shifted, more fully protonated bathorhodopsin intermediate. (This, incidentally, destabilizes the NH···N bond[32] and may contribute in part to the large energy storage observed in this first step.[22]) On the picosecond scale of this process there is little time for any other major conformational changes, but subsequent structural relaxation in the immediate active site vicinity (to give lumirhodopsin) followed by more global conformational changes (giving metarhodopsin I) can be envisaged as the protein relaxes to accomodate the new retinal configuration. To our minds this exhausts the number of plausible conformational changes that may be invoked without the intervention of additional chemical processes, and by this stage the active site conformation has changed to a sufficient extent to reduce the stabilizing influences on the Schiff base linkage and to allow access to solvent water and the start of hydrolysis. A plausible mechanism for this stage is sketched in Figure 10. Attack of water, base catalyzed by the proximal point charge (glutamate or aspartate), forms the carbinolamine species (step 1). The consequent change from trigonal to tetrahedral configuration results in relative reorientation of active site contacts, breaking the –NH··N– hydrogen bond and allowing conventional protonation (from the solvent) of the more basic carbinolamine (step 2). This is the proton uptake characteristic of the Meta I → II transition.[13] Simple deprotonation of the carbinol by proton release to the solvent, required to form the zwitterionic species as the next stage of hydrolysis,[2] is inhibited by the adjacent carboxylate anion but could occur by proton transfer to this group (step 3), consistent with changes in carboxylate protonation revealed by FTIR difference spectra.[37] The linkage now finally breaks (step 4) to give the retinal aldehyde, held in place by noncovalent interactions. This noncovalent complex will be unstable, however, because of the sterically unfavorable trans configuration of the retinal and irreversible retinal dissociation can now take place (step 5), though this is not necessarily a straightforward process and could involve transimination and transient, nonspecific Schiff base formation with adjacent amines along the way, giving a plausible explanation for the later metarhodopsin III and indicator-yellow intermediates.

There remain some paradoxes, however, and it is not clear at this stage which of the various species in Figure 10, following water attack on Meta I, are to be identified with the spectral Meta II state. The model compound stopped-flow experiments indicate that the retinal carbinolamine has spectroscopic properties similar to the parent Schiff base in detergent micelles, rather than the somewhat lower λ_{max} that might be anticipated by comparison with more stable pentaenes. It is difficult to predict the additional effects of point-charge interactions and possible chromophore strain during the metarhodopsin transition, but the 380-nm λ_{max} of Meta II is identical with that of free retinal and suggests the presence of the aldehyde at this stage. By contrast, the Raman spectrum of Meta II points more to some form of the carbinolamine. It seems feasible that the spectroscopically identified Meta II state is actually a dynamic mixture of the various chemical species that cannot be resolved in the UV/visible region, or which are sampled to differing extents by the different spectroscopic techniques. But, regardless of these uncertainties about the finer mechanistic details, we note that the significant change from trigonal to tetrahedral configuration at the retinal–opsin linkage during carbinolamine formation could be responsible, either directly or indirectly by inducing protein conformational changes, for triggering the G-protein activation and subsequent biochemical steps thought to be involved in the photoreceptor response and which have been shown to be initiated by the metarhodopsin II intermediate.[34,38]

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Deuterium Isotope Effects on the Carbon-13 Chemical Shifts in 2-Substituted 2-Norbornyl Cations

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Abstract: Deuterium isotope effects on ^{13}C chemical shifts have been examined as a function of location of deuterium in the C_3-exo or C_3-endo positions and as a function of increasing electron demand in the series 2-norbornanone, 2-aryl-2-norbornyl cations, and 2-methyl-2-norbornyl cation. Comparison with isotope shifts in 2-aryl-2-propyl cations demonstrates a change in the type of response to isotopic perturbation in 2-aryl-2-norbornyl cations as electron demand increases. The results are consistent with the onset of σ-bridging as electron demand increases. The observed isotope shift at a cation center is suggested to be a sum of contributions from a small upfield shift due to perturbation of the σ-framework (inductive-type perturbation), a downfield shift due to perturbation of hyperconjugation, and a potentially large upfield shift from perturbation of three-center, two-electron bonding. NMR isotope shifts may be a particularly sensitive probe of σ-bridging because of the vibrational origin of the isotope effect.

We present here deuterium isotope effects on the ^{13}C chemical shifts of several 2-substituted 2-norbornyl cations and related compounds. The variation of NMR isotope shifts as a function of aryl substituents in 2-aryl-2-norbornyl cations is examined with the aim of detecting bonding changes that may occur with increasing electron demand. The results are analyzed in terms of possible mechanisms of isotopic perturbation of the vibrationally averaged structure that could lead to the observed effects on shielding.

Substitution for hydrogen by deuterium produces small but measurable changes in ^{13}C NMR chemical shifts.[2-4] Intrinsic

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NMR isotope shifts result from perturbations of the motional averaging of nuclear shielding in a single molecular species due to changes in nuclear masses.[5-7] While the distinction between intrinsic and equilibrium isotope shifts has proven to be an exceptionally valuable tool for distinguishing between rapid equilibria and resonance phenomena in carbocations and other species,[8,9] it is now apparent that the intrinsic shifts themselves are a useful probe of structure. Although the chemical shift response to isotopic perturbation is often complex, it has been possible in many instances to find regularities that can be related to specific structural features. Isotopic perturbation of steric interactions has been detected via intrinsic isotope shifts,[10-12] and some long-range isotope shifts appear to be determined by the efficiency of coupling between certain vibrations along the intervening bond system.[13,14] When a C–H bond is involved in hyperconjugation with an adjacent π-system, deuterium substitution perturbs the effectiveness of the interaction through alteration of the portion of the electronic surface over which vibrational averaging occurs; this change in vibrational averaging leads to small changes in electron distribution and accompanying changes in shielding.[10,15-18] Thus, appropriate isotopic substitution has proven useful for probing electron distributions via the isotope shift.[15,19]

For nonequilibrating carbocations, the intrinsic chemical shift response to isotopic perturbation depends on the type of bonding involved, whether localized or π- or σ-delocalized.[15] In several cases in which the carbocation is believed to have a σ-delocalized structure, β-deuteriation produces an unusually large (>1.0 ppm) upfield shift at the cationic center.[15] Such isotopic perturbation of the three-center, two-electron bond has been used to establish that bridged mercurinium ions and bromonium ions have fundamentally different electronic structures.[20] We have interpreted these results to indicate that the large intrinsic shifts occur because of a shallow potential surface for the bending motion associated with σ-bridging and that such a potential surface is likely to be present even in slightly bridged structures.[21] If this interpretation is correct then the isotope shift should be a very sensitive probe for the onset of σ-bridging.

Results

Isotope shifts, $^{n}\Delta C(D)$,[22] were measured at 75.4 or 67.9 MHz from ^{13}C spectra of mixtures of labeled and unlabeled compounds. The proportions of the labeled and unlabeled materials in the mixtures were varied in repeat measurements so as to make certain the assignments of the direction of the isotope shifts. The estimated precision in the $\Delta C(D)$ is 0.010 ppm, based on the digital resolution. However, line widths are typically broad in carbocation spectra (3–10 Hz is common), so that some small isotope shifts of about 0.02 ppm or less were not resolved in the carbocations. Also, some isotope shifts at C_3 either were not measured or are less reliable because of the low intensity of multiplet signals for the directly deuteriated carbons. Nonetheless, the precision of measurement still appears to be about 0.010 ppm, based on repeat measurements. In some cases, resolution-enhancing weighting functions were applied to the FID signals before Fourier transformation in order to improve resolution.

Since the C_3 methylene hydrogens in the bicyclo[2.2.1]heptane system are diastereotopic, deuterium substitution for either the exo or endo C_3 hydrogen will, in principle, produce different isotope effects. For reference data in noncationic norbornyl compounds, ^{13}C isotope shifts were determined for exo and endo deuteriation

Chart I

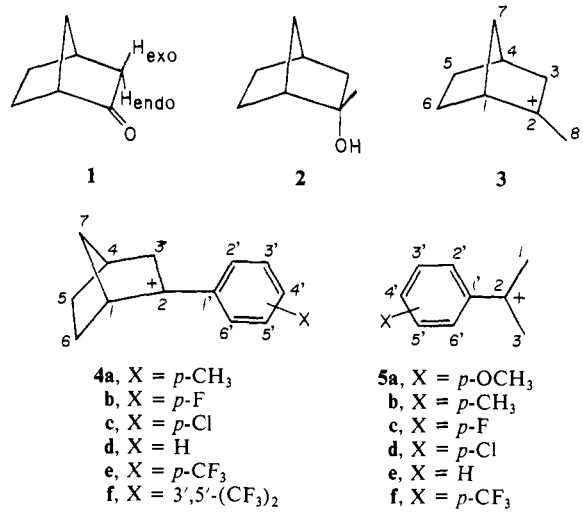

Table I. ^{13}C NMR Isotope Shifts in 2-Methyl-*endo*-2-norbornanol, 2-Norbornanone, and 2-Methyl-2-norbornyl Cation

carbon	δ_C,[a] ppm	n[b]	$^{n}\Delta C(D)$, ppm: 3,3-d_2	exo-3-d	endo-3-d
		2-Methyl-*endo*-2-norbornanol[c]			
C_1	49.0	3	0.00	0.00	0.00[d]
C_2	76.9	2	−0.11	0.00	−0.11[d]
C_3	47.5	1	−0.83	−0.43	−0.40[d]
C_4	37.8	2	−0.20	−0.11	−0.09[d]
C_5	22.5	3	−0.08	0.00	−0.08[d]
C_6	28.7	4	0.00	0.00	0.00[d]
C_7	39.0	3	−0.03	0.00	−0.03[d]
C_8	30.6	3	−0.07	0.00	−0.07[d]
		2-Norbornanone[e]			
C_1	49.8	3	0.000	0.000	0.008
C_2	217.7	2	0.096	0.050	0.048
C_3	45.2	1	−0.682	−0.342	−0.340
C_4	35.2	2	−0.188	−0.091	−0.096
C_5	27.2	3	−0.081	−0.028	−0.054
C_6	24.2	4	0.010	0.000	0.014
C_7	37.6	3	−0.056	−0.018	−0.039
		2-Methyl-2-norbornyl Cation[f]			
C_1	80.4	3	0.67	0.47	0.20
C_2	270.8	2	−2.51	−1.64	−0.87
C_3	55.3	1	−0.9[g]	−0.47	−0.4[d]
C_4	42.8	2	−0.23	−0.12	−0.12
C_5	23.6	3	0.00	0.00	0.00
C_6	35.2	4	0.12	*h*	*h*
C_7	40.1	3	−0.20	−0.10	−0.10
C_8	28.3	3	−0.22	−0.11	−0.11

[a] ^{13}C shifts of nondeuteriated compound relative to tetramethylsilane. [b] Minimum number of bonds separating the carbon and the deuterium. [c] Measured in C_6D_6 at 67.9 MHz; error less than 0.005 ppm. [d] Calculated assuming additivity of 3,3-d_2 and exo-3-d results. [e] Measured in $CDCl_3$ at 125.8 MHz; error less than 0.003 ppm. [f] Measured at 67.9 MHz and −90 °C; error less than 0.010 ppm. [g] Limited accuracy because of unresolved deuterium coupling. [h] No resolved shift, but line is broadened.

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(22) The notation $^{n}\Delta X(Y)$ indicates the incremental change in the chemical shift of nucleus X induced by substitution by the heavy nucleus Y at a distance of n bonds from X. Positive isotope shifts are downfield, following the usual sign convention for substituent effects on ^{13}C chemical shifts.

Table II. ^{13}C NMR Isotope Shifts[a] in 2-Aryl-2-norbornyl Cations at −60 to −90 °C Due to C_3 Deuteriation

cation	isotopomer	C_1	C_2^+	C_3	C_4	C_5	C_6	C_7	$C_{1'}$	$C_{2'}$	$C_{4'}$	$C_{6'}$
4a	d_2	*b*	*0.012*[c]	*−0.768*	*−0.227*			*−0.084*				
	exo-*d*	—[d]	0.048	−0.446	−0.134	—	—	−0.031	0.058	0.046	0.120	0.096
	endo-*d*	0.040	−0.036	−0.332	−0.093	−0.041	0.083	−0.053	—	—	—	—
	endo-*d*[e]	0.044	−0.038	—	−0.087	−0.043	−0.079	−0.050	—	—	—	—
4b	d_2	0.045	0.029	−0.7	−0.219	−0.050	0.104	−0.087	0.062	0.054	0.066	0.134
	exo-*d*	—	*0.077*	−0.46	−0.136	—	*0.019*	−0.030	0.062	0.054	0.062	0.116
	endo-*d*	0.052	−0.048	—	−0.087	—	0.085	−0.056	*0.000*	*0.000*	*0.004*	*0.018*
4c	d_2		*0.035*		*−0.216*		*0.111*	*−0.094*				
	exo-*d*	—	0.090	—	−0.137	—	0.019	−0.027	0.058	0.047	0.112	0.101
	endo-*d*	0.058	−0.055	—	−0.079	—	0.092	−0.067	—	—	—	—
4d	d_2	0.045	0.056	−0.7	−0.213	−0.06	0.112	−0.066	0.050	0.04	0.10	0.126
	exo-*d*	*−0.007*	0.113	−0.47	−0.135	—	0.033	—	0.056	0.051	0.088	0.104
	endo-*d*	0.052	−0.054	−0.32	−0.071	—	0.077	−0.063	*−0.006*	—	—	*0.026*
4e	d_2		*0.002*		*−0.200*							
	exo-*d*	—	0.131	—	−0.131	—	—	—	—	—	0.05	—
	endo-*d*	0.073	−0.129	—	−0.069	−0.026	0.099	−0.065	—	—	—	—
4f	d_2	0.20	−0.15	−0.8	−0.20	—	0.24	—	—	—	—	—
	exo-*d*	*0.09*	0.05	−0.4	—	—	*0.06*	—	—	—	—	—
	endo-*d*	0.11	−0.19	−0.4	—	—	0.18	—	—	—	—	—

[a] In ppm. Positive sign indicates downfield isotope shift. Estimated error ±0.010 ppm except where fewer than three significant figures are given. [b] No entry indicates no experimental measurement. [c] Entry in italics is determined by additivity from two experimental values. [d] Dash indicates unresolved isotope shift because of small magnitude, line broadening (aryl rings in **4e** and **4f**), or weak multiplet signal (C_3). [e] Measured by difference between d_2 and exo-*d* isotopomers rather than endo-*d* and d_0.

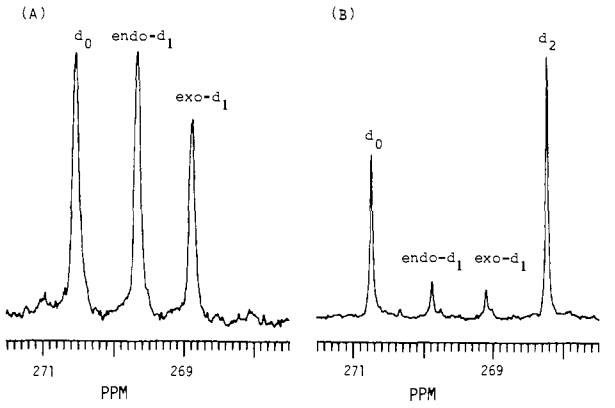


Figure 1. Comparison of the C_2^+ signals in the ^1H-decoupled ^{13}C spectrum of **3** prepared from *endo*-2-methyl-2-norbornyl chloride and (A) *endo*-2-methyl-2-norbornyl-*exo*-3-*d* chloride or (B) *endo*-2-methyl-2-norbornyl-3,3-d_2 chloride.

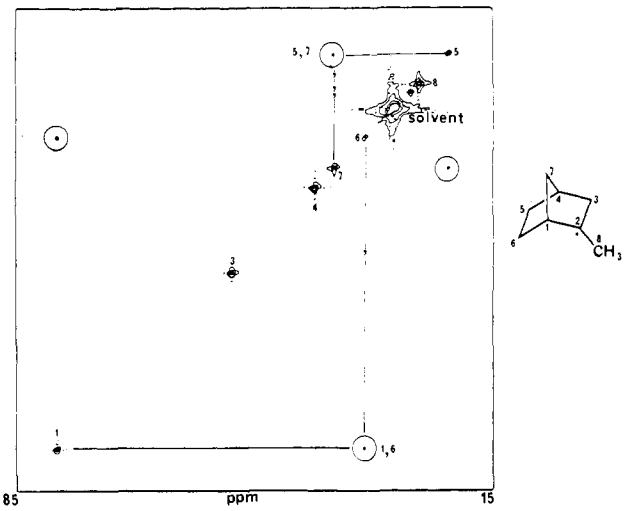
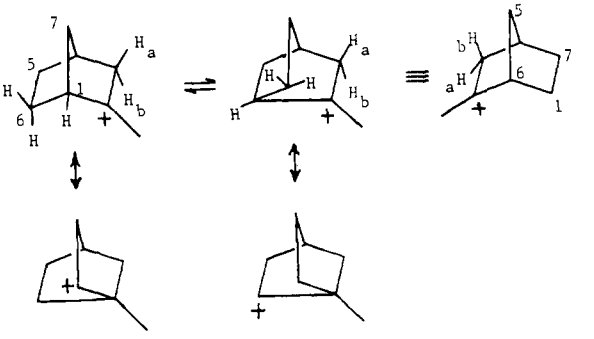


Figure 2. Contour plot of the 2D NMR exchange spectrum acquired for **3**.

in 2-norbornanone (**1**) and 2-methyl-*endo*-2-norbornanol (**2**) as reported in Table I. The issue of additivity of effects was examined carefully for **1**, where isotope shifts were determined separately for the 3,3-d_2, exo-3-*d*, and endo-3-*d* isotopomers. The values we have determined for 2-norbornanone are at variance with those reported by Morris and Murray,[23] which appear to have been determined by using separate solutions of the deuteriated and nondeuteriated samples instead of mixtures of the isotopomers.[4] The sum of the ΔC(exo-3-*d*) and ΔC(endo-3-*d*) for each position of **1** (Table I) matches very closely the corresponding experimental value for the 3,3-d_2 compound. Thus, with additivity observed for **1**, additivity of effects has been assumed in some of the other determinations of ΔC(D) in this study.

Isotope shifts due to C_3 deuteriation are also listed in Table I for the 2-methyl-2-norbornyl cation (**3**). The 2-methyl-2-norbornyl cation was first prepared by the procedure of Kelly et al.,[24] but with deuteriated compounds this procedure led to the scrambling of deuterium from the 3-position to other positions in the molecule. Therefore, this ion was prepared by a more careful procedure at lower temperatures and the spectrum was measured at −90 °C.[21] However, while avoiding scrambling to other positions, this attempt to prepare the 2-methyl-2-norbornyl-*exo*-3-*d* cation gave only an equilibrium mixture of the exo-3-*d* and endo-3-*d* cations. The two peaks in the region for C_2 in the spectrum of the cation were of unequal intensity (see Figure 1). The sum of the isotope shifts for these two peaks adds up to the isotope shift for C_2 in the 3,3-d_2 isotopomer. The less intense peak can be assigned to the exo-3-*d* isotopomer based on the expectation[25] of stronger hyperconjugative interactions with

Scheme I



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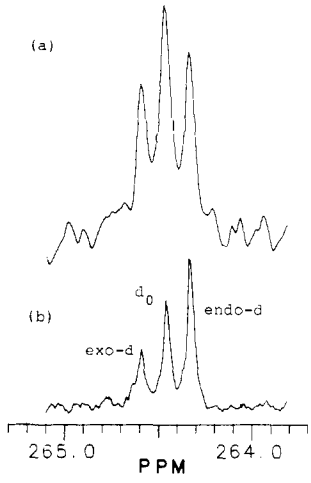

Figure 3. ^{1}H-decoupled ^{13}C spectra of the C_2^+ region for **4e** as a mixture of the nondeuteriated cation with (a) an equilibrium mixture of the endo-*d* and exo-*d* isotopomers at −80 °C or (b) a nonequilibrium mixture of the exo-*d* and endo-*d* isotopomers prepared from the endo-*d* alcohol at −130 °C and measured at −107 °C.

the exo C–H bond which should lead to deuterium being found preferentially in the more tightly bound endo position.

In an attempt to clarify the process which exchanges deuterium between endo and exo positions at C_3 in **3**, several 2D NMR experiments were undertaken. Using the pulse sequence $((\pi/2)_x, t_1, (\pi/2)_y, D, (\pi/2)_x$, acquire), the 2D chemical exchange spectrum[26] of **3** was obtained. A contour plot of the exchange spectrum at −53 °C is shown in Figure 2. The presence of off-diagonal peaks for C_1 and C_6 and for C_5 and C_7 establish that, at this temperature, these sets of carbon are undergoing chemical exchange. The exchange process which accounts for these results is shown in Scheme I.[27] A full study of this exchange process is in progress and will be reported at a later time.[28]

^{13}C NMR isotope shifts are reported in Table II for a series of 2-aryl-2-norbornyl cations (**4a–f**) substituted with deuterium at C_3. The ^{13}C chemical shifts of the unlabeled cations are in good agreement with previous reports[29] and are listed in the supplementary material. Separate measurements of isotope shifts for exo-3-*d*, endo-3-*d*, and 3,3-d_2 isotopomers were made for **4b** and **4d**; these ΔC(D) display additivity within the limits of experimental error. Another indication of additivity is the agreement between ΔC(D) values for endo deuteriation in **4a** when determined in two ways: (i) the typical direct measurement from a mixture of the endo-3-*d* isotopomer and unlabeled **3a**, and (ii) measurement from chemical shift differences in a mixture of the 3,3-d_2 and exo-3-*d* isotopomers.

The 2-aryl-2-norbornyl cations were prepared from the corresponding endo alcohols using SbF_5 in SO_2ClF at −78 °C (dry ice–acetone bath) or 1:1 FSO_3H–SbF_5 in SO_2ClF at −78 or −130 °C (pentane–liquid N_2 bath). Isotope shifts for **4b**-*exo-3-d* and **4d**-*exo-3-d* were measured in both SbF_5 and FSO_3H–SbF_2, with no significant difference in the results. Attempts to prepare the 2-(3,5-bis(trifluoromethyl)phenyl)-2-norbornyl-*exo-3-d* cation gave only an equilibrium mixture of the exo-3-*d* and endo-3-*d* cations. As was the case with the 2-methyl-2-norbornyl cation, the two peaks for the cation center were unequal in intensity and the less intense peak was assigned to the exo-3-*d* isotopomer. Similarly, preparation of the 2-(4-(trifluoromethyl)phenyl)-2-norbornyl cation (**4e**) at −78 °C from either the exo-3-*d* or endo-3-*d* alcohols gave an equilibrium mixture of exo- and endo-labeled cations. However, for **4e** the rearrangement leading to scrambling is sufficiently slow that preparation of the ions at lower temperature (−130 °C) and measurement of the spectra at −107 °C allowed each labeled ion to be identified prior to complete exo/endo equilibration of the label (Figure 3). Again, at equilibrium deuterium is found preferentially in the endo position, but this time with unequivocal isotopomer identification based on the separate measurements.

Attempts to prepare the 2-(4-methoxyphenyl)-2-norbornyl cation in FSO_3H–SbF_5 resulted in mixtures which contained the cation, based on comparisons of chemical shifts with previous data,[29] but several additional peaks were present. Thus, the spectra were not considered reliable sources for isotope shift data and the results have not been included in Table II.

The ΔC(D) for **4a–f** show a pronounced dependence on the aryl substituent. In order to better evaluate the dependence of ΔC(D) on aryl substitution, a series of 2-aryl-2-propyl cations **5a–f** were prepared as the unlabeled and 1,1,1,3,3,3-d_6 (methyl deuteriated) cations **5a–f**. Isotope shifts for **5a–f** are listed in Table III. The ^{13}C chemical shifts are in good agreement with previous reports[30] and are listed in the supplementary material.

Table III. ^{13}C NMR Isotope Shifts[a] in 2-Aryl-2-propyl-d_6 Cations at −80 °C

cation	C_2^+	$C_{1'}$	$C_{2',6'}$	$C_{3',5'}$	$C_{4'}$	CD_3
5a	−0.265	0.058	0.083	——[b]	0.143	−0.91
5b	−0.049	0.073	0.134	0.028	0.250	−0.92
5c	——	0.069	0.18	——	0.246	−0.94
5d	——	0.079	0.19	——	0.136	−0.94
5e	0.049	0.067	0.175	0.029	0.223	−0.94
5f	0.211	0.063	——	——	0.184	−0.98

[a] In ppm. Positive sign indicates downfield isotope shift. Estimated error is ±0.010 ppm. [b] Dash indicates no resolved isotope shift. Estimated value is 0.00 ± 0.02 ppm.

Discussion

Since nuclear shielding in a molecule is a function of internuclear separation, the isotope effects on chemical shifts could, in principle, be calculated by integrating the nuclear shieldings over the vibrational potential surface for the two isotopomers.[7] The integrated nuclear shieldings vary with nuclear mass, not because of a violation of the Born–Oppenheimer approximation but rather because vibrational potential wells are in general anharmonic. While full dynamical calculations of the variation of shielding with internal coordinate have been reported for a few diatomic molecules,[7] such studies are not readily extended to the polyatomic molecules of general interest.[31] Thus, we have chosen in this paper to adopt the empirical approach and explore the variation in isotope shifts with systematic changes in structure. The response of ^{13}C chemical shifts to isotopic perturbation in norbornane derivatives is examined as a function of location of deuterium in the exo or endo position at C_3 and as a function of increasing electron demand in the series 2-norbornanone, 2-aryl-2-norbornyl cations, and 2-methyl-2-norbornyl cation. Because of the rigid norbornane structure, isotopic perturbation of conformational equilibria can be excluded as the cause of these isotope effects, and perturbation of chemical equilibria can be ruled out also for the tertiary 2-norbornyl cations.[15]

2-Norbornanone and 2-Methyl-*endo*-2-norbornanol. Isotope shifts at C_2 in **1** are downfield while nearly all of the other ΔC(D) in **1** and **2** are upfield (Table I). The largest isotope shifts are at the directly deuteriated C_3 position. Typical isotope shifts are upfield and resemble an inductive effect which is attenuated by

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the intervening bonds.[2-4] One-bond effects are generally well accounted for by increased electron density and increased shielding at carbon arising from the bond-shortening effect of deuterium substitution due to an anharmonic potential for the C–H stretching vibration.[7,31,32] The downfield $^2\Delta C_2(D)$ at the carbonyl carbon in **1** is presumably due to perturbation of hyperconjugation in which C–D bonds are poorer hyperconjugative donors than C–H bonds, again because of the effectively shorter C–D bond.[17,32,33] The isotope shift in carbonyl compounds appears to be a balance between the "inductive" shielding effect, which is typically an upfield shift of about −0.1 ppm per deuterium,[4] and the hyperconjugative deshielding effect, with the deshielding effect dominating in the more electron-withdrawing types of carbonyl compounds.[18,34]

The $^2\Delta C_2(D)$ are nearly the same for exo and endo C_3 deuteriation in **1**. The exo and endo C–H bonds in **1** should have similar dihedral angles with respect to the p orbital of the carbonyl carbon, but with a slightly better hyperconjugative alignment for the exo C–H bond.[25] The exo C–D does induce a slightly larger downfield shift of +0.050 ppm vs +0.048 ppm for the 3-endo-*d* isotopomer.

Long-range isotope shifts in **1** and **2** are small and mostly upfield, but endo deuteriation at C_3 produces larger effects than exo deuteriation. Both upfield and downfield long-range $\Delta C(D)$ have been noted previously for ring systems, where it is likely that deuteriation affects the ring vibrations.[12-14,35] Long-range isotope shifts may also occur when steric interactions are perturbed.[10-12] Thus, it is not unexpected that alteration of the vibrational motions of the C–H at the more crowded endo position would have a greater effect on vibrational averaging of shielding at other carbons throughout the ring system. Perhaps noteworthy in this respect in Table I are the larger $^3\Delta C(D)$ at C_5 and C_7, which are likely to be involved in steric interactions, compared to C_1. However, the isotope shifts are quite small and may not be easily rationalized in detail.

2-Aryl-2-propyl and 2-Aryl-2-norbornyl Cations. Isotope shifts are downfield at the C_2 cation center in the exo-3-*d* series of cations **4a–f** and upfield at C_2 in the endo-3-*d* series (see Table II). As in the case of **1**, the downfield $^2\Delta C_2$(exo-3-*d*) can be attributed to isotopic perturbation of hyperconjugation, wherein a C–D bond acts as a poorer electron donor than a C–H bond due to the mass effect on vibrational averaging over the electronic surface. An exo C_3–H bond in a classical 2-norbornyl cation is better aligned for hyperconjugation than an endo C_3–H bond.[25] One manifestation of the different alignment is indicated by our observations of the deuterium being preferentially found at the endo position in equilibria which scramble the label between exo and endo positions in **4e**, **4f**, and **3**. Hyperconjugation should weaken the bending and stretching force constants of the exo C–H bond, leading to the observed equilibrium isotope effect. Other experimental and theoretical evidence supports this difference between exo and endo hyperconjugative interactions.[25] Thus, the upfield isotope shifts at C_2 in the endo-3-*d* series are probably observed because the normal upfield isotope shift is *not* counterbalanced in this case by a strong downfield effect of perturbed hyperconjugation.

Long-range isotope shifts in the aryl ring are found in the exo-3-*d* series but not in the endo-3-*d* series of **4a–f**. Downfield isotope shifts in the aryl ring are found at the positions $C_{2'}$, $C_{6'}$, and $C_{4'}$, which are ortho and para to the benzylic cation center. No isotope shifts are found at the meta positions, $C_{3'}$ and $C_{5'}$. This pattern indicates increased positive charge delocalization to the aryl ring in the deuteriated ions as a result of perturbed hyperconjugation which reduces electron supply from the alkyl group.[36] As discussed above, the exo C_3–H bond is better aligned for hyperconjugation than the endo C_3–H bond. The lack of long-range isotope shifts in the aryl ring in the endo-3-*d* series reflects the poorer alignment. Comparable results have been reported for deuterium isotope effects on the ^{19}F chemical shift of **4b** where exo deuteriation at C_3 produces a downfield shift of 0.202 ppm and endo substitution produces no measurable effect.[25]

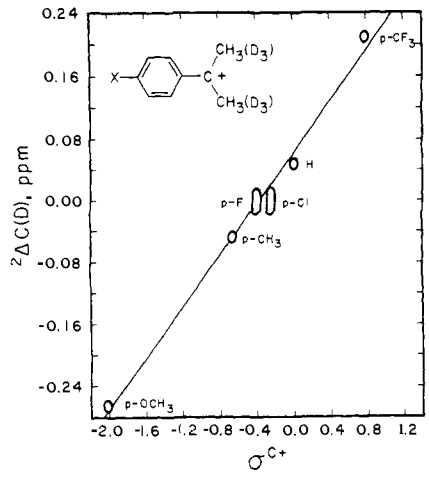

Figure 4. Plot of the $^2\Delta C(D)$ isotope shifts at C_2^+ due to methyl deuteriation in **5a–f** vs σ^{C+}.

Table IV. Correlations of C_2 Isotope Shifts with σ^{C+} in $\Delta C_2(D) = \rho\sigma^+ + i$

cation	isotopomers	ρ	i	corr coeff
5a–f	d_6	0.166	0.06	0.994
4a–f	3,3-d_2	−0.078	0.00	0.615
4a–d	3,3-d_2	0.064	0.05	0.986
4a–d	3-exo-*d*	0.096	0.11	0.998
4a–d	3-endo-*d*	−0.028	−0.06	0.857

Long-range isotope shifts in the phenyl ring were not observed in the 4-(trifluoromethyl)phenyl and 3,5-bis(trifluoromethyl)phenyl cations, **4e** and **4f**. Three factors are involved, one simply being coupling to ^{19}F which results in multiplets[29] or line broadening that make it more difficult to observe the isotope shifts at the aryl carbons. The other two factors are related to the extent of conjugation of the phenyl ring with the electron-deficient p orbital at C_2. Conjugation of the phenyl ring with the cation center leads to hindered rotation about the C_2–$C_{1'}$ bond axis. If rotation is slow, separate resonances may be observed for $C_{2'}$ and $C_{6'}$, and for $C_{3'}$ and $C_{5'}$, as is the case for **4a–e**. However, the rate of rotation depends upon how the substituent affects the strength of the π-bonding between C_2 and $C_{1'}$. With the electron-withdrawing 4-CF_3 group in **4e**, rotation is still slow enough to observe separate resonances for $C_{2'}$ and $C_{6'}$, but the signals are broadened by the exchange process. With 3,5-$(CF_3)_2$ substitution in **4f**, rotation of the phenyl ring is fast enough to give averaged signals, but these are also broadened by exchange. Broad line widths will obscure small isotope shifts at $C_{2'}$ and $C_{6'}$, but should not be a factor at $C_{4'}$ with is not exchange broadened. A factor that will influence $C_{4'}$ is reduced charge delocalization into the electron-withdrawing rings. This is likely to reduce also the magnitude of the long-range isotope shifts that arise from a perturbation of the charge delocalization. The isotope shifts are similarly small and difficult to measure in **5f**.

The key data that can provide insight regarding bonding in the 2-aryl-2-norbornyl cations is the substituent dependence of isotope shifts at the cation center. Before discussing these results, we must first examine the substituent dependence of isotope shifts in a reference system, the 2-aryl-2-propyl cations, **5a–f**. The isotope shifts at C_2 in **5a–f** vary with substituent electronic character in the same way as the C_2 chemical shifts themselves vary. The C_2 chemical shifts of 2-aryl-2-propyl cations have been used to define σ^{C+} constants, a set of Hammett-type substituent constants used to account for enhanced resonance interactions in stable carbocations.[30c] When the $^2\Delta C_2(D)$ for **5a–f** in Table III are plotted

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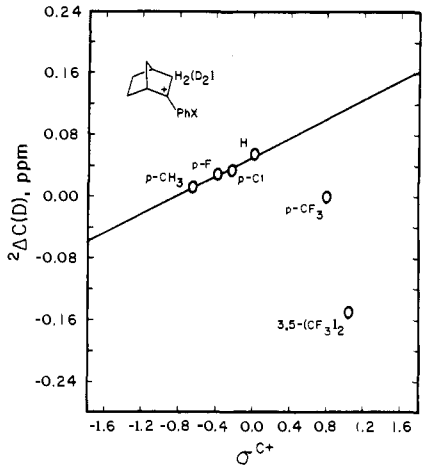

Figure 5. Plot of the $^2\Delta C(D)$ isotope shifts at C_2^+ from the 3,3-d_2 isotopomers of **4a–f** vs σ^{C+}.

vs. σ^{C+} constants (Figure 4), an excellent linear correlation is found (see Table IV).

As seen in Figure 4, the isotope shift is downfield when the substituent is electron withdrawing, as in **5f**, but changes to upfield with electron-donating substituents, as in **5a**. The sign of the isotope shift apparently depends on the balance of the deshielding effect of isotopic perturbation of hyperconjugation and the shielding effect of the inductive perturbation. Hyperconjugation will be more important for a more electron-deficient cation center. Also any perturbation of hyperconjugation is less likely to be compensated for by electron release from the aryl ring when the substituent is electron withdrawing. It is essential also to note that despite the upfield shifts at the cation centers of **5a** and **5b**, perturbation of hyperconjugation is still evident by way of downfield isotope shifts at the ortho and para positions of the phenyl group. Thus, all of the 2-aryl-2-propyl cations show decreased electron supply to the π-system upon β-deuteriation, but the effect is more concentrated at the cation center when the substituent is electron withdrawing.

Figure 5 shows the plot of isotope shifts from Table II for C_2 in 2-aryl-2-norbornyl-*3,3-d*$_2$ cations vs σ^{C+} constants. If the data for the *p*-CH_3, *p*-F, *p*-Cl, and parent ions (**4a–d**) are used to define a straight line (Table IV), it is clear that the ΔC_2(3,3-d_2) of **4e** and **4f** deviate substantially from the line. Figure 6 shows similar treatments separately for ΔC_2(exo-3-*d*) and ΔC_2(endo-3-*d*) in **4a–f**. Again, linear correlations can be defined from data for **4a–d**, with the points for **4e** and **4f** deviating from these lines. The deviant isotope shifts are more upfield than expected, with the ΔC_2(exo-3-*d*) showing greater deviation than the ΔC_2(endo-3-*d*).

The C_2 chemical shifts of 2-aryl-2-norbornyl cations also deviate in the upfield direction from a linear correlation with σ^{C+} constants when the substituents are strongly electron withdrawing.[29b,d,37] Farnum, Olah, et al. have interpreted such "tool of increasing electron demand" plots of 2-aryl-2-norbornyl cation C_2 chemical shifts as demonstrating the onset of σ-bridging.[37] The increased electron density, bonding, and change in coordination at C_2 if there is bridging from C_6 to C_2 are expected to shield C_2. Figures 5 and 6, which show that the isotope shifts at C_2 of **4e** and **4f** are more upfield than expected, indicate a change in type of response to deuteriation as the substituents become more electron withdrawing. The upfield direction of the deviations for the C_3 deuteriated cations **4e** and **4f** is consistent with isotopic perturbation of three-center, two-electron bonding toward enhanced σ-bridging in the deuteriated isotopomers.

It is important to remember that any apparent electronic differences between isotopomers are due to vibrational effects on the average structure within the same potential energy surface. An explanation within the vibrational context can be advanced for the upfield deviations in Figures 5 and 6, keeping in mind the related isotope shifts for the 2-methyl-2-norbornyl cation discussed below and in the accompanying paper.[21] Increasing electron demand should lower the energy requirement for bending the C_2–C_1–C_6 angle in the direction of bridging.[38] If the surface is sufficiently shallow with respect to the C_2–C_1–C_6 bending motion, some of the bridged portion of the surface will be included in populated vibrational states. β-Deuteriation at C_3 will lower the vibrational energy content of the more bridged portion of the surface more than the open portion, because force constants of β C–H bonds should be stronger in a bridged structure where there is less demand for C–H hyperconjugation. Thus, the result will be a vibrationally averaged structure that is more σ-bridged for the C_3-deuteriated isotopomers than for the nondeuteriated cation when the substituent is electron withdrawing.

The NMR isotope shifts appear to be a more sensitive probe of the behavior interpreted as the onset of σ-bridging than are the chemical shifts themselves. The deviations of isotope shifts for **4e** and **4f** from the correlation line in Figure 5 are more pronounced than the corresponding deviation of C_2 chemical shifts from correlation with σ^{C+}.[29,37] The greater sensitivity can be seen in Figure 7, where ΔC_2(3,3-d_2) are plotted vs the C_2 chemical shifts. Clearly, while the magnitude of the deviations from the correlation line is reduced, the isotope shifts at C_2 in **4e** and **4f** are much more upfield than expected from the chemical shifts. We suggest that the isotope shifts will start to show behavior characteristic of σ-bridging as soon as the energy barrier for the bending motion along the bridging coordinate is lowered sufficiently that the vibration occurs in a shallow potential well, even if the vibrationally averaged structure is only slightly bridged.

Isotope shifts at positions other than C_2 in the norbornyl rings of **4a–f** (Table II) are larger for the endo-3-*d* series than the exo-3-*d* series, as was the case with 2-norbornanone (Table I). However, in **4a–f**, the downfield shifts at C_1 and C_6 are larger than in **1**. The ΔC(endo-3-*d*) for C_1, C_4, C_6, and C_7 do not vary much outside the range of experimental error in the series **4a–e**. Attempted correlations with σ^{C+} give poor results, as the slopes of the lines are rather small. Only the two points for C_1 and C_6 in **4f** deviate obviously, in the downfield direction, which is consistent with increased bridging in the most electron-deficient ion.

2-Methyl-2-norbornyl Cation. Unusually large upfield isotope shifts at the cation center are associated with β-deuteriation at the methyl group or at C_3 in the 2-methyl-2-norbornyl cation (**3**).[21] We have attributed the large isotope shifts to isotopic perturbation of the average position on an energy surface which is unusually flat with respect to the bending/bridging motion that alters the C_2–C_1–C_6 bond angle.[21] The upfield direction indicates that the deuteriated isotopomers are more bridged than the unlabeled ion due to different vibrational averaging over this flat surface. From Table I, it may be seen that the separate exo-3-*d* and endo-3-*d* effects are also upfield, with the $^2\Delta C_2$(exo-3-*d*) at −1.64 ppm being nearly twice the magnitude of the $^2\Delta C_2$(endo-3-*d*) at −0.87 ppm. It is interesting to note that the upfield deviations of $^2\Delta C_2$(exo-3-*d*) for **4e** and **4f** from the correlation line in Figure 6 are also about twice the magnitude of the upfield deviations of $^2\Delta C_2$(endo-3-*d*) from the endo correlation line. The upfield isotope shifts at C_2 for **3** are an order of magnitude larger than for the upfield deviations of C_2 for **4f**, but this would seem a reasonable extrapolation of the same type of effect to a more electron demanding cation.

As discussed earlier for other differences between exo and endo isotope effects, the most likely source of the exo/endo difference for isotope effects in **3** is the better alignment of the exo C_3–H bond for hyperconjugation. The bending and stretching force constants for the exo C–H are likely to vary more as hyperconjugative demand varies between open and more bridged forms of the cation, so that deuteriation at the exo position would be likely to have a greater effect on the relative vibrational energy content

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(38) One indication that this is likely to be true is the lower energy barrier for the rearrangement shown in Scheme I for the more electron deficient cations.

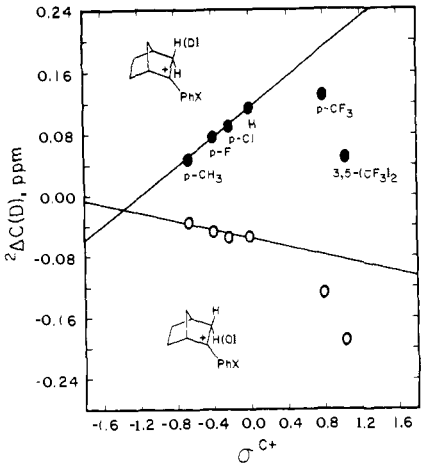

Figure 6. Separate plots of the $^2\Delta C(D)$ isotope shifts at C_2^+ from the 3-exo-*d* (upper) and 3-endo-*d* (lower) isotopomers of **4a–f** vs σ^{C+}.

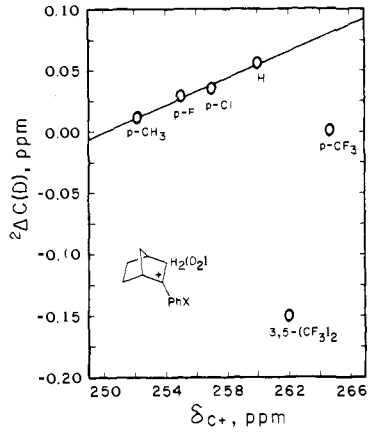

Figure 7. Plot of the $^2\Delta C(D)$ isotope shifts at C_2^+ from the 3,3-d_2 isotopomers of **4a–f** vs the chemical shifts at C_2^+ in **4a–f**.

and hence a greater isotope effect on the average C_2–C_1–C_6 bond an gle.

Conclusions

Intrinsic NMR isotope shifts in carbocations are very sensitive to structural changes and hence are a potentially powerful probe of structure. The complex vibrational origin of the isotope shifts have so far prevented direct theoretical predictions of isotope effects on shieldings more than one bond from the site of isotopic substitution in molecules of even moderate complexity. However, we feel that patterns of chemical shift response to isotopic perturbation can be established empirically which allow structural interpretation. We interpret the observed $^2\Delta C(D)$ isotope shift at a particular cation center to be a sum of contributions from a small upfield isotope shift due to perturbation of the σ-framework (inductive-type perturbation), a downfield shift due to perturbation of hyperconjugation, and a potentially large upfield shift from perturbation of three-center, two-electron bonding. All apparent electronic effects can be explained as mass-induced variations in vibrational averaging of nuclear shielding.

The ^{13}C isotope shift at the cation center arising from deuteriation at adjacent alkyl C–H bonds progresses systematically downfield with increasing electron demand in 2-aryl-2-propyl cations. The behavior of the less electron demanding members of the 2-aryl-2-norbornyl cations is similar to that of the 2-aryl-2-propyl cations. The structural feature of different alignments for the C_3 hydrogens with respect to the cation center is indicated by the upfield isotope shift at the cation center for endo deuteriation and downfield isotope shift for exo deuteriation. However, the type of response to isotopic perturbation changes with increasing electron demand in the 2-norbornyl system. With electron-withdrawing substituents in 2-aryl-2-norbornyl cations, the isotope shifts are more upfield than expected at the cation center. This response is more pronounced in the more electron demanding 2-methyl-2-norbornyl cation, where isotope shifts are large and upfield. These results can be interpreted as indicating the onset of σ-bridging with increasing electron demand. We suggest that the energy barrier for bending the C_2–C_1–C_6 toward a bridged structure becomes sufficiently low that the bending vibration occurs in a shallow potential well and isotopic substituion is then able to perturb the vibrationally averaged structure toward a more bridged position. The chemical shift response to isotopic perturbation may become dominated by this perturbation of the bending motion along the bridging coordinate as electron demand increases. The results reported here, together with the isotope shift data for the 2-methyl-2-bicyclo[2.2.2]octyl cation,[21] indicate that the NMR isotope shift may be a very sensitive probe of three-center, two-electron bonding because of the vibrational origin of the isotope effect.

Experimental Section

NMR Spectroscopy. ^{13}C NMR spectra of cations were acquired at 68.9 MHz with an IBM model WP-270 SY NMR spectrometer or at 75.4 MHz with a Varian model XL-300 spectrometer, as previously described.[21]. Spectra of 2-norbornanone were obtained on a Bruker WM-500 spectrometer at 125.8 MHz. The 2D exchange spectrum was acquired on the IBM spectrometer over a 72 h period at −53 °C with the standard chemical exchange sequence which included quadrature phase cycling in both dimensions. The number of data points in the F1 dimension was set equal to 512 words and zero filled to 1K, while the number of data points in the F2 dimension was 2K. A mixing time of 0.20 s was employed. The data set was weighted by a sine bell function in the F2 dimension and a sine squared bell function in the F1 dimension before 2D Fourier transformation. The standard liquid N_2 evaporator purchased with the spectrometer was modified to include a three valve system that would allow filling the Dewar without dissassembling the variable temperature unit. Filling was performed after forcing the lock to be lost when liquid N_2 was added so that variations in sample spinning would not distort the spectrum.

Cation Preparation. The 2-aryl-2-norbornyl and 2-aryl-2-propyl cations were prepared by ionization of the corresponding 2-aryl-*endo*-2-norbornanol or 2-aryl-2-propanol precursors as mixtures of isotopomers by either of two procedures. (i) Cations **4a–e** and **5a–f**: A precooled solution of about 2 mmol of the alcohol precursor in SO_2ClF (1 mL) was added dropwise to a vigorously stirred (vortex mixer) solution of about 5 mmol of 1:1 FSO_3H-SbF_5 in SO_2ClF (2 mL) at −78 °C (Dry Ice-acetone bath). About 0.1 mL CH_2Cl_2 was added for internal chemical shift reference. Cation **4e** was also prepared at −130° (pentane-liq. N_2 bath). The solution was transferred via precooled pipets to precooled NMR tubes. (ii) Cations **4b**, **4d**, and **4f**: A solution containing 1.5 g (6.9 mmol) SbF_5 dissolved in 0.8 to 1.2 mL of SO_2ClF was slowly stirred into a 10 mm NMR tube, cooled to −78°, containing about 2 mmol of the alcohol precursor dissolved in SO_2ClF (0.8 mL). The lock solvent and reference were contained in a 5 mm concentric insert.

Cation Precursors. The alcohols were synthesized in standard Grignard reactions on 2-norbornanone and its isotopomers in 65-80% yield.[29] Each of the alcohols was purified by recrystallization in 98% n-hexane, by flash column chromatography on silica gel (>230 mesh) with ethyl acetate-hexanes as eluant, or by preparative gas chromatography on a 6 m column packed with 5% Carbowax on 80/100 mesh Chromosorb W High Pack. 2-Methyl-2-norbornanol and its isotopomers were converted to the chlorides using the procedure of Brown et al.,[39] and the chlorides were used without further purification.

The *3,3-d*$_2$, *3-exo-d*, and 3-*endo-d* isotopomers of 2-methyl-2-norboranone were prepared as previously described,[25] or by the following improved procedures.

2-Norbornanone-*exo*-3-*d* was prepared by heating in a pressure vessel 10.0 g of 2-norbornanone and 20.0 mL of 5 wt% Na_2CO_3 in D_2O at 40 °C for 30 h with continuous vigorous stirring. The product was extracted with diethyl ether and dried over anh. $MgSO_4$. MS and ^{13}C NMR analysis showed 1.1% 2-norbornanone-*3,3-d*$_2$, 92.6% 2-norbornanone-*3-exo-d*, and 6.2% 2-norbornanone.

2-Norbornanone-*3,3-d*$_2$ was prepared by heating in a pressure vessel 10.0 g of 2-norbornanone and 12.5 mL of 1.0 M NaOD at 100 °C for 72 h while vigorously stirring. Workup gave a product consisting of 95% 2-norbornanone-*3,3-d*$_2$ and 5% 2-norboranone-*3-exo-d*. This procedure was found to be superior to that of Weinberg and Djerassi.[40]

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Supplementary Material Available: ^{13}C chemical shifts for **4a–f** and **5a–f** are provided for comparison with previous studies[29] (2 pages). Ordering information is given on any current masthead page.

Large Intrinsic Nuclear Magnetic Resonance Isotope Shifts Associated with Bending Motion along the Bridging Coordinate in Carbocations

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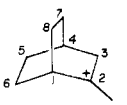
Abstract: Deuterium isotope effects on the ^{13}C NMR chemical shifts have been determined for the 2-methyl-2-bicyclo[2.2.2]octyl and 2-methyl-2-bicyclo[2.2.1]heptyl cations. These tertiary carbocations have isotope shifts that are larger than 1 ppm per deuterium, which is an order of magnitude larger than ordinary intrinsic shifts found in nonionic model compounds and in other carbocations. For deuteriation at the C_3 methylene or methyl group, the same pattern occurs in both cations: isotope shifts that are large and upfield at C_2, downfield at C_1, and upfield at the remaining carbon directly bonded to C_2. The similarity in the pattern of the isotope shifts suggests that the force field and shielding influences in both ions are similar. The specific results are interpreted as indicating the presence of a shallow potential surface for the bending motion along the direction associated with σ-bridging. Since the existence of the shallow potential does not depend on the actual extent of bridging, the magnitude of the isotope effect is not proportional to the extent of bridging.

Typical intrinsic isotope effects on ^{13}C NMR chemical shifts (the isotope shift, $^{n}\Delta C(D)$) are upfield displacements of a few tenths of a ppm per deuterium at the carbon bearing the deuterium and smaller effects at the next carbon and more remote positions.[2,3] NMR isotope shifts have been especially valuable in distinguishing equilibrium processes from resonance phenomena in structural studies of carbocations.[4,5] Isotopic perturbation of rapid degenerate equilibria in carbocations typically produces large, temperature-dependent $\Delta C(D)$ while isotopic substitution in a static species gives small, intrinsic $\Delta C(D)$. However, in nonequilibrating cations with σ-delocalized structures, isotopic perturbation produces relatively large intrinsic shifts.[6] In further exploration of intrinsic isotope shifts in carbocations, we now report additional two-bond isotope shifts, $^{2}\Delta C(D)$, which are larger than 1 ppm per deuterium in "static" tertiary carbocations. While these $^{2}\Delta C(D)$ are smaller than typical equilibrium isotope shifts in carbocations, they are an order of magnitude larger than and of opposite sign to intrinsic shifts in other nonequilibrating carbocations. These unusual isotope shifts indicate a response to isotopic substitution which appears to differ from both the usual equilibrium and intrinsic effects in carbocations.

Unusually large, upfield isotope shifts resulting from β-deuteriation are found at the cation center in the 2-methyl-2-bicyclo[2.2.2]octyl cation (**1**) and the 2-methyl-2-bicyclo[2.2.1]heptyl cation (**2**). Previously, Servis and Shue found upfield $^{2}\Delta C(D)$



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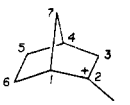

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in static carbocations capable of nonclassical σ- or π-bridging: the "methylcyclobutyl" cation, 7-methyl-7-norbornenyl cation, and **2**.[6] The $^{2}\Delta C(CD_3)$ at the cation center due to methyl deuteriation in these carbocations were notable relative to typical intrinsic effects in being larger than a few tenths of a ppm and being upfield rather than downfield. The upfield $^{2}\Delta C(D)$ were ascribed to isotopic perturbation of resonance which increases the relative contribution of the canonical forms that involve bonding to the cation center from the bridging atom. In contrast, downfield $^{2}\Delta C(D)$ were observed for classical static carbenium ions such as the 2-methyl-2-propyl, 2-methyl-2-butyl, and 1-methylcyclopentyl cations. The downfield $^{2}\Delta C(D)$ at C^{+} apparently originate from reduced hyperconjugative electron release from C–D bonds relative to C–H bonds,[6] an interpretation which has been supported by similar findings in several other studies.[7-10] The contrasting

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