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THE ANOMERIC EFFECT IN SEVEN-MEMBERED RINGS: A CONFORMATIONAL STUDY OF 1-OXA AND 3-OXA DERIVATIVES OF BENZOCYCLOHEPTENE BY NMR

S. Désilets and M. St-Jacques

Département de Chimie, Université de Montréal
C.P. 6128, Succ. A, MONTRÉAL, Québec, H3C 3J7, CANADA

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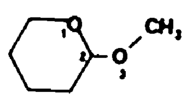
Abstract - The 2-methoxy derivatives 5 and 7 of 3- and 1-benzoxepine (4 and 6 respectively) have been investigated by ^{13}C and ^{1}H dynamic NMR methods. The results reveal the presence of two conformer, C_a and C_e (94:6), for 5 due to a strong endo-anomeric effect while for 7, the C_a:C_e population (5:95) is opposite. Based on UV $\pi\rightarrow\pi^*$ spectral characteristics, it is deduced that delocalization of the n electrons of oxygen into the aromatic ring is not the major factor governing this behavior. A large departure from coplanarity for the n-σ^* orbitals, revealed by the :-O-C-OMe torsional angle calculated for 7, explains the weakening of the endo-anomeric effect in 7. Finally, a stronger exo-anomeric effect is expected to contribute to the stability of the C_e form of 7.

The anomeric effect is a well-known stereoelectronic phenomenon documented extensively by both experimental and theoretical studies[1]. In six-membered cyclic molecules such as 2-methoxytetrahydropyran (1)[2], it is usually expressed in terms of the preferential stabilization of the axial chair conformation (C_a; 1a) relative to the equatorial chair form (C_e; 1b), while from a more general point of view[3], in systems such as R-O-C-O-R', it consists in the preferential stabilization of the g^+g^+ arrangement (g = gauche) about the acetal moiety. Recently, Praly and Lemieux[4] stressed the importance of considering both C-O bonds of the acetal function in 1, for which a preferred gauche arrangement about the O(1)-C(2) bond is termed the endo-anomeric effect and a gauche disposition about the C(2)-O(3) bond is called the exo-anomeric effect.



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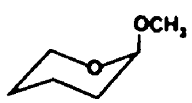
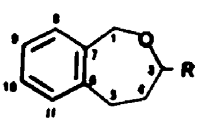
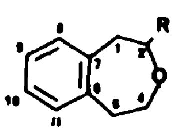


1a

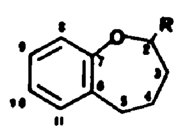
1b



2 R = H
3 R = OCH_3



4 R = H
5 R = OCH_3



6 R = H
7 R = OCH_3

The use of six-membered cyclic molecules as probes for the anomeric effect has certain limitations because the range of geometric dispositions available is normally restricted to those of conformers 1a and 1b because the conformations of the boat and twist-boat family (B and TB respectively) are virtually absent owing to their high conformational energies relative to the chair forms. Recently[5], it was observed that seven-membered rings derived from benzocycloheptene (namely 2 and 3) provide a more flexible model to investigate the anomeric effect. Dynamic NMR results showed that 3 exists as a mixture of three conformations, C_a, C_e and TB while the parent compound 2 exists solely in the C form. The stabilisation of the TB form by the single methoxy substituent is a manifestation of the anomeric effect not observed in the six-membered analog 1.

In order to characterize more completely the anomeric effect in seven-membered rings, 3-benzoxepin (4), 1-benzoxepin (6) and their 2-methoxy derivatives (5 and 7) were prepared and investigated by variable temperature high field ^1H and ^{13}C NMR methods. In both 5 and 7, the methoxy substituent is located at the same position on the seven-membered ring so that conformational differences ought to reflect largely on the difference in the nature of the ring oxygen atom and therefore on the possible effect of conjugation between the ring oxygen and the aromatic ring in 7.

RESULTS AND DISCUSSION

Spectral and Conformational Analyses

All four compounds studied (4 to 7) showed spectral modifications on lowering the temperature: for the methoxy derivatives 5 and 7 both the ^1H and ^{13}C spectra revealed changes while for the parent molecules 4 and 6 only the ^1H spectra showed a spectral modification.

The proton decoupled 100.62 ^{13}C NMR spectrum of 4 was recorded in two solvents (CHF_2Cl and CH_3OCH_3) at high and low temperatures. No dynamic spectral change was observed and the results of the analysis are given in Table 1. The assignments were made readily using the known chemical shifts of benzocycloheptene as reference[6]. This observation indicates that 4 exists as a single conformation.

In contrast, the 400.13 MHz ^1H NMR of 4 showed a dynamic spectral modification characteristic of the ring inversion of the chair conformation identified earlier[7] from a variable temperature study of this molecule at 100 MHz.

Figure 1 illustrates the 100.62 MHz proton decoupled ^{13}C NMR spectral changes observed for the methoxy derivative 5 in CHF_2Cl. Assignment of the signals at -20°C is straighforward using the known chemical[6] shifts of 2-methoxybenzocycloheptene as model. All signals split into two lines as the temperature is reduced such that the intensities are in the ratio 94:6 at -120°C. The results are illustrated in Figure 1 and summarized in Table 1.

The nature of the two conformations thus identified for 5 is best deduced from the chemical shift difference of C-4 at -120°C. The large difference of 7.4 ppm is indicative of the gauche effect as would exist in the axial chair conformation[6]. Therefore C_a is the major conformation while C_e is the minor one as shown in Figure 1. The chemical shift differences between 4 and 5 yields the so-called α, β and γ substituent shift effects[8]. These parameters, given in Table 1, are comparable to those published[5] for 3 (C_e: α = +34.1; β = +4.3; γ_0 = -5.7 and C_a: α = +25.1; β = +3.5, γ_0 = -13.1).

A solvent change to the less polar CH_3OCH_3 changes the C_a:C_e ratio to 84:16. Kinetic and thermodynamic parameters obtained[9] from the spectra of 5 are summarized in Table 3.

The 400.13 MHz ^1H NMR spectrum of 5 in CHF_2Cl also reveals a spectral change characterized by line broadening near -70° and line narrowing at lower temperatures together with a shift in some of the signals. This behavior is in accord with the slowing down of the $C_a \rightleftharpoons C_e$ inversion for which the signals of only the major C_a form are clearly resolved at -120°C. The results of the spectral analysis at -20°C and of the signals of the major conformation at -120°C are summarized in Table 2.

The ^{13}C NMR spectrum of 6 has recently been reported[10] to show no changes down to -120°C while the ^1H spectrum showed splitting characteristic of chair inversion. This compound therefore exists solely as the C form. The pertinent NMR parameters are summarized in Table 1.

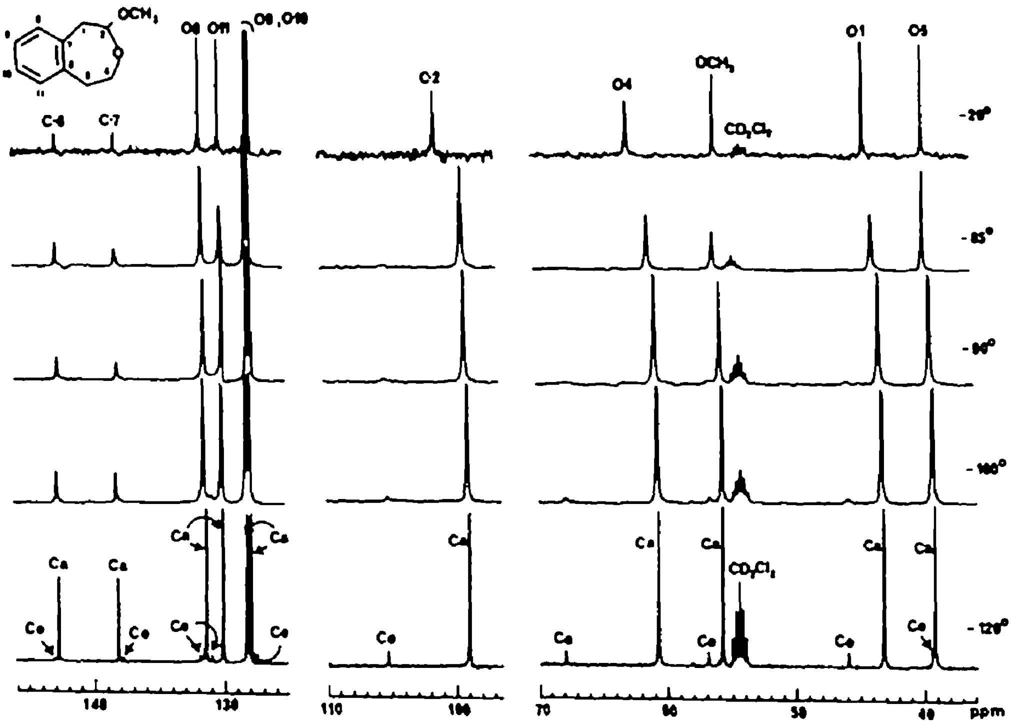


Fig. 1. Variable temperature 100.62 MHz ^{13}C NMR spectra of 5 in CHF_2Cl. (C_a = chair axial, C_e = chair equatorial)

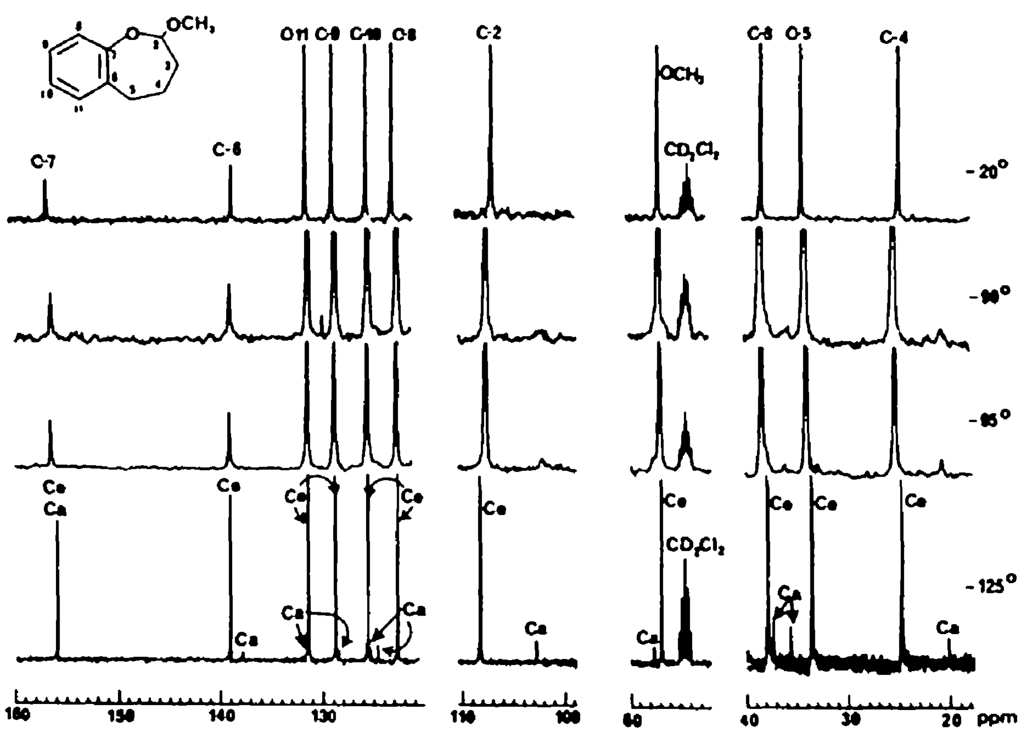


Fig. 2. Variable temperature 100.62 MHz ^{13}C NMR spectra of 7 in CHF_2Cl. (C_a = chair axial, C_e = chair equatorial)

TABLE 1. Carbon-13 chemical shifts of compounds 4-7 at high and low temperatures.

Compound	Solvent	t°	Conformation	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	OCH_3	α	δ	γ	δ_{C-5}
4	CHF_2Cl[a]	-15°		41.00	71.37	-	71.37	41.00	143.21	143.21	130.46	127.43	127.43	130.46	-				
		-120°	C >98%[b]	40.37	70.89	-	70.89	40.37	143.18	143.18	130.51	127.43	127.43	130.51	-				
	CH_3OCH_3	-15°		40.88	71.01	-	71.01	40.88	142.72	142.72	129.98	127.00	127.00	129.98	-				
		-120°	C >98%[b]	40.30	70.60	-	70.60	40.30	142.65	142.65	130.00	127.04	127.04	130.00	-				
5	CHF_2Cl[a]	-20°		44.25	101.07	-	62.56	39.68	142.59	138.03	131.47	127.62	127.88	130.02	55.84				
		-120°	C_e(6%)[c]	45.95	105.17	-	67.85	39.38	142.92	137.63	131.76		127.98	130.81	56.85	+34.4	+5.6	-3.0	-1.0
			C_a(94%)	43.18	98.98	-	60.68	39.11	142.57	137.98	131.24	127.75	128.10	129.92	55.72	+28.1	+2.8	-10.2	-1.2
	CH_3OCH_3	-20°		44.19	101.13	-	62.70	39.47	142.01	137.84	131.20	126.96	127.14	129.42	55.10				
		-120°	C_e(16%)[c]	45.71	104.97	-	67.37	39.26	142.45	137.58	131.13	127.40	127.50	130.26	55.89	+34.4	+5.4	-3.2	-1.0
			C_a(84%)	43.03	98.66	-	~60.5[d]	39.10	142.18	138.03	131.29	126.96	127.16	129.13	54.92	+28.1	+2.7	-10.1	-1.2
6	CHF_2Cl[a]	-25°		-	74.88	33.75	27.41	35.54	137.64	161.86	122.37	128.37	124.62	131.54	-				
		-120°	C>98%[e]	-	75.04	33.42	26.93	35.31	138.12	161.38	122.61	128.40	124.82	131.66	-				
	CH_3OCH_3	-25°		-	74.15	33.74	27.46	35.36	136.74	161.78	122.08	128.05	124.12	131.08	-				
		-120°	C>98%[e]	-	74.03	33.50	27.10	35.07	136.88	161.37	122.13	128.09	124.30	131.08	-				
7	CHF_2Cl[a]	-20°		-	108.46	38.06	24.59	34.12	138.44	156.32	122.75	128.68	125.32	131.27	56.74				
		-125°	C_e(95%)[c]	-	108.85	37.85	24.72	33.52	139.06	155.97	122.71	128.74	125.58	131.41	56.89	+33.8	+4.4	-2.2	-
			C_a(5%)	-	103.29	37.29	20.09	35.59	137.82	155.97[f]	124.59	128.48	125.32	131.50	57.63	+28.3	+3.9	-6.8	-
	CH_3OCH_3	-20°		-	107.69	37.91	24.55	34.02	137.79	156.38	122.56	128.35	124.76	130.82	56.07				
		-120°	C_e(95)[c]	-	108.35	38.06	25.13	33.50	138.18	156.36	122.32	128.52	125.03	130.86	55.91	+34.3	+4.6	-2.0	-
			C_a(5%)	-	102.30	37.61	20.22	35.77	136.80	156.36[f]	124.25	127.81		131.26	56.50	+28.3	+4.1	-6.9	-

(a) Chemical shifts in CH_3OCH_3 are similar.
(b) Chair conformation determined in ref. 7.
(c) Conformer populations are determined by integration of C-2 and C-4 in the ^{13}C spectra.
(d) Signal superposed with solvent.
(e) Conformational analysis and assignment of ^{13}C has been obtained from ref. 10.
(f) Signal C-7 of the minor conformer is superposed with the same signal of the major conformer.

TABLE 2. Proton ^{1}H chemical shifts[a] of compounds 5, 7 in CHF_2Cl at high and low temperatures.

Compound	Solvent	t° Conformation	H-1	H-2	H-3	H-4	H-5	OCH_3
5	CHF_2Cl	-20°C	3.00 (dd, H-1') $^2J_{1'1}$: -13.0 Hz $^3J_{1'2}$: 5.1 Hz 3.24 (d, H-1) $^2J_{11'}$: -13.0 Hz	4.60 (dd, H-2) $^3J_{21'}$: 5.1 Hz $^3J_{21}$: 1.2 Hz	—	3.70 (ddd, H-4') $^2J_{4'4}$: -12.1 Hz $^3J_{4'5}$: 6.2 Hz $^3J_{4'5'}$: 1.5-2.0 Hz 3.09 (td, H-4) $^2J_{44'}$: -12.1 Hz $^3J_{45}$: 10.0 $^3J_{45'}$: 1.0 Hz	2.83 (dd, H-5') $^2J_{5'5}$: -15.1 Hz $^3J_{5'4}$: 6.2 Hz 3.16 (ddd, H-5) $^2J_{55'}$: -15.1 Hz $^3J_{54}$: 10.0 Hz $^3J_{54'}$: 1.5-2.0 Hz	3.31 (s)
		-120°C C_a (94%)	2.98 (dd, H-1e) $^2J_{1e-1a}$: -13.3 Hz $^3J_{1e-2}$: 3.7 Hz 3.40 (d, H-1a) $^2J_{1a-1e}$: 13.3 Hz	4.89 (d, H-2) $^3J_{2e-1e}$: 3.7 Hz	—	3.77 (t, H-4a) $^2J_{4a-4e}$: 12.4 $^3J_{4a-5a}$: 12.4 3.02 (dd, H-4e) $^2J_{4e-4a}$: -12.4 $^3J_{4e-5a}$: 3.9	2.78 (dd, H-5e) $^2J_{5e-5a}$: -15.6 Hz $^3J_{5e-4e}$: 3.9 Hz 3.3 (H-5a) (superpose)	3.30 (s)
7	CHF_2Cl	-15°C	—	4.45 (d) $^3J_{23}$: 7.9 Hz	2.10 (m, H-3) 1.9-2.0 (H-3') (superpose)	1.33 (qd, H-4') $^2J_{4'4}$: -11.7 Hz $^3J_{4'3}$: 11.7 Hz $^3J_{4'5}$: 11.7 Hz $^3J_{4'5'}$: 2.0 Hz 1.9-2.0 (H-4) (superpose)	1.71 (dd, H-5') $^2J_{5'5}$: -14.6 Hz $^3J_{5'4}$: 6.1 Hz $^3J_{5'4'}$: 2.0 Hz 2.03 (td, H-5) $^2J_{55'}$: -14.6 Hz $^3J_{54'}$: 11.7 Hz $^3J_{54}$: 2.0 Hz	3.37 (s)
		-120°C C_e (95%)	—	4.32 (d, H-2a) $^3J_{2a-3a}$: 9.2 Hz	1.93 (q, H-3a) $^2J_{3a-3e}$: -13.2 Hz $^3J_{3a-4a}$: 13.2 Hz $^3J_{3a-2a}$: 13.2 Hz 2.13 (d, H-3e) $^2J_{3e-3a}$: -13.2 Hz	1.47 (q, H-4a) $^2J_{4a-4e}$: -13.2 Hz $^3J_{4a-5a}$: 13.2 Hz $^3J_{4a-3a}$: 13.2 Hz 2.02 (d, H-4e) $^2J_{4e-4a}$: -13.2 Hz	2.71 (dd, H-5e) $^2J_{5e-5a}$: -13.4 Hz $^3J_{5e-4e}$: 4.3 Hz 2.85 (t, H-5a) $^2J_{5a-5e}$: -13.4 Hz $^3J_{5a-4a}$: 13.2 Hz	3.40 (s)

(a) All aromatics signals were superposed with solvent.

Table 3. Thermodynamic, kinetic and geometrical data for compounds 2 to 7 and 9.

Compound	Solvent	Conformation	Population	$-\Delta G°$ (Kcal/mol)	$\Delta G^{\ddagger}$ (Kcal/mol)	θ_c	ΔH_{TB-C} in parent compound (kcal/mol)
2	CHF_2Cl	C_a	50%[a]	0.23 (C_a/C_e, -120°)[a]	8.8 (TB → Ca, -90°)[a]	5°	1.9 in 2
		C_e	23%	0.18 (C_a/TB, -120)	11.1 (Ca → TB, -90°)		
		TB	27%	0.05 (TB/C_e, -120)			
	CH_3OCH_3	C_a	61%	0.43 (C_a/C_e, -120)			
		C_e	15%	0.28 (C_a/TB, -120)			
		TB	24%	0.14 (TB/C_e, -120)			
5	CHF_2Cl	C_a	94%	0.84 (C_a/C_e, -120°)[b]	[c] 8.8 (Ca → Ce, -85°)	8°	2.7 in 4
		C_e	6%				
	CH_3OCH_3	C_a	84%	0.50 (C_a/C_e, -120°)			
		C_e	16%				
7	CHF_2Cl	C_a	5%	0.89 (C_e/C_a, -125°)[b]	8.4 (Ce → Ca, -90°)[c]	35°	1.5 in 6
		C_e	95%				
	CH_3OCH_3	C_a	5%	0.87 (C_e/C_a, -120°)			
		C_e	95%				
9	—	—	—	—	—	5°	—

(a) Parameter from ref. 5.

(b) Determination of these parameters are given in Experimental Section.

(c) Dihedral angle θ and ΔH_{TB-C} calculated with MM2 85[13] program obtained form QCPE (No. 395).

Figure 2 illustrates the 100.62 MHz proton decoupled ^{13}C NMR spectral change observed for 7. Most of the signals split into two lines of intensity 95:5 in CHF_2Cl at -125°C. Chemical shifts are assigned through a comparison with substituent effects relative to the parent compound 6 and by selective proton irradiation of the H-4a and H-3a at -120°C. Substituent effect parameters for the two conformers are given in Table 1 and the γ effect clearly shows that the major conformer, which has the smaller γ effect, is the C_e form. This result is a complete reversal from the situation observed for the other methoxy derivative 5. Kinetic and thermodynamic parameters obtained from the spectra of 7 are summarized in Table 3.

The 400.13 MHz ^1H NMR spectrum observed for 7 in CHF_2Cl also change at low temperature. At -120°C, the signals detected belong to the major C_e form whereas those of the minor C_a form are not well resolved. The H-2 doublet at 4.32 ppm shows a splitting of 9.2 Hz due to a large $^3J_{HH}$ coupling with one of the H-3 protons. This large vicinal coupling indicates that the two coupled protons are axially oriented as in C_e. The pertinent ^1H parameters are summarized in Table 2.

The Anomeric Effect in 3, 5 and 7

The currently accepted view of the anomeric effect is that it results from a combination of two factors: a stereoelectronic orbital interaction[11] and an electrostactic or dipole-dipole interaction.[12] However, the relative contribution of each factor has not been quantified, although it is believed that the orbital contribution may be more important[11b]. Recently, Praly and Lemieux[4] stressed the importance of considering electron pairs from both oxygen atoms of the acetal function (endo- and exo-anomeric effects) to explain conformer stabilization by such stereoelectronic interactions. In particular, these authors pointed out that, for the axial-anomer 1a, competition exists between the endo- and exo-anomeric effects for the electron deficiency at the anomeric carbon and consequently, that the exo effect is stronger in 1b than in 1a.

An example of seven-membered cyclic molecules exhibiting the anomeric[5] effect is 3 for which both the C_a and TB forms are stabilized by the methoxy group as seen from Table 3. In both of these conformations an endo n → σ* interaction is possible geometrically and is deemed to impart stability. The behavior of compounds 5 and 7 observed in this work is markedly different from that of 3 in that they do not reveal the presence of the TB form. Furthermore 5 shows a much greater amount of C_a than 3 whereas, for 7, the C_e form is predominant. Why do 5 and 7 show opposite conformational preference and why is the TB form not observed for both compounds?

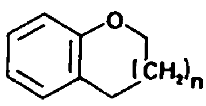
Detection of the TB form for compounds of the benzocycloheptene family results in large part from two basic factors, namely the conformational energy difference between C and TB in the basic ring skeleton of each heterocycle and the magnitude of stabilization caused by stereoelectronic and electrostatic interactions involving polar bonds. The experimental determination of the energy difference between the C and TB forms of the unsubstituted compounds 2, 4 and 6 is not possible by the NMR method and calculated values will be used. Conformational energies obtained from molecular mechanics calculations using the MM285 program[13] are reported in Table 3. It is seen that the calculated energy difference between TB and C (ΔE_{TB-C}) decreases in the order 4 > 2 > 6. In other words, as the oxygen atom is displaced away from the aromatic ring, the TB-C energy difference increases.

Because more energy must be overcomed for the TB form of 4 to become detectable by NMR, this form is less likely to be detected for 5 because the energy difference might not be compensated by the anomeric stabilization energy arising from the presence of the methoxy group. This explains the observation that 5 exists as a $C_a \rightleftharpoons C_e$ equilibrium without any TB form being present. Such is not the case in 3 for which the anomeric stabilization is sufficient to overcome the ΔE_{TB-C} term. In contrast, molecular models of the TB form for 7 show a serious non-bonded repulsive interaction between the methoxy group and the C(5)-H proton so that anomeric stabilization in TB is not sufficient.

The larger amount of C_a form for 5 relative to 1 or 3 can be attributed largely to a reduced steric interaction in C_a owing to the replacement of a syn-1,3 axial proton by the π-cloud of the benzo ring. This kind of steric interaction has been shown to favor the axial position in the reference compound 4-methoxybenzocycloheptene.[6]

In the case of 7, a complete reversal in conformational preference relative to 5 is observed whereby the C_e form has become highly dominant. The similar steric environment of the methoxy group in both 5 and 7 suggests that non-bonding repulsive interactions ought not to be responsible for the change in conformation stability. On the other hand, the structural difference between the two seven-membered rings is such that, in 7, the ring oxygen might conjugate with the aromatic ring. Could delocalization of an oxygen lone pair with the aromatic ring modify the conformation stability in favor of the C_e form?

A UV spectroscopic study carried out by Mandolini and Masci[14] on a series of cyclic phenolic ethers 8 has shown significant differences between the seven-membered 6 and the other cyclic ethers as measured by the λ_{max} and ϵ_{max} of the $\pi \rightarrow \pi^*$ transition. Our results for 7 are essentially identical to those reported for 6. The parameters observed for 6 and 7 suggest that there is less oxygen lone pair conjugation than in the corresponding six-membered analog 8 (n = 1). This conclusion is supported by calculated angles (using the MM2S5 program[13]) between the π orbitals of the aromatic ring and the adjacent oxygen lone pairs of electrons treated as localized sp^3 orbitals in both 7 and 9 as shown by structures 10 and 11 respectively. Thus the angle of 5° calculated for 9 indicates near perfect overlap and strong delocalization whereas the angle of 40° for 7 (see 10) indicates poorer overlap and less delocalization. This calculated 35° difference is similar to an experimental difference of angle of twist deduced from UV measurements[15].



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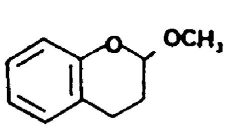

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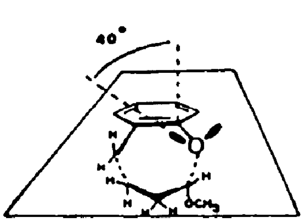

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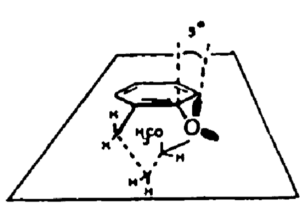

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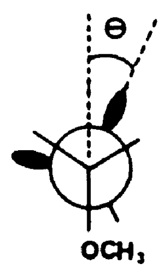

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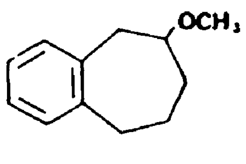
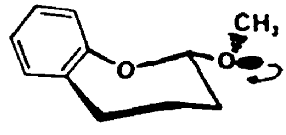
In addition, the NMR data for 7 and 9 reveal strikingly different conformational preferences for the two ring sizes whereby 7 is predominantly C_e while 9 is predominantly C_a[16]. It would appear that delocalization of the oxygen lone pair in 9 does not alter the axial preference associated with the endo-anomeric effect. The conformational specificity of 7 therefore cannot be attributed directly to lone pair conjugation with the aromatic ring.

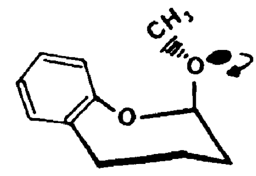
Because the $n \rightarrow \sigma^*$ stereoelectronic orbital interaction at the origin of the anomeric effect is maximum when the lone pair is anti-coplanar to the C-O bond, it is useful to determine the :-O-C-OMe dihedral angles (12) for compounds 3, 5, 7 and 9 as it has been shown that there exists an angular dependence for the anomeric effect[17]. The observation that the calculated dihedral angles (see Table 3) are very similar for 3, 5 and 9 indicates that near anti-coplanarity exists for these three compounds while there is appreciable departure from coplanarity for 7. This fact ought to weaken the $n \rightarrow \sigma^*$ interaction in 7 and attenuate its stabilising effect on the C_a form. This corresponds to a weakening of the endo contribution which should shift the $C_e \rightleftharpoons C_a$ equilibrium towards the C_e form. Furthermore, results[6] for 13 show that the amount of C_e is larger for 7 than 13. It is possible that the dihedral angular difference could also slightly modify the dipole-dipole contribution to conformational stability in 7, but the fact that the conformer populations of 7 are similar in both CHF_2Cl and CH_3OCH_3 suggests that this contribution is not overriding.



13



14



15

In addition to the attenuation of the $n \rightarrow \sigma^*$ interaction, the work of Praly and Lemieux[4] suggests that it is also necessary to assess the *exo* interaction term for **7** relative to **3** and **5**.

From the examination of structures **14** and **15**, the rotamers of the C_e and C_a forms of **7** exhibiting anti-coplanarity between a lone pair of electrons and the ring C–O bond, indicates that **15** is less favored than **14** due to greater steric interaction involving the methyl group. As a consequence, back-donation of electrons is stronger in C_e than in C_a. Furthermore, even though it was shown above that delocalization of the ring oxygen lone pair with the aromatic ring is not strong, it may still be sufficient to impart a slightly larger partial positive charge in **7** than in **3** and **5**. Such a situation would increase back-donation in **14** (C_e), further strengthen the *exo* interaction term and stabilize the C_e conformation.

In conclusion, it appears that the strong equatorial preference for **7** is due mainly to a combination of two factors: Firstly, poor overlap between the n and σ^* orbitals because of the non-coplanarity of the two orbitals resulting in a weakening of the *endo* contribution and secondly, a strengthening of the *exo* contribution term due to lone-pair back donation from the methoxy substituent. Both of these factors stabilize the C_e form.

EXPERIMENTAL SECTION

The variable temperatures ^{1}H NMR spectra were obtained using a Bruker WH-400 spectrometer equipped with a B-VT-1000 variable temperature unit. Calibration using a copper-constantan thermocouple inside a solvent containing NMR tube indicates that the temperature reported are precise within ±3°C. The proton samples were prepared as solution in chlorodifluoromethane (15–20 mg in 0.55 mL of solution) containing 18% of CD_2Cl_2 (for locking purpose) and a small quantity of Me_4Si in 5 mm tubes which were then degassed and sealed. The ^{1}H NMR spectra were recorded at 400.13 Hz and the following instrumental parameters are typical: flip angle = 10°: SW = 5000 Hz; data size 16 K data points; acquisition time = 1.64 s. Gaussian multiplication was applied. The number of scan varied from 200–1000.

The variable ^{13}C NMR spectra were recorded at 100.62 MHz. The samples were studied as solution in chlorodifluoromethane and in dimethyl ether (120–150 mg in 2.2 mL of solution) containing 18% of CD_2Cl_2 (for locking purpose) and a small quantity of Me_4Si in 10 mm tubes which were degassed and sealed. The following instrumental parameter are typical: flip angle = 60–90°; SW = 20 000 Hz; data size = 16 K; acquisition time = 0.41 s; number of scan = 500–2000; power decoupler (attenuation 5 dB on high rank of the standard decoupler). The ^{13}C NMR data were treated by a exponential multiplication with LB varying from 3–8. Reliable integrations from the ^{13}C spectra were obtained using a 0.1–0.2 s delay between pulses and by comparing results for at least two other set of carbon resonances of the same compound.

The values of $\Delta G°$ for **5** and **7** were calculated from the equation $\Delta G°\ C_a/C_e = RT \ln K$ where K is the population ratio $[C_a]/[C_e]$ at -120°C. The rate constants for **5** and **7** were determined by ^{13}C NMR at coalescence temperature using the equation[9] for two unequal population $k_A = 2\pi\rho_B\delta_v$ where ρ_B is the population of conformer B and δ_v the difference in Hz between the two carbons of conformers A and B. The free energy barrier for these compounds was calculated from standard equations using a transmission coefficient of one[18].

The UV spectrum of **7** was recorded in methanol using a Perkin-Elmer model 552 spectrophotometer.

Tetrahydro-3-benzoxepin (**4**)

1,2-Benzenediethanol was prepared by a $LiAlH_4$ (8.0 g, 0.21 mol) reduction of 1,2-benzenediacetic acid (Aldrich) (10 g, 0.05 mol) in 100 mL of anhydrous THF at reflux for 14 h and using a standard procedure and workup[19]. The solid was crystallized from a mixture of dichloromethane-hexane to give 6.0 g. ^{1}H NMR (90 MHz) δ = 7.21 (s, 4H, aromatics), 3.87 (t, 4H, ^3J = 6.6 Hz, CH_2O), 2.94 (t, 4H, ^3J = 6 Hz, Ar CH_2O), 2.04 (s, 2H, OH). IR 3500–3200 cm^{-1} (OH), 3020 and 3070 cm^{-1} (CH aromatic), 2980–2860 cm^{-1} (CH aliphatic) 1040 cm^{-1} (CO), 740 cm^{-1}.

The 1,2-benzenediethanol (0.5 g, 3.01 mmol) was tosylated by a standard method[20] using the equivalent of *p*-toluene sulfonyl chloride. Monotosyl and ditosyl (2:1) derivatives were separated with flash chromatography on silica gel 230–400 mesh to give 0.4 g of 1,2-benzenediethanol monotosylate. ^{1}H NMR (90 MHz): δ 7.71 and 7.30 (AB spectra, 4H, aromatics), 7.2 (m, 4H, aromatics), 4.20 (t, 2H, ^3J = 7.3 Hz, CH_2OSO_2), 3.80 (t, 2H, ^3H = 7.2 Hz, CH_2O) 3.03 (t, 2H, Ar CH_2) 2.82 (t, 2H, ar CH_2) 2.44 (s, 3H, CH_3Ar).

The above monotosylate (0.8 g, 2.5 mmol) was cyclized in THF by the addition of NaH (6.3 mmol). After 14 days, a mixture of 1,2,4,5-tetrahydro-3-benzoxepin and 1,2-dihydro-3-benzoxepin (75:25) was obtain and purified with gas chromatography (column SE-30% on chromosorb P) to yield 0.21 g of 1,2,4,5-tetrahydro-3-benzoxepin whose ^{1}H NMR spectrum is identical to that already published[7].

2-Methoxy-1,2,4,5-tetrahydro-3-benzoxepin (5)

The 1,2-benzenediethanol (2.9 g, 17.5 mmol) described above was monoacetylated with 97% acetic anhydride (1.8 g, 17.5 mmol) in 30 mL of pyridine. After 48 h, the mixture was coevaporated twicely with 50 mL of toluene (monoacetate:diacetate = 6:1) and the mixture was purified with Flash chromatography using silica gel 230–400 mesh to give 1.5 g of liquid corresponding to the monoacetate of 1,2-benzenediethanol. ^{1}H NMR (90 MHz): δ 7.2 (s, 4H, aromatics), 4.27 (t, 2H, ^{3}J = 7.3 Hz, CH_2OAc), 3.85 (t, 2H, ^{3}J = 6.8 Hz, CH_2O), 3.78 to 2.88 (2t, 4H, 2 X Ar CH_2), 2.05 (s, 3H, CH_3), 1.6 (s, 1H, OH).

The above monoacetate (1.5 g, 7.2 mmol) was oxydized with pyridinium chlorochromate using the method developed by Corey[21]. The liquid was rapidly passed through flash chromatography on silica gel 230–400 mesh to give 1.2 g of 2(2-acetoxyethyl)phenylacetaldehyde. ^{1}H NMR (90 MHz) δ 9.76 (t, 1H, ^{3}J: 2.0 Hz, CHO), 7.26 (s, 4H, aromatics, 4.23 (t, 2H, CH_2O), 3.80 (d, 2H, CH_2 aldehyde), 2.92 (t, 2H, ^{3}J: 7.2 Hz, Ar CH_2), 2.04 (s, 3H, CH_3).

Cyclization of this compound (1.0 g, 4.85 mmol) and purification was carried out using the same method as published[22] for a similar methoxy compound to yield 0.5 g of liquid 1,2,4,5-tetrahydro-2-methoxy-3-benzoxepin (5). ^{1}H NMR (400 MHz, Table 2) ^{13}C NMR (100.62 MHz, Table 1, Fig. 1). Mass spectra EI, calcd for $C_{11}H_{14}O_2$: 178.100. Found: 178.103.

2,3,4,5-Tetrahydro-1-benzoxepin (6)

This compound was synthetized and characterized by A. Lachapelle and M. St-Jacques[10].

2-Methoxy-2,3,4,5-tetrahydro-1-benzoxepin (7)

The starting product 2,3,4,5-tetrahydro-1-benzoxepin-3-ol[10] (1.0 g, 6.09 mmol) was tosylated using 1 equivalent of p-toluene sulfonylchloride. Flash chromatography on silica gel 230–400 mesh gave 1.5 g of solid 2,3,4,5-tetrahydro-3-tosyloxy-1-benzoxepin. ^{1}H NMR (90 MHz) δ 7.9 and 7.3 (AB spectra, 4H aromatics), 7.1-7.0 (m, 4H, aromatics), 4.8 (m, 1H, CH), 3.95 (m, 2H, OCH_2), 3.0–2.5 (m, 2H, Ar CH_2) 2.47 (s, 3H, CH_3Ar), 2.2–1.8 (m, 2H, CCH_2).

The above compound (1.35 g, 4.4 mmol) was left standing overnight with potassium-t-butoxyde (1.5 g, 13.4 mmol) in anhydrous THF under a flow of Argon. After water-ether extraction and drying with $MgSO_4$, the organic compound was purified with flash chromatography using silica gel 230–400 mesh to give 0.6 g of 4,5-dihydro-1-benzoxepin liquid whose ^{1}H NMR spectrum is identical to that already reported[23].

2-Methoxy-2,3,4,5-tetrahydro-1-benzoxepin (7) (0.2 g, 1.36 mmol) was synthetized using 4,5-dihydro-1-benzoxepin and mercuric acetate in methanol using a published method[24]. The product was purified with flash chromatography on silica gel 230-400 mesh to give 0.12 g of 7. The ^{1}H and ^{13}C NMR data are listed in Tables I, II. Mass spectra EI calcd for $C_{11}H_{14}O_2$: 178.100. Found: 178.099.

The UV spectrum of 7 in methanol (10^{-3}M) gave λ_{max} = 266.9 nm and ε = 583.

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