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Note

Steric requirement of a methyl group in simple models of anhydropyranoses

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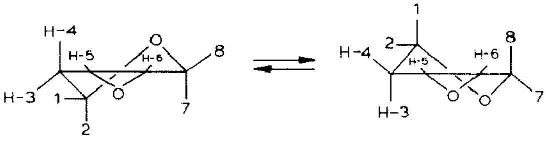
The conformational analysis of pyranoses is often made difficult by the presence on the six-membered ring of several substituents, which, apart from their steric requirements, can interact through hydrogen bonds or be subject to dipole–dipole interactions[1].

A study of simple model compounds derived from tetrahydropyran can provide useful information by isolating particular effects on the conformational equilibria. In 3,4-epoxytetrahydropyran (**1**), the simplest model for 2,3- or 3,4-anhydropyranoses, there is a significant preference[2] ($-\Delta G^\circ$ ~0.8 kcal/mol) for the conformation **A****, which was attributed to an electrostatic repulsion between dipoles in conformer **B**. We have now further elaborated this approach by studying the ^{1}H-n.m.r. spectra of the diastereomeric *trans*- (**2**) and *cis*-2-methyl-3,4-epoxytetrahydropyrans (**3**), which are simple models of the 3,4-anhydrohexopyranoses, in order to assess the conformational requirements of a C_1 substituent at position 5.



A **B**

1 1,2,7,8 = H
2 1,2,7 = H, 8 = Me
3 1,2,8 = H, 7 = Me
4 1 = ^{t}Bu, 2,7,8 = H
5 1,7,8 = H, 2 = ^{t}Bu

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According to the rules of nomenclature[3], conformations **A and **B** correspond, respectively, to $^1H_0$ and $^0H_1$ if **1** is considered as a model for a 3,4-anhydropyranose, and to $^0H_5$ and $^5H_0$ for a 2,3-anhydropyranose.

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TABLE I

CHEMICAL SHIFTS CALCULATED FOR **2** AND **3**[a]

Atom	**2** *$(CDCl_3)$*	**2** *(C_6D_6)*	**3** *$(CDCl_3)$*	**3** *(C_6D_6)*
H-1	3.59	3.34	3.32	2.87
H-2	3.41	3.33	3.75	3.48
H-3	1.92	1.48	2.03	1.68
H-4	2.01	1.58	1.85	1.20
H-5	3.31	2.88	3.38	2.85
H-6	2.95	2.57	3.00	2.48
H-7	3.89	3.79	—	—
H-8	—	—	3.92	3.52
CH_3	1.32	1.08	1.34	1.27

[a]Expressed in p.p.m. (Me_4Si internal standard).

TABLE II

VICINAL COUPLING CONSTANTS (Hz) CALCULATED FOR 3,4-EPOXYTETRAHYDROPYRANS

Coupling constant	**1**[a] *(C_6D_6)*	**2** *$(CDCl_3)$*	**2** *(C_6D_6)*	**3** *$(CDCl_3)$*	**3** *(C_6D_6)*	**4**[a] *$(CDCl_3)$*	**5**[a] *$(CDCl_3)$*
$J_{1,2}$	−12.5	−12.0	−12.0	−12.4	−12.0	—	—
$J_{1,3}$	5.5	1.6	1.6	10.0	9.6	—	11.6
$J_{1,4}$	5.5	6.0	6.0	4.5	4.4	—	3.6
$J_{2,3}$	4.5	3.3	3.0	5.8	5.8	2.4	—
$J_{2,4}$	8.2	11.9	11.2	3.3	4.0	11.4	—
$J_{3,4}$	−15.0	−14.0	−14.0	−15.5	−15.3	−14.4	−13.4
$J_{3,5}$	1.5[b]	1.8	1.8	0.7	0.7	2.3	0.0
$J_{4,5}$	3.0	2.0	2.0	4.8	4.7	2.2	6.7
$J_{5,6}$	4.4[b]	4.2	4.2	4.4	4.2	4.4	3.9
$J_{6,7}$	0.0	0.4	0.4	—	—	0.0	0.0
$J_{6,8}$	3.1	—	—	1.5	1.5	4.0	0.0

[a]Ref. 2. [b]Calculated for 2,2,6,6-tetradeuterio-3,4-epoxytetrahydropyran[2].

The spectra (200 MHz, in $CDCl_3$ and in C_6D_6) of **2** and **3** were interpreted using the LEQUOR programme[4], a special version[5] of LAOCOON/III, that can be extended to 7-spin systems. This simplification neglects the couplings involving the methyl protons, but should not prevent the use of the data for conformational analysis, since it should affect only the multiplicity of the signal of the proton geminal to methyl (H-7 for **2** and H-8 for **3**).

The chemical shifts and coupling constants obtained from the analysis are given in Tables I and II, and Figs. 1–4 show the experimental and computed spectra. The computed spectra reproduce fairly well the experimental ones, except for the signals of H-7 of **2** and H-8 of **3** (for the reasons stated above), and for the broadening of some signals (possibly due to small long-range couplings that were not included in the computations). The data in Tables I and II show that, whereas

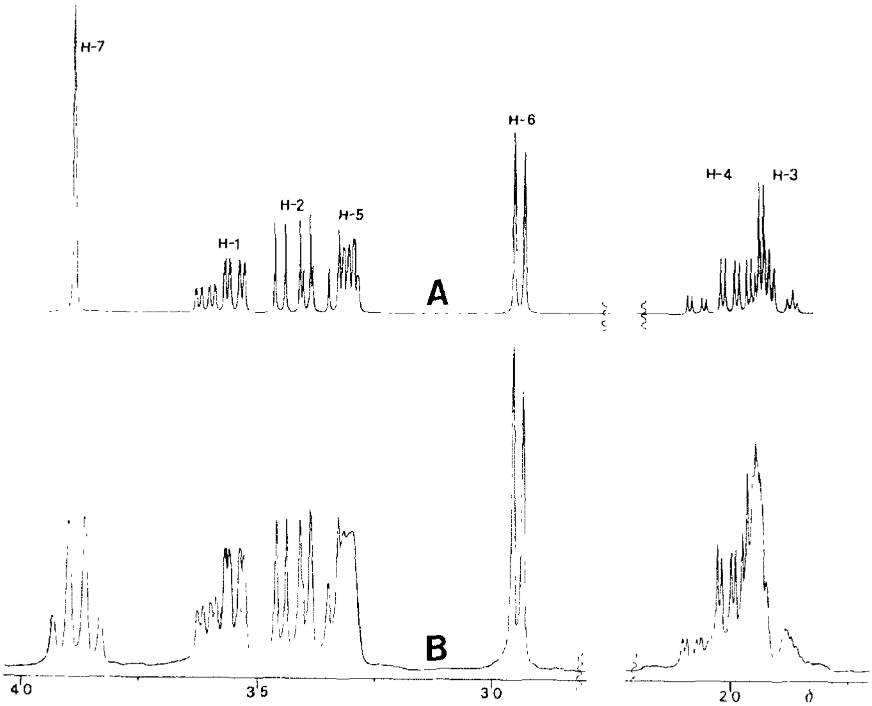


Fig. 1. Observed (B) and calculated (A) spectra of a solution of *trans*-2-methyl-3,4-epoxytetrahydropyran (**2**) in $CDCl_3$.

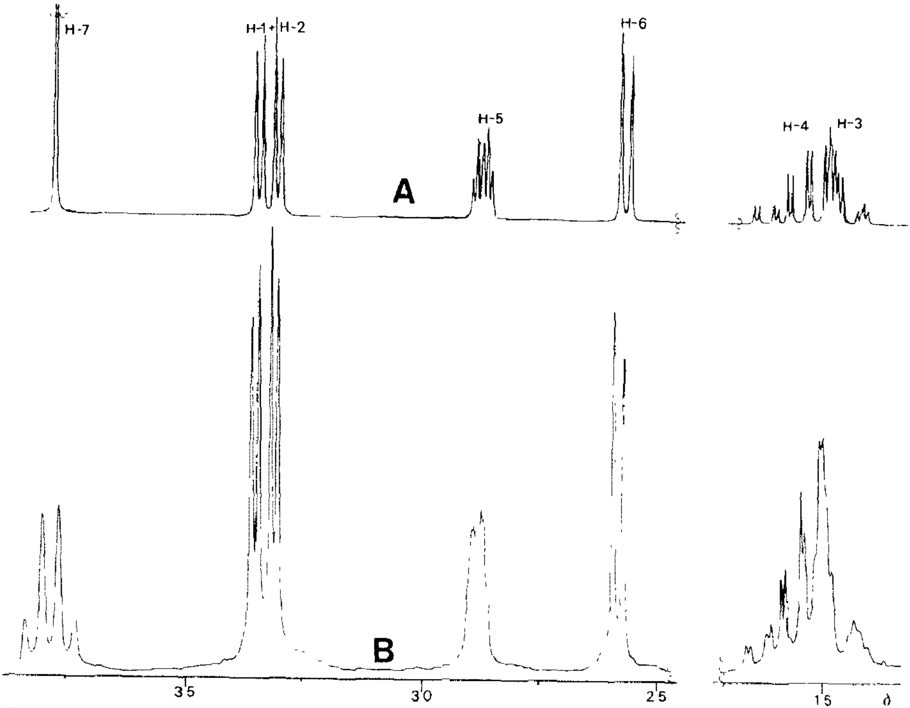


Fig. 2. Observed (B) and calculated (A) spectra of a solution of *trans*-2-methyl-3,4-epoxytetrahydropyran (**2**) in C_6D_6.

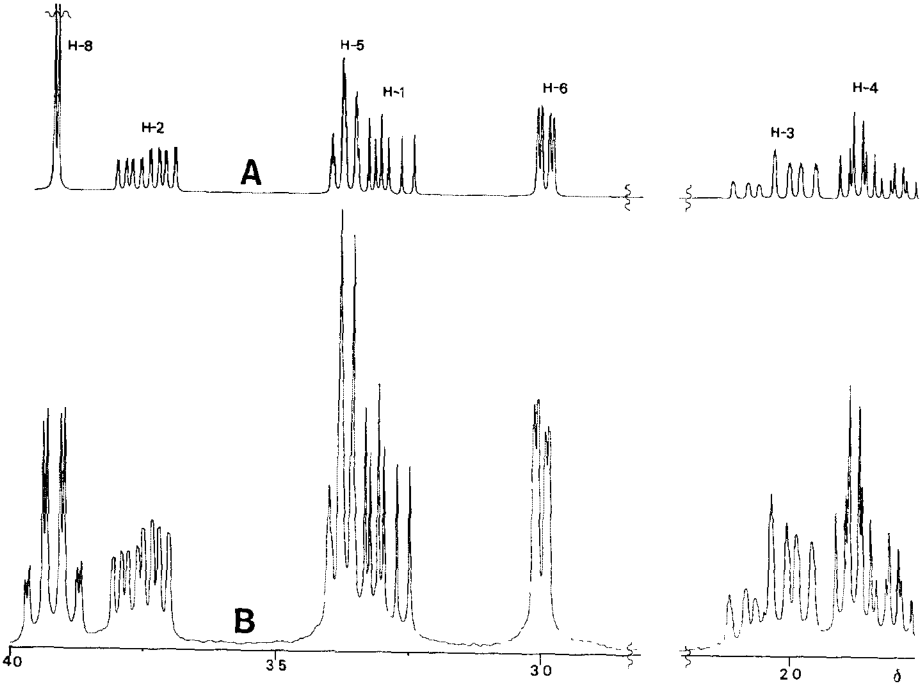


Fig. 3. Observed (B) and calculated (A) spectra of a solution of *cis*-2-methyl-3,4-epoxytetrahydropyran (**3**) in $CDCl_3$.

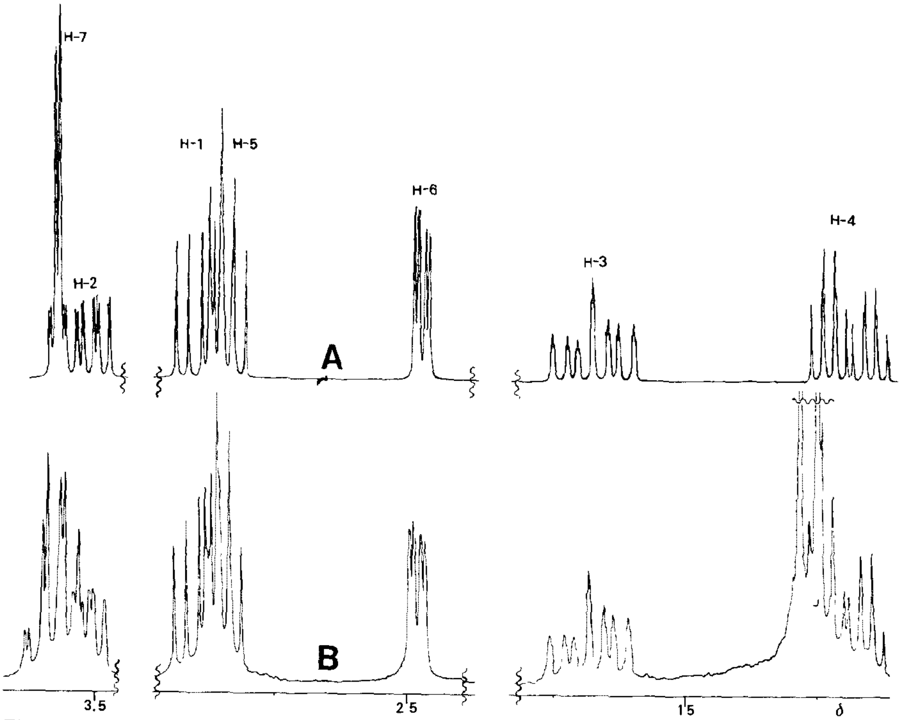
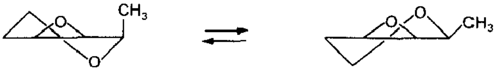


Fig. 4. Observed (B) and calculated (A) spectra of a solution of *cis*-2-methyl-3,4-epoxytetrahydropyran (**3**) in C_6D_6.

the change of solvent from $CDCl_3$ to C_6D_6 significantly affects the chemical shift values because of anisotropic effects, the coupling constants change very little, showing that the conformations are similar in spite of the different polarity and solvating powers, as previously found[2] for **1**. The spectrum of a solution of **2** in C_6D_6 is an example of a "deceptively simple" system, owing to the fortuitous isochronicity of H-1 and H-2 ($\Delta\delta$ 0.01) that reduces the corresponding signals to only 4 lines, as compared with the 8 doublet and 8 narrow lines for the spectrum of a solution in $CDCl_3$.



3A **3B**

The coupling constants for **2** are similar to those for the conformationally rigid model **4**, indicating that the *trans*-epoxide **2** exists essentially in conformation **A**, with an equatorial methyl group. This finding was expected, since the equatorial conformer is favoured also by the electrostatic effect mentioned above. On the other hand, for the *cis*-epoxide **3**, the steric effect of the methyl group and the oxygen dipole-interaction should be opposed, with the former favouring conformer **B** and the latter conformer **A**. The coupling constant data confirm this assumption since the values for **3** lie between those for **4** (model for conformer **A**) and **5** (model for conformer **B**), pointing to conformational mobility of **3**, with a significant contribution from both conformers. A rough assessment of the conformational equilibrium can be made on the basis of Eq. *1*, which allows an estimation of the molar fractions of conformers **A** and **B** (X_A and X_B) at equilibrium. The values obtained for $J_{4,5}$ and $J_{6,8}$ agree well and indicate a 60:40 ratio of **B** to **A** (Table III), whereas a higher preference for conformer **B** (68:32) would be deduced from the $J_{3,5}$ value. The latter value is less reliable, because of the higher error expected in applying Eq. *1* as a result of the smaller difference in the J values of the two rigid models. A value of 60 ±5% is therefore assumed as an estimate of the amount of equatorial conformer present at equilibrium, which corresponds to a $-\Delta G°$ value of 0.24 ±0.12 kcal/mol. If the previously established value of ~0.8 kcal/mol for the destabilisation of **B** versus **A** conformation is taken into account and this value is added to $-\Delta G°$, then a value of 1.04 ±0.13 kcal/mol is obtained for the contribution of the steric hindrance of the methyl group to the conformational equilibrium of **3** and therefore of a 3,4-anhydro-6-deoxyhexopyranose. Surprisingly, such a value is lower than the $-\Delta G°$ value of 2.86 kcal/mol reported[6] for the conformational energy of the methyl group in 2-methyltetrahydropyran. This difference could be accounted for by a decrease of the repulsive interaction of the pseudo-axial methyl group and H-6*a*, owing to the slightly greater distance in the half-chair conformation of the epoxide compared to that in the corresponding chair conformation of 2-methyltetrahydropyran, and possibly because the methyl group in **3A** interferes less with the *cis*-epoxide group than it does with H-6*a* in 2-methyltetrahydro-

TABLE III

CONFORMATIONAL EQUILIBRIUM FOR 3,4-EPOXYTETRAHYDROPYRANS[a]

Coupling constant	**1** *($CDCl_3$)*	**1** *(C_6D_6)*	**2** *($CDCl_3$)*	**2** *(C_6D_6)*	**3** *($CDCl_3$)*	**3** *(C_6D_6)*
$J_{4,5}$	80[b]	82[c]	100	100	42	44
$J_{6,8}$	78[c]	78[c]	—	—	38	38

[a]Expressed as percentage of conformer **A**; the error in the given values is ±5% (see Experimental). [b]Determined from the *J* values of 2,2,6,6-tetradeuterio-3,4-epoxytetrahydropyran[2]. [c]Ref. 2.

pyran. It may be assumed further that, because of the greater flexibility of the half-chair conformation of **3** compared with that of a normal chair conformation, small strain-releasing deformations may contribute to a decrease in conformational energy.

$$J_{\text{mobile}} = X_A J_A + X_B J_B \qquad (1)$$

Thus, even if the data reported are not rigorously quantitative, the previously assumed repulsive effect between epoxide and tetrahydropyran ring oxygens is confirmed and found to affect significantly the conformational equilibrium of **3**, producing an unexpectedly low value for the conformational energy of its methyl group.

EXPERIMENTAL

N.m.r. spectra were recorded for 10% solutions in $CDCl_3$ or C_6D_6 with a Varian XL200 instrument.

To compute the final chemical shifts, proton–proton couplings, and theoretical spectra, an iterative programme (LEQUOR[4]), based on the method of Castellano and Bothner-By[5], was applied and solved with an IBM 370/3332 computer equipped with a Calcomping accessory. The parameters obtained should be correct to within ±0.2 Hz. A similar error value determined a standard deviation in the conformer percentage of ±5% when Eq. *1* was applied to $J_{4,5}$ and $J_{6,8}$, and ±10% when applied to $J_{3,5}$.

Compounds **2** and **3** were prepared as previously reported[7].

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