^{13}C Nuclear Magnetic Resonance Spectra of Methoxycyclohexane Derivatives. Rotamer Populations about C-OMe Bonds as indicated by ^{13}C Chemical Shifts of Methoxy- and Ring-carbons and $^{3}J_{C,H}$ Coupling Constants

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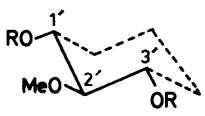
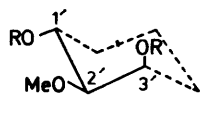
Methoxy ^{13}C chemical shifts in methoxycyclohexane derivatives may be rationalized in terms of rotamer populations about the C–OMe bond and δ_1-effects caused by steric interaction of the methoxy-group with substituents at the neighbouring 2- and 6-positions. Information on rotamer populations is obtained also from the ^{13}C chemical shifts of C-2 and C-6, and from the three-bond coupling between the proton at C-1 and the methoxy-carbon atom.

ATTENTION has been drawn to the dependence of the ^{13}C chemical shifts of methoxy-groups on six-membered rings upon the presence and orientation of oxygen-containing groups at neighbouring positions. Thus, an equatorially oriented methoxy-group in a methylated methyl glycopyranoside, which is situated between two equatorially disposed methoxy-groups as in (a; R = Me) resonates approximately 2—3 p.p.m. to lower field than a methoxy-group which has one equatorially and one axially disposed methoxy-group, as in (b; R = Me), on the adjacent carbon atoms.[1—3] Similar effects are

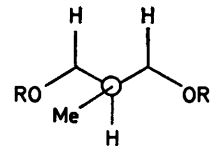


(a)

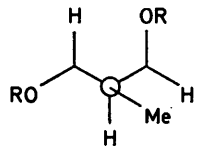


(b)

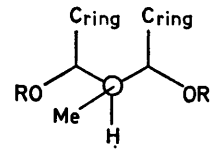
observed if the groups neighbouring the central methoxy-group are hydroxy-groups. Thus, it has been noted [4,5] that methoxy-carbon nuclei in partially *O*-methylated inositols absorb near 60 p.p.m. (from Me_4Si) if flanked by two equatorial hydroxy-groups, as in (a; R = H), but at 58 p.p.m. if flanked by one axial and one equatorial group as in (b; R = H). There is also limited evidence [3,4,6] that similar methoxy-shift dependence on



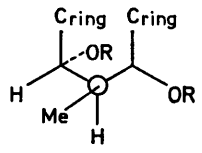
(c)



(d)



(e)



(f)

stereochemistry occurs with the central methoxy-group occupying an axial position, that is (a) and (b) with OMe axially disposed.

Related observations have been made with polymethoxyflavonols;[7] methoxy-groups on the fully aromatic rings resonated in the range 55—57 p.p.m. except where they were flanked by two oxygen atoms, in which case they appeared further downfield, at 60—62 p.p.m.

A rationalization of the stereochemical dependence of the ^{13}C-methoxy-shifts in the alicyclic systems, based on preferred rotamer populations and deshielding δ-effects, was proposed by us [3] and independently by others.[6] The major rotamers about the MeO–C-2′ bond in (a) will be (c) and the equivalent arrangement, in which the methyl group lies close to the other neighbouring oxygen atom.† For (b), the major rotamer about the MeO–C-2′ bond will be (d) since steric interactions are minimum in this conformation. The spatial arrangements of the methyl group, the nearest oxygen atom on an adjacent ring carbon, and the four intervening bonds in (c) and its equivalent arrangement is, essentially, that of the *syn*-axial disposition of a methyl group and an oxygen atom occupying 1,3-diaxial positions on a cyclohexane ring. This orientation has been designated [9,10] δ_1 to distinguish it from others which are possible for two groups separated by four bonds. With few exceptions,[11] δ_1-arrangements, or closely analogous dispositions, produce appreciable *downfield* shifts in the ^{13}C resonance of a methyl group,[9—20] and downfield shifts are also induced in the resonances of methylene carbon atoms when they are involved in δ_1 interactions.[10,21] On the other hand, in rotamer (d), no such δ_1 interaction occurs with the nearest adjacent oxygen atom. It is noteworthy that the stereorelationship between the methyl group in (d) and the carbon atom bearing the axially disposed oxygen substituent is γ-gauche, and it is well recognised [22,23] that such interactions lead to *upfield* shifts in the terminal carbon nuclei of the fragment.

When the central methoxy-group on an alicyclic ring is axially disposed [(a) and (b) with OMe axially orientated] the favoured rotamers are (e) and (f) respectively.

† Analysis of the rotameric behaviour of methoxy-groups in some aldopyranoses, by measurement of ^{1}H chemical shift increments for ring protons at the geminal and vicinal positions, suggests [8] that the rotamer with the *O*-methyl group *gauche* to both vicinal carbons might be a minor component of the rotameric equilibrium in some cases.

The downfield shift which is observed [3,4,6] for the methoxy-carbon resonance when in the stereo-arrangement (e) compared to stereo-arrangement (f) may be rationalized in a similar manner to that described above for the analogous shift, which is found for the equatorially placed methoxy-group in rotamer (c) compared to rotamer (d).

The dependence [7] of methoxy ^{13}C-carbon shifts in methoxyflavonols on the substitution pattern *ortho* to the methoxy-group can be explained in terms related to those used for the alicyclic derivatives. In derivatives possessing no, or only one *ortho*-oxygen substituent atom, rotameric forms are available about the C–OMe bond in which the methyl group avoids interactions of the δ_1-type. However, when there are two *ortho*-oxygen substituents, and the methoxy-group interacts mesomerically with the aromatic ring, then the methyl group must interact sterically with one of the *ortho*-oxygen atoms, leading to δ_1-type * interactions and downfield shifts in the ^{13}C-methoxy-resonance.†

The general equivalence of hydroxy- and methyl-shielding effects in ^{13}C spectra [29] led us to suggest [3] that 1-methoxy-2,6-dimethylcyclohexanes, and related compounds, should also show similar changes in ^{13}C-methoxy-carbon resonances with changes of configuration at the 2- and 6-positions. A desire to test this suggestion, coupled with a realization that δ-effects in the ^{13}C n.m.r. spectra of such systems might provide a valuable aid to stereochemical assignment and rotamer population analysis in related compounds, led us to examine the ^{13}C n.m.r. spectra (Table 1) of methoxycyclohexane (1), a series of substituted methoxycyclohexanes (2)—(15) ‡ and, in addition, the methoxybenzenes (16)—(18).

TABLE 1

^{13}C Chemical shifts of methyl ethers (1)—(18)

Cmpd.	Carbon atom: OCH_3	C-1	C-2	C-3	C-4	C-5	C-6	CCH_3	$C(CH_3)_3$
(1)	55.4	78.8	31.9	24.1	26.0	24.1	31.9		
(2)	56.2	85.3	38.3	33.9	25.6	25.0	30.5	18.8	
(3)	58.4	91.6	38.4	34.6	25.6	34.6	38.4	18.9	
(4)	56.3	87.1	31.4	32.5	20.0	30.9	29.6	13.1_{ax}, 18.4_{eq}	
(5)	57.2	86.7	35.4	38.8	21.8	24.1 [a]	25.6 [a]	20.5_{ax}, 28.6_{eq}	
(6)	62.2	94.3	36.8	40.2	21.5	34.9	34.8	19.1_{ax}, 19.3_{eq}, 29.5_{eq}	
(7)	63.1	95.0	37.2	40.2	18.6	40.2	37.2	20.9_{ax}, 32.3_{eq}	
(8)	56.2	80.5	34.6	29.8	24.0	21.7	27.8	16.1	
(9)	62.0	85.8	37.9	28.5	26.0	28.5	37.9	18.9	
(10)	48.2	73.3	36.1	22.2	25.9	22.2	36.1	24.0	
(11)	55.5	79.8	32.3	25.6	47.6	25.6	32.3		$27.6(CH_3)$, 32.3(C)
(12)	55.5	74.7	30.1	21.4	48.1	21.4	30.1		$27.5(CH_3)$, 32.6(C)
(13)	48.3	72.3	36.3	22.4	47.8	22.4	36.3	24.9	$27.7(CH_3)$, 32.4(C)
(14)	48.4	74.7	36.9	24.5	48.0	24.5	36.9	20.2	$27.7(CH_3)$, 32.3(C)
(15)	63.1	95.2	37.2	41.4	38.7	41.4	37.2	21.0_{ax}, 32.9_{eq}	$27.6(CH_3)$, 31.6(C)
(16)	54.9	159.6	113.9	129.4	120.6	129.4	113.9		
(17)	55.1	157.7	126.5	130.5	120.2	126.8	109.8	16.2	
(18)	59.5	156.9	130.7	128.7	123.7	128.7	130.7	16.0	

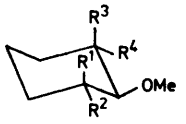
[a] Assignments may be interchanged.

The methoxy-compounds were all prepared by methylation of the corresponding hydroxy-compounds, the ^{13}C n.m.r. spectra of which were also recorded (Table 2). When necessary, compounds were purified by preparative gas–liquid chromatography. With the exception of 2,2,6,6-tetramethyl-4-t-butylcyclohexanol, all the alcohols were either commercially available or had been reported in the literature. 2,2,6,6-Tetramethyl-4-t-butylcyclohexanone was conveniently prepared by *C*-methylation of 4-t-butylcyclohexanone using potassium hydride–methyl iodide.[30] Reduction of the tetramethylketone with sodium borohydride gave an alcohol as the major product, which was isolated by column chromatography, and then *O*-methylated. Based on the similarity of the ^{13}C chemical shift of C-3 (C-5) in the alcohol with that of C-3 (C-5) in the starting ketone, and a comparison of the ^{13}C chemical shifts of the ring-carbons

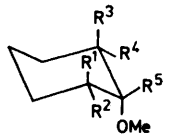
* The four bonds forming the δ-arrangement in this case do not form exactly the same spatial arrangement that occurs in the 1,3-diaxial arrangement in cyclohexane derivatives. Nevertheless, the molecular geometry in such 'δ_1-type' interactions ensure that the end groups in the fragment are brought into close proximity.

† Related downfield shifts in the ^{13}C-resonances of methyl groups in aromatic hydrocarbon derivatives have been observed, in particular for *o*-t-butyltoluene,[24] 1,8-dimethylnaphthalene,[12,25–27] and certain polymethylanthracenes.[28]

‡ The formulae depict favoured chair conformations only, and when compounds exist as racemic mixtures, only one enantiomer is drawn. Rotameric forms (g)—(y) may, in some cases, refer to the opposite enantiomer to that depicted in the formula.

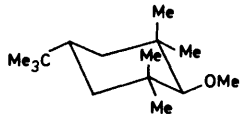


(1) $R^1 = R^2 = R^3 = R^4 = H$
(2) $R^1 = R^3 = R^4 = H, R^2 = Me$
(3) $R^1 = R^3 = H, R^2 = R^4 = Me$
(4) $R^1 = R^4 = H, R^2 = R^3 = Me$
(5) $R^1 = R^2 = Me, R^3 = R^4 = H$
(6) $R^1 = R^2 = R^4 = Me, R^3 = H$
(7) $R^1 = R^2 = R^3 = R^4 = Me$



(8) $R^1 = R^3 = R^4 = R^5 = H, R^2 = Me$
(9) $R^1 = R^3 = R^5 = H, R^2 = R^4 = Me$
(10) $R^1 = R^2 = R^3 = R^4 = H, R^5 = Me$

(11) $R^1 = OMe, R^2 = H$
(12) $R^1 = H, R^2 = OMe$
(13) $R^1 = Me, R^2 = OMe$
(14) $R^1 = OMe, R^2 = Me$



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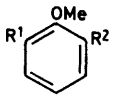
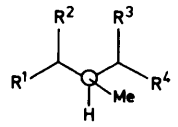


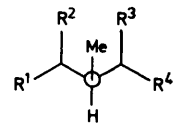
(16) $R^1 = R^2 = H$
(17) $R^1 = Me, R^2 = H$
(18) $R^1 = R^2 = Me$

in the methyl ether with those in related members of the series, the methyl ether was identified as *trans*-1-methoxy-2,2,6,6-tetramethyl-4-t-butylcyclohexane (15).

^{13}C *Chemical Shifts of Methoxy- and Certain Ring-carbons.*—Methoxy-shifts in *trans*- and *cis*-4-t-butylmethoxycyclohexane (11) and (12), [δ_C(OMe) 55.5 in both compounds], and in methoxycyclohexane (1) [δ_C(OMe) 55.4], indicate the chemical shift of an isolated methoxy-group on a cyclohexane ring to be virtually



(g) $R^1 = R^2 = R^3 = R^4 = H$
(h) $R^1 = R^4 = H, R^2 = R^3 = C_{ring}$
(i) $R^1 = Me, R^2 = R^3 = R^4 = H$
(j) $R^1 = Me, R^2 = R^3 = C_{ring}, R^4 = H$
(k) $R^1 = R^3 = R^4 = H, R^2 = Me$
(l) $R^1 = R^2 = R^4 = H, R^3 = Me$
(m) $R^1 = R^4 = Me, R^2 = R^3 = H$
(o) $R^1 = R^4 = Me, R^2 = R^3 = C_{ring}$
(q) $R^1 = R^3 = Me, R^2 = R^4 = H$
(r) $R^1 = R^2 = Me, R^3 = R^4 = H$
(s) $R^1 = R^2 = R^4 = Me, R^3 = H$
(t) $R^1 = R^3 = R^4 = Me, R^2 = H$
(v) $R^1 = R^2 = R^3 = R^4 = Me$



(n) $R^1 = R^4 = Me, R^2 = R^3 = H$
(p) $R^1 = R^4 = Me, R^2 = R^3 = C_{ring}$
(u) $R^1 = R^2 = R^4 = Me, R^3 = H$
(w) $R^1 = R^2 = R^3 = R^4 = Me$

independent of the equatorial/axial nature of the group, a result substantiated by measurements of other workers.[31,32] The similarity of the methoxy-shifts in (1), (11), and (12) is readily rationalized, since the immediate steric environment of an equatorial and an axial methoxy-group in these compounds, shown in rotamers (g) and (h), respectively, are very little different.

Introduction of a methyl group at the 2-position produces a relatively small (<1 p.p.m.) downfield

TABLE 2

^{13}C Chemical shifts of hydroxy-compounds corresponding to ethers (1)—(18)

Compound [a]	Carbon atom C-1	C-2	C-3	C-4	C-5	C-6	CCH_3	$C(CH_3)_3$
(1)-OH	70.0	35.5	24.4	25.7	24.4	35.5		
(2)-OH	76.4	40.3	33.7	25.7	25.2	35.5	18.6	
(3)-OH	82.1	39.8	34.3	25.6	34.3	39.8	18.9	
(4)-OH	77.7	33.4 [b]	31.6	20.0	30.7	33.7 [b]	13.7_{ax} 18.1_{eq}	
(5)-OH	77.2	35.4	38.5	21.7	24.5	30.6	19.3_{ax} 28.6_{eq}	
(6)-OH	83.6	35.7	40.0	21.5	34.7	34.7	18.3_{ax} 19.2_{eq} 29.5_{eq}	
(7)-OH	84.2	35.9	40.1	18.6	40.1	35.9	19.9_{ax} 32.0_{eq}	
(8)-OH	71.1	35.9	28.9	24.5	20.8	32.5	16.86	
(9)-OH	75.1	37.3	27.4	25.9	27.4	37.3	18.7	
(10)-OH	69.9	39.5	22.7	25.7	22.7	39.5	29.6	
(11)-OH	71.1	36.0	25.6	47.2	25.6	36.0		$27.7(CH_3)$ $32.3(C)$
(12)-OH	65.9	33.4	20.9	48.0	20.9	33.4		$27.5(CH_3)$ $32.6(C)$
(13)-OH	68.9	39.3	22.7	47.7	22.7	39.3	31.4	$27.6(CH_3)$ $32.4(C)$
(14)-OH	71.0	40.9	25.0	47.7	25.0	40.9	25.3	$27.7(CH_3)$ $32.2(C)$
(15)-OH	84.3	36.2	41.3	38.9	41.3	36.2	20.2_{ax} 32.5_{eq}	$27.6(CH_3)$ $31.7(C)$
(16)-OH	154.8	115.4	129.7	121.0	129.7	115.4		
(17)-OH	153.5	123.9	131.0	120.8	127.0	115.0	15.7	
(18)-OH	152.0	123.0	128.5	120.2	128.5	123.0	15.8	

[a] The descriptor (1)-OH, *etc.*, refers to the hydroxy-compound corresponding to methyl ether (1), *etc.* [b] Assignments may be interchanged.

methoxy-shift, as indicated by shifts in *trans*-1-methoxy-2-methylcyclohexane (2) [δ_C(OMe) 56.2] and *cis*-1-methoxy-2-methylcyclohexane (8) [δ_C(OMe) 56.2]. In the *trans*-compound (2), which exists overwhelmingly in the diequatorial form, the preferred rotameric form about the C-1–OMe bond should be that shown in (i) in which the *O*-methyl group is γ-gauche disposed to C-6, and in which δ_1 interactions are avoided. The predominance of this rotameric form is supported [22,23] by the shift to high field of C-6 in (2) [δ_C(C-6) 30.5] compared to that in (1) [δ_C(C-6) 31.9].* In the *cis*-compound (8) the conformer with an equatorial methyl group should predominate.[31,34] In either the favoured or unfavoured conformation, the preferred rotameric forms about the C-1–OMe bond [(j), and (k) or (l), respectively] are such that the *O*-methyl group avoids δ_1 interactions with the methyl group at C-2. The importance of rotamer (j) is reflected by the high-field shift of C-6 [δ_C(C-6) 27.8] compared to that in (1) [δ_C(C-6) 31.9].

In *r*-1-methoxy-*t*-2,*t*-6-dimethylcyclohexane (3), the rotameric form (m), which possesses just one γ-gauche interaction, also possesses a δ_1-interaction between the *O*-methyl group and the neighbouring *C*-methyl group. This δ_1 interaction, which could only be relieved in an unfavourable rotamer (n) possessing two γ-gauche interactions, is reflected in the methoxy-resonance of (3) [δ_C(OMe) 58.4] which is 3 p.p.m. to lower field than that of (1) and 2.2 p.p.m. to lower field than those of (2) and (8). That a significantly greater proportion of a conformer of type (n) might be present in compound (3) compared to (1), (11), and (12) is suggested by the greater three-bond coupling ($^3J_{C,H}$) between the methoxy-carbon atom and H-1 in (3) (7.3 Hz) compared to that in (1) (3.7 Hz), (11) (3.8 Hz), and (12) (3.9 Hz). Accumulated evidence [35–37] suggested that there is a dihedral dependence for $^3J_{C,H}$ which is qualitatively similar to the Karplus relationship [38,39] for $^3J_{H,H}$.

r-1-Methoxy-*c*-2,*c*-6-dimethylcyclohexane (9), which would be expected to be, predominantly, in that conformation with the methoxy-group axially disposed, cannot escape δ_1-interactions in any of its three staggered rotameric forms about the C-1–OMe bond. Thus, the *O*-methyl group interacts with the methyl groups at C-2 or C-6 in rotamers of type (o), and in the rotamer (p), in which the Me–O bond points towards the ring, it interacts simultaneously with 3-CH_2 and 5-CH_2. This highly hindered environment is reflected in the chemical shift of the methoxy-carbon atom [δ_C(OMe) 62.0]. The coupling constant, $^3J_{C,H}$, at 9.2 Hz is the highest in the whole series studied here.

In direct contrast, *r*-1-methoxy-*t*-2,*c*-6-dimethylcyclohexane (4), in the chair conformation with the methoxy-group equatorially placed, has available to it one rotameric form about the C-1–OMe bond, (q), which lacks δ_1-interactions, and the methoxy-carbon chemical shift [δ_C(OMe) 56.3] is similar to that in (2) and (8). The relatively large change towards higher field in the chemical shift of C-6 on methylation of the hydroxy-group in the alcohol corresponding to (4) [δ_C(C-6) (ROH) 33.7 to δ_C(C-6) (ROMe) 29.6] is reminiscent of the change in shift reported [4,40,41] for related compounds, with hydroxy-groups replacing *C*-methyl groups, in which it is the β-carbon bearing the axial hydroxy-group which is most affected on *O*-methylation at the α-position. The similarity of $^3J_{C,H}$ (4.6 Hz) in this compound with that in (2) is certainly in keeping with related rotameric forms (q) and (i), respectively, for the two compounds. Calculation † suggests that the probable free-energy difference between the two possible chair conformers for (4) is relatively small (approximately 0.84 kJ mol^{-1}) and is less than the corresponding difference calculated for the related alcohol (1.92 kJ mol^{-1}).[43] However, even in the alternative chair conformation to that actually shown for (4), an axially disposed methoxy-group may still avoid δ_1-interactions in a conformation of type (j) where it is γ-gauche to C-2.

1-Methoxy-2,2-dimethylcyclohexane (5) with a methoxy-shift [δ_C(OMe) 57.2] between that of (1) and (3) appears to present a difficulty for interpretation in steric terms. Initially, a rotameric form (r) might seem reasonable, and, therefore, a smaller shift expected. However, in view of the uncertainty in the conformation of the related 1,1,2-trimethylcyclohexane,[44] it is possible that an interpretation based on chair conformations is too simplistic.‡

It may reasonably be expected that *r*-1-methoxy-2,2,*t*-6-trimethylcyclohexane (6) will adopt a chair conformation with three equatorial substituents. In none of the staggered rotamers (s), (t), or (u), can δ_1-interactions be avoided, and this is reflected in the methoxy-carbon shift [δ_C(OMe) 62.2]. The value of $^3J_{C,H}$ (7.3 Hz) for methoxy-carbon to H-1 coupling is similar to that in (3) and in (7) and (15) (see below).

The favoured chair conformation for 1-methoxy-2,2,6,6-tetramethylcyclohexane, based on the assumptions used to calculate conformational energies for (4), appears to be that with an axial methoxy-group. However, the marked similarities in the ^{13}C shifts of C-1 and C-2 in this compound with those of corresponding carbons in (15), and comparisons with spectra of related compounds in the series, argue strongly that the favoured conformation for the ether is that with an equatorially disposed methoxy-group, as shown in formula (7). Ethers (7) and (15) have the same methoxy-carbon chemical shifts [δ_C(OMe) 63.1], this value being consistent with the δ_1 interactions present in either of the staggered rotameric forms (v) or (w). Also, the $^3J_{C,H}$ values in compounds (7) and (15) are very similar (7.5 and 7.7 Hz, respectively) and in view of the severe steric hindrance

* The γ_e effect of a methyl group in cyclohexanes is known to be negligible.[33]

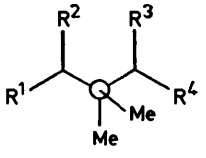
† Parameters used: CH_{3ax} 7.28,[34] OCH_{3ax} 3.14 kJ mol^{-1}.[31] It is assumed here that the mutual conformational energies of vicinal methyl and methoxy-groups are the same as those of vicinal methyl and hydroxy-groups.[42]

‡ The energy difference between the two chair forms for (5) may be calculated to be 0.84 kJ mol^{-1}, with the same assumptions used in the calculation of the conformational energy difference for (4).

likely to be encountered in rotamer (w), it is tempting to explain these large coupling constants, compared to those in (1), (11), and (12), in terms of a conformation of the type (v) in which the dihedral angle between Me–O and C-1–H bonds is significantly less than 60°.

Experimental evidence suggests [45] that 1-methoxy-1-methylcyclohexane (10) should exist in a conformational equilibrium containing approximately 60—65% of the conformer with an equatorial *C*-methyl group. The γ-interactions suffered by the *O*-methyl group in either the axial position [rotamer (x)] or the equatorial position [rotamer (y)] are indicated by the resonance of the methoxy-carbon [δ_C(OMe) 48.2] which is at a considerably higher field than that of methoxycyclohexane (1).

The methoxy-carbon shift for *r*-1-methoxy-1-methyl-*c*-4-t-butylcyclohexane (13) [δ_C(OMe) 48.3] most probably corresponds to rotamer (x) and that in *r*-1-methoxy-1-



(x) $R^1 = R^4 = H, R^2 = R^3 = C_{ring}$
(y) $R^1 = R^2 = R^3 = R^4 = H$

methyl-*t*-4-t-butylcyclohexane (14) [δ_C(OMe) 48.4] to rotamer (y). The similarity in δ_C(OMe) values of (13) and (14) suggests that a methoxy-shift is independent of the axial/equatorial nature at a tertiary centre, when vicinal substituents are absent.

To broaden the scope of this study, ^{13}C n.m.r. spectra of anisole (16), 2-methylanisole (17), and 2,6-dimethylanisole (18) were measured, and δ_C(OMe) values of 54.9, 55.1, and 59.5, respectively, were obtained. The approximately 4 p.p.m. difference in δ_C(OMe) values of (18) and those of (16) and (17), and the small difference between the shifts for (16) and (17), provide strong evidence for the influence which δ_1-type interactions have on methoxy-carbon chemical shifts.

C-*Methyl Chemical Shifts*.—For compounds (3), (6), (7), (9), and (15), in which the methoxy-carbon atoms show a marked downfield shift compared to (1) as a result of δ_1-interactions with methyl groups at C-2 and C-6, corresponding downfield shifts should be apparent in the ^{13}C resonances of the C-2- and C-6-methyl groups, when compared with the resonances for these carbon atoms in the corresponding alcohol. Although small downfield shifts are observed in some of the *C*-methyl resonances, they are, generally, smaller than might be expected for a δ_1-interaction between methyl groups.[11-16,19,20,24,28] Also, the *C*-methyl resonance in (18) [δ_C(Me) 16.0] is close to that in 2,6-dimethylphenol [δ_C(Me) 15.8], even though the methoxy ^{13}C resonance in (18) is >4 p.p.m. to lower field than that in (16). We can offer no explanation for the relative insensitivity of the ^{13}C-shifts of these *C*-methyl groups towards the δ_1 interactions.

^{13}C-*Shifts of Ring Atoms compared to Those in Corresponding Hydrocarbons*.—Roberts and his co-workers [29] reported that for a series of acyclic and alicyclic alcohols, the carbon chemical shifts were linearly related to those in the corresponding hydrocarbon, wherein a methyl group takes the place of the hydroxy-group. Such a correlation was observed for carbons at the site of hydroxy substitution (α), at the carbon atom next removed (β), and so on, and, most strikingly, there was a remarkable fit to lines of unit slope for the resonances of β-, γ-, and δ-carbon atoms. For the resonances of α-carbons, a line of unit slope did not seem correct.

We have conducted a similar analysis by plotting, separately, the chemical shifts of the α-, β-, γ-, and δ-carbon atoms in the methyl ether (1)—(15) against the ^{13}C-shift of the corresponding carbon atom in the corresponding hydrocarbon.* For the α-, γ-, and δ-carbon resonances, good linear plots are obtained with the following parameters [equations (1)—(3)].

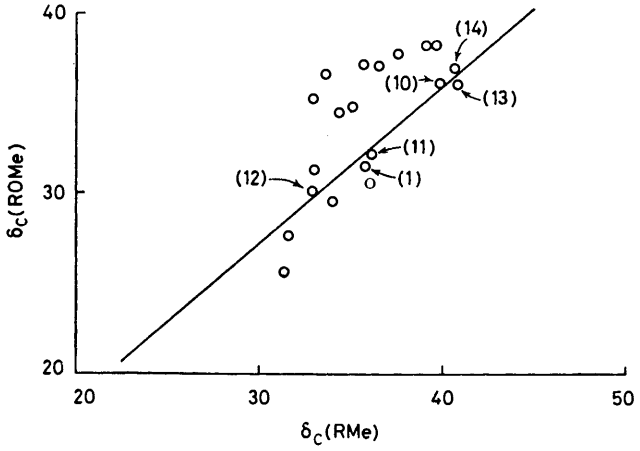
$$\delta_C(\text{ROMe})(\alpha) = 1.03\ \delta_C(\text{RMe})(\alpha) + 44.31 \quad (1)$$
$$r \text{ (linear correlation coefficient)} = 0.9855$$
$$\delta_C(\text{ROMe})(\gamma) = 0.96\ \delta_C(\text{RMe})(\gamma) - 0.35 \quad (2)$$
$$r = 0.9901$$
$$\delta_C[\text{ROMe} = 0.99\ \delta_C(\text{RMe})(\delta) - 0.40 \quad (3)$$
$$r = 0.9988$$

The plot obtained for δ_C(ROMe)(β) against δ_C(RMe)(β) is shown in the Figure. In striking contrast to the alcohol–hydrocarbon plot for β-carbon chemical shifts in the earlier [29] and the present work (neglecting data for the pairs of compounds 2,2,6,6-tetramethylcyclohexanol and 1,1,2,6,6-pentamethylcyclohexane, and *trans*-2,2,6,6-tetramethyl-4-t-butylcyclohexanol and *trans*-*r*-1,2,2,6,6-pentamethyl-4-t-butylcyclohexane), there is no linear correlation.

The reason for the lack of a linear correlation may find its origin in the δ_1-interactions which may occur in certain rotamers of members of this series of compounds, and the γ-gauche interactions which occur between the *O*-methyl groups and C-2 or C-6. Stothers and his co-workers [13-15] have made the important observation that shifts of as much as 10—11 p.p.m. occur for carbon atoms *bearing* sterically crowded nuclei in a γ- or δ-relationship, upon comparison of the observed shieldings with those

* The ^{13}C n.m.r. spectra of the hydrocarbons corresponding to (6) and (7) have not, to our knowledge, been measured, but the required chemical shifts may be calculated using the ^{13}C-shift parameters for methylcyclohexanes.[33,44] However, compound (7) contains one important structural feature not included in the original analysis [33,44] of methylcyclohexanes, that is the 1,3-diaxial arrangement. It is clear from our graphical correlation (see text) of the β-shifts of alcohols with hydrocarbons, that the calculated shift of C-1 [C-6] in 1,1,2,6,6-pentamethylcyclohexane (eq. Me–C-2) is too small by approximately 7.3 p.p.m. On this basis, the 1,3-diaxial interaction between two methyl groups on a cyclohexane ring requires a chemical-shift parameter of approximately +7.3 p.p.m. for the ring carbons *bearing* the interacting groups; the calculated shift of C-1 [C-6] in 1,1,2,6,6-pentamethylcyclohexane was corrected, accordingly. The shifts for ring carbons in hydrocarbons corresponding to (13) and (14), and to (15), were obtained from those of 1,1-dimethylcyclohexane and 1,1,2,6,6-pentamethylcyclohexane, respectively, by applying a substituent-parameter correction for the t-butyl group.

predicted on the basis of simple additivity of substituent effects. The deviations are upfield for a γ-interaction and downfield for a δ-interaction. Most importantly, in the case of a δ-interaction, the deviations from expected shifts are much greater than those found for carbon atoms in terminal positions. The potential of such shifts for use in stereochemical analysis has been recognised.[15]



^{13}C Chemical shifts of β-carbon atoms in methoxycyclohexanes (ROMe) plotted against the corresponding β-carbon shifts in the corresponding methylcyclohexanes (RMe). The straight line is the best fit obtained by linear regression analysis (r 0.9929) from data points for (1), (10), (11), (12), (13), and (14) and the corresponding hydrocarbons. β-Carbon shifts for the methoxycyclohexanes are recorded in Table 1 and those for the methylcyclohexanes were taken from the literature,[31,33,34] or calculated (see text)

We suggest that deviations of this type in the ^{13}C shifts of carbons bearing δ-related, sterically interacting substituents are partly responsible for the divergence of the ^{13}C shifts of the C-2 and C-6 ring-carbon atoms in the 1-methoxycyclohexanes (that is, β with respect to the site of substitution) from values which might be predicted. Because of the large deviations produced in the resonances of penultimate carbons of a sterically crowded δ-fragment, the C-2 and C-6 resonances will reflect the presence of rotameric forms possessing δ_1 interactions *even if these constitute a relatively minor proportion of the population of conformers*. It may be expected, therefore, that if C-2 or C-6 bears a methyl group which may suffer a δ_1-interaction with the *O*-methyl group, the resonances of C-2 or C-6 will be to lower field than predicted. On the other hand, when the *O*-methyl group is γ-gauche with respect to C-2 or C-6, and does not at the same time suffer δ_1-interactions with substituents present on C-2 or C-6, then the resonances of these carbons will be to higher field than expected, as a result of the well known γ-gauche effect.[22,23] Members of the series lacking any substituents at C-2 and C-6, that is (1), (10), (11), (12), (13), and (14), provide a basis to test this proposed rationalization, since the resonances of C-2 (C-6) in these compounds may be used to predict the expected values of other members of the series. Thus, after placement of the best straight line through the points on the graph obtained for the β-resonances of these six compounds and the corresponding hydrocarbons (see Figure), then expected values of β-resonances in the other members of the series can be obtained by interpolation of the β-resonances in the corresponding hydrocarbon. It is readily seen that points on the graph which lie to the upper-left of the straight line correspond to methoxy-compounds having resonances of β-carbon carbons to *lower* field than expected, and those to the lower-right, to *higher* field than predicted. All the β-carbon resonances lying to the upper-left of the straight line arise from just those carbon atoms which are the penultimate atoms in a δ_1-arrangement, albeit in some cases in a relatively unfavoured rotameric form. On the other hand, those points to the lower-right of the line arise from carbon atoms which are γ-gauche to the *O*-methyl group in the preferred rotamer, and which lack δ_1-interactions.

It is pertinent that in 2,6-dimethylanisole (18), the resonance of the penultimate carbon atom in the group of atoms forming the δ_1 type arrangement, C-2 (C-6) is approximately 7 p.p.m. to lower field than that calculated[35] (123.4 p.p.m.) on the basis of additivity tables. However, in 2,6-dimethylphenol, in which the methyl group at C-2 suffers a γ-interaction with the oxygen atom, the resonance of the penultimate carbon atom in the γ-arrangement resonates approximately 2 p.p.m. to higher field than that expected (125.1 p.p.m.).

Methoxy ^{1}H-*Chemical Shifts.*—Previous work[1-3] suggested that changes in the ^{1}H- and ^{13}C-chemical shifts of a methoxy-group, induced as a result of involvement of the group in δ_1-interactions, were both in the same direction, and to lower field. This correspondence in the direction of shift changes is in contrast to previously observed[46] inverse shielding effects on ^{1}H and ^{13}C nuclei caused by steric interactions of the γ-type.

The ^{1}H-chemical shifts of the methoxy-groups in compounds (1)—(18) are recorded in the Experimental section. For the ethers of the cyclohexanol derivatives, the general trends in these shifts are in agreement with previous results,[1-3] that is, those compounds exhibiting marked low-field ^{13}C-shifts compared to (1) show, correspondingly, low-field ^{1}H-shifts compared to (1). However, a comparison of ^{13}C- and ^{1}H-methoxy-shifts for the pairs of compounds (1) and (10), (11) and (14), and (12) and (13) shows that increasing the number of γ-interactions suffered by a methoxy-group causes both ^{13}C- *and* ^{1}H-shifts to move to higher field.

The ^{1}H- and ^{13}C-methoxy-resonance in (18) are both at lower field than the corresponding resonances in (16), as expected from a consideration of the δ-interactions in the former compound. It is curious, however, that the ^{1}H-methoxy-resonance in (17) is at a lower field than that in (18), even though the magnitude of its ^{13}C-shift compared to (16) suggest that no significant δ interactions are present.

EXPERIMENTAL

^{13}C N.m.r. spectra were recorded using a JEOL FX100 spectrometer at 25.05 MHz at *ca.* 27 °C. Samples were prepared as approximately 0.5M-solutions in [^{2}H]chloro-

form–1,4-dioxan–tetramethylsilane (87 : 10 : 3 v/v/v). Chemical shifts were found not to vary significantly over the concentration range used. The field-frequency lock was provided by the [^{2}H]chloroform. Spectra were recorded at a sweep-width of 2 500 Hz and FIDs were accumulated into 8K addresses giving a digital resolution of 0.61 Hz, equivalent to 0.024 p.p.m. Chemical shifts were measured relative to Me_4Si and the reproducibility in each spectrum of the chemical shift of 1,4-dioxan (average value δ_C 67.09, standard deviation 0.045 p.p.m.) gave an indication of the accuracy of the shift measurements. ^{1}H N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer on *ca.* 0.5M-solutions in [^{2}H]chloroform–1,4-dioxan–tetramethylsilane (87 : 10 : 3 v/v/v) at a sweep width of 50 Hz in the methoxy-proton region; internal Me_4Si was used as a reference for field-frequency locking and spectra were calibrated using a pen-coupled, digital frequency-counter. Analytical gas–liquid chromatography (g.l.c.) was performed on a Perkin-Elmer F11 machine, between 140 and 210 °C, using a column (72 × $\frac{1}{8}$ in) containing a stationary phase of Carbowax 20M on Chromosorb W. Preparative g.l.c. was performed with a Perkin-Elmer F21 machine using a column (72 × $\frac{3}{8}$ in) of Carbowax 20M supported on Chromosorb W.

Ethers (1)—(18) were prepared by methylation of the corresponding hydroxy-compounds by procedures A (alcohols) or B (phenols) as described below. The hydroxy-compounds corresponding to ethers (1), (2), (16), (17), and (18) were commercially available, whereas those corresponding to (3), (4), and (9), and to (11) and (12) were commercially available as mixtures of isomers. These mixtures were fractionated by preparative g.l.c. before methylation, but complete separation of the isomeric 2,6-dimethylcyclohexanols was not achieved. Literature procedures were used to prepare 2,2-dimethylcyclohexanol,[47] *cis*-2-methylcyclohexanol,[48] and 1-methylcyclohexanol.[49] *r*-1-Methoxy-2,2,*t*-6-trimethylcyclohexane (6) was isolated, contaminated by two unidentified minor components, by preparative g.l.c. of the mixture obtained on methylation of the sodium borohydride reduction product of 2,2,6-trimethylcyclohexanone. The major product of this reduction was identified as *r*-1,2,2,*t*-6-trimethylcyclohexanol on the basis of the coupling constant $J_{1,6}$ 10 Hz in its ^{1}H n.m.r. spectrum (see ^{1}H n.m.r. data reported [50] for the stereoisomeric 2,2,6-trimethylcyclohexanols). 2,2,6,6-Tetramethylcyclohexanol has been described,[51] but a more convenient preparation uses the potassium hydride–methyl iodide alkylation of cyclohexanone,[30] followed by sodium borohydride reduction of the product. Separation, by chromatography on silica gel, of the *ca.* 1 : 1 mixture of diastereoisomeric alcohols, obtained [52] by reaction of methylmagnesium iodide on 4-t-butylcyclohexanone gave the known [52] *cis*- and *trans*-1-methyl-4-t-butylcyclohexanols, which were methylated to afford (13) and (14) respectively.

2,2,6,6-*Tetramethyl*-4-*t*-*butylcyclohexanone*.—4-t-Butylcyclohexanone (8 g) was treated with potassium hydride (60 ml; 20—25% dispersion in mineral oil) and methyl iodide (22 ml) in tetrahydrofuran (350 ml) essentially as described for the preparation of 2,2,6,6-tetramethylcyclohexanone,[30] and the *C*-alkylated products were distilled from the mineral-oil mixture, after work-up, to yield a product (6.7 g), b.p. 118—128 °C at 15 mmHg. G.l.c. analysis of this product indicated one major and several minor components. The distillate was purified by column chromatography on silica gel (220 g) (Merck Kieselgel 60, 70—230 mesh) using toluene–light petroleum (b.p. 60—80 °C) (3 : 2 v/v) as eluant, and a portion of the major component was isolated and recrystallised from light petroleum to give the *ketone*, m.p. 99—100° (Found: C, 79.65; H, 12.9%; M^+, 210.1992. $C_{14}H_{26}O$ requires C, 79.9; H, 12.5%; *M*, 210.1984); δ_C ($CDCl_3$) 220.8, 44.2, 41.7, 38.8, 31.9, 28.4, 28.0, and 27.5. (Signal at 220.8 p.p.m. measured from spectrum of sweep width 6 024 Hz.)

trans-2,2,6,6-*Tetramethyl*-4-*t*-*butylcyclohexanol*.—To a stirred solution of 2,2,6,6-tetramethyl-4-t-butylcyclohexanone (1 g) in a mixture of ethanol (6 ml) and water (1 ml) was added a solution of sodium borohydride (0.11 g) in water (1 ml) over 3 h. After 18 h at room temperature, the ethanol was removed on a rotatory evaporator and the remaining aqueous solution was acidified with 2.5M-hydrochloric acid, then extracted with chloroform (4 × 5 ml). The combined extracts were concentrated to give a residue (0.5 g), $\nu_{max.}$ (Nujol) 3 600—3 400, no absorption near 1 700 cm^{-1}. G.l.c. indicated only one component was present, and crystallisation from light petroleum gave the *product*, m.p. 104—105 °C (Found: C, 78.7; H, 13.5%; M^+, 212.2198. $C_{14}H_{28}O$ requires C, 79.2; H, 13.3%; *M*, 212.2140).

Methylation of Hydroxy-compounds.—*Procedure A*. To a stirred solution of the alcohol (5 mmol) in anhydrous ether (15 ml) was added sodium hydride (20 mmol), and after formation of the sodium salt was complete (lack of effervescence), a solution of methyl iodide (25 mmol) in ether (10 ml) was added over 0.5 h. The mixture was heated under reflux for 24—48 h. In the case of some hindered alcohols, when g.l.c. indicated incomplete methylation, a further amount (5 mmol) of sodium hydride and methyl iodide was added, and heating was continued for a further 24 h. Water (5 ml) was added, the ether layer separated, and the aqueous solution further extracted with ether (3 × 15 ml). The combined, dried extracts were concentrated to give the crude methyl ether which, in nearly all cases, was purified by preparative g.l.c.

Procedure B. To a stirred and cooled (0 °C) solution of the phenol (60 mmol) in 2.7M-aqueous sodium hydroxide (30 ml) was added, dropwise, dimethyl sulphate (73 mmol), over 0.5 h. The mixture was then heated under reflux for 2 h, and after allowing it to cool, water (30 ml) was added. The layer were separated and the aqueous layer was extracted with ether (5 × 25 ml). The combined organic phases were washed with water (25 ml), 1M-sulphuric acid (2 × 25 ml), and then water (3 × 25 ml). The dried organic solution was concentrated to afford the crude ether, which was purified by distillation at 15 mmHg.

^{1}H *Chemical Shifts of Methoxy-protons*.—Chemical shifts, measured at 100 MHz, are given in Hz from 1,4-dioxan (mean chemical shift of 1,4-dioxan from Me_4Si was 366.3 Hz, standard deviation 0.9 Hz); positive values indicate resonances to high field of 1,4-dioxan: compound (1), δ_H 35.0; (2), 34.3; (3), 27.2; (4), 36.6; (5), 36.2; (6), 20.5; (7), 16.7; (8), 37.1; (9), 23.0; (10), 51.0; (11), 34.7; (12), 39.1; (13), 53.9; (14), 45.8; (15), 16.0; (16), 9.9; (17), −12.9; (18), −3.5.

$^3J_{C,H}$ *Values for Methoxy-carbon to H-1 Coupling in* (1)—(9), (11), (12), and (15).—Compound (1), $^3J_{C,H}$ 3.7; (2), 4.9; (3), 7.3; (4), 4.6; (5), 5.5; (6), 7.3; (7), 7.5; (8), 4.3; (9) 9.2; (11), 3.8; (12), 3.9; (15), 7.7.

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