Isochronous and Anisochronous O-Methylene Protons in Cyclic and Acyclic Acetals

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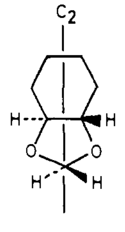
Abstract: Configurational assignments are made to some cyclic and acyclic acetals on the basis of the nature of the signals for their O-methylene protons in their pmr spectra. The three known 4,5:9,10-biscyclohexano-1,3,6,8-tetraoxacyclodecanes are assigned the *trans-syn-trans*, *trans-anti-trans*, and *cis-anti-cis* configurations and the di-(*trans*-2-hydroxycyclohexyloxy)methanes with mp 80–82° and mp 102.5–103.5° are assigned to the *meso* form and *dl* modification, respectively.

The reaction of *dl*-cyclohexane-*trans*-1,2-diol with methylene halides and sodium hydride in N,N-dimethylformamide is known[1] to yield mainly *trans*-hexahydro-1,3-benzodioxolane (**1**) together with small amounts of *trans*-hexahydro-1,3,5-benzotrioxepane (**2**) and a 4,5:9,10-biscyclohexano-1,3,6,8-tetraoxacyclodecane (**3**). On the basis of an AB quartet for the O-methylene protons in the pmr spectrum of the tetraoxacyclodecane (**3**), it was concluded[1] that the ten-membered ring is conformationally stable and exists in the BCB conformation,[2] which contains anisochronous[3] O-methylene protons. This conformation (**3a**) may be obtained from the tetraoxacyclodecane with the *trans-syn-trans* configuration **3**. In this paper we seek to correct some misinterpretations of the significance of isochronous[3] and anisochronous O-methylene protons in 4,5:9,10-biscyclohexano-1,3,6,8-tetraoxacyclodecanes and to assign configurations to some cyclic and acyclic acetals by comparison of the symmetry relationships of their O-methylene protons with the nature of the signals of these protons in their pmr spectra.



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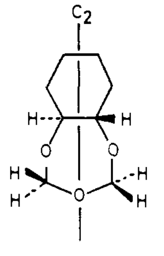

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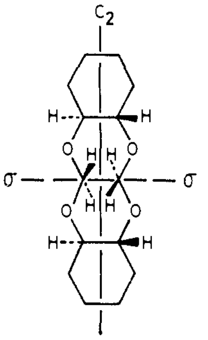

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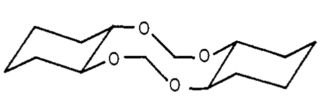
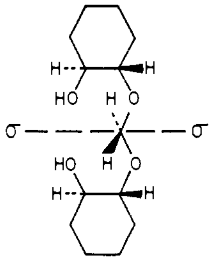


BCB CONFORMATION

3a

Examination of the symmetry properties[4,5] of the tetraoxacyclodecane **3** with a conformationally unstable ten-membered ring shows that it has a σ plane perpendicular to a C_2 axis (point group, C_{2h}). Thus, while the two O-methylene groups are equivalent,[3] each pair of O-methylene protons is diastereotopic.[3] The pmr spectrum of **3** shows a four-proton AB quartet (τ 5.15, $\Delta\nu_{AB} = 20.6$ Hz, $J_{AB} = 7.2$ Hz at 33°) indicating that each pair of O-methylene protons is anisochronous as is to be expected from their diastereotopic relationship. Therefore, a careful consideration of the symmetry properties of the tetraoxacyclodecane with the *trans-syn-trans* configuration **3** shows that it is not necessary to propose[1] conformational stability of the ten-membered ring to explain the observation that the O-methylene protons are anisochronous.

Head[6] has shown that acid-catalyzed reaction of *dl*-cyclohexane-*trans*-1,2-diol with formaldehyde yields, among other products, the diastereomeric *meso*-di-(*trans*-2-hydroxycyclohexyloxy)methane (**4**) and *dl*-di-(*trans*-2-hydroxycyclohexyloxy)methane (**5**), but was unable to assign structures to the two crystalline isomeric forms. Comparison of the symmetry properties of the two isomers shows that **4** has a σ plane (point group, C_s), while **5** has a C_2 axis (point group, C_2).



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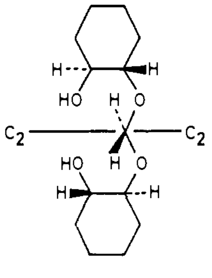

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[1] J. S. Brimacombe, A. B. Foster, B. D. Jones, and J. J. Willard, *Chem. Commun.*, 174 (1965); *J. Chem. Soc., C*, 2404 (1967); J. S. Brimacombe, *Chem. Brit.*, 2, 99 (1966).

[2] (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, 86, 4854 (1964); (b) J. B. Hendrickson, *ibid.*, 89, 7036 (1967); (c) J. B. Hendrickson, *ibid.*, 89, 7047 (1967).

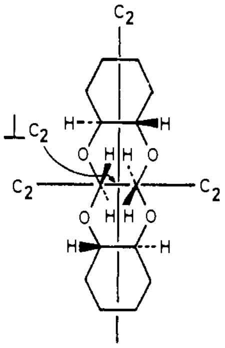
[3] The terms "isochronous," "anisochronous," "equivalent," "enantiotopic," and "diastereotopic" are used as described or defined by Mislow and Raban[4] in a recent review article.

[4] K. Mislow and M. Raban, in "Topics in Stereochemistry," N. L. Allinger and E. L. Eliel, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 1.

[5] K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966, p 23.

[6] F. S. H. Head, *J. Chem. Soc.*, 1778 (1960).

Thus, in the *meso* isomer **4**, the O-methylene protons are diastereotopic, whereas they are equivalent in the *dl* isomer **5**. Hence, in the pmr spectra, the O-methylene protons of **4** and **5** should be anisochronous and isochronous, respectively. Indeed, this result was observed. The isomer with mp 80–82° exhibited a two-proton AB quartet (τ 4.11, $\Delta\nu_{AB} = 14.2$ Hz, $J_{AB} = 6.9$ Hz at 33°) and so has been assigned to *meso*-di(*trans*-2-hydroxycyclohexyloxy)methane (**4**). The other isomer with mp 102.5–103.5° gave a sharp two-proton singlet (τ 5.18) and has been assigned to *dl*-di(*trans*-2-hydroxycyclohexyloxy)methane (**5**). The tetraoxacyclodecane **3** may be obtained[1] from the *meso* isomer **4** by base-catalyzed methylenation, and hence there is additional evidence that **3** has the *trans-syn-trans* configuration. Another 4,5:9,10-biscyclohexano-1,3,6,8-tetraoxacyclodecane (**6**) may be obtained[1] from the *dl* isomer **5** by base-catalyzed methylenation, and hence **6** must have the *trans-anti-trans* configuration. Examination of the symmetry properties of **6** shows that it has three mutually perpendicular C_2 axes (point group, D_2). Thus, the four protons of the O-methylene groups are all equivalent and hence would be expected to be isochronous. Indeed, a singlet was observed[1] in the pmr spectrum at τ 5.13.



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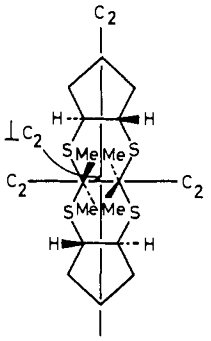
Kyan and Owen[7] have recently reported the preparation from *dl*-cyclopentane-*trans*-1,2-dithiol of a 2,2,7,7-tetramethyl-4,5:9,10-biscyclopentano-1,3,6,8-tetrathiacyclodecane, a sample of which was kindly given to us by Dr. Owen. Since this compound showed a sharp 12-proton singlet (τ 8.46 in chloroform-*d*) for the four methyl groups in its pmr spectrum, it has been tentatively[8] assigned the *trans-anti-trans* configuration **7**, which like **6** has three mutually perpendicular C_2 axes (point group, D_2).



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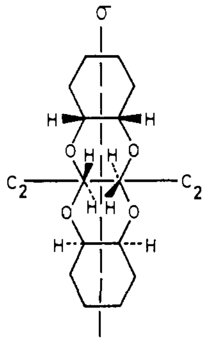
Reaction of cyclohexane-*cis*-1,2-diol with methylene bromide and sodium hydride in N,N-dimethylformamide as described[1] yielded a 4,5:9,10-biscyclohexano-1,3,6,8-tetraoxacyclodecane which has either a *cis-anti-cis* (**8**) or *cis-syn-cis* (**9**) configuration as well as the main product, *cis*-hexahydro-1,3-benzodioxolane (**10**).



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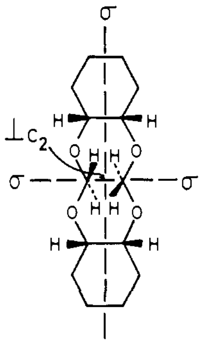

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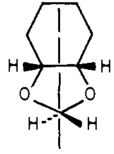

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Comparison of the symmetry properties of the two conformationally unstable tetraoxacyclodecane isomers shows that one (**8**) has a σ plane perpendicular to a C_2 axis (point group, C_{2h}) and the other (**9**) has two perpendicular σ planes which intersect on a C_2 axis (point group, C_{2v}). Thus, in the *cis-anti-cis* arrangement, the two O-methylene groups are enantiotopic[3] and each pair of O-methylene protons is equivalent, while in the *cis-syn-cis* arrangement, although the two O-methylene groups are equivalent, each pair of O-methylene protons is diastereotopic. Since the pmr spectrum shows a sharp four-proton singlet (τ 5.20) for the O-methylene protons, the isomer was tenatively[8] assigned the *cis-anti-cis* configuration **8**.

Comparison of the symmetry properties of *cis*-hexahydro-1,3-benzodioxolane (**10**) with those of the *trans* isomer **1** shows that the former has a σ plane and the latter a C_2 axis. The O-methylene protons of **10** are diastereotopic so it is not surprising that an AB quartet with $J_{AB} \simeq 1$ Hz was observed[1] at τ 5.95 in the pmr spectrum. The O-methylene protons of **1** are equivalent and the expected singlet is observed[1] at τ 4.93 in the pmr spectrum.[10] The other product, *trans*-hexahydro-1,3,5-benzotrioxepane (**2**), of the based-catalyzed methylenation of *dl*-cyclohexane-*trans*-1,2-diol also has a C_2 axis. Thus, although the O-methylene groups are equivalent, each pair of O-methylene protons is diastereotopic. The pmr spectrum of this trioxepane showed a four-proton AB quartet (τ 5.09, $\Delta\nu_{AB} = 4.14$ Hz, $J_{AB} = 6.0$ Hz at 33°) indicating that each pair of O-methylene protons is anisochronous.

Experimental Section

Melting points are uncorrected and were determined on a Fisher-Johns apparatus. Proton magnetic resonance (pmr) spectra were

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[7] M. Kyan and L. N. Owen, *J. Chem. Soc.*, 1298 (1965).

[8] The observation that the protons are isochronous does not entirely rule out the possibility that the methyl groups in **7** and the O-methylene protons in **8** are diastereotopic. Cases of accidental coincidence of pmr signals are known (see, for example, ref 4 and 9).

[9] M. van Gorkom and G. E. Hall, *Quart. Rev.* (London), **22**, 14 (1968).

[10] It is also worth drawing attention to the fact that the O-methylene protons of methyl 4,6-O-benzylidene-2,3-O-methylene-α-D-gluco- and galactopyranosides are diastereotopic. Thus, the isochronous O-methylene protons of the glucose derivative[1] constitute a case of accidental coincidence of pmr signals.[4] It is not necessary to invoke the explanation[1] of preferential shielding of one of the O-methylene protons in the galactose derivative to account for their anisochronous nature.

measured by a Varian A-60A spectrometer on 10% (w/v) solutions in chloroform-*d*-carbon disulfide (1:1, v/v)[11] with tetramethylsilane (τ 10.00) as internal standard.

trans-**Hexahydro-1,3,5-benzotrioxepane (2) and** ***trans-syn-trans*****-4,5:9,10-biscyclohexano-1,3,6,8-tetraoxacyclodecane (3)** were prepared according to the procedure of Brimacombe, *et al.*[1] The trioxepane **2** had bp 34–37° (0.02 mm) and n^{20}D 1.4659 (lit.[1] n^{20}D 1.4657). The tetraoxacyclodecane **3** had mp 164.5–165.5° (lit.[1] mp 166–167.5°).

meso*- (4) and** ***dl**-di-(*****trans*****-2-hydroxycyclohexyloxy)methane (5)** were prepared according to the procedure described by Head.[6] The *meso* compound **4** had mp 80–82° (lit.[6] mp 81–82°) and the *dl* modification **5** had mp 102.5–103.5° (lit.[6] mp 104–105°).

cis-anti-cis**-4,5:9,10-Biscyclohexano-1,3,6,8-tetraoxacyclodecane (8)** was prepared according to the procedure described by Brimacombe, *et al.*[1] It had mp 139–140° (lit.[1] mp 142–143°).

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[11] This mixed solvent system was used because it was suitable for low-temperature studies, which will be reported elsewhere at a later date.

Stereochemistry of Some Reactions of Phospholane Derivatives[1]

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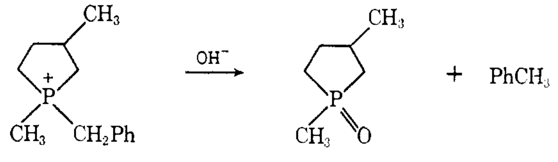
Abstract: The pure geometric isomers of 1-benzyl-1,3-dimethylphospholanium bromide (**1a** and **1b**) have been prepared and were subjected to treatment with aqueous sodium hydroxide. This resulted in the formation of the isomeric 1,3-dimethylphospholane 1-oxides (**2a** and **2b**) with complete retention of configuration. Arguments are presented favoring a stereospecific apical-equatorial displacement reaction. Reaction of **1a** and **1b** with sodium *n*-butoxide gave **2a** and **2b** with a high degree of retention but with detectable inversion. The pure oxides (**2a** and **2b**) yielded identical mixtures of these oxides when treated separately with concentrated hydrochloric acid. Pseudorotation of an intermediate phosphorane is suggested as being responsible for the formation of product mixtures. The oxide **2b** was observed to be reduced smoothly by phenylsilane to the corresponding phosphine (**4b**) with complete retention of configuration. Phosphines **4a** and **4b** are configurationally stable for long periods at 150°. Unlike **1**, 1,1-dimethylphospholanium bromide (**22a**) underwent slow cleavage with aqueous sodium hydroxide forming ring-opened product (**23**) as well as manifesting cleavage external to the ring (**22b**).

In a preliminary communication,[2] it was reported that both geometric isomers of 1-benzyl-1,3-dimethylphospholanium bromide (**1a** and **1b**) undergo cleavage with aqueous sodium hydroxide to produce exclusively toluene and the corresponding oxide (**2a** and **2b**) *with complete retention of configuration at the phosphorus atom.*



1a, mp 168.5–169.5°
b, mp 180–180.5°

2a, mp 22°
b, mp 72–73.5°

Although no definite assignment of the geometric configuration of the phosphonium salts has yet been made,[3] it was nevertheless possible to demonstrate the stereochemistry of the reaction in the following way. A mixture of **2a** and **2b** was prepared by catalytic reduction of 1,3-dimethyl-3-phospholene 1-oxide (**3**).[4] Reduction of the oxide mixture with trichlorosilane[5] produced a mixture of phosphines (**4a** and **4b**) which, after careful distillation, provided two fractions: pure **4a** and a mixture of the two phosphines enriched in **4b**. The configurational stability of **4** was evidenced by heating a mixture of **4a** and **4b** at various temperatures up to 150° for a 3-day period without any change occurring in the nmr spectrum when it was recorded again at room temperature.[6] Quaternization of **4a** with benzyl bromide yielded **1a**, which upon cleavage with aqueous sodium hydroxide yielded **2a**. The oxide **2a** was also produced by oxidation of **4a** with *t*-butyl hydroperoxide, a reaction known to occur with retention of configuration at phosphorus.[7] Isomer **1b**, obtained by quaternizing the

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[1] This investigation was supported by National Institute of General Medical Sciences Special Research Fellowship 1-F3-GM-36,717-01 and in part by National Science Foundation Grant GP-7407.

[2] K. L. Marsi, *Chem. Commun.*, 846 (1968).

[3] The structure of **1b** is presently being determined by X-ray analysis by Dr. C. N. Caughlin, Montana State University.

[4] L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).

[5] (a) L. Horner and W. D. Balzer, *Tetrahedron Lett.*, 1157 (1965); (b) H. Fritsche, U. Hasserodt, and F. Korte, *Chem. Ber.*, **97**, 1988 (1964); **98**, 171 (1965); S. E. Cremer and R. J. Chorvat, *J. Org. Chem.*, **32**, 4066 (1967); S. E. Cremer, *Chem. Commun.*, 1132 (1968).

[6] By comparison, methyl-*n*-propylphenylphosphine racemized somewhat after 3-hr refluxing in toluene, showed about 20% racemization when distilled *in vacuo* [bp 86–88° (2.5–3.0 mm)], and was completely racemized during atmospheric distillation. See L. Horner, H. Fuchs, H. Winkler, and A. Rapp, *Tetrahedron Lett.*, 965 (1963). S. E. Cremer, R. J. Chorvat, C. H. Chang, and D. W. Davis, *ibid.*, 5799 (1968), have shown that 1,2,2,3,4,4-hexamethylphosphetane is stable to inversion at 162° for 4 days, but that the 1-phenyl and 1-*t*-butyl analogs undergo racemization at lower temperatures and possess activation energies quite similar to that of methyl-*n*-propylphenylphosphine. 1-Methyl-4-ethyl-4-phosphorinanol has also been shown to be configurationally stable [L. D. Quin and H. E. Shook, Jr., *ibid.*, 2193 (1965); see also H. E. Shook, Jr., and L. D. Quin, *J. Amer. Chem. Soc.*, **89**, 1841 (1967)].

[7] D. B. Denney and J. W. Hanifin, Jr., *Tetrahedron Lett.*, 2177 (1963).