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STERIC SUBSTITUENT EFFECTS ON ^{13}C NMR CHEMICAL SHIFTS OF 8-(exo/endo)-SUBSTITUTED 1,5-DIMETHYLBICYCLO[3.2.1]OCTANES

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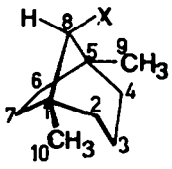
Abstract: The ^{13}C n.m.r. spectra of a series 8-(exo/endo)-substituted 1,5-dimethylbicyclo[3.2.1]octanes have been obtained and the effects of the present substituents X, and Y (=H, OR, alkyl) on the ^{13}C-chemical shifts of the skeleton carbon atoms determined. Especially the steric γ-high field effects are discussed within proposed mechanisms.

Substituent effects on ^{13}C-chemical shifts have been widely discussed because of their value as means of determining the stereochemistry of compounds and getting insight into the electronic structure. Especially the γ-substituent effects have been found to be particularly useful as stereochemical probes. The methyl group, for example, exhibit a shielding effect of -4 to -6.6 ppm on a methylene carbon atom in gauche - arrangement[1] compared to the corresponding anti - analogue. Parallel effects have been reported for heterosubstituents[2] indicating the existence of a "general γ-effect".

These shielding γ-gauche effects have been proposed to arise from steric nonbonding interactions resulting in the polarization of the terminal H-C bonds[3] towards the carbon atom and shifting hereby the corresponding absorption in the ^{13}C n.m.r. spectrum to higher field. This interpretation has recently received widespread reconsideration. From deshielding δ-syn-axial effects[4], and theoretical investigations[5] it was concluded that the primary source of the shielding effects is not the electron density change at the relevant carbon atoms. Other mechanisms for the transmission of the γ-gauche shielding effect have been proposed, e. g. bond angle distortions[6], classical electric field effects[7,8], and the idea that a large part of this high field effect derives from removed hydrogen atoms on the ß-carbon atom[9]. If the γ-effects of heterosubstituents are studied also γ-anti effects can cause significant shielding due to a kind of hyperconjugative electronic interactions including the heteroatom lone pairs[10]. Others[11] state that the degree of substitution of the intervening and the functionalized carbon atoms is the major factor in determining the direction and the size of the γ-anti effect[11]. More recently the hypothesis that a 1,3-diaxial H,H - interaction serves as pathway for transmission of the γ-anti effect[12] has been widely proved[13]. The application of the γ-anti effect to stereochemical assignments however, has been proposed to be used cautiously[14].

In continuation to our studies about the orign of steric γ-substituent effects in ^{13}C n.m.r. spectroscopy[1,15] and their phenomenological application in stereo-

chemical analysis[16] we did synthesize a series of different 8-(exo/endo)-substituted 1.5-dimethylbicyclo[3.2.1]octanes, 1 - 3 (^{13}C NMR spectra- see Table 1)



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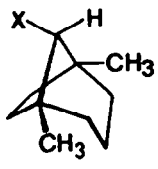

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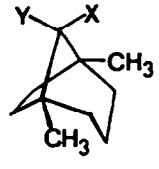


3

1a - X = -H
1b - -OH
1c - -O-COCH$_3$
1d - -Cl
1e - -Br
1f - -I
1g - -O-CHO
1h - -O-CONH-C$_6$H$_5$
1i - -O-CO-C$_6$H$_4$-^{5}NO$_2$(p)
1k - -OCH$_3$
1l - -O-tosyl

2b - X = -OH
2c - -O-COCH$_3$
2d - -Cl

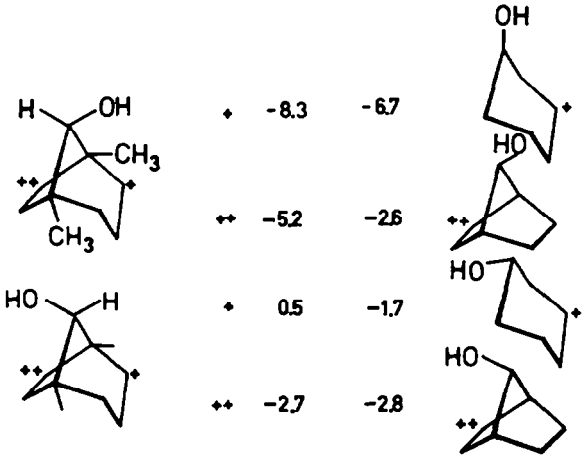
3b X = -OH Y = -CH$_3$
3c -O-COCH$_3$ -CH$_3$
3d -OH -C$_2$H$_5$
3e -OH -C$_5$H$_{11}$
3f -OH -C$_6$H$_5$

The ^{13}C n.m.r. spectra of these compounds and the discussion of the present γ-effects on the ^{13}C-chemical shifts are the major topics of this study. Related compounds, tricyclo[3.2.1.0^{2,4}]octanes, have been investigated in detail [17,18].

(a) Comparing the γ-effects of the hydroxy group in comp. 1b and 2b with analogous values in cyclohexane and norbornane, respectively, results in the following general remarks, represented in Scheme 1:

- Comparable steric conditions in the present γ-fragments result in comparable γ-effects on the ^{13}C-chemical shifts.
- If the hydroxy group and the C^3 - bridge (comp. 1b) are syn positioned both the γ-anti and the γ-gauche carbon atoms are more high field shifted than in the reference compounds.
- If the hydroxy group and the C^2 - bridge (comp. 2b) are syn positioned the opposite is true: the two effects are high field reduced (the γ-anti effect on C-6/7 even is a down field effect).

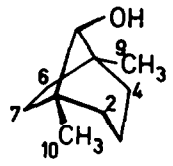
Scheme 1



(b) The γ-effects in the alcohols 1b, and 2b (and also in the related compounds 1, and 2) strongly support the idea that the γ-effect is of steric origin,

especially in that cases where direct steric interactions between the terminal atoms are possible - Scheme 2. The more the hydroxy group and the hydrogen(s)

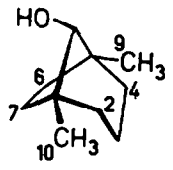
Scheme 2



$\theta_{OH/C-2}$ = 40° $\theta_{OH/C-9}$ = 80°

$r_{O...H-2}$ = 1.9 Å $r_{O...H-9}$ = 2.7 Å

$\Delta\delta_{C-2}$ = -8.3 ppm $\Delta\delta_{C-9}$ = -1.6 ppm



$\theta_{OH/C-6}$ = 75° $\theta_{OH/C-9}$ = 45°

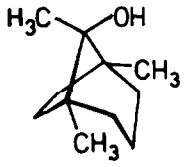
$r_{O...H-6}$ = 2.7 Å $r_{O...H-9}$ = 2.1 Å

$\Delta\delta_{C-6}$ = -2.7 ppm $\Delta\delta_{C-9}$ = -5.2 ppm

on the γ-carbon atom interact sterically (both the dihedral angle $\theta_{OH/C-\gamma}$, and distance $r_{O...H-\gamma}$ get smaller) the more high field shifted are the γ-carbon atoms in the adequate ^{13}C n.m.r. spectrum.

(c) If C-8 is substituted twice (comp. 3b in Scheme 3) the γ-effect of the hydroxy group on C-2/4 with respect to comp. 1b is still the same. Comparable steric conditions at the C^3 - bridge side of both compounds 1b, and 3b, will support this result. Moreover the γ-anti effect of the methyl group can be neglected[1]. The ^{13}C-absorptions of the C-9/10 methyl carbon atoms in 3b are further high field shifted with reference to comp. 1b (-6.7 ppm according to -1.6 ppm in comp. 1b). This is the result of remarkable steric interactions of the 8-methyl substituent and the mentioned γ-carbon atoms C-9/10 - another support for the steric origin of the γ-effect.

Scheme 3



Δδ (C-2/4 = -8.1 ppm)
(C-6/7 = -4.0 ppm)
(C-9/10 = -6.7 ppm)

The γ-anti effect of the hydroxy group on C-6/7 in comp. 3b is reduced to -4.0 ppm (in comp. 1b still - 5.2 ppm). One major reason therefore seems to be the eliminated 1,3-diaxial H,H - interaction by replacing one of the two hydrogen atoms (H-8) by the 8-methyl substituent because the intact 1,3-diaxial H,H - arrangement has been found to be the major precondition[12] for the transmission of this effect. So the elimination of the latter should result in the reduced high field effect, just mentioned, but being still surprisingly large.

(d) Variations of the substituents X in comp. 1, and 2 are negligible for steric informations about the investigated bicyclo[3.2.1]octane skeleton. With the exception of C-8 (substituent carriing carbon atom -α-substituent effect being directly proportional to the substituent electronegativity[19]) variations in the present ß- and γ-substituent effect due to different substituent electronegativities are small (± 0.6 ppm) and the series of substituents too limited to search for polar substituent effects to contribute to the observed substituent-induced-^{13}C-chemical-shifts.

Table 1: ^{13}C-chemical shifts of 8-(exo/endo)-substituted 1,5-dimethylbicyclo-[3.2.1]octanes (δ /ppm)

compound item	subst. X	C-1/5	C-2/4	C-3	C-6/7	C-8	C-9/10	Subst. X
1a	-H	41.1	39.3	21.2	37.0	53.4	27.1	-
1b	-OH	41.4	31.0	19.9	32.4	83.1	25.5	-
1c	$-OCOCH_3$	41.2	32.0	20.0	32.0	82.7	25.1	170.9, 21.0
1d	-Cl	42.8	31.5	19.7	33.1	76.2	25.5	-
1e	-Br	42.4	32.9	19.6	32.4	73.0	25.8	-
1f	-I	42.6	32.5	19.8	34.8	60.7	27.0	-
1g	-O-CHO	41.2	32.0	19.8	32.0	82.8	25.0	160.8
1h	$-OCONH-C_6H_5$	41.1	31.9	20.0	32.2	83.8	25.2	153.7, 138.2, 129.1, 123.3, 118.7
1i	$-OCOC_6H_4-NO_2$	41.8	32.0	20.0	32.4	85.8	25.2	164.5, 150.5, 136.1, 130.7, 123.6
1k	$-OCH_3$	40.4	30.7	18.9	31.0	92.6	24.9	59.2
1l	-O-tosyl[20]	41.4	31.4	19.6	31.9	92.3	25.0	not stated
2b	-OH	45.1	39.8	20.2	34.3	88.1	21.9	-
2c	$-OCOCH_3$	44.8	39.6	20.0	34.8	89.4	22.0	173.4, 21.0
2d	-Cl	46.8	41.0	19.8	34.1	83.1	24.5	-
3b	CH_3/OH	42.1	31.2	18.0	33.0	78.2	20.4	18.3
3c	CH_3/$OCOCH_3$	43.6	32.6	19.5	34.5	79.8	21.7	175.7, 21.7, 19.4
3d	C_2H_5/OH	44.9	32.5	19.6	35.4	80.4	22.8	24.4, 9.4
3e	C_5H_{11}/OH	45.0	32.5	19.5	35.4	78.7	22.8	33.7, 30.1, 29.6, 22.7
3f	C_6H_5/OH	45.7	33.5	18.8	36.2	85.3	22.4	143.7, 128.7, 127.1, 126.2

CONCLUSIONS

(a) The possibility to discuss the general γ-high field effect quantitatively as the result of steric nonbonding interactions in the γ-fragment is still useful, even when other, often chemically less understandable mechanisms have been proposed in the literature instead of it.

(b) Though the transmission of the γ-anti effect to high field through the polarization of 1,3-diaxial protons on C_α and C_γ has been proved[13], a low field effect in comp. 2 has been observed ($\Delta\delta_{C-2/4}$ = +0.5 to 1.7 ppm). The reason therefore may be found in the C^3 - bridge of the bicyclo[3.2.1]octane skeleton which is flattened compared to the strainless cyclohexane[21]. Hereby the steric interactions of the two 1,3-diaxial protons probably become less effective.

EXPERIMENTAL SECTION

Gas chromatograms were recorded on a Varian Moduline 2700 apparatus modified for using of glass capillary columns (100 m Carbowaxs 20M and 100 m OV 1). Preparative chromatography was carried out on Kieselgel 100, 70-230 mesh (Merck, Darmstadt) and n-hexane as eluent. IR spectra (film, cm^{-1}) were registered on an UR 20 apparatus of VEB Carl Zeiss, Jena; Mass spectra (MS, 70 eV) were recorded on a Varian MAT CH-6 apparatus, signals are given in m/e (rel. %); n. m. r. spectra ($CDCl_3$, internal standard TMS) were recorded on a Tesla BS 487 C (^1H n.m.r., 80 MHz), on a Bruker HX 90 (^{13}C n.m.r., 22.63 MHz) and on a Bruker WP 200 (^1H n.m.r., 200.13 MHz, ^{13}C n.m.r., 50.33 MHz).

The ^{13}C chemical shifts are listed in table 1. By using the off-resonance splittings, the relative signal intensities, and literature values [21] the assignment of the carbon atoms C-1/5, C-3, C-8, and C-9/10 is given. Second order effects in the C-2/4 off-resonance multiplets contrary to the sharp C-6/7 off-resonance triplets as well as an independent LIS-study ($Yb(fod)_3$) of the alcohols 1b, 2b, and 3b are used to differentiate the ^{13}C n.m.r. signals of the carbon atoms C-2/4 and C-6/7, respectively.

Synthesis of the compounds

The compounds 1b up to 1i have been synthesized from 1,5-dimethylcycloocta-1,5-diene. This, as well as the preparation of 2b, 2c and 2d, have been described elsewhere[22].

1,5-dimethylbicyclo[3.2.1]octane (1a)

A mixture of 2.3 g (100 mg atoms) sodium in 50 ml dry liquid ammonia was treated with a solution of 2.6 g (15 mmol) 2d[22] in 25 ml dry ether with stirring at -70 °C. The stirring was continued for 2 h, then the sodium was carefully destroyed by addition of 5.4 g (100 mmol) NH_4Cl. The ammonia was allowed to evaporate over night, an additional 100 ml portion of ether and 25 ml water were added. Usual work up gave 1.2 g (60 %) 1a: bp_{30} 36-37 °C; MS: 138 (M^+, 4 %), 123 (M^+-CH_3, 10), 110 ($M^+-C_2H_4$, 10), 109 ($M^+-C_2H_5$, 100), (cf. ref. [23]). Anal. calcd. for $C_{10}H_{18}$: C 86.88, H 13.12, found: C 86.52, H 13.02.

exo-8-methoxy-1,5-dimethylbicyclo[3.2.1]octane (1k)

A solution of 1.54 g (10 mmol) 1b [22] in 30 ml dry THF was treated with 0.6 g (25 mmol) NaH and refluxed for 24 h. Then 7.1 g (50 mmol) CH_3I were added and refluxed for further 10 h. After cooling to 0°C 100 ml water were added. The mixture was extracted with ether. Usual work up gave 1.1 g (65 %) 1k: bp_{10} 66-68 °C; MS: 168 (M^+, 50%), 153 (M^+-CH_3, 5), 136 (M^+-CH_3OH, 66), 107 (100); IR: 2831, 1107; ^1H n.m.r.: 3.41 (s, 3H, $-OCH_3$), 2.66 (s, 1H, $C\underline{H}-OCH_3$), 1.5-1.1 (m, 10 H, $-CH_2-$), 0.85 (s, 6H, $-CH_3$). Anal. calcd. for $C_{11}H_{20}O$: C 78.51, H 11.98, found: C 78.35, H 11.80.

Grignard syntheses of the compounds 3

To a solution of the Grignard reagent prepared from 0.72 g (30 mg atoms) magnesium shavings and 30 mmol of the alkyliodide or bromide in 25 ml of dry ether was droped a solution of 3.04 g (20 mmol) 1,5-dimethylbicyclo[3.2.1]octan-8-one [22] in 10 ml dry ether. The mixture was refluxed for 2 h. After hydrolysis with ice water and ammonium chloride solution the organic layer was separated and worked up as usual.

1,5,8-trimethyl-exo-bicyclo[3.2.1]octan-8-ol (3b)

Yield: 2.85 g (85%); bp_1 73°C; mp 46-47 °C (lit. [24] bp_1 74 °C); MS: 168 (M^+, 47%), 153 (M^+-CH_3, 30), 150 (M^+-H_2O, 42), 135 ($M^+-CH_3-H_2O$, 39), 43 (100); IR: 3480, 1053; ^1H n.m.r.: 1.7-1.2 (m, 11H, -OH, $-CH_2-$), 1.00 (s, 3H, $-CH_3$), 0.81 (s, 6H, $-CH_3$).

8-ethyl-1,5-dimethyl-exo-bicyclo[3.2.1]octan-8-ol (3d)

Yield (after chromatography) 2,48 g (68%); bp_2 74°C; mp 49-50°C (lit. [24] bp_1 68°C); MS: 182 (M^+, 0.2%), 167 (M^+-CH_3, 0.2), 164 (M^+-H_2O, 0.5), 154 ($M^+-C_2H_4$, 2), 153 ($M^+-C_2H_5$, 4), 41 (100); IR: 3485, 1065; ^1H n.m.r.: 1.72 (bs, 1H, -OH), 1.48-1.39 (m, 8H, $-CH_2-$), 1.36-1.18 (m, 4H, $-CH_2-$ and $-C\underline{H}_2CH_3$), 0.96 (t, 3H, $-CH_2C\underline{H}_3$), 0.89 (s, 6H, $-CH_3$).

8-isoamyl-1,5-dimethyl-exo-bicyclo[3.2.1]octan-8-ol (3e)

Yield: 3,16 g (7o%); bp_1 100°C; MS: 224 (M^+, 2%), 209 (M^+-CH_3, 1), 206 (M^+-H_2O,3), 191 ($M^3-CH_3-H_2O$, 2), 181 ($M^+-C_3H_7$, 3), 163 ($M^+-C_3H_7-H_2O$, 5), 153 ($M^+-C_5H_{11}$, 100), 135 ($M^+-C_5H_{11}-H_2O$, 37); IR: 3515, 1052; ^1H n.m.r.: 1.7-1.2 (m, 15H, >CH- and $-CH_2-$), 1.65 (bs, 1H, -OH), 0.83 (d, 6H, $-CH(C\underline{H}_3)_2$), 0.81 (s, 6H, $-CH_3$). Anal. calcd. for $C_{15}H_{28}O$: C 80.29, H 12.58, found: C 80.45, H 12.41.

1,5-dimethyl-8-phenyl-exo-bicyclo[3.2.1]octan-8-ol (3f)

Yield (after chromatography): 2.80 g (61%). bp_2 125°C; MS: 230 (M^+, 6%), 215 (M^+-CH_3, 0.6), 212 (M^+-H_2O, 4), 197 ($M^+-CH_3-H_2O$, 0.4), 154 ($M^+-C_6H_4$, 10), 77

(100); IR: 3485, 1058; ^{1}H n.m.r.: 7.8-7.2 (m, 5H, phenyl), 1.92 (m, 2H), 1.81 (m, 4H), 1.77 (bs, 1H, -OH), 1.60 (m, 2H), 1.21 (q, 2H), 0.69 (s, 6H, $-CH_3$); Anal. calcd. for $C_{16}H_{22}O$: C 83.43, H 9.63; found: C 83.21, H 9.51.

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