(40) A locally written computer program, NLLSQ, based on the Marquardt algorithm,[41] was used. We thank Dr. Eric Enwall for kindly obtaining for us the computer-drawn plot shown in Figure 3.
(41) D. W. Marquardt, *J. Soc. Ind. Appl. Math.*, **11**, 431 (1963).
(42) The observed values of $J_{^{14}NCCH}$ measured in ^{15}N-enriched amino acids measured approximately at their isoelectric points agree remarkably well with the values predicted on the basis of the curve shown in Figure 3, e.g., $J^{trans}_{^{14}NCCH} = 3.6$ and $J^{gauche}_{^{14}NCCH} = 1.3$ Hz.[43]
(43) R. L. Lichter and J. D. Roberts, *J. Org. Chem.*, **35**, 2806 (1970).
(44) $J_{^{14}NCCH}$ values for torsion angles, ϕ, of 60 and 180° are predicted to have *opposite* signs "due to a substituent effect involving the lone pair electrons on the nitrogen and the π-electrons of the carbonyl groups".[28b]

Proton and Carbon-13 Nuclear Magnetic Resonance Studies of the Conformational Dynamic Properties of Seven-Membered Rings. 2,4-Benzodioxepin and Its Derivatives

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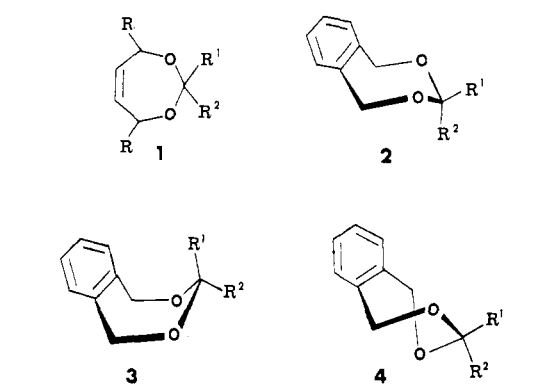
Abstract: The conformational and dynamic properties of 1,3-dioxa-5,6-benzocycloheptene (**5**, 2,4-benzodioxepin) and three of its 2,2-disubstituted and two of its 2-monosubstituted derivatives have been investigated by ^1H and ^{13}C DNMR methods. Analysis of the spectra of low temperatures (below coalescence) indicates that the most stable seven-membered ring conformations detected for solutions in CHF_2Cl are C (79%) and TB (21%) for **5**, TB for **6**, **7**, and **8** (the disubstituted derivatives), C for the 2-methyl-derivative (**9**), and TB for the 2-methoxy derivative (**10**). Thus the polar nature of the single methoxy substituent causes a change in the ring conformation as a consequence of the anomeric effect. Free-energy barriers were determined for the chair inversion of **5** (8.0 kcal/mol) and for the twist-boat pseudorotation of **6**, **7**, **8**, and **10** (10.0, 9.0, 9.9, and 6.7 kcal/mol, respectively). The substituent effects on both the conformational and dynamic properties of the seven-membered rings are discussed and explained.

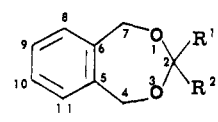
Recent theoretical and expermental investigations[1-5] of the conformational dynamic properties of seven-membered carbocycles have provided much valuable information concerning this fundamental cyclic system. The need for extending such knowledge to rings with heteroatoms has given rise to several studies concerned with the conformation of six-,[6-8] seven-,[9-12] and eight-membered[13] heterocycles containing the OCH_2O unit. However, the results for seven-membered rings have revealed that quantitative experimental characterization is apparently more elusive than for the other two ring systems.

The family of molecules derived from 1,3-dioxacycloheptene (1,3-dioxepin) and 1,3-dioxa-5,6-benzocycloheptene (1,5-dihydro-3*H*-2,4-benzodioxepin[14]) constitutes a fundamental system whose conformational properties compared to those of the cycloheptene–benzocycloheptene system[1,5] should permit characterization of the effects of the OCH_2O, OCHRO, and OCR_2O fragments in the seven-membered ring.

It appears that previous works on this class of molecules have not provided the quantitative results required to fully characterize the important conformational and dynamic effects associated with the OCH_2O unit. On one hand, Gianni and co-workers[11] have studied the carbon-13 magnetic resonance spectra of several methyl and alkyl derivatives of 1,3-dioxacycloheptene (**1**) at ambient temperature. The unknown conformation of the unsubstituted compound used as reference for calculating γ shifts and the impossibility to detect mixtures of conformations significantly limit the scope of their conclusions. On the other hand, preliminary ^1H DNMR results[15] at 60 MHz and moderately low temperatures suggested that, among the three possible conformations (chair (**2**), boat (**3**), or twist-boat (**4**)), 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene exists as a twist-boat (TB) whereas the stable conformation of the parent compound was not identified.

In order to gain a more quantitative understanding of the conformational dynamic properties of the seven-membered ring involved we undertook a DNMR investigation of compounds **5–10.** Our specific objectives were first to characterize





5; $R^1 = R^2 = H$
6; $R^1 = R^2 = CH_3$
7; R^1, R^2 = tetramethylene
8; R^1, R^2 = pentamethylene
9; $R^1 = H$, $R^2 = CH_3$
10; $R^1 = H$, $R^2 = OCH_3$

the conformation(s) of the parent compound (**5**), the 2,2-disubstituted derivatives (**6**, **7**, and **8**), and the 2-monosubstituted derivatives (**9** and **10**) and secondly to determine the effect of the various substituents on the ring dynamics. The well-known axial preference of 2-methoxy-1,3-dioxane,[6] because of the anomeric effect, adds special interest to the investigation of **10** whose conformational properties could be determined by this particular effect.

Consequently we report results from ^1H (100 MHz) and ^{13}C

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Table I. ^{1}H NMR[a] Spectral and Dynamic Parameters for Compounds **5–10**

Compd	Temp, °C	δ_A	δ_{av}	δ_B	$-^2J_{AB}$, Hz[b]	T_c, °C	$\Delta G^{\ddagger}$, kcal/mol
5	25		4.832				
	−130	4.961		4.842[c]	14.6	−108	7.7 ± 0.5
	25		5.004				
	−130	5.402		5.017[d]	7.6	−102	8.0 ± 0.3
6	25		4.853				
	−107	5.212		4.567[c]	15.1	−64	10.0 ± 0.3
7	25		4.891				
	−130	5.077		4.642[c]	14.6	−86	9.0 ± 0.3
8	25		4.848				
	−111	5.255		4.554[c,e]	15.3	−64	9.9 ± 0.3
		5.090		4.471	15.2		
9	25		4.816				
	−100	4.972		4.773[c]	15.0		
10	25	5.056		4.674	14.6		
	−150	5.354		4.507[c,e]	14.8[f]		
		5.041		4.834	15.3	−131	6.7 ± 0.5

[a] At 100 MHz in CHF_2Cl containing internal Me_4Si. [b] The uncertainty is ±0.3 Hz unless otherwise mentioned. [c] Methylene protons on C-4 and C-7. [d] Methylene protons on C-2. [e] Two AB patterns are observed at low temperature. [f] Owing to the broadness of the lines at −150 °C, the uncertainty is about 0.5 Hz.

Table II. Carbon-13 Chemical Shift Data for Compounds **5–10** at High and Low Temperature[a]

Compd	Temp, °C	C-5, C-6	C-8 to C-11	C-2	C-4, C-7	Substituents on C-2		
5	25	141.03	128.55	100.54	73.96			
	−130	140.72 (c)[b]	129.59, 129.37 (c)	103.09 (c)	76.25 (c)			
		139.64 (b)	128.08, 127.86 (b)	96.84 (b)	70.38 (b)			
6	25	140.05	127.96, 127.38	103.79	66.09	24.31 (CH_3)		
	−120	139.21	128.03, 127.51	103.66	65.51	23.79 (CH_3)		
7	25	140.12	127.91, 127.30	116.38	67.71	36.55 (C-2′)	24.94 (C-3′)	
	−130	139.34	127.95, 127.52	116.38	67.40	36.55 (C-2′)	25.24 (C-3′)	
8	25	140.29	127.99, 127.39	103.87	65.29	33.87 (C-2′)	24.51 (C-3′)	27.06 (C-4′)
	−101	139.47	127.91, 127.39	103.78	65.03[c]	34.26 (C-2′)[c]	24.29 (C-3′)[c]	26.32 (C-4′)
					64.43	31.67	23.73	
9	25	141.09	128.74	107.04	72.72	21.51 (CH_3)		
	−130	140.51	129.39	109.31	74.67	22.49 (CH_3)		
10	25	139.13	128.21, 127.52	115.35	66.02	53.98 (OCH_3)		
	−150	138.31	128.20, 127.28	114.35	67.84[c]	54.33 (OCH_3)		
					62.57			

[a] Solutions in CHF_2Cl containing internal Me_4Si and CD_2Cl_2 (13%) for field locking purpose. [b] The lines labeled c are more intense than the b lines (c = 79%; b = 21%). [c] The indicated carbon signal has undergone a splitting into two lines of equal intensities at low temperatures.

(22.6 MHz) DNMR studies which provide rather significant new insight into the conformational dynamics of seven-membered rings.

Results

Compounds **5, 6, 7, 8,** and **10** gave dynamic proton magnetic resonance (^{1}H NMR) spectral changes on going to low temperatures whereas only **5, 8,** and **10** gave carbon-13 magnetic resonance (^{13}C NMR) spectral changes. Spectral and dynamic parameters for all the compounds studied are listed in Tables I and II.

Figure 1 illustrates both the ^{13}C NMR (A) and ^{1}H NMR (B) spectral modifications observed for the parent 1,3-dioxa-5,6-benzocycloheptene (**5**) in CHF_2Cl. Figure 1A shows that all the ring carbon signals have split into doublets of unequal intensities at −130 °C. The more intense lines (labeled c) account for 79% while the less intense lines (b) account for 21% of the total intensity. The aromatic carbon signals also undergo a similar change as reported in Table II. A free energy of activation of 7.9 ± 0.5 kcal/mol was estimated at −101 °C, the coalescence temperature (T_c), using a transmission coefficient of one.

Owing to solubility problems at low temperatures, we were able to study the ^{13}C NMR spectrum of this compound at lower concentration only in one other solvent, namely, dimethyl ether. A similar spectral change to that described in Figure 1A was observed. Integration of the signals at −128 °C, however, revealed 33% for the less intense lines and 67% for the major ones.

Figure 1B shows that the two methylene proton singlets of **5** in CHF_2Cl each change into an AB quartet below −110 °C for which spectral parameters at −130 °C are reported in Table I. Free energies of activation were calculated from the coalescence of each AB pattern. The value of 8.0 ± 0.3 kcal/mol was calculated from the low-field signal and 7.7 ± 0.5 from the high-field signal using a transmission coefficient of one half (vide infra). The larger chemical shift difference of the low-field AB pattern permitted a more accurate estimation of coalescence and therefore should give a parameter more representative of the dynamics of **5.**

In addition to two AB patterns similar to those observed in Figure 1B, the ^{1}H NMR spectrum of **5** in dimethyl ether at −135 °C revealed the presence of two additional singlets apparently due to the minor conformer identified in the ^{13}C NMR spectra. These lines were visible because of solvent effects on the methylene proton chemical shifts. However, because of appreciable overlap with the more intense AB lines of the major conformation, the two singlets, separated by 4.7

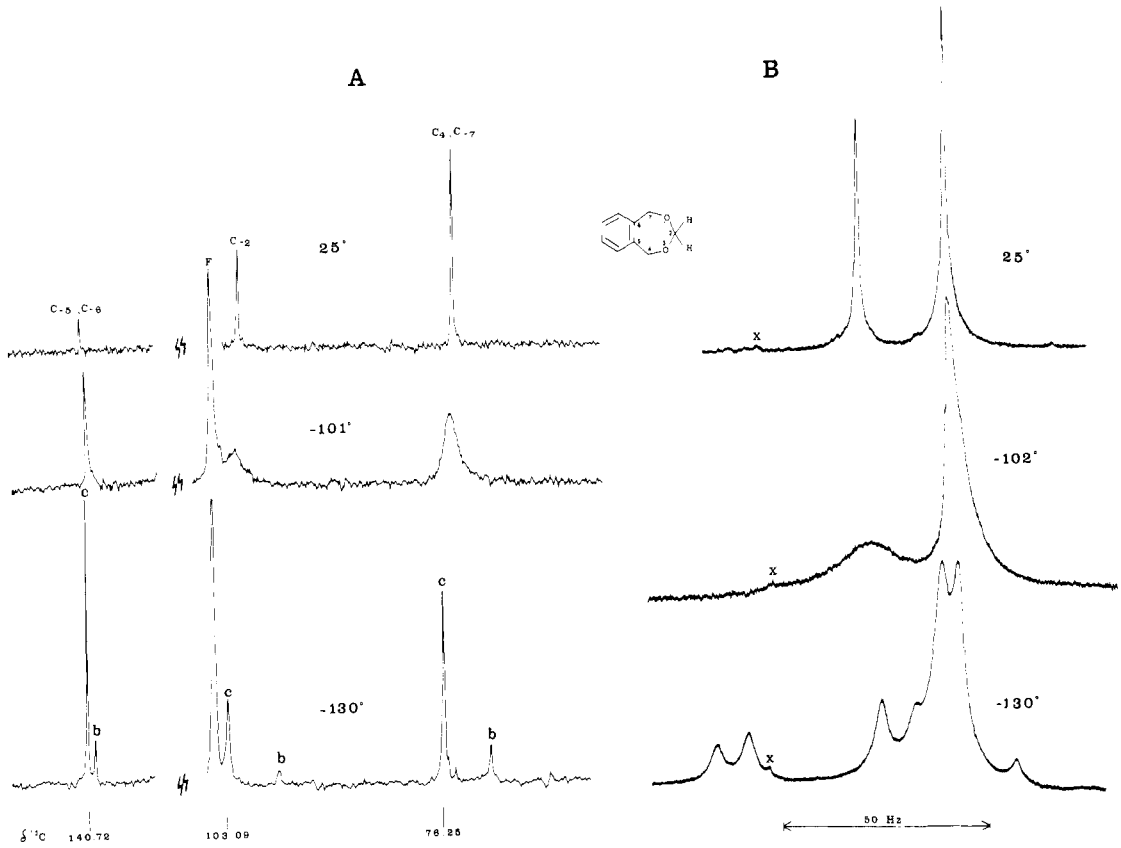

Figure 1. (A) The 22.6-MHz ^{13}C NMR spectra of the seven-membered ring carbons of **5** in CHF_2Cl at several temperatures. (F denotes a CHF_2Cl line). (B) The 100-MHz ^1H NMR spectra of the methylene protons of **5** in CHF_2Cl at several temperatures (x denotes an impurity).

Hz, could not be assigned reliably. Furthermore, because the sample froze near −140 °C, spectra at lower temperatures could not be recorded.

Compound **6** (2,2-dimethyl) showed only a ^1H NMR spectral change similar to that reported earlier[15] whereby only the methylene singlet became an AB below −64 °C (T_c). Its spectral and dynamic parameters are listed in Tables I and II. The ^{13}C NMR spectrum remained unchanged down to −160 °C.

Compound **7** (2,2-tetramethylene) exhibited only a ^1H NMR spectral change similar to that of **6** whereby the methylene singlet has split into an AB spectrum below −86 °C. All characteristic parameters are listed in Tables I and II.

The ^1H NMR spectrum of **8** (2,2-pentamethylene) showed a spectral change for the C-4 and C-7 methylene protons from a singlet at 25 °C into two AB patterns at −111 °C. The complex upfield signal of the six-membered ring also changed at lower temperatures in a complex manner. Spectral and dynamic parameters are reported in Table I. The ^{13}C NMR spectrum of **8** also showed a spectral change whereby three singlets (those of C-4,7, C-2′,6′, and C-3′,5′) split into doublets with components of equal intensities. In addition to the parameters listed in Tables I and II, it is relevant to point out that $\Delta G^{\ddagger}$ calculated from the ^{13}C NMR spectral change is identical with that reported in Table I.

Only the ^1H NMR spectrum of **9** (2-methyl) showed a spectral modification whose origin is not related to a dynamic process but rather to an important temperature effect on chemical shifts of the nonequivalent C-4,7 methylene protons which appear as an A_2 pattern at high temperatures and an AB at −100 °C. The other proton signals as well as the ^{13}C NMR spectrum remained unchanged down to −150 °C.

The ^1H NMR spectrum of **10** (2-OCH_3), illustrated in Figure 2B, shows a unique spectral modification whereby the higher temperature AB quartet of the C-4,7 methylene protons has split into two AB patterns of equal intensity at −150 °C. The C-2 methine proton singlet shown on the left side of Figure 2B remains unchanged through the temperature range studied. Spectral and dynamic parameters are reported in Table I.

The ^{13}C NMR spectrum of **10** also exhibits a spectral change (Figure 2A) at low temperatures whereby only the C-4,7 singlet splits into a doublet with components of equal intensity. In addition to the chemical shift data reported in Table II, a free energy of activation of 6.7 ± 0.3 kcal/mol was calculated at −125 °C (T_c). This value agrees very well with that estimated from the ^1H NMR spectral change (Table I).

Discussion

Conformations of the Seven-Membered Rings. ^1H NMR results have shown that the chair is the only conformation detected for benzocycloheptene,[16] 5-oxabenzocycloheptene,[17] and several 5,5-disubstituted benzocycloheptenes.[18] By contrast, the existence of two conformers (79:21 in CHF_2Cl) for **5** is clearly revealed by its ^{13}C NMR spectrum at −130 °C (Figure 1A). Furthermore, the observation of only two AB patterns in its ^1H NMR spectrum at −130 °C (Figure 1B) suggests that the signals of the minor conformation are hidden under those of the major form. Nevertheless the observed nonequivalence of the C-2 methylene protons rules out the TB conformation (**4**, $R^1 = R^2 = H$) as the major one, but is compatible with either the chair (**2**, $R^1 = R^2 = H$) or the boat (**3**, $R^1 = R^2 = H$) forms. Consequently only the minor conformer can be TB, but because this form is generally less energetic than the boat (B),[1,19] then the major conformer is unlikely to be B and should be the chair (C). This conclusion is further confirmed later from the analysis of ^{13}C chemical shifts.

The existence of a larger amount of TB for **5** relative to benzocycloheptene is readily rationalizable in terms of the stabilizing effect associated with the more favorable disposition

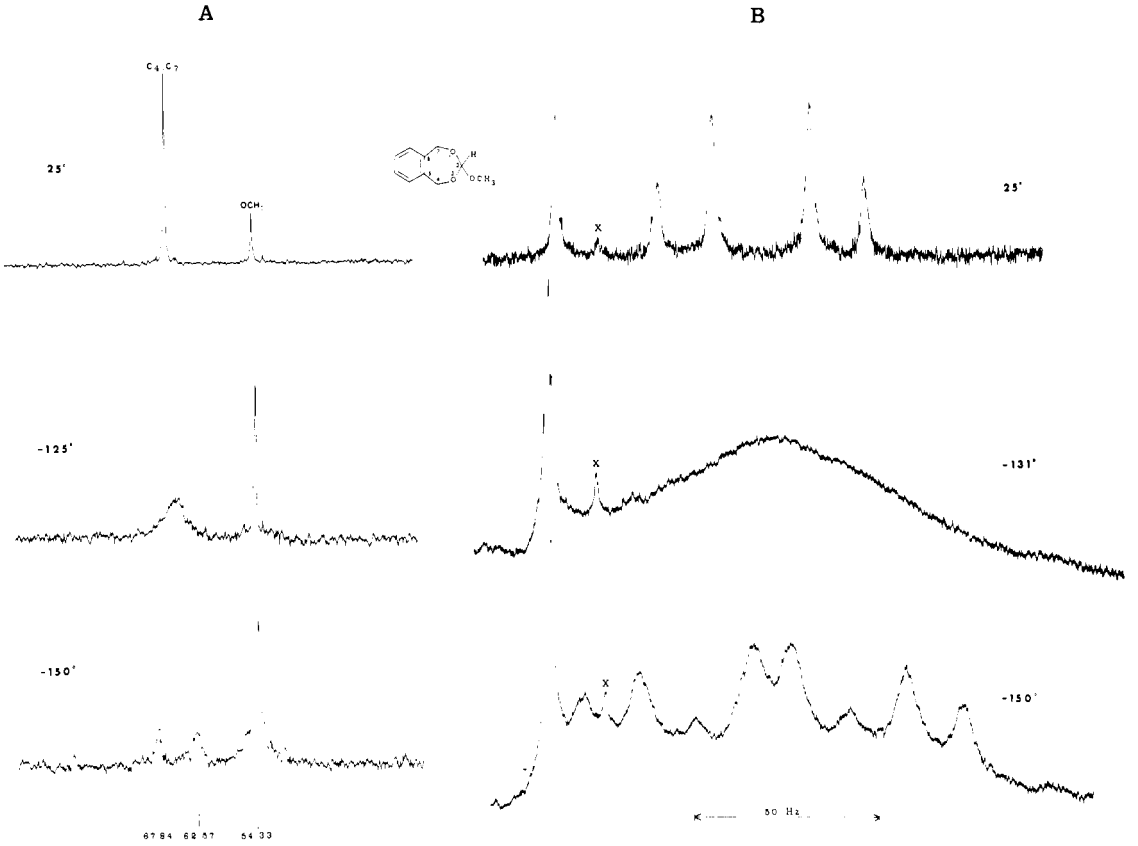

Figure 2. (A) Partial 22.6-MHz ^{13}C NMR spectra of **10** in CHF_2Cl at several temperatures. (B) The 100-MHz ^1H NMR spectra of the C-2 methine proton and the C-4,7 methylene protons of **10** in CHF_2Cl at several temperatures (x denotes an impurity).

of the $-CH_2OCH_2OCH_2-$ fragment in TB relative to C and B. Only in the TB form can these atoms take up a + gauche + gauche arrangement similar to that found most stable for dimethoxymethane.[20] The free-energy difference ($\Delta G°$) between C and TB of **5** at −130 °C in CHF_2Cl is 0.57 kcal/mol taking into account the existence of two equivalent TB forms. In dimethyl ether the difference is reduced to 0.40 kcal/mol at −128 °C.

This solvent effect is in line with that expected from the consideration that the C to TB conformational change is a manifestation of the generalized anomeric effect[21] whereby the preference for a gauche arrangement of the ROCOR moiety (as exists in TB) is increased in the solvent of lower polarity, namely, dimethyl ether, which has a smaller dipole moment[22] (1.30 D) than CHF_2Cl (1.48 D).

In contrast, it has been shown that 1,3-dioxacyclohexane[8] and 1,3-dioxacyclooctane[13] and their simple derivatives exist in only one detectable conformation, namely, a chair and a boat-chair, respectively.

Both the ^1H and ^{13}C NMR spectra of **10** at −150 °C (Figure 2) indicate that the benzylic carbon atoms are nonequivalent in the stable conformation. Furthermore the lack of splitting for the C-2 and C-H signals is compatible with a single conformation which must be TB since the benzylic carbons are equivalent in both C and B. The examination of **11** actually shows that, in TB, C-7 is gauche to OCH_3 whereas C-4 is anti to it.

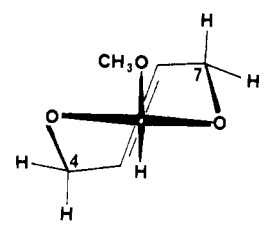

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Figure 3 illustrates the carbon-13 shift data for all compounds studied together with the identification of the C and TB lines for **5** and **10** revealed from the above analysis.

The absence of a ^{13}C NMR spectral change for **6** and the observed ^1H NMR spectral modification only for the signal of the methylene protons are compatible with a single detectable conformation with identical environments for both methyl groups unless, of course, shift equivalence is merely accidental. The TB form best explains these observations. More conclusive evidence in favor of this conformation is revealed from Figure 3 where it is seen that both the C-5,6 and C-8 to C-11 chemical shifts of **6** are very close to those characterizing the TB form of the parent compound (**5**). The distance between the site of substitution (i.e., C-2) and the protonated aromatic carbons is sufficiently large for there being no significant substituent effect caused by methyl substitution (or any of the other nonpolar substituents) on the TB ring skeleton.

Similar reasoning for **7** leads to the conclusion that it also exists as a single detectable TB form. The small chemical shift difference of the C-4,7 signals between **6** and **7** is apparently attributable to the effect of the five-membered ring.[23]

The similar chemical shifts for the various sp^2 carbons of **5**TB, **6**, **7**, and **8** shown in Figure 3 suggest that **8** also exists in a single detectable TB form. Thus at −101 °C the inversion of both the six- and seven-membered rings should be slow on the ^{13}C NMR time scale. The absence of symmetry in the stable conformation of **8** revealed from the low-temperature spectra, although by itself not characteristic of any particular seven-membered ring conformation, is compatible with TB for which C-4 and C-7 are nonequivalent. The small shift difference observed for these carbons is in line with its originating from slightly different relationships [24]with the nonequivalent C-3′ and C-5′ of the six-membered ring of **8**.

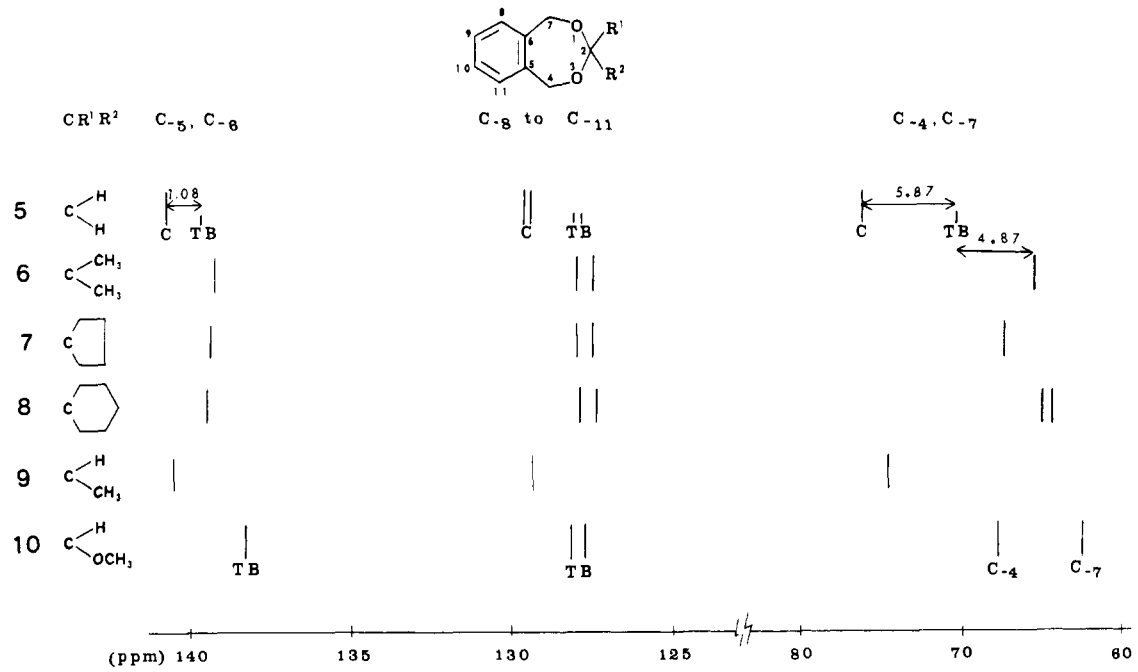


Figure 3. Carbon-13 chemical shift diagrammatic representation for compounds **5–10** at low temperatures as specified in Table II.

The examination of Figure 3 further shows that the carbon signals of **9** have shifts markedly different from those of **6, 7,** and **8** but which are very close to those of the c lines of the parent compound (**5**). This observation together with the absence of dynamic ^1H and ^{13}C NMR spectral changes for **9** are compatible with a single detectable chair conformation on which the methyl group is equatorial.

The results therefore show that disubstitution on C-2 strongly destabilizes the C form relative to TB and consequently **6, 7,** and **8** all exist in TB forms. Presumably strong nonbonded repulsive interactions between the axial substituent on C-2 and the axial protons on C-4 and C-7 of C are responsible for the TB preference of 2,2-disubstituted derivatives of **5.**

The results for **9** and **10** show that the conformational effect of a single substituent on C-2 is strongly dependent on its nature. The substitution with the nonpolar methyl group is seen to stabilize the chair form with an equatorial methyl relative to the TB form with an isoclinal methyl. Presumably an isoclinal methyl would participate in a significant nonbonded repulsive interaction with one of the syn-hydrogen atoms of the methylene group gauche to it.

Contrastingly, substitution by the polar methoxy group as in **10** has been found to lead to a conformational change—from C for **9** to TB for **10.** Were **10** to exist in the C form, a large amount of molecules would contain axial methoxy groups as is the case for 2-methoxy-1,3-dioxane,[6,7] because of the so-called anomeric effect.[21] The steric strain arising from axial substitution, which has been shown to destabilize C relative to TB for **6, 7,** and **8,** is believed to be largely responsible for the greater relative stability of the TB form of **10** because the methoxy group is more favorably located in TB compared to the equatorial position of the chair available as the other alternative. In fact, the isoclinal methoxy groups in TB are characterized by one stabilizing + gauche + gauche (or − −) arrangement whereas the equatorial methoxy group[20,21] is not. Furthermore the isoclinal position is not expected to be appreciably less stabilized from anomeric effects than is the axial position which is similarly characterized by only one + gauche + gauche (or − −) arrangement. By comparison methyl and methoxy substitutions on C-2 of 1,3-dioxane do not produce a ring conformational change similar to that observed for **9** and **10** because of the much larger energy difference[8] between the C and TB forms of 1,3-dioxane compared to our observed difference for **5.**

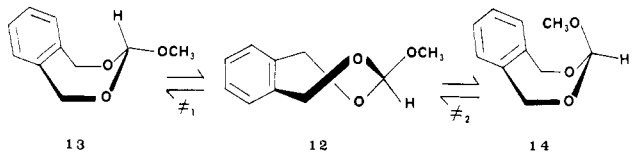
Conformational Averaging Processes. The chair inversion of benzocycloheptene and 5-oxabenzocycloheptene is known to involve a rate-determining chair to boat step characterized by free energies of activation of 10.9 and 9.5 kcal/mol, respectively.[5,17] The $\Delta G^{\ddagger}$ value of 7.9 ± 0.5 kcal/mol estimated from the ^{13}C NMR spectral change (Figure 1A) of **5** characterizes the chair to boat interconversion whereas the 8.0 ± 0.3 kcal/mol value calculated from the ^1H NMR spectral change (Figure 1B), using a transmission coefficient of one half, characterizes the chair to boat step of the chair inversion itinerary. Consequently the inversion barrier of 8.0 kcal/mol for **5** is smaller than those of the two above compounds and is indicative of easier ring deformation along the inversion pathway.

On the other hand, the conformational process averaging the environment of the methylene protons of **6** and **7** must involve the pseudorotation of the TB form which does not involve the chair form.[1]

The averaging process responsible for the spectral changes of **8** could be either the ring inversion of the six-membered ring or the pseudorotation of the seven-membered ring or a combination of both. In fact model compounds, namely, **6** and dimethylcyclohexane,[25] suggest that both processes should involve similar activation energies and thus not influence individually the appearance of the spectral changes of **8.**

Finally, the averaging process for **10** must also be the pseudorotation of the TB form. The lower barrier observed (6.7 kcal/mol) relative to that of **6** (10.0 kcal/mol) no doubt reflects on the nature of the interactions involved in the transition state and possibly in the ground state.

The pseudorotation pathway of the TB form is known to involve a TB ⇌ B step through a transition state (‡) containing five coplanar carbons.[1] The examination of molecular models shows that for **6** the transition state contains a syn-1,3 interaction between one of the C-2 methyl group and a C-4 (or C-7) hydrogen atom. On the other hand, two nonequivalent pathways exist for the inversion of the TB form of **10:** one of them (**12** ⇌ **14**) involves the transition state $‡_2$ containing a syn-1,3 interaction between the methoxy group and a C-4 hydrogen



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whereas the other (**12** ⇌ **13**) involves a transition state $\neq_1$ containing only a syn-1,3 hydrogen–hydrogen interaction. The latter pathway is expected to be less energetic than the first one and also easier than the pseudorotation of **6** in agreement with the lower $\Delta G^{\ddagger}$ value of **10** relative to that of **6** (Table I).

It is interesting to point out that the free-energy barriers for 2,2-dimethyl-1,3-dioxane,[26] 2-methoxy-1,3-dioxane,[27] and 1,3-dioxane[28] are 8.0, ~9.0, and 9.9 kcal/mol, respectively. This trend is characteristic of chair inversion for which nonbonded repulsion in the transition state and electrostatic effects[26] are less important than torsional effects. The marked difference in the relative order of the $\Delta G^{\ddagger}$ values of **6** and **10** compared to their dioxane analogues appears compatible with the earlier suggestion that nonbonded repulsive interactions in the pseudorotation transition state are mainly responsible for the $\Delta G^{\ddagger}$ difference for the seven-membered rings. Other reports[2,3] have noted that a *gem*-dimethyl group similarly raises the pseudorotation barriers of other seven-membered cyclic molecules.

Extrapolation from the data characterizing **10** suggests that the pseudorotation of the TB form of the parent compound (**5**), which involves a transition state similar to $\neq_1$, ought to be characterized by a $\Delta G^{\ddagger}$ barrier near 6 kcal/mol. Unfortunately this value cannot be confirmed from our data because ^{13}C NMR spectroscopy cannot provide such information while the ^1H NMR signals of TB in CHF_2Cl were not detected distinctly from those of the more abundant C form as seen from Figure 1B. Furthermore the dimethyl ether solution froze at temperatures above the expected coalescence temperature for a spectral modification associated with the pseudorotation of **5**TB.

The smaller barrier of **7** relative to **6** is more delicate to rationalize. It is, however, interesting to note that the trend is opposite to that observed for analogous derivatives of 1,3-dioxane whereby the 2,2-tetramethylene substituent leads to a barrier higher than that of 2,2-dimethyl-1,3-dioxane by 0.4 kcal/mol.[28] It is not obvious at the moment whether changes in bond and torsional angles or nonbonded repulsive interactions can best account for the 1 kcal/mol decrease in $\Delta G^{\ddagger}$ of **7** relative to **6.**

Carbon-13 Chemical Shifts. The observation of signals characteristic of both the C and TB forms of **5** allows the determination of the effect of the conformational change on the chemical shifts of the various seven-membered ring and aromatic carbons without the complicating effect of substituents.

The data for **5** at −130 °C (Table II) reveal that the C-2, C-4,7, and C-5,6 signals of C are all downfield from those of TB. The observed differences are 6.25 ppm for C-2, 5.87 ppm for C-4,7, and 1.08 ppm for C-5,6. These shift differences no doubt reflect on differences in both bond and torsional angles,[29] and it is very difficult to rationalize them quantitatively. It is nevertheless easy to see from models of C (**2**) and TB (**4**) that the relationship between C-4 and O-1 (or C-7 and O-3) is significantly different in each form. For example, in TB the torsional arrangement about the $-OCH_2O-$ segment is similar to that found for dimethoxymethane (i.e., + gauche + gauche or − gauche − gauche)[20] whereas it is + gauche − gauche in C. The upfield chemical shift observed for the TB carbons is in line with recent observations for 1,3-dioxanes and 1,3-dithianes.[30]

The shift differences measured constitute basic reference data characterizing the effect of the C ⇌ TB conformational change which must be distinguished from substituent effects when considering substituted derivatives. Thus, when dealing with molecules whose skeleton conformation can take up different forms, it is important to account for any conformational change in the skeleton before calculating substituent effects for a given conformation. Information on possible conformational changes then appears to be a prerequisite to quantitative work. It therefore appears that the absence of equivalent information for the 1,3-dioxepins could have introduced significant distortions in the interpretation of the carbon-13 data obtained at ambient temperature.[10]

The upfield γ shift of C-4,7 brought about by the substitution on C-2 is undoubtedly the most conformationally (and stereochemically) significant carbon-13 parameter.[31] Because **6, 7,** and **8** exist only as TB forms, this parameter must therefore be calculated from the TB lines of **5** (at low temperature) which are taken as reference point.

Thus the 4.87-ppm upfield shift of C-4,7 of **6** (determined from the data in Table II at low temperatures) caused by the dimethyl substitution on C-2 is characteristic of the seven-membered TB skeleton. It is somewhat smaller than the value of 7.49 ppm reported for analogous substitution on the 1,3-dioxane chair form[7] as well as the averaged value of 6.0 ppm for the C-4 and C-8 carbons of the BC-1,3 form of 1,3-dioxacyclooctane.[13]

Similarly the γ shifts caused by the spirotetramethylene (**7**) and spiropentamethylene (**8**) substituents on C-2 are 2.98 and 5.65 ppm, respectively. Accordingly the trend observed for **6, 7,** and **8** relative to **5**TB is parallel to that previously reported for identical substituents in six-membered cyclic molecules.[23]

The fact that **10** contains only one substituent (i.e., OCH_3) on C-2 results in the nonequivalence of the benzylic carbons (namely, C-4 and C-7) as seen from the TB projection **11.** The large chemical shift difference between the C-4 and C-7 lines can be explained readily by assigning a large upfield γ shift (7.81 ppm) to C-7 which is gauche to the OCH_3 group and a smaller upfield γ shift (2.54 ppm) to C-4 which is antiperiplanar to the methoxy substituent. This latter value is very similar to anti γ shifts observed for an equatorial methoxy group in six-membered rings.[32]

Finally, because **9** exists as a chair with an equatorial methyl group, it is interesting to compare the methyl effect with that reported for 2-methyl-1,3-dioxane, which also exists as a chair with an equatorial methyl group. An upfield γ shift of 1.58 ppm is observed for **9** at −130 °C compared to 0.33 ppm for the six-membered ring at room temperature.[7] Part of the difference may be related to the relatively large temperature effect on the chemical shift of the C-4,7 signal of **9** which could be either of intrinsic origin or arise as a consequence to the existence of a small amount of TB form for **9** at higher temperatures. It is, however, pertinent to point out that the γ shift of 5-methylbenzocycloheptene at 25 °C is 1.63 ppm[33] and 1.24 ppm at −85 °C. Consequently, differences in bond and torsional angles between six- and seven-membered rings might be responsible for the difference in magnitudes of the γ shifts for the equatorial methyl group.

The α shifts caused by substitution on C-2 of TB are 6.82, 19.54, and 6.94 ppm for **6, 7,** and **8,** respectively. These values are slightly larger than analogous observations in six-membered rings,[7] although they show a very similar trend.[23] Bond angle changes[29] in the two ring systems could easily account for the differences.

The δ shifts of the C-5,6 signals caused by substitution are essentially negligible for **6, 7,** and **8,** which show very similar chemical shifts to that of **5**TB, and for **9,** which has a chemical shift very similar to that of **5**C. On the other hand, the methoxy group in **10** causes appreciable shifts whereby the C-5,6 line has moved 1.34 ppm upfield from that of **5**TB whereas the C-8

to C-11 lines have moved downfield. Such shifts can be explained in terms of Π-polarization effects.[34]

Proton Chemical Shifts. Because bond anisotropy effects are more important for proton chemical shifts, the observed differences for the individual protons of various compounds are more difficult to rationalize completely. A significant trend has been noted, however, and its qualitative description in terms of the chemical shift difference ($\Delta\nu$) between the two geminal protons on C-4 (or C-7) is significant because this parameter appears to be sensitive to the nature of substitution.

The value of $\Delta\nu$ (Hz at 100 MHz) for **5** is 11.9 Hz (Table II, −130 °C) and characteristic of the chair form. This value is very similar to the 10.6 Hz observed for the benzylic protons of benzocycloheptene[16] which exists exclusively as a chair. The negligible effect of oxygen in C is confirmed by the chemical shift difference of 38.5 Hz for C-2 methylene protons of **5** which is very similar to the 40.7 Hz observed for benzocycloheptene.[16] The value of 19.9 Hz for **9** therefore indicates that an equatorial methyl group has a relatively small effect on $\Delta\nu$ of the C-4 (or C-7) protons, although it is significantly larger than in methylcyclohexane.[35]

On the other hand, the $\Delta\nu$ values for **6, 7,** and **8** which exist as TB forms are 64.5, 43.5, and (70.1 and 61.9), respectively. These values are representative of TB forms disubstituted on C-2. Unfortunately the $\Delta\nu$ value of the TB form of **5** could not be measured in both CHF_2Cl and dimethyl ether, so that the effect of the substituents cannot be determined.

Finally, the two AB patterns observed for **10** at −150 °C reveal $\Delta\nu$ values of 20.7 and 84.7 Hz. The examination of structure **11** shows that the environment of the C-7 methylene group is closer to that of the methylene groups of **6, 7,** and **8** than is the environment of the C-4 methylene group. Consequently the larger $\Delta\nu$ value should be associated with the protons on C-7 and the smaller value with the protons on C-4. Thus the proximity of a 2 substituent increases the $\Delta\nu$ value. Corroborative information comes from the observation of analogous $\Delta\nu$ values for the axial and equatorial conformers of 5-substituted derivatives of 4,4,6,6-tetradeuteriobenzocycloheptene.[36] The spectra at −90 °C show that the $\Delta\nu$ values of the benzylic protons of the equatorial conformer are very small because A_2 singlets are observed for various substituents whereas the axial conformers show AB patterns characterized by $\Delta\nu$ values ranging between 60 and 130 Hz depending on both substituent and solvent.

Extrapolation from the data for **10** therefore suggests that the $\Delta\nu$ value for the methylene protons on C-4 and C-7 of the TB conformation of **5** could be relatively small and possibly only slightly different from that of the methylene protons of its C form.

Experimental Section

Melting points are uncorrected and were determined using a Büchi melting point apparatus. High-resolution mass spectra at 70 eV were recorded using an associated Electrical Industries Model MS-902 spectrometer.

The variable temperature ^1H NMR spectra at 100 MHz were obtained using a JEOL JNM-4H-100 spectrometer equipped with a temperature control unit Model JES-VT-3. Temperatures were measured accurately with a calibrated copper-constantan thermocouple placed inside a solvent-containing dummy NMR tube. A precision of ±1 °C is expected. The samples were studied as solutions in chlorodifluoromethane (20–30 mg in 0.55 mL of solution) containing a small quantity of Me_4Si in standard 5-mm tubes which had been degassed and sealed.

The variable temperature ^{13}C NMR spectra were recorded in the FT mode with a Bruker WH-90 spectrometer operating at 22.63 MHz and equipped with the Bruker variable temperature accessory. All ^{13}C NMR spectra were recorded with proton noise decoupling for solutions in chlorodifluoromethane (200–270 mg in 2.5 mL of solution) containing Me_4Si and about 13% of CD_2Cl_2 (for locking purpose) in standard 10-mm tubes which had been degassed and sealed. The following instrumental parameters were used: flip angle = 45°; SW = 4000 Hz; pulse delay = none, except for the integration of the signals of **5** at −130 °C, where a pulse repetition rate of 5 s was used. Temperatures were controlled with a JEOL JES-VT-3 unit and cooling system; they were measured accurately with a thermocouple as described above for the ^1H NMR spectra.

The rate constants were determined at the coalescence temperature using the equation $k = \Pi\Delta\nu\sqrt{2}$ for singlet to doublet splitting in ^{13}C NMR spectra (i.e., for **5, 8,** and **10;** in the case of **5** where the lines are of unequal intensity the equation provides an acceptable estimate[37]) and the equation $k = \Pi(\Delta\nu^2 + 6J^2)^{1/2}/\sqrt{2}$ for singlet to AB splitting[38] in ^1H NMR spectra (i.e., for **5, 6, 7, 8,** and as an approximation for **10**). The free-energy barriers ($\Delta G^{\ddagger}$) were calculated from standard equations[13] using a transmission coefficient of one except for the ^1H spectral changes of **5,** for which a transmission coefficient of one half is most appropriate to describe the chair to boat step of its chair inversion. If a value of one had been used for the calculation from the ^1H spectral change of **5,** the $\Delta G^{\ddagger}$ value would have been higher by about 0.3 kcal/mol.

1,3-Dioxa-5,6-benzocycloheptene (5). Compound **5** was prepared by a procedure already published.[39] It was characterized by its melting point (37–38 °C)[14] and its ^1H NMR spectrum,[15] which were identical with those published. Its ^{13}C shift parameters are reported in Table II.

2,2-Dimethyl-1,3-dioxa-5,6-benzocycloheptene (6). A mixture of 8.0 g (5.79×10^{-2} mol) of 1,2-benzenedimethanol (Aldrich), 7.1 mL (5.79×10^{-2} mol) of 2,2-dimethoxypropane, 4.2 mL of acetone, 11 mL of benzene, and a catalytic amount of *p*-toluenesulfonic acid were heated near 65 °C for about 1 h to allow some methanol, benzene, and acetone to distill off. Dry benzene was added periodically to the reaction flask. The remaining benzene was then evaporated and the product was distilled under vacuum. A 60% yield of **6** (mp 101–102 °C) was thus obtained and its ^1H NMR spectrum was identical with that already published.[15] Its ^{13}C shift parameters are reported in Table II.

2,2-Tetramethylene-1,3-dioxa-5,6-benzocycloheptene (7). Compound **6** (5.2 g, 3.12×10^{-2} mol), 2.8 mL (3.16×10^{-2} mol) of cyclopentanone, 10 mL of benzene, and a catalytic quantity of *p*-toluenesulfonic acid were mixed and heated during 7 h using a Dean-Stark collector. Dry benzene was periodically added to the reaction flask to replace the quantity trapped in the collector.

After cooling, the organic solution was washed with a saturated potassium carbonate solution and dried over anhydrous magnesium sulfate. After filtration the solvent was evaporated and the product was distilled under reduced pressure. A 72% yield of **7** (mp 59–60 °C) was then obtained. The product was characterized by its ^1H and ^{13}C NMR spectra (Tables I and II) and by its high-resolution mass spectrum.

Anal. Calcd for $C_{13}H_{16}O_2$: mol wt, 204.1150. Found (mass spectrum at 70 eV): mol wt, 204.1150.

2,2-Pentamethylene-1,3-dioxa-5,6-benzocycloheptene (8). Compound **8** was prepared by the same procedure as for **7** using 2.0 g (1.20×10^{-2} mol) of **6** and 1.3 mL of cyclohexanone. A 70% yield of distilled product (mp 85–86 °C) was obtained. Its ^1H and ^{13}C NMR spectra (Tables I and II) and its high-resolution mass spectrum confirmed its identify as **8.**

Anal. Calcd for $C_{14}H_{18}O_2$: mol wt, 218.1307. Found (mass spectrum at 70 eV): mol wt, 218.1308.

2-Methyl-1,3-dioxa-5,6-benzocycloheptene (9). This compound was prepared by the same procedure as for **5** using 0.493 g (3.56×10^{-3} mol) of 1,2-benzenedimethanol and an excess of acetaldehyde together with a catalytic amount of *p*-toluenesulfonic acid and 7 mL of benzene. An 85% yield of distilled product (mp 55–57 °C) was obtained. Its ^1H and ^{13}C NMR spectra (Tables I and II) and its high-resolution mass spectrum confirmed its identity as **9.**

Anal. Calcd for $C_{10}H_{12}O_2$: mol wt, 164. Found (mass spectrum at 70 eV): mol wt, 164.0833.

2-Methoxy-1,3-dioxa-5,6-benzocycloheptene (10). A mixture of 3.0 g (0.0217 mol) of 1,2-benzenedimethanol, 2.4 mL (0.0219 mol) of trimethyl orthoformate, 3 mL of benzene, and 20 mg of *p*-toluenesulfonic acid was stirred for 2 h at room temperature. After having been washed with a saturated potassium carbonate solution the benzene solution was dried over anhydrous magnesium sulfate. The benzene was then evaporated and the product purified by column

chromatography on basic alumina using carbon tetrachloride as eluent. A quantity of 1.3 g of compound (mp 38–39 °C) was obtained which crystallized on cooling after the eluent had been evaporated. Its ^1H and ^{13}C NMR spectra (Tables I and II) and its high-resolution mass spectrum confirmed its identity as **10.**

Anal. Calcd for $C_{10}H_{12}O_3$: mol wt, 180.0786. Found (mass spectrum at 70 eV): mol wt, 180.0781.

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Electron-Impact and Field-Ionization Mass Spectrometry of α-Ketol Phosphate Salts. Gas-Phase Thermolysis of Phosphodiester to Monomeric Alkyl Metaphosphate. Appearance and Origins of Original Salt Cations in Mass Spectra

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Abstract: The electron-impact (EI) and field-ionization (FI) mass spectra of two salts derived from α-ketol phosphates, 1-methyl-3-carbamylpyridinium 3-oxo-2-butyl phosphate and 1-methyl-3-carbamylpyridinium methyl(3-oxo-2-butyl) phosphate, have been measured. These salts undergo the expected facile thermal transmethylation to nicotinamide and the corresponding phosphodiester and -triester, methyl(3-oxo-2-butyl) phosphate and dimethyl(3-oxo-2-butyl) phosphate, respectively. The diester, but not the triester, undergoes further thermal decomposition to 3-oxo-2-butanol and presumably monomeric methyl metaphosphate, CH_3OPO_2. In addition, the EI and FI spectra obtained from the salts contain peaks at the mass of the original salt cation and a mass one unit greater. In the FI spectra, however, they are accompanied by arrays of additional peaks at precisely those mass numbers that one would expect to observe in field-desorption (FD) spectra of the salts, and which we interpret as a FD component in the nominally FI spectra. The data thus suggest that the salt is in thermodynamic equilibrium with an isomeric covalently bound molecule, which volatilizes and travels the ca. 1 cm from probe to anode via the gas phase, is adsorbed on the anode, reverts to the original salt, and undergoes conventional FD. This and analogous covalent intermediates are most probably the source also of the "salt cation" peaks in the EI spectra of these salts and of others reported in the literature—cinnolinium, tropylium, pyrylium, and 1,2-dithiolylium salts and the cationic dye crystal violet.

The original intent of this work was to examine the behavior in the mass spectrometer of diesters and triesters derived from α-ketol phosphates, that is, simple analogues of the sugar phosphates.[2] Our main objective was to search for evidence of monomeric metaphosphate intermediates, $ROPO_2$, in ionic or intervening thermal[3] reactions of derivatives of acetoin

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