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Tertiary 2-Benzonorbornenyl Cations[1]

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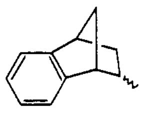
Abstract: The tertiary 2-methyl-, 2-ethyl-, and 1,2-dimethyl-2-benzonorbornenyl cations were prepared under stable ion conditions and characterized by ^{1}H and ^{13}C NMR spectroscopy. All three ions display very similar charge delocalization pattern of the benzo ring in their NMR spectra. The 2-methyl- and 2-ethyl-2-benzonorbornenyl cations are shown to be static unsymmetrical carbenium ions with less benzonortricyclyl-like nature than the parent secondary 2-benzonorbornenyl cations; while the 1,2-dimethyl-2-benzonorbornenyl cation is a symmetrical carbenium ion undergoing rapid 1,2 Wagner–Meerwein shift. The 2-ethyl-2-benzonorbornenyl cation undergoes ring expansion reaction upon heating to give the 2-methyl-2-benzobicyclo[3.2.1]octenyl cation. Although charge delocalization into the benzo ring in both 2-benzonorbornenyl and 2-benzobicyclo[3.2.1]octenyl cations is substantial, the interaction between C(1)–C(11) σ bond and the empty p orbital at C(2) in the former is much stronger than that of the C(1)–C(12) σ bond and the empty p orbital at C(2) in the latter.

The importance of phenyl-ring participation in the solvolysis of secondary benzonorbornenyl derivatives (**1**) has been clearly demonstrated.[2] The solvolytic reactions generally have been considered to involve assisted ionization for *exo*-2-benzonorbornenyl derivatives to give symmetrically bridged nonclassical ions **2,** rather than unsymmetrical classical ions **3.** Ambiguous interpretations have been given of the solvolysis of tertiary benzonorbornenyl derivatives (**4**).[3] Goering et al.[4] have recently been able to show that solvolysis of optically active tertiary 2-benzonorbornenyl derivatives (**5**) gave exclusively optically active products and thus concluded that the reactions involved the unsymmetrical carbenium ions, rather than nonclassical ions.



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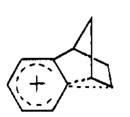

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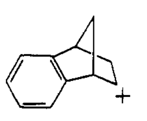

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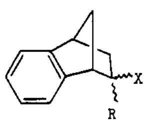

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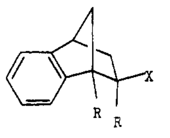
R= CH_3 or C_6H_5



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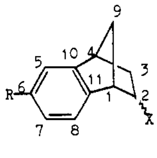
R= CH_3

In earlier work we have shown that the ionization of secondary 2-benzonorbornenyl derivatives (**6**) under stable ion conditions gives symmetrical benzonortricyclyl cations (**7**) rather than rapidly equilibrating unsymmetrical 2-benzonorbornenyl cations (**8**).[5] The strong participation of the benzo ring into the developing empty p orbital at C(2) thus results in formation of sterically constrained tricyclic carbenium ions of ethylenebenzenium ion type,[6] clearly indicated by the observation of the aliphatic spiro carbon absorption (C(11)) in their ^{1}C NMR spectra.



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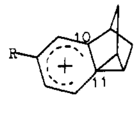

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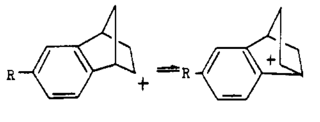

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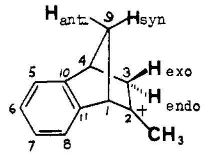
R = H, CH_3, Cl, OCH_3

In continuation of our studies, we now report our investigation of the structure of tertiary 2-benzonorbornenyl cations under stable ion conditions, showing that they are either static or rapidly equilibrating carbenium ions with expected charge delocalization into the benzo ring, but with rather limited contribution from benzonortricyclyl structures.

Results and Discussion

Preparation of 2-Benzonorbornenyl Cations. 2-Methyl-2-benzonorbornenyl cation (**9**) was prepared by careful ionization of 2-methyl-*endo*-2-benzonorbornenol (**10**)[7] or 1-methyl-*exo*-2-chlorobenzonorbornene (**11**) with SbF_5-SO_2ClF at −78 °C. The ^{1}H NMR spectrum (60 MHz) of **9** (Figure 1) consists of a sharp singlet at δ 3.08 (3 H); a multiplet centered at δ 3.20 (2 H); a broad singlet at δ 3.84 (1 H); a multiplet centered at δ 4.10 (2 H); a broad singlet at δ 6.08 (1 H); and aromatic multiplets extending from δ 7.70 to 8.46 (4 H). The proton noise-decoupled FT ^{13}C NMR spectrum (Figure 1) of **9** at −85 °C shows *12* carbon resonances, clearly indicating that the ion is unsymmetrical. The ^{1}H and ^{13}C NMR spectroscopic data are summarized in Table I along with their assignments. Assignments for carbon shifts were made with the aid of the proton coupled ^{13}C NMR spectrum. There are three singlet carbon resonances at $\delta_{^{13}C}$ 199.1, 177.2, and 104.5, which are assigned to C(2), C(10), and C(11), respectively. The two doublets at $\delta_{^{13}C}$ 80.8 ($J_{^{13}C-H}$ = 180.4 Hz) and 41.6 ($J_{^{13}C-H}$ = 158.7 Hz) are assigned to the two bridgehead positions C(1) and C(4), respectively. The two doublet of doublets centered



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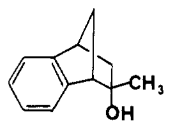

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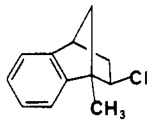

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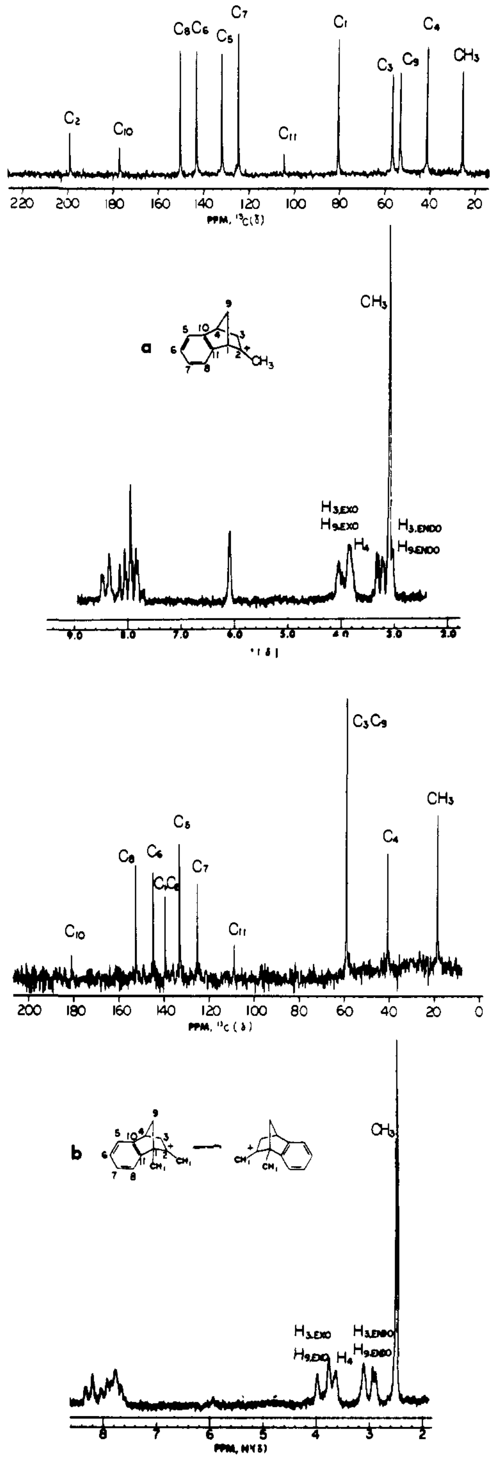


Figure 1. ^{1}H and ^{13}C NMR spectra of (a) 2-methyl- and (b) 1,2-dimethyl-2-benzonorbornenyl cations in SbF_5-SO_2ClF (−85 °C) and FSO_3H-SO_2ClF (−85 °C) solution, respectively.

at $\delta_{^{13}C}$ 56.9 and 53.4 are assigned to C(3) and C(9), respectively (they are, however, interchangeable). The four doublets in the aromatic region are assigned as summarized in Table I.

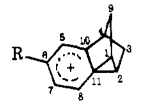
The ^{1}H NMR spectrum of **9** is temperature independent (−125 to −10 °C) and slow decomposition of the ion takes place at higher temperatures. The temperature-independent behavior of **9** is very different from that previously reported for the 2-methyl-2-norbornyl cation (**12**)[8,9] which has been shown to display line-broadening effects in its NMR spectra above −80 °C by undergoing rapid 1,2 Wagner–Meerwein shift.[9]

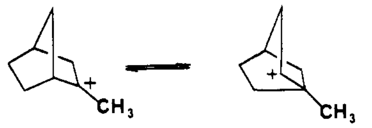
Table I. ^{1}H and ^{13}C NMR Parameters of the 2-Benzonorbornenyl and Related Cations[a]

Ion	1	2	3	4	5	6	7	8	9	10	11	12
9[b] $\delta_{^1H}$	6.08		exo 3.95[c] endo 3.20	3.84		7.70 to 8.46			syn 3.95[c] anti 3.20			
$\delta_{^{13}C}$	80.8 (d, 180.4)	199.1 (s)	56.9 (d–d, 139.4, 136.7)	41.6 (d, 158.7)	132.0 (d–d, 5.3, 174.0)	143.1 (d–d, 5.8, 170.6)	124.7 (d–d, 5.8, 169.3)	152.3 (d–d, 7.4, 171.9)	53.4 (d–d, 139.7, 142.7)	177.2 (s)	104.5 (s)	
12[d] $\delta_{^{13}C}$	80.3	271.1	55.6	42.8	23.6	35.8	40.2					
13[e] $\delta_{^1H}$	6.08		exo 3.98[c] endo 3.18	3.70		7.70 to 8.40			syn 3.98[c] anti 3.18			
$\delta_{^{13}C}$	78.7 (d, 180.0)	207.6 (s)	54.0 (d–d, 139.0, 136.8)	41.3 (d, 158.4)	131.4 (d–d, 5.4, 173.5)	142.6 (d–d, 5.3, 170.0)	124.7 (d–d, 5.8, 169.8)	149.5 (d–d, 7.4, 170.5)	52.7 (d–d, 139.0, 141.5)	176.4 (s)	103.7 (s)	
15[f] $\delta_{^{13}C}$	56.2 (d, 148.0)	243.7 (s)	44.9 (t, 137.0)	25.6 (t, 134.2)	44.9 (d, 141.0)	130.5 (d, 170.4)	138.8 (d, 169.6)	129.9 (d, 169.9)	153.6 (d, 170.2)	26.5 (t, 136.9)	165.6 (s)	134.5 (s)
17[g] $\delta_{^{13}C}$	66.3 (d, 153.6)	321.6 (s)	58.2 (t, 137.5)	30.1 (t, 136.8)	35.5 (d, 142.2)	23.1 (t, 134.4)	30.1 (t, 136.8)	23.1 (t, 135.8)				
21[h] $\delta_{^1H}$			exo 3.85[c] endo 3.00	3.62		7.60 to 8.40			syn 3.85[c] anti 3.00			
$\delta_{^{13}C}$	138.5 (s)	138.5 (s)	38.5 (t, 138.1)	40.2 (d, 161.0)	132.1 (d–d, 5.3, 173.0)	143.8 (d–d, 5.2, 170.1)	124.1 (d–d, 5.6, 168.9)	151.5 (d–d, 7.2, 171.2)	58.5 (t, 138.1)	180.2 (s)	108.1 (s)	

[a] Proton and carbon shifts are in parts per million from external Me_4Si (capillary). Multiplicities and coupling constants are given in parenthesis: d = doublet; d–d = doublet of doublets; s = singlet; t = triplet; q = quartet. [b] CH_3: $\delta_{^1H}$ 3.08 (s); $\delta_{^{13}C}$ 26.0 (q, 130.4). [c] AB quartet, J = 13.5 Hz. [d] $\delta_{^{13}C}$ (CH_3) 28.3. [e] CH_3: $\delta_{^1H}$ 1.45 (t, J = 7 Hz), $\delta_{^{13}C}$ 13.0 (q, 130.0); CH_2: $\delta_{^1H}$ 3.42 (t, 7.0), $\delta_{^{13}C}$ 35.0 (t, 132.8). [f] CH_3: $\delta_{^{13}C}$ 28.1 (q, 130.5). [g] CH_3: $\delta_{^{13}C}$ 38.6 (q, 132.0). [h] CH_3: $\delta_{^1H}$ 2.50 (s), $\delta_{^{13}C}$ 18.1 (q, 130.7).

Table II. Characteristic ^{13}C Chemical Shifts of Secondary Benzonortricyclyl Cations

	R	δC(1), C(2)	δC(10)	δC(11)	ΔδC(10)−δC(11)
 7	H	96.1	193.9	84.1	109.7
	Cl	93.6	193.4	80.9	112.5
	CH_3	86.0	194.1	75.6	118.5
	OCH_3	70.5	189.2	61.3	132.9



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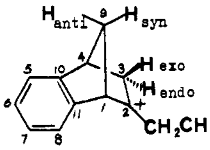
The 2-ethyl-2-benzonorbornenyl cation (**13**) was obtained by ionizing 2-ethyl-*endo*-2-benzonorbornenol (**14**) in SbF_5-SO_2ClF solution at −78 °C. Both ^1H (60 MHz) and ^{13}C (25.16 MHz) NMR spectra of **13** show that the ion is unsymmetrical, similar to its methyl analogue **9**. NMR spectroscopic data are summarized in Table I, along with their assignments.



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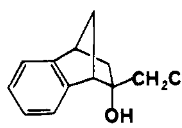

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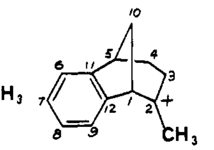

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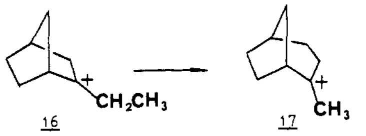
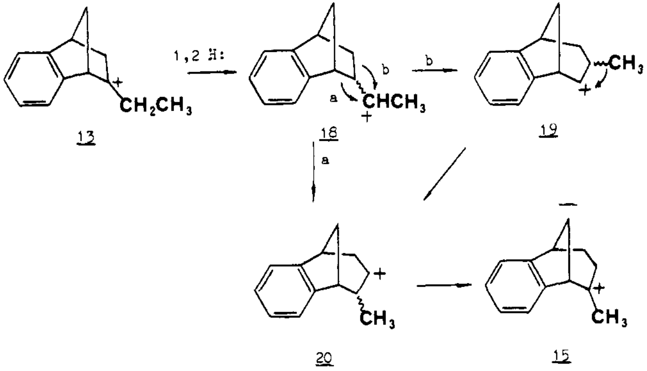
In contrast to **9**, ion **13** is only stable below −60 °C and it slowly undergoes ring expansion at higher temperatures to the 2-methyl-2-benzobicyclo[3.2.1]octenyl cation (**15**). The thermal rearrangement of **13** is not unexpected as we have previously reported a similar reaction taking place in the case of 2-ethyl-2-norbornyl cation (**16**), which upon heating cleanly rearranges to the 2-methyl-2-bicyclo[3.2.1]octyl cation (**17**)[10]

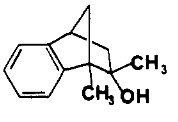


The ring expansion reaction of **13** can be depicted to take place as shown in Scheme I.

Scheme I



1,2-Dimethyl-2-benzonorbornenyl cation (**21**) was prepared by addition of 1,2-dimethyl-*endo*-2-benzonorbornenol (**22**)[4,7] to FSO_3H-SO_2ClF solution at −78 °C. The temperature-independent (−135 to −20 °C) ^1H NMR (60 MHz, Figure 1) spectrum shows two equivalent methyl groups at δ 2.48 (singlet, six protons); two sets of methylene protons (H(3) and H(9)) as an AB quartet centered at δ 3.00 and 3.85 (J = 13 Hz); the bridgehead proton H(4) as a broad singlet at δ 3.62; and the four aromatic protons as a multiplet between δ 7.6 and 8.4.



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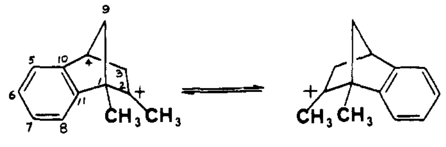

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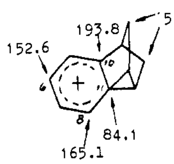
The proton noise-decoupled ^{13}C NMR spectrum of ion **21** shows *ten* carbon resonances, also indicating the symmetrical nature of the ion. Carbon shifts, coupling contants ($J_{^{13}C-H}$, in hertz), and assignments are summarized in Table I (assignments were made with the aid of the proton-coupled spectrum).

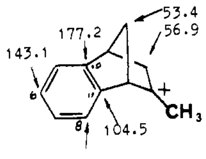
Structure of Tertiary 2-Benzonorbornenyl Cations. We have previously shown that the stable carbocations formed from secondary 2-benzonorbornenyl derivatives **6** bear the benzonortricyclyl skeleton **7**.[5] The presence of an aliphatic spiro carbon (C(11)) in these ions confirms their structure. Delocalization of positive charge into the fused benzo ring is significant, as seen from the deshielding of both the ortho (C(8) and C(10)) and para (C(6)) carbons in **7**.

Introduction of substituents at C(6) ranging from hydrogen to chlorine, to methyl, and to methoxy gradually causes both C(1) and C(11) to become less deshielded, while the C(10) positions are not much affected. As delocalization of the positive charge into the benzo ring increases along this sequence of substitution, carbon C(11) becomes more aliphatic in nature and less positive charge is delocalized into the cyclopropane ring (Table II). The difference between the carbon shifts of C(10) and C(11), $\Delta\delta_{C_{10}-C_{11}}$ on the other hand, increases from 109.7 in the parent ion **7** (R = H) to 132.9 in 6-methoxy-substituted ion **7** (R = OCH_3).

The introduction of alkyl groups at either or both C(1) and C(2) leads to static unsymmetrical or rapidly equilibrating symmetrical 2-benzonorbornenyl cations, respectively. One immediately notices that delocaliztion of the positive charge into the benzo ring has been decreased; both ortho and para positions in **9**, **13**, and **21** are less deshielded than those in the secondary ions **7**. In addition, C(11) in the tertiary 2-benzonorbornenyl cations is about 20-ppm deshielded from that of **7** (R = H). This fact no doubt indicates the decrease in the aliphatic nature of this carbon (C(11)) going from secondary ions **7** to tertiary ions. On the other hand, the methylene carbons (C(3) and C(9)) in tertiary ions **9** ($\delta_{^{13}C}$ 53.4 and 56.9), **13** ($\delta_{^{13}C}$ 52.7 and 54.0), and **21** ($\delta_{^{13}C}$ 58.5) are deshielded by almost a similar extent as those in the parent secondary ion **7** (R = H, $\delta_{^{13}C}$ 51.2). The differences in carbon shifts between C(3) and C(9) in tertiary ions **9** and **13** are very small (in the order of 2–3 ppm). These observations may indicate that the tertiary 2-methyl-, 2-ethyl-, and 1,2-dimethyl-2-benzonorbornenyl cations also bear a certain degree of benzonortricyclyl



7(R=H)



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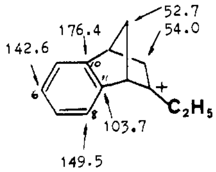

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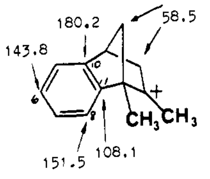

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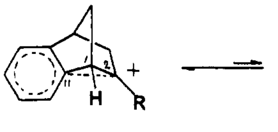
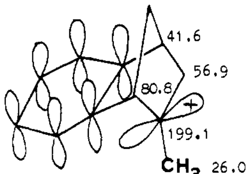
character; however, this contribution is only minor. Carbon shifts of $\delta_{^{13}C}$ 104 in **9** and 108.1 in **21** for C(11) show that this carbon cannot have fully sp^2 nature in the tertiary 2-benzonorbornenyl cations. The large differences in carbon shifts between C(1) and C(2) in **9** (~119 ppm) and **13** (~130 ppm), however, show that positive charge is heavily shared by the carbocationic centers (C(2)), causing the ions to be unsymmetrical. Tertiary 2-benzonorbornenyl cations thus can be best described as the partially delocalized benzonortricyclyl cations with positive charge being predominately shared between C(2) and benzo ring carbons. The bridging carbon C(11) bears hybridization intermediate between sp^2 and sp^3.



The 2-methyl-2-norbornyl cation (**12**) has been shown to be a partially σ-delocalized carbocation in which the exo proton at C(6) is more deshielded than the endo proton resulting from the interaction between the back lobe of the C(6)-H$_{exo}$ orbital and the empty p orbital of C(2).[9] The aromatic π orbitals in benzonorbornenyl cations may interact in a similar fashion with the empty p orbital at the carbocationic center (C(2)), causing positive charge to be delocalized into the benzo ring (homobenzylic delocalization).[3] This pattern is reflected by the deshielding of the aromatic carbon resonances in the ^{13}C NMR spectrum of the ions. Strong interaction to induce charge delocalization into the benzo ring is also evident from the fact that the carbocationic center of tertiary benzonorbornenyl cation **9** ($\delta_{^{13}C}$ 199.1) is highly shielded in comparison with that of the 2-methyl-2-norbornyl cation (**12**) ($\delta_{^{13}C}$ 271.1).[9]



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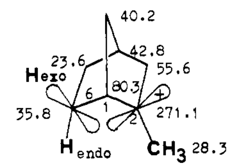

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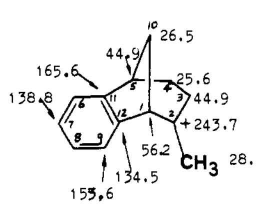
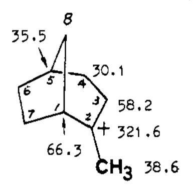
The interaction between the empty p orbital and the fused benzo ring in the 2-methyl-2-benzobicyclo[3.2.1]octenyl cation (**15**) seems to be much weaker than that in the 2-methyl- and 2-ethyl-2-benzobicyclo[2.2.1]heptenyl (or benzonorbornenyl) cations when comparison is made between the ^{13}C NMR data of these ions. First of all, the carbocationic center of **15** (C(2), $\delta_{^{13}C}$ 243.7) is about 50 ppm more *deshielded* and at the same time the bridgehead carbon α to the carbocationic center, C(1) ($\delta_{^{13}C}$ 56.2), is about 25 ppm more *shielded* than those in **9** (C(2), $\delta_{^{13}C}$ 199.1; C(1), $\delta_{^{13}C}$ 80.1). Second, both the ortho (C(11)) and para (C(7)) carbons in **15** are more *shielded* than those (C(10) and C(6), respectively) in **9**, while the ipso carbon (C(12)) in the former is about 30 ppm more *deshielded* than that in the latter. Third, the carbon shift difference between the two bridgehead carbons in **15**, (C(1) and C(5)) is only about 12 ppm with similar J_{CH} values (<150 Hz), while that of **9** and **13** is about 40 ppm with much larger J_{CH} values at C(1) (~180 Hz) than C(4) (<160 Hz). Fourth, the methylene bridge carbon (C(10)) in **15** is much less *deshielded* than those (C(9)) in **9** and **13**. One further notices that the ipso carbons gradually become more *deshielded* going from the parent benzonortricyclyl (**7**, R = H, δ C(11) 84.1) to the 2-methyl-2-benzonorbornenyl (**9**, δ C(11) 104.5), to the 1,2-dimethyl-2-benzonorbornenyl (**21**, δ C(11) 108.1), and to the 2-methyl-2-benzobicyclo[3.2.1]octenyl (**15**, $\delta_{^{13}C(12)}$ 134.5) cations. At the same time the ortho and para carbons become less *deshielded*. Based on these observations we can conclude that the bridging interaction between the C(2) empty p orbital and neighboring σ bonds (C(1)-C(11) bond in **9** and C(1)-C(12) in **15**) becomes more significant in going from the benzobicyclo[3.2.1]octenyl to the tertiary benzobicyclo[2.2.1]heptenyl and to the secondary benzobicyclo[2.2.1]heptenyl cations, in accordance with the increase of positive charge delocalization into the benzo ring. Indeed, ionization of secondary benzobicyclo[2.2.1]heptenyl (benzonorbornenyl) derivatives yields benzonortricyclyl cations (**7**) in which the cyclopropane ring is fully formed. In contrast, tertiary 2-benzonornenyl cations (**9**, **13**, and **21**) are best described as partially bridged, unsymmetrical carbocations with charge delocalization into the fused benzo ring, while tertiary 2-benzobicyclo[3.2.1]octenyl cations are charge-delocalized carbocations without significant bridging. A similar difference is also found between the tertiary 2-methyl-2-norbornyl and 2-methyl-2-bicyclo[3.2.1]octyl cations (**12** and **17**, respectively). The carbocationic center (C(2)) in **12** is about 50 ppm *less deshielded* than that in **17**. As reported previously, ion **12** should be described as a partially σ-bridged carbocation and **17** as a carbenium ion without significant bridging.

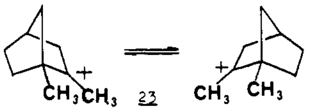


15



17

The previously studied 1,2-dimethyl-2-norbornyl cation (**23**) has been shown to be a partially σ-delocalized *carbenium* ion undergoing rapid 1,2 Wagner-Meerwein equilibration.[11] The degree of charge delocalization in **23** is found to be virtually identical with that present in the 2-methyl-2-norbornyl cation (**12**).[8,11] A comparison between **21** and **23** clearly indicates that the former also undergoes rapid 1,2 Wagner-Meerwein shift. This can be substantiated by comparing the calculated and observed averaged carbon shifts using the 2-methyl-2-benzonorbornenyl cation (**9**) as model. As seen, the calculated average carbon shifts for C(1) and C(2) and the two methyl carbons are in good agreement with the observed values. The carbon shift of $\delta_{^{13}C}$ 108.1 observed for the ipso carbon (C(11)) of **21** also excludes a significant contribution of benzonortricyclyl structure. The introduction of a second methyl group at C(1) into ion **9**, although it does not alter the pattern of charge delocalization, which is similar in extent in both **9** and **21** (as reflected by their carbon-13 shifts), but sufficiently lowers the barrier for the 1,2 Wagner-Meerwein shift, as it can not be frozen out on the NMR time scale even at −135 °C. Thus both the static 2-methyl- and 2-ethyl-, as well as the



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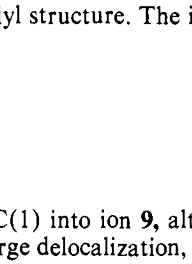
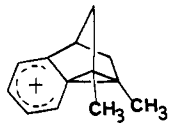


	δ_{C_1}	δ_{C_2}	$\delta_{C_1-CH_3}$	$\delta_{C_2-CH_3}$
calculated	85	200	15	26
$\delta_{^{13}C,ave}$:				
cal.	$\frac{1}{2}(85+200)$ =143		$\frac{1}{2}(15+26)$ =20.5	
obs.	138.5		18.5	



24

rapidly equilibrating 1,2-dimethyl-2-benzonorbornenyl cations are best pictured as partially bridged carbenium ions with charge delocaliztion into the fused benzo ring, wherein the related benzonortricyclyl structures are considered only as minor contributors.

Experimental Section

Materials. 2-Methyl-2-*endo*-benzonorborneol (**10**) and 1,2-dimethyl-2-*endo*-benzonorborneol (**22**) were prepared according to the procedures reported by Goering et al.[4,7]

1-Methyl-2-*exo*-chlorobenzonorbornene (**11**) was prepared by chlorination of **10** with concentrated hydrochloric acid at room temperature for two hours. The product was extracted with petroleum ether (30-60 °C), washed, dried ($MgSO_4$), and distilled: bp 54-56 °C (0.02 mm); ^1H NMR ($CDCl_3$, capillary Me_4Si) δ 1.70 (s, 2 H), 2.08 (s, 3 H), 2.60 (m, 2 H), 3.70 (m, 1 H), 4.20 (m, 1 H), and 7.60 (s, 4 H).

2-Ethyl-2-*endo*-benzonorborneol (**14**) was prepared from 2-benzonorbornenone with ethylmagnesium bromide in anhydrous ether: mp 59-60 °C (pentane).

Preparation of Carbocations. In general, benzonorbornenyl cations were prepared by careful addition of a suspension of appropriate benzonorbornenyl precursors in SO_2ClF to either FSO_3H, FSO_3H-SbF_5, or SbF_5 solution in SO_2ClF at dry ice-acetone temperature (ca. -78 °C) with vigorous stirring to give $\sim$10% solutions of the ions. An appropriate portion of the resulting solutions were immediately transferred to precooled NMR tube for NMR measurement. Details are as reported previously.[5]

Proton and Carbon-13 NMR Spectroscopy. Both proton and carbon-13 NMR spectra were obtained as previously reported.[5]

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Structures of Modified Cardenolides. 1. Lactam Analogues of Isodigitoxigenin

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Abstract: The crystal structures of two synthetic lactam derivatives of digitoxigenin have been determined by x-ray crystallography. The crystal data for the major product: (20*S*,21*R*)-3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4a**) hydrate, orthorhombic system, $P2_12_12_1$, $a = 11.953$, $b = 23.611$, $c = 7.502$ Å, $Z = 4$. The crystal data for the minor product: (20*R*,21*S*)-3β-hydroxy-14,21-epoxy-5β,14β,20-cardanolactam (**4b**), monoclinic, $P2_1$, $a = 11.472$, $b = 7.7771$, $c = 11.463$ Å, $\beta = 97.71°$, $Z = 2$. These crystal structures establish the stereochemistry of the C(20), C(21) ring junctions as cis-equatorial-axial and cis-axial-equatorial for **4a** and **4b**, respectively. The structure of **4a** also indicates that isodigitoxigenin also has a cis-equatorial-axial configuration. There are no unusually short intramolecular nonbonded contacts involving the lactam rings in either structure, although models had indicated these configurations would require close contacts. The only conformational differences between these two structures and digitoxigenin occur in the region of the lactam ring despite the strain introduced by the formation of a ring to O(14).

Cardiac glycosides and aglycones have an inotropic effect in both the failing heart and isolated cardiac preparations. They also are known to inhibit cardiac microsomal Na^+/K^+-ATPase at the same concentration levels. These observations have led to proposals involving a direct casual relationship between the enzymic inhibition and the positive inotropic response.[2] Other studies, however, suggest a dissociation of the two biological responses.[3-5] Several derivatives of digitoxigenin (**1**) were used in the studies showing the dissociated responses. However, some conflict concerning the stereochemistry of these derivatives (**3, 4a,** and **4b**) has arisen.

Figure 1 shows part of the pathway[3,6] leading to the three digitoxigenin derivatives (**3, 4a,** and **4b**) in question. Ammonolysis of digitoxigenin (**1**) in 75% aqueous methanol afforded two isomeric lactolamides **2a** and **2b**. Heating **2a** to 200 °C or treatment with warm glacial acetic acid caused rapid cyclization to lactam **4a.** Similar treatment of lactol-amide **2b** gave the epimeric lactam **4b.**

The configuration of the E/F rings in isodigitoxigenin (**3**) was first postulated on conformational and steric grounds to have a trans-diequatorial junction,[7] Figure 2c. The alternate trans configuration, Figure 2d, was eliminated on conforma-