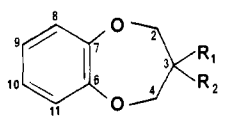
High-Field Proton and Carbon-13 Nuclear Magnetic Resonance Studies of the Conformational Dynamic Properties of Seven-Membered Rings. 3-Substituted Derivatives of 1,5-Benzodioxepin

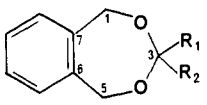
D. Mênard and M. St-Jacques*

Contribution from the Département de Chimie, Université de Montréal, C.P. 6210, Succ. A, Montréal, Québec H3C 3V1, Canada. *Received June 15, 1983*

Abstract: The conformational and dynamic properties of the 3-methyl (**6**), 3-methoxy (**7**), and 3-methoxy-3-methyl (**8**) derivatives of 1,5-benzodioxepin **1** have been investigated by high-field ^1H and ^{13}C NMR methods. Analyses of the spectra at low temperatures (below coalescence) indicate that in CHF_2Cl **6** exists as a mixture of three stable conformations in a 58:32:10 ratio which are found to be Ce (chair form with an equatorial methyl group), TB, and Ca, respectively. Compound 7 exists as a 67:33 mixture of TB and Ca conformations in CHF_2Cl whereas **8** exists as a TB and C mixture (77:23) for which the methoxy group is axial in the C form. Whereas in dimethyl ether **6** still exists as a mixture of three conformers, both **7** and **8** exist exclusively in the TB form. Free energy barriers were determined for the various inversion processes characterizing each compound. The striking differences noted between the conformational properties of the seven-membered heterocycles bearing substituents on C-3 with those of the analogous 1,3-dioxane derivatives are explained in terms of steric, electrostatic, and bond–antibond interactions.

We have recently reported[1] direct NMR observations showing that 1,5-benzodioxepin **1** and its 3,3-dimethyl derivatives (**2**) exist as mixtures of chair (C) and twist-boat (TB) conformations, the





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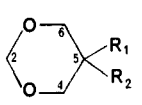

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1: $R_1 = R_2 = H$
2: $R_1 = R_2 = CH_3$
4: $R_1 = OH, R_2 = CH_2NHR'$
6: $R_1 = H, R_2 = CH_3$
7: $R_1 = H, R_2 = OCH_3$
8: $R_1 = CH_3, R_2 = OCH_3$

C form being favored by **1** and the TB form by **2**. A comparison of these initial results with those reported for compounds of the 2,4-benzodioxepin family[2] (**3**) suggested that the study of other derivatives of **1** is required to fully characterize the stereodynamic properties of this seven-membered heterocyclic family.

Interest in this class of compounds is also derived from the pharmaceutical activity[3] associated with closely related compounds such as **4** as well as from structural similarities with 5-substituted derivatives of 1,3-dioxane (**5**). A more complete study of this seven-membered heterocycle should not only provide valuable insight into the effect of heteroatoms on conformational preference but also help define the limitations to applying conformational conclusions derived from studies of six-membered rings to larger cyclic molecules. Whereas TB forms rarely need to be considered for 1,3-dioxanes, previous studies indicate that stabilization of this form is more frequently observed[1,2] for seven-membered rings. Therefore complete investigation of systems other than six-membered rings are important to identify the effect of substituent interactions on the relative stability of twist-boat forms.

We report the results of a high-field DNMR investigation of the 3-methyl (**6**), 3-methoxy (**7**), and 3-methoxy-3-methyl (**8**) derivatives of 1,5-benzodioxepin that, through conformational observations for nonpolar and polar substituents, help delineate between the steric and electronic forces acting competitively between the ring oxygen atoms and the substituents.

Results

All three compounds, **6**–**8**, gave dynamic ^1H and ^{13}C NMR spectral changes at low temperatures. Spectral parameters for these compounds are listed in Tables I and II.

Figure 1 illustrates the 100.62-MHz ^{13}C NMR spectral modifications observed for **6** in CHF_2Cl. The observation in the spectrum at −135 °C that all three sp^3 carbon signals (CH_3, C-3, and C-2,4) exhibit three lines of unequal intensity (58:10:32 ratio) reveals a very unique behavior for **6**. These lines are labeled Ce, Ca, and TB, respectively, in conformity with assignments to the various conformations made in the next section of the text. The signal of the quaternary carbons (C-6,7), on the other hand, splits only into a doublet with the more intense line (labeled C) accounting for 68% of the total intensity and the less intense line (labeled TB) for 32%. A similar spectral change was observed in dimethyl ether for which integration of the upfield signals gave a Ce:Ca:TB intensity ratio of 42:9:49.

The 400.13-MHz ^1H NMR spectrum of **6** in CHF_2Cl, shown partially in Figure 2, reveals that the methyl doublet ($^3J_{HH}$ = 7.0 Hz) recorded at high temperature also gives rise to three distinct signals at −135 °C that show no well-resolved splitting, although the smaller one appears as a broadened doublet. The intensity ratio is the same as that reported for the ^{13}C NMR spectrum. The H-3 signal (not on the figure) also splits at low temperature to give two signals at 2.49 and 2.01 ppm with relative intensity 90:10. Figure 2 reveals that the H-2,4 region of **6**, appearing as a pair of quartets at room temperature, has changed into six signals at −135 °C (see also Table I). Only large splittings are resolved at −135 °C and a $^2J_{HH}$ value of −11 Hz is observed for the doublet signals at 4.33, 4.25, and 3.79 while the upfield triplet at 3.3 ppm further reveals the existence of a large vicinal coupling (10–11 Hz) between one of the H-2,4 protons and H-3, as was confirmed by the effect of irradiating the signal at 2.49 ppm (H-3a). Smaller $^3J_{HH}$ couplings with H-3 (less than 3–4 Hz) are unresolved at low temperature owing to viscosity and residual averaging effects that lead to appreciable line broadening. In contrast to the Ca and Ce signals, those labeled TB did not show any well-resolved splitting. As described in details in the next section, this spectral change was simulated through calculations with the DNMR-2 computer program[4] in which the low-temperature H-2,4 region of the spectrum was considered as the sum of the AM part of three exchanging AMX patterns arising from three three-spin systems corresponding to the Ca, Ce, and TB forms (vide infra). Pertinent chemical shifts are shown schematically in Figure 2 under the

(1) Mênard, D.; St-Jacques, M. *Can. J. Chem.* **1981**, *59*, 1160.
(2) Blanchette, A.; Sauriol-Lord, F.; St-Jacques, M. *J. Am. Chem. Soc.* *100*, **1978**, 4055.
(3) Rooney, C. S.; Stuart, R. S.; Wasson, B. K.; Williams, H. W. R. *Can. J. Chem.* **1975**, *53*, 2279.
(4) Binsch, G. *J. Am. Chem. Soc.* **1969**, *91*, 1304. A copy of the program was obtained from *QCPE*.

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Table I. ^{1}H NMR Spectral Parameters for 6, 7, and 8

compd	temp, °C	conformation	H-2,4	H-3	substituent on C-3
6	−10		4.25 dd (J = −11.9, 4.3 Hz) 3.71 dd (J = −11.9, 7.5 Hz)	2.36 m	0.97 d (J = 6.9 Hz)
	−135	Ce	4.33 d (H-2e ≡ H-4e) (J = −11.0 ± 0.5 Hz) 3.30 t (H-2a) (sep ≈ 10–12 Hz)	2.49 s[a]	0.79 s
		Ca	4.25 d (H-2e) (J = −11.0 Hz) 3.79 d (H-2a) (J = −11.0 Hz)	2.01 s	1.33 s
		TB	4.4 br (H-2 anti) 4.0 br (H-2 syn)	2.49 s	1.04 s
7	−5		4.27 m	3.78 quint (sep ≈ 4.6 Hz)	3.43 s
	−135	C	4.63 d (J = −12.2 Hz) 3.75 d (J = −12.2 Hz)	3.54 s	3.56 s
		TB	4.3 br 4.29 br	3.95 s	3.43 s
8	−10		4.26, 3.92 (AB; J = −12.3 Hz)		3.35 s (OMe) 1.25 s (Me)
	−135	C	4.39 d (J = −12.5 Hz) 3.57 d (J = −12.5 Hz)		3.45 s (OMe) 1.04 s (Me)
		TB	4.04 br 4.17 br 4.38 br		3.32 s (OMe) 1.35 s (Me)

[a] The low-temperature signals labeled s actually represent broadened signals owing to the unresolved couplings because of increased viscosity.

Table II. Carbon-13 Chemical Shifts for 6-8 at High and Low Temperatures[a]

compd	solvent	temp, °C	conformation	C-6,7	C-8 to C-11	C-2,4	C-3	substituent on C-3
6	CHF_2Cl	−10		152.84	124.52, 122.58	77.26	37.17	13.66
		−135	Ce[b]	153.47	125.73, 123.82	78.25	38.12	11.86
			Ca	153.47	125.73, 123.82	77.21	36.64	13.81
			TB	150.94	125.42, 121.49	75.97	34.99	15.16
	CH_3OCH_3	−20		152.56	123.85, 122.17	76.59	37.00	13.86
		−133	Ce	153.72	124.96, 123.43	77.38	38.19	11.71
			Ca	153.72	124.96, 123.43	76.43	36.82	13.87
			TB	151.01	123.43, 121.42	75.33	35.39	15.03
7	CHF_2Cl	−10		151.67	124.40, 122.09	72.45	79.85	57.58
		−125	C	153.39	126.15, 123.70	72.38	78.86	56.85
			TB	150.46	124.08, 121.71	71.26	78.86	57.46
	CH_3OCH_3	−20		151.29	123.56, 121.57	72.01	79.49	
		−130	TB	150.67	123.45, 121.37	71.02	78.78	56.62
8	CHF_2Cl	0		151.26	124.40, 121.97	76.31	78.23	50.25 OMe 18.22 Me
		−130	C	153.31	126.28, 123.64	76.32	77.49	49.90 OMe 15.82 Me
			TB	151.26	124.12, 121.66	78.09 73.08	78.51	50.22 OMe 18.59 Me
	CH_3OCH_3	25		151.52	123.60, 121.56	76.57	77.80	50.31 OMe 19.54 Me
		−130	TB	150.50	123.11, 121.26	76.43 73.25	77.59	49.66 OMe 18.95 Me

[a] Solutions containing internal Me_4Si and CD_2Cl_2 (19%) for field lock purpose. [b] The letters Ce, Ca, and TB refer to conformations described in the text.

simulated spectrum at −135 °C. The intensity ratio of the three three-spin systems was taken as equal to that observed for the three methyl lines whose spectral change was also simulated as shown on the right hand side of Figure 2.

The changes observed at low temperature in the ^{13}C and ^{1}H NMR spectra of the 3-methoxy derivative **7** in CHF_2Cl are illustrated in Figures 3 and 4, respectively. The ^{13}C NMR spectra of **7** show that all ring carbon signals, except that of C-3, have split into doublets with an intensity ratio of 67:33 at low temperature. The coalescence temperature is about −112 °C. In contrast, no spectral change was observed in the ^{13}C NMR spectrum of **7** in dimethyl ether as the temperature was lowered to −130 °C. Table II shows that the ^{13}C chemical shifts in dimethyl ether are similar to those of the taller set of lines (labeled TB) observed in CHF_2Cl.

The 400.13-MHz ^{1}H NMR spectrum of **7** (Figure 4) shows that the signal of the methoxy protons which appears as a singlet at 3.42 ppm at room temperature broadens and splits into a doublet below −115 °C, the coalescence temperature. The more intense high-field component (labeled TB in the spectrum at −120 °C) of the doublet accounts for ~70% of the total intensity while the less intense component (labeled C) accounts for ~30% of the total intensity. This latter component seems to be overlapping partially with a small signal (labeled H-3e in the spectrum at −130 °C) at 3.54 ppm. The H-3 methine signal, which appears as a quintet at room temperature (splitting = 4.6 Hz), broadens significantly at −105 °C, and its band shape suggests that the less intense component after splitting is located at higher field in accord with the above observation.

The H-2,4 signal appearing as a triplet at room temperature (splitting ≈3 Hz) broadens and splits near −103 °C. The peaks then sharpen and at −120 °C four signals are observed at 4.63, 4.43, 4.29, and 3.75 ppm, respectively. These methylene peaks, labeled C, TB, TB, and C, respectively, are effectively broadened doublets as illustrated with a stick diagram under the spectrum recorded at −120 °C. Both smaller doublet signals observed at 4.63 and 3.75 ppm show improved resolution at −135 °C, and a 12.2-Hz splitting is observed. A selective homonuclear decoupling experiment of the signal at 3.75 ppm collapses the signal at 4.63 ppm into a singlet, thus confirming the existence of a $^2J_{HH}$ coupling

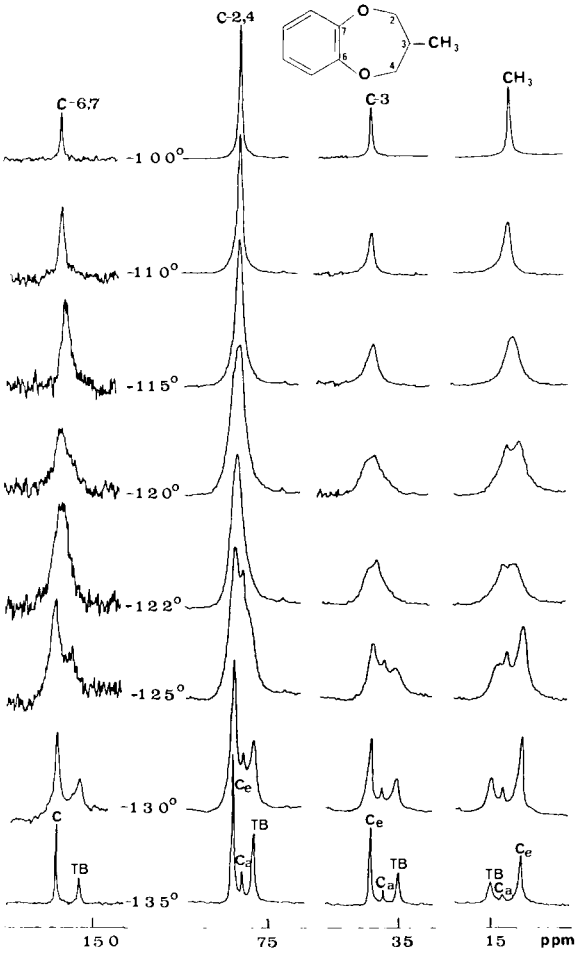


Figure 1. 100.62-MHz ^{13}C NMR spectra of the seven-membered ring carbons of **6** in CHF_2Cl at several temperatures. The letters Ce, Ca, and TB refer to conformations described in the text.

between the protons involved. Below −125 °C, the TB signals at 4.43 and 4.29 ppm undergo further broadening, but this second spectral change does not lead to a recognizable pattern at lower temperature probably because sharpening of the lines would occur much below −135 °C. However, it is clear from the spectrum at −130 °C that the upfield TB signal (~4.29 ppm) broadens much more than the lower field one. In contrast, the two signals of H-2,4 labeled C as well as the two H-3 and the two OCH_3 signals are not affected by this second spectral broadening process.

Figure 5 illustrates the partial ^{13}C NMR spectra of **8** in CHF_2Cl at several temperatures. All carbon signals shown broaden and split. The coalescence temperature for the C-6,7 and CH_3 signals is about −105 °C while it is about −115 °C for the C-2,4 signal and −122 °C for the C-3 and OCH_3 signals. Except for the C-2,4 signal which gives rise to three lines at −130 °C, all other carbon signals split into doublets with components of unequal intensity in the ratio 77:23. Of the three lines observed for the C-2,4 signal, the middle one (labeled C on the expanded partial spectrum) is sharper and accounts for about 24% of the total intensity while the two broader lines (labeled TB, one on each side of line C) each account for about 38% of the total intensity. The lines labeled C′ and TB′ in the same region belong to C-3.

The ^{13}C NMR spectrum of **8** in dimethyl ether showed no spectral change as the temperature was lowered to −140 °C. The ^{13}C chemical shifts in dimethyl ether listed in Table II are found to be similar to those of the taller set of lines (labeled TB) for spectra recorded in CHF_2Cl.

Figure 6 shows that the methyl and methoxy singlets in the ^1H NMR spectrum of **8** in CHF_2Cl split into doublets whose components, labeled C and TB, are of unequal intensity at low temperature. The coalescence temperature of the CH_3 signal is −112 °C while T_c for the methoxy signals is −118 °C. The more intense lines account for 78% and the less intense lines account for 22% of the total intensity. The H-2,4 region, which appears as an AB pattern at room temperature (see also Table I), undergoes asymmetrical broadening at low temperature. The high-field half of the AB pattern broadens first and attains maximum broadening near −100 °C. A splitting diagram shows that the larger component (labeled TB) is at 4.05 ppm while the smaller component (labeled C) appears near 3.6 ppm. The low-field half of the high-temperature AB pattern attains maximum broadening between −115 and −120 °C to give at −122 °C a broad doublet with components (labeled C and TB) of unequal intensity. At −122

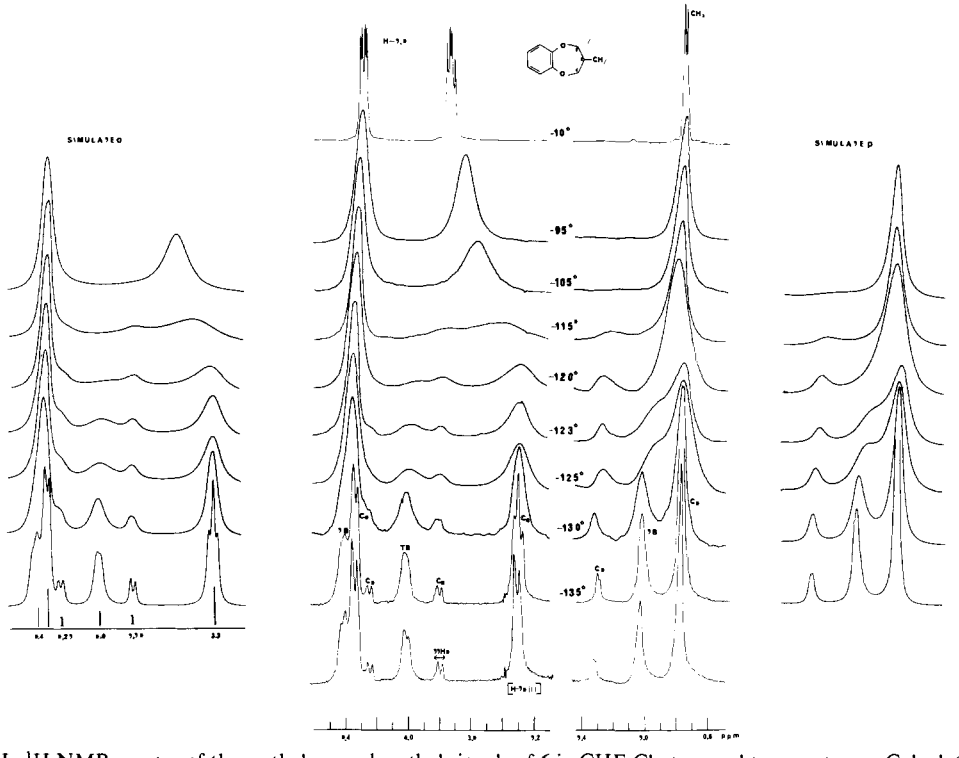


Figure 2. 400.13-MHz ^1H NMR spectra of the methylene and methyl signals of **6** in CHF_2Cl at several temperatures. Calculated spectra are shown on both sides of the experimental spectra.

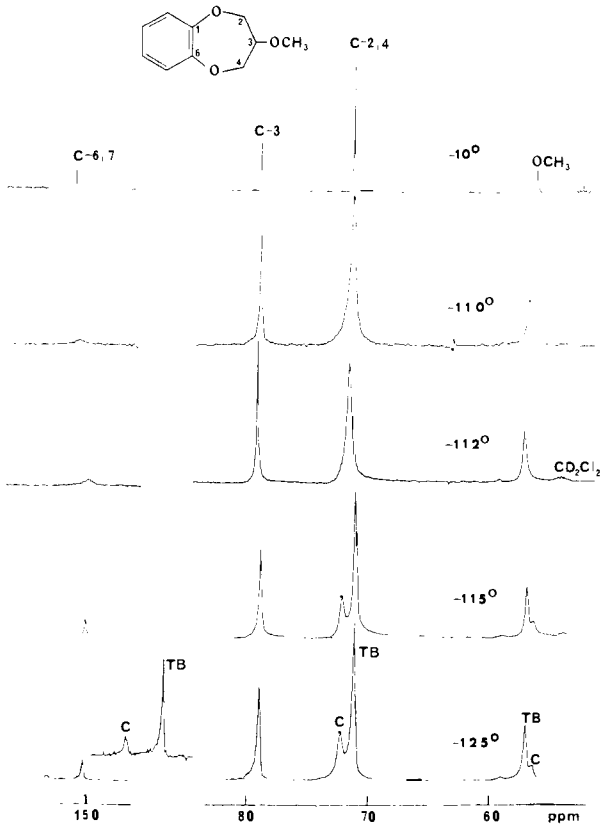


Figure 3. 100.62-MHz ^{13}C NMR spectra of the seven-membered ring carbons of 7 in CHF_2Cl at several temperatures.

°C, the ratio of the intensity of the more intense TB signal to that of the less intense C signal is about 3:1 for both parts of the H-2,4 spectrum. Furthermore, additional broadening is observed at −130 °C and below for the TB signals while the C signals at **4**.39 and 3.57 ppm become doublets with a $^2J_{HH}$ values of about −12.5 Hz.

The second spectral change noted for the H-2,4 signals labeled TB (in the spectrum at −122 °C) is such that the signal at 4.05 ppm does not reveal additional splitting whereas the downfield one at 4.3 changes into a doublet with components at 4.17 and 4.38 ppm, as illustrated with a splitting diagram above the spectrum recorded at −135 °C. Homonuclear decoupling of the C doublet at 3.57 ppm collapsed one of the overlapping signals at 4.38 ppm into a sharp singlet (labeled C) showing more clearly the broader TB signal as a shoulder.

Discussion

Spectral Analysis and the Conformations of the Seven-Membered Rings. The spectral modifications observed in the ^1H and ^{13}C NMR spectra of compound **6** (Figures 1 and 2) reveal the existence of a mixture of three conformers (in a ratio of 58:32:10 in CHF_2Cl) at −135 °C. Such an occurrence is quite rare and was not predictable for a single methyl group. The identification of the nature of the three conformations present is made below through the analysis of the chemical shifts of the three methyl signals in both the ^1H and ^{13}C NMR spectra of **6** and a comparison with those observed[1] in the spectra of the dimethyl derivative **2**.

The methyl region of the low-temperature ^1H NMR spectrum of **6** contains three lines at 1.33, 1.04, and 0.79 ppm. Similarity with methyl chemical shifts for **2** (1.24, 1.01, and 0.74 ppm[1]) suggests the following assignment: **6**-TB, **6**-Ca, and **6**-Ce in the ratio 32:10:58 in CHF_2Cl (Figure 2).

It is now well established that the ^1H NMR chemical shifts of protons bound to carbons β to an oxygen atom (i.e., in fragments such as $-O-C_\alpha-C_\beta-H$) exhibit a stereodependent behavior whereby β-protons anti to the oxygen atom undergo a strong upfield shift.[5]

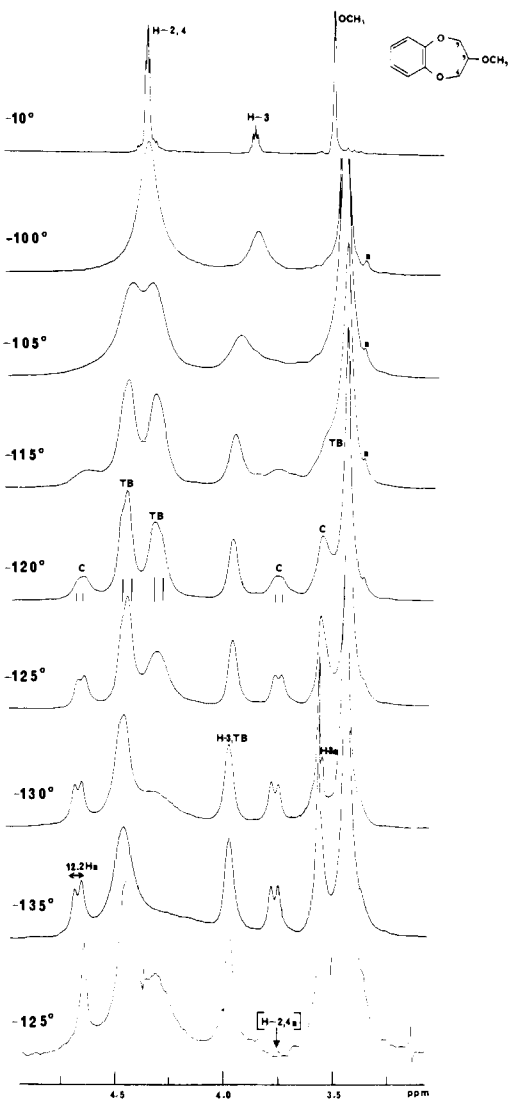


Figure 4. Variable-temperature partial 400.13-MHz ^1H NMR spectra of 7 in CHF_2Cl. The stick diagram under the spectrum at −120 °C refers to the spectral analysis described in the text.

Studies on the 1,3-dioxane system[6,7] have shown that an axial proton or a methyl group at the 5-position appears at lower field (5-Ha = 2.0 ppm; 5-CH_3a = 1.16 ppm) than an equatorial proton or methyl group (5-He = 1.3 ppm; 5-CH_3e = 0.74 ppm). The methyl chemical shifts previously reported[1] for **2** and those for **6** suggest that a similar trend exists for both ring sizes. The assignment of the Ca and Ce methyl signals is made accordingly in Table I and in the ^1H spectrum of **6** at −135 °C shown in Figure 2.

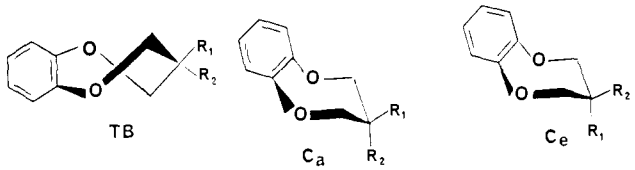
Confirmation is provided by the variable-temperature ^{13}C NMR spectra of **6** (Figure 1). Again by analogy with previous observations in 5-alkyl-1,3-dioxane derivatives[8] and recent observations[1] for **2**, the smallest methyl line at 13.81 ppm, in the spectrum at −135 °C, is assigned to the axial methyl of the chair form (**6**-Ca) while the most intense signal at 11.86 ppm is assigned to the equatorial methyl carbon in **6**-Ce. Unfortunately, no TB parameters exist for the six-membered ring, but analogy with **2** allows the assignment of the signal at 15.16 ppm (which represents 32% of the total intensity) to the twist-boat conformer (**6**-TB).

(5) Lambert, J. B.; Goldstein, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 5689 and references cited therein.

(6) (a) Delmau, J.; Duplan, J. C.; Davidson, M. *Tetrahedron* **1967**, *23*, 4371. (b) Schmid, H. G.; Friebolin, H.; Kabuss, S.; Mecke, R. *Spectrochim. Acta* **1965**, *22*, 623.

(7) (a) Eliel, E. L.; Rao, V. S.; Vierhapper, F. W.; Juaristi, G. Z. *Tetrahedron Lett.* **1975**, *49*, 4339. (b) Tavernier, D.; Antenuis, M. *J. Magn. Reson.* **1974**, *13*, 181.

(8) Jones, A. J.; Eliel, E. L.; Grant, D. M.; Knoeber, M. C.; Bailey, W. F. *J. Am. Chem. Soc.* **1971**, *93*, 4772.



6: R_1 = H, R_2 = CH_3
7: R_1 = H, R_2 = OCH_3
8: R_1 = CH_3, R_2 = OCH_3

It is interesting to note that the three aromatic carbon signals (only C-6,7 is shown in Figure 1) do not give rise to triplets at −135 °C but to doublets with lines of different intensity in the ratio of 68:32. It appears that because these carbons are quite remote from the site of substitution, their chemical shifts are not influenced significantly by the axial or equatorial orientation of the methyl group in the chair form. They therefore appear to be sensitive only to the ring conformation, and consequently the low-field component (153.47 ppm) is characteristic of the chair conformation and it actually represents two nonresolved lines, one from **6**-Ca and the other from **6**-Ce. Their sum (58% for **6**-Ce and 10% for **6**-Ca) accounts for 68% of the total intensity.

The chemical shift difference between the two components of the C-6,7 signal of **6** is 2.53 ppm, a value very similar to the 2.34 and 2.70 ppm values observed for **1** and **2**, respectively.[1] These similarities strongly suggest that the C-6,7 signal constitutes a probe for the identification of the ring conformations adopted by 1,5-benzodioxepins substituted on C-3.

The H-2,4 region of the ^1H NMR spectrum of **6** at −135 °C in CHF_2Cl (Figure 2) can now be analyzed in light of the above conclusions. The relative intensities of the six signals observed at −135 °C allow the assignment of the tall doublet at **4**.33 ppm and the triplet at 3.3 ppm to **6**-Ce while the two small doublets at 4.25 and 3.79 ppm belong to **6**-Ca. The remaining two broader signals at 4.4 and 4.0 ppm arise from **6**-TB. The multiplicity of these signals leads to the assignment given in Table I. The single-frequency decoupling of the H-3a signal (2.49 ppm) at −135 °C produces a change in the multiplicity of the signal at 3.3 ppm from triplet to doublet, thus confirming the identity of H-2a (=H-4a) in **6**-Ce. As a consequence, the triplet multiplicity suggests that this signal ought to constitute a useful probe for the Ce form of other 3-monosubstituted derivatives of **1**. As will be discussed in more detail in the next section, the broader line width of the **6**-TB form (4.0 and 4.4 ppm) is related to the fact that the pseudorotation process between the two equivalent forms of **6**-TB is not slow at −135 °C. Consequently, the resulting averaged chemical shifts cannot be assigned to specific proton environments in **6**-TB.

It is noteworthy to point out that the ^{13}C methyl signal of **6**-TB (15.16 ppm) at −130 °C does not fall between those for **6**-Ca (13.81 ppm) and **6**-Ce (11.80 ppm), as might have been expected from a rapid analysis in terms of the number of γ-gauche and γ-anti relationships involving the two oxygen atoms. Whereas the methyl group in **6**-Ce is anti to each of the ring oxygens and gauche to both oxygen atoms in **6**-Ca, it is observed that for **6**-TB a gauche and an anti arrangement exist. Because the gauche and anti dispositions in **6**-TB are not identical with those in **6**-Ca and **6**-Ce, the extent of electronic communications between the oxygen atom and the C-2–C-3 could be conformation dependent and affect C-3 differently.[9] Furthermore angular differences might also contribute to the apparent nonadditivity.[10]

The spectral modifications observed in the ^{13}C NMR spectrum of compound **8** (Figure 5) indicate that it exists as a mixture of two conformers in a 77:23 ratio in $CHFCl_2$ at −130 °C. The chemical shift difference between the two components of the C-6,7 signal is 2.08 ppm at −130 °C, with the intense high-field component appearing at 151.26 ppm and the less intense one at 153.31 ppm. These values are in line with those previously observed for compounds **1**, **2**, and **6** and suggest that the twist-boat is the predominant conformation adopted by **8** while a chair form is the minor one.

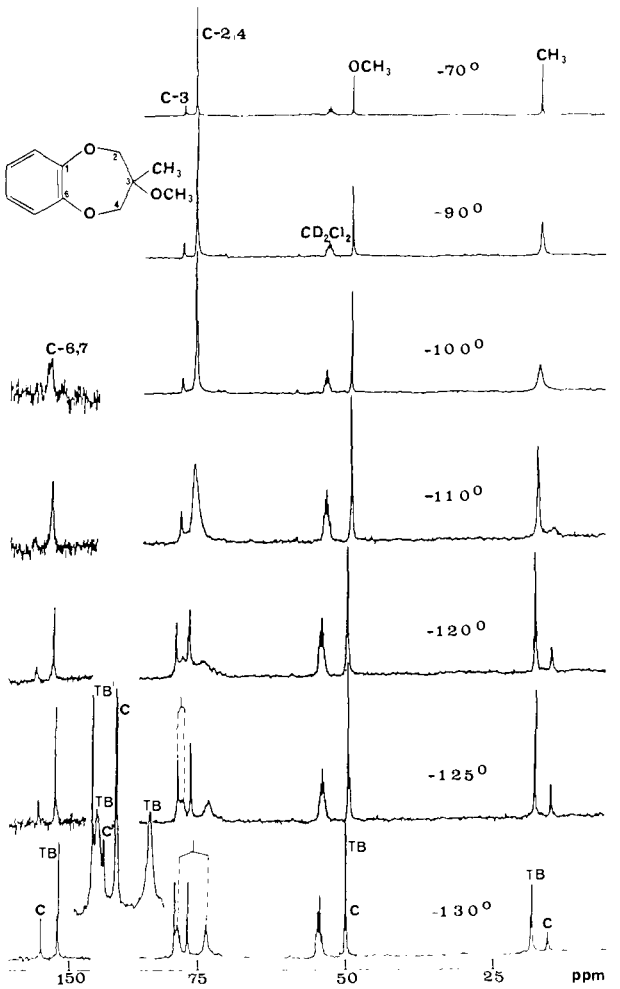


Figure 5. Variable-temperature 100.62-MHz ^{13}C NMR spectra of the seven-membered ring carbons of **8** in CHF_2Cl. The inset over the spectrum at −130 °C is an expansion of the C-3 and C-2,4 region of this spectrum.

The above suggestion is confirmed by the observation of two equally intense lines for the C-2,4 signal at −130 °C (labeled TB in Figure 5). The absence of symmetry, indicated by the nonequivalence of these carbon atoms, is compatible only with a nonaveraging TB conformation. The intensity of these two TB signals relative to the singlet at 76.32 ppm (labeled C in Figure 5) is the same as that observed between the two components of the C-6,7, C-3, OCH_3, and CH_3 signals.

In dimethyl ether, only one set of ^{13}C NMR signals is observed at −140 °C. The presence of two equally intense lines for the C-2,4 carbons indicates that the TB form is the only conformation adopted by **8** in this solvent.

The observation of only one chair signal for each carbon of **8** indicates that only one of the two possible chair conformations (namely **8**-Ca or **8**-Ce) is detected by the NMR technique. Differentiation between these two forms can readily be achieved from the chemical shift of the methyl proton signals in the ^1H NMR spectrum of **8** at −138 °C (Figure 6 and Table I). It has been shown that the equatorial methyl signal for **2** and **6** (at 0.74 and 0.79 ppm, respectively) appears upfield from the TB-methyl signal while the axial methyl signal (at 1.24 and 1.33 ppm, respectively) appears downfield from the TB methyl signal. In addition, it is known that for 5-methyl-5-methoxy-1,3-dioxane, the equatorial methyl group appears at 0.93 ppm while the chemical shift of the axial methyl is 1.42 ppm.[11] Thus the observation that the smaller C signal of **8** at 1.04 ppm is upfield

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(10) Lambert, J. B.; Vagenas, A. R. *Org. Magn. Reson.* **1981**, *17*, 265.
(11) Eliel, E. L.; Enamoza, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 8072.

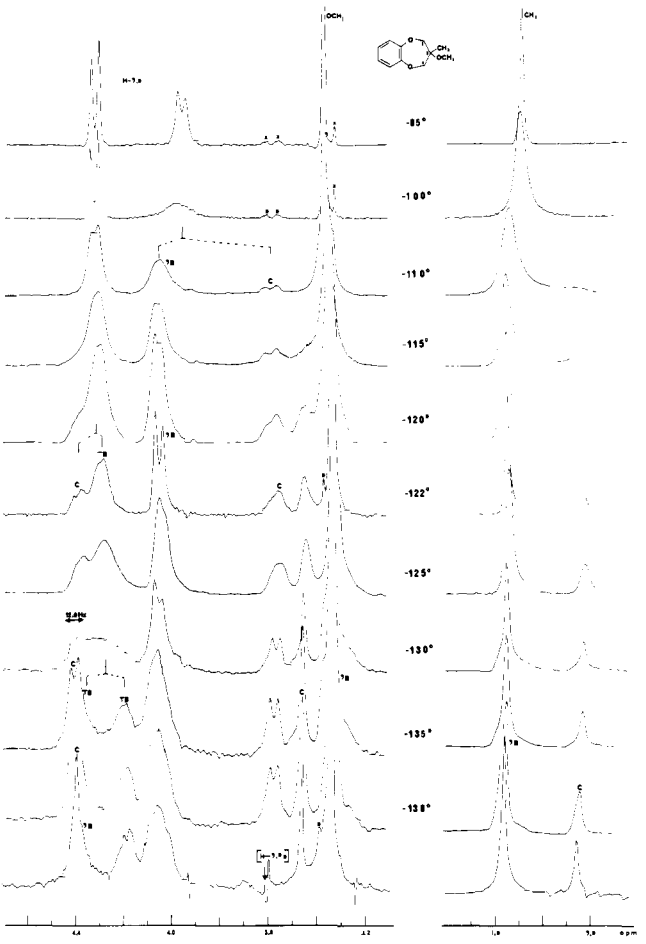


Figure 6. Partial 400.13-MHz ^1H NMR spectra of **8** in CHF_2Cl at several temperatures (× denotes impurity).

from the more intense TB-methyl signal at 1.35 ppm suggests that the methyl group on C is equatorial and that the correct substituent disposition on the chair conformer of this compound is as for **8**-Ca in which the methoxy group is axial.

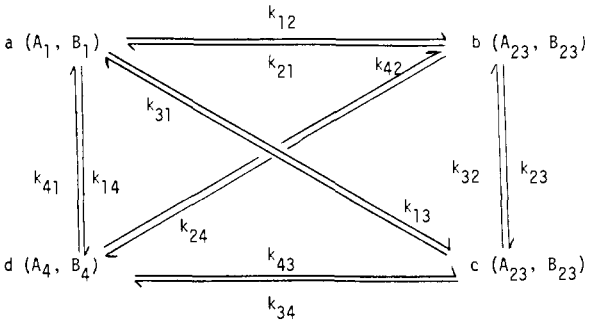
As the temperature is lowered, the H-2,4 region of the ^1H spectrum of **8** (Figure 6) undergoes complex changes whereby two separate spectral changes can be distinguished. The first one occurs between −75 and −123 °C; it corresponds to the slowing down of the C ⇌ TB interconversion. The second spectral change is clearly evident below −125 °C and is still not completed at −138 °C. It corresponds to the slowing down of the pseudorotation between the two TB forms (the next section contains more details on the dynamic aspects). Thus, the doublets observed at 4.39 and 3.57 ppm belong to the chair conformation and the broader signals at 4.38, 4.17, and 4.04 ppm to the twist-boat conformation.

The low-temperature ^{13}C NMR spectrum of compound **7** in CHF_2Cl (Figure 3) reveals the presence of two conformers in a 67:33 equilibrium. Analysis of the C-6,7 ^{13}C NMR signals in the same manner as described above for **8** indicates that the major form (150.46 ppm) is the twist-boat conformation while the minor one (153.39 ppm) is a chair form for which two possibilities exist, namely **7**-Ca and **7**-Ce, with the methoxy group either in an axial or equatorial environment. A solvent effect on the TB:C ratio was observed. In dimethyl ether the C-6,7 signal gave only a singlet at 150.67 ppm, indicating that **7** exists exclusively in the twist-boat conformation in this less polar solvent.

The ^1H NMR spectra of **7** in CHF_2Cl (Figure 4) confirm the predominance of the twist-boat conformation. As was the case for **8**, two spectral changes are observed for the methylene proton signals of the major conformation. The second broadening occurring below −125 °C corresponds to the slowing down of the TB pseudorotation.

The exact nature of the chair form of **7** can be determined from the multiplicity of the axial H-2,4 protons in the ^1H spectrum at

Scheme I



−125 °C. Results for **6** indicate that when a single substituent adopts an equatorial position, the axial H-2a and H-4a protons should appear as a triplet whereas when the substituent is axial, the signal should appear as a doublet. Thus, the observation of a doublet for the axial H-2,4 protons at 3.75 ppm in Figure 4 indicates that **7**-Ca is the correct structure for the chair form adopted by **7**. This conclusion is supported by the fact that the H-3 proton of the chair form appears at 0.41 ppm upfield from the signal of H-3 in the TB form. A similar difference of 0.48 ppm was observed between the chemical shifts of the equatorial H-3 proton of **6**-Ce and the H-3 proton of **6**-TB.

Conformation Averaging Processes. We have previously shown that the chair inversion of 1,5-benzodioxepin **1** involves an activation energy ($\Delta G^{\ddagger}$) of 6.5 kcal/mol and that dimethylation at the 3-position raises this energy barrier to 7.5 kcal/mol.[1] A similar increase of 1 kcal/mol has been noted for the chair inversion process of benzocycloheptene[12] and 1,3-dioxane upon dimethylation at the 5-positions.[13]

Because of the presence of three stable conformers for **6**, its kinetic parameters cannot be obtained from approximate equations and must be derived from a complete line-shape analysis. The variable-temperature ^1H NMR spectra of **6** were therefore calculated with a modified version[1] of the DNMR-2 computer program that is capable of handling four different spin systems of unequal populations.[1,4] The exchange mode selected is slightly different from that used previously for **2** and is represented in Scheme I.

Four configurations (a, b, c, and d), corresponding to Ce, TB, TB*, and Ca, are considered whose populations in CHF_2Cl are 58%, 16%, 16%, and 10%, respectively. Each configuration contains two nonequivalent methylene (H-2,4) protons, which are labeled A_1 and B_1 for a, A_{23} and B_{23} for b and c, and A_4 and B_4 for d. At this point it should be noted that the observation of only two broadened signals for **6**-TB indicates that pseudorotation of the TB form is still rapid on the NMR time scale at −135 °C. If it were slow, two AB patterns would be expected because each TB form contains two different methylene groups. Because the chemical shifts for these four TB methylene protons cannot be predicted, the calculations were carried out by using, for A_{23} and B_{23}, the averaged chemical shifts observed for the two TB signals shown in Figure 2 at −135 °C for **6**-TB. These actually represent averaged chemical shifts for the two syn protons (H_s) and the two anti protons (H_a) relative to the methyl group, as illustrated in Scheme II for one of the methylene groups.

Various trial calculations have suggested that the itinerary of the first proton (labeled H_1 in Scheme II) involves the axial position in **6**-Ca (3.3 ppm) which adopts the syn proton position in **6**-TB (4.03 ppm) and then becomes the equatorial proton in **6**-Ce (4.25 ppm) while the second proton (H_2) starts off at the equatorial position in **6**-Ca (4.3 ppm) to become an anti proton in **6**-TB (4.4 ppm) and ends up at the axial position in **6**-Ce (3.8 ppm). The following relationships were respected: $k_{12} = k_{13}$, $k_{23} = k_{32}$, $k_{24} = k_{34}$, $k_{43} = k_{42}$, and $k_{21} = k_{31}$. Because of the relative populations of the four conformations and the inversion mechanism

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Scheme II

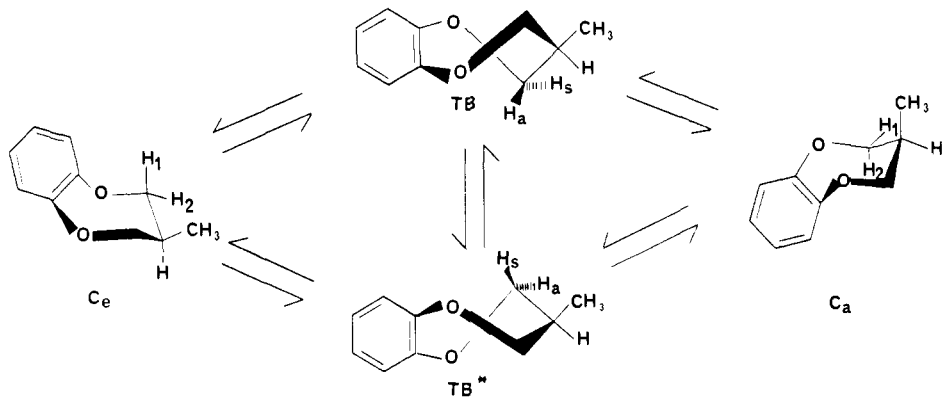

Table III. Kinetic and Thermodynamic Parameters for 1,5-Benzodioxepin 1 and Its Derivatives

compd	solvent	$\Delta G^{\ddagger}$(C → TB)[a]	$\Delta G^{\ddagger}$(C → C*)	$\Delta G^{\ddagger}(\psi)$[b]	$-\Delta G^{\circ}$(C/TB)[c]
1	CHF_2Cl	6.5	6.7		0.35 (−147)
	CH_3OCH_3				0.30 (−147)
2	CHF_2Cl	7.1	7.5	6.8	−0.17 (−128)
	CH_3OCH_3				−0.29 (−142)
6	CHF_2Cl	7.3 (Ce → TB)	7.4 (Ce → Ca)		0.48 (Ce/Ca, −135)[d]
	CH_3OCH_3				0.41 (Ce/Ca, −140)
7	CHF_2Cl	7.4 (Ca → TB)			−0.005 (Ca/TB, −130)
	CH_3OCH_3				>−1.5 (Ca/TB, −130)
8	CHF_2Cl	7.5		6.8	−0.16 (−130)
	CH_3OCH_3				>−1.5 (−140)

[a] All values are in kcal/mol. [b] The symbol ψ refers to the pseudorotation motion involved in the TB inversion process. [c] The temperatures at which the values were determined are given in parentheses in °C. [d] Because three conformers are detected for compound 6, three $-\Delta G^{\circ}$ values can be calculated, namely $-\Delta G^{\circ}$(Ce/Ca) = 0.48 (0.41 in CH_3OCH_3), $-\Delta G^{\circ}$(Ce/TB) = 0.35 (−0.04 in CH_3OCH_3), and $-\Delta G^{\circ}$(Ca/TB) = −0.13 (−0.45 in CH_3OCH_3).

involved (Scheme II), the order $k_{12} > k_{24} > k_{14}$ was initially respected. Best values for the rate constants at each temperature were then obtained by a trial and error method using visual comparison of calculated and experimental spectra as test. A spectral simulation of the methyl region was also carried out by using a similar exchange mode for a two-spin system, one spin representing the three equivalent protons of the methyl group and the other, the H-3 proton. Calculated spectra for the H-2,4 and CH_3 regions are shown in Figure 2.

Plots of ln (k/T) vs. $1/T$ for k_{12} and k_{24}, which represent respectively $k_{Ce\rightarrow TB}$ and $k_{TB\rightarrow Ca}$, yield $\Delta G^{\ddagger}$ values of 7.3 and 7.4 kcal/mol at −140 °C for **6**. These values are similar to the activation energies found for the analogous interconversions for **2** as summarized in Table III. Unfortunately, a $\Delta G^{\ddagger}$ value for the TB pseudorotation of **6** cannot be obtained from the simulation because, as explained above, this process is still rapid at −135 °C.

The activation energy of the TB ⇌ Ca interconversion of **7** can be estimated with reasonable precision from the coalescence of the C-6,7, C-2,4, and OCH_3 signals observed for the ^{13}C NMR spectra. The coalescence temperature is −112 ± 2 °C for all three sets of signals, which leads to a $\Delta G^{\ddagger}$ of 7.4 ± 0.3 kcal/mol using a two-site approximation[14] and a transmission coefficient of 1. Similarly a value of 7.5 kcal/mol is derived from the coalescence of the methoxy signal in the ^1H spectrum of **7**.

Finally, an activation energy of 7.5 ± 0.3 kcal/mol is estimated for the TB ⇌ C interconversion by using the coalescence temperature of −105 °C for the CH_3 and C-6,7 signals of the ^{13}C NMR spectrum of **8**. In this case, the slowing down of the pseudorotation is complete at −130 °C, and $\Delta G^{\ddagger}$ for this process can be estimated from the coalescence temperature of −115 °C observed for the two components of the C-2,4 signal in **8**-TB. A value of 6.8 ± 0.5 kcal/mol is found by using a transmission coefficient of 1. This value is similar to that previously reported[1] for the pseudorotation of **2**.

The dynamic parameters for **6**, **7**, and **8** summarized in Table III are all in line with previous observations[1,2,15] that the presence of oxygen atoms in the seven-membered ring lead to easier ring deformation and lower inversion barriers.

Origin of the Conformation Preferences. The striking differences in conformational identity and population between the seven-membered molecules studied and analogous six-membered ones as well as the solvent-induced shifts in conformational equilibria can be understood in the framework of an analysis combining a mix of factors of which the most important are steric, electrostatic,[16] and bond–antibond interactions.[17,18]

Because the TB form is observed only for the seven-membered cyclic molecules, it is important, at the outset, to identify the origin of the accrued stability of this form for **1** relative to that of benzocycloheptene. Recent results have shown that the methoxy groups in *o*-dimethoxybenzene prefer a nonplanar disposition in the gas phase and in solution in spite of no obvious steric hindrance in the planar form.[19] Because **1** constitutes a cyclic analogue of *o*-dimethoxybenzene, it is reasonable to expect that similar electronic effects involving the oxygen atoms will stabilize the TB form relative to C because the former has a spatial disposition close to that of the preferred nonplanar conformation.

The results for **6**, showing the coexistence of three conformations in both CH_3OCH_3 and CHF_2Cl (Ca, Ce, and TB), are most informative. The nonpolar nature of the substituent suggests that here bond–antibond interactions in the fragment O–C–C–CH_3 should have negligible effect on conformation stability.[17,18] The relative high stability of the Ca form then appears to be a consequence of a weaker steric interaction between the axial methyl group and the oxygen lone pairs. By comparison nonbonding interactions with axial benzylic hydrogens in 5-methylbenzocycloheptene are much more destabilizing so that only the Ce form is detected by NMR,[20] while for methylcyclohexane an *A* value

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of 1.74 kcal/mol has been determined.[21] Furthermore, the $-\Delta G°$(Ce/Ca) value of 0.48 kcal/mol for **6** in CHF_2Cl is smaller than the value of 0.88 kcal/mol for 5-methyl-1,3-dioxane in $CHCl_3$.[22] Finally results[1] published for **2** indicate steric destabilization of the C form relative to TB by an axial methyl group, but this effect is not very large. The presence of a significant amount of the three forms then shows that a single methyl group has relatively small conformational biasing properties in **6**.

The observation of a Ca/TB ratio of 33:67 for **7** in CHF_2Cl, corresponding to a $-\Delta G°$ value of −0.005 kcal/mol at −130 °C (taking into account the statistical effect of the existence of two equivalent TB forms), is quite different from observations made on 5-methoxy-1,3-dioxane in $CHCl_3$. Equilibration studies on 2-isopropyl-5-methoxy-1,3-dioxane[23] show that only axial and equatorial forms exist for which the equatorial predominance is characterized by a $-\Delta G°$(Ce/Ca) of 0.16 at 25 °C in $CHCl_3$. Decreasing the polarity of the solvent increases the TB amount for **7** ($-\Delta G°$(Ca/TB) > −1.5 kcal/mol in dimethyl ether) whereas for the corresponding dioxane derivative, the Ce form becomes more favored ($-\Delta G°$(Ce/Ca) = 0.83 kcal/mol in diethyl ether[23]). Notwithstanding differences in temperature, it appears that whereas the **7**-Ce form might have been expected by extrapolating the dioxane results, compound **7** has preferred the TB form instead.

The published qualitative analysis of the conformational features of 5-heterosubstituted 1,3-dioxanes, in terms of a simple formalism[16,24] based on two factors, provides a useful framework for the analysis of **7**. The first term, E_D, is the dipole–dipole interaction (maximum in the vapor phase, it tends toward zero in polar solvents) while the second terms E_S is the solvation stabilization energy (zero in the vapor phase, it becomes important in polar solvents favoring that conformation with the larger dipole moment). In this context solvent changes are useful to identify the electrostatic component of certain conformational preferences assuming that quadrupolar interaction can be ignored and that bond–antibond interactions are not solvent dependent. The underlying concepts suggest that in a relatively nonpolar solvent, such as dimethyl ether, the intramolecular dipolar interactions should achieve greater importance while in the more polar CHF_2Cl solvent, these interactions should be significantly reduced while solvation effects should become more important.

In addition to these two factors, quantum mechanical analyses[17] predict that conformations containing gauche dispositions for the fragment –O–C–C–O– (as in **7** and **8**) should also show stabilization from bond–antibond interactions involving the C–O orbitals. Furthermore, the quantitative application[18] of this concept to the conformational preference of the furanose ring has confirmed the importance of this factor (the so-called gauche effect) and shown that a quantitative assessment of its importance requires precise geometrical information.

Firstly, the solvent change from CHF_2Cl to CH_3OCH_3 is observed to favor the TB form for compounds **1** and **2** in accord with the existence of a destabilizing dipolar repulsion between the two ring oxygen dipoles of the C form and a stabilizing dipolar attraction between the dipoles of the two oxygen atoms in the TB form. In addition, because the C form is more polar than TB, it is also better solvated in CHF_2Cl. The results for **6** show that the presence of a methyl group does not alter the C → TB shift on solvent change.

Extending the above analysis to **7** is more complex because the substituent dipole (and possibly that of the benzo group[20]) must also be considered together with bond–antibond interactions involving the exo C–O bond. A quantitative analysis of the behavior observed for **7** is unfortunately not possible because calculation of electrostatic and bond–antibond interactions is fraught with uncertainties[18,24,25] in the absence of precise geometrical information for the various conformers detected. Consequently, only a qualitative rationalization of the results for **7** and **8** is attempted next.

Because solvation effects are expected to be weak in nonpolar solvents, it is best to first analyze the results obtained for CH_3OCH_3 solutions. As in the case of analogous 1,3-dioxane derivatives,[24] dipolar electrostatic interactions are expected to be repulsive in **7**-Ca and weakly attractive or slightly repulsive for **7**-Ce, while for **7**-TB attractive dipolar interactions are predicted.[16] On the other hand, the effect of bond–antibond interactions, as estimated from a phenomenological potential equation,[18] suggest that **7**-Ce, which contains two *trans*–O–C–C–O arrangements, should be disfavored relative to both the **7**-Ca and **7**-TB forms, which are both significantly stabilized by this term. Thus, it is seen that both of these factors contribute to TB being the most stable conformation of **7**, as observed in CH_3OCH_3. In contrast, because the conformational energy of the TB form of the 1,3-dioxane ring is much larger, the TB signals are undetectable experimentally and only the Ca ⇌ Ce equilibrium is modified by a solvent change.[23]

Changing the solvent from dimethyl ether to the more polar CHF_2Cl shifts the **7**-TB ⇌ **7**-Ca equilibrium to the right, so that **7**-Ca becomes detectable by NMR. The apparent increase in stabilization of **7**-Ca is believed to result from bond–antibond stabilization together with changes in E_D and E_S. The relative magnitude of the dipole moment of each conformation is required to appreciate the effect of solvation, and to this end results for analogous 1,3-dioxanes are pertinent. The dipole moment of the Ca and Ce forms for 2-isopropyl-5-methoxy-1,3-dioxane were determined as 2.85 and 1.30 D,[24] and it appears that this order should carry over to **7**-Ca and **7**-Ce even if the effect of the benzo group is considered. In addition, estimates for **7**-TB suggest that it ought to have a relatively small dipole moment,[26] either smaller than or comparable to that of **7**-Ce. Thus the observed **7**-TB → **7**-Ca shift in the more polar solvent is caused by a decrease in the electrostatic stabilization of **7**-TB, an attenuation of the electrostatic repulsion in **7**-Ca and better solvation of **7**-Ca. It then appears that the absence of stabilizing intramolecular interactions in conformation **7**-Ce explains why it has not been detected.

Further insight into the effect of a 3-methoxy group is gained from the interpretation of the results for **8**. As was the case for **7**, this compound also exists solely in the TB form in dimethyl ether, in large part as a consequence of greater overall stabilization from intramolecular interactions in **8**-TB. A change to the more polar CHF_2Cl solvent shifts the **8**-TB ⇌ **8**-Ca equilibrium toward **8**-Ca so that its signals become detectable (23%). Better solvation of **8**-Ca, attenuation of the destabilizing E_D term in **8**-Ca, and strong bond–antibond stabilization are likely responsible. In contrast, chair conformations with axial or equatorial methoxy were found[11] for the analogous 2-isopropyl-5-methoxy-5-methyl-1,3-dioxane in the ratio of 58:43 in $CHCl_3$ while in the less polar diethyl ether, the proportion becomes 36:64. Thus the results for the six-membered ring would be misleading if used as a model for the seven-membered ring. The absence of conformation **8**-Ce (equatorial methoxy) therefore supports the suggestion made for **7** concerning the apparent unfavorableness of the equatorial position for the polar methoxy group as a result of the absence of stabilizing intramolecular interactions.

Experimental Section

Melting points are uncorrected and were determined with a Buchi melting point apparatus. The VPC analyses and separations were carried out on a Varian-Aerograph Model 920 instrument using helium as carrier gas.

The variable-temperature ^1H and ^{13}C NMR spectra were recorded in the FT mode with a Bruker WH-400 instrument operating at 400.13 and 100.62 MHz, respectively, and equipped with a standard Bruker variable-temperature accessory. Temperatures were read off the B-VT-1000 control unit and compared to a calibration curve previously established by using a Fluke Model 2165A digital display thermometer equipped

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with a copper–constantan thermocouple placed inside a solvent containing dummy NMR tube inserted in the probe. A precision of ±3 °C is expected. All ^{13}C NMR spectra were recorded with broad-band proton decoupling, and the following instrumental parameters are typical: flip angle 45°; SW = 21 700 Hz; data size = 8K; AQ = 0.19 s; pulse delay = 0.2 s. For proton, the typical instrumental parameters used are as follow: flip angle = 45°; SW = 3800 Hz; data size = 4K; AQ = 0.54 s; pulse delay = 1.0 s. The ^1H spectra were resolution enhanced by Gaussian multiplication.

All variable-temperature studies were performed on $CHFCl_2$ or dimethyl ether solutions of the sample containing Me_4Si and about 18% of CD_2Cl_2 (for field locking purposes) in standard 5-mm (^1H) or 10-mm (^{13}C) NMR tubes that had been degassed and sealed. The ^1H NMR tubes contained 5–10 mg of the sample in 0.5 mL of solvent while the ^{13}C NMR tubes contained 80–120 mg of the sample in 2.2 mL of the solvent.

Some rate constants were estimated at the coalescence temperature with the equation $k = \pi\Delta\nu/2^{1/2}$ for singlet to doublet splitting. The free energies of activation values ($\Delta G^{\ddagger}$) were calculated from standard equations by using a transmission coefficient of 1.[27]

Spectra calculations were carried out with a slightly modified version of the DNMR-2 program on a CDC Cyber 835 computer. Spectra were traced by a Zeta 3653 sx plotter. Free energies of activation were calculated from a ln (k/T) vs. $1/T$ plot by using the Eyring equation.

Ditosylate of 2-Methyl-1,3-propanediol. A solution of 1.35 g of 2-methyl-1,3-propanediol (0.015 mol) in 4 mL of pyridine was added to a solution of 8.18 g of *p*-toluenesulfonyl chloride (0.043 mol) in 13 mL of pyridine. The solution was stirred at 0 °C for 2 h and left to stand at room temperature overnight. It was then poured on 25 mL of ice–water. The mixture was filtered and washed successively with 5% H_2SO_4, diluted Na_2CO_3, and water to yield 4.62 g (77%) of a white solid: mp. 59–61 °C; ^1H NMR ($CDCl_3$) δ 0.9 (3 H, d, CH_3), 2.17 (1 H, m, H-2), 2.45 (6 H, s, CH_3-Ar), 3.9 (4 H, d, OCH_2), 7.6 (8 H, AB-quartet, Ar); mass spectra calcd for $C_{18}H_{22}O_6S_2$, M_r 398.0858; found (70 eV), M_r 398.0847.

3-Methyl-1,5-benzodioxepin (6). To a solution of 1.1 g of catechol (0.01 mol) in 25 mL of Me_2SO was added in small portions 1.13 g (0.021 mol) of sodium methoxide. To the dark mixture was then added dropwise a solution of 3.98 g (0.01 mol) of the ditosylate prepared above in 50 mL of Me_2SO. The mixture was stirred at 90 °C under nitrogen for 6 h and then cooled and poured into 100 mL of water. It was then extracted with ether (2 × 200 mL, 1 × 100 mL), and the combined organic fractions were washed with water and dried over $MgSO_4$. The ether was evaporated, and the residue distilled under reduced pressure to yield 0.89 g (54%) of a colorless liquid: bp 70 °C (0.25 mm); ^1H NMR ($CDCl_3$) δ 1.01 (3 H, d, CH_3), 1.33 (1 H, m, H-3), 3.6–4.2 (4 H, m, CH_2O), 6.93 (4 H, s, Ar); mass spectrum, m/e 164 (M^+), 121 ($M - C_3H_7$)$^+$, 110 $(C_6H_6O_2)^+$.

3-Oxo-1,5-benzodioxepin. This compound was prepared by a three-step procedure already published[3] and was characterized by its ^1H NMR spectrum, which was identical with that reported.

3-Hydroxy-1,5-benzodioxepin.[28] A solution of 1.6 g (0.0096 mol) of the ketone prepared above in 15 mL of anhydrous ether was slowly added to a suspension of 0.76 g of $LiAlH_4$ in 25 mL of anhydrous ether. The mixture was stirred at room temperature overnight, and the excess of hydride was decomposed with 20 mL of 10% H_2SO_4. The phases were separated, and the aqueous layer was extracted with ether (2 × 30 mL). The combined organic fractions were dried over $MgSO_4$. Evaporation of the solvent yielded 1.2 g of a yellow oil which was used in the next reaction without further purification: ^1H NMR ($CDCl_3$) δ 4.11 (5 H, d + m, CH_2O + H-3), 3.14 (1 H, br s, OH), 6.95 (4 H, s, Ar).

3-Methoxy-1,5-benzodioxepin (7). A solution of 1.2 g (0.0072 mol) of 3-hydroxy-1,5-benzodioxepin in 10 mL of diglyme was cooled in an ice bath and 4 g of CH_3I (0.028 mol) was added followed by 0.5 g of NaH. The mixture was stirred at room temperature for 5 h, and the excess hydride was decomposed with methanol. Water and ether were added and the phases were separated. The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic fractions were washed with water (4 × 30 mL) and dried over $MgSO_4$. A yellow oil was obtained after evaporation of the solvent and was purified by gas chromatography on a SE-30 5% column (1.5 m × 0.6 cm, T = 125 °C). Thus 0.58 g (45%) of a colorless liquid was obtained and characterized: ^1H NMR ($CDCl_3$) δ 3.43 (3 H, s, OCH_3), 3.78 (1 H, s, H-3), 4.27 (4 H, s, CH_2O), 6.9 (4 H, s, Ar); mass spectrum, m/e 180 (M)$^+$, 148 ($M - CH_3OH$)$^+$, 135 ($M - CH_3OHCH$)$^+$, 121 ($M - CH_3OHC_2H_3$)$^+$.

3-Hydroxy-3-methyl-1,5-benzodioxepin. A solution of 0.281 g of CH_3I (0.002 mol) in 2 mL of anhydrous ether was slowly added to 0.09 g of magnesium in 3 mL of anhydrous ether. After the formation of the Grignard reagent had been completed, a solution of 0.23 g (0.0014 mol) of 3-oxo-1,5-benzodioxepin prepared above in 2.5 mL of anhydrous ether was slowly added, and the mixture refluxed for 1 h. After cooling, 10 g of ice, a few drops of HCl, and 20 mL of ether were added. The phases were separated, and the organic fraction was washed with water and dried over Na_2SO_4. The solvent was evaporated and the solid recrystallized in a mixture of benzene–hexane (1:3) to yield 0.14 g (55%) of a white solid: mp 77–79 °C [lit.[29] mp 77–79) °C]; ^1H NMR (CD_2Cl_2) δ 1.11 (3 H, s, CH_3), 3.65–4.07 (4 H, AB quartet, OCH_2), 5.28 (1 H, s, OH), 6.93 (4 H, s, Ar).

3-Methoxy-3-methyl-1,5-benzodioxepin (8). A solution of 65 mg (0.00036 mol) of 3-hydroxy-3-methyl-1,5-benzodioxepin in 1 mL of diglyme was cooled in an ice bath, and 0.5 g of CH_3I (0.0035 mol) was added followed by 125 mg of NaH in 1 mL of diglyme (in small portions). The mixture was stirred at room temperature overnight, and the excess hydride was decomposed with 4 mL of methanol. Water and ether were added, and the phases were separated. The organic fraction was washed 4 times with water and then dried over $MgSO_4$, and the solvent was evaporated to a volume of 1.5 mL. The product was purified by gas chromatography on a SE-30, 5% column to yield 65 mg (93%) of a colorless liquid: ^1H NMR (CF_2Cl_2) δ 1.26 (3 H, s, CH_3), 3.35 (3 H, s, OCH_3), 4.35–3.84 (4 H, AB quartet, CH_2O), 6.82 (4 H, s, Ar).

Acknowledgment. We wish to acknowledge the technical contribution of Robert Mayer and the assistance of Dr. Phan Viet Minh Tan of the "Laboratoire Régional de RMN à haut champ" in Montréal. We thank the Natural Sciences and Engineering Research Council of Canada and the Ministère de l'Education du Québec for financial assistance. We also thank a referee for bringing ref 18 to our attention.

Registry No. 4, 88657-40-3; **7**, 88657-41-4; **8**, 88657-42-5; 2-methyl-1,3-propanediol ditosylate, 24330-53-8; 2-methyl-1,3-propanediol, 2163-42-0; catechol, 120-80-9; 3-oxo-1,5-benzodioxepin, 27612-17-5; 3-hydroxy-1,5-benzodioxepin, 30067-20-0; 3-hydroxy-3-methyl-1,5-benzodioxepin, 68281-26-5.

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