The Ring Inversion Barriers of 1,4-Dioxane and *cis*-2,3-Dimethyl-1,4-dioxane. ^{13}C Coupling-Induced Nonequivalence of Vicinal Protons[1]

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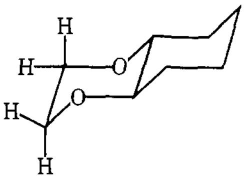
Abstract: The center band proton spectrum of 1,4-dioxane exhibits no spectral changes with temperature. One explanation is that the axial and equatorial protons are coincident, or nearly coincident, and this hypothesis is found to hold in the model, locked 1,4-dioxane, *trans*-2,5-dioxa[4.4.0]bicyclodecane. In contrast, the ^{13}C side band spectra of 1,4-dioxane and a specifically deuterated analog (*trans*-2,3-*trans*-5,6-dioxane-d_4) show temperature dependent spectral changes ascribable to the ring inversion process. These side bands allow calculation of proton-proton coupling constants of J_{aa} = 11.7 Hz and $J_{ee} \simeq 1$ Hz, consistent with 1,4-dioxane existing in the normal chair form. Ring inversion barriers (chair → twist) have been determined for 1,4-dioxane-d ($\Delta F^{\ddagger}$ = 9.7 kcal/mol at −93.6°) and for *cis*-2,3-dimethyl-1,4-dioxane ($\Delta F^{\ddagger}$ = 9.2 kcal/mol at −86.0°).

Considerable effort has been devoted to the study of the stereochemical relationships and energies of 1,3-dioxane and its substituted derivatives,[2] and some work has been performed in the 1,2-dioxane system.[3] With the exception of a report[4] of a ring inversion barrier for a 1,4-dioxane-d_6 which appeared concurrently with our preliminary report,[1] 1,4-dioxane and its substituted analogs have received little attention. One of the reasons for this has been the inability of workers to obtain the inversion barrier for the ring reversal reaction in the parent compound. Various investigators have reported that the protons of 1,4-dioxane remain equivalent at very low temperature.[5] In one investigation, the ring protons of 1,4-dioxane revealed a narrower absorption line than TMS at −160°.[6] This behavior could be attributed to a low chair-to-chair inversion barrier (<5 kcal/mol), a predominant boat form which pseudorotates with a low-energy barrier, or a coincidence (or near coincidence) of the axial and equatorial proton resonances at low temperature. In view of the normal behavior of most heterocyclohexanes (especially those with bond lengths and angles similar to those of carbon), the first two possibilities seem unlikely. The present investigation, which demonstrates the occurrence of the third possibility, closes a gap in the study of saturated six-membered ring systems.[5]

Results and Discussion

Examination of the NMR spectrum of a "locked" 1,4-dioxane provided information on the chemical shifts of the axial and equatorial protons in the 1,4-dioxane ring system. Although use of a *tert*-butyl group as a locking substituent is common, it was rejected because of the possibility of ring distortion.[7] Also, the *tert*-butyl group might have a relatively low "*A* value" in the 1,4-dioxane system[8] and, thus, not exist predominantly in the equatorial conformation as in cyclohexane. Therefore, the locked *trans*-decalin system, *trans*-2,5-dioxa[4.4.0]bicyclodecane (I), was chosen as a model (compound I is called 1,4-dioxadecalin in the discussion below). Inherent strain in this system should be small, as it is in the *trans*-decalin system. Any effect of the methylene groups on the chemical shifts of the four ring protons of interest should be small because of the equatorial position of these "substituents".



I

In the 100 MHz spectrum of *trans*-1,4-dioxadecalin in carbon disulfide (Figure 1), a typical broad band for the cyclohexyl ring protons (eight protons) is found between δ 1.0 and 2.0. There is an unresolved multiplet for the bridgehead protons at δ 2.95 (two protons) and a sharp singlet at δ 3.72 (four protons) for the four ring protons of interest. This sharp singlet for these four ring protons supports the hypothesis of equivalent (or nearly equivalent) chemical shifts for the axial and equatorial ring protons of the parent 1,4-dioxane.

The 100 MHz spectrum of *cis*-1,4-dioxadecalin, on the other hand, is complex and is composed of a typical broad cyclohexyl ring proton band between δ 1.0 and 2.2 (eight protons) and a complex multiplet between δ 3.2 and 3.8 (six protons) which can be identified as an A_2B_2 multiplet with a narrower multiplet superimposed on it. On cooling, the spectrum of the cis isomer broadens, passes through coalescence, and at −85° becomes a nonexchanging spectrum. When the spectrum of the trans isomer was observed at various temperatures down to −100°, no change in the spectrum was detected. These observations (as well as the method of preparation, see the Experimental Section) are in accord with the assignment of ring fusion geometry for these two compounds.

In connection with a study of the geometry of the *cis*- and *trans*-2,3-dimethyl-1,4-dioxanes (by means of their spectral properties), Gatti, Segre, and Morandi[9] found that the cis isomer had a temperature dependent NMR spectrum which revealed two methyl resonances of equal intensity at low temperature. Unfortunately, no data were presented which could be used to estimate the barrier to inversion for this substituted 1,4-dioxane.

In order to estimate the magnitude of this inversion barrier, *cis*- and *trans*-2,3-dimethyl-1,4-dioxane were synthesized and the cis isomer was investigated by variable temperature NMR spectroscopy. At −111° two separate methyl resonances of equal intensity are observed at δ 1.14 and 0.89. Coupling with the adjacent methine proton is equal to 6.6 Hz for both methyl groups. Using line shape analysis (see the Experimental Section) a free energy of activation ($\Delta F^{\ddagger}$) of 9.2 ± 0.2 kcal/mol at −86.0° is calculated for the chair-to-half-chair process. This "normal" barrier for a substituted 1,4-dioxane supports the hypothesis of a normal barrier for 1,4-dioxane itself.

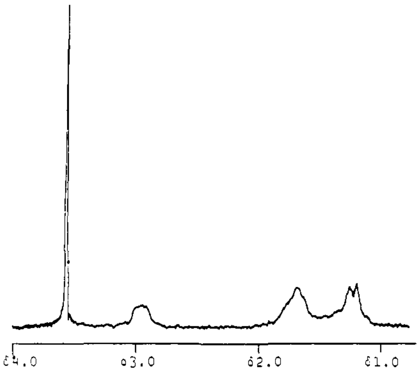


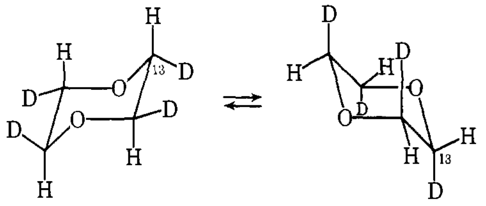
Figure 1. The 100 MHz spectrum of *trans*-1,4-dioxadecalin in carbon disulfide at normal probe temperature (ca. 33°).

In an effort to determine a barrier for the ring inversion process of 1,4-dioxane itself, the ^{13}C side band spectrum of 1,4-dioxane was examined at low temperature. These side bands consist of multiplets which arise from the hydrogens on ^{13}C coupling with the adjacent hydrogens on ^{12}C.[10] In other words, because the hydrogens are coupled with the ^{13}C atoms to which they are attached, an apparent chemical shift difference (equivalent to $J_{^{13}C-H}/2$) is produced between the protons on ^{12}C and ^{13}C.

In the case of 1,4-dioxane the proton ^{13}C side band multiplet should consist of a combination of geminal and vicinal axial and equatorial splitting.

At low temperature, the observed coupling in the ^{13}C side band spectrum should be one resulting from slow exchange while the coupling observed at room temperature should be attributable to fast exchange (chair to chair). A complex spectrum is especially expected for the low temperature spectrum of each ^{13}C side band if superposition of the resonances of the axial and equatorial protons attached to the ^{13}C nucleus occurs.

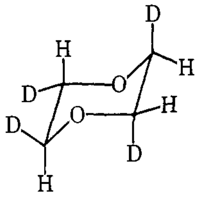
Upon cooling a sample of 1,4-dioxane, a change was observed in the ^{13}C side band spectrum. However, the spectrum is broad, complex, and difficult to analyze. In order to simplify this spectrum, *trans*-2,3-*trans*-5,6-dioxane-d_4 (II, eq 1) was synthesized. Because of the method of synthesis, IIa and IIb were both obtained. They are expected to exhibit (almost) identical spectra.



(1)

J_{aa} coupling
IIa

J_{ee} coupling
IIa



IIb

At low temperature (slow exchange) each ^{13}C side band should consist of an equatorial proton doublet with a small J_{cc} centered within an axial proton doublet with a J_{aa} = ~12 Hz (assuming a normal chair geometry for 1,4-dioxane and that $J_{^{13}C-H_a} = J_{^{13}C-H_e}$) (Figure 2). At the fast exchange limit, both halves of the ^{13}C side band spectrum should consist of a doublet with an average coupling constant of $J = \frac{1}{2}(J_{aa} + J_{ee})$.

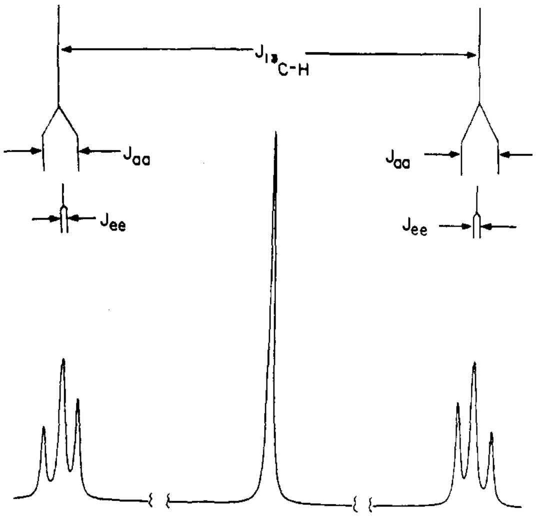


Figure 2. Calculated spectrum of *trans*-2,3-*trans*-5,6-dioxane-d_4 using program DNMR3 with slow exchange: J_{aa} = 11.7 Hz, J_{cc} = 0.8 Hz, $\delta H_a = \delta H_e$, $J_{^{13}C-H_a} = J_{^{13}C-H_e}$ (side band intensities magnified).

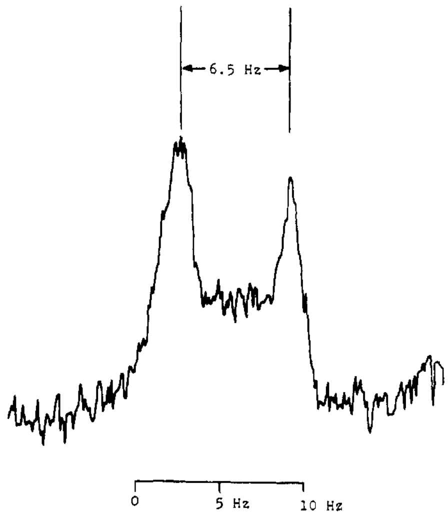


Figure 3. Upfield ^{13}C side band of *trans*-2,3-*trans*-5,6-dioxane-d_4 (100 MHz, deuterium decoupled, 14 scans) at room temperature showing the averaged coupling $J = \frac{1}{2}(J_{aa} + J_{ee})$ = 6.5 Hz. Solvent: 10% TMS, 37% vinyl chloride, 37% CH_2Cl_2, and 16% dioxane-d_4 (vol %).

The upfield ^{13}C side band spectrum (the downfield side band was too close to side bands of the solvents for investigation) of compound II at room temperature is shown in Figure 3. As expected, the room temperature spectrum of the side band consisted of a doublet with J = 6.5 Hz. At low temperature (Figure 4), the two expected doublets (J = 11.7 Hz and an unresolved doublet with J = ~1 Hz) were found, but the unresolved J_{ee} doublet was not centered within the J_{aa} doublet as expected (compare Figure 2). The explanation for this behavior becomes apparent upon examination of the center band spectrum of this deuterated 1,4-dioxane, for it is no longer a singlet, but two well resolved singlets (deuterium decoupled) at δ 3.629 and 3.657.

These chemical shifts represent an upfield chemical shift from 1,4-dioxane-d_0 (in a solution containing both deuterated and nondeuterated dioxane). The upfield shift amounts to 1.3 Hz for the resonance at δ 3.657 and 4.1 Hz for the resonance at δ 3.629. A similar upfield chemical shift with deuterium substitution in the α position has been noted in

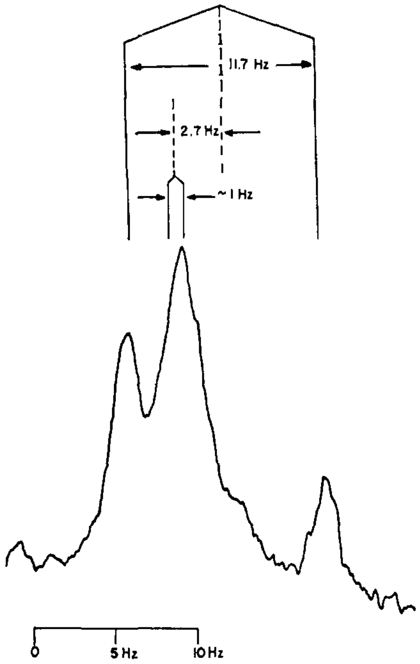


Figure 4. Upfield ^{13}C side band of *trans*-2,3-*trans*-5,6-dioxane-d_4 (100 MHz, deuterium decoupled, computer enhanced, 10 scans) at −104° showing the J_{aa} coupling equal to 11.7 Hz and the unresolved J_{ee} coupling less than 1.5 Hz. The J_{ee} "doublet" is displaced 2.7 Hz downfield from the center of the J_{aa} doublet. Same solvent as indicated in Figure 3.

acetone-d_5 (0.034 ppm upfield)[11] and α-deuteriotoluene (0.015 ppm upfield).[12] The separation of the axial and equatorial resonances in this deuterated 1,4-dioxane indicates that either the induced upfield chemical shift for the axial and equatorial protons is different,[13] or an inherent chemical shift difference (small) which is normally collapsed by the large coupling constants becomes evident in the abscence of coupling.[4]

A computer simulation of the slow exchange spectrum (including ^{13}C side bands) of compound II expected for noncoincident chemical shifts of the axial and equatorial protons (axial proton upfield from the equatorial proton) is shown in Figure 5. Comparison of this computer simulation with that of Figure 2 (overlapping axial and equatorial chemical shifts) shows that in the upfield side band the axial-axial doublet appears upfield relative to the equatorial-equatorial "doublet". From this comparison, the upfield center band signal (δ 3.629) is assigned to the axial protons and the signal at δ 3.657 to the equatorial protons.

To test whether the chemical shift difference arises from an across-ring effect, possibly through 1,3-diaxial interactions, 2,2,3,3-dioxane-d_4 was synthesized and investigated by low temperature NMR. At −104° this compound shows only line broadening in the center band spectrum centered at δ 3.66 and therefore it is concluded that an across-ring effect, if present, is small.

Since *trans*-2,3-*trans*-5,6-dioxane-d_4 exists as two compounds (as in eq 1) the broadness of the observed low temperature peaks is, perhaps, not unexpected. It appeared that if the same differential chemical shift occurred in 1,3-dioxane-d_7, this compound would be more suitable for analysis to obtain the inversion barrier. For this purpose, 1,4-dioxane-d_8 was prepared and shown to contain 7% 1,4-dioxane-d_7 by mass spectral analysis. This compound gives a sharp singlet at room temperature (deuterium decoupled) which broadens as the temperature is lowered and becomes two sharp singlets with a separation of 3.3 Hz at −104° (δ 3.64 and 3.61).

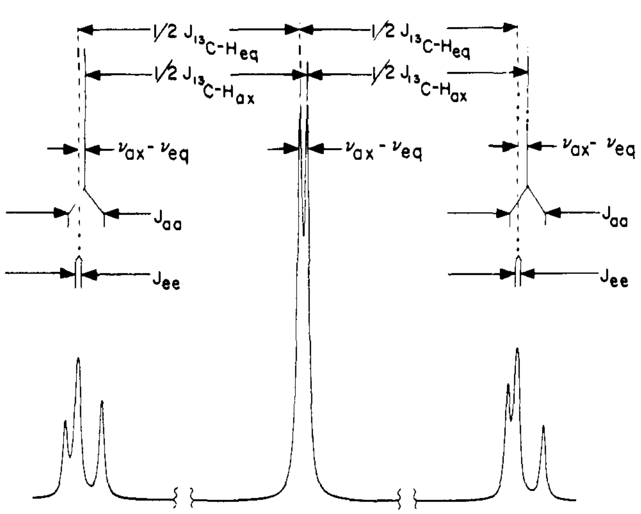
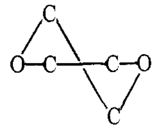
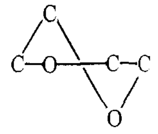


Figure 5. Calculated spectrum of *trans*-2,3-*trans*-5,6-dioxane-d_4 using program DNMR3 with slow exchange (J_{aa} = 11.7 Hz, J_{ee} = 0.8 Hz, $J_{^{13}C\text{-}H_a} = J_{^{13}C\text{-}H_e}$) and the chemical shift of the equatorial protons 2.8 Hz downfield from the axial protons. Side band intensities magnified.

The spectrum of 1,4-dioxane-d_7 was recorded at various temperatures and compared to the simulated spectrum obtained by use of computer program DNMR3. However, significant spectral changes only occur over a temperature range of 2.5°. Calculation of a meaningful enthalpy and entropy of activation with accuracy from such data is not possible. However, the enthalpy of activation can be estimated if the reasonable assumption is made that the major contribution to the entropy of activation is the degeneracy of reaction pathways to the half-chair transition state.[14] One would expect this to be true for such a simple process which does not involve charged species or highly distorted bonds. If the half-chair is assumed to be the transition state, then there are two types of half-chair transition states possible for 1,4-dioxane (III and IV).



III



IV

The degeneracy of reaction pathways for transition state III is two, and for transition state IV it is four. If both III and IV are of equal energy the degeneracy is six and $\Delta S^\ddagger \simeq R \ln 6 = 3.6$ eu. This latter possibility is unlikely and $\Delta S^\ddagger$ probably lies between the values 1.4 eu ($R \ln 2$) and 3.6 eu. Using this estimated entropy of activation range and a value of $\Delta F^\ddagger = 9.7$ kcal/mol (temp = −93.6°, chair to half-chair), $\Delta H^\ddagger$ is calculated to be 9.95–10.35 kcal/mol.

1,4-Dioxane is, thus, "normal" in all respects. A free energy of activation for the chair to half-chair process of 9.7 kcal/mol is close to that predicted by Pickett and Strauss (10.1 kcal/mol).[15] An axial-axial coupling constant of 11.7 Hz and an equatorial-equatorial coupling constant of ~1 Hz are evidence of the normal chair character of 1,4-dioxane in solution. Finally, all of the evidence indicates that a fortuitous coincidence (or near coincidence) of axial and equatorial chemical shifts exists in this compound.

Experimental Section

A Varian 100 MHz NMR spectrometer equipped with a specially constructed low temperature NMR probe[16] was used for all spectra. This probe allowed calibration of the temperature to ±0.1°. Deuterium decoupling was achieved with an SD-60 spin decoupler from NMR Specialties Co. (modified for 100 MHz by the manufacturer). Computer enhancement was obtained with a Varian Associates C-1024 Time Averaging Computer.

Computer program DNMR3 was obtained from Quantum Chemistry Program Exhange[17] and adapted[13] to the CDC 6400 computer at the University of California, Berkeley. Because of the limitations of the program (having to do with the number of nuclei which the program can handle), *cis*-2,3-dimethyl-1,4-dioxane could not be analyzed by computer simulation. Instead, the line separation method[19] using correction factors for coupled spectra as outlined by Beck[20] was used to analyze the methyl region of this compound.

All dioxanes discussed in this paper were purified by preparative gas chromatography on a 10 ft × 0.50 in. 20% QF-1 on 60–80 Chromosorb W column.

All NMR samples were prepared by vacuum transfer of the compounds and solvents from the appropriate drying agent into an NMR tube (drying agents: vinyl chloride-P_2O_5; methylene chloride-P_2O_5; TMS-CaH_2; all dioxanes-CaH_2). The mixed solvent used for the dioxane studies was found to be necessary to increase the solubility of the relatively insoluble dioxane, especially for the ^{13}C side band studies.

***trans*-2,5-Dioxa[4.4.0]bicyclodecane.** To a solution of 11.6 g of *trans*-1,2-cyclohexanediol (0.1 mol) in 200 ml of dry tetrahydrofuran at 0° was added 0.4 g of concentrated sulfuric acid. The flask was attached to a Dry Ice/acetone condenser and 8 g of ethylene oxide (0.18 mol) was introduced. The solution was magnetically stirred for 10 min, and then the tetrahydrofuran was removed with an aspirator. The white solid which remained was heated to 150° for 2.5 hr.[21] A black tar formed and the volatiles were distilled under reduced pressure (aspirator). Two liquid layers were found in the receiver. Each layer was gas chromatographed and found to contain the same three major components, one layer containing more water than the other. Both layers contained different quantities of the major products as well as a number of minor products. *trans*-1,4-Dioxadecalin is the major product, followed by 1,4-dioxaspiro[4.5]decane (cyclohexanone–ethylene glycol ketal) and 1,3-dioxa-2-cyclopentylcyclopentane (cyclopentane carboxaldehyde–ethylene glycol acetal). No *cis*-1,4-dioxadecalin was detected by gas chromatography. Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.86. Found: C, 67.64; H, 9.88.

***cis*-2,5-Dioxa[4.4.0]bicyclodecane.** The same procedure was used as for the trans isomer, except that the starting diol was *cis*-1,2-cyclohexanediol.[22] The yield in this reaction was considerably lower and the product mixture contained the same impurities as in the trans isomer. However, no *trans*-1,4-dioxadecalin was detected by gas chromatography. Anal. Calcd for $C_8H_{14}O_2$: C, 67.60; H, 9.86. Found: C, 67.38; H, 10.05.

***cis*- and *trans*-2,3-Dimethyl-1,4-dioxane.** The procedure of Astle and Jacobson[21] was used to prepare a mixture of the two compounds. These were separated by preparative GLC on a 10 ft × 0.50 in. QF-1 column at 90°.

2,2,3,3-Dioxane-d_4, *trans*-2,3-*trans*-5,6-Dioxane-d_4, and 1,4-Dioxane-d_8. These were prepared by the addition of the appropriately deuterium substituted ethylene glycol to the corresponding deuterium substituted ethylene glycol ditosylate in the presence of 2,6-di-*tert*-butylpyridine as previously described.[23]

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