -0.57)	
4	trans-4,7-Dimethyl-	-4.28(-5.15)	-4.13(-7.22)	+2.16(+0.42, 1.55)	
5	r-2-tert-Butyl-cis-			,	
	4, cis-7-dimethyl- ^a	-6.50(-6.42)	-5.07 (-4.08)	+0.93 (+1.06)	
6	r-2-tert-Buty1-cis-				
	4, trans-7-dimethyl- ^a	-6.50(-1.84, -9.20)	-5.07 (-6.93)	+0.93 (+4.34)	

^a Values compared to 2-tert-butyl-1,3-dioxacyclohept-5-ene. ^b Values in parentheses are from the corresponding 1,3-dioxacycloheptanes, ref 4.

substitution on the ring. There is no indication of an axial tert-butyl group.⁴ Substituents at C4 and C7 do affect the signals at C5 and C6 but a substituent at C2 does not.

Carbon-13 Substituent Effects. Table II lists the carbon-13 chemical shift substituent effects produced on each carbon of unsubstituted 1,3-dioxacyclohept-5-ene by introduction of alkyl groups at several positions. Table III summarizes these same effects but lists them as to origin, *i.e.*, α , β , γ , and δ . This table also lists sbstituent effects produced by substitution on 2-*tert*-butyl-1,3-dioxacyclohept-

5-ene. The values in parentheses are for corresponding 1,3-dioxacycloheptanes.

The α and β effects are generally consistent with those for cyclohexane, 1,3-dioxacyclohexane, and 1,3-dioxacycloheptane. A *tert*-butyl substituent at C2 gives α values of -14.43 and -13.50 ppm. These values compare with -11.06 and -15.25 ppm for 1,3-dioxacyclohexane and 1,3dioxacycloheptane, respectively. A *gem*-dimethyl substitution at C2 gives an α shift of -5.35 ppm which compares with -3.21 ppm for 2,2-dimethyl-2,3-dioxacyclohexane. The relation of the γ effect to conformation is probably the best understood of the chemical shift substituent parameters.^{1,5,11} It reflects a paramagnetic shift due to a 1,3diaxial steric compression. The δ effect reflects the same kind of compression for a 4,7-diaxial interaction.

The γ effect for the 2,2-dimethyl derivative (+5.72 ppm) is smaller than that for 2,2-dimethyl-1,3-dioxacyclohexane (7.51 ppm).^{1,12} This was unexpected because models indicate that the distance between the 1,3-diaxial methyl and hydrogen atoms is smaller for 2,2-dimethyl-1,3-dioxacyclohept-5-ene than for the dioxacyclohexane homolog. Thus for a chair conformation a bigger γ shift for the 1,3dioxacyclohept-5-ene was expected. In a twist-boat conformation the distance between the axial C2 methyl group and the axial C4 hydrogen is considerably larger than it is for the chair conformation. The small γ shift is consistent with a twist-boat conformation but an unequivocal assignment cannot be made.

The 3.12 ppm γ shift at C2 for *cis*-4,7-dimethyl-1,3-dioxacyclohept-5-ene, 1, is consistent with a twist-boat conformation. A chair conformation would require a very small or no γ shift. For example the γ shift at C2 for *cis*-4,6-dimethyl-1,3-dioxacyclohexane is +0.7 ppm. In contrast the γ shift at C2 for the trans isomer is +7.6 ppm.^{12a}

The twist-boat conformation has a 1,3-methyl-hydrogen interaction but models indicate that the distance between the C4 methyl group and the C2 hydrogen is greater than in the corresponding chair conformation. This accounts for the small γ shift compared to +7.6 ppm for *trans*-4,6-dimethyl-1,3-dioxacyclohexane. Therefore the evidence indicates that the twist-boat conformation is more favorable than the chair conformation for which both methyl groups are equatorial.^{12b} The angle strain imposed by the C5,6 double bond and the generalized anomeric effect may well account for this rather surprising conclusion. A twist-boat should relieve the angle strain and the dipolar repulsions due to the generalized anomeric effect.

A boat conformation is not a reasonable alternative since it does not account for the γ shift at C2. The situation here is analogous to that for cycloheptene,¹³ in which the boat conformation is estimated to be least stable by 3.37 kcal/ mol. It is reasonable to expect the boat conformation for 1,3-dioxacyclohept-5-ene to be of even higher energy, when compared to its chair conformation, than boat cycloheptene, compared to its chair, because of the shorter COC bonds. This shorter distance makes the interaction between the prow of the boat and the double bond even more severe than in cycloheptene.¹⁵ Therefore it is reasonable to exclude the boat conformation from consideration.

A twist-boat conformation has also been assigned to the trans isomer, 2. This assignment is consistent with the 2.61 ppm γ shift at C2. This value is considerably smaller than the +7.6 ppm found for *trans*-4,6-dimethyl-1,3-dioxacyclohexane.

A rapid equilibrium between two chair conformations would account for the A_2 spectrum of the C2 protons. However, the chair conformation has a 1,3-diaxial methyl-hydrogen interaction across COC bonds and a 4,7-methylhydrogen interaction. It is known that the sum of the energies of these interactions is sufficiently high that such conformations must be excluded from the conformational array of 4,7-dimethyl-1,3-dioxacycloheptanes. These interactions are at least as severe as those found in the 1,3-dioxacyclohexanes which are estimated at 2.9 kcal/mol.¹⁴ Therefore it is reasonable to exclude the chair conformation from consideration.

The γ shift (+0.93 ppm) for r-2-tert-butyl-cis-4,cis-7dimethyl-1,3-dioxacyclohept-5-ene is consistent with a chair conformation. This value is in accord with +0.7 ppm for cis-4,6-dimethyl-1,3-dioxacyclohexane and -0.1 ppm for r-2-cis-4,cis-6-trimethyl-1,3-dioxacyclohexane. Examination of models indicates that the twist-boat conformation has a severe 1,3-tert-butyl-methyl interaction. This interaction should manifest a γ shift at both the methyl carbon and the tert-butyl group.⁴ This is not in accordance with the carbon-13 data.

A twist-boat conformation is assigned to r-2-tert-butyl-cis-4,trans-7-dimethyl-1,3-dioxacyclohept-5-ene. This conformation has neither a 1,3-diaxial nor a 4,7-diaxial methyl-hydrogen interaction. It is consistent with the small value of the γ shift at C2 and the absence of a paramagnetic shift at the C7 methyl carbon. The C2 γ shift for



r-2-cis-4,trans-6-trimethyl-1,3-dioxacyclohexane is +2 ppm. This compound is known to have an axial methyl group. It is reasonable to conclude that there is no axial methyl group and therefore no chair conformation for the corresponding 1,3-dioxacyclohept-5-ene.¹⁶

Experimental Section

Proton nmr spectra were recorded on a Varian A-60A nmr spectrometer. Samples were run as 10% solutions in carbon tetrachloride. All chemical shifts are reported in hertz downfield from internal TMS. The carbon-13 spectra were recorded at 25.15 MHz on a Varian HA 100D nmr spectrometer interfaced with a Digilab NMR-FTS-3 pulse and data system. The number of data points was 8K or 16K as required to obtain satisfactory resolution. Spectra were recorded with broad-band proton decoupling. All chemical shifts were referenced to internal TMS and reported in ppm. All mass spectra were determined on a AEI-9 high resolution mass spectrometer. The infrared spectra were recorded on a Beckman IR-8 instrument and the absorption values are reported in microns.

1,3-Dioxacyclohept-5-ene was prepared as described in the literature.¹⁷

2-tert-Butyl-1,3-Dioxacyclohept-5-ene. The general procedure for the preparation of these compounds is that of Brannock and Lappin.¹⁷ The preparation of 2-*tert*-butyl-1,3-dioxacyclohept-5-ene is described as a general example. A mixture of 8.8 g (0.1 mol) of *cis*-2-butene-1,4-diol, 8.6 g (0.1 mol) of pivaldehyde, 50 ml of benzene, and 50 mg of *p*-toluenesulfonic acid was refluxed under a Dean-Stark distillation trap until 1.8 ml of water was collected. The mixture was fractionally distilled at reduced pressure to give a 75% yield of the desired product: bp 38-40° (2 Torr); ir 3.4, 3.65 6.1, 6.7, 7.2, 9.5, and 10.0; *m/e* 156 (parent peak).

4,7-Dimethyl-1,3-dioxacyclohept-5-ene. The mixture of isomers had bp 25° (0.3 Torr) and the yield was 40%. The isomers were separated by glpc (12 ft 5% 1,2,3-tris(cyanoethoxy)propane on Chromosorb). The cis-trans ratio was 4:1 and the trans isomer was the first peak: ir (mixture) 3.3, 3.6, 6.9, 7.3, 9.0, 9.7, 10.8, 11.3; m/e 128 (parent peak).

2-tert-Butyl-4,7-Dimethyl-1,3-Dioxacyclohept-5-ene.¹⁸ The mixture of isomers had a bp $36-40^{\circ}$ (1 Torr) and the yield was 70%. The cis-trans ratio was 4:1 and the first peak was r-2-tert-butyl-cis-4,cis-7-dimethyl-1,3-dioxacyclohept-5-ene: ir (neat) 3.4,

6.9, 7.3, 7.8, 8.2, 8.9, 9.7, and 10.8; m/e 184 (parent peak). The isomers were best separated by glpc (8 ft Carbowax 20 M 10% on Chromosorb).

2.2-Dimethyl-1.3-dioxacyclohept-5-ene. A mixture of 8.8 g (0.1 mol) of 2-butene-1,4-diol, 20.0 g of anhydrous copper sulfate, 50 mg of p-toluenesulfonic acid, and 50 ml of anhydrous acetone was placed in a pressure bottle which was sealed and heated to 50° for a period of 2 weeks. Fractional distillation gave a 50% yield of the desired product: bp 18-20° (1 Torr); ir (neat) 3.3, 3.5, 6.9, 9.9, 11.6, 13.1; m/e 128 (parent peak).

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provided the original indication that twist-boat conformations might be more common in these compounds than was previously believed. It was expected that the double bond in 1,3-dioxacyclohept-5-ene would spread the dioxamethylene (OCO) bond angle with respect to 1,3-dioxacycloheptane. In so far as these coupling constants relate to the diox-amethylene bond angle the data suggest that the angle is not larger but smaller. This observation is not inconsistent with a twist-boat conformation for 1.3-dioxacvclohept-5-ene. The coupling constants have an accuracy of 0.5 Hz at best and the change in values is small and therefore not conclusive. The values for diethoxymethane, which is assumed to be strain free, and 1.3-dioxacvclooctane, which was expected to be strain free, give testimony to the idea that the coupling constants are sensitive to bond angle. The ¹³C-H coupling constants are as follows: 1,3-dioxacyclopentane, 164; 1,3-dioxacyclohexane, 163; 1,3-dioxacycloheptane, 164; 1,3-dioxacyclooctane, 161; 1,3-dioxacyclohept-5-ene, 164.5; and diethoxymethane, 161 Hz.

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Synthesis and Enol Determinations of 2,2-Disubstituted 6-Cyanocyclohexanones

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A series of 14 new 2-R-2-R'-6-cyanocyclohexanones was synthesized. The enol-keto contents of 19 compounds of this type were determined by quantitative ir study of conjugated CN (enol) and unconjugated (keto) absorbances. Application of the concept that steric inhibition of enclization was important in this system seemed appropriate. The per cent enol found for the R, R' compounds were 37 (H, H), 24 (Ph, Ph), 20 (Me, Me), 18 (Et, Et), 19 (Me, Ph), 13 (CH₂CH₂Ph, Ph), 10 (Et, Ph), 10 (Pr, Ph), 10 (Am, Ph), 6 (*i*-Bu, Ph), 6 (*c*-Hex, Ph), 5 (*i*-Pr, Ph), 4 (CH₂Ph, Ph), and 5 (n-Bu, Ph). The series can be classified in four categories by percentage: A, only parent compound, ~37; B, four compounds, ~20; C, four compounds, ~10; and D, five compounds, ~5. The equivalency or extent of dissimilarity (branching) of substituents, number of conformations, and the 2-alkyl ketone effect rationalize the data with one exception and support the view that steric interference decreases enolization in these β keto nitriles.

Large differences in the relative rates of hydrolysis of a series of α, α -disubstituted α' -cyanocycloalkanone imines (1) to their corresponding cyano ketones (2) have been observed.²⁻⁴ The results were qualitative and the availability of a number of these β -keto nitriles or extension of the series by their ready synthesis suggested that quantitative date on the enolization of the latter might be useful.

The imines were more difficult to hydrolyze as their steric requirements increased. The isoelectronic imine (>C==N) and carbonyl bonds (>C==O) are not only chemically similar⁵ but are also subject to similar steric limitations on the degree of enolization.^{6,7} Whereas steric hindrance afforded a satisfactory explanation for the conversion of >C=N to >C=O in our previous work, this is an irreversible reaction. The enolization process, however, is an

equilibrium condition. The concept that there can be steric inhibition of enolization has been employed to account for decreased enol contents in a series of compounds with increasing steric requirements^{8a} but exceptions are also known.^{8b} Steric requirements can have a profound effect.^{8c} Studying our compounds seemed to offer an opportunity to contribute to the developing knowledge of enol-keto equilibria.^{8d} Therefore, the percentage enol in a series of 2,2-disubstituted 6-cyanocyclohexanones (2_K) was obtained.

The compounds listed in Table I were either on hand from earlier work or were synthesized from the appropriate disubstituted acetonitriles by alkylation with 5-chloropentanenitrile and cyclization in one reaction to the cyanocyclohexanone imines 3 (eq 1) which were subsequently hydrolyzed to keto nitriles. The effectiveness of the two-step,