Carbon-13 Nuclear Magnetic Resonance Chemical Shifts in β-Substituted Bicyclo[3.2.1]octan-8-one Derivatives. Unusually High Anti-γ-Substituent Effects

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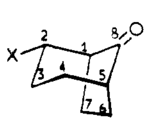
Considerable attention has been focussed on the study of substituent effects on ^{13}C shieldings in order to get useful data for analytical purposes. Although the usefulness of the additivity of substituent increments has often been demonstrated,[2] a recent account by Stothers et al.[3] shows that, in disubstituted compounds, deviations of up to 11 ppm from the calculated values were found at the penultimate carbons of δ fragments. This phenomenon is observed only when the substituents are in a syn-axial relationship. In uncrowded situations, the effects are much smaller. However, recent findings[4] in β-substituted cyclohexanone derivatives[5,6] demonstrate that additivity rules may even fail in 1,3-disubstituted molecules exhibiting no steric compression.[7]

We now have studied the 2-substituted bicyclo[3.2.1]-octan-8-one derivatives **1a–c** and **2a–c** and found that the anti-γ-substituent effect can in some cases be appreciably larger than the steric γ effect.



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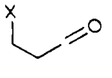
a: X = OH
b: X = OAc
c: X = Cl
d: X = H

Considering first the α-carbon (C-2), it can be seen from Table I that this carbon generally exhibits lower shieldings in exo compounds **2a–c** (axial substituent, syn orientation to the carbonyl group) than in the epimeric endo molecules **1a–c.** This agrees with findings in the structurally related bicyclo[3.3.1]nonan-9-one[5] and adamantanone[6] systems. However, in the corresponding 2-substituted hydrocarbons (X = OH, OAC), the α-carbon is more shielded in the exo isomer.[8] These shielding effects in the keto compounds 1 and 2 can be rationalized by steric and/or electronic arguments. In addition to the possible heteroatom lone pair donation[9] from the substituent to the spacially neighbored carbonyl group resulting in polarization of the C–X bond, steric interactions should be considered. Thus, the pseudo-syn-axial δ arrangement 7 may formally explain the deshielding of C-2 in exo isomers due to the steric interaction of the axial substituent and the carbonyl function.[3] Although the interpretation of C_α shifts as a response to γ or δ steric crowding may be useful in some cases,[10] we think that a generalization is not valid. Indeed it has been shown in equatorial and axial monosubstituted cyclohexanes that a bromine and iodine substituent[11] affect the α-carbon in an opposite manner than OH,[12] CH_3,[13] F,[11] and NO_2[14] groups. Thus shielding or deshielding of carbons in crowded molecular fragments appears to depend on the nature of the substituent (e.g., polarizability) and is not necessarily a general crowding phenomenon.[15] Confirmation of this suggestion for δ-crowded situations can be found at C-α in β-substituted adamantanones, provided that syn orientation of the substituent at C-4 toward the 2-keto group is realized. In this case upfield *and* downfield deviations from calculated values are observed.[6]



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γ Effects are found for carbons 4, 7, and 8 (see Table I). For carbon-8 (carbonyl carbon) a high-field shift is observed irrespective of the stereochemistry of the functional group X. While this effect is purely due to nonsteric interactions in endo compounds 1, the situation is more complicated in compounds 2. In addition to electronic through-bond effects (polarization of the σ-bond framework) steric and through-space effects (polarization of the C=O π bond) (8) may compete.[4,16] The carbon-4 and carbon-7 are similarly shifted in 2 and 1, respectively. While the well-known γ-substituent effects caused by gauche interactions are observed at C-4 in 2 and at C-7 in 1, unusual diamagnetic shifts of up to 8.4 ppm are found for

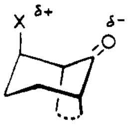

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Table I. ^{13}C Chemical Shifts and Substituent Effects of Derivatives of Bicyclo[3.2.1]octan-8-one[a,b]

	registry no.	C-1 (β)	C-2 (α)	C-3 (β)	C-4 (γ)	C-5 (δ)	C-6 (δ)	C-7 (γ)	C-8 (γ)
1d, X = H	55679-31-7	44.9	37.1	17.4	37.1	44.9	22.6	22.6	222.9
1a, X = OH	25548-53-2	53.4	74.1	26.3	28.9	43.4	22.5	17.4	218.0
		(8.5)	(37.0)	(8.9)	(−8.2)	(−1.5)	(−0.1)	(−5.2)	(−4.9)
1b, X = OAc[c]	69257-95-0	49.7	74.8	23.3	28.7	43.5	22.3	18.2	215.7
		(4.8)	(37.7)	(5.9)	(−8.4)	(−1.4)	(−0.3)	(−4.5)	(−7.2)
1c, X = Cl	40441-28-9	53.2	61.8	28.5	31.5	43.2	21.9	18.4	215.7
		(8.3)	(24.7)	(11.1)	(−5.6)	(−1.7)	(−0.6)	(−4.2)	(−7.2)
2a, X = OH	25548-51-0	51.4	78.4	24.9	32.4	44.5	21.5	20.8	219.3
		(6.5)	(41.3)	(7.5)	(−4.7)	(−0.4)	(−1.1)	(−1.8)	(−3.6)
2b, X = OAc[d]	69257-96-1	47.4	79.5	22.6	32.0	44.0	21.3	20.1	216.8
		(2.5)	(42.5)	(5.2)	(−5.1)	(−0.9)	(−1.3)	(−2.5)	(−6.1)
2c, X = Cl	67403-65-0	51.0	65.7	26.4	30.8	43.6	20.8	22.3	214.6
		(6.1)	(28.6)	(9.0)	(−6.3)	(−1.3)	(−1.8)	(−0.3)	(−8.3)

[a] Chemical shifts in ppm relative to Me_4Si. [b] Greek letters and values in parentheses represent the substituent effects relative to bicyclo[3.2.1]octan-8-one (**1d**); a minus sign denotes a highfield shift. [c] Values for the acetyl group: 169.7 (CO); 21.1 (CH_3). [d] Values for the acetyl group: 170.2 (CO); 21.1 (CH_3).

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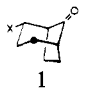
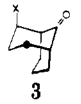
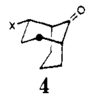
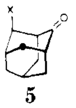
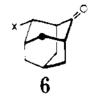
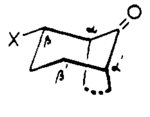
Table II. Comparison of γ-Substituent Effects at C-4 (●) in β-Substituted Bicyclo[3.2.1]octan-8-ones, Bicyclo[3.3.1]nonan-9-one,[a] and Adamantan-2-one Derivatives[b]

X	 2		 1	 3		 4	 5		 6
OH	−4.7		−8.2	−5.1		−6.5	−6.5		−6.4
Δ[c]		+3.5			+1.4			−0.1	
OAc	−5.1		−8.4	−5.4		−6.5	−5.4		−6.5
Δ		+3.3			+1.1			+1.1	
Cl	−6.3		−5.6	−5.8		−4.4	−6.3		−4.3
Δ		−0.7			−1.4			−2.0	

[a] Reference 5. [b] Reference 6. [c] Δ represents the difference between the steric and nonsteric γ effect. A plus sign denotes that the anti-γ effect is larger.

the anti-γ-carbon at position 4 in **1**. Such an enhanced anti-γ-effect is also observed in the related systems shown in Table II. These observations suggest that i–v may be necessary conditions for the large anti-γ-effect: (i) a carbonyl group is present in the substituted cyclohexane ring; (ii) the carbon bearing the substituent and the γ-carbon are β with respect to the carbonyl group; (iii) the substituent is equatorial (anti to the C=O group) (**9**), (iv) the substituent is not on a bridgehead carbon,[17] and (v) the cyclohexanone ring is in the chair conformation.[18] Thus, in disubstituted compounds, uncrowded molecular arrangements may give rise to appreciable high-field shifts. These shifts can even be higher (e.g., X = OH, OAc) than those caused by the well-established steric γ effect. This is true when comparing the chemical shifts of carbon-4 in the two epimers **1** and **2** (see Table II), but it is also true if one compares carbon-4 (anti) and carbon-7 (steric) of the endo isomer **1** (see Table I).



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Although there might be a relationship between ring strain and the magnitude of the anti-γ-shift (derived from the increased diamagnetic shielding in the bicyclo[3.2.1]octane systems, see Table II), other factors such as deviations from coplanarity in the antiperiplanar arrangements and angular distortion[19] of the propanic fragment could play an important role.

Experimental Section

For details concerning ^{13}C PFT spectra, see ref 5.

The bicyclic compounds used in this study were all prepared by known methods: **1a** and **2a**;[20] **1b** and **2b**;[21] and **2c**.[22]

The endo/exo mixture of **1a** and **2a** was separated by column chromatography on silica gel 60 (Merck, 70–230 mesh ASTM) using pentane–ether mixtures (0–50%) as an eluent.

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