A Variable-Temperature NMR Study of Several 2-Aryl-3-methyl-6-methoxy-4-tetrahydropyranones

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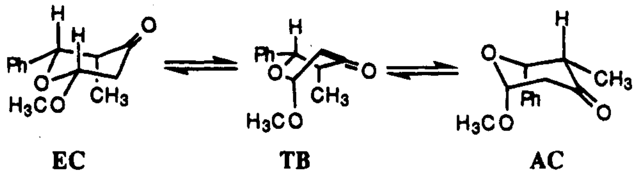
Received March 31, 1994[⊗]

A study by variable-temperature NMR indicates rapid equilibrium occurring among conformational isomers in several 4-tetrahydropyranones (THPN) even at −100 °C. A small preference (~0.3 kcal/mol) for the diequatorial conformer (EC) is observed in several solvents. This preference is decreased in some of the solvents, and the order of favoring the EC form is $CHCl_3$ > $C_6H_5CH_3$ > CH_3COCH_3 > CH_3OH.

Introduction

The conformational profile of 4-tetrahydropyranone (4-THPN) is directly relevant to the current interests in diastereofacial selectivity.[1−9] A survey of literature by Cieplak found that the hydride reduction of 4-THPNs suffered from a universally higher percentage of axial attack than their corresponding cyclohexanone derivatives.[2] This observation was explained on the basis of the stabilization of the incipient antibonding orbital, $\sigma_{\neq}^*$. No consideration was given to the difference in conformational behavior between 4-THPN and cyclohexanone. Our earlier computational study points out the possibility of a nonhomogeneous conformational mixture for the 4-THPN system.[1] As a rule, computational predictions should always be assessed by comparison with experimental results. Therefore, we have sought experimental evidence that can be used to judge the quality of the computational results. Now we wish to present the variable-temperature NMR data for several 4-THPNs (*cis*- and *trans*-**1** and **2**). The results corroborate our computational study in that they show that 4-THPNs have a mobile ring structure. On the other hand, the experimental results also show that the diequatorial conformer (EC) form is slightly favored (by ~0.3 kcal/mol). This differs from the MM2 study, which predicts that the diaxial conformer (AC) form is favored by 0.51 kcal/mol.[1] This small energy difference between experiments and theory may be due to a number of reasons, such as the solvent effect. Therefore, several different solvents have been studied and the results are discussed in the following report.



EC **TB** **AC**

Experimental Section

The 4-THPNs are synthesized according to the procedure developed by Danishefsky.[3] The variable-temperature NMR experiments are performed on a 300-MHz Bruker instrument with a variable-temperature probe.[10] Typically a total of 128 000 data points are collected over a window of 2000 Hz centered on the anomeric proton resonance. The digital resolution of such measurements is about ±0.02 Hz. The data collected at various temperatures are reproducible to 0.05 Hz in duplicate runs. A typical sample concentration is ~0.05 M. Pure nitrogen or argon gas is passed through the sample solution to purge oxygen before each run.

Results and Discussion

A. Qualitative Analysis. The variable-temperature NMR data in several solvents for the 4-THPN derivatives are listed in Table 1. To interpret the coupling constant change with temperature, it is easy to first focus on the Karplus type of relationship between the dihedral angle and the magnitude of the three-bond coupling.[11] We have concentrated our efforts on the compound *cis*-**1** since this particular structure was the focus of the previous discussion.[1] Because the orientations of the protons H_a and H_b shift from diaxial in the EC form to diequatorial in the AC form, the three-bond coupling $^3J_{ab}$ should experience a greater change than either $^3J_{de}$ or $^3J_{ac}$ if there is an equilibrium between these two forms. This is indeed the case (Table 1). The greatest change in $^3J_{ab}$ occurred in polar solvent, methanol. The $^3J_{ab}$ should have a greater magnitude in the EC form since for *cis*-**1** the dihedral angle involving H_a and H_b is close to 180° in this conformer.

The $^3J_{ab}$ should be small in the AC form and even smaller in the TB form since the corresponding dihedral angles are close to 60 °C and 90 °C in these two conformations, respectively. Although on the basis of the molecular mechanics, the TB form is nearly as stable as

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[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1994.

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Table 1. Selected Chemical Shifts (δ, ppm) and Coupling Constants (Hz) for 4-THPN Derivatives 1 and 2 at Various Temperatures

T (K)	δH_d	δH_a	$\delta(-OCH_3)$	J_{de} (Hz)	J_{ab} (Hz)	J_{ac} (Hz)
cis-**1**						
In Chloroform						
243	4.798	4.698	3.606	broad	9.23	3.13
253	4.796	4.696	3.602	2.63	9.21	3.16
263	4.793	4.695	3.599	2.70	9.09	3.18
273	4.791	4.696	3.597	2.71	9.09	3.19
283	4.791	4.697	3.593	2.74	9.07	3.22
295	4.791	4.699	3.590	2.82	8.98	3.20
305	4.787	4.702	3.588	2.74	8.93	3.21
315	4.795	4.707	3.585	2.84	8.86	3.23
In Acetone						
183	4.94	4.81	3.49	2.58	9.48	2.66
193	4.95	4.81	3.50	2.72	9.49	2.77
213	4.95	4.82	3.50	2.79	9.34	2.89
223	4.96	4.83	3.52	2.79	9.29	2.93
243	4.97	4.84	3.52	2.82	9.13	3.01
253	4.97	4.84	3.53	2.85	9.04	3.05
263	4.97	4.85	3.53	2.87	8.95	3.09
273	4.97	4.85	3.53	2.90	8.85	3.15
295	4.97	4.85	3.54	3.00	8.62	3.28
325	4.98	4.86	3.55	2.98	8.30	3.50
In Toluene						
223	4.32	4.13	3.47	2.41	broad	3.22
243	4.38	4.21	3.47	2.68	9.16	3.18
263	4.43	4.27	3.47	2.81	9.13	3.12
273	4.45	4.30	3.47	2.83	9.13	3.12
295	4.50	4.36	3.48	2.90	9.02	3.11
325	4.55	4.43	3.48	2.92	8.82	3.17
In Methanol						
223	4.93	4.80	3.58	2.68	9.12	3.02
243	4.93	4.81	3.58	2.70	8.94	3.12
263	4.93	4.81	3.58	2.89	8.70	3.27
273	4.93	4.82	3.57	2.93	8.62	3.34
295	4.93	4.82	3.57	2.90	8.28	3.56
325	4.93	4.83	3.56	3.05	7.78	3.96
trans-**1**						
In Chloroform						
223	5.221	5.250	3.286	2.50	4.81	
243	5.247	5.259	3.312	2.37	4.85	1.10
263	5.256	5.244	3.316	2.44	4.94	1.16
273	5.252	5.244	3.318	2.43	4.91	1.16
295	5.262	5.233	3.324	3.01	4.96	1.22
325	5.273	5.219	3.334	3.14	5.06	1.25
cis-**2**						
In Chloroform						
223	4.758	4.701	3.606	2.50	9.09	3.36
243	4.749	4.692	3.596	2.62	9.03	3.26
263	4.744	4.688	3.587	2.74	9.08	3.43
273	4.740	4.686	3.583	2.75	8.98	3.36
295	4.743	4.692	3.578	2.64	8.85	3.20
325	4.746	4.702	3.571	2.61	8.70	3.25
trans-**2**						
In Chloroform						
223	5.184	5.251	3.297	2.65	4.79	
243	5.185	5.237	3.297	2.54	4.93	
263	5.191	5.228	3.301	2.96	4.91	1.14
273	5.195	5.224	3.304	2.78	4.92	1.17
295	5.203	5.206	3.311	2.55	4.95	1.15
325	5.217	5.203	3.323	2.53	5.10	1.22

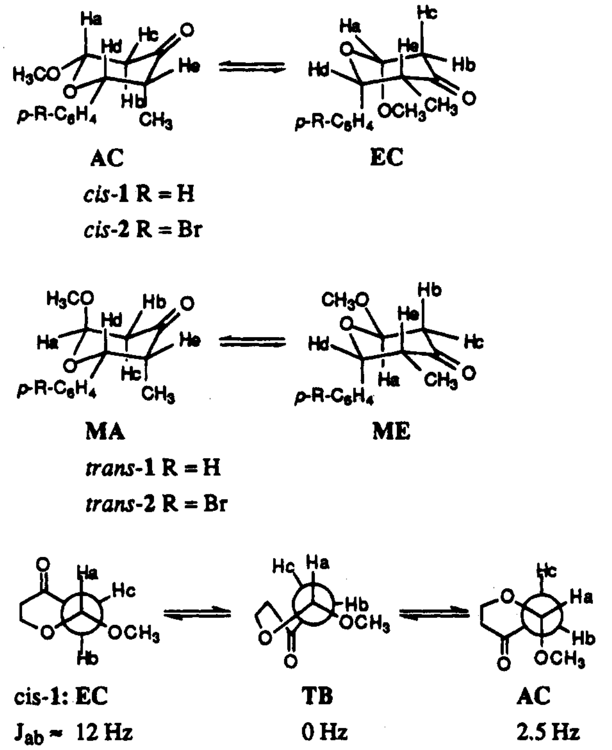

Figure 1. Structure and conformations involved in the equilibrium of 2-aryl-3-methyl-6-methoxy-4-tetrahydropyranones.

the EC form, *ab initio* calculations on 2-hydroxy-4-THPN places the TB form 2.72 kcal/mol higher in energy than the AC form.[1] Therefore, we assume that the TB form is negligible in the following discussion.[12] As the temperature is lowered, the observed coupling constant, $^3J_{ab}$, increases steadily, an indication that the diaxial form AC is shifting toward the EC form. According to the Boltzman distribution law, this indicates that the diequatorial form (EC) is more stable than the diaxial form (AC) in solution. Therefore Danishefsky's intuition was correct in assigning the diequatorial form as the ground-state conformation.[3] However, at temperatures as low as −100 °C, the ^1H NMR spectra of **1** remains sharp, and the coupling constants change gradually indicating rapid equilibrium among the conformational isomers. A similar trend is also observed for the bromophenyl analog of **1**, i.e., *cis*-**2**. Thus, even though the diequatorial form is preferred, the 4-THPN derivatives *cis*-**1** and *cis*-**2** exist in solution as a nonhomogeneous conformational mixture.

The $^3J_{ab}$ for the *trans* isomers (*trans*-**1** and -**2**, Figure 1) are much smaller than those for the *cis* forms indicating that the stable conformer contains an axial methoxy group (MA). In this conformation (MA), both H_a and H_b are in the equatorial orientation and the torsional angle H_aCCH_b is ~60°. The coupling between them should be small. In the other conformation, where the methoxy group is equatorially placed (ME), both H_a and H_b are in the axial orientation and the torsional angle H_aCCH_b is ~180°. Consequently, the coupling between them should be large. The three-bond coupling $^3J_{ab}$ increases as the temperature rises, indicating that the population of the isomer ME becomes greater at higher temperatures. This is consistent with our earlier calculations[1] and also consistent with the consideration of the steric and anomeric effects.[13] However, it is surprising to see that the *trans* isomers also exhibit considerable conformational interconversion. That is even when a phenyl group works (sterically prefers the equatorial position) in unison

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(12) As one reviewer pointed out, the AC form of *cis*-1 contains a 1,3-diaxial interaction, which is absent in 2-hydroxy-4-THPN. Therefore caution should be excised in using this assumption.

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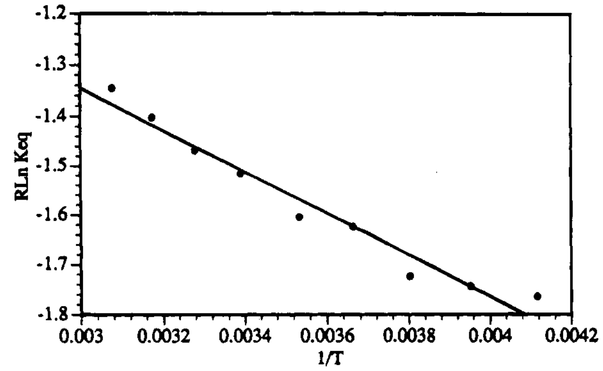

Figure 2. Van't Hoff plot with best fit straight line for *cis*-**1** in $CDCl_3$ (r = 0.96).

with a methoxy group (electronically favors the axial position), for reasons beyond the scope of this report, the disfavored conformation (ME) is still present to a significant amount.

B. Quantitative Analysis. Quantitatively, it is possible to calculate the energy difference between the EC and the AC form by the standard van't Hoff analysis if we assume that the TB form is negligible. The van't Hoff equation uses the relationship between the equilibrium constant and the temperature to obtain the enthalpic and entropic differences. The fractional populations of the conformational isomers are related to the observed coupling constants by the J-averaging method.[14] In order to use this methodology, two standard coupling constants, characteristic of the EC and the AC isomers, J_{EC} and J_{AC} must be found. One must be careful in the choice of J_{EC} and J_{AC} since they make a difference in the final values of the enthalpy and entropy. The J_{EC} and J_{AC} are carefully chosen based on two criteria. First, we searched the literature for similar compounds with known coupling constants.[15] Second, by using a linear regression analysis program, the best values of J_{EC} and J_{AC} are found by fitting the experimental VT NMR data with varying J_{EC} and J_{AC}, which must be within the reasonable range set by the known compounds and give the smallest mean standard error. Part of the analysis is compiled in the table of the supplementary material.

The final values chosen to be used in the van't Hoff analysis are $J_{EC} = 12.0$ and $J_{AC} = 2.5$ Hz. As shown in Figure 2, the VT NMR data does not provide a straight line. A most likely explanation is that the ΔH and the ΔS values are temperature dependent, i.e., heat capacity $[\Delta C_p^\circ = (\partial \Delta H^\circ / \partial T)_p]$ is different for the two conformers. A recent treatment of the temperature dependency of ΔH by Dougherty is applied here.[16] Thus, the van't Hoff equation is rewritten as eq 1.

$$R \ln K eq = -\left(\frac{\Delta H_0}{T}\right) + \Delta C_p^\circ \ln T + (\Delta S_0 - \Delta C_p^\circ) \tag{1}$$

$$\Delta H^\circ = \Delta H_0 + T\delta C_p^\circ \tag{2}$$

$$\Delta S^\circ = \Delta S_0 + \Delta C_p^\circ \ln T \tag{3}$$

The plot according to eq 1 has a better fit and is shown in Figure 3. The thermodynamic parameters obtained through this treatment are collected in Table 2. The free-energy differences are from 250 to about 450 cal/mol between the conformers EC and AC. These are small values indicating that there are significant amounts of AC forming at equilibrium. It is interesting to note that in the polar solvent methanol, although the enthalpic difference is relatively large, the free-energy difference is the smallest (ΔG°_{298} = 247 cal/mol) among all solvents studied. This is due to a positive entropy term in going from the EC to the AC form. Why is the AC form entropically favored? The solvent effect on conformational behavior of organic molecules has not been studied extensively. A recent report described a very similar conformational change in taxol.[17] The conformation of taxol changed from a stretched form in nonpolar solvents to a compact form in water. This was described as "hydrophobic collapse" after similar reports for peptidic enzyme inhibitor.[18] These observations appear to be similar to the classical hydrophobic effect,[19] i.e., the tendency for nonpolar groups to aggregate in micelles, in the centers of proteins, and in cell membranes. In the current case, since the entropy term is the largest (ΔS°_{298} = 3.2 eu) in the polar solvent methanol, it appears that the AC form restricts less of the mobility of the solvent molecules surrounding the solute than the EC form. The AC form is more compact than the EC form. Since the "order" of the solvent or the entropy of the solvation process is proportional to the surface area (bulk) of the solute,[19] the EC form causes more negative entropy. A systematic study in the area of solvent effect on conformational changes of medium-sized molecules seems to be in order.

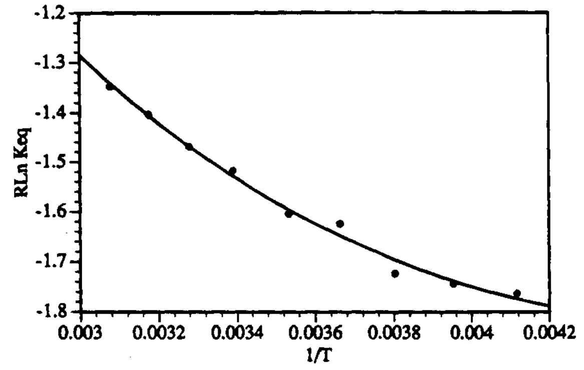

Figure 3. Van't Hoff plot with best fit curve following eq 1 for *cis*-**1** in $CDCl_3$ (r = 0.99).

Table 2. Thermodynamic Parameters for *cis*-1 in Various Solvents

solvent	ΔG°_{298} (cal/mol)	ΔH°_{298} (cal/mol)	ΔS°_{298} (cal/mol K)	ΔC_p° (cal/mol K)
$CDCl_3$	450	530	0.3	6.2
Acetone	340	860	1.7	6.6
Methanol	250	1200	3.2	11.8
Toluene	370	580	0.7	15.6

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(14) The equations involved in the J-averaging method are supplied in the supplementary material. For examples of applications of this method, see: (a) Bothner-By, A. A.; Castellano, S.; Ebersole, S. J.; Gunther, H. *J. Am. Chem. Soc.* **1966**, *88*, 2466. (b) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008.

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Summary

The variable-temperature NMR study indicates that the 4-THPN derivatives have a rapid equilibrium among the isomeric conformations. According to the Curtin–Hammett principle,[20] isomeric product ratio depends only on the energy difference of the diastereomeric transition states. Since we have shown that both the diaxial and the diequatorial conformers (AC and EC) are present, the product (equatorial alcohols) in the L-Selectride reduction[1-3] could have come from the diaxial isomer (AC) resulting from an equatorial attack even though the diaxial isomer (AC) is less populated than the diequatorial form (EC). The greatest change in the three-bond coupling $^3J_{ab}$ occurs in the solvent methanol, followed by acetone, indicating that the diaxial form (AC) is relatively favored in more polar solvent. The hydride reduction of **1** was performed in methanol, a solvent promoting more of the diaxial form, AC. Therefore the AC form must be taken into account when one tries to interpret the product ratio in terms of diastereofacial selection.[1]

Acknowledgment. This research is supported by grants from the National Institutes of Health (GM44260 and GM49745) and the Petroleum Research Fund (PRF 26684-AC4). We thank the National Science Foundation for grants (CHE-9012532 and CHE-8951897) for the purchase of the 300-MHz Bruker FT-NMR and the HP GC-MS.

Supplementary Material Available: Table of J_{EC} and J_{AC} and the equations for J-averaging method (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) For an excellent review, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.